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REVIEW

Micronutrients deficiences in patients after bariatric surgery

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Abstract

Bariatric surgery is an effective option for managing obesity and has gained general acceptance among patients in recent years. Generally, despite the high caloric intake, a bad nutritional habit of obese people results in the deficiency of several vitamins, minerals, and trace elements essential for body metabolism and normal physiological processes. Additionally, the current bariatric surgical approaches such as sleeve gastrectomy (SG), Roux-en-Y-gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), and jejunoileal bypass (JIB) can cause or exacerbate these deficiencies. Based on several reports, it appears that the various bariatric surgical procedures affect nutrient absorption differently. Being purely restrictive, LAGB and SG affect the absorption of iron, selenium, and vitamin B_{12}, while RYGB, JIB, and biliopancreatic diversion have a more profound impact on the absorption of essential vitamins, minerals, and trace elements. Nutritional deficiencies in vitamins, minerals, and trace elements may follow bariatric surgery and are associated with clinical manifestations and diseases, including anemia, ataxia, hair loss, and Wernicke encephalopathy. The present review summarizes some of the major vitamin and micronutrient deficiencies associated with bariatric surgery, particularly those presented post-surgically. To avoid any adverse consequences of vitamin and trace element deficiency, proper monitoring and tests are recommended at any stage, from pre- to post-surgery (periodical check-up), followed by specific and individual nutritional supplementation treatments and a proper healthy diet.

Keywords Bariatric surgery · Nutritional supplements · Micronutrients deficiency · Trace elements deficiency · Vitamins deficiency

Introduction

Obesity has become a global public health issue with an increased incidence in recent decades [1]. Alarmingly, a higher prevalence rate of obesity has also fueled other health epidemics such as type 2 diabetes mellitus, dyslipidemia, insulin resistance, and cardiovascular disorders [1]. Bariatric surgery has recently gained attention as an effective option to manage obesity, and the acceptance of this surgical procedure has increased in the past few years [2, 3]. The strategies for the management of obesity include lifestyle changes, medications, and surgery. Generally, individuals with very

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high body mass index (BMI) (> 40) or obese subjects with BMI in the range of 35–39.9 and suffering from one of the obesity-associated metabolic complications are advised for weight-loss surgery. For individuals with BMI around 30, the decision to conduct bariatric surgery can be taken after consideration [4]. According to the International Diabetes Federation, those patients with type 2 diabetes mellitus who have suboptimal blood glucose control on a background of adequate medical therapy are recommended bariatric surgery even though their BMI could be just 30 kg/m^2 [5]. In bariatric surgery, the stomach size is reduced to limit the calorie intake of the obese patient leading to reduced food intake and a progressive loss of weight with time. For instance, the stomach size is reduced by 80% in the sleeve gastrectomy (SG), thus significantly reducing solid food and calories. SG spares the upper part of the intestine and is today one of the most common surgical procedures for weight loss as it is widely performed in the USA, Canada, Europe, and several Asian countries [6]. In a biliopancreatic diversion with the duodenal switch (BPD/DS), the stomach is resected in the same way as in SG with a subsequent connection of the intestine end portion to the duodenum near the stomach [7]. In another type of bariatric surgery, called the Roux-en-Y-gastric bypass (RYGB), the stomach is divided into two parts: the smaller upper part and the bigger lower part. The small intestine is rearranged into a Y-configuration to connect to both parts of the stomach, and as a result, the major part of the small intestine is preserved from nutrients absorption. The reversal of RYGB is possible but might technically be demanding compared with removing a gastric band [8]. Laparoscopic adjustable gastric banding (LAGB) is an alternative procedure but less effective in achieving weight loss than RYGB and SG [2, 3, 9]. Another type of bariatric surgery, the jejunoileal bypass (JIB), was the first bariatric surgery performed and led to dramatic weight loss in patients. However, subjects who undergone JIB showed severe side effects, and many died due to liver failure and other complications making this bariatric procedure out of favor. Since then, SG and RYGB have been the two commonest bariatric procedures to effectively manage obesity and weight loss [9–11]. However, these surgical procedures still have some side effects, and individuals who have undergone bariatric surgery often display the signs of vitamin and micronutrient deficiencies (Table 1) [2, 3, 10].

Different types of bariatric surgeries impact the absorption of micronutrients differently. Being purely restrictive, LAGB and SG affect the absorption of iron, zinc, selenium, folate, and B12, while RYGB, JIB, and biliopancreatic diversion (BPD) have a more profound impact on the absorption of essential vitamins, minerals, and trace elements [12]. Over the past decade, several international publications tried to address the issue of micronutrient supplementation in post-bariatric patients [13–15]. The present review summarizes some of the major vitamin and micronutrient deficiencies associated with bariatric surgery, focusing particularly on those presented post-surgically. Further, the co-existent pathologies and the most common symptoms associated with them are discussed.

Methods

A comprehensive search through the scientific literature on bariatric surgery and micronutrient deficiencies was carried out via Pubmed and Cochrane Library databases to meet the review goal fully. All searches in Pubmed were performed

Table 1 Deficiencies of vitamins and trace elements after bariatric surgery and the associated clinical manifestations and diseases

Deficiency	Clinical manifestations—diseases
Vitamins	
Vitamin B12	Lost of body coordination, numbness, neurological complications, memory impairment, macrocytic anemia, leucopenia, infertility
Vitamin B1	Wernicke–Korsakoff syndrome, constipation, nausea, fatigue, anorexia, numbness, weakness
Vitamin A	Insomnia, acne, hyperkeratosis, night blindness, fatigue, immune impairment, dry hair
Vitamin K	Blood clotting disorders, osteoporosis
Vitamin C	Fatigue, delayed wound healing, depression, scurvy
Minerals	
Iron	Anemia, immunodeficiency, fatigue, weakness, pale skin, headaches, dizziness, heart palpitations, shortness of breath, cold extremities, hair loss, gastrointestinal complaints
Calcium	Osteoporosis, tooth decay, depression, heart problem, weak nails, dermatitis, hypertension, muscle spams, sleeplessness
Zinc	Slow healing, hair loss, acrodermatitis, anxiety, depression, hormone disturbance, poor concentration, immune dysfunction
Copper	Fatigue, weakness, pallor, join pains, muscle pain, numbness, tingling, osteoporosis, anemia, frequent illness, skin inflammation, cold sensitivity
Selenium	Immune system dysfunction, vulnerability to infection, fatigue, hair loss, liver dysfunction, thyroid dysfunction, reproductive disorders

with the help of the following keywords: ["Bariatric Surgery" (MeSH)] OR ["Gastric Bypass" (MeSH)] OR ["Gastroplasty" (MeSH)] OR ["Jejunoileal Bypass" (MeSH)] AND ["Micronutrients" (MeSH)] OR ["Trace Elements" (MeSH)]. The search was limited to papers in the English language published from inception to 30 April 2021. According to their titles, all papers were initially screened to decide about their relevance for the scope of the review. As a next step, all papers were evaluated based on their abstracts with subsequent selection of papers meeting the inclusion criteria: (i) publications reporting about micronutrient deficiencies associated with bariatric surgery; (ii) studies on human subjects; and (iii) studies published in the English language.

As for the exclusion criteria, the following filters were applied: (i) unavailability of the full text, (ii) studies of low methodological quality (i.e., case reports, letters, or commentaries), and (iii) studies published in languages other than English. As soon as all irrelevant publications were excluded, a check for duplicates was performed, and the final list of papers to be included in the present review was prepared. Finally, all full texts were accessed and analyzed to exclude papers not meeting the inclusion criteria.

An initial version of the review was drafted after extracting data from the selected papers and followed a structure of the review. This initial draft was discussed between all co-authors, which helped obtain ideas and suggestions to reflect the review scope better. After the initial draft was amended based on the suggestions made, the final version of the review was prepared, repeatedly sent to all co-authors for re-evaluation and approval. After all, co-authors ranted the permission for publication, and the corresponding author was assigned.

Bariatric surgery techniques and risk of deficiencies

Bariatric surgery aims to manage weight gain by primarily reducing the calorie intake of an individual. Bariatric surgeries are classified into restrictive and malabsorptive categories based on the mechanism used to reduce calorie intake. In the restrictive type to which SG belongs, the stomach size is reduced to reduce food intake and early satiety. However, in the malabsorptive type, the amount of calories absorbed by the body is reduced by bypassing the food route [16, 17]. This leads to reduced contact between the food and the digestive juices secreted by the pancreas. In another strategy, the main absorptive regions of the small intestine (the duodenum and the proximal jejunum) are bypassed to prevent the absorption of calories. However, the ultimate reduction in energy intake and absorption of nutrients also depends on the overall manipulations with the gastrointestinal tract.

In malabsorptive procedures, the main cause of vitamin, mineral, and trace element deficiencies is bypassing the main sites where the absorption of micronutrients occurs. Besides, created bypass excludes the "intestinal phase" of pancreatic secretion, induced by food entering the duodenum. Instead, the bypass results in the permanent ileal brake stimulation since undigested food particles enter the ileum stimulating the secretion of glucagon-like peptides 1 and 2 and peptide YY, which suppress pancreatic secretion and further exacerbate malabsorption [18]. As for restrictive procedures, the resected gastric fundus decreases the absorption of certain micronutrients, including iron, zinc, selenium, and vitamin B12. Moreover, the resulting caloric restriction contributes to folic acid, vitamin B1, vitamin B6, and copper deficiencies [19]. RYGB is one of the most commonly performed bariatric surgeries and, together with SG, constitutes approximately 95% of the total bariatric surgeries performed [20]. RYGB drastically reduces the gastric capacity by 90–95%, leading to a massive decline in calorie intake [16, 17]. Such a drastic reduction in consumed calories may be associated with adverse side effects and gastrointestinal symptoms. The prevalence of anemia in RYGB is twofold within 12 months of the surgery, and such patients showed a reduction in hemoglobin/hematocrit with time. Osteopenia and secondary hyperparathyroidism were also attributed to RYGB because of reduced calcium absorption, and this may even result in an increased rate of fractures, especially two years after the surgery. This happens due to the bypass of the duodenum, which has the highest concentration of calcium transporters [21].

Similarly, malabsorptive procedures like biliopancreatic diversion (BPD) and biliopancreatic diversion with duodenal switch (BPD/DS) also induce vitamin, mineral, and trace element deficiencies [22]. A recent study by Homan et al. [22] demonstrated that patients with BPD and BPD/DS frequently suffered from anemia, and deficiency of fat-soluble vitamins was common in post-surgery even after vitamin supplementation. However, it is important to remember that lack of supplementation is associated with worse outcomes, and thus, it was proposed to enable life-long monitoring at a specialized bariatric center and possibly a better micronutrient supplementation [23]. The other study reported on nutrient deficiency post SG, which has been shown to reduce protein absorption by 25%, while fat absorption is reduced by 72%. This leads to a reduction in the absorption of various fat-soluble vitamins and zinc [24].

Besides, increased gallstones formation secondary to a rapid weight loss after surgery and enhanced lithogenicity of bile was reported. Hyperoxaluria is also a side effect of bariatric surgery, and it may lead to oxalate nephropathy and even renal failure [25]. Another dangerous side effect is rhabdomyolysis, associated with acute kidney injury but occurs quite seldom [26].

Based on the above-cited studies, it is evident that various bariatric surgical procedures affect nutrients absorption differently. Furthermore, the high frequency of micronutrients and vitamin deficiencies in obese patients before bariatric surgery, which could aggravate the surgical procedure and lead to postoperative complications, should be considered carefully.

Deficiencies before bariatric surgery

Obesity is generally a consequence of excessive consumption of energy-dense foods leading to a positive energy balance. Thus, it is intriguing that individuals suffering from obesity and overweight also show signs of nutritional deficiency (Fig. 1).

Several scientific studies have shown that obese and overweight individuals suffer from micronutrient deficiency, with the deficiency more pronounced in individuals with extreme obesity (BMI > 40 kg/m^2) [27]. The coexistence of obesity and diabetes leads to altered vitamin D status associated with low serum calcium concentrations and induced secondary hyperparathyroidism [28]. Decreased vitamin D levels are also observed in obese patients with associated cardiovascular disease [29]. Iron deficiency is also common in obese subjects because chronic low-grade inflammation, a characteristic feature of obesity, stimulates the synthesis of hepcidin, which blocks the iron absorption in the body [30, 31]. This inflammation further reduces iron absorption secondary to the inhibition of duodenal ferroportin expression with a simultaneous increase in hepcidin levels [32].

It is important to highlight that intake of energy-dense foods and a higher number of calories does not necessarily bring adequate quantities of vitamins, minerals, and trace elements needed for the body. In other words, individuals with obesity and overweight often consume less fruits, vegetables, and nutritionally poor-quality and more processed foods [27]. For example, a study has shown that increased consumption of fat-rich foods leads to a deficiency of several vitamins such as folate, vitamin A, and vitamin C [33, 34]. In another observation, increased fat in the body decreases fat-soluble vitamins such as vitamin D in the serum [35]. Similarly, increased intake of sugar-rich beverages generally reduces milk consumption, leading to deficiency of milk-derived nutrition such as calcium and vitamin D [36]. In the European population, obese individuals have lower vitamin D concentrations regardless of the season when measured

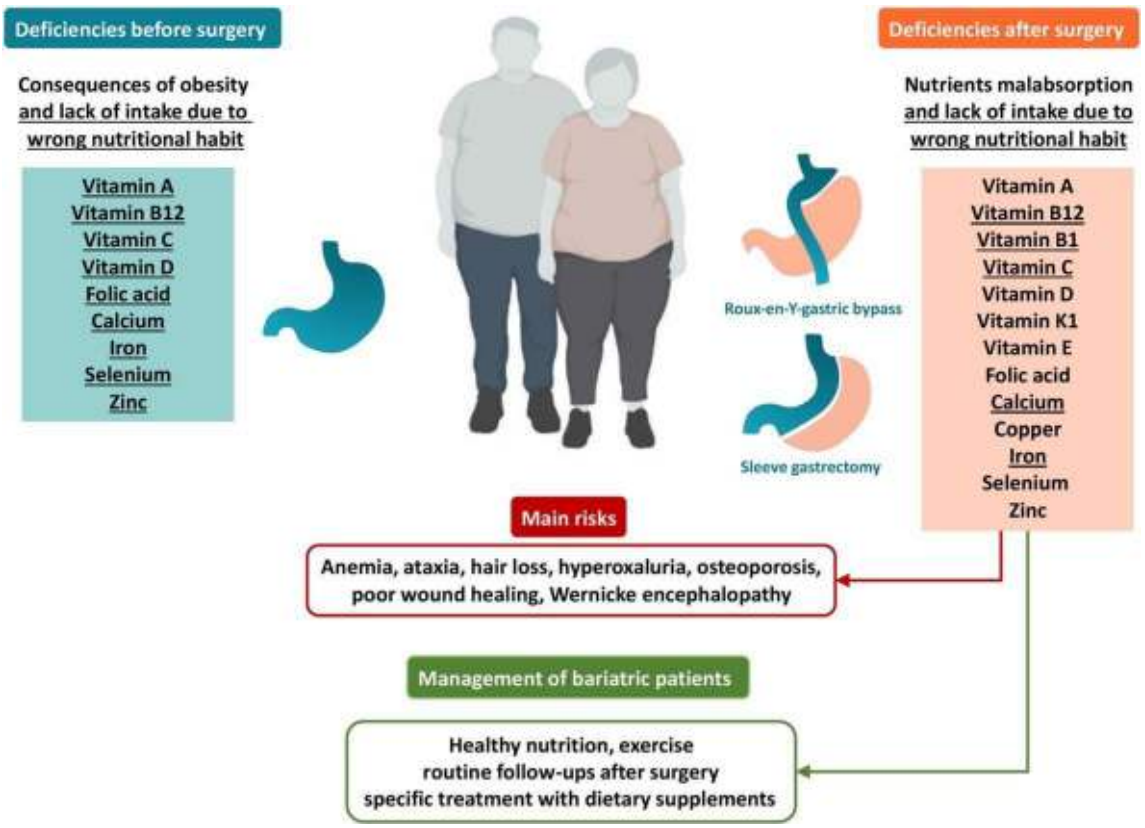

Fig. 1 Micronutrient deficiencies in obesity and after bariatric surgery, risks and management

[37], and similar findings have been obtained for the Asian population [38].

Thus, obese individuals exploring the possibility of bariatric surgery are often diagnosed with a deficiency of micronutrients and vitamins. Ernst et al. [39] measured the serum levels of important micronutrients including zinc, calcium, magnesium, the vitamins D3, B1, B3, and B6, copper, selenium, and parathyroid hormone in 232 individuals before bariatric surgery. The results showed that individuals suffer from very high degrees of micronutrient deficiency, with 25.4% subjects faced vitamin D3 deficiency, 32.6% showed selenium deficiency, 24.6% displayed zinc deficiency, and 18.1% were found with vitamin B12 deficiency. In a study by Schweiger et al [40], 114 patients were recruited, and the plasma levels of various vitamins, minerals, and trace elements were examined. It was observed that 35% of subjects were iron deficient while 24% had too little folic acid and/or ferritin, 3.6% had vitamin B12 deficiency, 2% had too little phosphorus, and 0.9% had calcium deficiency. Nineteen percent of the subjects showed hemoglobin deficiency, defined as a level below 12 gm/dL for women and a level below 14 gm/dL for men. These cut-offs corresponded with the definition of anemia given by the World Health Organization. At the same time, higher levels of parathyroid hormone were reported in 39% of patients [41]. De Luis et al. [18] supported similar findings in which women undergoing bariatric surgery showed lower blood levels for several essential vitamins, minerals, trace elements, and proteins such as folic acid (25.2%), zinc (73.9%), vitamin D (67.8%), and prealbumin (21.7%). Thus, based on the studies cited, it is quite common for obese subjects to face micronutrient deficiency, and the same has to be taken into consideration while and after performing the surgery [42, 43].

Meanwhile, it is very important to prevent or timely treat nutrient deficiencies as failure to do this may lead to undesirable consequences. For example, altered DNA methylation patterns were identified in such tissues of diabetic patients as pancreatic islets, adipose tissue, and skeletal muscle. Potentially, epigenetic changes may alter gene expression and contribute to hyperglycemia and impaired metabolism. Since a methyl donor supply-consumption imbalance could induce these changes, nutrient deficiencies, like folate deficiency, may influence DNA methylation levels and affect gene expression and cell functions [44]. Except for folate, all the B vitamins are involved in at least one step of the energy-production system within the cell, and thus, a shortfall in any of the B vitamins limits energy production with potential metabolic and health consequences [45].

Another example could be made of vitamin D deficiency, contributing to the development of initial insulin resistance and β-cell death secondary to excessive Ca^{2+} and reactive oxygen species signaling with subsequent onset of diabetes. Vitamin D also maintains the epigenome as it increases the expression of DNA demethylases, which protect against hypermethylation of multiple gene promoter regions of many diabetes-related genes [46]. Besides, vitamin C is needed to produce two dioxygenase enzymes, which take part in the carnitine biosynthesis. In turn, carnitine serves as an essential cofactor in the transport of long-chain fatty acids into the mitochondria, and so, impaired carnitine metabolism that may be due to vitamin C deficiency can lead to weakness and physical fatigue [47].

Deficiencies after bariatric surgery

Deficiencies of vitamins

As reported earlier, obese individuals face the deficiency of several vitamins, minerals, and trace elements essential for body metabolism and normal physiological processes. However, it has been observed that several patients who had undergone bariatric surgery also suffer from micronutrient deficiency post-surgery (Fig. 1) [48]. The deficiencies of these micronutrients are associated with several clinical manifestations and disorders (Table 1).

For instance, the American Society of Hematology reported anemia in 33–49% of the cases within 2 years after bariatric surgery [7]. One of the most common causes of anemia post-bariatric surgery is the deficiency of vitamin B12, which develops due to poor its absorption, as the major sites of its absorption are bypassed during bariatric surgery [49]. However, other causes, such as lower secretion of intrinsic factor (IF), a glycoprotein crucial for vitamin B12 absorption, also reduces the absorption secondary to BPD and RYGB [7, 50]. Generally, the body shows the symptoms of vitamin B12 deficiency after a certain period since body reserves of vitamin B12 are considerable, and clinical symptoms appear when the reserves deplete to 5–10% of the initial deposits [7, 50]. The duration of this period varies, depending on the amount of dietary B12 intake and the extent of effective absorption. It has to be noted that intolerance of and, thus, limited consumption of animal proteins may also occur, contributing to exacerbation of vitamin B12 deficiency [51].

Folic acid deficiency is also one aspect in individuals after bariatric surgery and affects 9 to 39% of individuals exposed to restrictive and malabsorptive procedures, respectively [52]. Still, folate deficiency could also be attributed to an inadequate intake of this essential dietary nutrient. Folic acid is absorbed throughout the small intestine, and its deficiency can be easily corrected by oral supplementation [7]. Moreover, the deficiency of folate has a direct correlation with vitamin B12 deficiency because the latter is essentially required for the inactive folate form (methyltetrahydrofolic acid) to be activated (tetrahydrofolic acid) [53].

Bariatric surgery also leads to vitamin D deficiency, with 10% of individuals suffering from this post-surgery issue, although the incidences can also reach as high as 73% [54]. Vitamin D deficiency is primarily due to reduced calcium absorption because the main absorption sites, the duodenum, and the proximal jejunum, are bypassed during the surgical intervention. Vitamin D deficiency leads to increased bone loss post-surgery, and the situation may also aggravate if the intake of milk products is low [55]. It might appear logical that malabsorptive procedures result in a higher reduction of Vitamin D levels, but according to a meta-analysis by Chakhtoura et al. [54] the effect of the surgical procedure, restrictive versus malabsorptive, is inconsistent.

Interestingly, as already mentioned, lower vitamin D levels are observed in 48.7% of the subjects before bariatric surgery [56]. The lower absorption of dietary fat post-bariatric surgery is one reason for decreased vitamin D absorption since it is a fat-soluble vitamin and requires bile salts. Bariatric surgery removes/bypasses critical sites of vitamin D absorption in the small intestine leading to its deficiency, which is more prominent in malabsorptive procedures like RYGB [56]. Bariatric surgery may also lead to the deficiency of other fat-soluble vitamins such as vitamins A, E, and K [57]. For instance, vitamin A deficiency was reported in 69% of the subjects.

Lower levels of vitamin K are developed in patients after bariatric surgery and lead to health complications associated with blood clotting, given the critical role of vitamin K in the blood clotting process [27, 58]. According to the recent systematic review by Sherf-Dagan et al., patients who undergo major malabsorptive surgeries are at a higher risk of developing vitamin K deficiency. Still, it is unknown if supplementation is required and what oral dose of vitamin K normalizes serum levels. Thus, the protocol for the management of vitamin K deficiency in post-bariatric patients is still uncertain [59]. However, a recent study by Homan et al. observed that individuals who have undergone biliopancreatic diversion (BPD) and BPD with duodenal switch (BPD/DS) generally did not decrease the coagulation factor and did not show sign of bleeding. According to the authors, the synthesis of vitamin K2 in the large intestine compensated for the loss of vitamin K1 activity due to BPD or BPD/DS. This synthesis helped maintain liver stores of vitamin K2 needed for the coagulation process [60].

Apart from the deficiency of fat-soluble vitamins, bariatric surgery also increases the risk of developing vitamin B1 (thiamine) and vitamin C deficiency. According to an estimate, thiamine deficiency can develop in 49% of the subjects after sleeve gastrectomy [61]. The primary cause of poor absorption of thiamine is jejunum bypassing, continuous vomiting, and inadequate nutrition. Moreover, certain complications due to the surgery, such as abnormal bowel movements and stenosis, can also contribute to thiamine deficiency. Finally, individuals skipping the doses of multivitamin supplements [12] also develop thiamine deficiency. Thiamine deficiency leads to the development of Wernicke Encephalopathy (WE) after bariatric surgery [62]. A recent study by Oudman et al. recruited 118 WE patients and observed that bariatric procedures led to an early onset of the disease (median age 33 years) compared to other medical procedures where the mean age was 39.5 years. Moreover, bariatric WE patients often displayed other symptoms such as vomiting, abnormal eye movements, and mental issues. The study suggested that individuals must be tested for thiamine deficiency post-surgery, and appropriate supplementations must be provided to prevent the WE [63].

Vitamin C deficiency is also observed in bariatric subjects. It has been observed that vitamin C deficiency is mainly due to poor diet selection post-surgery and may lead to scurvy. However, scurvy can be managed by proper vitamin-C supplementation [64].

The above-cited studies show that the deficiency of several essential vitamins may occur post-bariatric surgery, and the use of multivitamin supplements [12] may be an effective strategy to combat the health complications resulting from this deficiency. Hair loss, peripheral neuropathies, anemia, and poor wound healing are common postoperative ailments most pronounced during the weight reduction phase. As underlying micronutrient deficiencies provoke these ailments, prescription of vitamins, minerals, and trace elements was reported to cause a speedy recovery [65].

Deficiencies of minerals and trace elements

Like the deficiency of vitamins, bariatric surgery also leads to the deficiency of several minerals and trace elements such as iron, zinc, copper [66], calcium [67], and selenium [68] (Fig. 1). This section describes some of the trace elements and mineral deficiencies associated with bariatric surgery.

Iron

Iron deficiency is one of the most common trace element deficiencies and affects around 33% of patients undergoing bariatric procedures. Iron absorption sites are mainly located in the duodenum and proximal jejunum, and bypassing them severely reduces iron absorption [16, 69]. Moreover, dietary changes such as lower intake of meat and iron-fortified dairy products post-surgery may aggravate the iron deficiency. Of these, oral iron supplementation appears to be the most effective tool [70]. Prospective studies based on iron supplementation strategies are urgently needed.

Calcium

Bariatric surgery also causes calcium deficiency, a critical component of several cell signaling processes and an essential element for bone and teeth health. It has been reported that the prevalence of hypocalcemia after RYGB and BPD ranges from 1 to 25%, depending on the surgical technique adopted [71, 72]. In a more recent retrospective study involving patients that undergo bariatric surgery from 2008 to 2014, it was shown that, in about 1000 patients, the prevalence of hypocalcemia after bariatric surgery was 3.6%. In particular, the prevalence was 10% in the BPD-DS group, 9.3% in the SG group, and 1.9% in the RYGB group, respectively [55]. It is important to highlight that vitamin D deficiency can further exacerbate calcium deficiency because vitamin D is required for normal calcium absorption in the intestine and plays a central role in its homeostasis [16, 73–75]. A strategy based on adequate calcium and vitamin D supplementation should be carefully monitored, particularly in patients at high risk for developing symptomatic hypocalcemia in case of pre-existing renal insufficiency and vitamin D deficiency [55, 75].

Copper

Copper acts as a cofactor for several enzymes associated with various pathways in the cell. For instance, copper is a cofactor for superoxide dismutase (antioxidant pathway), cytochrome C oxidase (involved in energy generation), and amine oxidases (involved in the synthesis of neurotransmitters). Thus, deficiency of copper can have severe clinical consequences. Moreover, copper is also needed for iron mobilization in the system. Hence, copper deficiency can also cause symptoms of iron deficiency, such as anemia. It has been observed that malabsorptive bariatric surgery can cause copper deficiency because it bypasses the duodenum. The concentration of blood copper is reduced post BPD and RYGB and may cause severe deficiency in certain individuals [7]. Studies have shown that copper deficiency affects 10–15% of individuals after RYGB surgery [76]. The other cause of copper deficiency is inadequate intake of copper from the diet [16].

Zinc

Zinc is another important essential divalent cation for which individuals develop deficiency post-bariatric surgery [77]. Zinc is absorbed in the proximal intestine, and bypassing the absorption route leads to poor absorption. It is important to note that 42–65% of patients develop zinc deficiency within 6–18 months post-surgery, indicating a direct and strong association between them. Zinc supplementation early after bariatric surgery is necessary to reach significant clinical and echocardiographic improvement [78]. However, studies have also shown that in some cases, zinc levels can decrease after surgery [16, 79].

Selenium

Selenium is primarily absorbed in the duodenum and proximal jejunum and its deficiency has been evidenced in postoperative bariatric surgery (RYGB and SG) with a prevalence from 11 to 46% [79–81]. Selenium deficiency is strictly associated with cardiomyopathy, myopathy, arrhythmias, muscle wasting, and hypothyroidism complications. Screening for selenium levels should be recommended before and after surgery in particular in case of unexplained anemia, fatigue, metabolic bone disease, chronic diarrhea, or cardiomyopathy, followed by specific supplementation [82]. However, studies with large cohort and longer follow-up, also in dependence of the different type of surgical procedure, are still lacking.

Consequences of micronutrients deficiencies

The deficiency of trace elements and minerals can have severe consequences for human health because several trace elements are essentially required to activate several enzymatic reactions and biochemical pathways in cells [16, 83]. The deficiency of these trace elements manifests in symptoms associated with cardiac, neurological, and gastrointestinal systems (Table 1). Thiamine (vitamin B1) deficiency can lead to Wernicke encephalopathy, constipation, nausea, fatigue, and anorexia. Inadequate absorption of fat due to bariatric surgery reduces the absorption of vitamin D. Vitamin D deficiency can severely compromise bone health and manifests in lower bone density. Calcium deficiency also reduces bone density and impairs several cellular signaling pathways because calcium acts as a secondary messenger in the cell. Vitamin D and calcium deficiency can have similar clinical manifestations, and one deficiency can exacerbate another deficiency. Still, bariatric surgery is not the only cause behind the observed deficiency, and reduction in certain food items such as meat, milk, and other dairy products can also lead to deficiencies of vitamin D and calcium.

Zinc deficiency post-bariatric surgery can cause poor wound healing and promotes hair loss [16]. As for copper deficiency, it can cause weak bones, issues with normal learning, fatigue, vision loss, and hair graying. Selenium deficiency is also observed in post-bariatric patients, and it can cause goiter, thyroid issues, and fatigue [84]. Vitamin C deficiency ranges from 10 to 50% following bariatric surgery [7] and may also cause fatigue, delayed wound healing, depression, and even scurvy [27, 85]. Iron

deficiency and the related iron deficiency anemia is also frequently observed and is associated with low baseline ferritin level [86].

It is pertinent to mention that clinical manifestations of vitamin, mineral, and trace element deficiencies are not specific, and ultimate clinical symptoms may be due to deficiencies of many vitamins, minerals, and trace elements. Some of the consequences of micronutrient deficiencies are briefly discussed here.

Anemia

Anemia is one of the most common consequences of micronutrient deficiency post-bariatric surgery [86, 87]. It develops due to a change in food habits, which prohibits the use of meat, leading to reduced iron intake. Gastric hypochlorhydria is another reason for lower iron absorption after bariatric surgery. Moreover, bypassing the duodenum also prevents the reduction of iron to the ferrous state, the main absorbable form of iron. Thus, it is recommended that routine laboratory check-ups to determine iron deficiency must be performed in patients after RYGB, which includes testing complete blood count and measurement of ferritin and total iron-binding capacity [88]. These check-ups are needed to prescribe timely treatment for iron deficiency anemia, which reaches 45–50% after RYGB [7]. With anemia progression, the patients often become symptomatic and complain about fatigue, pallor, and dyspnea on exertion. Moreover, anemia was reported to increase the risk of hospitalizations by two-fold along with the duration of in-hospital stay [89].

Impaired absorption of vitamin B12 and folate is a consequence of both restrictive and malabsorptive bariatric procedures. For instance, vitamin B12 deficiency can reduce body coordination, cause numbness in different parts of the body, various neurological complications, and memory impairment. Along with folate, vitamin B12 deficiency can also lead to the development of macrocytic anemia and leucopenia. In pregnant women, growth retardation and congenital disabilities in the newborn may be possible [90].

Wernicke encephalopathy

Wernicke encephalopathy (WE) is observed in alcoholics, undernourished individuals, and cancer patients. However, lower absorption of thiamine (vitamin B1) post-bariatric surgery also causes WE in patients. Some of the common symptoms of WE are nystagmus, confusion, and issues with body coordination. According to a survey, 49% of patients develop the symptom of WE after bariatric surgery. However, some individuals develop it even after sleeve gastrectomy [61].

Ataxia

Ataxia is a medical condition with impaired voluntary body coordination and displays abnormal body and eye movement. Ataxia is a consequence of neurological complications arising out after bariatric surgery. It is observed in 4.6–16% of subjects after bariatric surgery. Some associated medical complications are peripheral neuropathy, burning feet syndrome, lumbosacral plexopathy, and Wernicke-Korsakoff encephalopathy [91].

Hair loss

Hair loss is a common health issue due to the inadequate availability of several micronutrients such as zinc and iron. However, sudden and excessive weight loss after bariatric surgery contributes to hair loss [92]. A recent large cohort study involving 555 subjects reported that the most frequent nutritional deficiency linked to hair loss is essentially connected to deficiency in blood iron and related proteins than zinc and B vitamins, both in the short term and long term follow-up [93].

Taken together, patients after bariatric surgery can develop several health complications due to weight loss, vitamin deficiency, and dietary changes. Thus, a diet rich in proper nutrients and multivitamin supplements may help ameliorate the health consequences of micronutrient deficiency.

Deficiencies and pregnancy after bariatric surgery

Pregnancy post-bariatric surgery requires special attention and care. The impact of bariatric surgery on pregnancy becomes more important because most of these patients are women of reproductive age [94]. It has been observed that women after bariatric surgery show reduced incidences of pregnancy-associated complications such as hypertension, gestational diabetes, and they are mostly successful [95]. A retrospective study considering 287 women between 18 and 45 years of age who underwent RYGB evidenced this surgical practice's safety without any adverse outcomes [96]. One of the major concerns for pregnant women post-bariatric surgery is the deficiency of essential nutrients and trace elements that can prevent normal growth and development of the fetus [97]. For example, anemia is commonly observed in 10.2% of subjects and generally a direct indication of iron deficiency. Studies have shown that weight loss has a positive impact on fertility due to its direct role in improving hormonal balance in the body. Women should plan the pregnancy 12–24 months after the bariatric surgery when their maximum weight loss is achieved [95, 98]. The American

College of Obstetricians and Gynecologists (ACOG) has prescribed special guidelines for women conceiving after bariatric surgery to improve pregnancy outcomes. As per the guidelines, the following points must be considered [99].

Contraception and preconception counseling

Women of reproductive age should be provided with counseling for contraception and preconception after surgery. It has been observed that oral contraceptives are less effective in women after bariatric surgery due to poor absorption. Thus, a higher conception rate has been observed in women of reproductive age post-bariatric surgery than normal women of reproductive age.

Monitoring of nutritional status

As discussed, it is very common to develop a nutritional deficiency after bariatric surgery. Some of the common deficiencies are iron, folate, vitamin B12, vitamin D, and calcium. As per the guidelines, a dedicated team of doctors and specialists must monitor the nutritional status of pregnant women conceived after bariatric surgery. The use of multivitamins and other nutritional supplements must be considered if needed [100].

Antenatal period

Pregnancy-related complications such as nausea, abdominal pain, and vomiting must be taken seriously because these complications may be due to bariatric surgery. A complete evaluation of symptoms by a bariatric surgeon is highly recommended [95].

Labor and delivery

Bariatric surgery does not affect labor and delivery, but a higher cesarean delivery rate has been observed in women after bariatric surgery [101]. However, if the pregnant woman had a complicated bariatric surgery, a pre-labor consultation with a bariatric surgeon is highly advisable as per the ACOG guidelines [102].

Conclusion

Obesity is a disorder of excessive energy surplus, and its unprecedented rise in recent decades is one of the major causes behind other lifestyle-related disorders such as diabetes, non-alcoholic fatty liver disease, and cardiovascular disorders. Bariatric surgery is a surgical intervention to manage weight gain; it involves bypassing the stomach and the jejunum portions to reduce the calorie intake. It has been well-established that the most common types of bariatric surgery, like SG and RYGB, are associated with deficiencies of several essential vitamins, minerals, and trace elements, and those are being more profound for RYGB. This deficiency is mainly attributed to lower absorption of the vitamin, minerals, and trace elements since the proximal duodenum is an important absorption site. The lack of essential micronutrients severely compromises the normal functioning of the body systems because trace elements, minerals, and vitamins are involved in various biological processes and cell signaling. For instance, iron deficiency can hinder normal oxygen transport, and vitamin C deficiency can lead to scurvy. Paradoxically, obesity and overweight are also associated with a deficiency of several vitamins, minerals, and trace elements. Thus, individuals undergoing bariatric surgery should be checked before and after the surgery to detect and correct nutrient inadequacies or deficiencies effectively. Then again, periodic screening for micronutrient deficiencies after bariatric surgery is necessarily required. However, further prospective studies are needed to determine which categories of patients might benefit most and the primary cause of malnutrition, such as surgery or a pre-existing health problem, as this will have economic consequences and an influence for related public health recommendations.

In conclusion, bariatric patients need routine follow-ups after surgery and individual treatment with specific dietary supplements to manage their deficiency of vitamins, minerals, and trace elements. International practice guidelines generally agree that multivitamin and calcium supplementation with added vitamin D is required for all post-bariatric patients and is best administered orally, while intravenous administration should only be applied in situations when oral supplementation is insufficient. Furthermore, healthy nutrition with a targeted diet is recommended for preventing the deficiency of specific micronutrients.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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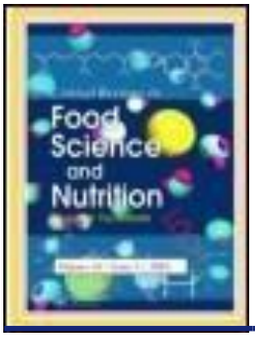
I. Lucrări relevante

2. Gasmi A, Bjørklund G, Noor S, Semenova Y, Dosa A, Pen JJ, Menzel A, Piscopo S, Wirth N, **Costea DO**. Nutritional and surgical aspects in prostate disorders. *Critical Reviews in Food Science and Nutrition* 2022, 1-17. doi: 10.1080/10408398.2021.2013158. PMID: 35021909. (IF din 2021/2022=11.208). 17 PAGINI



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REVIEW

Nutritional and surgical aspects in prostate disorders

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ABSTRACT

Prostate disorders are commonplace in medicine, especially in older men, with prostatitis, benign prostatic hyperplasia, and prostate cancer being the most abundant pathologies. The complexity of this organ, however, turns treatment into a challenge. In this review, we aim to provide insight into the efficacy of alternative treatments, which are not normally used in conventional medicine, with a particular focus on nutrients. In order to understand why and how nutrition can be beneficial in diseases of the prostate, we give an overview of the known characteristics and features of this organ. Then, we provide a summary of the most prevalent prostate illnesses. Finally, we propose nutrition-based treatment in each of these prostate problems, based on in-depth research concerning its effects in this context, with an emphasis on surgery. Overall, we plead for an upgrade of this form of alternative treatment to a fully recognized mode of therapy for the prostate.

KEYWORDS

benign prostatic hyperplasia;
nutrients;
nutrition;
prostate;
prostate cancer;
prostatitis

Introduction

Prostate disorders comprise prostatitis, prostate cancer (PCa), and benign prostate hyperplasia (BPH). PCa is by far one of the most frequent cancers in humans, and it is the second leading cancer site among non-skin cancers in men worldwide (Wild, Weiderpass, and Stewart 2020). Upon autopsy, up to 30% of males above the age of 50 were found to have prostate cancer. The prevalence of prostate cancer has greatly increased in many countries of the world since the 1970s due to improved diagnosis via prostate-specific antigen (PSA) testing. Therefore, prostate cancer poses a serious threat to the public and the aging population worldwide. The benign form of prostate tissue proliferation is BPH. Even though no solid evidence suggests that BPH contributes to prostate cancer, it is suspected that both diseases are caused by irregular modulation of hormone secretion in male physiology. The normal prostate tissue starts developing in men near age 25 after maturation. Evidence from the US showed that at 60 years of age, 50% of males show BPH. The frequency is further elevated over the age of 80 to 80% of the male population (Langan 2019).

The largest medical approach commonly used to treat BPH and prostate cancer is surgical excision. The procedure has a high survival rate for people diagnosed with prostate cancer at the initial stage of the disorder. Nevertheless, the survival rate for the patients with mid to late cancer stage is poor due to the absence of effective drug treatment (Teo, Rathkopf, and Kantoff 2019). PSA is the most significant biomarker for an early diagnosis of prostate cancer. The prostate epithelial cells release PSA under the activation of androgens and other growth factors, like TGF-β. The normal PSA level in human serum is 1-4 ng/ml, but PSA concentration in PCa patients is often above this limit; and the PSA concentration in BPH is also substantially greater than the normal range, probably because of the irregular hormonal activity in prostate cancer and BPH patients (Gat and Goren 2010). Surgical and drug therapies for BPH and prostate cancer patients reduce PSA serum level, which often indicates a higher rate of survival or disease relief.

Consequently, PSA levels may function as a model system for detecting possible successful therapies with multiple mechanisms of action. Recent research has shown that the prostate acts as a secreting organ and has an immune function against the invasion of bacterial and pathogenic microorganisms through the development of immunoglobins and zinc synthesis, which affects the production of antibacterial polypeptides. As such, non-surgical therapies give an advantage against surgery to retain the prostate organ's biological function (Wild, Weiderpass, and Stewart 2020).

Currently, for clinical use, there are four types of drug therapies carried out for BPH: antiandrogens that specifically suppress the activity of dihydrotestosterone (DHT); 5

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alpha-reductase inhibitors that partially suppress the activity of DHT; alpha1-adrenaline receptor blockers that primarily suppress smooth muscle contraction and relaxation; and natural products. Since BPH is a chronic disorder and its therapy often takes a long period, adverse effects like reduced libido, incontinence, and others sometimes prohibit patients from pursuing care. Accordingly, there is an urgent need to identify effective alternative treatments of prostate pathophysiological disorders with much-improved side effects (Lu et al. 2006). Herbal medicine is becoming increasingly popular worldwide. Patients with prostate cancer and those with benign prostatic hyperplasia are increasingly considering the use of supportive alternative medicine, particularly due to the mortality risk and long-term morbidity correlated with surgical interventions. Since prostate disorders are steadily increasing, the efficacy of herbal medicine provides relief similar to that of traditional treatment methods (Steenkamp 2003). The present review summarizes the nutritional and surgical aspects of prostate disorders. The particular focus is made on alternative treatments, which are not commonly used in prostate disorders, but may potentially postpone surgical intervention. The review discusses molecular mechanisms of some of the most promising supplemental substances with a particular focus on nutrients.

Materials and methods

We conducted the comprehensive literature searches in the following databases: MEDLINE, EMBASE, Trip Medical Database, and Cochrane Library. The search queries were performed using the following terms: ["Cancer, prostate" (MeSH)] OR ["Cancer of prostate" (MeSH)] OR ["Prostatic neoplasms" (MeSH)] AND ['Adenoma, prostatic" (MeSH)] OR ['Benign Prostatic Hyperplasia" (MeSH)] OR ['Benign Prostatic Hypertrophy" (MeSH)], ["Prostatitis" (MeSH)] OR ['Disease, prostatic" (MeSH)] AND ["Nutritional Status" (MeSH)] OR ["Nutrition Therapy" (MeSH)] OR ["Nutrition Assessment" (MeSH)] OR [Nutrition* (title/abstract;TIAB)] AND [Surgery [Subheading]]. All searches were limited to studies published in English-language from inception to 31 July 2021. As a next stage, the titles and abstracts of all papers were evaluated to determine the suitability for inclusion in the present review. Besides, the reference lists of all eligible papers were also screened, which helped to identify additional relevant articles.

The inclusion criteria were as follows: (i) studies that included patients with prostate disorders or animal models of prostate disease; (ii) studies that addressed the issue of nutrition in relation to prostate health and disease; (iii) studies that described the principles of surgical management in patients with prostate disorders; and (iv) studies that were published in English language. The following exclusion criteria were applied: (i) studies that did not analyze the nutritional and/or surgical aspects of prostate disorders; (ii) unavailability of the full text; (iii) studies that involved children as research subjects; (iv) studies that were published in non-English language.

At the stage of initial search the titles and abstracts of all articles were screened for eligibility and the publication was excluded if the inclusion criteria were not met. As a next step, the full texts of all articles were obtained and analyzed. This helped to create a "pool" of eligible publications, from which the data could be extracted for inclusion into the present review. Those papers that fall outside the review's scope were excluded along with duplicate articles. Likewise, the publications with unavailable full texts or publications in non-English languages were also excluded. Finally, the draft of this literature review was prepared and sent to all coauthors for consideration and contribution.

Anatomy, physiology, and metabolism of the prostate

The male prostate is a basic endoderm derivative that grows from the cloaca during embryogenesis. The linked vas deferens and seminal vesicles emerge from the mesonephric ducts that secrete semen-containing fluid. The prostate is a pyramid-shaped fibromuscular gland that surrounds the male urethra. It is encircled by peri-prostatic fascia. The true capsule is constructed by a thin layer of connective tissue. The pseudo capsule, developed by three fascia layers on the anterior, posterior, and lateral prostate part, is analogous to the true capsule. Superiorly, the neck of the bladder extends to the prostate. The urethra extends from the anterior boundary into the prostate base. Inferior to that, the gland apex rests on the bladder's lateral sphincter. The pubic symphysis is anterior to the prostate, isolated from it by the extraperitoneal fat of the retro-pubic area (Retzius Grotto). The peri-prostatic venous plexus lies within this area. The puboprostatic ligaments attach the prostate apex to the pubis. Denovilliers' fascia resides behind the penis, distinguishing it from the rectum, while the levator ani muscle laterally fuses with the prostate's lateral fascia (Kim et al. 2015). The vas deferens and the seminal vesicles attach to establish the ejaculatory ducts on either side of the verumontanum in the super-posterior portion of the gland and expand in the prostatic urethra.

The prostate's main function is to supply the electrolytes and proteins, which make up a large portion of the seminal fluid. Also, the prostate helps to retain continence by autonomous control of the sphincter of the internal urethra. For males with BPH, the urethra is squeezed by the enlarged prostate. As a result, the bladder wall gets thickened due to hyperplasia of the bladder wall's muscle fibers, and consequently, the ability of the bladder to empty reduces, because it weakens, and some urine remains in the bladder. The confluence of urethra narrowing and incomplete bladder emptying can result in urinary incontinence via secondary detrusor overexpression (Hayward and Cunha 2000). In the adult male, the prostate is a tubule-alveolar gland consisting of semi-stratified columnar epithelium-filled ducts. The cells, which line with the ducts, are column-shaped with basal nuclei and are secretory. The basement membrane is generated by a persistent film of basal epithelial cells. In addition, the prostatic epithelium is lined with a thick

fibromuscular stroma. Prostate embryological development starts at nearly ten weeks of human fetus development, forming prostatic buds from the urogenital sinus. Within the urogenital sinus, testicular androgens stimulate the androgen receptors (AR) to trigger epithelial lining for budding, differentiation, and propagation to form ductal structures. In the adult prostate, androgens play function to sustain a completely differentiated, growth-quiescent epithelium by acting on the AR expressing prostatic smooth muscle. This happens through interactions of stromal epithelial cells mediated by regulating growth factors (Nehikhare et al. 2018).

In aerobic cells, the intermediary metabolic pathways are regulated by the synthesis and oxidation of citrate through the Krebs cycle. Through this mechanism, glucose and fats are oxidized. It is because of citrate synthesis and oxidation that cells produce their main source (about 80%) of cellular energy (production of ATP) by coupled phosphorylation. Furthermore, the Krebs cycle and the processing of its substrates offer important mechanisms for amino acid metabolism through processes of biosynthesis and degradation. The acetyl-CoAS, which is necessary for lipogenesis, is obtained from synthesized citrate. As such, the synthesis and oxidation of citrate are essential for the regular metabolism, efficient capabilities, development and reproduction, and longevity of aerobic mammalian cells through an operational process of Krebs. As can be seen from the fatal effects of fluoroacetate inhibiting the mitochondrial aconitase process, which is the first step in the oxidation of citrate oxidation, aerobic mammalian cells are generally compromised through a disrupted Krebs cycle.

In particular instances, mammalian cells possess adaptive characteristics that enable alternate metabolic mechanisms to be integrated to meet the cell's energetic and synthetic needs. However, the importance of citrate-related intermediate metabolism and an active Krebs cycle in mammalian cells is most obvious (Farnsworth and Brown 1963).

The human prostate gland's main functions include the production and release of exceptionally high quantities of citrate and zinc. Now, it is clear that this feature is directly associated with the peripheral zone glandular epithelium. As such, in the human prostate, citrate-producing and highly diverse zinc-accumulating cells are the secretory epithelial cells of the peripheral region. In comparison, the central zone glandular cells do not absorb zinc and oxidize the citrate, which is characteristic of many mammalian cells. There are no cells other than these present in the body which possess these metabolic and functional capacities that specifically distinguish secretory epithelial cells in the peripheral zone. Prostate physicians and scholars should learn to understand this concept. Using such terms that suggest the presence of a certain particular secretory epithelial cell category correlated with the human prostate is misleading and contributes to misrepresentations and misunderstandings. This refers in particular to the classification and characterization as indicative of natural prostate epithelial cells of primary and immortalized prostate epithelial cells in cultures. A cell that lacks those functional and metabolic attributes correlated with the accumulation of zinc and citrate synthesis could not be classified as representing the peripheral zone's normal secretory epithelial cells, and it is useless to identify these cells as 'normal prostate epithelial cells.' The following listed relationships are thus entirely correct and straightforward, except when specified, only attributable to citrate-synthesizing prostate epithelial cells, which are indicative of the secretory epithelial cells of the peripheral zone in the human prostate (Costello and Franklin 2000).

Prostate disorders in general

Prostate disorders are pretty common throughout the aging process. Prostatitis, prostate adenoma (prostate cancer), and benign prostatic hyperplasia (BPH) are some common disorders of the prostate. Prostatitis is commonly recognized as prostate inflammation; it occurs due to some infection or may occur without any infection at all. Prostatitis-related symptoms include nausea, nullifying symptoms such as nocturia, frequent urgency of urination, intermittent voiding, and reduced urinary stream intensity and intermittency, dysfunction, and infertility. The cause of prostatitis associated with non-infection is unknown and thus difficult to treat. It is well known that both acute and chronic bacterial prostatitis are treated successfully with antibiotics. Typically, antibiotics and anti-inflammatory drugs are being used to treat acute and chronic pelvic pain disease. Alpha-blockers may be recommended for relieving prostate muscle tension and increasing urinary discharge. Alpha-blockers, however, are costly, need to be used in high doses continuously, can have serious side effects, and do not treat the root problem, nor do they eliminate recurrences. It can be helpful to relieve the inflammation produced by prostatitis through anti-inflammatory drugs or hot sitting baths, but such rem- edies are limited and do not eradicate the disease.

Benign prostatic hyperplasia

Benign prostatic hyperplasia corresponds to a prostate enlargement caused by nonmalignant hyperplasia, frequently seen in elderly individuals (AUA Practice Guidelines Committee 2003). BPH is often detected when the prostate becomes swollen up to the point that urination gets painful. Several fibro adenomatous nodules form in the prostate's peri-urethral area, usually arising in the peri-urethral glands instead of the true fibromuscular prostate, i.e., surgical capsule, which is substituted peripherally via progressive nodular development. As the prostatic urethra lumen shrinks and elongates, the outflow of urine is increasingly obstructed. Increased micturition and bladder distention associated pressure will lead to bladder detrusor hypertro- phy, trabeculation, cell development, and diverticula. Incomplete bladder emptying induces stasis, which predis- poses to the development of infection and calculus. The prolonged incomplete blockage of the urinary tract may also cause hydronephrosis and impair renal function (Lepor 2005; Foo 2017).

Symptoms include frequent urination or urinary hesitancy. When the prostate becomes enlarged, the urethra can be narrowed and impedes the urine flow, causing painful urination, which even may be entirely impossible in severe cases, resulting in urine retention. Inability to drain the bladder entirely and, over time, prolonged accumulation may cause bladder enlargement and allow urine to flow back toward kidneys, known as hydronephrosis (Thorpe and Neal 2003).

Most researchers think that androgens (testosterone and associated hormones) play a permissive function in BPH development. It suggests that for BPH to appear, androgens would have to be available, but they do not necessarily cause the disorder directly. It is supported that no sign of BPH development is observed in previously castrated boys during aging. An exceptional survey of 26 eunuchs of the Qing dynasty palace residing in Beijing in 1960 showed that in 81% of them, the prostate was non-palpable (Wu and Gu 1991). On the other side, few research studies indicate that a significant increase in the likelihood of BPH symptoms is not correlated with the use of exogenous testosterone. Therefore, the effect of testosterone in BPH and PCa is still uncertain. Further systematic, controlled experiments are required with a greater number of participants to measure the role of providing external testosterone therapy (Liverman and Blazer 2004).

Studies show that nutritional habits can influence BPH development, but additional research is required to explain any significant association (Zhang et al. 2003). Chinese studies indicate that increased protein intake might be a factor for BPH growth. Men over 60 living in rural areas had very low clinical BPH levels, whereas men living in towns and eating more meat and dairy products had a greater BPH incidence (Heber 2002; Gu 1997). Research on Japanese-American males in Hawaii, on the other hand, demonstrated a strong negative correlation with the intake of alcohol; however, a moderate positive correlation with beef consumption did exist (Chyou et al. 1993).

Medication, minimally invasive surgery, or, in serious cases, a removal of the prostate gland are used to treat BPH. Generally, therapy frequently starts with an alpha-1 adrenergic receptor inhibitor drug, like tamsulosin, which decreases the stiffness of the smooth muscle located in the ureter, allowing an easier urine flow through it.

Prostatitis

Prostatitis is prostate gland inflammation. It may be induced by a bacterial infection or other noninfectious factors. Representatives of the Enterobacteriaceae species often cause bacterial prostatitis (BP), but pathogens from other families may be accountable and are much more likely to occur in certain populations at high risk. Escherichia coli may be the most prevalent isolated bacteria from urine cultures and is the cause of the disease in most cases (around 50-90%). Some other isolates comprise the species *Klebsiella, Proteus, Serratia, Enterobacter,* and *Pseudomonas*. Gram + bacteria like *Enterococcus*, *Staphylococcus* species, and some sexually transmitted bacteria, e.g., *Chlamydia trachomatis, Neisseria gonorrhoeae, and Ureaplasma urealyticum*, are also implicated in this disorder (Lee et al. 2016). The pathways suggested for BP all include invasion of pathogenic organisms capable of overcoming the normal immune defenses of the prostate gland. Most generally, BP develops secondary to ascending urethritis, cystitis, and epididymal inflammation, but BP is often also caused by overt prostate biopsy or drug inoculation. More generally, sepsis or other types of infection in the body may cause BP through hematogenous or lymphatic seeding. The pathophysiology of chronic bacterial prostatitis (CBP) is less clearly understood; however, it might include bacterial biofilm formation (Davis and Silberman 2019). Prostate inflammation may cause painful urination or ejaculation, pain in the abdomen, discomfort during urination, or constipation (Fried 2018).

Antibiotics are used for the treatment of acute and chronic bacterial prostatitis. Non-bacterial chronic prostatitis or male chronic pelvic pain disorder is addressed with a wide range of therapies comprising alpha-blockers, nonsteroidal anti-inflammatory medications, and amitrip- tyline. Some therapies may involve physical therapy, nerve modulators, psychotherapy, antihistamines, anxiolytics, herbal medicine, chemotherapy, and more. In addition, a range of therapeutic approaches has recently emerged, including specific pelvic floor physiotherapy, local heat application, relaxation exercises, and psychological treatment (Coker and Dierfeldt 2016; Zaidi, Thomas, and Chughtai 2018).

Prostate cancer

Out of the most prevalent types of cancer, prostate cancer is the one that typically affects elderly men in different countries, like the UK, Northern Europe, and the USA. It is also a major cause of death among elderly males in these countries. An individual often has no symptoms, but may experience urinary urgency, frequency, hesitancy, and other BPH-related symptoms. In advanced stages, these cancers might lead to weight loss, retention of urine, and other symptoms, like back pain, which are associated with external prostate lesions (Dunn and Kazer 2011).

A rectal examination and an assessment of prostate-specific antigen (PSA) level are the typical screening tests for prostate cancer. However, it is difficult to interpret the PSA values since an elevated value in an individual lacking cancer may be present, and a poor value may be seen in those who have cancer. Taking a biopsy to determine the Gleason score and estimate the tumor aggressiveness is the next testing phase. Screening for prostate cancer remains problematic due to the high risk of misdiagnosis with routine testing in the general population (Smailova et al. 2020). If a tumor is identified, the existence of tumor metastases in other areas of the body can be tested by medical imaging, like magnetic resonance imaging (MRI) or bone scanning (Klotz 2013).

Localized prostate cancer is most often controlled by delivering either prostate surgery or radiotherapy that may be conducted utilizing small radioactive particles, known as

brachytherapy. Hormone therapy is typically used for the treatment of advanced cancer. This is sometimes achieved by using gonadotropin-releasing hormone (GnRH) analogues or other substances that inhibit the action of androgens on receptors, i.e., result in hypogonadism. Prostate cancers that are non-responsive to hormonal therapy or fail to improve following the treatment provided might be handled via chemotherapy. Radiotherapy can also be used to alleviate pain related to bone metastases (Sandhu and Andriole 2012). At times, it may be the best option not to treat prostate cancer, but to provide active surveillance. In small and localized cancers, it can be chosen to assess the tumor activity and delay intervention until its definite progression. If a person has a lifespan of fewer than ten years due to frailty or other medical conditions, the effects of treatment can exceed any possible benefits (Sandhu et al. 2013).

Intervention protocol

Surgery

Open prostatectomy or radical transurethral prostate resection (TURP) are perhaps the most common surgical techniques to treat prostate disorders and are typically provided when all other treatment options fail. TURP is usually used in BPH, but may also be indicated for patients with PCa and prostatitis. In this procedure, the prostate is visualized through the urethra, and sharp dissection or electrocauterization are applied to remove the prostate tis- sue, which pushes against the upward portion of the urethra, and limits the urine flow. Although TURP is commonly associated with a low rate of erectile dysfunction, it carriesa high risk of retrograde ejaculation (Wada et al. 2019). Because various prostates disorders are subjected to different surgical interventions, it is worth considering them separately.

Prostatitis

Commonly, prostatitis is not treated surgically, but in situations of recurrent chronic prostate infection TURP or transurethral vaporization of the prostate (TUVP) may be indicated. This helps to remove a nidus of infection, which may be in the form of prostatic stones that are almost impossible to cure with antibiotic therapy alone. Radical prostatectomy is indicated for patients with chronic prostatitis more seldom and is mostly used as a last resort to resolve the prostatitis-related symptoms. However, because there is lack of randomized controlled trials dedicated to surgical management of prostatitis, currently available evidence does not provide a base for clinical decisions (Schoeb et al. 2017).

Benign prostatic hyperplasia

Since TURP is associated with side effects, minimally invasive alternatives have been developed nowaday, and these include transurethral microwave thermotherapy (TUMT), prostate transurethral needle ablation (TUNA), transurethral incision of the prostate (TUIP), Rezūm water vapor therapy, and the UroLift system. When TUMT is performed, the microwave energy released through the transurethral antenna destroys the excess prostate tissue, while in TUNA, the tissue is destroyed by means of radiofrequency needles that are placed in the lateral lobes of the prostate. As an alternative to TURP, TUIP envisages endoscopic incisions of the prostate to reduce urethral constriction and is indicated for men with relatively small prostate glands (30 g or less). Rezūm is a novel thermal therapy that delivers heat through water vapor or steam to treat the excess prostate tissue, and the UroLift system is a permanent implant that lifts and holds the enlarged prostate tissue, preventing the blockade of the urethra (Madersbacher, Roehrborn, and Oelke 2020).

Prostatic neoplasms

If minimally invasive techniques are mostly used to treat BPH, open or laparoscopic prostatectomy is used to treat prostate neoplasms. In subtotal prostatectomy, only a part of the prostate is removed, and this approach is preferred for benign prostate lesions, while in radical prostatectomy, the entire prostate gland, along with the seminal vesicles and the vas deferens, is removed. Radical prostatectomy is the technique of choice for PCa. There are various approaches to radical prostatectomy: open (through the lower abdomen) and laparoscopic (through the urethra or the perineum). Robotic-assisted devices have been recently proposed to make this procedure minimally invasive. Prostatectomy is like any radical intervention associated with several complications that may seriously compromise the quality of life. Impotence was reported in more than 50% of cases, erectile dysfunction is observed in 100% of men, orgasmic dysfunction is seen in 50% of cases, and incontinence ranges from less than 5% to 30% (McCullough 2005).

It is noteworthy to mention that in certain instances, treating obesity might be an efficient way to reduce the volume of the prostate (Black et al. 2006; Silva, Silva, and Cruz 2014). However, because surgery is an effective solution reserved for clinically prominent or advanced disease cases, there is a need for a continuous search of safe but working approaches that could be beneficial for delaying the surgical intervention. Nutraceuticals present one of such options, and their potential in postponing a surgery will be discussed in more detail in the next sections of this review.

Nutrition

Total energy intake and intake of certain macronutrients may affect many facets of the cause of underlying BPH and improve the symptoms related to the urinary tract. As such, 8-year community-based research surveying the diet specifics of a large cohort of health professionals with BPH identified a modest direct association between the disease and intakesof total energy, animal proteins, and long-chain polyunsat- urated fatty acids. Although energy-adjusted total protein intake was positively associated with BPH and BPH surgery, no association between intakes of total fat or carbohydrates

and BPH occurrence was found (Suzuki et al. 2002). A greater association between BPH and animal protein intake was established as compared to the intake of vegetable protein (Espinosa 2013). A diet that includes high-quality plant-based and cold water fish-based protein may be ben- eficial instead of eating a lot of animal protein. Heavy intake of unsaturated fatty acids might lead to the peroxidation of cell membrane lipids and cell membrane components and fluidity, influencing the function of 5a-reductase (Weisser and Krieg 1998). Foods with high cholesterol and saturated fat levels are also rich in arachidonic acid, which is the major contributor to inflammation. Reduction in these foods' intake will help patients with BPH by decreasing the inflammatory triggers. Low-glycaemic nutrition and exercise can improve the symptoms associated with both BPH and dyslipidaemia in individuals with metabolic syndrome (Kopp 2018).

Foods high in omega-three fatty acids consist of cold-water fish (mackerel, halibut, tuna), fruits, and ground flaxseed oil. A diet that contains high omega-3 fatty acids reduces prostaglandin and leukotriene effects on the inflammatory portion of BPH (Das and Buchholz 2019). Whole flaxseed seeds (flaxseed oil, also commercially available as 500 mg capsules) have the additional advantage of lignan fibers, which tend to bind estrogen in the intestine and thereby facilitate the release of estrogen. As a consequence, they affect BPH's progression. In several trials, the combination of glycine, alanine, and glutamic acid (in the form of two 6-grain capsules given three times daily for two weeks and one capsule three times daily after that) has been shown to relieve multiple BPH symptoms. In one controlled study, nocturia was reduced by 95%, and symptom severity decreased by 81%, the incidence decreased by 73%, and deferred micturition decreased by 70% (Espinosa 2013). Amino acids are the possible solution, as they act as inhibitory neurotransmitters, decreasing a full bladder feeling. However, treatment by amino acids only alleviates signs.

Even if beer only increases prolactin levels, BPH might be linked to higher alcohol intake. For example, during a 17-year analysis involving 6581 males in Hawaii, alcohol consumption of a minimum of 25 oz/month was strongly associated with BPH diagnosis (Chyou et al. 1993).

Prostatitis is among the most predominant urological pathologies. Typical foods commonly observed to disturb the symptoms of prostatitis are caffeine and alcohol. Chili foods may comprise capsaicin, which in men with irritable bowel syndrome may improve rectal sensitivity. A high intake of sodium can enhance signs of the urinary tract related to prostate disease. Gluten exposure might cause inflammation in sensitive individuals, and thus a gluten-free diet can help alleviate symptoms of prostatitis. In many countries globally, prostate cancer (PCa) is one of the major types of cancer in males, causing many deaths, along with non-melanoma skin cancer (Smailova et al. 2019). Clinical trials showed a substantial benefit of different nutrients, dietary components, and food patterns on the development or progress of PCa, but their results are inconclusive (Sandhu et al. 2013).

Numerous studies have investigated the hypothesis that carbohydrates will delay PCa development by increasing serum insulin levels or modifying the insulin-like growth factor (IGF), which has had a mitogen and anti-apoptotic impact on epithelial cells of the prostate (Mavropoulos et al. 2006; Chan et al. 1998). Animal studies have shown that a ketogenic non-carbohydrate or low-carbohydrate diet (20% kcal) can slow the growth of prostate tumor. Castrated rats, depicting a more sophisticated castration-resistant PCa, consumed a low-carbohydrate, high-protein diet rather than a Western diet (Freedland et al. 2008; Tewari et al. 2009; Masko et al. 2010; Drake et al. 2012; Fokidis et al. 2015). Dietary fiber has been proposed to support PCa patients by reducing the secretion of estrogen and androgen, by increasing the sex hormone linking globulin or the fecal excretion of these hormones (Pusateri et al. 1990; Longcope et al. 2000). Fiber can also decrease the risk of PCa via raising insulin sensitivity and lowering the carcinogenic IGF in the prostate (Barnard et al. 2002). Preclinical studies have shown that a low-carbohydrate, high-protein diet, and a protein-restrictive diet can minimize PCa development (Fontana et al. 2013). Human clinical trials that specifically investigate the impact of the quantity of different types of protein on PCa are hard to design, and this influence is preferably studied under the framework of the dietary pattern in general. A number of studies on PCa have shown the benefits of eating poultry and fish compared to red meat (Lin, Aronson, and Freedland 2015). However, intake of these foods may indicate a trend beyond protein and may include contributions from other dietary factors. Milk products have provided fairly inconsistent findings within the framework of animal protein research. Components such as sugar, calcium, iron, and particularly dairy amino acids may potentially affect PCa. A cross-sectional analysis found a positive correlation between dairy protein and serum IGF-1, which might trigger the initiation or progression ofPCa. The findings of the Physicians' Health Study indicatethat a higher intake of milk after a diagnosis of PCa could be linked to higher PCa-related mortality (Young et al. 2012; Yang et al. 2015). In a meta-analysis of 32 prospective studies, higher average dairy consumption was also found to increase the overall risk of PCa (Aune et al. 2015). Numerous preclinical studies showed the possible benefits of isoflavone-genistein on PCa. Potential pathways includereducing hepatic aromatase, 5α-reductase, androgen receptor expression, all of which FOXA1, which influence urogenital tract tissues and development of the PCa tumor (Christensen et al. 2013). Human studies were, however, rare, low-quality, and contradictory. A meta-analysis found no significant impact of soy consumption on PSA levels, globulin (sex binding hormone), testosterone, and estradiol/dihydrotestos- terone (Ngo et al. 2003; Huang et al. 2012; Liang et al. 2016). In a randomized controlled trial (RCT), it has been found that no PSA, serum total testosterone, free testoster- one, total estrogen, estradiol, or total cholesterol effects are seen in pre-prostatectomy patients (van Die et al. 2014; Hamilton-Reeves et al. 2013). The 2-year RCT showed that soy protein supplementation in males with a high risk of

disease did not influence the risk of PCa recurrence after radical prostatectomy. In case-control trials, PCa risk was not correlated with either plasma or urinary genistein. In comparison, the treatment with genistein in a dose of 30 mg resulted in a significant reduction of androgen-related markers of PCa progression, as was demonstrated by a phase 2 placebo-controlled RCT. The RCT has demonstrated substantially fewer pro-inflammatory cytokines and immunosuppressive cells in PCa patients who consumed isoflavone-rich soy bread (Lazarevic et al. 2012; Bosland et al. 2013; Travis et al. 2012; Jackson et al. 2010; Lesinskiet al. 2015).

A range of preclinical studies on PCa progression demonstrated that decreased dietary fat slows down tumor growth compared to high-fat diets, particularly those containing animal fat and maize oil. A high-fat diet consisting of fish oil (omega-3) substantially decreased the volume of PCa tumor, along with the gene expression of macrophages M1 and M2, the related cytokines, and CCL-2 chemokines (Ngo et al. 2003; Huang et al. 2012; Liang et al. 2016). Rather than simply looking at fat, it may be important to investigate the relationship between PCa and the type of fat, especially animal and omega-6 fatty acids. PCa development can include modulation of the function of fatty acid synthase by high-level inflammatory cytokines (IGF-1) and suppressing GPx3 expression, which may result in prostate epithelial cell growth and intraepithelial neoplasia (Huang et al. 2016; Xu, Jiang, and Ding 2015). A diet rich in fat can also essentially facilitate the infiltration of immune cells into prostate tissues and luminal differentiation (Kwon et al. 2016). An overview of the surgical and lifestyle interventions used in the management of prostate disorders is presented in Figure 1.

Micronutrients

A greater amount of zinc is found in the prostate as compared to most other tissues. For people with BPH, zinc levels in plasma and prostate tissue tend to decline, in contrast to prostatitis. Zinc has shown the ability to alleviate lower urinary tract symptoms (LUTS), possibly because it can inhibit 5-alpha-reductase and/or prolactin (Li et al. 2005; Gómez et al. 2007; Om and Chung 1996; Login, Thorner, and MacLeod 1983). Prolactin has been shown to enhance testosterone secretion by the prostate, thereby supplying more substrate, leading to increased dihydrotestosterone

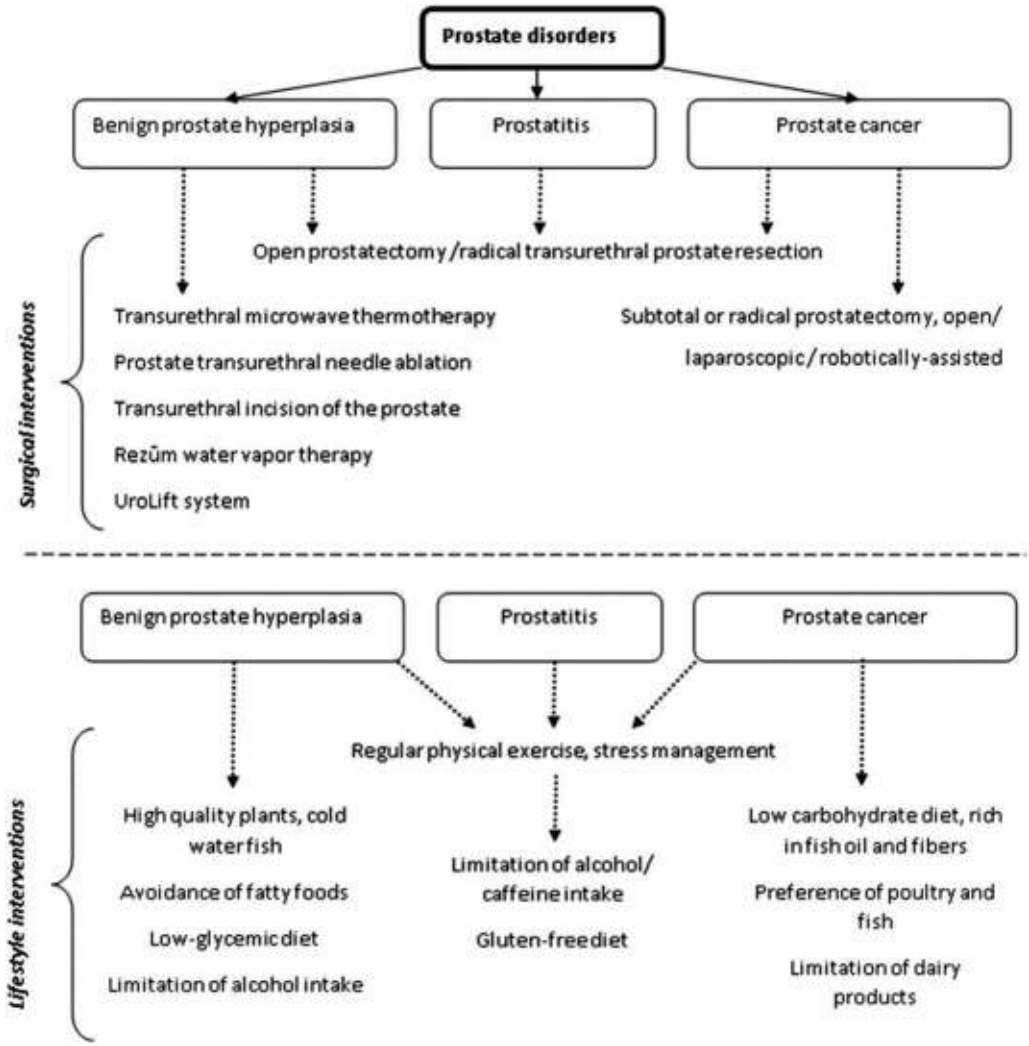

Figure 1. Flow chart of surgical and lifestyle interventions applied for the treatment of prostate disorders.

(DHT). In the context of this preclinical research, tests have shown that proper zinc status in males can benefit both patients with BPH and prostate cancer. However, the outcomes of the Health Professionals Follow-Up Study have shown that men who took zinc supplements for more than ten years developed advanced prostate cancer more often than non-users did. Still, this finding has to be interpreted with caution since the researchers did not control other confounders, such as calcium supplementation (Leitzmann et al. 2003).

The increased consumption of vitamin D with diet or as a supplement has been linked to a decline in BPH incidence. Vitamin D binds to the receptors of the prostate and bladder, inhibits the growth of the prostate, and decreases inappropriate contractility and inflammation. It also has a detrimental impact on the RhoA/ROCK pathway and the expression of the cyclooxygenase-2 and prostaglandin E2 in BPH stromal cells. BPH patients consuming vitamin D analogues in a dose of up to 6,000 IU/day were shown to achieve a reduced prostate volume (Adorini et al. 2010; Espinosa et al. 2013).

In animal models of several cancers, including PCa, retinoids – both natural and synthetic analogues of vitamin A – have been demonstrated to prevent carcinogenesis, but the underlying mechanism remains unknown. In the mouse prostate model, fenretinide, a synthetic cretinoid, has been shown to minimize prostate tumor occurrence. Supplementation with fenretinide in a dose of 200 mg/day for four weeks did not increase retinoids in the prostate tissue to the degree that may be effective or affect retinoid receptor expression in PCa patients (Slawin et al. 1993; Lotan et al. 2000; Thaller et al. 2000). The introduction of fenretinide in a dose of 900 mg/m^2 twice a day for one week, every three weeks a year, demonstrated mild clinical changes in 23 patients with biochemically recurring PCa. Of these 23 cases, seven (30%) were stable on PSA. More work is required to explore safe and effective dosages of fenretinide in PCa patients. In the link between Vitamin A and PCa, broad observational experiments have found contradictory results that the types of vitamin A can explain. In large pooled studies, circulating retinol was positively associated with overall PCa risk (Cheung et al. 2009; Endogenous Hormones Nutritional Biomarkers, 2015; Nash et al., 2015). Still, retinoic acid and retinyl palmitate have demonstrated poor efficacy. Retinol was, however, shown to suppress the development of metastatic PCa in a dose-dependent manner.

Preclinical research indicates that folate depletion can delay tumor growth, although supplementation does not affect growth or progression, but may lead to epigenetic changes through increased DNA methylation. Three meta-analyses demonstrated a correlation between dietary folate and PCa occurrence. Nonetheless, one of these meta-analyses found that serum folate was inversely linked with PCa risk (Li et al. 2016; Bistulfi et al. 2011; Collin2013; Wang, Zheng, et al. 2014). ARCT also found that dietary folate was unrelated to the chance of PCa recurrence. Folate consumption was inversely correlated with PCa risk in a comparative Danish cohort, which was supplementary, but not absolute, on the dietary plane. The study suggested that folate can perform a double role in prostate cancer (Tomaszewski et al. 2014; Roswall et al. 2013; Rycyna, Bacich, and O'Keefe 2013).

Few studies have investigated dietary or supplemental vitamin treatment regardless of the potential use of vitamin C as an antioxidant for cancer treatment. A follow-up analysis of the Physicians' Health Study II also revealed a little effect of vitamin C on PCa incidence (Wang, Sesso, et al. 2014). Probably, data analysis may have been hampered by the perception that high doses of vitamin C can behave rather as a pro-oxidant than an antioxidant.

Laboratory studies show that vitamin E as γ-tocopherol and δ-tocopherol causes the inhibition of PCa cell growth by stimulating cell cycle arrest and apoptosis through AKT activation, induced by the tyrosine kinase receptors (Chen et al. 2016). A mixture of tocotrienols blocked human prostate tumor xenograft development, along with CDK inhibitors p21 and p27 up-regulation. Human experiments have, sadly, been less supportive. An elevated serum-containing α-tocopherol, and not tocopherol, was linked with a reduced risk of PCa, and the correlation might be affected by muta- tions in the genes associated with vitamin E (Huang et al. 2017; Antwi et al. 2015a; Weinstein et al. 2012; Cui, Liu, and Xu 2014; Major et al. 2014). Even among European Americans, dietary α- and γ-tocopherols were inversely related to the aggressiveness of PCa.

In comparison, two observational studies (Cancer Prevention Research II Nutrition Cohort and NIH-AARP Diet and Health Review) found no correlation between supplementation with vitamin E and risk of PCa (Antwi et al. 2015b; Lawson et al. 2007; Calle et al. 2002). Once the treatment with vitamin E has been tested in RCTs, these findings were somewhat incoherent. In a RCT on males of about 50 years of age, supplementation with vitamin E in a dose of 400 IU every other day for an average of 10.3 years did not show an imminent or long-term impact on any cancer, including the incidence of PCa. A follow-up analysis of the Physicians' Health Study II found that supplementation with both vitamin E and C had no effects on PCa cases. However, a modest dose of vitamin E supplement (50 mgr~75 IU) resulted in lower PCa incidence among 29,133 male smokers (Virtamo et al. 2014).

Only a few preclinical studies have examined the role of calcium in PCa patients. Many longitudinal studies and meta-analyses have indicated a positive relationship between calcium intake and PCa incidence, while other trials imply no relation (Ma and Chapman 2009; Bristow et al. 2013). Total and dairy calcium intake, but not nondairy calcium or supplementary calcium intake, have been significantly correlated to total PCa frequency in a meta-analysis of 32 randomized trials. Additional calcium increased the risk of catastrophic PCa, too. Another study indicated the existence of "U-shaped" interactions, according to which very low calcium or creatine levels were also correlated with PCa. Calcium consumption in a dose of 42,000 mg/d was linked to a higher frequency of fatal and high-grade PCa in the

Health Professionals Follow-up Study (Williams et al. 2011; Wilson et al. 2015). Such interactions were, however, attenuated and became statistically insignificant after accounting for phosphorus intake. In this study, phosphorus intake was linked to increased high-grade PCa occurrence, irrespective of calcium and red meat, white meat, dairy, and fish intakes. Phosphorus can also interact separately, with the potential of fatal and high-grade PCa as a consequence.

Plants and essential oils

Achillea wilhelmsii volatile oil has anticancer activity against prostate cancer cells. For normal cells, no cytotoxic effect was found. Ethanol extract of *Acorus calamus* root has been shown to inhibit cell proliferation and angiogenesis and promote rapid apoptosis in left supraclavicular lymph node carcinoma prostate (LNCaP) cancer cell lines, relying on dosage and time. Intake of onion (*Allium cepa*) and garlic (*Allium sativum*) delays the development of BPH (Galeone et al. 2007; Koca et al. 2018; Gautam, Mantha, and Mittal 2014). Sulforaphane (one of the *Brassica oleracea L. var Italica* compounds) decreases the development of prostate cancer by activating phase 2 enzymes in the prostate cells of humans. The anti-androgenic effect of *Mentha spicata* on testis had been determined in a male rat trial. *Mentha spicata* is considered to be used to treat prostate disorders because of its anti-androgenic effect [69] (Brooks, Paton, and Vidanes 2001; Kumar et al. 2008).

Many publications have reported on the role played by a plant-based diet in people with prostate cancer without considering physical activity or stress management. In these trials, the plant-based diet was usually high in fruits, vegetables, whole grains, legumes (beans) and was often low in total fat. The results showed some increase in PSA levels, which was not substantial enough to be statistically significant, or a drop in other cancer-related markers. While the outcomes of plant-based diet trials differed, generally, they showed some positives for preventing cancer, changes in eating habits, and general health. Li and coauthors discussed improved cholesterol profile and body composition. The in vivo analysis of extracts obtained from *Tribulus terrestris* and *Cornus officinalis* revealed a marked improvement of ICP and cAMP levels (Kam et al. 2012).

Extracts from *T. terrestris* and *C. officinalis* can enhance erectile functionality. The reduction of erectile dysfunction, one of the treatment effects in prostate disorders, is believed to improve the patients' quality of life (Kam et al. 2012). *Urtica dioica* extract (UR102) inhibits the activity of 5 α-reductase enzymes, depending on their concentration. UR102 can only influence enzyme activity at high concen- trations (including 12 mg/mL) and was measured at 14.7 mg/ mL ED50 (Hartman, Mark, and Soldati 1996). *Urtica dioica* is believed to be particularly effective in treating prostate disorders by inhibiting the enzyme 5-α-reductase. It has been determined that *Carthamus tinctorius* ethanol extract is an important 5α-reductase inhibitor and promoter of hair growth (Kumar et al. 2012). 5α-reductase is an essential enzyme in the metabolism of androgens and is needed for the conversion of testosterone (T) into the more active dihydrotestosterone (DHT). Dihydrotestosterone is efficacious in prostate gland development. *Carthamus tinctorius* is thought of being used as a 5α-reductase blocker to prevent the prostate gland from developing. β-Sitosterol, present in the oil of *Cucurbita pepo*, was shown to be a significant promoter in the biosynthesis of prostaglandin in prostate tissue of BPH patients (Nakić et al. 2006). *Cucurbita pepo* is believed to be used to manage inflammation because it prevents prostaglandin biosynthesis and symptoms associated with prostaglandin effects (Younis, Ghirmay, and Al-Shihry 2000). In a previous study, 2245 BPH patients underwent a multicentre clinical trial. According to the American Urological Association, urinary symptoms were measured by the International Prostate Symptom Score (I-PSS), and the influence on life quality was measured trough the Life Quality (LQ Index) questionnaire. According to this report, the patient was administered capsules comprising a 500 mg extract of pumpkin seed.

I-PSS declined by 41.4% during therapy, and the life quality at the end of treatment increased by 46.1% (Friederich, Theurer, and Schiebel-Schlosser 2000). It is known that *Viola odorata* contains β-ionone. Studies of β-ionone cytotoxic activity have shown that it prevents cancer cell proliferation in a concentration-dependent manner in β-ionone DU145, LNCaP (human prostate carcinoma cells), and prostate adenocarcinoma cells (PC-3) (Jones et al. 2013). Furthermore, it was observed that maysin, an effective flavonoid contained in maize tassel (*Zea mays*), prevents the development of PC-3 (androgen-dependent human prostate cancer cells) by inducing apoptotic cell death, which depends on mitochondria. This has a potential therapeutic impact in managing human prostate cancer that is chemotherapy-resistant or androgen-independent (Lee et al. 2014). A pigmented variety of maize, known as purple corn, has been cultivated in the Andean Region of South America for hundreds of years. In animal studies, purple corn was found to be successful in inhibiting prostate carcinogenesis. Three major purple corn anthocyanins (cyanidin-3-glucoside, pelargonidin-3-glucoside, and peonidin-3-glucoside) were evaluated on an androgen-dependent prostate cancer cell line, LNCaP. The results showed that the active compounds were cyanidin-3-glucoside and pelargonidine-3-glucoside, which may potentially lead to chemoprevention in PCa (Long et al. 2013).

Lifestyle advice

Understanding the direct impact of lifestyle changes on the prostate gland is constrained by many challenges, since it requires the extraction of prostate tissue from healthy men before and after introducing such changes. However, some factors were reported to play an inflammatory role, including excessive estrogen, insulin, and IGF-I plasma levels. Hopefully, they are all likely to be decreased by appropriate changes in lifestyle. Epidemiological studies identified that a high-calorie diet containing carbohydrates and polyunsaturated fatty acids increases the risk of BPH, while intake

of fruits and vegetables decreases this (Suzuki et al. 2002; Rohrmann et al. 2007; Bravi et al. 2006). Also, physical activity was documented to lower the risk of BPH and/or LUTS. According to clustered analyses, light to intense physical exercise is correlated with a non-significant risk reduction for BPH and LUTS. Regular exercise (5 days a week), paired with a low-fat diet consisting of whole grains, fruits, and vegetables, reduced insulin and IGF-1 and increased levels of IGFBP-1, which was associated with a reduction in apoptosis relative to mitosis in prostate cells. Besides, inflammatory cytokines released through the nuclear factor-kB (NF-kB) mechanism were also declined, stimulat- ing growth and blocking apoptosis. Further research showed that regular exercise combined with low-fat diet results in downregulated RAS oncogenes, such as RAN, RAB14, RAB8A, and SHOC2, that synthesize proteins necessary for MAPK activation through growth factors, thus minimizing the incidence of BPH (Ornish et al. 2008).

Giubilei and coauthors reported a strong impact of aerobic exercises on patients with prostatitis, leading to a decrease of symptoms (Giubilei et al. 2007). When assessing the frequency and predisposing factors for prostatitis in African-American males, Wallner observed that physical activity was linked to lower chances of prostatitis (Wallner, Clemens, and Sarma 2009). Similarly, in a report assessing the incidence and psychosocial association of symptoms indicative of prostatitis in the population of the Boston area, Link and coauthors observed that males with elevated physical activity were less likely to experience signs of this disorder (Link et al. 2008). Collins and colleagues have discovered that a diagnosis of prostatitis was associated with a sedentary lifestyle and obesity (body mass index ≥ 27 kg/m^2) (Collins et al. 2002).

For many years, it has been known that a mode of living, which involves a balance of diet and physical activity, is effective in the treatment and prevention of chronic diseases, including cardiovascular disease and diabetes. In 2005, a similar lifestyle plan was studied in a group of patients with PCa, who had opted to undergo active monitoring. This research examined the impact of a low-fat vegan diet with added soy and a number of dietary supplements, along with mild aerobic activity and stress management. There was a small decline in PSA after one year in males following the lifestyle program, and there was an improvement in the control group (males getting standard treatment). This research suggests that maintaining a healthy lifestyle can slow the progression of PCa in males with early-phase disease. After a period of active surveillance that lasted for two years, fewer males in the lifestyle plan group compared with the controls needed treatment for PCa. Finally, people who adopted this plan reported moderate weight loss and decreased blood cholesterol levels, which provided an opportunity for significant health effects besides PCa. The effects of lifestyle programs in people with PCa were tested in randomized controlled research. The researchers recruited people with elevated PSA levels following treatment and men with more advanced cancer (Bourke et al. 2011). Although these findings did not show significant changes in PSA and cancer growth markers, they led to a substantial increase in feeding sense, exercise habits, fatigue, and muscle strength advancements. Therefore, it may be concluded that exercise plans can have potentially major health effects on people with PCa. However, direct comparisons between such experiments are difficult to make, due to differences in food and physical activity systems and the length and mode of therapy.

The significance of mental health treatment in PCa patients has become evident due to epidemiological studies indicating a higher risk for mental distress, e.g., stress, depression, and sleeplessness in PCa patients. For example, one study documented a 6.5-fold elevated suicide risk in newly diagnosed patients as compared to control subjects of the same age. Thus, several strategies were proposed to promote healthy habits and boost the quality of life in patients, addressing cancer symptoms and negative effects of cancer therapy (Zuniga et al. 2020).

Integrative approach

The inadequacy of Western medicine in treating chronic diseases has been noted by health care workers worldwide. Integrative health care has many dimensions and could range from simple incorporation of comprehensive and alternative medicine (CAM), into conventional medicine, to an independent form of medical practice. The health benefits of the integrated approach are well-known. With the recognition of this, a new center has been founded within the National Institutes of Health, the USA, to tackle CAM problems. However, regulatory bodies of the US, UK, and EU countries do not approve the use of herbal medicines in their respective countries, citing safety issues and lack of clinical evidence of efficacy. Nevertheless, those patients who did not benefit from Western medicine pursue CAM interventions, and it was estimated that around 25%–50% of PCa patients use at least one CAM modality (Klempner and Bubley 2012).

Considering that most countries are trying to develop sustainable universal health care, an innovative healthcare approach is of great global importance. According to the World Health Organization, over 1 billion users utilize herbal medicines, and in India, over 65% of rural people use medicinal plants (Rao 2015). According to a study by Joos and coauthors, more than two-thirds of the patients in Germany use CAM. Based on their report, CAM is highly valued by many families and is already making a significant contribution to primary care in Germany. One in ten people in the UK are currently using alternative drugs, and so do 50% of patients during their lifespan. Thus, a recent report by the House of Lords expressed great concern in the need for more studies on both health effects and efficacy of these treatment modalities.

Khorsan et al. systematically reviewed integrative studies in health care, including randomized controlled trials, controlled clinical studies, and meta-analyses. In their search, which yielded 11,891 citations, they concluded that there is not enough evidence to judge the effectiveness of integrative treatment regimens, but they appear to be safe (Khorsan et al. 2011). Because patients with prostate disorders are

increasingly using CAM to improve their symptoms, there is a need for more studies dedicated to this emerging public health problem. At the same time, it is not easy to conduct such trials for several reasons. Firstly, it is not easy to find a reliable CAM source since there is a lot-to-lot variability. Secondly, more reliable biomarkers have to be identified, and pharmacokinetics must be better understood to make sound recommendations considering the dose and administration schedule. Thirdly, most clinical trials on novel pharmacological agents are sponsored by the manufacturers, which have little interest in initiating such trials because the market is already full, and approval from the side of regulatory bodies is not required. Thus, in the presence of multiple experimental studies demonstrating the efficacy of CAM, there are very few clinical trials.

Nevertheless, there are many clinical trials on incorporating CAM therapies to treat prostate disorders, which deserve to be described in more detail. A blend of 8 herbs consisting of chrysanthemum (*Dendranthema morifolium*), Baikal skullcap (*Scutellaria baicalensis Georgi*), Panax ginseng (*Panax pseudoginseng var.*), Isatis (*Isatis indigotica fortune*), Ganoderma (*Ganoderma lucidum*), licorice (*Glycyrrhiza glabra licorice*), saw palmetto (*Serenoa repens*), and Hara (*Rabdosia rubescens*) was tested in a phase II RCT, in comparison to diethylstilbestrol (DES), in patients with castrate refractory PCa. This trial showed that more than 40% of patients, randomized to a blend of 8 herbs, had a 50% reduction in PSA levels, and the median time to progression constituted 5.5 months, in contrast to 2.9 months in the group receiving DES (Oh et al. 2004). Still, the trial was terminated because DES was found in the herbal formulation in concentrations up to 3.1%.

Zyflamend is a blend of herbal extracts (turmeric, barberry, hu zhang, ginger, oregano, Chinese goldthread, *Scutellaria baicalensis*, green tea, and holy basil), which in LNCaP cancer cell lines caused inhibition of COX-1 and COX-2, induced cell cycle inhibitory proteins and suppressed AR expression (Bemis et al. 2005). Furthermore, it was demonstrated that Zyflamend and/or metformin, prescribed to patients with castration-resistant PCa, exerted antitumor effects and could be considered as a useful supplementation to conventional treatment (Bilen et al. 2015).

Prostate Health Cocktail (PHC) is another combination herbal supplement (selenium, vitamin E, vitamin D3, saw palmetto, green tea extract, lycopene, and soy derivatives), which was evaluated in PCa cell lines and men with biochemically recurrent PCa. The in vitro effects of PHC included a strong anti-proliferative activity that was dose-dependent. Besides, PHC induced the suppression of androgen receptor expression. Although the primary end- point of 50% PSA reduction was not met, PHC induced some PSA declines without reducing the levels of serum androgens (Dorff et al. 2014).

To provide robust evidence on the effectiveness of CAM in the management of biochemically recurrent PCa, Die and coauthors conducted a systematic review of randomized controlled trials. The interventions tested included herbal medicinal extracts (turmeric, pomegranate, green tea, and broccoli sprout) or plant-derived dietary items (soy and lycopene). All eligible studies reported stabilizing serum PSA levels that decreased or rose more slowly in a significant proportion of patients. The authors concluded that all herbal medicinal interventions were safe and well-tolerated, but more studies of good methodological quality are needed to judge their place in managing PCa patients (Van Die et al. 2016). Figure 2 summarizes the micronutrients, plants, and essential oils of interest to manage prostate disorders.

Nutrition and surgery

Eventually, many patients will need to undergo surgery for their prostate disease. The *European Society for Clinical Nutrition and Metabolism* (ESPEN) provides straightforward and hands-on guidelines for nutritional support in this case, which will be discussed below. Despite the quite high Level of Recommendation, however, the Level of Evidence is usually fairly low due to the lack of RCTs of sufficient quality. Moreover, the guidelines are based on the type of pathology rather than the type of surgery (with some exceptions).

ESPEN provides guidelines for various types of surgery; in this case, those for perioperative care in rectal/pelvic surgery are applicable (although most evidence in this region exists for rectal cancer) (Nygren et al. 2012). These directives, obtained in association with two other international societies, overarch the entire perioperative period, from pre- to postoperative period. Special attention is paid to a fluidic replacement, also because prostate surgery can sometimes take a whole working day (depending on the technique of surgery), causing even more fluid loss in an already compromised patient group; excessive hydration, however, is to be avoided at any cost. In practice, preoperative counseling is required, leading to nutritional support is necessary; also, exercise therapy is highly recommended. The perioperative period is marked by a heavy carbohydrate load (unless the patient has diabetes) and fluid intake preoperatively. Postoperatively, it is recommended that patients have oral intake (with oral nutritional supplements if needed) as soon and as much as possible, with an emphasis on protein intake.

Based on an *Enhanced Recovery After Surgery* (ERAS) program, these guidelines are complimentary to the ESPEN guidelines for nutrition in surgery in general (Weimann et al. 2017). Importantly, the general guidelines emphasize limiting preoperative fasting and resuming oral intake as soon as possible in the postoperative period (with oral nutritional supplements if needed); both especially apply for the intake of clear fluids. Classical pathways involving the quick start of enteral and/or parenteral nutrition (including for ease) can be considered completely obsolete; both are only indicated in case of insufficient oral intake (e.g., due to comorbidities). In any case, both pre- and postoperative nutrition assessment is heavily needed to conform to these directives; in case of severe nutritional risk preoperatively, a nutritional intervention needs to be performed for no less than 1-2 weeks before surgery (although this can also be done ambulatory in many cases, omitting the need for a longer hospital stay), even in the case of cancer, to improve

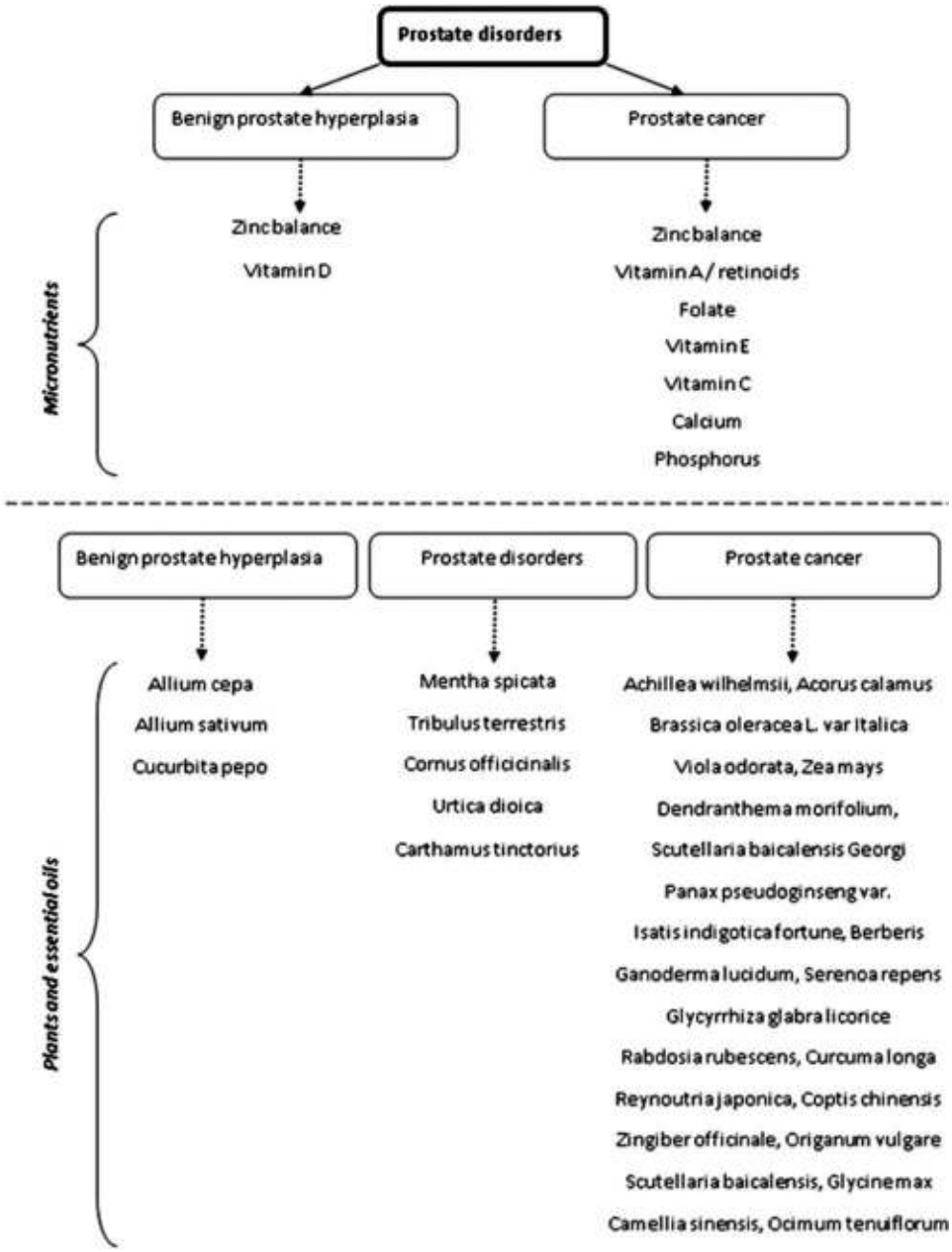

Figure 2. Micronutrients, plants, and essential oils of interest for the management of prostate disorders.

outcome. Specific recommendations for both enteral and parenteral nutrition are provided to minimize the duration of these modes of therapy.

Taking the typically advanced age of patients with prostate pathology (especially PCa) into account, the above guidelines should be completed with the ESPEN guidelines specifically aimed at geriatric patients (Volkert et al. 2019), as this group classically yields multiple pathologies pathology (such as cognitive impairment), complicating the patients' self-sustainability. When dealing with prostate cancer specifically, ESPEN only provides for cancer guidelines in general (Muscaritoli et al. 2021), referring to the ERAS programs mentioned above. The *European Society for Medical Oncology* (ESMO) mostly underwrites the ESPEN guidelines through their handbook for members (ESMO 2011 online Handbook of Nutrition and Cancer, conceived with the aid of ESPEN members), although recommendations concerning surgery remain general. Despite detailed guidelines concerning the specific treatment of PCa (Parker et al. 2020), no actual recommendations for nutritional support exist. Many PCa patients are typically much older than other cancer patients; in this age group, it is well-known that malnutrition of any cause is already much more abundant.

However, it should be stressed that these are European guidelines, which cannot be applied everywhere in the world. For instance, the American recommendations, especially those concerning clinical nutrition, differ vastly from the European ones. This is mostly due to a different healthcare system. Therefore, these guidelines can only be applicable when it remains affordable for both the patient as well as the healthcare system.

Concluding remarks

Altogether, nutraceuticals can be considered a viable mode of treatment in prostate disease, including prostatitis, BPH, and prostate cancer. Ample evidence exists for the immediate hands-on application of nutrition therapy in these prostate disorders. However, there is a need to continue research with a focus on future perspectives. The sample could be put forward of *omega-6/omega-3* PUFA ratio, the role of which has been well established in other diseases; more and more is becoming known about prostate disease, particularly of BPH and prostate cancer. While more preclinical research is needed, PUFA can already be administered safely and effectively to patients with prostate disorders, possibly also in a preventive way, based on the current nutritional guidelines, as proposed by the European Society for Clinical Nutrition and Metabolism.

Concerning prostate cancer, the value of nutrition therapy should be further elucidated, as hormonal changes could result from a nutritional change. In particular, limiting carbohydrates (which yields no surprise, as many other diseases are also caused by carbohydrate overconsumption), the addition of fibers, and the fat-soluble vitamins A, D, and E have much potential. As for proteins, their role is less obvious, and quality might be more important than actual quantity.

The beneficial effects of exercise therapy are known to be the same in other forms of cancer, although clear evidence is lacking. Moreover, while studies can easily demonstrate a positive effect, attention should be given to the implementation potential of the patients, for which it may be a bigger challenge than the application of nutrition therapy.

Classical, alternative therapies, including plant-based treatments and natural oils, are less supported by hard-boiled evidence, due to the relative lack of interven- tional trials as compared to the abundance of observational trials. However, the few interventional trials that do exist are showing favor toward CAM. While mechanisms are often not well known (if at all), clinical evidence yields high hopes for this mode of treatment. We conclude that, although alternative treatments can and are already being applied worldwide, more elucidation on its mechanisms is hotly demanded.

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I. Lucrări relevante

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New Challenges in Surgical Approaches for Colorectal Cancer during the COVID-19 Pandemic

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Abstract: (1) Background: The COVID-19 pandemic put a great burden on national healthcare systems, causing delays and disruptions in the medical care of non-COVID-19 patients. This paper aims to analyze the COVID-19 pandemic impact upon the quality of care in colorectal surgery. (2) Materials and Methods: We performed a retrospective study on the colorectal cancer cases operated in the Fourth Department of General Surgery, Emergency Hospital Bucharest Romania, over the period March 2020–February 2021 (pandemic group) vs. March 2019–February 2020 (non-pandemic group). (3) Results: The number of patients in the pandemic group decreased by 70% (36 vs. 118 patients), with lower accessibility from rural areas (11.1% vs. 37.2%, $p = 0.035$). Most cases in the pandemic group were emergencies (69% vs. 37.3%, $p = 0.009$), admitted for bowel obstruction (63.8% vs. 27.9%, $p = 0.008$). There was no in-hospital COVID-19 infection in patients operated for colorectal cancer. The 30-day mortality was significantly higher in the pandemic group (25% vs. 6.7%, $p = 0.017$), mostly due to septic shock (36.1% vs. 5%, $p = 0.0001$). (4) Conclusions: Colorectal cancer surgery may be performed safely during the COVID-19 pandemic, with strict adherence to the SARS-CoV-2 prevention protocols. However, the significant increase in colorectal cancers in the emergency was associated with worse outcomes and higher mortality during the COVID-19 pandemic.

Keywords: COVID-19 pandemic; colorectal cancer; surgery; quality of care; outcomes

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1. Introduction

The COVID-19 pandemic has put enormous pressure on national health systems around the world for more than two years, both through a large number of hospitalizations,

exceeding the capacity of intensive care beds and the frequent disruptions in health care for other conditions, conducting national screening programs during lockdown periods [1,2].

The standards of quality and safety were deeply affected by the rapid spread of the COVID-19 in all elements of Donabedian's triad—structure, process, and outcomes, the global impact being difficult to quantify [3,4]. Hospitals encountered difficulties in balancing the resources of intensive care needed for COVID-19 patients while struggling to continue the routine hospital care. The prioritization of COVID-19 by health systems, non-COVID patients failed to receive appropriate care, missed scheduled check-ups for screening or procedures by imposed lockdowns, or were postponed by patients for fear of SARS-CoV-2 infection. Moreover, the staffing shortage, crush of work, and burnout among medical personnel had a direct impact on patient care, resulting in delayed or rushed care [5,6].

COVID-19 has reduced life expectancy in four-fifths of OECD countries [7]. Many studies raised concerns about the increased vulnerability of cancer patients during the COVID-19 pandemic, by limiting early access to diagnosis and treatment, discontinuation in treatment, and remission of controls due to travel restrictions and limited hospitalization [8–10]. A report on the COVID-19 pandemic impact on accessibility to chronic healthcare services in Romania showed a decrease by 35% in the oncological hospitalizations in 2020, in comparison with previous years [11]. Taking into account the gravity of oncological diseases and the importance of early diagnosis, there was a concern that this vulnerable segment could become a "silent collateral victim" of the COVID-19 pandemic [12–14]. After the first pandemic lockdown, national healthcare systems prioritized the access of oncological patients to adequate treatment facilities. However, in current practice, elective surgeries for digestive cancers were often delayed due to the lack of availability of intensive care beds. Colorectal cancer is the third most frequent malignancy worldwide, with an overall incidence of more than a million new cases per year [15], and one of the top causes of death by cancer [16].

This paper aims to analyze the challenges in surgical approaches to colorectal cancer encountered during the COVID-19 pandemic.

2. Materials and Methods

We conducted a retrospective comparative study on the patients diagnosed with colorectal cancer that underwent surgery in the Fourth Department of General Surgery, Emergency Hospital Bucharest, Romania, between March 2020 and February 2021 (pandemic group) vs. March 2019–February 2020 (non-pandemic group). March 2020 marked the beginning of the COVID-19 pandemic in our country. The data from the observation sheets and the operating protocols regarding emergency presentation, TNM staging, tumor location, therapeutic management, and changes in surgical practice protocols imposed by the COVID-19 pandemic were analyzed. The patients with colorectal cancer admitted for evaluation, for whom surgery was not performed, and patients admitted for bowel transit reconstruction after a temporary stoma were excluded. Quality of care was analyzed in terms of postoperative 30-day mortality and morbidity. Descriptive statistics were reported as percentages. The Student's *t*-test was used to assess statistically significant correlations between continuous variables in the 2 study groups, and Wilcoxon (chi-squared) test for categorical variables. A *p*-value less than 0.05 was considered statistically significant. Data analysis was performed with the Statistical Software of SciStat® available at www.scistat.com (accessed on 15 January 2022) and IBM-SPSS22. Moreover, we also used the following statistical tests and models: Fisher's exact test for contingency tables of dimension 2 × 2 (in order to compare frequencies) and dimension N × 2 for N > 2 (to compare discrete distributions); nonparametric Mann–Whitney U-test; binary multivariate logistic models and OR, the odds ratio statistic.

3. Results

3.1. Changes in Structure and Surgical Protocol during COVID-19 Pandemic

Before the COVID-19 pandemic, there were 54 hospital beds in our department. Between March 2019 and February 2020, 2404 patients were treated in our department, of which 1017 cases were admitted in emergency (42.3%), 1022 (42.5%) by planned admission and 365 (15.2%) were transferred from other departments. We identified 362 patients admitted with the ICD-10 code of colorectal cancer (codes C18-C20) between February 2019 and March 2020, out of which 118 were operated for the primary tumor and included in the present study.

During the first year of the COVID-19 pandemic (March 2020–February 2021), there were significant changes in the structure and circuits, to comply with the new regulations: social distancing for patients, with a minimum distance of 1.5 m between hospital beds and separate circuits for COVID-19 negative and COVID-19 suspects. The total number of beds decreased to 19 for COVID-19 negative patients and an additional area of 7 hospital beds for COVID-19 suspects, isolated one per room, until the result of the RT-PCR was obtained. A total of 1089 patients were hospitalized in the period March 2020–February 2021 in our department, out of which 514 (47.2%) in emergency, 313 (28.7%) by scheduled appointment and 262 (24%) were transferred from other departments. Our research identified 61 patients hospitalized with diagnostic codes C18-C20, out of which 36 were operated for colorectal cancer.

RT-PCR testing was routinely performed 24–48 h before the planned admission for elective surgery. Taking into account the early evidence of poor outcome in COVID-19 patients who underwent surgery [17,18], the admission was postponed in case of a positive result. For emergency presentations, RT-PCR was taken at admission, and the patient followed the circuits for COVID-19 suspects. If the patient's condition permitted, surgery was delayed until the result of the RT-PCR was obtained. If the surgery had to be performed in emergency, all the precautions for a possible COVID-19 positive case were taken: full personal protective equipment (PPE), with N95 or FFP 2 or 3 (filtering facepiece) masks, eye protection, gowns, and gloves, limiting the maneuvers with risk of aerosolization, such as laparoscopy and limiting the exposure of healthcare personnel in the operating room to a minimum necessary, according to the current regulations for preventing SARS-CoV-2 infection [19,20]. Family visits were not permitted during the COVID-19 pandemic, except for special circumstances, such as imminent patient death.

3.2. General Data of the Patients Included in the Study Groups

The total number of colorectal cancer patients treated in our department between March 2020 and February 2021 was 70% lower when compared to the non-pandemic group (36 vs. 118 patients). Moreover, there was a significantly decreased addressability of patients from rural areas (11.1% vs. 37.2%, p = 0.035). This finding may be explained by several factors: the limitations in free circulation during lockdowns, the discontinuities in primary care, and patients' decisions to postpone presentations due to fear of SARS-CoV-2 infection (Table 1).

Table 1. General data of the patients that underwent surgery for colorectal cancer in the 2 study groups (the percentages are calculated based on the total of the corresponding column, namely 118 and 36, respectively).

Parameter	Non-Pandemic Group (March 2019–February 2020)	Pandemic Group (March 2020–February 2021)	p Value
No. of cases	118	36	
Females (no. of cases; %)	36 (30.5%)	16 (44.4%)	0.158 [(a)]
Age (years)	66.6+/−11.3	70.2+/−10.4	0.180 [(b)]
Rural vs. urban (no. of cases; %)	44; 74 (37.2%; 72.8%)	4; 32 (11.1%; 88.9%)	0.003 * [(a)]

Table 1. *Cont.*

Parameter	Non-Pandemic Group (March 2019–February 2020)	Pandemic Group (March 2020–February 2021)	*p* Value
Emergency presentation (cases; %)	44 (37.3%)	25 (69%)	0.009 * [a]
• Occlusion	33 (27.9%)	23 (63.8%)	0.008 * [a]
• Perforation	2 (1.6%)	1 (2.7%)	0.367 [a]
• Inferior digestive hemorrhage	9 (5%)	1 (2.7%)	0.685 [a]
Location of the tumor (no. of cases; %):			
• Cecum and right colon	30 (25.4%)	10 (27.7%)	0.829 [a]
• Transverse colon	4 (3.3%)	4 (11.1%)	0.087 [a]
• Left colon	51 (43.2%)	17 (47.2%)	0.704 [a]
• Rectum/rectosigmoid	33 (27.9%)	5 (13.8%)	0.121 [a]
Chemotherapy before admission (no. of cases; %):	16 (15.6%)	2 (5.5%)	0.354 [a]
Comorbidities (no. of cases; %):			
• Arterial hypertension	40 (33.9%)	16 (44.4%)	0.322
• Ischemic coronary disease	30 (25.4%)	20 (55.6%)	0.001
• Chronic respiratory diseases	18 (15.3%)	0 (0.0%)	0.008
• Diabetes mellitus	10 (8.6%)	4 (11.1%)	0.741
• Other	30 (25.4%)	10 (27.8%)	0.828
No. of comorbidities per patient:			0.273
• ≥3	14 (11.8%)	6 (16.6%)	
• 2	49 (41.5%)	9 (25%)	
• 1	39 (33%)	13 (36.1%)	
• 0	16 (13.5%)	8 (22.2%)	
TNM Stage (no. of cases; %)			
T			
T2	12 (10.1%)	0	
T3	67 (56.7%)	12 (33.3%)	0.163
T4	24 (20.3%)	21 (58.3%)	
Tx	9 (7.6%)	3 (8.3%)	
N			
N0	32 (27.1%)	8 (22.2%)	
N1	72 (61%)	18 (50%)	0.373
N2	6 (5.1%)	6 (16.6%)	
Nx	8 (6.8%)	4 (11.1%)	
M			
M1	27 (22.8%)	6 (16.6%)	0.623
Mx	91 (77.2%)	30 (83.4%)	
Histopathological forms (cases; %)			
• Colonic conventional adenocarcinoma	80 (67.68%)	8 (22.1%)	<0.001
• Colonic mucinous adenocarcinoma	21 (17.8%)	26 (72.2%)	<0.001
• Rectal adenocarcinoma NOS	11 (9.3%)	0	0.196
• Rectal squamous cell carcinoma	2 (1.6%)	0	0.586
• Neuroendocrine tumor	2 (1.6%)	2 (5.5%)	0.193
• Colonic stromal tumor	2 (1.6%)	0	0.586

Footnote: * Statistically significant ($p < 0.05$); [a] Fisher's Exact Test for 2 × 2-Table; [b] Mann–Whitney U-test.

There were no statistical differences in sex ratio between the 2 groups ($p = 0.273$). Age at presentation was slightly higher in the pandemic group (70.16+/−10.2 years vs. 66.6+/−11.2), but not statistically significant ($p = 0.06$). In both groups, the most frequent associated comorbidities were arterial hypertension, cardiac ischemic disease, and diabetes mellitus (Table 1). Preoperative chemotherapy was initiated at admission in 15.6% of cases in the non-pandemic group and only 5.5% of patients in the pandemic group. However, the statistical analysis did not find a significantly decreased value ($p = 0.354$).

Most patients in the pandemic group presented in emergency (69% vs. 37.3%, $p = 0.009$), with signs of bowel obstruction (63.8% vs. 27.9%, $p = 0.008$). The statistical analysis of the

distribution of cases according to TNM stage revealed a higher incidence of loco-regional advanced colorectal tumors in the pandemic groups (T4 58.3% vs. 20.3%; N2 16.6% vs. 5.1%), but not statistically significant (p-value = 0.163).

An interesting finding in the histopathological exam was a significantly higher proportion of mucinous adenocarcinomas moderately differentiated (G2) in the pandemic group (72.2% vs. 17.6%. p = 0.002), while in the non-pandemic group, the most prevalent were conventional G2 colonic adenocarcinomas (59.3%). This type of colorectal tumor is generally associated with a delayed diagnosis until advanced stage, partial response to chemotherapy and worse outcomes compared with conventional colorectal adenocarcinoma [21,22].

3.3. Postoperative Outcomes in Pandemic and Non-Pandemic Groups

Tumor resection in intended oncological safety limits was performed in most cases in both groups (76.3% in the non-pandemic group, and 88.9% in the pandemic group, respectively). In the remaining cases, a colostomy or ileostomy was decided, either palliative or temporary, to resolve a bowel obstruction in emergency, in patients with multiple comorbidities and insufficiently explored as oncological status. Statistical analysis of the type of surgery showed no significant difference between the 2 study groups (Table 2).

Table 2. Types of surgery, mortality and postoperative complications in the 2 study groups.

	Non-Pandemic Group	**Pandemic Group**	***p*-Value**
Type of surgery (no. of cases; %):			0.168 [c]
• Rectum amputation	16 (13.5%)	4 (11.1%)	
• Colostomy/ileostomy	29 (24.5%)	5 (13.8%)	
• Hartman surgery	23 (19.4%)	13 (36.1%)	
• Right hemicolectomy	27 (22.8%)	8 (22.2%)	
• Left hemicolectomy	21 (17.7%)	2 (5.5%)	
• Segmental resection	2 (1.7%)	4 (11.1%)	
Hospital stays (days)	15.82+/−11.7	12.72+/−5.3	0.278 [b]
Postoperative hospital stays (days)	11.59+/−9.4	11+/−4.94	0.798 [b]
Systemic postoperative complications (no. of cases; %):			
• Clostridium infection	12 (10.1%)	5 (13.8%)	0.452 [a]
• Septic shock	6 (5%)	13 (36.1%)	<0.001 * [a]
• Pulmonary acute edema	4 (3.3%)	2 (5.5%)	0.677 [a]
• Myocardial infarction	2 (1.7%)	0	NS
• Malign arterial hypertension	3 (2.5%)	0	NS
• Urticaria	1 (0.9%)	0	NS
• Urinary infection	2 (1.7%)	0	NS
Wound related complications (no. of cases; %):			
• Bleeding	3 (2.5%)	0	NS
• SSI	16 (13.5%)	4 (11.1%)	NS
• Infected hematoma	4 (3.3%)	0	NS
• Anastomotic leak	8 (6.7%)	4 (11.1%)	NS
• Colostomy detachment	1 (0.9%)	0	NS
Death at 30 days after surgery (no. of cases; %):	8 (6.7%)	9 (25%)	0.017 * [a]
Causes of death (no. of cases; %):			
• Septic shock	4 (3.3%)	8 (22.2%)	<0.001 * [a]
• Myocardial infarction	2 (1.7%)	0	NS
• Pulmonary acute edema	2 (1.7%)	1 (2.75%)	NS

Footnote: * Statistically significant; NS: non-significant/irrelevant statistics; [a] Fisher's Exact Test for 2 × 2-Table; [b] non-parametric Mann–Whitney U-test for comparison of distributions; [c] Fisher's Exact Test for N × 2-Table, N > 2.

The mean hospital stay was slightly lower in the pandemic group (12.72+/−5.3 days vs. 15.82+/−11.7 days). There was no in-hospital COVID-19 infection in patients operated for colorectal cancer, which proves the efficiency of the newly established circuits and

procedures. The surgical wound infections were lower in the pandemic group, but not statistically significant. As a general guideline, colo-colic or colo-rectal anastomosis was avoided in cases operated in emergency, due to a high incidence of anastomotic leaks in such conditions. When analyzing the postoperative complications according to the Clavien Dindo classification (Table 3), the chi-square test did not show a significant difference among the 2 groups (p = 0.085). However, statistical analysis revealed worse outcomes in the pandemic group in terms of mortality (25% vs. 6.7%, p = 0.017) and postoperative septic shock (36.1% vs. 5%, p = 0.0001).

Table 3. Postoperative morbidity in pandemic and non-pandemic groups according to the Clavien Dindo Classification of severity.

Clavien Dindo Classification of Postoperative Complications	Non-Pandemic Group (No. of Cases, %)	Pandemic Group (No. of Cases, %)
Grade I (SSI, minor complications treated pharmacologically)	17 (14.4%)	2 (11.1%)
Grade II (treated pharmacologically)	16 (13.5%)	3 (16.6%)
Grade III	13 (11%)	4 (11.1%)
IIIA (reintervention without general anesthesia)	4 (3.3%)	0
IIIB (reintervention with general anesthesia)	9 (7.6%)	4 (11.1%)
Grade IV	10 (8.4%)	5 (13.8%)
IVA (requiring ICU)	4 (3.3%)	2 (5.5%)
IVB (with multiple organ failure)	6 (5%)	3 (8.3%)
Grade V	8 (6.7%)	9 (25%)

Furthermore, we assessed the differences in quality of care between the two study groups in terms of postoperative morbidity and in-hospital mortality. We found no significant differences in terms of hospital stay, wound related complications, Clostridium infection and acute cardiovascular complications, such as heart attack, malign arterial hypertension and acute pulmonary edema. However, we found an increased incidence of septic shock (p < 0.001) and death (p = 0.017) in the pandemic group.

A multivariate analysis was carried out in order to identify the main factors related to the worse outcome among the study groups (namely pandemic group and non-pandemic group). We investigated as covariates age, sex, emergency presentation, bowel occlusion, the associated diseases and major postoperative complications.

We used two logistic regression models: to compare pandemic/non- pandemic (Table 4); to compare death/non-death (Table 5).

The logistic regression model found for bowel occlusion an odds ratio OR (pandemic/non-pandemic) = exp(1.542) = 4.673 with 95% confidence interval CI = (1.905, 11.466) and for the septic shock, an odds ratio OR (pandemic/non-pandemic) = exp(2.87) = 17.932 with 95% confidence interval CI = (5.001, 64.301). The frequency of bowel occlusion and septic shock were significantly higher in pandemic period (the significance of goodness of fit test of Hosmer and Lemeshow Test is p = 0.592).

Table 4. Logistic regression model for dependent variable pandemic/non-pandemic.

Independent Variable	B	S.E.	Wald	df	Sig.	OR [b] = Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Bowel occlusion01 [a]	1.542	0.458	11.334	1	0.001	4.673	1.905	11.466
Septic shock01 [a]	2.887	0.652	19.628	1	0.000	17.932	5.001	64.301
Constant	−2.327	0.358	42.278	1	0.000	0.098		

Footnote: [a] parameters with binary distribution; for logistic regression model calculation, it was used 0 = absent; 1 = present. [b] OR= odd ratio.

Table 5. Logistic regression model for dependent variable death.

Independent Variable	B	S.E.	Wald	df	Sig.	OR[(b)] = Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
age	0.236	0.065	13.174	1	0.000	1.266	1.115	1.438
Number of comorbidities	0.986	0.415	5.648	1	0.017	2.681	1.189	6.049
Septic shock 01 [(a)]	2.762	0.858	10.357	1	0.001	15.828	2.944	85.094
Sample group × Diabetes01 [(a)]	3.696	1.521	5.905	1	0.015	40.271	2.044	793.365
Constant	−22.389	5.495	16.603	1	0.000	0.000		

Footnote: [(a)] parameters with binary distribution; for logistic regression model calculation, it was used 0 = absent; 1 = present. Sample group = 1 for pandemic group and sample group = 0 for non-pandemic group; in the logistic regression model, diabetes resulted to be a risk factor for death only for the pandemic group; [(b)] OR= odd ratio.

In a multivariate analysis of the factors that were associated with fatal outcome, we found that higher age (OR: 1.266, CI: 1.115–1.438), a higher number of comorbidities (OR: 2.681, CI: 1.189–6.049), the septic shock (OR: 15.828; CI: 2.944–85.094) and diabetes for the patients in the pandemic group (OR: 40.271; CI: 2.044–793.365) increased the death risk. For this model, the significance of Hosmer and Lemeshow Test is $p = 0.606$. Interestingly, for the patients in the non-pandemic group, diabetes was not associated with increased risk for fatal outcome. This may reflect an increased vulnerability of diabetic patients during the COVID-19 pandemic.

Septic shock was the most frequent cause of death in both groups, leading to a fatal outcome in 57.1% and 50% of cases with septic shock, respectively. However, the incidence of septic shock was significantly higher in patients admitted during COVID-19 pandemic, and this finding correlates significantly with emergency presentation.

Furthermore, we analyzed the possible correlations between emergency presentation and septic shock. We considered the questions, "Q1: Is emergency presentation a risk factor for septic shock?", and, "Q2: To what extent did the COVID-19 pandemic influence the response to Q1?". If all 154 cases are considered, statistical analysis shows that emergency presentation a risk factor for septic shock, with an estimate of odds ratio OR (Septic shock|Emergency presentation) = 5.155 and 95% confidence interval CI = (1.611, 16.488). However, this could be a misleading result for normal circumstances, with an OR of 1.714, but a wide 95% confidence interval CI = (0.233, 12.624).

When the statistical analysis was performed only on the pandemic group, the OR was considerably higher, of OR (septic shock|emergency presentation) = 4.154 with 95% confidence interval CI = (0.743, 23.229). The significance of this finding is yet of limited clinical value, due to the wide range of 95% CI, with subunitarian inferior limit. An explanation could be the small number of patients in pandemic-sample. On the other hand, multiple factors could impact the hospital care of patients admitted in emergency that experienced postoperative septic shock.

4. Discussion

The benchmarks of the quality of care in medical services are patient safety, effectiveness, timeliness, and patient-centered health service [23]. COVID-19 pandemic affected the quality of specialized healthcare services by multiple mechanisms. Kopel et al. found a significant decrease in diagnosis of colorectal cancers during the pandemic period, which could result in the long term in a devastating rise in late-stage CRC cases, and the overall loss of life years for these patients [24]. Health policy measures to save resources by reducing the overall number of surgeries during the COVID-19 pandemic also affect oncological colorectal resections [25]. While national health regulations promote a continuation of oncological surgical services, to prevent delays in diagnosis and treatment, the strained resources and manpower fatigue affect the quality of cancer care [26,27]. Discontinuities in screening, reduced referral, and accessibility to medical staff may result in delayed presentation, while discontinuity in regular check-ups may result in delayed diagnosis of recurrences [26]. Confronted with severe limitation of the resources and staff, several

studies reported issues related to prioritization of cases, minimization of the risk of infection, and balancing the therapeutic options available [27,28]. Our hospital implemented major changes in structure and procedure, to safely treat both COVID-19-positive and COVID-19-negative patients during the entire pandemic period. The bed structure of the clinical departments was modified to create new available beds for COVID-19 patients, to the detriment of surgical departments. We were also confronted with reduced availability of intensive care beds, due to the increased number of COVID-19 patients requiring ventilatory support. All these changes led to a significant limitation of the number of complex surgeries during the COVID-19 pandemic, including colorectal cancers operations. On the other hand, the safety precautions and the new established circuits proved to be effective in SARS-CoV-2 infection prevention in the study group.

The surgical protocols in our department pay special attention to patient safety and the decrease in the postoperative complications, by routinely use of large spectrum antibiotics, perioperative anticoagulation for prevention of the thrombotic events, close perioperative care to prevent cardiac acute events, optimization of glycemia in diabetic patients, and prevention of postoperative pneumonia. However, operating complicated colorectal cancers in emergency remains challenging and it is associated with high postoperative mortality. While surgery for elective colorectal cancers is well standardized by national and local guidelines, the best option in cases of bowel obstruction in emergency is still a subject of debate. Min et al. found that all patients with obstruction due to colorectal cancer should undergo subtotal colectomy, based on the fact that staged operations are associated with higher mortality and morbidity and longer hospital stay in comparison to immediate resections [29]. However, adherence to traditional surgical oncologic principles and the goal to achieve R0 resection should be balanced with the patients' biological status at presentation [30]. Clinical studies found 30-day postoperative mortality of 20% in patients with colorectal cancer operated in emergency in UK [15,31], and of 24% in Denmark [32] advising for damage-control surgery, such as colostomy, ileostomy, stenting or internal by-pass to solve obstruction. Patients with malignant colonic perforation face a high risk of peri-operative death, making septic source control the priority in the acute setting [31,33]. Age, Charlson comorbidity index, and tumor stage IV were associated with increased mortality of colorectal cancers operated in emergency [32].

The COVID-19 pandemic has brought important challenges in surgical practice, which we have never been confronted with before. In a systematic review of Mazidimoradi et al., the COVID-19 pandemic was found to have a negative effect both on the diagnosis and treatment of colorectal cancer [34]. Decreased diagnosis of new cases of colorectal cancer was seen in most countries, varying from 43.1% to 73.1% among different studies, with important discontinuities reported in screening programs and patients' usual visits [34–37]. Clinical studies found a significant increase in emergency presentations, for bowel obstruction or perforation [33–35]. Suarez et al. found an increase in emergency presentation for colorectal cancer in Spain from 3.6% in 2019 to 12.1% in 2020 [38]. Shinkwin et al. found an increase in neoplastic bowel obstruction from 4.3% in 2019 to 8.6% in 2020, and draw attention that only a short delay of 4 months in referral and diagnosis leads to an increase in patients presenting with large bowel obstruction [39]. Our department is a tertiary center in the biggest emergency hospital in the country. This fact explains the increased proportion of complicated colorectal cases treated in emergency (37% before the COVID-19 pandemic and 72% during the first year of the COVID-19 pandemic), in comparison with other published studies.

In our research, we found significantly higher mortality in the pandemic group, which may be explained by the higher percentage of acute complicated cases. Emergency presentation of colorectal cancers has a severe impact upon patients' survival and should be prevented. On the other hand, healthcare providers should balance the increased risk of death from COVID-19 exposure with preventable deaths from undertreating cancer patients [25,28,40]. Previously published reports found that elective colorectal surgical procedures may be safely performed during the pandemic, in the condition of establishing

COVID-19 and non-COVID-19 circuits, strict visitor policy, and triage questionnaire for possible COVID-19 symptoms and RT-PCR testing before admission [24,27,41,42]. Our results verify previous reports, as we also registered no in-hospital SARS-CoV-2 infection in the pandemic group. This result may be a solid argument for encouraging colorectal elective surgery during COVID-19 pandemic, and preventing the future burden of advanced cases and the loss of life years for these patients.

The findings in the present research may support some recommendations to improve the outcomes of colorectal cancers patients admitted for surgery during the COVID-19 pandemic. In case of patients admitted in emergency for obstructive bowel cancer, minimal procedures, such as stenting or colostomy/ileostomy could be preferable to more extensive surgery, to decrease the risk of postoperative morbidity and mortality. Extensive lavage of peritoneal cavity, avoiding colonic anastomosis per primam, broad spectrum intravenous antibiotics and careful postoperative monitoring could be useful to prevent and treat septic shock.

Treating emergency colorectal patients is associated with worse outcomes, when compared to elective colorectal cancer surgery. In our country, oncological cases were treated continuously during pandemic waves, except the first lockdown period. However, in clinical practice, admission of elective oncological cases was often put on hold because of the lack of available ICU beds. Ensuring intensive care resources necessary for elective oncological surgery is mandatory for maintaining the standard of care in colorectal cancer surgery.

An increased mortality in the pandemic arm of the study has brought into question the use of strategies for bridging to elective surgery (BTS) such as self-expandable metal stents and decompression colostomies. Right sided colon malignancies are difficult to stent due to longer segments of poorly prepared bowel that need to be traversed compared to left sided obstructive lesions [43]. This is why we believe that in these cases, stoma is a more feasible alternative of BTS. Additionally, many authors advocate that inherent tumor manipulation during stenting could lead to local spreading or perforation rendering endoscopic procedures more dangerous and less compliant with the rigors of oncological principles [43–46]. However, one should consider that choosing decompression colostomies implies a three-stage procedure [47], while stenting offers a single stage surgery with primary anastomosis [45,46,48]. None of the patients in our study benefited of BTS because of the local policy and surgeon preferences, but we believe that the adoption of BTS should be considered in order to reduce mortality in emergency cases.

Our study has some limitations. The small number of patients included in the study may impact the statistical significance of the results. On the other hand, our hospital is an emergency hospital, and one may argue that chronic cancer patients were moreover treated in non-emergency hospitals. However, in our country, many of these hospitals were transformed in dedicated centers for COVID-19 patients only. Longer period and multicentric analysis could provide more comprehensive insight upon the effects of COVID-19 pandemic on the quality of care in colorectal oncological surgery. However, being a tertiary center, in the biggest emergency hospital in the country, our results raised awareness of the negative outcome of surgeries in emergency for colorectal cancer and postponing elective oncological surgeries.

5. Conclusions

The COVID-19 pandemic has deeply affected the quality of care in colorectal surgery, by decreasing the accessibility to healthcare surgical services, especially of people living in rural areas, and severe limitation of resources needed for perioperative intensive care. Colorectal cancer surgery may be performed safely during the COVID-19 pandemic, with strict adherence to the SARS-CoV-2 prevention protocols. However, the significant increase in colorectal cancers presentation in emergency is associated with worse outcomes and higher mortality during the COVID-19 pandemic and should be prevented.

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I. Lucrări relevante

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Review

Acute Mesenteric Ischemia in COVID-19 Patients

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Abstract: Acute mesenteric ischemia is a rare but extremely severe complication of SARS-CoV-2 infection. The present review aims to document the clinical, laboratory, and imaging findings, management, and outcomes of acute intestinal ischemia in COVID-19 patients. A comprehensive search was performed on PubMed and Web of Science with the terms "COVID-19" and "bowel ischemia" OR "intestinal ischemia" OR "mesenteric ischemia" OR "mesenteric thrombosis". After duplication removal, a total of 36 articles were included, reporting data on a total of 89 patients, 63 being hospitalized at the moment of onset. Elevated D-dimers, leukocytosis, and C reactive protein (CRP) were present in most reported cases, and a contrast-enhanced CT exam confirms the vascular thromboembolism and offers important information about the bowel viability. There are distinct features of bowel ischemia in non-hospitalized vs. hospitalized COVID-19 patients, suggesting different pathological pathways. In ICU patients, the most frequently affected was the large bowel alone (56%) or in association with the small bowel (24%), with microvascular thrombosis. Surgery was necessary in 95.4% of cases. In the non-hospitalized group, the small bowel was involved in 80%, with splanchnic veins or arteries thromboembolism, and a favorable response to conservative anticoagulant therapy was reported in 38.4%. Mortality was 54.4% in the hospitalized group and 21.7% in the non-hospitalized group ($p < 0.0001$). Age over 60 years ($p = 0.043$) and the need for surgery ($p = 0.019$) were associated with the worst outcome. Understanding the mechanisms involved and risk factors may help adjust the thromboprophylaxis and fluid management in COVID-19 patients.

Keywords: acute mesenteric ischemia; COVID-19; thromboemboembolism; SARS-CoV-2; endotheliitis; cytokines; hypercoagulability

1. Introduction

Acute mesenteric ischemia (AMI) is a major abdominal emergency, characterized by a sudden decrease in the blood flow to the small bowel, resulting in ischemic lesions of the intestinal loops, necrosis, and if left untreated, death by peritonitis and septic shock. In non-COVID patients, the etiology may be mesenteric arterial embolism (in 50%), mesenteric arterial thrombosis (15–25%), venous thrombosis (5–15%), or less frequent, from non-occlusive causes associated with low blood flow [1]. Several systemic conditions, such as arterial hypertension, atrial fibrillation, atherosclerosis, heart failure, or valve disease are risk factors for AMI. Portal vein thrombosis and mesenteric vein thrombosis can be seen with celiac disease [2], appendicitis [3], pancreatitis [4], and, in particular, liver cirrhosis and hepatocellular cancer [5].

Acute intestinal ischemia is a rare manifestation during COVID-19 disease, but a correct estimation of its incidence is challenging due to sporadic reports, differences in patients' selection among previously published studies, and also limitations in diagnosis related to the strict COVID-19 regulations for disease control and difficulties in performing imagistic investigations in the patients in intensive care units. COVID-19 is known to cause significant alteration of coagulation, causing thromboembolic acute events, of which the most documented were pulmonary embolism, acute myocardial infarction, and lower limb ischemia [6].

Gastrointestinal features in COVID-19 disease are relatively frequently reported, varying from less than 10% in early studies from China [7,8] to 30–60%, in other reports [9,10]. In an extensive study on 1992 hospitalized patients for COVID-19 pneumonia from 36 centers, Elmunzer et al. [7] found that the most frequent clinical signs reported were mild and self-limited in up to 74% of cases, consisting of diarrhea (34%), nausea (27%), vomiting (16%), and abdominal pain (11%). However, severe cases were also reported, requiring emergency surgery for acute bowel ischemia or perforation [5,8].

The pathophysiology of the digestive features in COVID-19 patients involves both ischemic and non-ischemic mechanisms. ACE2 receptors are present at the level of the intestinal wall, and enterocytes may be directly infected by SARS-CoV-2. The virus was evidenced in feces and enteral walls in infected subjects [4,11–13]. In a study by Xu et al., rectal swabs were positive in 8 of 10 pediatric patients, even after the nasopharyngeal swabs became negative [14]. However, the significance of fecal elimination of viral ARN is still not fully understood in the transmission chain of the SARS-CoV-2 infection. On the other hand, disturbance of lung-gut axis, prolonged hospitalization in ICU, and the pro coagulation state induced by SARS-CoV-2 endothelial damage was incriminated for bowel ischemia, resulting in intestinal necrosis and perforation [8,9,15]. Early recognition and treatment of gastrointestinal ischemia are extremely important, but it is often challenging in hospitalized COVID-19 patients with severe illness.

The present review aims to document the risk factors, clinical, imagistic, and laboratory findings, management, and outcomes of acute intestinal ischemic complications in COVID-19 patients.

2. Materials and Methods

A comprehensive search was performed on PubMed and Web of Science with the terms "COVID-19" AND ("bowel ischemia" OR "intestinal ischemia" OR "mesenteric ischemia" OR "mesenteric thrombosis"). All original papers and case reports, in the English language, for which full text could be obtained, published until November 2021, were included in the review. Meeting abstracts, commentaries, and book chapters were excluded. A hand search was performed in the references of the relevant reviews on the topic.

2.1. Data Extraction and Analysis

The review is not registered in PROSPERO. A PRISMA flowchart was employed to screen papers for eligibility (Figure 1) and a PRISMA checklist is presented as a Supple-

mentary File S1. A data extraction sheet was independently completed by two researchers, with strict adherence to PRISMA guidelines.

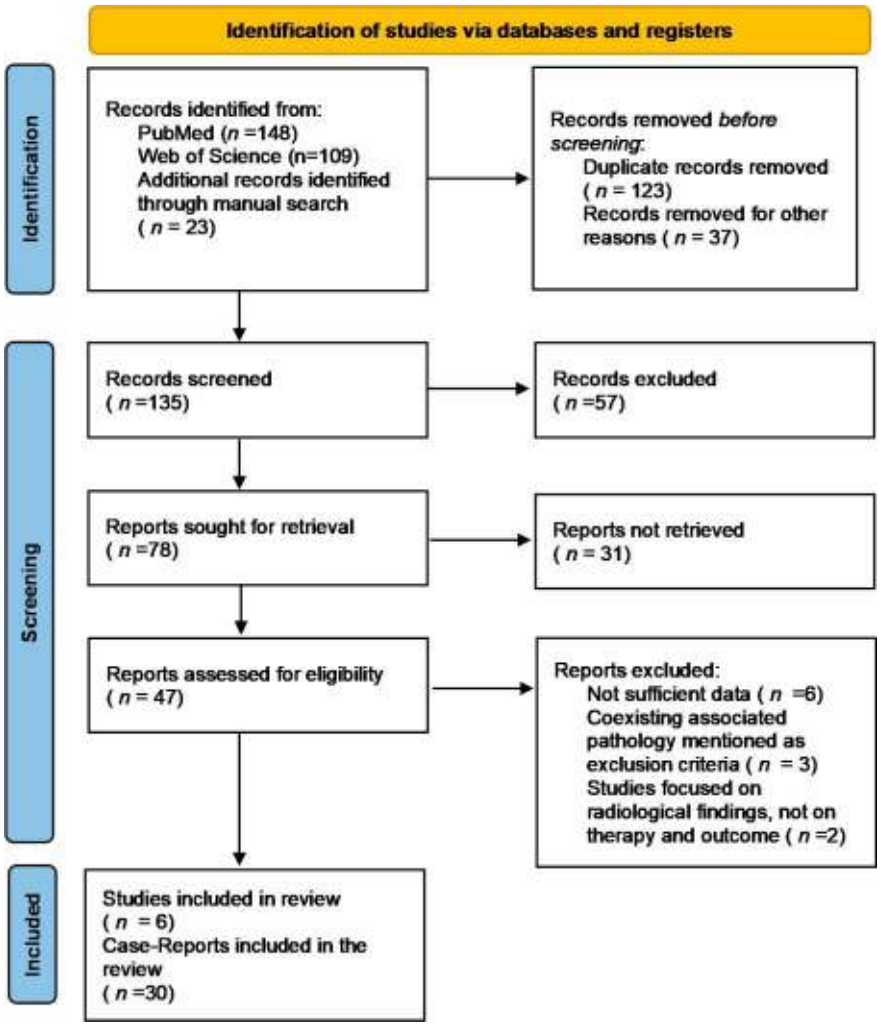

Figure 1. PRISMA 2020 flowchart for the studies included in the review.

The relevant data abstracted from these studies are presented in Tables 1–3. COVID-19 diagnosis was made by PCR assay in all cases. All patients reported with COVID-19 disease and mesenteric ischemia were documented in terms of age, sex, comorbidities, time from SARS-CoV-2 infection diagnosis, presentation, investigations, treatment, and outcome. A statistical analysis of the differences between acute intestinal ischemia in previously non-hospitalized vs. previously hospitalized patients was performed. The potential risk factors for an adverse vital prognosis were analyzed using SciStat® software (www.scistat.com (accessed on 25 November 2021)).

Papers that did not provide sufficient data regarding evaluation at admission, documentation of SARS-CoV-2 infection, or treatment were excluded. Patients suffering from other conditions that could potentially complicate intestinal ischemia, such as liver cirrhosis, hepatocellular carcinoma, intraabdominal infection (appendicitis, diverticulitis), pancreatitis, and celiac disease were excluded. Any disagreement was solved by discussion.

Table 1. Patients with intestinal ischemia in retrospective studies on hospitalized COVID-19 patients.

Study	No of Patients with Gastrointestinal Ischemia (Total No of COVID-19 Patients in ICU)	Sex (M; F)	Age (Mean)	BMI	Time from Admission to Onset (Days)	Abdominal CT Signs	Intraoperative/Endoscopic Findings	Treatment	Outcomes
Kaafarani HMA [16]	5 (141); 3.8%	1;3	62.5	32.1	51.5 (18–104) days	NA	Cecum-1—patchy necrosis Cecum_ileon-1 Small bowel-3; yellow discoloration on the antimesenteric side of the small bowel; 1 case + liver necrosis	Surgical resection	NA
Kraft M [17]	4 (190); 2.1%	NA	NA	NA	NA	NA	Bowel ischemia + perforation (2) Bowel ischemia + perforation (1) MAT+massive bowel ischemia (1)	Right hemicolectomy (2) Transverse colectomy (1) Conservative, not fit for surgery	Recovery (3) Death (1)
Yang C [18]	20 (190 in ICU; 582 in total); 10.5%	15:5	69	31.2	26.5 (17–42)	Distension Wall thickness Pneumatosis intestinalis Perforation SMA or celiac thrombosis	no info	Right hemicolectomy 7(35%) Sub/total colectomy12 (60%) Ileocecal resection 1(5%)	Recovery (11) Death (9)
Hwabejire J [19]	20	13:7	58.7	32.5	13 (1–31)	Pneumatosis intestinalis 42% Portal venous gas (33%) Mesenteric vessel patency 92%	large bowel ischemia (8) small bowel ischemia (4) both (8) yellow discoloration of the ischemic bowel	resection of the ischemic segment abdomen left open + second look (14)	Recovery (10) Death (10)
O'Shea A [20]	4 (142); 2.8%	NA	NA	NA	NA	bowel ischemia, portal vein gas, colic pneumatosis	NA	NA	NA
Qayed E [21]	2 (878); 0.22%	NA	NA	NA	NA	NA	diffuse colonic ischemia (1) Small + large bowel ischemia and pneumatosis (1)	Total colectomy (1) Extensive resection (1)	Recovery (1) Death (1)

NA: not acknowledged; MAT: mesenteric artery thrombosis; SMA: superior mesenteric artery.

Table 2. Case reports and case series presenting gastrointestinal ischemia in hospitalized COVID-19 patients under anticoagulant medication.

Article	Sex	Age	Comorbidities	Time from COVID-19 Time from Admission (Days)	ICU; Type of Ventila-tion	Clinical Signs at Presenta-tion	Leukocytes (/mm³)	CRP (mg/L)	Lactat mmol/L	Ferritin (ng/mL)	LDH (U/L)	Thrombocytes (/mm3)	(ng/mL)	Abdominal CT Signs	Treatment	Outcome
Azouz E [22]	M	56	none	1; 2 (hospitalized for acute ischemic stroke)	No info	abdominal pain and vomiting	No info	-	-	-	-	-	-	Multiple arterial thromboembolic complications: AMS, right middle cerebral artery, a free-floating clot in the aortic arch	Anticoagulation (no details), endovascular thrombectomy Laparotomy + resection of necrotic small bowel loops	No info
Al Mahrugi G [23]	M	51	none	26; 24	yes, in-tubated	Fever, metabolic acidosis, required inotropes	30,000	-	7	687	-	-	2.5	Non-occlusive AMI Hypoperfused small bowel, permeable aorta, SMA, IMA + deep lower limb thrombosis	enoxaparin 40 mg/day from admission; surgery refused by family	death
Ucpinar BA [24]	F	82	Atrial fibrillation, hyperten-sion, chronic kidney disease	3; 3	no	-	14,800	196	5.1	-	-	-	1600	SMA thrombosis; distended small bowel, with diffuse submucosal pneumatosis portomesenteric gas	fluid resuscitation; continued ceftriaxone, enoxaparin 0.4cc twice daily; not operable due to fulminant evolution	Death
Karna ST [25]	F	61	DM, hyper-tension	4; 4	Yes, HFNO	diffuse abdominal pain with distention	21,400	421.6	1.4	-	-	464,000	No	thrombosis of the distal SMA with dilated jejunoileal loops and normal enhancing bowel wall.	Iv heparin 5000 ui, followed by 1000 ui, Ecospin and clopidogrel. Laparotomy after 10 days with segmental enterectomy of the necrotic bowel	Death by septic shock and acute renal failure
Singh B [26]	F	82	Hypertension, T2DM	32; 18	Yes, Ventila-tor support	severe diffuse abdominal distension and ten-derness	22,800	308	2.5	136	333	146,000	1.3	SMA—colic arteries thrombosis pneumatosis intestinalis affecting the ascending colon and cecum	laparotomy, ischemic colon resection, ileostomy; heparin in therapeutic doses pre- and post-surgery	slow

Table 2. *Cont.*

Article	Sex	Age	Comorbidities	Time from COVID-19 Diagnosis; Time from Admission (Days)	ICU; Type of Ventila-tion	Clinical Signs at Presenta-tion	Leukocytes (/mm³)	CRP (mg/L)	Lactat mmol/L	Ferritin (ng/mL)	LDH (U/L)	Thrombocytes (/mm3)	D-Dimers (ng/mL)	Abdominal CT Signs	Treatment	Outcome
Nakatsutmi K [27]	F	67	DM, diabetic nephropathy requiring dialysis, angina, post-resection gastric cancer	16; 12	ICU, in-tubation	hemodynamic deteriora-tion, abdominal distension	15,100	32.14	-	-	-	-	26.51	edematous transverse colon; abdominal vessels with sclerotic changes	laparotomy, which revealed vascular micro thrombosis of transverse colon—right segment resection of the ischemic colonic segment, ABTHERA management, second look, and closure of the abdomen after 24 h	death
Dinoto E [28]	F	84	DM, hyper-tension, renal failure	2; 2	no	Acute abdominal pain and disten-sion;	18,000	32.47	-	-	431	-	6937	SMA origin stenosis and occlusion at 2 cm from the origin, absence of bowel enhancement	Endovascular thrombectomy of SMA; surgical transfemoral thrombectomy and distal superficial femoral artery stenting	Death due to respira-tory failure
Kiwango F [29]	F	60	DM, hyper-tension	12; 3	no	Sudden onset abdominal pain	7700	-	-	-	-	-	23.8	Not performed	Not performed due to rapid oxygen desaturation Massive bowel acute ischemia	death

Table 3. Case reports and case series presenting gastrointestinal ischemia in non-hospitalized COVID-19 patients.

Article	Sex	Age	Comorbidities	Time from COVID-19 Diagnosis (Days)	Clinical Signs at Presentation	Leukocyte Count (/mm³)	CRP (mg/L)	Lactate mmol/L	Ferritin (ng/mL)	LDH (U/L)	Thrombocytes (/mm³)	D-Dimers (ng/mL)	Abdominal CT Signs	Treatment	Outcome
Sevella, P [30]	M	44	none	10	Acute abdominal pain constipation, vomiting	23,400	-	-	-	1097	360,000	1590	Viable jejunum, ischemic bowel, peritoneal thickening with fat stranding; free fluid in the peritoneal cavity	LMWH 60 mg daily Piperacillin 4g/day Tazobactam 500 mg/day Extensive small bowel + right colon resection	death
Nasseh S [31]	M	68	no info	First diagnosis	epigastric pain and diarrhea for 4 days	17,660	125	-	-	-	-	6876	terminal segment of the ileocolic artery thrombosis; thickening of the right colon wall and the last 30 cm of the small bowl	unfractionated heparin laparoscopy -no bowel resection needed	recovery
Aleman W [32]	M	44	none	20	sev dom p ab pelvic in	36,870	-	-	456.23	-	574,000	263.87	absence of flow at SMV, splenic, portal vein; Small bowel loop dilatation and mesenteric fat edema	enoxaparin and pain control medication 6 days, then switched to warfarin 6 months	recovery
Jeilani M [33]	M	68	Alzheimer disease, COPD	9	S rp abdo inal pain +distension	12,440	307	-	-	-	318,000	897	a central venous filling defect within the portal vein extending to SMV; no bowel wall changes	LMWH, 3 months	recovery
Randhawa J [34]	F	62	none	First diagnosis	right upper quadrant pain and loss of appetite for 14 days	Normal limits	-	-	-	346	-	-	large thrombus involving the SMV, the main portal vein with extension into its branches	Fondaparinux 2.5. mg 5 days, then warfarin 4 mg (adjusted by INR), 6 months	recovery
Cheung S [35]	M	55	none	12 (discharged for 7 days)	Nausea, vomiting and worsening generalized abdominal pain with guarding	12,446	-	0.68	-	-	-	-	low-density clot, 1.6 cm in length, causing high-grade narrowing of the proximal SMA	continuous heparin infusion continued 8 h postoperative, Laparotomy with SMA thromboembolectomy and enterectomy (small bowel)	recovery

Table 3. *Cont.*

Article	Sex	Age	Comorbidities	Time from COVID-19 Diagnosis (Days)	Clinical Signs at Presentation	Leukocyte Count (/mm³)	CRP (mg/L)	Lactate mmol/L	Ferritin (ng/mL)	LDH (U/L)	Thrombocytes (/mm³)	D-Dimers (ng/mL)	Abdominal CT Signs	Treatment	Outcome
Beccara L [36]	M	52	none	22 (5 days after discharge and cessation prophylactic LWMH)	vomiting and abdominal pain, tenderness in epigastrium and mesogastrium	30,000	222	-	-	-	-	-	arterial thrombosis of vessels efferent of the SMA with bowel distension	Enterectomy (small bowel) LMWH plus aspirin 100 mg/day at discharge	recovery
Vulliamy P [37]	M	75	none	14	abdominal pain and vomiting for 2 days	18,100	3.2	-	-	-	497,000	320	intraluminal thrombus was present in the descending thoracic aorta with embolic occlusion of SMA	Catheter-directed thrombolysis, enterectomy (small bowel)	recovery
De Barry O [38]	F	79	none	First diagnosis	Epigastric pain, diarrhea, fever for 8 days, acute dyspnea	12600	125	5.36	-	-	-	-	SMV, portal vein, SMA, and jejunal artery thrombosis Distended loops, free fluid	anticoagulation Resection of affected colon+ ileum, SMA thrombolysis, thrombectomy	death
Romero MCV [39]	M	73	smoker, DM, hypertension	14	severe abdominal pain, nausea. fecal emesis, peritoneal irritation	18,000	-	-	-	-	120,000	>5000	RX: distention of intestinal loops, inter-loop edema, intestinal pneumatosis	enoxaparin (60 mg/0.6 mL), antibiotics (no info) enterectomy, anastomotic fistula, reintervention	death
Posada Arango [40]	M F F	62 22 65	None Appendectomy 7 days before left nephrectomy,	5 3 15	colicative abdominal pain at food intake; unsystematized gastrointestinal symptoms; abdominal pain in the upper hemiabdomen	20,100 - -	- - -	- - -	1536 - -	534 - -	- - -	- - -	Case 1: thrombus in distal SMA and its branches, intestinal loops dilatation, hydroaerical levels, free fluid thrombosis of SMV Case 2: SMV thrombosis and adiacent fat edema Case 3: thrombi in the left jejunal artery branch with infarction of the corresponding jejunal loops	Case 1: Laparotomy: extensive jejunum + ileum ischemia; surgery could not be performed Case 2: Anticoagulation analgesic and antibiotics Case 3: segmental enterectomy	Case 1: death Case 2: recovery Case 3: recovery

Table 3. *Cont.*

Article	Sex	Age	Comorbidities	Time from COVID-19 Diagnosis (Days)	Clinical Signs at Presentation	Leukocyte Count (/mm³)	CRP (mg/L)	Lactate mmol/L	Ferritin (ng/mL)	LDH (U/L)	Thrombocytes (/mm³)	D-Dimers (ng/mL)	Abdominal CT Signs	Treatment	Outcome
Pang JHQ [41]	M	30	none	First diagnosis	colicky abdominal pain, vomiting	-	-	-	-	-	-	20	SMV thrombosis with diffuse mural thickening and fat stranding of multiple jejunal loops	conservative, anticoagulation with LMWH 1mg/kc, twice daily, 3 months; readmitted and operated for congenital adherence causing small bowel obstruction	recovery
Lari E [42]	M	38	none	First diagnosis	abdominal pain, nausea, intractable vomiting, and shortness of breath	Mild leukocytosis	-	2.2	-	-	-	2100	extensive thrombosis of the portal, splenic, superior, and inferior mesenteric veins + mild bowel ischemia	Anticoagulation, resection of the affected bowel loop	No info
Carmo Filho A [43]	M	33	Obesity (BMI: 33), other not reported	7	severe low back pain radiating to the hypogastric region	-	58.2	-	1570	-	-	879	enlarged inferior mesenteric vein not filled by contrast associated with infiltration of the adjacent adipose planes	enoxaparin 5 days, followed by long term oral warfarin	recovery
Hanif M [44]	F	20	none	8	abdominal pain and abdominal distension	15,900	62	-	1435.3	825	633,000	2340	not performed	evidence of SMA thrombosis; enterectomy with exteriorization of both ends	recovery
Amaravathi U [45]	M	45	none	5	Acute epigastric and periumbilical pain	-	Normal value	1.3	324.3	-	-	5.3	SMA and SMV thrombus	i.v. heparin; Laparotomy with SMA thrombectomy; 48 h Second look: resection of the gangrenous bowel segment	No info
Al Mahruqi G [23]	M	51	none	4	generalized abdominal pain, nausea, vomiting	16,000	-	-	619	-	-	10	SMA thrombosis and non-enhancing proximal ileal loops consistent with small bowel ischemia	unfractionated heparin, thrombectomy + repeated resections of the ischemic bowel at relook (jejunum+ileon+cecum)	Case 2: recovery

Table 3. *Cont.*

Article	Sex	Age	Comorbidities	Time from COVID-19 Diagnosis (Days)	Clinical Signs at Presentation	Leukocyte Count (/mm³)	CRP (mg/L)	Lactate mmol/L	Ferritin (ng/mL)	LDH (U/L)	Thrombocytes (/mm³)	D-Dimers (ng/mL)	Abdominal CT Signs	Treatment	Outcome
Goodfellow M [46]	F	36	RYGB, depression, asthma	6	epigastric pain, irradiating back, nausea	9650	1.2	0.7	-	-	-	-	abrupt cut-off of the SMV in the proximal portion; diffuse infiltration of the mesentery, wall thickening of small bowel	IV heparin infusion, followed by 18,000 UI delteparin after 72 h	recovery
Abeysekera KW [26]	M	42	Hepatitis B	14	right hypochondrial pain, progressively increasing for 9 days	-	-	-	-	-	-	-	enhancement of the entire length of the portal vein and a smaller thrombus in the mid-superior mesenteric vein, mural edema of the distal duodenum, distal small bowel, and descending colon	factor Xa inhibitor apixaban 5 mg ×2/day, 6 months	- recovery
Rodriguez-Nakamura RM [27]	M F	45 42	-vitiligo -obesity	14	severe mesogastric pain, nausea, diaphoresis	16,400 18,800	367 239	- -	970 -	- -	685,000 -	1450 14,407	Case 1: SMI of thrombotic etiology with partial rechanneling through the middle colic artery, and hypoxic-ischemic changes in the distal ileum and the cecum Case 2: thrombosis of the portal and mesenteric veins and an abdominopelvic collection in the mesentery with gas	Case 1: resection with entero-enteral anastomosis; rivaroxaban 10 mg/day, 6 months Case 2: Loop resection, entero-enteral manual anastomosis, partial omentectomy, and cavity wash (fecal peritonitis)	Case 1: Recovery Case 2: death
Plotz B [47]	F	27	SLE with ITP	First diagnosis	acute onset nausea, vomiting, and non-bloody diarrhea	-	-	-	-	-	-	5446	diffuse small bowel edema	enoxaparin, long term apixaban at discharge	recovery

Table 3. *Cont.*

Article	Sex	Age	Comorbidities	Time from COVID-19 Diagnosis (Days)	Clinical Signs at Presentation	Leukocyte Count (/mm³)	CRP (mg/L)	Lactate mmol/L	Ferritin (ng/mL)	LDH (U/L)	Thrombocytes (/mm³)	D-Dimers (ng/mL)	Abdominal CT Signs	Treatment	Outcome
Chiu CY [48]		49	Hypertension, DM, chronic kidney disease	28	diffuse abdominal pain melena and hematemesis	-	-	-	-	-	-	12,444	distended proximal jejunum with mural thickening	laparotomy, proximal jejunum resection	no info
Farina D [49]	M	70	no info	3	abdominal pain, nausea	15,300	149	-	-	-	-	-	acute small bowel hypoperfusion, SMA thromboembolism	not operable due to	Death

SMA: superior mesenteric artery; SMV: superior mesenteric vein; DM: diabetes mellitus; T2DM: type 2 diabetes mellitus; AMI: acute mesenteric ischemia; IMV: inferior mesenteric vein; RYGB: Roux-en-Y gastric bypass (bariatric surgery).

2.2. Risk of Bias

The studies analyzed in the present review were comparable in terms of patient selection, methodology, therapeutic approach, and the report of final outcome. However, there were differences in the reported clinical and laboratory data. The sample size was small, most of them being case reports or case series, which may be a significant source of bias. Therefore, studies were compared only qualitatively.

3. Results

After duplication removal, a total of 36 articles were included in the review, reporting data on a total of 89 patients. Among these, we identified 6 retrospective studies [16–21], documenting intestinal ischemia in 55 patients admitted to intensive care units (ICU) with COVID-19 pneumonia for whom surgical consult was necessary (Table 1).

We also identified 30 case reports or case series [22–51] presenting 34 cases of acute bowel ischemia in patients positive for SARS-CoV-2 infection in different clinical settings. 8 cases were previously hospitalized for COVID-19 pneumonia and under anticoagulant medication (Table 2). In 26 cases, the acute ischemic event appeared as the first symptom of COVID-19 disease, or in mild forms treated at home, or after discharge for COVID -19 pneumonia and cessation of the anticoagulant medication (Table 3).

3.1. Risk Factors of Intestinal Ischemia in COVID-19 Patients

Out of a total of 89 patients included in the review, 63 (70.7%) were hospitalized for severe forms of COVID-19 pneumonia at the moment of onset. These patients were receiving anticoagulant medication when reported, consisting of low molecular weight heparin (LMWH) at prophylactic doses. The incidence of acute intestinal ischemia in ICU patients with COVID-19 varied widely between 0.22–10.5% (Table 1). In a study by O'Shea et al. [20], 26% of hospitalized patients for COVID-19 pneumonia who underwent imagistic examination, presented results positive for coagulopathy, and in 22% of these cases, the thromboembolic events were with multiple locations.

The mean age was 56.9 years. We observed a significantly lower age in non-hospitalized COVID-19 patients presenting with acute intestinal ischemia when compared to the previously hospitalized group ($p < 0.0001$).

There is a slight male to female predominance (M:F = 1:68). Obesity might be considered a possible risk factor, with a reported mean BMI of 31.2–32.5 in hospitalized patients [16,18,19]. However, this association should be regarded with caution, since obesity is also a risk factor for severe forms of COVID-19. Prolonged stay in intensive care, intubation, and the need for vasopressor medication was associated with increased risk of acute bowel ischemia [8,18,19].

Diabetes mellitus and hypertension were the most frequent comorbidities encountered in case reports (8 in 34 patients, 23%), and 7 out of 8 patients presented both (Table 4). There was no information regarding the comorbidities in the retrospective studies included in the review.

3.2. Clinical Features in COVID-19 Patients with Acute Mesenteric Ischemia

Abdominal pain, out of proportion to physical findings, is a hallmark of portomesenteric thrombosis, typically associated with fever and leukocytosis [4]. Abdominal pain was encountered in all cases, either generalized from the beginning, of high intensity, or firstly localized in the epigastrium or the mezogastric area. In cases of portal vein thrombosis, the initial location may be in the right hypochondrium, mimicking biliary colic [26,34].

Fever is less useful in COVID-19 infected patients, taking into consideration that fever is a general sign of infection, and on the other hand, these patients might be already under antipyretic medication.

Table 4. Demographic data of the patients included in the review.

Nr. of Patients	**89**
M	48 (61.5% *)
F	30 (38.5% *)
NA	11
The first sign of COVID-19	6 (6.7%)
Home treated	17 (19.1%)
Hospitalized • ICU	63 (70.7%) 58 (92% of hospitalized patients)
Discharged	3 (3.3%)
Time from diagnosis of COVID-19 infection • Non-Hospitalized • Hospitalized (*when mentioned)	8.7 ± 7.4 (1–28 days) 9.6 ± 8.3 (1–26 days)
Time from admission in hospitalized patients	1–104 days
Age (mean) • Hospitalized • Non-hospitalized	59.3 ± 12.7 years 62 ± 9.6 years. ($p < 0.0001$) 52.8 ± 16.4 years.
BMI	31.2–32.5
Comorbidities • Hypertension • DM • smokers • Atrial fibrillation • COPD • Cirrhosis • RYGB • Vitiligo • Recent appendicitis • Operated gastric cancer • Alzheimer disease • SLE	 8 7 2 1 2 1 1 1 1 1 1 1 1

*: percentage calculated in known information group; BMI: body mass index; COPD: chronic obstructive pulmonary disease; SLE: systemic lupus erythematosus.

Other clinical signs reported were nausea, anorexia, vomiting, and food intolerance [23,31,38,45]. However, these gastrointestinal signs are encountered in 30–40% of patients with SARS-CoV-2 infection. In a study by Kaafarani et al., up to half of the patients with gastrointestinal features presented some degrees of intestinal hypomotility, possibly due to direct viral invasion of the enterocytes and neuro-enteral disturbances [16].

Physical exam evidenced abdominal distension, reduced bowel sounds, and tenderness at palpation. Guarding may be evocative for peritonitis due to compromised vascularization of bowel loops and bacterial translocation or franc perforation [35,39].

A challenging case was presented by Goodfellow et al. [25] in a patient with a recent history of bariatric surgery with Roux en Y gastric bypass, presenting with acute abdominal pain which imposed the differential diagnosis with an internal hernia.

Upcinar et al. [24] reported a case of an 82-years female that also associated atrial fibrillation. The patient was anticoagulated with enoxaparin 0.4 cc twice daily before admission and continued the anticoagulant therapy during hospitalization for COVID-19 pneumonia. Bedside echocardiography was performed to exclude atrial thrombus. Although SMA was reported related to COVID-19 pneumonia, atrial fibrillation is a strong risk factor for SMA of non-COVID-19 etiology.

In ICU patients, acute bowel ischemia should be suspected in cases that present acute onset of digestive intolerance and stasis, abdominal distension, and require an increase of vasopressor medication [19].

3.3. Imagistic and Lab Test Findings

D-dimer is a highly sensitive investigation for the prothrombotic state caused by COVID-19 [45] and, when reported, was found to be above the normal values. Leukocytosis and acute phase biomarkers, such as fibrinogen and CRP were elevated, mirroring the intensity of inflammation and sepsis caused by the ischemic bowel. However, there was no significant statistical correlation between either the leukocyte count (p = 0.803) or D-dimers (p = 0.08) and the outcome. Leucocyte count may be within normal values in case of early presentation [34]. Thrombocytosis and thrombocytopenia have been reported in published cases with mesenteric ischemia [30,35,42,46,50].

Lactate levels were reported in 9 cases, with values higher than 2 mmol/L in 5 cases (55%). LDH was determined in 6 cases, and it was found to be elevated in all cases, with a mean value of 594+/−305 U/L.

Ferritin is another biomarker of potential value in mesenteric ischemia, that increases due to ischemia-reperfusion cellular damage. In the reviewed studies, serum ferritin was raised in 7 out of 9 reported cases, with values ranging from 456 to 1570 ng/mL. However, ferritin levels were found to be correlated also with the severity of pulmonary lesions in COVID-19 patients [52]. Due to the low number of cases in which lactate, LDH, and ferritin were reported, no statistical association could be performed with the severity of lesions or with adverse outcomes.

The location and extent of venous or arterial thrombosis were determined by contrast-enhanced abdominal CT, which also provided important information on the viability of the intestinal segment whose vascularity was affected.

Radiological findings in the early stages included dilated intestinal loops, thickening of the intestinal wall, mesenteric fat edema, and air-fluid levels. Once the viability of the affected intestinal segment is compromised, a CT exam may evidence pneumatosis as a sign of bacterial proliferation and translocation in the intestinal wall, pneumoperitoneum due to perforation, and free fluid in the abdominal cavity. In cases with an unconfirmed diagnosis of COVID-19, examination of the pulmonary basis during abdominal CT exam can add consistent findings to establish the diagnosis.

Venous thrombosis affecting the superior mesenteric vein and or portal vein was encountered in 40.9% of reported cases of non-hospitalized COVID-19 patients, and in only one case in the hospitalized group (Table 5). One explanation may be the beneficial role of thrombotic prophylaxis in preventing venous thrombosis in COVID-19 patients, which is routinely administrated in hospitalized cases, but not reported in cases treated at home with COVID-19 pneumonia.

In ICU patients, CT exam showed in most cases permeable mesenteric vessels and diffuse intestinal ischemia affecting the large bowel alone (56%) or in association with the small bowel (24%), suggesting pathogenic mechanisms, direct viral infection, small vessel thrombosis, or “nonocclusive mesenteric ischemia” [16].

3.4. Management and Outcomes

The management of mesenteric ischemia includes gastrointestinal decompression, fluid resuscitation, hemodynamic support, anticoagulation, and broad antibiotics.

Once the thromboembolic event was diagnosed, heparin, 5000IU iv, or enoxaparin or LMWH in therapeutic doses was initiated, followed by long-term oral anticoagulation and/or anti-aggregating therapy. Favorable results were obtained in 7 out of 9 cases (77%) of splanchnic veins thrombosis and in 2 of 7 cases (28.5%) with superior mesenteric artery thrombosis. At discharge, anticoagulation therapy was continued either with LMWH, for a period up to 3 months [33,36,41], either, long term warfarin, with INR control [32,34,41] or apixaban 5 mg/day, up to 6 months [26,47]. No readmissions were reported.

Table 5. Comparative features in acute intestinal ischemia encountered in previously hospitalized and previously non-hospitalized COVID-19 patients.

Parameter	Hospitalized (63)	Non-Hospitalized (26)	*p* * Value
Type of mesenteric ischemia:			
• Arterial	5 (14.7% *)	10 (38.4%)	
• Venous	1 (2.9%)	11 (42.3%)	
• Mixt (A + V)	0	2 (7.6%)	
• Diffuse microthrombosis	30 (88.2%)	3 (11.5%)	$p < 0.0001$
• Multiple thromboembolic locations	2 (5.8%)	1 (3.8%)	
• NA	29	0	
Management:			
• Anticoagulation therapy only	0	10 (38.4%)	
• Endovascular thrombectomy	2 (1 + surgery) (3%)	2 (+surgery)	
• Laparotomy with ischemic bowel resection	60 (95.4%)	15 (57.6%)	$p < 0.0001$
• None (fulminant evolution)	2 (3%)	1 (3.8%)	
Location of the resected segment:	35 (56%)	0	
• Colon	10 (16%)		$p < 0.0001$
• Small bowel	15 (24%)	3 (20%)	
• Colon+small bowel	6	0	
• NA			
Outcomes:	26 (46.4%)	17 (79.3%)	
• Recovery	30 (54.4%)	5 (21.7%)	$p = 0.013$
• Death	7	3	
• NA			

* calculated for Chi-squared test.

Antibiotic classes should cover anaerobes including *F. necrophorum* and include a combination of beta-lactam and beta-lactamase inhibitor (e.g., piperacillin-tazobactam), metronidazole, ceftriaxone, clindamycin, and carbapenems [4].

In early diagnosis, during the first 12 h from the onset, vascular surgery may be tempted, avoiding the enteral resection [25,53]. Endovascular management is a minimally invasive approach, allowing quick restoration of blood flow in affected vessels using techniques such as aspiration, thrombectomy, thrombolysis, and angioplasty with or without stenting [40].

Laparotomy with resection of the necrotic bowel should be performed as quickly as possible to avoid perforation and septic shock. In cases in which intestinal viability cannot be established with certainty, a second look laparotomy was performed after 24–48 h [43] or the abdominal cavity was left open, using negative pressure systems such as ABTHERA [51], and successive segmentary enterectomy was performed.

Several authors described in acute bowel ischemia encountered in ICU patients with COVID-19, a distinct yellowish color, rather than the typical purple or black color of ischemic bowel, predominantly located at the antimesenteric side or circumferentially with affected areas well delineated from the adjacent healthy areas [18,19]. In these cases, patency of large mesenteric vessels was confirmed, and the histopathological reports

showed endothelitis, inflammation, and microvascular thrombosis in the submucosa or transmural. Despite early surgery, the outcome is severe in these cases, with an overall mortality of 45–50% in reported studies and up to 100% in patients over 65 years of age according to Hwabejira et al. [19].

In COVID-19 patients non hospitalized at the onset of an acute ischemic event, with mild and moderate forms of the disease, the outcome was less severe, with recovery in 77% of cases.

We found that age over 60 years and the necessity of surgical treatment are statistically correlated with a poor outcome in the reviewed studies (Table 6). According to the type of mesenteric ischemia, the venous thrombosis was more likely to have a favorable outcome (recovery in 80% of cases), while vascular micro thombosis lead to death in 66% of cases.

Table 6. Risk factors for severe outcome.

Parameters	Outcome: Death	*p*-Value
Age • Age < 60 • Age > 60	27.2% 60%	0.0384 * 0.043 **
Surgery • No surgery • surgery	0% 60%	0.019 **
Type of mesenteric ischemia • Arterial • Venous • Micro thrombosis	47% 20% 66%	0.23 **
D dimers	Wide variation	0.085 * 0.394 **
Leucocytes	Wide variation (9650–37,000/mmc)	0.803 0.385 **

* One-way ANOVA test; ** Chi-squared test (SciStat® software, www.scistat.com (accessed on 25 November 2021)).

4. Discussions

Classically, acute mesenteric ischemia is a rare surgical emergency encountered in the elderly with cardiovascular or portal-associated pathology, such as arterial hypertension, atrial fibrillation, atherosclerosis, heart failure, valve disease, and portal hypertension. However, in the current context of the COVID-19 pandemic, mesenteric ischemia should be suspected in any patient presenting in an emergency with acute abdominal pain, regardless of age and associated diseases.

Several biomarkers were investigated for the potential diagnostic and prognostic value in acute mesenteric ischemia. Serum lactate is a non-specific biomarker of tissue hypoperfusion and undergoes significant elevation only after advanced mesenteric damage. Several clinical trials found a value higher than 2 mmol/L was significantly associated with increased mortality in non-COVID-patients. However, its diagnostic value is still a subject of debate. There are two detectable isomers, L-lactate, which is a nonspecific biomarker of anaerobic metabolism, and hypoxia and D-lactate, which is produced by the activity of intestinal bacteria. Higher D-lactate levels could be more specific for mesenteric ischemia due to increased bacterial proliferation at the level of the ischemic bowel, but the results obtained in different studies are mostly inconsistent [53,54].

Several clinical studies found that LDH is a useful biomarker for acute mesenteric ischemia, [55,56]. However, interpretation of the results may be difficult in COVID-19 patients, as both lactate and LDH were also found to be independent risk factors of severe forms of COVID-19 [57,58].

The diagnosis of an ischemic bowel should be one of the top differentials in critically ill patients with acute onset of abdominal pain and distension [50,59]. If diagnosed early, the

intestinal ischemia is potentially reversible and can be treated conservatively. Heparin has an anticoagulant, anti-inflammatory, endothelial protective role in COVID-19, which can improve microcirculation and decrease possible ischemic events [25]. The appropriate dose, however, is still a subject of debate with some authors recommending the prophylactic, others the intermediate or therapeutic daily amount [25,60].

We found that surgery is associated with a severe outcome in the reviewed studies. Mucosal ischemia may induce massive viremia from bowel epithelium causing vasoplegic shock after surgery [25]. Moreover, many studies reported poor outcomes in COVID-19 patients that underwent abdominal surgery [61,62].

4.1. Pathogenic Pathways of Mesenteric Ischemia in COVID-19 Patients

The intestinal manifestations encountered in SARS-CoV-2 infection are represented by inflammatory changes (gastroenteritis, colitis), occlusions, ileus, invaginations, and ischemic manifestations. Severe inflammation in the intestine can cause damage to the submucosal vessels, resulting in hypercoagulability in the intestine. Cases of acute cholecystitis, splenic infarction, or acute pancreatitis have also been reported in patients infected with SARS-CoV-2, with microvascular lesions as a pathophysiological mechanism [63].

In the study of O'Shea et al., on 146 COVID-19 hospitalized patients that underwent CT-scan, vascular thrombosis was identified in 26% of cases, the most frequent location being in lungs [20]. Gastrointestinal ischemic lesions were identified in 4 cases, in multiple locations (pulmonary, hepatic, cerebellar parenchymal infarction) in 3 patients. The authors raised awareness about the possibility of underestimation of the incidence of thrombotic events in COVID-19 patients [20].

Several pathophysiological mechanisms have been considered, and they can be grouped into occlusive and non-occlusive causes [64]. The site of the ischemic process, embolism or thrombosis, may be in the micro vascularization, veins, or mesenteric arteries.

Acute arterial obstruction of the small intestinal vessels and mesenteric ischemia may appear due to hypercoagulability associated with SARS-CoV-2 infection, mucosal ischemia, viral dissemination, and endothelial cell invasion vis ACE-2 receptors [65,66]. Viral binding to ACE2Receptors leads to significant changes in fluid-coagulation balance: reduction in Ang 2 degradation leads to increased Il6 levels, and the onset of storm cytokines, such as IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, IgG -induced protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein 1-alpha, and tumor necrosis factor α [67], but also in the expression of the tissue inhibitor of plasminogen -1, and a tissue factor, and subsequently triggering the coagulation system through binding to the clotting factor VIIa [68]. Acute embolism in small vessels may be caused by the direct viral invasion, via ACE-2 Receptors, resulting in endothelitis and inflammation, recruiting immune cells, and expressing high levels of pro-inflammatory cytokines, such as Il-6 and TNF-alfa, with consequently apoptosis of the endothelial cells [69].

Capillary viscometry showed hyperviscosity in critically ill COVID-19 patients [70,71]. Platelet activation, platelet–monocyte aggregation formation, and Neutrophil external traps (NETs) released from activated neutrophils, constitute a mixture of nucleic DNA, histones, and nucleosomes [59,72] were documented in severe COVID-19 patients by several studies [70,71,73].

Plotz et al. found a thrombotic vasculopathy with histological evidence for lectin pathway complement activation mirroring viral protein deposition in a patient with COVID-19 and SLE, suggesting this might be a potential mechanism in SARS-CoV-2 associated thrombotic disorders [47].

Numerous alterations in fluid-coagulation balance have been reported in patients hospitalized for COVID-19 pneumonia. Increases in fibrinogen, D-dimers, but also coagulation factors V and VIII. The mechanisms of coagulation disorders in COVID-19 are not yet fully elucidated. In a clinical study by Stefely et al. [68] in a group of 102 patients with severe disease, an increase in factor V > 200 IU was identified in 48% of cases, the levels determined being statistically significantly higher than in non-COVID mechanically

ventilated or unventilated patients hospitalized in intensive care. This showed that the increased activity of Factor V cannot be attributed to disease severity or mechanical ventilation. Additionally, an increase in factor X activity was shown, but not correlated with an increase in factor V activity, but with an increase in acute phase reactants, suggesting distinct pathophysiological mechanisms [74].

Giuffre et al. suggest that fecal calcoprotein (FC) may be a biomarker for the severity of gastrointestinal complications, by both ischemic and inflammatory mechanisms [75]. They found particularly elevated levels of FC to be well correlated with D-dimers levels in patients with bowel perforations, and hypothesized that the mechanism may be related to a thrombosis localized to the gut and that FC increase is related to virus-related inflammation and thrombosis-induced ischemia, as shown by gross pathology [76].

Non-occlusive mesenteric ischemia in patients hospitalized in intensive care units for SARS-CoV-2 pneumonia requiring vasopressor medication may be caused vasospastic constriction [19,64,65]. Thrombosis of the mesenteric vessels could be favored by hypercoagulability, relative dehydration, and side effects of corticosteroids.

4.2. Question Still to Be Answered

Current recommendations for in-hospital patients with COVID-19 requiring anticoagulation suggest LMWH as first-line treatment has advantages, with higher stability compared to heparin during cytokine storms, and a reduced risk of interaction with antiviral therapy compared to oral anticoagulant medication [77]. Choosing the adequate doses of LMWH in specific cases—prophylactic, intermediate, or therapeutic—is still in debate. Thromboprophylaxis is highly recommended in the absence of contraindications, due to the increased risk of venous thrombosis and arterial thromboembolism associated with SARS-CoV-2 infection, with dose adjustment based on weight and associated risk factors. Besides the anticoagulant role, some authors also reported an anti-inflammatory role of heparin in severe COVID-19 infection [66,78,79]. Heparin is known to decrease inflammation by inhibiting neutrophil activity, expression of inflammatory mediators, and the proliferation of vascular smooth muscle cells [78]. Thromboprophylaxis with enoxaparin could be also recommended to ambulatory patients with mild to moderate forms of COVID-19 if the results of prospective studies show statistically relevant benefits [80].

In addition to anticoagulants, other therapies, such as anti-complement and interleukin (IL)-1 receptor antagonists, need to be explored, and other new agents should be discovered as they emerge from our better understanding of the pathogenetic mechanisms [81]. Several studies showed the important role of Il-1 in endothelial dysfunction, inflammation, and thrombi formation in COVID-19 patients by stimulating the production of Thromboxane A2 (TxA2) and thromboxane B2 (TxB2). These findings may justify the recommendation for an IL-1 receptor antagonist (IL-1Ra) which can prevent hemodynamic changes, septic shock, organ inflammation, and vascular thrombosis in severe forms of COVID-19 patients [80–82].

5. Conclusions

Understanding the pathological pathways and risk factors could help adjust the thromboprophylaxis and fluid management in COVID-19 patients. The superior mesenteric vein thrombosis is the most frequent cause of acute intestinal ischemia in COVID-19 non-hospitalized patients that are not under anticoagulant medication, while non-occlusive mesenteric ischemia and microvascular thrombosis are most frequent in severe cases, hospitalized in intensive care units.

COVID-19 patients should be carefully monitored for acute onset of abdominal symptoms. High-intensity pain and abdominal distension, associated with leukocytosis, raised inflammatory biomarkers and elevated D-dimers and are highly suggestive for mesenteric ischemia. The contrast-enhanced CT exam, repeated, if necessary, offers valuable information regarding the location and extent of the acute ischemic event. Early diagnosis and treatment are essential for survival.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11010200/s1, File S1: The PRISMA 2020 statement.

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I. Lucrări relevante

5. Șerban D, Popa Cherecheanu A, Dascalu AM, Socea B, Vancea G, Stana D, Smarandache GC, Sabau AD, **Costea DO**. Hypervirulent Klebsiella pneumoniae Endogenous Endophthalmitis - A Global Emerging Disease. *Life* 2021, 11(7),676. doi: 10.3390/life11070676. PMID: 34357049; PMCID: PMC8304989. (IF din 2021=3.253). 16 PAGINI. **Lucrare premiată** - **PN-III-P1-1.1-PRECISI-2021-61494** (revisită cotată în zona galbenă, 2021)

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Review

Hypervirulent *Klebsiella pneuMoniae* Endogenous Endophthalmitis—A Global Emerging Disease

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Abstract: The review aims to document the new emerging hypervirulent *Klebsiella pneumoniae* (Kp) endogenous endophthalmitis (EKE) in terms of incidence, microbiological characterization of the pathogenic agent, associated risk factors, management, and outcomes. Hypervirulent (hv) strains of KP (hvKp) induce invasive liver abscesses (LA) with specific clinical features. Up to 80–90% of cases have hepatic liver abscess as a primary focus of infection, followed by renal or lung hvKp infections. However, the incidence of EKE in patients with KPLA varied between 3.4% (19) and 12.6% (13), with a total of 95 cases of endophthalmitis in 1455 cases of KPLA (6.5%). Severe visual loss was encountered in 75% of cases, with 25% bilateral involvement. Intravitreal antibiotics are the mainstay therapeutic approach. Pars plana vitrectomy is a subject of controversy. HvKp strains present mostly natural "wild-type" antibiotic resistance profile suggestive for community-acquired infections, being highly susceptive to the third and fourth generation of cephalosporins and carbapenems. Antimicrobial resistance in hypervirulent strains was recently documented via plasmid transfer and may result in extremely difficult to treat cases. Global dissemination of these strains is a major epidemiologic shift that should be considered in the diagnostic and therapeutic management of patients with endogenous endophthalmitis. Ophthalmologic screening in patients with KPLA and other hvKp infections and a multidisciplinary therapeutic approach is extremely important for early diagnosis and preservation of the visual function.

Keywords: hypervirulent *Klebsiella pneumoniae*; invasive liver abscess syndrome; percutaneous drainage; endophthalmitis; early diagnosis; intravitreal antibiotherapy

1. Introduction

Klebsiella pneumoniae (Kp) is a Gram-negative opportunistic bacterium, from the Enterobacteriaceae family, which classically produces lobar pneumonia, particularly in immunocompromised patients, and it is known to cause hospital-acquired pneumonia, meningitis, bloodstream, and urinary tract infections [1,2].

In recent decades, new challenges regarding Kp have emerged. One concerns the growing evidence of multidrug resistance strains [3]. Therapeutic management is threatened by the complex mechanisms of multidrug resistance, mainly due to extended-spectrum

beta-lactamases (ESBL), AmpC beta-lactamases, or carbapenemases [4,5], of the strains, encountered in the hospital environment [6–8].

Another problem is the global spread of hypervirulent Kp (hvKp), an evolving pathotype, characterized by increased virulence that may cause disabling and life-threatening diseases in previously healthy individuals [6,7]. The first hypervirulent Kp endogenous endophthalmitis was reported in 1986 in Taiwan, in a patient with hepatic abscess without any underlying hepatobiliary pathology, raising attention about a new invasive strain [8–10]. Subsequent clinical trials reported that an epidemiologic shift in the epidemiology of cryptogenic liver abscess, with a growing number of case reports and subsequent clinical studies on larger patient groups signaling endemic growth of hvKp infections, accounting for 80% of cases in the Asian Pacific rim [11–17], and emerging in other regions such as the US, Australia, South Africa and recently in Europe [18–27], characterized by a high rate of metastatic septic dissemination, endophthalmitis and CNS complications being among the most common.

Hypervirulent Kp strains are recognized presently as the primary cause of endogenous endophthalmitis, whereas endogenous endophthalmitis is rarely seen with cKp, excepting on rare occasions in the setting of neutropenic or otherwise immunocompromised patients [28]. Moreover, the endogenous endophthalmitis in the clinical setting hepatic, or less frequently urinary, the pulmonary focus of infection is highly suggestive for hvKP [28–31].

Particular Features of the Hypervirulent K. pneumoniae (hvKp) Strains

Most of the hypervirulent strains express a hypermucous phenotype, according to the string test: formation of mucoviscous strings greater than 5 mm, when a standard bacteriological loop is passed through a colony [32–44]. These strains are characterized by a super capsule, more resistant to complementary, neutrophil-mediated bactericidal activity and phagocytosis. While some authors contest the clinical significance of K2 serotype, K1 seems to more resistant to serum resistance assay and more than 40% of infected patients are free from diabetes or other comorbidities [35]. The K1 capsular polysaccharide is thought to be related with the resistance to phagocytosis, but the mechanism is not yet fully understood. A "Trojan horse" mechanism has been postulated with hvKp strains being able to survive and migrate within neutrophils and delay their apoptosis, within 24 h [6,36,37].

Another marker of virulence characteristic for hvKp is the magA gene, which is located in the K1 strain-specific wzy allele. The magA gene codes an outer membrane protein essential for the formation of a protective exopolysaccharide web associated with mucoviscosity and virulence of the K1 strain [38]. Two plasmid-encoded virulence factors have been well characterized, rmpA, a regulator of mucoid phenotype that upregulates capsule synthesis, and the iron siderophores (aerobactin, yersiniabactin, salmochelin) which enable the bacterium to obtain iron essential for growing, by chelating the Fe-binding proteins of the host [40–45]. Other virulence factors include the chromosome-encoded virulence genes kfu/PTS, which codes for an iron uptake system (kfu) and a phosphoenolpyruvate, and allS gene, which is associated with the anaerobic metabolism of allantoin [21,39,41].

HvKp strains identified in previously published paper present in most cases a natural "wild-type" resistance to antibiotic profile, suggestive for community-acquired infections, with uniform resistance to ampicillin and piperacillin and susceptibility to cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems [10]. A small group of cases exhibits extended spectrum beta-lactamases (ESBL), up to 10 % in various studies. Recently, the emergence of carbapenem-resistant, hypermucoviscous *K. pneumoniae* strains is mentioned in a hospital outbreak in China [46–50], causing severe, untreatable infections in healthy individuals. These may occur by several mechanisms involving plasmids transfer: either a hvKp strain acquires an antimicrobial-resistant plasmid, or a cKp strain acquires the hvKp

specific virulence plasmid or a hybrid plasmid that contains both virulence elements and antimicrobial resistance genes (Table 1) [6].

Table 1. Differences between common *K. pneumoniae* (cKp) and hypervirulent *K. pneumoniae* (hvKp).

	cKp	hvKp
Acquisition of infection	mostly hospital acquired	mostly community acquired
Host status	immunocompromised, old, hospitalized	previously healthy, all ages;
Geographic region	globally spread	first endemic in South East Asia, with progressive global spreading [51]
Locus of primary infection	lungs, urinary tract, blood stream, meningitis	liver, less frequently kidney, lungs, others
Co-pathogens	unfrequently; mostly monomicrobial	may be plurimicrobial, especially is digestive, hepatobiliary, urinary or soft tissue infections [6,51]
Metastatic spread	unfrequently	Frequent: endophthalmitis, meningitis, central nervous system (CNS), psoas, prostatic abscess, necrotizing fasciitis) [51,52]
Phenotype	String < 5 mm	hypermucoviscosity, string > 5 mm
Serotypes	K1–79	mostly K1, K2; other serotypes identified: K5, K16, K20, K54, K57, KN1
Multidrug resistance (MDR)	Frequent, especially in hospital acquired infections (to cephalosporins, fluoroquinolones, carbapenems)	less than 10–15% (but on a emerging trend)
Siderophores	enterobactin, yersiniabactin [6,53]	enterobactin, aerobactin, yersiniabactin, salmochelin [6,53]

This review aims to document the endogenous hvKp endophthalmitis (EKE) in terms of epidemiology, risk factors, clinical features, therapeutic management, and outcomes. We performed a comprehensive review of literature on PubMed and additional databases (Science direct-Elsevier, Springer Nature, Web of Science), by the terms "hypervirulent *Klebsiella pneumoniae*" and "endogenous endophthalmitis". Case reports and clinical studies in the English language, reporting clinical data, and therapeutic management were included. The elements taken into account for further analysis were: type of article (case report/clinical study), length of the follow-up period (if existed), number of patients with EKE included; comorbidities; bilateral ocular involvement; associated septic disseminations; hvKp strain, if documented; ophthalmic findings; general and local treatment; outcomes in terms of preserved visual acuity.

The reports and clinical studies included in this review were comparable in terms of patient selection, methodology, and documentation of the results. However, due to the relatively new emergence of this *Klebsiella pneumoniae* pathologic association, we encountered significant differences regarding the documentation of cases, therapeutic approach—both general and local, ophthalmic treatment, according to the development of knowledge and therapeutic protocols.

2. Epidemiology of Endogenous hvKp Endophthalmitis (EKE)

Since the first case described in 1986, EKE has become currently the most frequent cause of endogenous endophthalmitis in Asian countries, with an incidence of up to 9%, and with an emergent trend in US, Australia, and European countries [22,54]. Epidemiological studies evidenced an incidence of 100 higher of metastatic spread in hvKp vs. other microorganisms. The incidence is higher in middle-aged adults, 50–60 years, with a slight male predominance and associated metabolic disorders, diabetes mellitus being a constant association.

Up to 80–90% of cases appear in the context of hepatic liver abscess. However, the incidence of EKE in patients with KPLA varied between 3.4% [17] and 12.6% [55], with a total of 95 cases of endophthalmitis in 1455 cases of KPLA (6.5%). One of the reasons for this wide variation may be the fact that the incidence was reported to all patients with a pyogenic liver abscess in some studies (19), while others analyzed only hypervirulent K1, K2 KPLA [56], as a different pathogenic entity. In a systematic review performed by

Hussain et al., in 2020, on 15 studies, totaling 11,889 patients with KPLA, an incidence of 4.5% (217 cases) of EKE was found, with a 95% confidence interval 2.4% to 8.2%. Among infections with K1serotype KPLA, Wang et al. found a 19% incidence of metastatic ocular or central nervous system complications [30], and 84.2% of these patients developed irreversible catastrophic disabilities, including loss of vision, quadriplegia, paraparesis, and/or impairment of the higher cortical function [38,57]. This highlights the need for clinical awareness about the possibility of catastrophic septic ocular or CNS complications from KPLA in previously healthy individuals. Location in the right hepatic lobe, segment VII and VIII [27,58–62], size larger than 5 cm and thrombosis of the suprahepatic vein are associated with a higher risk of metastatic spread.

Although hvKp commonly causes a hepatic abscess, and endophthalmitis may occur in this clinical setting, endophthalmitis can occur from hvKp in conjunction with non-hepatic sites of infection, such as the urinary tract (5.5–8%) or lung infections (4–11%) [63,64]. Only one study [30] found an equal incidence of 40% each for liver and lungs as the primary focus of EKE. Post-spider bite cellulitis [65,66], prostate abscess, endocarditis [30], and osteomyelitis were reported as unusual causes of hvKp endophthalmitis,

The entry gate is considered to be the gastrointestinal tract [15], oropharyngeal [67], or recent urinary tract infections [62]. Oropharyngeal colonization could lead to infection with aspiration, but it is still unclear what the mechanism of entry is via the GI tract since many individuals subsequently infected have no apparent GI pathology. Entry through micro-breaks in the skin, similar to *Staphylococcus aureus* is also a theoretical possibility. However, the exact mechanism and necessary time lapsed between inoculation and the onset of the invasive systemic infection is not fully understood [41].

Chung et al. found a significant fecal carriage of K1 and K2 pathogenic stains in stools in a cohort of healthy South Korean residents [15]. Fujita et al. found a correlation with previous treatments with ampicillin or amoxicillin, leading to the hypothesis that these antibiotics may increase the risk for KPLA by selection pressure [67–69]. Diabetes, by impaired gastrointestinal permeability, may favor bacterial translocation into the portal bloodstream [68,69]. In a two-case report, Fujita et al. found KPLA and endophthalmitis appeared in patients previously incompletely treated with amoxicillin/clavulanic acid for sore throats and upper respiratory infections and postulated the possibility of systemic dissemination following incomplete eradication of the pathogen [67].

3. Risk Factors

This emerging epidemiological issue was initially attributed to the association with the Asian race and diabetes [10,27,36,59,60]. However, a significant number of published papers documented the presence of the infectious strain in young, previously healthy subjects, of all ethnic groups [18,19,22,25]. In recent years, cases from United States, Belgium, Spain, UK, Germany, Sweden, Romania, Saudi Arabia have been reported, indicating global dissemination of these strains causing invasive liver abscesses and endogenous endophthalmitis in both Asian and non-Asian patients, independent from their immunocompetent status or coexistence, or coexistence with diabetes [70].

Diabetes was frequent comorbidity [18,25,26,71] with an incidence between 35–92%, although it may appear in previously healthy adults (Tables 2 and 3). The role of poor glycemic control in the impaired phagocytosis of capsular serotypes K1 or K2 of *Klebsiella pneumoniae* was postulated for the pathogenesis of serious metastatic complications in diabetic patients [72], but the hypothesis was not supported by further experimental studies [73]. On the other hand, Coburn et al. demonstrate that a possible explanation of the frequent association of diabetes with EKE following KPLA may be the specific diabetic ocular environment, with increased retinal blood barrier permeability [74]. Another possible explanation may be the disturbing gastrointestinal defense mechanisms in diabetes, which may favor the bacterial translocation from the gastrointestinal lumen into the bloodstream [15].

Table 2. Demographics, clinical characteristics and treatment of patients with *Klebsiella pneumoniae* endogenous endophthalmitis (EKE) from case reports.

Author, Country, Year	Sex Age	Underlying Diseases	Serotype	Focus of Infection	Ophthalmic Findings	Associated Septic Spread	General Treatment	Opththalmic Treatment	Outcome
Seo, R[58] Japan, 2016	F, 64	-	K2A, rmpA positive	KPLA [a] right lobe	VA [b]: NLP [c] Chemosis, corneal, vitreal haze	thrombocytopenia, coagulopathy	iv [d] meropenem (3 g/day), changed to ceftriaxone (2 g/day) percutaneous drainage of KPLA	Early VIT [e]	VA: NLP
Saccente M[18], US, 1999	M, 38	diabetes	No info	KPLA right lobe,	VA: 20/400, Hypopyon, chemosis, vitreal haze	meningitis	iv ceftriaxone (21 days), metronidazole (17 days), followed by oral levofloxacin and metronidazole, 30 days	Intravitreal ceftazidime and vancomycin; Topic ciprofloxacin, cefazolin and corticosteroids 1 drop/1–2 h	VA: 20/60
Maruno T[38], Japan, 2013	M, 63	-	K1	KPLA right lobe,	VABE: LP [f], bilateral endophthalmitis and orbital cellulitis	lungs septic emboli	iv meropenem 1 g/kg every 8 h, changed to ceftriaxone Ultrasound-guided percutaneous transhepatic liver abscess drainage	No info	Bilateral total vision loss
Sobirk S[20], Sweden, 2010	M,45	-	Mucoid strain	KPLA multiloculated	VA: LP; Chemosis, vitreous hemorrhage	-	iv ceftazidime and vancomycin	Topic antibiotics	Vision loss
Baekby M[21], Denmark, 2018	M, 78	-	K1, hv CC23 clone	multiloculated KPLA > 12 cm	VA: LP, red painful eye	lumbar abscess	iv piperacillin/ tazobactam, followed by oral ciprofloxacin	Intravitreal ceftazidime and vancomycin	Vision loss
Fujita M[38], Japan 2015	F, 70; M, 50	-	K1	KPLA	Case1: VARE: LP; hypopyon, haze of ocular media [b] Case 2: VARE *: LP; hyperemia, corneal and vitreous haze,		case 1: iv sulbactam /cefoperazone; percutaneous drainage Case 2: iv clindamycin and cefazolin, then switch to cefepime	Case 1: VIT + PEA [g]+ antibiotics Case 2: VIT+ PEA, per secundam IOL [h], antibiotics	Case 1: Corneal melting; evisceration Case 2: preserved partial vision
Al Mahmood[71], Saudi Arabia, 2011	M, 43; F, 70	diabetes	No info	KPLA	Case 1: VA: LP, hemorrhagic purulent vitreous Case 2: VA BE **: LP; ocular hypertension, hypopyon		iv ceftazidime vancomycin	Case1: vancomycin 1 mg/0.1 mL, ceftazidime 2.25 mg/ 0.1 mL, amphotericin B 10 lg/0.1 mL and dexamethasone 0.4 mg/0.1 mL Case 2: + VIT	Case 1: VA: NLP Case 2:RE: evisceration; VA LE ***: LP
Wells JT[23], US, 2015	F, 67	-	K1	KPLA	RE: pan ophthalmitis, retinal detachment	peritoneal sepsis, septic shock	iv ceftriaxone, changed to imipenem, vancomycin, and fluconazole	Intravitreal Vancomycin and ceftazidime	deceased
Castle G[24], UK, 2020	M, 56	anti-IFN-3 [i] autoimmunity	No info	KPLA 9 cm, multiloculated	VARE:1; choroidal abscess VA in LE: HM, marked vitreous and anterior chamber haze	lung emboli	iv ceftriaxone, followed by oral ciprofloxacin	RE: Vitrectomy, lens removal, intravitreal antibiotics LE: evisceration	RE: LP, aphakic LE: NLP

Table 2. *Cont.*

Author, Country, Year	Sex Age	Underlying Diseases	Serotype	Focus of Infection	Ophthalmic Findings	Associated Septic Spread	General Treatment	Ophthalmic Treatment	Outcome
Paraschiv F[25], Romania, 2018	F, 53	diabetes	positive string test	KPLA	VA CF Uveitis, retinal hemorrhages	meningitis thrombocytopenia	iv vancomycin and ceftriaxone, percutaneous drainage	Intravitreal and topic antibiotics, topic corticosteroids	Partial recovered vision
Van Keer J[26], Belgium, 2017	M, 84	hypertension	No info	KPLA < 30 mm	VARE 20/250; proptosis, chemosis VALE: CF	-	iv ceftriaxone	Intravitreal ceftazidime, topic antibiotics and cs; LE: vitrectomy	RE: LP LE: partial vision recovery
Pichler C[5], Germany, 2017	M, 61	-	K2 serotype ST2398	KPLA	endophthalmitis	thrombosis of supra hepatic vein	percutaneous catheter drainage, i.v. piperacillin/tazobactam, and ciprofloxacin	No info	No info
Xu [29], China, 2019	M, 25	diabetes	KP587, ESBL [j]	KPLA	VA: LP, hypopyon		i.v. imipenem	Intravitreal imipenem, vancomycin and dexamethasone, VIT	CF [k] at 0.4 m
Abdul Hamid, A[63], UK, 2013	M, 36		No info	KPLA, 6 cm, segment VIII	VA: LP, chemosis, sever periorbital edema	tenosynovitis, urinary infection	oral ciprofloxacin, 10 weeks	Intravitreal amikacin 0.4 mg/0.1 mL and vancomycin 1 mg/0.1 mL topic antibiotics, CS, mydriatics	VA: NLP
Sridhar J[65], 2014, US	M,43 F, 58 F,60	DM DM Multiple mieloma	No info	KLPA Spider bite + celullitis unknown	VA: 2/200 VA:1/200 VA: LP	no info	no info	Vitreous tap+ Intravitreal vancomycin and ceftazidime – all patients + intravitreal CS – patient 1 + VIT – patient 2	Enucleation Evisceration enucleation
Hassanin F[75], 2021, Saudi Arabia	F, 55	DM	+ string test	Renal abscess	VA: LP, Chemosis, conjunctival injection, hypopion, panopthalmia with orbital cellulitis	-	iv ceftazidime, vancomycin, and metronidazole	VIT+ intravitreal vancomycin and ceftazidime evisceration	Anophthalmia
Dubey D[66], 20313, US	F, 41	DM	K1, sensitive to carbapemens only	Renal abscess	blurred vision, hypopion, endophthalmitis	lungs, CNS [l]	iv meropenem (2 g /8 h), 8 weeks	Intravitreal vancomycin and ceftazidime	No info
Martel A[76], 2017	M, 60	-		KPLA	VA 20/50 Anterior uveitis, subretinal abscess	urinary	iv ceftazidime	Intravitreal ceftazidime (2.25 mg/0.1 mL), 13 injections	VA 20/20

[a] KPLA: *K. pneumoniae* liver abscess; [b] VA: visual acuity, * RE: right eye; ** BE: both eyes; *** LE: left eye; [c] NLP: no light perception;[d] iv: intravenous; [e] VIT: pars plana vitrectomy; [f] LP: light perception; [g] PEA: phacoemulsification of the lens; [h] IOL: intraocular lens; [i] anti IFN-3: anti-interferon 3; [j] ESBL: extended spectrum beta lactamase; [k] CF: counting fingers; [l] CNS: central nervous system.

Table 3. *Klebsiella pneumoniae* endogenous endophthalmitis (EKE) in clinical studies.

Author, Country, Year	Study Period	No of Cases/No of Eyes	Sex (M/F)	Age (Mean)	Comorbidities	K.p. Strain	Focus of Infection (%)	Other Disseminations	Ocular Outcome	General Therapy	Ophthalmic Therapy
Chiu CT[59], Taiwan, 1988	1977–1986	3(5.2% incidence in KPLA)	2/1	65	diabetes (66.7%)	no info	hepatic	-	vision loss (3) enucleation (1)	iv cephalosporins	topic antibiotics, mydriatics, CS [a]
Liao HR[60], Taiwan, 1992	1983–1988	12 (25% bilateral)	no info	no info	diabetes (91.66%)	no info	hepatic (50%) Others (urinar, pulmonary)	-	no light perception (9); enucleation or evisceration (6) light perception (3)	iv cephalosporins percutaneous drainage of KPLA if necessary	topic cephalosporin + gentamicin, mydriatics, CS
Cheng DL[61], Taiwan, 1991	1981–1987	14; (14,2% bilateral)	no info	no info	diabetes (50%)	No info	hepatic	lungs (4) CNS (3) prostate (1)	12 -blindness 2—partial blindness	general	Topic antibiotics
Fung C[10], Taiwan, 2002	1991–1998	14 (10.44%); 134	3/1	56.4	diabetes (93%)	K1 (85.7%) K2 (14.3%)	hepatic	lungs (3) CNS (2)	deceased (4) vision loss/very low vision (8) vision recovery (2)	pigtail catheter drainage; iv 3rd generation cephalosporin + gentamicin, 2 weeks, continued with oral ciprofloxacin	No info
Fang CT[56], Taiwan, 2007	1997–2005	14 (12.6%); 177 28.5% bilateral	8/6	58.2	diabetes (93%; 78.4%)	K1 (92,85%) K2 (7.15%)	hepatic	meningitis (8) spondylitis/ diskitis (4) pneumonia (1) brain abscess (2) fasciitis (1)	vision loss (8; 57.1%) limited vison (2; 14.2%) partial recovery (4;28.5%)	pigtail catheter drainage; iv third generation cephalosporin + gentamicin	Intravitreal antibiotics and CS
Yang CS[55], Taiwan, 2007	1994–2001	22 (bilateral 22.7%)	19/3	54.6	diabetes (68%)	no info	hepatic	lungs (6) CNS (3) kidney (1) prostate (1)	vision loss (89%), of which 41% anophthalmia VA > 1/10 (3 cases)	iv cephalosporins and aminoglycosides	intravitreal antibiotic/CS enucleation/evisceration 41%
Sheu SJ[12], Taiwan, 2011	1991–2009	42(6.9%); 602 (26% bilateral)	26/16	60.2	diabetes (35%)	no info	hepatic	no info	VA of CF or better in 35.8%	iv cephalosporins, intravitreal antibiotics; VIT (9 cases)	intravitreal ATB [b] -40 (amikacin 400 mg/ 0.1 mL, gentamicin 0.05 mg/0.1 mL, ceftazidime 2.25 mg/0.1 mL, and vancomycin 1 mg/0.1 mL intravitreal CS -12 VIT-9 enucleation/evisceration- 11
Park IH[13], South Korea, 2015	2004–2013	12	7/5	64.3	diabetes (50%; 23.8%)	no info	hepatic (incidence in KPLA 6.1%)	no info	NLP$_c$(7) HM (3) Partial recovery (2)	iv cephalosporins and aminoglycosides	intravitreal ceftazidime 2.25 mg/0.1 mL and vancomycin 1 mg/0.1 mL; early VIT
Lee JY [14], South Korea, 2014	1997–2013	8;	5/3	71.1	diabetes (50%)	no info	hepatic	no info	vision loss (7) partial recovery (1)	iv ceftriaxone,	intravitreal antibiotics (7)
Pastagia M[19], US, 2008	2001–2007	1 (bilateral EKE)	no info	no info	diabetes (100%)	K1	hepatic	lungs, meninx (1)	bilateral vision loss	iv ceftriaxone /imipenem in cases with ESBL Intravitreal antibiotics	no info

Table 3. *Cont.*

Author, Country, Year	Study Period	No of Cases/No of Eyes	Sex (M/F)	Age (Mean)	Comorbidities	K.p. Strain	Focus of Infection (%)	Other Disseminations	Ocular Outcome	General Therapy	Ophthalmic Therapy
Chung CY[15], Hong Kong, 2016	2006–2015	19 (bilateral 26.3%)	12/7	67.89	diabetes (11) hypertension (5) cirrhosis (2) Guillain-Barre (1)	no info	liver 18 (94%) urinary 1 (6%)	coagulopathy (1), shock (1) psoas (1) CNS (1) pleura (3)	deceased (4) anophthalmia (9) total vision loss (3) VA > 0.3 (3)	iv cefuroxime, gentamicin;	intravitreal ceftazidime and amikacin+/− vancomycin 17/19 (89.47%) VIT 3 (15.8%) evisceration 9 (47.4%)
Ang M[16], Singapore, 2011	1986–2007	61/71 (18% bilateral)	49/12	55.7	diabetes (55.7%)	no info	liver 46 (77.5%) urinary 11 (9.9%) repiratory 3 (4.2) other 6 (8.4%)	lung (5) meningitis (5) urinary (7)	evisceration (10/26 (8%)) VA < 20/400 55 (77.5%) VA > 20/400 16 (22.5%)	iv ceftriaxone,	intravitreal vancomycin (2.0 mg/0.1 mL) ± ceftazidime (2.25 mg/0.1 mL) or amikacin (0.4 mg/0.1 mL).
Tan YM[17], Singapore, 2003	1995–2001	10 (3.4%); 289	6/10	45.7	diabetes 70%	no info	hepatic	skin emboli (1) pneumonia (1) ARDS [d] (2) pleural effusion (1)	evisceration (2) vision loss (4) poor vision -HM (4)	iv ceftriaxone and gentamicin/metronidazole	Intravitreal antibiotics, VIT
Odouard C[22], Australia	2011–2015	4 (50% bilateral)	3/1	39.2	diabetes (50%)	No info	hepatic liver 4 (40%)	lungs (1) prostate (1)	enucleation (1) vision loss (1) preserved vision >6/24 (2)	iv ceftriaxone, hepatic abscess drainage	intravitreal ceftazidime and vancomycin, VIT
Shields RA[30], 2017, US	2000–2017	10/12 (20% bilateral)	8/2	56	diabetes 7 (70%)		lungs 4 (40%) endocarditis 1 (10%) osteomyelitis 1 (10%)	no info	anophthalmia 5/12 vision loss 2/12 VA > 20/300—5/12	iv antibiotics	intravitreal antibiotics (1–33 injections)–10/12 enucleation, evisceration 5/12
Lim H[31], 2014, S. Korea	2005–2011	18/23 (27% bilateral)	14/4	68.7	diabetes-8 (44%) cirrhosis 4 (22%) psoriasis arthritis 1(5%)	no info	KPLA 15 (85%) lungs (11%) prostate abscess 1(5%)	no info	anophthalmia 1 (2.3%) total vision loss 13 (56%) VA> 0.05- 9 (39%)	iv ceftazidime/ceftriaxone+ amikacin/ metronidazole/ tazocin /meropenem	intravitreal vancomycin, ceftazidime +/ gentamicin/amikacin VIT- 7 (30%) evisceration 1 (2.3%)
Chen SC[84], 2016, Taiwan	2002–2013	48/58 (20.8% bilateral)	29/19	59.3	diabetes 34 (70.8%) hypertension 17 (35.4%) malignancy 7 (14.6%) cirrhosis 4 (8.3%)	no info	KPLA 33 (68.7%) Urinary 4 (8.3%) pneumonia 2 (4%) other 5 (10.4%)	no info	anophthalmia 12 (20.6%) total vision loss 27 (46.5%) VA > 1/60 -19 (32%)	iv antibiotics, according to antibiogram	intravitreal ceftazidime+/− vancomycin (3.8 + −2.6) − 100% intravitreal CS -27 (50%) VIT 18 (31%) evisceration/enucleation 12 (20.6%)
Wong JS[64], 2000	1986–1998	18/20 (11% bilateral)	10/8	49.3	KPLA 15 (83%) pneumonia 2 (11.1%) urinary 1 (5.5%)	No info	KPLA 15 (83%) pneumonia 2 (11%) urinary 1 (5%)	no info	vision loss 15 (83%) AV > 0.05 3(17%)	ceftriaxone+ imipenem/ gentamicin/ metronidazole	intravitreal cefazolin/ceftazidime + vancomycin/gentamicin -100%

[a] CS: corticosteroids; [b] ATB: antibiotics; [c] HM: hand movement; [d] ARDS: acute respiratory distress syndrome.

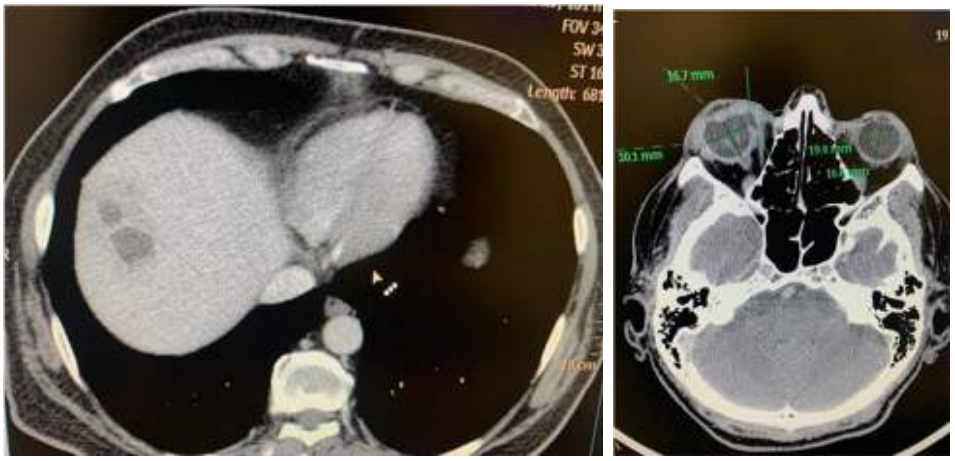
Chung et al. found also an increased incidence of other metabolic disorders, such as hypertension and fatty liver [15], but it is not clear what specific mechanisms may favor the invasive infection in these cases.

Other associated pathologies were: thrombocytopenia [12], anti-interferon type 3 (anti-IFN3) autoantibodies [24], hypertension [26,55], and less frequent cirrhosis and Guillain Barre syndrome [17]. IFN-3 is considered to be involved in the neutrophil response, hepatic macrophage activity, and mucosal immunity. IFN-3 signifies type 3 interferon, which is considered to be involved in the neutrophil response, hepatic macrophage activity, and mucosal immunity. The identification of the anti-IFN3 in the case reported by Castle et al. may explain the poor outcome, with bilateral vision loss, in a previously healthy patient [24].

4. Diagnostic of Endogenous hvKp Endophthalmitis

The distinctive clinical course of irreversible ocular injury caused by hvKp strains is still not complete elucidated. However, experimental animal studies showed a significant decrease in electric activity of the infected retina within 18 h from the onset [34].

In 25.8% (5–50%) of cases, the septic involvement was bilateral, resulting in permanent vision loss. Bilaterality was encountered in 5–50% of cases in the reviewed studies, in association with multiple septic determinations, such as lungs [38], meninges and CNS, coagulopathy, thrombocytopenia, urinary sepsis (Tables 2 and 3). There were a total of 78 bilateral cases in a total of 302 patients with EKE and KPLA (25.8%). In all cases with ocular determination, the localization of liver abscess was in the right hepatic lobe (Figures 1 and 2)



(a) (**b**)

Figure 1. (**a**) CT exam: multiloculated hepatic liver abscess, right lobe, segment VIII, 50/32/57 mm; (b) CT Exam: Right eye endophthalmitis, eyeball with irregular contour, with a hypodense area in the internal side (at the area of the insertion of the medial rectus muscle), with possible communication between posterior chamber and periorbital space (perforation) (archive of the Ophthalmology Department, Emergency University Hospital Bucharest).

4.1. Clinical Evaluation. Prognostic Factors

Various reports found that the ophthalmologic findings, with decreased vision and painful eye, may precede the signs related to the initial focus of infection [10,55,56,62,67]. The most common presentation was blurred vision and ocular pain. In the study of Park et al., ocular symptoms developed prior to the diagnosis of liver abscesses in 66.7% of cases [15]. These findings were confirmed by other case reports [26,67]. General signs are suggestive of an infectious syndrome, although the fever may not be present at admission.

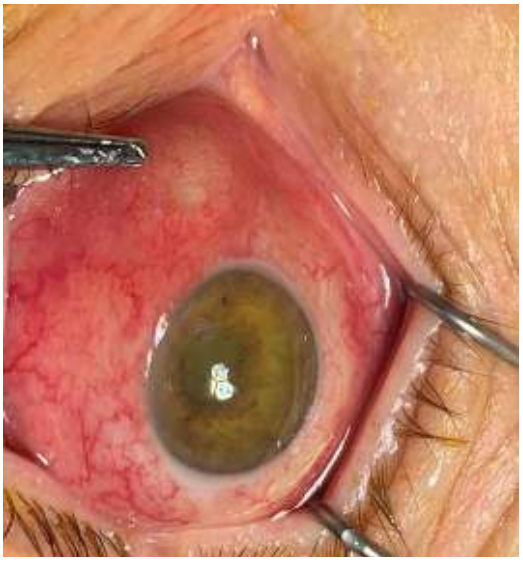


Figure 2. Endogenous hvKp endophthalmitis (EKE): corneal haze, intense hyperemia, scleral abscess in the internal angle, with impending ocular perforation (archive of the Ophthalmology Department, Emergency University Hospital Bucharest).

Ocular findings included chemosis, red painful eye, haze cornea, and vitreous. Decreased visual acuity at presentation of hand movement or less and hypopyon were associated with poor prognosis [15,68,72,75–77]. Patients with unilocular involvement were found to be a risk factor for evisceration, in comparison with bilateral infection, one possible explanation being the delay in presentation in cases in which only one eye was affected [16]. In a study by Ang et al [16], early onset of the ocular symptoms was also a factor of poor prognosis, in correlation with the virulence of the pathogen and bacterial load.

Hypopion may be present in 30–40% of cases and is considered a factor for adverse outcomes [15]. EKE is the result of the metastatic septic emboli in the choroid, with subsequent development of the infection through a blood–retina barrier, into the retina and vitreous body. Passage of the germs, leukocytes, and inflammatory products into the anterior segment of the eye may occur at the level of zonular fibers. The increased number of cellularity and fibrin at the level of the anterior chamber is an expression of intense inflammation in the posterior segment [15].

According to the focal or diffuse aspect, as well as the extension of the septic process, various clinical forms were described: subretinal abscess, posterior diffuse involvement, anophthalmia, scleral abscess with spontaneous perforation, orbital cellulitis.

4.2. Imagistic and Laboratory Tests

Ocular imagistic investigations (ultrasonography) CT and an IRM exam may indicate the increased density of vitreous body +/ − subretinal abscess, as well as the extension of the septic process with eyeball disorganization and infiltration of the orbital soft tissue. Documenting the initial focus of infection and the possible septic associations requires hepatic, renal pulmonary, and CNS imaging, or other locations suggested by clinical findings.

Aqueous humor and vitreous taps may identify the pathogen at the eye level in 30–40% of cases. Additionally, *K. pneumoniae* was isolated from the blood culture in most cases. A string test is an inexpensive tool, which can strongly suggest the involvement of a hypervirulent strain of *Klebsiella pneumoniae*. However, physicians should be aware that a negative string test does not exclude the presence of hvKp in cases with the clinically documented invasive syndrome. Extensive documentation of the serotype and virulence gene by genomic sequences and PCR was performed in recent studies and reports, revealing a high incidence of K1 serotype and magA gene [5,21,29].

5. Management of EKE

5.1. General Antibiotic Therapy and Assesment of the Primary Focus

The antibiotic regimen should be chosen considering the penetration of the available antibiotics in different tissues, like the eye and CNS, when the metastatic spread is encountered. In particular, third-generation cephalosporin is recommended due to its good penetration in the vitreous cavity and cerebral spinal fluid. Peak vitreous concentrations of at least 2 mg/l can be achieved [56]. The clinical management was based on 2–3 weeks intravenous antibiotic therapy with the 3rd or 4th generations of cephalosporins, which are considered to be superior to the first generation of cephalosporin in septic metastasis and recurrence prevention [15,16,18,19,37,68]. In some papers, metronidazole or piperacillin/tazobactam was added for anaerobic pathogens [20,23]. The use of aminoglycosides is debatable, due to the relatively low penetrance of the abscess capsule. However, they may be useful upon pathogens in the bloodstream, thus preventing septic dissemination [10,12,50,68]. After 2–3 weeks, if the criteria for favorable evolution are met, the patients were switched to oral fluoroquinolones, for 1–2 months, with periodic follow-up to identify possible recurrence early [10,23,26].

ESBL strains were identified in up to 10–13% of cases [40,57,58,61]. In a recent study on 110 patients with KPLA, with a mean follow-up period of 3.65 years, Wang et al. [76] found that ESBL was encountered significantly more frequently in the patients who experienced recurrence (30.0% vs. 8.89%). This finding supports the idea that ESBL should be considered an independent risk factor for the recurrence of KPLA [76]. and in these cases, cephalosporins should be replaced with imipenem or meropenem therapy [21]. In the absence of ESBL, such use of reserve antibiotics should be avoided, to preserve as long as possible the natural "wild-type" phenotype of hypervirulent KP strains.

In non-responding cases, percutaneous or surgical drainage of the primary infection focus should be performed to mitigate the hematogenous spread. Percutaneous drainage of the liver abscess, ultrasound or preferable CT guided, may be performed either needle assisted or by continuous catheter drainage with negative pressure. The indications for drainage include febrile patient after more than 48–72 h of adequate intravenous antibiotherapy, abscess of more than 6 cm in diameter, or impending perforation [50,78,79]. Multiple location and multiloculated abscesses are relative contraindications due to increased chances of failure. High locations may not be suited for guided drainage due to the increased risk of pneumoperitoneum. When a catheter is used, one must take into account the specific high viscosity of the KP strains, thus larger size and frequent flushing should be used to prevent blockage [68]. The catheter was usually maintained for 1–2 weeks and removed when drainage is sterile, less than 5 mL daily, and fever does not reappear when the tube is clamped [57].

Surgical drainage should be considered if a patient fails to improve at a satisfactory rate with percutaneous drainage and intravenous antibiotics, in cases of impossible percutaneous evacuation due to thick pus, multiloculated or multiple liver abscesses, located in the left hepatic lobe. Surgery is mandatory in cases of spontaneous rupture or if other biliary pathology should be addressed. Abscess spontaneous rupture is a serious complication, requiring immediate surgery. It is favored by: dimensions of more than 5 cm, thinned walls, intracavitary gas formation, and hyperglycemic dysregulation in diabetic patients [68].

5.2. Ocular Management and Visual Outcomes

Early case reports and clinical studies using topical antibiotics, corticoids, and mydriatics reported a poor outcome resulting in most cases in blindness and anophthalmia due to spontaneous eye perforation that required evisceration or enucleation [18,20,60,61].

5.2.1. Intravitreal Antibiotics

Today, the mainstay of ocular management is intravitreal antibiotics based on a combination of 3rd-generation cephalosporins +/— vancomycin +/− aminoglycoside. The role of intravitreal antibiotics is supported by evidence that vitreous samples are

still positive for *Klebsiella*, despite intensive systemic antibiotherapy. According to recent guidelines of endophthalmitis treatment, intravitreal antibiotics increase the third time chance to preserve some degree of vision in the affected eye and decreased by a third the risk for evisceration.

Intravitreal drugs used were: ceftazidime 2.25 mg/0.1 mL +/− vancomycin 1–2 mg/0.1 mL+/−amikacin 0.4 mg/0.1 mL [13,15,16,18,29,55]. There are no current guidelines regarding the number and frequency of intravitreal antibiotics administration, the therapeutical decision is based on the clinical response. The median number of administrations in the reviewed studies was 3–5 [12,58,67,77]. However, Martel successfully treated a Kp subretinal abscess with intensive intravitreal ceftazidime and vancomycin, daily for one week, then at 48 h, with a total of 13 administrations [80].

5.2.2. Intravitreal Steroids

There is no consensus regarding the utility of intravitreal triamcinolone in EKE. Intravitreal corticoids administration was found to be associated with vision gain of more than 6/60 [22,55] and may be performed after 2–3 intravitreal antibiotic injections. However, in the reviewed studies, corticoids were administrated in only 20–50% of cases.

5.2.3. Pars Plana Vitrectomy (PPV) and Subretinal Abscess Drainage

The benefits of early pars plana vitrectomy are still a subject of debate in the clinical management of EKE. The timing and indications for PPV are a challenging issue, with contradictory results. Some authors recommend early vitrectomy, considering as beneficial results the decrease of intraocular bacterial load and increased penetration of the antibiotics into the eye, preventing irremediable damage of the eye structures. Connel et al. reported a 0% evisceration and enucleation rate in eyes treated by PPV and intravitreal antibiotics when compared to 50% in eyes treated with intravitreal antibiotics only [79]. However, Ang et al. found that early vitrectomy is not associated with a better visual outcome [16]. Martel et al. raised concern about the efficacy and results of PPV on an inflamed necrotic retina [80]. A vitrectomy could result in supplementary damage of the retina, especially if the vitreous body is not detached due to vitreoretinal tractions. Another aspect to be taken into account is that removing the vitreous body will reduce the time of contact with the antibiotic with the infected retina. An absolute contraindication for PPV is the presence of life-threatening septic dissemination, such as meningitis or CNS abscess. Early removal of vitreous abscess can favor rapid evacuation of the pathogen load and mediators of inflammations. A more conservative approach would indicate PPV only in eyes with VA severely decreasing a worsening grade of relative afferent pupillary defect with no response to intravitreal antibiotics for 48 h [18,80]. Choosing the surgical timing should take into account the general status of the patient, hemodynamics, and coagulation parameters, which can be affected during *Klebsiella* infection.

In cases with abscesses larger than four disks areas, retinotomy and abscess drainage may be an option, but the risk for post-operative retinal detachment and vitreoretinal proliferation is higher due to active inflammation, laser photocoagulation is difficult on a fragile retina. Venkatesh used a conservative approach, by combining PPV with 41G needle abscess drainage, which has the advantage of an easily self-sealing retinal hole [81].

PPV alone may be also beneficial even in large-size retinal abscesses according to Xu et al. [29], by removal of the toxins and inflammatory products.

5.2.4. Lensectomy

Phacoemulsification of the lens was employed by some authors, but with limited results in vision improvement and the risk of corneal melting and spontaneous perforation [38].

5.2.5. Evisceration and Enucleation

Evisceration or enucleation was performed in cases non-responsive to other therapeutical options, with spontaneous perforation and total vision loss.

Despite immediate management, the visual outcome in patients with EKE is poor [82,83]. It ranges from hand motion visual acuity to evisceration or enucleation of the eye in more than 75% of cases [74,82]. In a study of Ang et al., on 71 eyes of 61 patients with EKE, the severe visual loss was encountered in 76% of cases, despite adequate treatment. with a high likelihood of bilateral blindness [16]. However, early intervention in the first 48 h from the onset, with intravenous 3rd or 4th generations of cephalosporins, intravitreal antibiotics +/−corticosteroids and, in severe, non-responsive cases, pars plana vitrectomy, may preserve a vision of more than 6/60 in 13.6% of cases [13]. Several reports showed that early treatment before severely decreased vision appears, based on systemic and intravitreal antibiotics may preserve vision in variable degrees [13,16,45]. The introduction of an ophthalmological screening program for patients with *KPLA* was useful in early diagnosis and reducing the risk of progression to enucleation of eyes due to earlier diagnosis and more aggressive treatment [16,72,75,84].

6. Conclusions

Global dissemination of hvKp is a major epidemiologic shift that should be considered in the diagnostic and therapeutic management of patients with endogenous endophthalmitis. There is a concern regarding the possibility of abelon further combination of virulence and resistance, causing severe, untreatable infections in healthy individuals, which would be extremely difficult to manage [34,73]. Ophthalmologic screening in patients with KPLA or other suspected primary hvKp infections is extremely important for early diagnosis that could preserve visual function. Once vision is severely decreased, the outcome of hvKP endophthalmitis is extremely severe, despite aggressive ophthalmological treatment. The dramatic evolution of the ocular damage, with loss of vision in most cases and anophthalmia in 25–50% of cases, requires awareness of this new pathological association and the need to follow up these patients in multidisciplinary teams and to initiate aggressive ophthalmic treatment early concomitantly with antibiotic treatment as this is essential for saving vision.

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Optimization of a GF-AAS method for lead testing in blood and urine: A useful tool in acute abdominal pain management in emergency

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Abstract. Suspicion of lead poisoning is confirmed by its concentration in blood and protoporphyrin red blood cells. At low concentrations, lead influences the synthesis of the heme in the sense of lowering it. Acute and chronic lead intoxication is extremely polymorphic in regards to its clinical manifestations, with digestive, hematological, cardiovascular, renal hepatic and neurological features. The aim of the study was to evaluate the presence of lead in human whole blood and urine harvested before and during chelation treatment in the case of lead poisoning. An atomic absorption spectroscopic method for the analysis of lead was developed using graphite furnace atomic absorption spectrophotometer (GF-AAS), Varian Spectra AA-880 with a hollow cathode lead lamp and a deuterium lamp for background correction, coupled to a GTA-100 atomizer and a programmable sample dispenser. Standard calibration solutions were used for the range 10-100 $\mu g/l$. The linearity range was 10.0 to 100.0 $\mu g/l$ with the correlation coefficient of 0.999. We established that the method can be applied for the determination of lead in whole blood and urine, and the results obtained are useful for monitoring chelation therapy in cases of acute lead poisoning, a neglected cause of abdominal colic pain in an emergency situation.

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Abbreviations: GF-AAS, graphite furnace atomic absorption spectrometry

Key words: lead toxicity, GF-AAS, biological samples, saturnine colic, acute abdominal pain

Introduction

Lead intoxication is an environmental health problem, with extremely severe consequences upon the human body (1). Acute lead poisoning manifests clinically with intense acute abdominal pain, being a challenging diagnosis in emergency situations (2). Development a quick and reliable method for lead determination in blood and urine, is important in clinical practice, both in diagnostics, but also in monitoring chelating therapy.

The main sources of lead that result in lead contamination include: Paint; leaded petrol; drinking water; car batteries, cables, glass; printers with lead-based technology; manufacture and use of war ammunition (3,4). In melters, the main danger is melting. The risk of exposure to lead increases with increasing temperature in industrial processes (5).

The main routes of absorption of lead are gastric and pulmonary. Gastric absorption in adults is about 10-15% of the total amount ingested and 40% in children. At the lung level it is absorbed at ~50-70% of the inhaled dose. In organic form, lead from tetraethyl lead is also absorbed at the skin level (6). Inhalation absorption depends on the form of lead (vapors or particles). Approximately 90% of inhaled particulate lead is absorbed into the respiratory tract (7). Once absorbed, 99% is

transported by the bloodstream and binds to hemoglobin in red blood cells (2,5).

The distribution is completed in three compartments, namely in the blood compartment, mineralized tissues (bones, teeth) and soft tissues (kidneys, bone marrow, liver and brain). Lead in the blood is distributed at a percentage of 99% in erythrocytes and 1% in plasma and is available for transport to tissues. The blood concentration does not reflect the actual amount of lead in the body, but ~90% is stored in tissues, with a maximum half-life of ≤30 years (8). Because lead is mobilized from these tissues, individuals who have been exposed may have high concentrations of lead, from a few months to several years from the time of exposure cessation (7). The level of lead in the blood, a traditional indication of absorption, reflects only recent exposure as the half-life in the blood is 36 days (3). In individuals with chronic exposure, there is a small correlation between a level once determined at a control and the cumulative absorption index or loading of the lead organism.

Suspicion of lead poisoning is confirmed by its concentration in blood and protoporphyrin red blood cells. At low concentrations, lead influences the synthesis of the heme in the sense of lowering it. Due to the fact that the level of erythrocyte protoporphyrin is not pathognomonic in children at levels of approximately 25 µg/dl, the best method remains to determine the level of blood lead (9,10). Lead binds to the sulfur groups of many enzymes by inactivating them. Lead poisoning has a multisystemic, hematological, cardiovascular, renal, hepatic, digestive and neurotoxic impact (5). Acute intoxication at blood levels >50 µg/dl causes saturnine colic, and biochemical dosing of lead when there is clinical suspicion is extremely important in emergency situation, in the differential diagnosis of acute abdomen, to avoid white laparotomies in patients with severe abdominal colic pain (11).

This work aims to present a method of determination for lead in blood and urine using graphite furnace atomic absorption spectrometry (GF-AAS) with a background correction. Atomic absorption spectrometry with graphite furnace atomization (GF-AAS) is a leading technique in analytical chemistry as a routine low-level assay for lead and other heavy metals, for a wide variety of sample types (12).

Materials and methods

Instrumentation. Lead analysis was performed using a graphite furnace atomic absorption spectrophotometer (GF-AAS) Varian Spectra AA-880, with a hollow cathode lamp (Agilent Technologies, Inc.) and a deuterium lamp (Agilent Technologies, Inc.) for background correction, coupled to a GTA-100 atomizer and a programmable sample dispenser (Varian). Addition instrumentation included: A monochromator (fully automatic computer-controlled Czerny-Tuner micromotor, focal length 0.33 mm; automatic sample dispenser PSD Varian with 54 positions for samples, standards, modifiers, quality control and buffer, maximum injected quantity 100 µl, injection precision 0.2 µl, automatic dilution and mixing, automatic re-injection of samples); Neslab CFT 33 water cooler for graphite oven working at temperature 15-25˚C; a nitrogen generator (Dominik Hunter) (purity, 99.999%); EBA 200 Hettich Centrifuge, Eppendorf automatic pipette 1,000 µl. Biochemical parameters were determined from blood on the Vitros 650 System (Ortho Clinical Diagnostics) and complete blood count on a Celltac-F Hematology Analyzer (Nihon Kohden).

Table I. Working parameters for determining lead by GF-AAS.

No.	Parameter	Method
1.	Injection mode	Automated dilution
2.	Calibration mode	Concentration
3.	Type of measurement	Peak height
4.	Replicate standard	3
5.	Replicate sample	3
6.	Smoothing	9
7.	Wavelength	283.3 nm
8.	Slit	0.5
9.	Lamp current	10 mA
10.	Background correction	Yes
11.	Standard 1	10 µg/l
12.	Standard 2	20 µg/l
13.	Standard 3	50 µg/l
14.	Standard 4	100 µg/l
15.	Recalibration rate	30
16.	Calibration algorithm	New rational
17.	Total volume	15 µl
18.	Sample volume	10 µl
19.	Dilution coefficient	2

GF-AAS, graphite furnace atomic absorption spectrometry.

Samples and reagents. Biological samples (20 urine samples and 20 blood samples) were collected during hospitalization (23 days) from a patient admitted to the Intensive Care II Unit, Toxicology Department within the Bucharest Emergency Clinical Hospital. Written informed consent was obtained after the study protocol was previously discussed and explained to the patient.

All chemicals were of analytical or certified-reagent grades. Lead standard solution Certipur® (Merck) (1,000 mg/l Pb) was used. A lead stock solution (100 µg/l) was prepared daily in 0.01% nitric acid. Concentrated nitric acid (Lach-Ner), with a lead content (<0.00005%) below the GF-AAS detection limit, was used. Solutions were prepared with grade doubly distilled, de-ionized water in polypropylene calibrated flasks. The required volumes were measured with air displacement pipettes (Eppendorf Research plus Models) with premium grade polypropylene tips. All glassware was cleaned with acid and rinsed thoroughly with distilled or unionized water before use.

Blood samples. Sodium heparin (Lilly) with a lead content below the GF-AAS detection limit was used. For analysis, 200 µl of blood was mixed together with 800 µl 5% anti-foam B (Sigma-Aldrich; Merck KGaA) solution and 1,000 µl 1.6 M solution of 65% HNO_3. They were allowed to stabilize for 10 min and then centrifuged for 5 min at 2,884 x g relative centrifugal force (RCF). The supernatant was collected and

Table II. Furnace GTA-100 Varian operating conditions for lead measurements.

Step	Temperature (˚C)	Time (sec)	Flow (liters/min)	Gas type	Read	Signal storage
	40	1.0	3.0	Normal	No	No
	85	5.0	3.0	Normal	No	No
	95	40.0	3.0	Normal	No	No
	120	10.0	3.0	Normal	No	No
	120	5.0	3.0	Normal	No	No
	400	5.0	3.0	Alternate	No	No
	400	1.0.	3.0	Alternate	No	No
	400	2.0	0.0	Alternate	No	Yes
	2,100	1.0	0.0	Alternate	Yes	Yes
	2,100	2.0	0.0	Alternate	Yes	Yes
	2,100	3.0	3.0	Normal	No	Yes
	40	2.0	3.0	Normal	No	No
	40	5.0	0.0	Normal	No	No

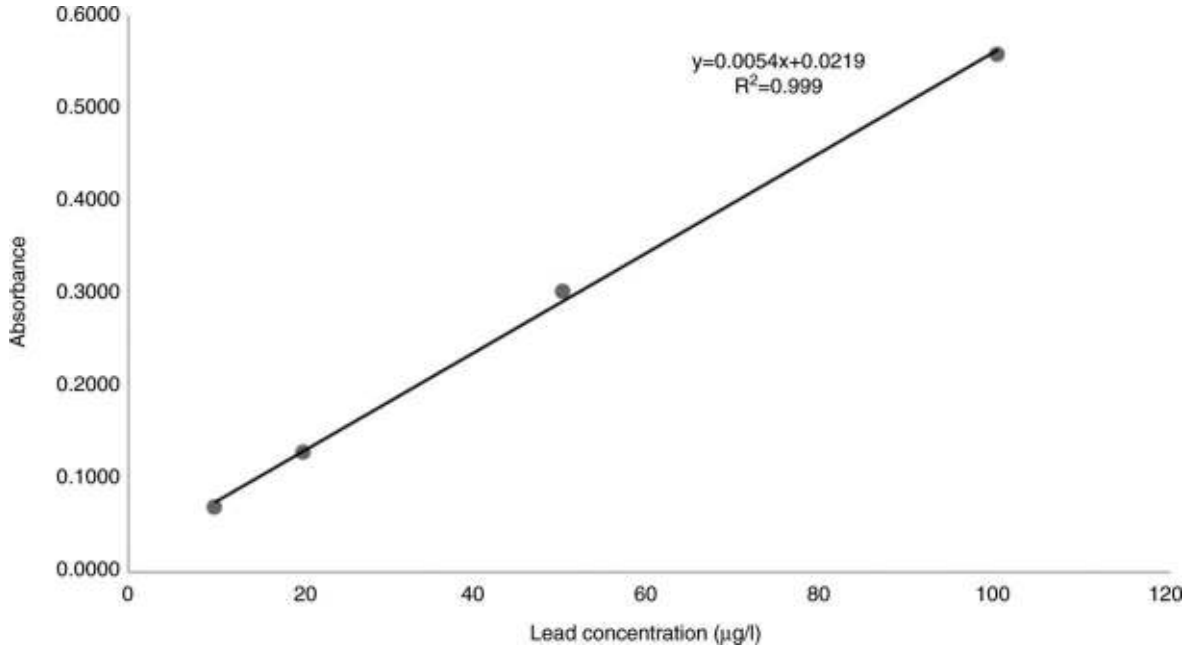

Figure 1. The linear regression curve for the determination of lead etalon model.

analyzed on the graphite furnace atomic absorption (GF-AAS) system.

Urine samples. A volume of 9 ml of urine was treated with 1 ml of 65% HNO_3. The sample was allowed to stabilize for 20 min and then centrifuged for 10 min at 2,884 x g relative centrifugal force (RCF). The supernatant was then analyzed on the GF-AAS system. There were several trials using different working parameters, to reach optimum conditions (Table I).

Results

Optimization of the working parameters. The atomization temperature was established by varying the atomization temperature between 1,600 and 2,100˚C. As expected, the lead signal increased with the increase in the atomization temperature up to 2,000˚C. For temperatures >2,100˚C, the signals remained almost constant, indicating that maximum atomization efficiency can be achieved in this range (Table II).

The application of the optimized temperature program made possible elimination of the whole matrix of the sample before the atomization step, as confirmed by the low background signals observed in the measurement of lead (13-15). To determine the performance parameters for the method (linearity, accuracy, precision and robustness) standard calibration solutions were used in the concentration range 10-100 µg/l (14). The detection and quantification limits were established according to ICH (International Conference on Harmonization) recommendations (16,17).

Table III. Performance parameters of the linear regression equation.

Denomination	Conc. (µg/l)	Abs	Media Abs	Abs without blank	R^2 coefficient of determination	Slope	Standard deviation of slope (STD)	Ordinate at origin b	Standard deviation (STD) of the ordinate at origin
Blank	0	0.0086	0.0085		0.9986	0.0054	0.0001	0.0219	0.0068
		0.0091							
		0.0079							
Standard 1	10	0.0726	0.0788	0.0703					
		0.0839							
		0.0799							
Standard 2	20	0.1393	0.1387	0.1302					
		0.1363							
		0.1406							
Standard 3	50	0.2943	0.3095	0.3009					
		0.3151							
		0.3190							
Standard 4	100	0.5744	0.5654	0.5569					
		0.5630							
		0.5589							

Abs, absorbance; conc., concentration.

Table IV. Validation parameters.

Cation	Pb^{2+}
Linearity range	10-100 µg/l
Regression equation	y=0.0054x + 0.0219
Correlation coefficient (R^2)	0.9990
Intercept	0.0219
Slope	0.0054 µg/l
SE of intercept	0.0068
SD of intercept	0.02633572
LOD	4.15 µg/l
LOQ	12.59 µg/l

SE, standard error; SD, standard deviation; LOD, limit of detection; LOQ, limit of quantification.

A linear relationship was found between the absorbance at 283.3 nm and the concentration of lead in the range of 10.0 to 100 µg/l. The representative linear equation was y = 0.0054x + 0.0219 where: y is the absorbance, x is the lead concentration (µg/l), calculated by the least squares method. The regression coefficient (R^2) standard curve was 0.9990 (Fig. 1) indicating good linearity.

The performance parameters of the linear regression equation are presented in Table III. The parameters of the GF-AAS analysis method of lead are presented in Table IV, and the calibration curve can be observed in Fig. 1. The limit of detection (LOD) and the limit of quantification (LOQ) were detected for the method based on the standard deviation of 6 readings of the standard solution blank and on the slope of the analytical curve (Table III).

LOD is the lowest concentration of an analyte that can be detected while LOQ is defined as the lowest concentration of an analyte that can be determined at the acceptable level of precision and accuracy and were calculated according to the formula below: LOD = 3.3x (SD of intercept/slope) and LOQ = 10x (SD of intercept/slope) (Table IV).

The accuracy of the assays (BIAS), expressed as the consistency between the real value and the analytical result, was calculated using three sources of blank matrix samples fortified at each level of concentration analyzed in duplicate. The calculated coefficient of variance (CV%) which describes the precision of the analytical method is shown in Table V. The CV% did not exceed 15% at each concentration and the BIAS was <15% at each level of concentration, which ensured a superior trust grade for each determination using this method. In other words, the difference between the real value and the determined value of concentration was minimal.

Clinical application. Lead level monitoring in humans is of great importance due to its high toxicity. In order to detect lead in whole blood, the authors developed a method using GF-AAS, for quantifying the lead level in blood which can be used for monitoring lead levels during chelation treatment time. The permissible concentration of lead in the blood is up to 20 µg/dl, and in urine ≤40 µg/l.

Acute lead poisoning manifests with acute abdominal pain, nausea and vomiting, being a neglected cause in the differential diagnosis of acute surgical abdomen. A careful anamnesis,

Table V. The performance parameters of the analytical method for lead determination.

Level	Standard solution concentration µg/ml	Measured concentration µg/ml	Average measured concentration µg/ml	Standard deviation	BIAS	CV%
1	10	9.41	10.56	1.06	-5.90	10.04
	10	11.50			15.00	
	10	10.76			7.60	
2	20	21.78	21.67	0.41	8.90	1.89
	20	21.22			6.10	
	20	22.02			10.10	
3	50	50.53	53.34	2.46	1.06	4.61
	50	54.38			8.76	
	50	55.11			10.22	
4	100	102.47	100.81	1.49	2.47	1.48
	100	100.36			0.36	
	100	99.60			-0.40	

BIAS, accuracy of the assays; CV%, coefficient of variance.

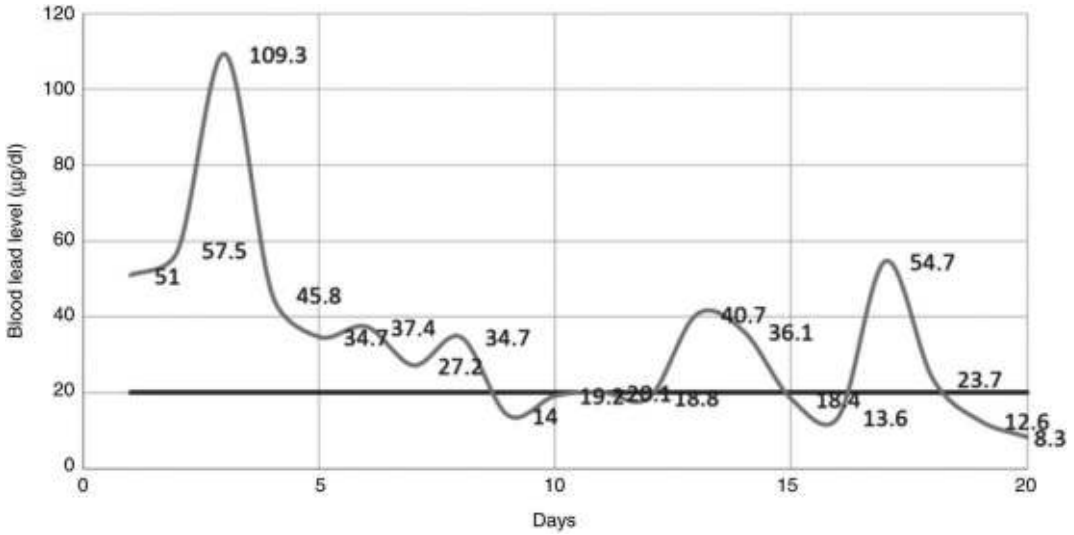

Figure 2. Variation of lead levels in whole blood, measured by the presented GF-AAS technique, during chelating treatment in a case of lead intoxication. GF-AAS, graphite furnace atomic absorption spectrometry.

revealing previous toxicological history, occupational risk or hobbies that might be associated with lead exposure, may reveal important information, but it may not be always accurate, due to patient multiple comorbidities, ignorance of the possible toxic risk or neuropsychiatric disorders. A frequent associated condition is anemia, due to the increased fragilization of the erythrocyte membranes and hemolysis. In suspect cases or patients with a non-conclusive clinical and imagistic exam, a prompt and reliable determination of lead concentration in blood is extremely important to avoid 'white' laparotomies and associated perioperative morbidity.

The therapeutic approach is based on sustaining vital functions and increased lead elimination through urine. Chelating therapy is usually initiated when lead concentration in blood is more than 50 µg/dl, due to the possible dangerous side effects.

The most commonly used chelating agents in lead intoxication include: Dimercaptosuccinic acid, dimercaprol and $CaNa_2$ EDTA. Among the current drawbacks of the chelation therapy, the clinician must take into account the hepatotoxicity and nephrotoxicity, essential metal loss, headaches, nausea, arrythmias, hypotension or hypertension, bone marrow depression, convulsions or even cardio-respiratory arrest (17,18). Another aspect is the redistribution of the lead among the body compartments, which may generate important fluctuation of blood and urine concentration during the first days of therapy. Prolonged treatment with $CaNa_2$ EDTA results in depletion of essential metals, especially Zn, Cu and Mn, requiring oral Zn supplementation (17).

Chelating therapy requires close monitorization and advanced medical skill (5). In our department, patients admitted for acute lead poisoning are closely followed

up by daily laboratory tests including: Hemoleucogram, transaminase, urea, creatinine, electrolytes (Na^+, K^+, Ca^{++}), as well as lead concentration in the blood and urine. The optimized method based on GF-AAS technique proves to be useful for monitoring chelation therapy in the cases of acute lead poisoning. It allows a close follow-up of the dynamic concentrations of lead in the blood and urine, as presented in Fig. 2.

Discussion

Saturnine colic is an infrequent cause of differential diagnosis of acute abdomen, which may appear in cases of acute lead poisoning, with blood lead levels exceeding 50-80 µg/dl (2,19-22). If undiagnosed, it can lead to avoidable surgeries, by mimicking acute appendicitis, perforated ulcer, acute pancreatitis or bowel obstruction (21-23). The abdominal pain is intense, colliquative, in the periumbilical area, resistant to usual antispastics (2,20-22). The pain diminishes at profound palpation of the abdomen, with no tenderness or contracture, being a key element of differential diagnosis with surgical acute abdomen. Other signs and symptoms are anorexia, nausea, vomiting, constipation or very rarely, diarrhea (23,24). Radiological abdominal exam shows hydroaeric images, with alternative sectors of spastic and moderate dilated intestinal loops. The patient may experience transient increased blood pressure, which comes back to normal after ceasement of abdominal pain with chelating therapy. Oliguria, increased serum urea and leukocytosis may be associated with acute poisoning (19).

It is well known that exposure to lead causes dose-dependent decreases in heme synthesis by inhibiting the enzyme δ-aminolaevulinic acid dehydrase (δ-ALAD). Hematologic tests such as hemoglobin concentration may suggest toxicity, but this is not specific for lead (25). The higher the level of blood lead levels, the lower the hemoglobin in the blood and the level of erythrocytes due to the increase in lead-induced membrane fragility resulting in the development of anemia (26). The toxicity of lead on the human hematological system has been established in numerous studies. Other effects of lead on the hematological system are decreased activity of erythrocyte enzymes (pyrimidine 5'-nucleotidase) and altered levels of plasma erythropoietin (27).

The effects of acute and chronic lead intoxication upon the nervous system have been studied for 100 years. Lead is a highly neurotoxic element, both for central nervous system and peripheric nerves. Even concentrations below 10 µg/dl, in children, are inversely correlated with the intelligence quotient (IQ). There are well-defined clinical features encountered in both adults and children: Decreased learning ability, memory loss, cognitive deterioration, reduced neural signaling and demyelination. At blood levels >70 µg/dl in children and >100 µg/dl in adults lead toxicity is increased and may cause paresis or paralysis and saturnine encephalopathy, with sudden seizures, changes in consciousness, coma and death (28,29). Furthermore, several studies have confirmed the pathogenic role of lead intoxication in Alzheimer disease and glaucoma, by increasing the tissular oxidative stress, through depletion of glutathione and thiol pools, as well as by disrupting the antioxidant defense system (30-35). Several studies revealed that probiotics may be useful for alleviation and treatment of lead toxicity, reducing the specific side-effects in heavily polluted areas (36,37). Accidental or occupational lead intoxication is an important public health problem, causing a significant burden especially in low- and middle-income countries (38). The Institute for Health Metrics and Evaluation (IHME) estimated that in 2017, lead exposure accounted for 1.06 million deaths and 24.4 million years of healthy life lost worldwide due to long-term effects on health (39). The most severe include the neurologic and cardiovascular effects of acute or chronic lead poisoning: 63.2% of the global burden of idiopathic developmental intellectual disability, 10.3% of the global burden of hypertensive heart disease, 5.6% of the global burden of the ischemic heart disease and 6.2% of the global burden of stroke (40).

Graphite furnace atomic absorption spectrometry (GF-AAS) is increasingly becoming the method of choice for the determination of lead and other heavy metals in blood and urine, as well as in other biological products (40-43), with several improvements developed in time to increase its power of detection and determination for lower concentrations.

Whole blood lead levels are the most widely used and most generally accepted measure of absorbed dose. A repeatable, reliable, cost-efficient method is an important tool for lead intoxication screening and chelation therapy monitoring in clinical practice.

GF-AAS is simpler, less expensive, quicker and more accurate than neutron activation or emission spectrometric technique. The absorbance signals obtained for lead in the optimizing conditions presented ensures a well-defined profile and a low background (42-44).

The reported method shows high precision and accuracy, as well as a wide applicability in routine lead determination and research assays. The methods developed are valuable for clinical diagnostics and biological monitoring of work-related exposure.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

MST, GC, OA, ADS and DS were responsible for the conception and design of this study. DMP, CGS, CT, AMD, CDB, DOC and BS were responsible for the data collection and analysis. MST, GC, OA, CT and DS were in charge of drafting the manuscript. AMD, MC, ADS, DOC and RS revised critical perspectives for important intellectual content. The final version for publication was read and approved by all the authors.

Ethics approval and consent to participate

Written informed consent was obtained after the study protocol was previously discussed and explained to the patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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I. Lucrări relevante

7. Dascalu AM, Stoian AP, Cherecheanu AP, Serban D, **Costea DO**, Tudosie MS, Stana D, Tanasescu D, Sabau AD, Gangura GA, Costea AC, Nicolae VA, Smarandache CG. Outcomes of Diabetic Retinopathy Post-Bariatric Surgery in Patients with Type 2 Diabetes Mellitus. *Journal of Clinical Medicine* 2021, 10(16), 3736. doi: 10.3390/jcm10163736. PMID: 34442032; PMCID: PMC8396947, (IF din 2021=4.964) 17 PAGINI.
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Review

Outcomes of Diabetic Retinopathy Post-Bariatric Surgery in Patients with Type 2 Diabetes Mellitus

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Abstract: Bariatric surgery is an emerging therapeutic approach for obese type 2 diabetes mellitus (T2DM) patients, with proven benefits for achieving target glucose control and even remission of diabetes. However, the effect of bariatric surgery upon diabetic retinopathy is still a subject of debate as some studies show a positive effect while others raise concerns about potential early worsening effects. We performed a systematic review, on PubMed, Science Direct, and Web of Science databases regarding the onset and progression of diabetic retinopathy in obese T2DM patients who underwent weight-loss surgical procedures. A total of 6375 T2DM patients were analyzed. Most cases remained stable after bariatric surgery (89.6%). New onset of diabetic retinopathy (DR) was documented in 290 out of 5972 patients (4.8%). In cases with DR at baseline, progression was documented in 50 out of 403 (12.4%) and regression in 90 (22.3%). Preoperative careful preparation of hemoglobin A1c (HbA1c), blood pressure, and lipidemia should be provided to minimize the expectation of DR worsening. Ophthalmologic follow-up should be continued regularly in the postoperative period even in the case of diabetic remission. Further randomized trials are needed to better understand the organ-specific risk factors for progression and provide personalized counseling for T2DM patients planned for bariatric surgery.

Keywords: bariatric surgery; diabetic retinopathy; progression; type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance and progressive failure of beta-pancreatic cells. The global prevalence

of T2DM is estimated to rise from 8.3% in 2011 to 9.9% in 2030 [1]. The increase in T2DM incidence is well correlated with the global burden represented by a high prevalence of obesity, especially in the younger ages. Recent studies documented the link between high body mass index (BMI) and diabetes via proinflammatory cytokines, insulin resistance, increased levels of circulating fatty acids, and impaired cellular metabolism [2]. The patients newly diagnosed with T2DM are advised to lose weight and perform physical exercise to improve glycemic control and to achieve a target HbA1c below 7%, as recommended by the American Diabetes Association [3–5]. However, patients that lose weight by lifestyle changes, diet, or medication are not likely to maintain the results over time.

Bariatric surgery offers more rapid, efficient, and long-lasting results compared to traditional weight loss methods [5–7]. Current indications for bariatric surgery are a BMI of more than 40 kg/m^2 or 35–40 kg/m^2 associated with at least 2 obesity-related comorbidities [6,8]. Several clinical studies demonstrated that bariatric surgery in obese T2DM patients led to remission of DM in up to 75% of cases [5] by increasing insulin secretion and decreasing tissular insulin resistance. The relative impact on glucose metabolism depends on the type of surgery, being more rapid and intense in bypass intestinal procedures than in gastric restrictive interventions. Treatment during the early course of the disease ensures better outcomes before advanced beta-pancreatic cell decompensation and clinical signs of micro and macrovascular diabetic complications appear [5,9,10].

Diabetic retinopathy (DR) is one of the common microvascular complications of diabetes mellitus. According to the United Kingdom Prospective Diabetes Study (UKPDS) study, 37% of patients are diagnosed with DR and up to 60% may present some degree of it after 2 decades [11,12]. The main risk factors for the onset of DR are hyperglycemia, arterial hypertension, and hyperlipemia, leading to specific chronic microvascular changes in retinal microvasculature, which in turn lead to retinal–blood barrier disruption, leakage, ischemia, and neovascularization [13,14]. Obtaining good glycemic control is important for preventing the onset and progression of diabetic retinopathy. The UKPDS study found that patients with an HbA1c below 7% had a 21% reduction in DR progression compared to those with conventional glycemic control, while Action to Control Cardiovascular Risk in Diabetes (ACCORD) suggested that an HbA1c below 6.0 may be efficient for ensuring a significantly lower rate of progression [15–17]. However, there is evidence that tight glycemic control with hypoglycemic episodes may lead to an early worsening of diabetic retinopathy [18–21]. This paradoxical phenomenon is not fully understood but seems to be related to impaired autoregulation in retinal circulation that cannot adapt properly to a sudden decrease in the availability of nutrients and insulin-related increase levels of growth factors [19–22].

Several studies evaluated the outcomes of bariatric surgery upon diabetic retinopathy, with conflicting results. In this paper, we review the clinical evidence regarding the onset and progression of diabetic retinopathy in obese T2DM patients who underwent weight-loss surgical procedures.

2. Materials and Methods

Extensive research was performed on PubMed, Science Direct, Springer, and Web of Science databases, by the terms “diabetic retinopathy” AND “bariatric surgery” OR “metabolic surgery” OR “Roux-en-Y gastric bypass,” OR “sleeve gastrectomy” OR “gastric bypass” OR “biliopancreatic diversion” OR “gastric band” OR “vertical sleeve gastrectomy and their combination. For the potentially relevant records, full-text articles were obtained. Meeting abstracts, commentaries, and book chapters were excluded. Furthermore, an additional hand search was performed in the reference list of the reviews focusing on the subject.

Original articles in English for which full texts could be obtained were included in the qualitative analyses. The strategy of research followed PICOS acronyms as recommended by PRISMA guidelines.

P: patients with T2DM

I: bariatric surgery (all types of procedures)

C: comparison to a matched cohort of medically treated T2DM patients was analyzed when available

O: new incidence of any DR in patients with no retinopathy at baseline; % of worsening and % of improvement of DR in patients treated by bariatric surgery during the follow-up period.

S: any types of clinical studies were included.

The type of bariatric procedure used, the number of patients, follow-up time, improvement in HbA1c, and resolution of T2DM were also documented.

Data Extraction and Analysis

A PRISMA flowchart was employed to screen papers for eligibility. A data extraction sheet was independently completed by two researchers. We evaluated the type of study, the number of patients enrolled, the percentage of patients with DR at baseline, type of bariatric surgery, the percentage of patients who experienced de novo onset of diabetic retinopathy, progression or regression of diabetic retinopathy, and changes in HbA1c, systolic blood pressure and lipid profile. Studies providing insufficient data regarding the pre and post DR status were excluded. Any disagreement was resolved by discussion.

The risk of bias (RoB) was assessed by Egger's test and Begg's test. Heterogenicity of studies was analyzed by Cochran's Q test and i^2 test for inconsistency after the pooled effect by the random effect model (SciStat® software, MedCalc Software Ltd, Ostend, Belgium).

The AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews 2) [23] chart for qualitative systematic reviews including randomized and non-randomized studies was employed to appraise the quality of the studies in the qualitative analysis. The checklist table is presented in Supplementary Material S1.

3. Results

The initial search resulted in 231 papers. After duplication removal and application of inclusion and exclusion criteria, 16 articles [24–39] were included in the qualitative analysis. The flowchart of the research strategy is presented in Figure 1.

The studies included in the qualitative analysis were published between 2012 and 2021, and the mean follow up ranged between 6 months and 5 years, with a median of 28.1 months. The sample size varied between 20 and 5321 participants for the surgical group, with a total of 6375 T2DM patients who underwent bariatric procedures. In 4 studies [28,35,37,38], a controlled matched group with T2DM patients treated only medically was used to compare the outcomes.

The most frequent bariatric procedures performed were: Roux-en-Y gastric bypass (RYGB), followed by laparoscopic sleeve gastrectomy (SG), laparoscopic adjustable gastric banding (GB), biliopancreatic diversion (BPD), and duodenal switch (DS).

3.1. Risk of Bias

The studies included in a review were comparable in terms of selection of patients, comparison, the strategy of research, and outcomes. However, some differences may be a potential source of bias when the total change in DR status is analyzed (Egger's test: 5.0064; p = 0.0014; Begg's test: −0.1757; p = 0.3424). The presence of any DR and the percentages of different stages of DR at baseline varied among studies, from no DR at baseline [38] to only proliferative DR [37]. This was the reason for assessing RoB and heterogeneity of studies within subgroups, based on the analyzed effect: de novo DR, progression, or regression in DR status. The method of collecting DR data varied across the reviewed papers. Some used the retrospective data from the national health registries [38], while others documented progression by prospective [25,26,28,31,34,36] or retrospective ophthalmological evaluation [27,29,30,32,33,35,37]. The definition of progression also varied: some authors used the criteria of at least 2 steps by the ETDRS scale; others defined progression as any change in the retinopathy score.

The comparative outcomes in the reviewed studies are presented in Table 1.

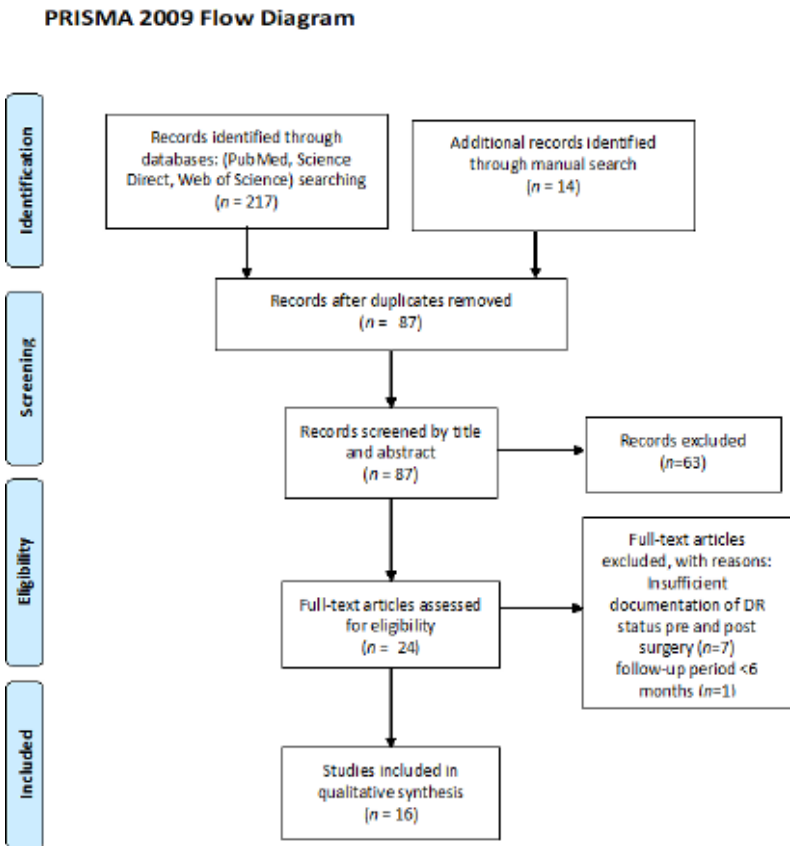

Figure 1. PRISMA flowchart for the studies included in the review. DR: diabetic retinopathy.

In the present review, we identified 16 studies [24–39], for a total of 6375 T2DM patients that underwent bariatric surgery in which pre- and post-DR status were analyzed. The percentage of patients with no DR at baseline varied between 30.3 and 100% in the study groups. Of the total, 5972 (93.6%) patients presented no DR at baseline and 403 patients were diagnosed with various stages of DR. There was no change in the baseline DR stage in 5714 out of 6375 patients (89.6%). After bariatric surgery, 65.2% (263) of the patients with previous DR and 91.2% of the patients with no DR at presentation remained stable.

3.2. *Incidence of De Novo DR in the Bariatric Surgery Group*

New cases of DR were documented after bariatric surgery in a total of 290 of 5972 patients (4.8%) that did not present DR at baseline during the follow-up period, with a wide variation of incidence between 0 and 29.4%. The limited number of cases included in most of the available studies, limited documentation of additional risk factors (e.g., smoking) but also different follow-up periods may explain the high heterogeneity (I^2: 91.7%) of reported outcomes (Table 2, Figure 2). For this reason, a meta-analysis could not be performed, which carried the risk of result overestimation according to the small-study effects. Risk of bias (RoB) analysis did not detect significant publication bias.

The onset of ocular microvascular complication was documented both in patients with a postsurgical total resolution of T2DM [29] and those who continued oral antidiabetic medication [24,27,28,30,32–34,38]. However, when the comparative incidences were compared to those of a matched group of medically treated T2DM patients, the incidence of new-onset DR was found to be significantly lower in the surgical group [38].

Table 1. Details of the studies included in the systematic review.

Study, Year	No of Patients (Surgical; Medical)	Type of Study	Follow-Up Period (Months)	Baseline No DR/DR	Type of Bariatric Procedure	New Onset of DR	% DR Worsening	%DR Improving	% No Change in DR Stage	Change in HbA1c (%)	Discontinuation of Oral Medication
Varadhan et al., 2012 [24]	22	retrospective	6–12	15/7	SG, RYGB	2/15 (13%)	2/7 (9%)	2/7 (9%)	16/22 (73%)	2.0% (0.3–4.2%)	No info
Miras et al., 2012 [25]	67	prospective	12–18	39/28	SG 22.6% RYGB 70.2% GB 7.1%	0/39	1/28(3.6%)	5/28 (17.8%)	61/67 (91%)	No info	No info
Abbatini et al., 2013 [26]	33	prospective	36–60	32/1	SG	0/32	0/1	0/1	33/33	−2.0%	76.9%
Thomas et al., 2014 [27]	38	retrospective	12	26/12	SG 35% RYBP 30% GB 10% BPD 25%	4/26 (15%)	3/12 (25%)	5/12 (42%)	26/38 (68%)	−1.5%	No info
Miras et al., 2015 [28]	56; 21	prospective	12	17/39 9/12	RYGB vs. med	5/17; 0/9	1/39 (2.5%) 3/12 (25%)	6/39 (15%) 1/12 (8.3%)	44/56(78%) 17/21(81%)	−3.3% +0.7%	decreased medication by 41% medication vs. increased medication by 27%
Kim et al., 2015 [29]	20	retrospective	12–46	12/8	RYGB	2/12 (16.6%)	7/8 (87.5%)	0%	11/20 (55%)	−2.4%	6(30%) remission T2DM; 3 cases experienced DR progression
Murphy et al., 2015 [30]	318	retrospective	12	218/100	RYGB 30.8% SG 65.7% DS 3.5%	38/218 (17%)	12/100 (12%)	35/100 (35%)	232/318 (73%)	−3.9%	18%
Brynskov et al., 2016 [31]	56	prospective	12	32/24	RYGB 94% SG 6%	1/32 (3%)	Any visit: 5/24 (21%) 12 mo: 3/24 (13%)	Any visit: 6/24 (25%) 12 mo: 4/24 (17%)	49/56 (87%)	−1.7%	59%
Amin et al., 2016 [32]	152	Retrospective cohort analysis	36	106/41	GB 70% RYGB 25% SG 4.6%	29/106 (27%)	5/41 (12%)	5/41 (12%)	113/152 (74%)	−0.9%	*n*/a
Moren et al., 2018 [33]	117	retrospective	16	73/44	RYGB	12/73 (12%)	7/44 (16%)	8/44 (18%)	90/117 (77%)	−1.9%	66%
Richardson et al., 2018 [34]	32 (64 eyes)	prospective	36	47/17	RYGB	9/47 (19%)	3/17 (17%)	11/17 (64%)	41/64 (64%)	*n*/a	*n*/a
Feng et al., 2019 [35]	40; 36	Retrospective controlled	12	34/6 29/7	RYGB Vs med	-	-	3/34 (8%) vs. 0%	37/40 (92%) vs. 100 36/36 (1 05)	−1.9% −0.3%	48 vs. 3%
Miras et al., 2019 [36]	24	prospective	60	*n*/a	RYGB, SG, GB	0/24	6/24 (25%)	5/24 (20.8%)	13/24 (54.2%)	−1.4%	43%

Table 1. *Cont.*

Study, Year	No of Patients (Surgical; Medical)	Type of Study	Follow-Up Period (Months)	Baseline No DR/DR	Type of Bariatric Procedure	New Onset of DR	% DR Worsening	%DR Improving	% No Change in DR Stage	Change in HbA1c (%)	Discontinuation of Oral Medication
Sever et al., 2020 [37]	21 (37 eyes) 27 (37 eyes)	Retrospective, comparative	12	PDR only	*n*/a	Increased % of complication in surgical vs. medical group: IOH, NVG, retinal vein occlusion (21.6, 16, 8 vs. 5.4, 2.7, 0)				−1.0% −0.7%	*n*/a
Akerblom et al., 2021 [38]	5321; 5321	Retrospective database analysis, comparative	54	No DR only	RYGB	188 (3.5%) 317 (5.9%)	-	-	5133 (94.3%) 5004 (94.1%)	*n*/a	*n*/a
Adam et al., 2021 [39]	26	prospective	12	21/5 (R1)	RYGB-21 (81) SG-5 (19%)	0%	0%	1(20%)	25/26 (96%)	−1.4%	*n*/a

DR: Diabetic retinopathy; HbA1c: Hemoglobin A1c; SG: sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; GB: Gastric banding; BPD: biliopancreatic derivation; DS: duodenal switch; STDR: sight-threatening DR; NPDR: non-proliferative DR; PDR: proliferative DR; IOH: intraocular hypertension; NVG: neovascular glaucoma.

Table 2. Incidence of de novo DR in screened studies: means and 95% credible intervals.

Study	Sample Size	Proportion (%)	95% CI	Weight (%)
				Random
Varadhan et al. [24]	15	13.333	1.658 to 40.460	5.75
Miras et al. [25]	39	0.000	0.000 to 9.025	7.32
Abbatini et al. [26]	32	0.000	0.000 to 10.888	7.05
Thomas et al. [27]	26	15.385	4.356 to 34.868	6.73
Miras et al. [28]	17	29.412	10.314 to 55.958	5.98
Kim et al. [29]	12	16.667	2.086 to 48.414	5.31
Murphy et al. [30]	218	17.431	12.640 to 23.131	8.60
Brynskov et al. [31]	32	3.125	0.0791 to 16.217	7.05
Amin et al. [32]	106	27.358	19.149 to 36.874	8.26
Moren et al. [33]	73	16.438	8.793 to 26.954	7.99
Richardson et al. [34]	47	19.149	9.149 to 33.260	7.55
Feng et al. [35]	34	0.000	0.000 to 10.282	7.13
Akerblom et al. [38]	5321	3.533	3.053 to 4.065	8.93
Adam et al. [39]	21	0.000	0.000 to 16.110	6.37
Total (random effects)	5993	9.818	4.784 to 16.397	100.00

Test for heterogeneity: Q: 156.56; DF: 13; $p < 0.0001$; I^2: 91.7%; Publication bias: Egger's test: 2.1131 ($p = 0.0521$); Begg's test: Kendall's Tau: −0.04420 ($p = 0.8257$).

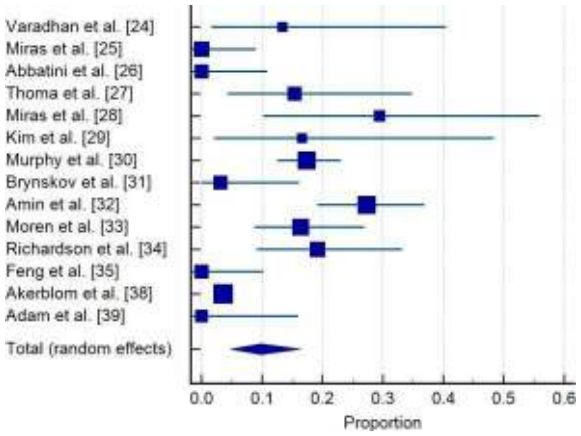

Figure 2. Incidence of de novo DR in screened studies. Forrest plot: pooled effects-random effects model [24–35,38,39].

3.3. Progression of DR after Bariatric Surgery and Clinical Correlations

The progression of DR after bariatric surgery was documented in 50 of 403 cases (12.4%). The heterogeneity among studies was substantial ($I^2 = 75.12\%$), but it was lower than the de novo incidence of DR, with Egger's ($p = 0.3979$) and Begg's ($p = 0.4263$) tests suggesting no publication bias (Table 3, Figure 3).

Table 3. Progression of DR in patients with DR at baseline: means and 95% credible intervals.

Study	Sample Size	Proportion (%)	95% CI	Weight (%)
				Random
Varadhan et al. [24]	7	28.571	3.669 to 70.958	4.93
Miras et al. [25]	28	3.571	0.0904 to 18.348	7.86
Abbatini et al. [26]	1	0.000	0.000 to 97.500	1.94
Thomas et al. [27]	12	25.000	5.486 to 57.186	6.14
Miras et al. [28]	39	2.564	0.0649 to 13.476	8.38
Kim et al. [29]	8	87.500	47.349 to 99.684	5.23
Murphy et al. [30]	100	12.000	6.357 to 20.024	9.37
Brynskov et al. [31]	24	20.833	7.132 to 42.151	7.58

Table 3. *Cont.*

Study	Sample Size	Proportion (%)	95% CI	Weight (%)	
				Random	
Amin et al. [32]	41	12.195	4.081 to 26.204	8.45	
Moren et al. [33]	44	15.909	6.644 to 30.065	8.55	
Richardson et al. [34]	17	17.647	3.799 to 43.432	6.90	
Feng et al. [35]	6	0.000	0.000 to 45.926	4.59	
Miras et al. [36]	24	25.000	9.773 to 46.711	7.58	
Sever et al. [37]	37	45.946	29.487 to 63.078	9.31	8.30
Adam et al. [39]	5	0.000	0.000 to 52.182	1.47	4.20
Total (random effects)	393	19.231	11.554 to 28.315	100.00	100.00

Test for heterogeneity: Q: 56.267; DF: 14; $p < 0.0001$); I^2: 75.12% (95% CI: 58.82 to 84.97); Publication bias: Egger's test: 1.1090 ($p = 0.3979$); Begg's test: Kendall's Tau: 0.1531 ($p = 0.4263$).

Progression was detected in any stage of DR. Some authors associated advanced stages with a higher risk of progression [30], but this finding was not supported by others [29]. Kim et al. [29] found that the duration of diabetes, preexistent DR and albuminuria were risk factors for DR progression following bariatric surgery. Murphy et al. [30] found a direct correlation between initial reduction in HbA1c from pre-operative to first post-operative values and worsening of diabetic retinopathy.

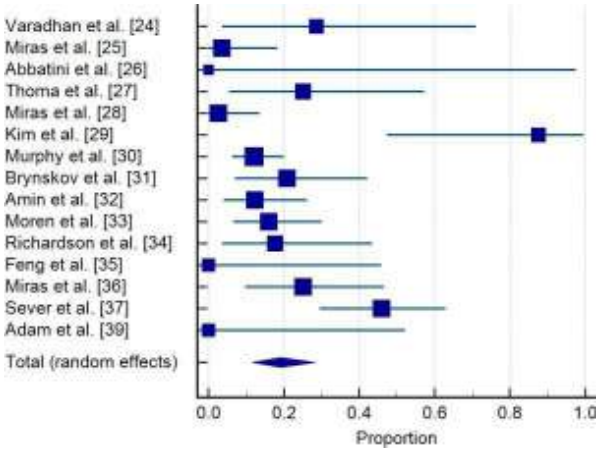

Figure 3. Progression of DR in patients with DR at baseline. Forrest plot: pooled effects–random effects model [24–37,39].

3.4. Regression of DR

The reviewed clinical studies documented a percentage of cases who experienced regression of DR following bariatric surgery, varying from 0 to 64% of patients with any stage of DR at baseline, with substantial heterogeneity (I^2: 76.88%) (Table 4, Figure 4).

Table 4. Regression of DR in patients with DR at baseline: means and 95% credible intervals.

Study	Sample Size	Proportion (%)	95% CI	Weight (%)
				Random
Varadhan et al. [24]	7	28.571	3.669 to 70.958	5.04
Miras et al. [25]	28	17.857	6.064 to 36.893	7.81
Abbatini et al. [26]	1	0.000	0.000 to 97.500	2.04
Thomas et al. [27]	12	41.667	15.165 to 72.333	6.21
Miras et al. [28]	39	15.385	5.862 to 30.528	8.29
Kim et al. [29]	8	0.000	0.000 to 36.942	5.33
Murphy et al. [30]	100	35.000	25.729 to 45.185	9.19
Brynskov et al. [31]	24	25.000	9.773 to 46.711	7.56

Table 4. *Cont.*

Study	Sample Size	Proportion (%)	95% CI	Weight (%)
				Random
Amin et al. [32]	41	12.195	4.081 to 26.204	8.36
Moren et al. [33]	44	18.182	8.192 to 32.714	8.44
Richardson et al. [34]	17	64.706	38.328 to 85.790	6.92
Feng et al. [35]	6	50.000	11.812 to 88.188	4.71
Miras et al. [36]	24	20.833	7.132 to 42.151	7.56
Sever et al. [37]	37	0.000	0.000 to 9.489	8.22
Adam et al. [39]	5	20.000	0.505 to 71.642	4.33
Total (random effects)	393	22.568	14.040 to 32.441	100.00

Test for heterogeneity: Q: 60.5611; DF: 14; $p < 0.0001$); I^2: 76.88%; Publication bias: Egger's test: 0.097 ($p = 0.9439$); Begg's test: Kendall's Tau: 0.1723 ($p = 0.3708$).

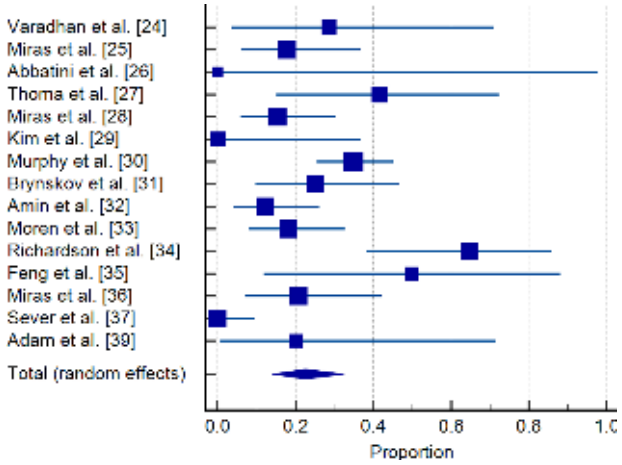

Figure 4. Regression of DR in patients with DR at baseline. Forrest plot: pooled effects–random effects model [24–37,39].

In the reviewed articles, a total of 90 of 403 cases (22.3%) were documented There was no information to indicate if this positive effect could be attributed to surgery or an additional ophthalmologic therapy (laser, anti-VEGF, surgery). The improvement could be correlated with T2DM remission in the postoperative period, but also with the positive effect of bariatric surgery on other recognized risk factors for DR progression, such as hypertension and dyslipidemia.

3.5. The Impact of Bariatric Surgery upon Systolic Blood Pressure (SBP), Cholesterol and Serum Triglycerides (TG)

Hypertension and altered lipidic metabolism are recognized to be a risk factors for DR onset and progression, so to better document the impact of bariatric surgery on the evolution of DR in patients with T2DM, we analyzed the available data in the studies regarding the impact of bariatric surgery on blood pressure (BP), cholesterol, and triglycerides (Table 5).

When analyzing the impact of bariatric surgery upon systolic blood pressure BP, most authors found a significant decrease of systolic BP in the follow-up period [28,36,39] and a reduced necessity of antihypertensive medications [26,35].

All authors found a significant decrease in TG and an increase of HDL-C levels, following bariatric procedures, but with no statistically significant change in LDL-C levels [35,36,39].

Abbatini et al. [26] found a significant decrease of patients with hypertension and dyslipidemia in the study group, after a 60 months follow-up period. In the study of Thomas et al. [27], there was no information on postoperative blood pressure. However,

there was a significantly higher preoperative BP mean value in the subgroup that experienced progression of DR, compared to "no change" and regression subgroups (180.3 mmHg, vs. 141.4 and 130.5, respectively). Kim et al. [29] also found an increased percentage of patients with hypertension in the group that presented progression of DR after surgery compared to the non-progression group (55 vs. 18.2%). However, this finding was not statistically significant when included in a multivariate analysis.

Table 5. The impact of bariatric surgery upon BP, LDL-C, HDL-C, and TG.

Study	Preop SBP Mean ± DS (mmHg)	Postop SBP (Mean ± DS), *p*-Value	Preop Cholesterol (mg/dL)	Postop Cholesterol (mg/dL), *p* Value	Preop TG	Postop TG, *p* Value
Abbatini et al., 2013 [26]	-	% patients with hypertension decreased from 54.5% to 15.1%	-	% patients with hypercholesterolemia decreased from 21 to 9%	-	% patients with hyperTG decreased from 18 to 9%
Thomas et al., 2014 [27]	DR progression: 180.3 ± 32.8 DR no change: 141.4 ± 17.0 DR regression: 130.5 ± 27.6	No info	181.7 (38.7)	166.3 ($p = 0.36$)	No info	No info
Miras et al., 2015 [28]	143 ±	130 ± 3 ($p < 0.001$)	No info	No info	No info	No info
Feng et al., 2019 [35]	134.0 ± 3.6	123.1 ± 2.9 ($p < 0.05$) complete remission in 14/24 (58%)	± 193.35 ± 7.73	154.68 7.73, $p < 0.001$	± 265.7 ± 35.43	97.43 8.857 $p < 0.001$
Miras et al., 2019 [36]	142 (103–195)	128 (104–196) $p < 0.0001$	Total C: 181.75 HDL-C: 42.54 LDL-C: 100.54	Total C: 170.15, $p = 0.21$ HDL-C: 54.14, $p < 0.0001$ LDL-C: 88.94, $p = 0.16$	159.43 (53.14–655.4)	115.15 (35.43–389.7), $p < 0.0001$
Adam et al., 2021 [39]	134 ± 15	119 15, $p < 0.001$	Total C: 144 ± 28.6 HDL-C: 33.2 (29.7–39.0) LDL-C: 81.9 ± 23.9	Total C: 162 ± 36.7, $p = 0.035$ HDL-C: 44.0 (38.6–50.6), $p < 0.001$ LDL-C: 93.8 ± 35.1, $p = 0.38$	134 (81.4–165)	100 (77.0–132), $p = 0.071$

SBP: systolic blood pressure; total C: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG and Cholesterol values converted from mmol/L.

4. Discussion

Bariatric surgery may influence the outcome of DR by multiple pathways. Achieving a target glycemic control, hypotriglyceridemia-increased insulin secretion, decreased insulin resistance, decreased inflammation and oxidative stress related to fatty tissue [40–45], and decreased blood pressure, are all well-documented factors that prevent the worsening of DR. Murphy et al. [30] and Brynskov et al. [31] raised awareness about the importance of the preoperative glycemic control to prevent a sudden decrease of HbA1c, which could be a factor for the early worsening of DR. As a consequence, DR screening for at least 5 years after bariatric surgery should be continued, particularly among those who achieved large reductions in HbA1c, as this may signal a higher risk of worsening in subsequent diabetic retinopathy screens [30]. However, in long-term follow-up, Chang et al. [46] found no differences between pre and post-surgery HbA1c in the progression vs. non-progression group. Moreover, though there is evidence that RYGB induces an earlier and

more important decrease in HbA1c, Amin et al. [32], could not find a significantly higher risk for DR progression in a comparative study of bariatric procedures.

Several large retrospective studies [46–49] investigated the long-term risk of microvascular complications in T2DM patients after bariatric surgery compared to medical treatment, and found a significant decrease in microvascular events: a reduced cumulative incidence of DR by 45% [47], a decreased incidence of STDR by 42% [46] and a lower risk of blindness and need for laser or ocular surgery [48] compared to medical treatment. Moreover, Carlsson et al. [49] found that those who achieved remission after surgery had a significantly lower incidence of microvascular events compared with those who were not in remission after 15 years (8.0 versus 25.2 events per 1000 person-years). Amin et al. [32] found a lower progression to STDR or maculopathy in patients with T2DM following bariatric surgery compared to routine care. All this clinical evidence reflects the beneficial metabolic effects of bariatric surgery [32].

On the other hand, Schauer [50] and Chang [51] found no significant differences in changes to the DR score in the follow-up period. One explanation may be the limited number of patients included in the study group.

Only one study analyzed the outcomes of bariatric surgery in a group of patients with proliferative DR baseline [37] and found an increased risk of complications, such as intraocular hypertension, neovascular glaucoma, and retinal vein thrombosis in surgical vs. medically treated matched patients. However, the authors acknowledged that the patients that underwent bariatric surgery missed their ophthalmological check-ups within the first 3 months, thus having a lower number of intravitreal anti-VEGF injections compared to the medically treated group. Whether this finding could be a contributor to increased complications should be analyzed in further studies.

In the present review, we found that, in most cases, DR remained stable after bariatric procedures. We also found a progression of retinal lesions in 12.4% of cases and regression in 22.3%. In 4.8% of cases with no retinopathy at baseline, retinal microvascular changes appeared after bariatric surgery, despite achieving a target glycemic control.

There are some limitations to the present review: the small number and the substantial heterogeneity of the studies, the lack of information about different methods to assess DR, the different treatments proposed in cases of severe DR either before or after bariatric surgery, and other important factors known to influence RD status, such as smoking, drug use, physical activity and nutrition. Moreover, the probable direct influence on DR of pre-surgical global management (physical activity, nutrition, motivational interviewing regular and frequent follow up by several health professionals) generally went from 6 to 12 months before the surgery procedure. In a long-term follow-up, other factors could influence the outcome more.

However, clinicians should be aware that there is a change of progression, despite even T2DM remission after surgery. The mechanisms involved are still a subject of research. Complex hormonal and metabolic changes following bariatric surgery may be responsible for the rapid improvement of glycemic control even before weight loss is achieved, and may be a cause for the early worsening of DR. Other factors for DR progression may involve vitamin and microelement deficiencies (A, D, B12, copper, and folate) which are secondary to malnutrition or the discontinuation of oral antidiabetic medication associated with a protective role for retinal damage, such as fenofibrate or angiotensin receptor blockers (ARBs) [36,52–55].

4.1. Gut Hormones and Metabolic Changes after Bariatric Surgery Procedures

Bariatric surgery nowadays offers a different therapeutic approach to T2DM associated with obesity. The intrinsic mechanisms responsible for diabetes resolution are still a subject of research. Several studies revealed a 25–47% early remission of diabetes after gastric restrictive procedures, up to 45–90% after Roux-en-Y anastomosis [37,49,56,57] and up to 95% following biliopancreatic derivation [49].

Weight loss is associated with negative energy balance and decreased tissular insulin resistance. On the other hand, the decrease in the amount of fat tissue reduces oxidative stress and chronic inflammation associated with lipotoxicity, including fatty acids and chemokines secreted by adipocytes [45,58].

The bariatric procedures may be classified according to the mechanism of weight loss in gastric restrictive and intestinal by-pass procedures. The gastric restrictive procedure uses approaches, such as a gastric sleeve or laparoscopic adjustable gastric banding [5] to reduce gastric volume, induce early satiety, and reduce caloric intake [59]. Moreover, removal of the gastric fundus decreases the level of ghrelin, thereby causing decreased hunger [59,60].

Intestinal bypass procedures, such as Roux-en-Y gastric bypass and biliopancreatic diversion have a deep impact on gastrointestinal physiology. By shortening the small intestine and altering the alimentary pathway in the digestive tract, they reduce the gastric reservoir and cause the selective malabsorption of fats and other nutrients [5,61,62]. The associated dumping syndrome is expected to limit patients' consumption of triggering food, such as those high in sugars.

The gastrointestinal tract has a complex role in metabolic regulation. The hindgut theory formulated by Cumming et al. [46] is based on the fact that the rapid delivery of incompletely digested food to the lower intestinal tract is triggers the secretion of incretins, such as gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), thus increasing the secretion of glucose-dependent insulin, suppressing glucagon, and inducing satiety. Peptide YY, normally secreted in the distal small bowel and responsible for satiety in response to food intake, is expressed earlier and at higher levels, especially in intestinal bypass procedures [63].

Rubino et al. formulated in 2002 the foregut hypothesis, showing that bypassing a short segment of the proximal intestine directly ameliorates type 2 diabetes, independently of the effects on food intake, body weight, malabsorption, or nutrient delivery to the hindgut [64]. In this way, a dysfunctional signal released by nutrient contact with the proximal duodenum, including the release of "anti-incretins" that lead to insulin resistance and T2DM, is inhibited [64,65].

Intestinal bypass procedures act aggressively on lowering blood sugar, even from the first week before weight loss occurs, via postprandial GLP-1-mediated insulin secretion. Recent studies found that GLP-1 acts on multiple levels, by decreasing hepatic glucose synthesis and regulating food intake by synergistic actions at the brain and gut levels [66,67]. Gastric restrictive procedures are considered to have a milder effect on glucose metabolism [68–70]. However, no study included in the review found significant differences between the type of surgery and risk for DR progression in a 12-month or longer follow-up.

4.2. *The Paradoxical Effect of Glucose-Lowering Therapy on Diabetic Retinopathy*

The retina is one of the most metabolically active tissues in the body because neural–retinal energy is exclusively represented by glucose [71]. The severity of DR at baseline is associated with decreased autoregulation in retinal microcirculation and increased vulnerability to osmotic or nutrient concentration changes [72]. Early worsening of DR was first documented in a Diabetes Control and Complications Trial (DCCT) with intensive glycemic lowering therapy [20]. Afterwards, clinical evidence was observed with the beginning of insulin therapy and GLP-1 analogs [73–75]. Similar concerns were also raised regarding bariatric surgery.

The biochemical mechanism by which hypoglycemia and high insulin levels can induce retinal damage is not completely understood [76,77]. A decreased level of blood sugar triggers osmotic changes that favor leakage and retinal edema from previously damaged capillaries. Low levels of oxygen and glucose are potential triggers for VEGF retinal production [22].

Experimental studies in vitro showed a synergistic interaction between insulin and VEGF on blood vessels on endothelial bovine cells, a disruption of the blood–retinal barrier, increased ROS [78], and expression of hypoxia-inducible factor (HIF-1) ion diabetic rats following intensive insulin therapy [22,79] with subsequent inflammation and neovascularization.

4.3. DR Phenotypes and Risk for Progression

Classically, HbA1c was considered a powerful clinical tool for predicting the progression of diabetic retinopathy [80,81]. However, clinical observations showed that there are patients who maintain good vision despite poor glycemic control, and vice-versa. Recent research characterized 3 DR phenotypes associated with different dominant retinal alterations and different risks of progression to vision-threatening complications [82]. Microaneurysm turnover was defined as the number of new microaneurysms and vanished microaneurysms over a preset period of 6 months as evaluated by fundus photography with or without retinal angiography. Microaneurysm (MA) turnover and macular thickness measured by optical coherence tomography may be considered organ-specific markers for predicting the long-term outcomes and maybe suggesting the predominance of a different pathogenic mechanism. Cunha-Vaz et al. [83,84] defined phenotype A, with a MA turnover of <6 and normal retinal thickness, characterized by apoptosis, vessel regression, and loss of pericytes, with limited progression over time. Phenotype B was characterized by MA turnover <6 but associated with an increased retinal thickness measured by OCT, which should suggest a predominant role of blood–retinal barrier disruption and inflammation. Phenotype C, associated with a MA turnover > 6 and variable retinal thickness, was characterized as having a higher risk for visual impairment due to ischemia and angiogenesis. Further clinical validation of these different phenotypes may lead to the development of targeted treatments and personalized approaches in the management of DR [83–85].

5. Conclusions

Although diabetic retinopathy in most cases is stable after bariatric surgery, there is still little information about the prediction of DR outcomes in individuals in remission, cured or with T2DM. The careful preoperative preparation of HbA1c, blood pressure, and lipidemia should be provided to minimize the expectation of DR worsening. Ophthalmologic postoperative follow-ups should be continued regularly, despite diabetic remission for early detection and treatment of possible diabetic retinopathy progression. Further randomized trials are needed to better understand the organ-specific risk factors for progression and provide adequate personalized counseling to the T2DM patients that are planned to have bariatric surgery.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10163736/s1.

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I. Lucrări relevante

8. Șerban D, Papanaș N, Dascălu AM, Kempler P, Raz I, Rizvi AA, Rizzo M, Tudor C, Silviu Tudosie M, Tănăsescu D, Pantea Stoian A, Gouveri E, **Costea OD**. Significance of Neutrophil to Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) in Diabetic Foot Ulcer and Potential New Therapeutic Targets. *The International Journal of Lower Extremity Wounds* 2021, 18, 15347346211057742. doi: 10.1177/15347346211057742. Epub ahead of print. PMID: 34791913. (IF din 2021/2022=1.922).

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Significance of Neutrophil to Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) in Diabetic Foot Ulcer and Potential New Therapeutic Targets

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Abstract

Diabetic foot ulcer (DFU) is a well-known complication of diabetes and a significant burden on the national health systems. The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio are inexpensive and easily accessible biomarkers that have proved to be useful in several inflammatory, infectious and cardiovascular diseases. We carried out a comprehensive review examining the association of NLR and PLR with the onset and progression of DFU. PLR and NLR were signi ficantly increased in patients with DFU, compared with a control group of T2DM patients without DFU, and correlate well with DFU severity, evaluated by Wagner and IWGDF grading scales. In patients with diabetic foot infections (DFI), elevated NLR and PLR were correlated with osteomyelitis, increased risk of amputation, and septic complications. The significance of the elevated value of these biomarkers in DFU is related to chronic hyperglycemia and low-grade systemic inflammation, atherosclerotic and vascular complications, and also the associated septic factor. Serial, dynamic follow-up can provide useful information in planning and monitoring DFU treatment, as well as in risk stratification of these vulnerable patients. Further randomized studies are needed to set the cut-off values with clinical significance.

Keywords

diabetic foot ulcer, neutrophil-to-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), diabetes, inflammation

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Diabetic foot (DF) is a well-known complication of DM and an important cause of morbidity in individuals with diabetes.[1] It is estimated that at least one limb is lost due to diabetic foot ulcer (DFU) somewhere in the world every 20 to 30 s, and this condition accounts for over 50% of non-traumatic amputations.[2,3] The annual incidence of DFU is estimated at 1 to 4% and its prevalence at 5 to 10%.[4,5] Many cases of DFU are complicated by infection, which leads to adverse clinical outcomes, deeply impacting the quality of life.[6] Of note, DFUs are also associated with a 5-year mortality rate of approximately 40%.[7] The main pathological factors involved in the onset and progression of the diabetic foot are diabetic neuropathy and peripheral arterial disease. Micro and macrovascular changes share common mechanisms and progress simultaneously as a continuum.[8,9] Oxidative stress, low-grade inflammation, atherosclerosis, and chronic hypoxia lead to an increased vulnerability to trauma and infections, resulting in chronic, non-healing ulcers.

The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are inexpensive and accessible inflammatory biomarkers, easily calculated from the complete blood count (CBC), fast responding to stress and inflammation with high sensitivity and low specificity, which has proved to be useful in several inflammatories, infectious and cardiovascular diseases.[10] PLR and NLR correlate well with metabolic syndrome and the severity of metabolic perturbations in T2DM.[11,12] Moreover, Duman et al found that NLR is a reliable measure of glycemic control in addition to HbA_{1c} in subjects with T2DM[13]. More recently, platelet to lymphocyte ratio (PLR) has been posited as a potential biomarker, revealing shifts in platelet and lymphocyte counts due to acute inflammatory and prothrombotic states in rheumatologic, cardiovascular, and neoplastic diseases.[14–16]

Therefore, we carried out a comprehensive review on PubMed, Web of Science, Science direct databases examining the clinical evidence regarding the significance of NLR and PLR with the onset and progression of DFUs. The terms "diabetic foot" OR" diabetic ulcer" and "neutrophil-lymphocyte ratio" OR/AND "platelet lymphocyte ratio" and their combinations were used. All original, English-language studies regarding the neutrophil-lymphocyte ratio (NLR) and/or platelet lymphocyte ratio (PLR) in patients with DFU were included in the initial search. For potentially relevant records, full-text articles were obtained.

Due to the known association of NLR with other conditions, the following exclusion criteria were used about the studies: age less than 18 years, pregnancy, malignancy, autoimmune disorder, underlying hematological disease, glucocorticoid use, other active infections, and previous antibiotic use.

Clinical Studies Evaluating the Role of NLR and PLR in Patients with Diabetic Foot

After duplicates removal and applying of the exclusion criteria, a total of 14 studies were identified. Among these, 4 studies evaluated both the significance of NLR and PLR, while 8 evaluated only NLR and 2 only PLR. The ensuing comments are based on the analysis of 2066 patients with diabetic foot of variable severity according to Wagner classification, enrolled in 10 clinical studies evaluating NLR, presented in Table 1 and on 1701 patients with DFU enrolled in 6 clinical studies evaluating PLR presented in Table 2.

Most studies were retrospective and non-randomized.[17,18,20,21,23,24,28] The retrospective nature of these studies may be a source of bias related to difficulties in the documentation of the exact size and depths of wounds, potentially impacting the outcomes and conclusions. There were only 2 comparative prospective studies, one testing NLR,[22] and one for PLR.[29] Studies analyzed in the present review were comparable in terms of patient selection and methodology, however, frequencies of severe DFU and outcomes measured differed.

PLR and NLR Correlations with DFU

PLR and NLR were significantly increased in patients with DFU, compared with a control group of T2DM patients without DFU, and correlate well with DFU severity, evaluated by Wagner and IWGDF grading scales.[17,18,27,29] Higher values of NLR were found to be an independent factor for wound non-healing [17] and major amputation.[19,21,24,26,27]

Zhang et al showed that PLR, along with smoking status, and HbA_{1c} were independent risk factors for DFU in T2DM patients (all $p < .05$).[29] Increased PLR is an expression of both chronic inflammation and prothrombotic state encountered in diabetic patients, and is considered to have more clinical significance and prognostic value than the 2 factors taken separately. While Zhang et al found an increased platelet count in patients with DFU, Mineoka et al found that higher PLR values in the DFU group are due to decreased lymphocyte counts among the study groups, while the platelet count was similar in the DFU group and non-DFU group.[27,30]

NLR and PLR in Diabetic Foot Infections (DFI)

In patients with diabetic foot infections (DFI), elevated NLR and PLR were correlated with osteomyelitis, increased risk of amputation and septic complications.[14,17,19–22,26] The association between NLR and outcome of DFI was examined by Yapici et al in a randomized prospective study on a group of 75 patients who were managed with amputation,

Table 1. Studies Evaluating NLR in Patients with DFU.

Study, country, year	Type	No of patients, type	NLR cut-off value	Mean NLR value	Associated correlations of NLR	Endpoints
Chen W,[17] 2021	non-randomized, retrospective,	348, DFU Wagner 2 to 5, who underwent amputation	postop NLR 2.76 sensitivity of 69.2% and specificity of 62.6%	3.21 ± 2.59 (postoperative values)	age, FBG, WBC, duration of diabetes, Wagner grade	survival in (1,2, 5 years) low NLR: 96.8%, 84%, 80.1% high NLR: 85.2%,58.6% and 23.9%
Eren MA,[18] 2019	non-randomized, retrospective, 2016 to 2017	78 DFI patients 18 (Wagner 2 group) 44 (Wagner 3 group) 16 (Wagner 4 group)	no info	2.8 ± 0.9 (Wagner 2 group) 6.0 ± 5.2 (Wagner 3 group) 6.9 ± 5.3 (Wagner 4 group)	Wagner's grade	hospital stays and costs: no correlation to NLR
Demirdal T[19] 2018	non-randomized, prospective, 2010 to 2016	280 patients with DFI (diabetic foot infection)	>6.5 for arterial disease (53.3 sensitivity; 63% specificity) >8.2 for amputation (53.2 sensitivity; 77.1 specificity)	11.2 ± 9.4 in amputation group (higher in major amputation group) 6 ± 3.4 in debridement/ drainage group	no info	predicting peripheral arterial disease, and need for amputation in DFI Significant higher in amputation
Ong E,[20] 2017	non-randomized, retrospective, 2013 to 2014	379 patients with DFU	elevated WBC and NLR>3.5 (sensitivity 52.5% and specificity 91.7% for DFI)	3.51 ± 2.42 non-infected ulcer 5.49 ± 5.56 infected ulcer without osteomyelitis 7.59 ± 8.19 DFU and osteomyelitis	WBC, ESR	The severity of infection in DFI NLR correlates with osteomyelitis
Metineren H,[21] 2017	non-randomized, retrospective, 2012 to 2016	56 patients, DFU with gangrene who underwent amputation and amputation	no info	preop NLR survivors: 7.15 postop NLR survivors: 3.5 preop NLR deceased: 8.65 postop NLR deceased: 7.55	CRP	prognosis of mortality in septic DFU: CRP – significant; NLR - not significant both CRP and DFU decreased significantly postoperatively in patients that survived
Yapici O,[22] 2017	prospective, comparative, 2012 to 2015	75 patients with DFI	no info	6.0 ± 2.8 no-surgery group 9.980 ± 5.6 debridement/ drainage group	ESR, CRP	NLR good correlation with osteomyelitis and amputation risk

(continued)

Table 1. (continued)

Study, country, year	Type	No of patients, type	NLR cut-off value	Mean NLR value	Associated correlations of NLR	Endpoints
				15.7 ± 10.3 amputation group		
Vatankhah N,[23] 2016	non-randomized, retrospective, 2011 to 2014	101 patients with DFU	4.19 (sensitivity 0.63, specificity 0.71)	not info	no info	high NLR independent factor for predicting wound non-healing
Gocer H,[24] 2017	non-randomized, retrospective, 2006 to 2012	258 DFU admitted for amputations	not calculated	9.2 (0.9-36) – deaths within 6 months 5.5 (1.3-17.1)- deaths within 6 months -1 year 6.3 (2.9-15.5)- deaths within 1 to 3 years 5.6 (0.0-29.2) survivors	PLR	high preoperative NLR predictor for amputation and risk of wound complications, reamputation, and mortality
Kahraman C,[25] 2014	randomized, retrospective	32 T2 DM without DFU	no info	1.6 ± 0.7 (T2DM without DFU)	Age, serum urea, creatinine, WBC, neutrophil %, lymphocyte % (inversely), total cholesterol	NLR risk factor for DFU in T2DM
		32 T2 DM with DFU		4.3 ± 3.9 (T2DM with DFU)		
Altay FA,[26] 2019	a non-randomized, 5-year prospective study	136 T2 DM with DFI	no info	Wagner severe versus mild grade: 6.7 versus 4.2 PEDIS severe versus mild grade: 6.3 versus 3.6 amputation versus no amputation: 9.2 versus 4.1 vascular interventions: 12.6 versus 4.6	no info	NLR correlates with severity of DFI, the risk for amputation, need for long term hospitalization, aggressive treatment
Arican G,[27] 2020	non-randomized, retrospective	250 patients with DFU	<4.3 – complete healing >6.73 – major amputation	8.7 ± 2.2 major amputation 3.5 ± 1.3 minor amputation 4.1 ± 2.6 chronic wound 2.4 ± 2.1 complete healing	no info	high NLR – predictive for major amputation; NLR useful for DFU management
Aragon Sanchez J,[28] 2021	non-randomized, retrospective	245 patients with DFI	> 4.52 – severe infections	3.0 (1.8- 4.8) moderate infections	ESR > 94 mm/h	High NLR predictive for severe infections; higher rate of

(continued)

Table 1. (continued)

Study, country, year	Type	No of patients, type	NLR cut-off value	Mean NLR value	Associated correlations of NLR	Endpoints
				5.0 (2.2- 8.3) severe infections	albumin < 2.8 g/dl	amputations and recurrences, longer duration of antibiotic treatment and longer hospital stays

debridement/drainage, or no surgical intervention.[22] He found that higher NLR was observed in patients with osteomyelitis (12.3 ± 8.6) and those requiring amputation (mean 15.7, p = .001), versus debridement only (9.9) or conservative approach (6.0).[22]

Regarding the correlation of NLR and PLR with hospital stay and costs, the results differ among the reviewed studies. Altay et al found that NLR was correlated with duration of both intravenous antibiotic treatment (r = .374; p = .005) and hospitalization (r = .337; p = .02).[26] However, Eren et al found NLR was not correlated with duration and cost of hospitalization, while PLR was significantly associated with increased hospital expenses[18]. A recent study of Aragón- Sánchez et al, on 245 patients with DFI, found a significant correlation between NLR and the severity of infection, with a risk of amputation, and duration of hospitalization, while PLR was not significantly correlated with the severity of septic process.[28]

NLR and PLR as Prognostic Factors for Short and Mid-Term Mortality

When NLR was tested as a prognostic factor of mortality in DFI patients who underwent amputation, Chen et al found that a postoperative cut-off value of 2.76 can predict a higher short and middle-term mortality, while Metineren et al found no significant effect.[17,21] Importantly, Metirenen et al found that post-operative NLR was significantly decreased in surviving patients.[21] Gocer et al found that the preoperative value of NLR was significantly higher in patients with DFI who underwent amputation who died within 6 months (mean value 9.2), but did not differ between survivors and those who died within 1 to 3 years. PLR value was insignificantly higher in patients who did not survive.[24]

One aspect that should be taken into account is that patients with diabetic feet have usually more extensive micro and macrovascular changes, including cardiovascular disease. NLR was associated with an increased risk of cardiovascular events, and a biomarker for multivessel disease, coronary calcification, and atherosclerosis.[31,32] Circulating aggregates formed by platelets and neutrophils play an important role in acute thrombosis of the atherosclerotic plaque.[33] CRP, interleukin-6, and interleukin-1 receptor antagonists were strongly related to accumulations of neutrophils and neutrophil-platelet aggregates in peripheral blood in patients with unstable angina.[32] Several studies showed that high NLR values are linked with increased mortality in patients with cardiovascular surgery.[34,35] In several clinical studies, a value of NLR of more than 5 to 5.25 is a strong predictor for short term mortality in patients who underwent amputation with chronic limb ischemia and may be useful to select a subgroup of patients at risk of acute cardiovascular events, who should be managed more carefully, aiming more aggressively to control the other risk factors.[36–39]

All studies reported their outcomes concerning a "cut-off" value of NLR and PLR calculated on the partici- pants included in the study groups. Although outcomes lead to similar conclusions, the cut-off values show wide variation. One explanation was the different outcomes followed by the researchers and the different criteria of selection applied.

On the other hand, even though a large number of papers have been published regarding NLP and PLR in various infectious and non-infectious pathologies, there are still no universally accepted normal values for the 2 parameters.

NLR and PLR Values in the Healthy Adult Population

There are few studies published to document the normal values of NLR and PLR in the healthy adult population. Forget et al found that in an adult, non-geriatric, the population in good health NLR varies between 0.78 and 3.53.[40]. In a cohort of 10255 healthy Iranian subjects aged 35 to 70 years, Moozasadeh et al found a mean NLR value of 1.70 ± 0.70, and a mean PLR value of 117.05 ± 47.73, which were significantly higher in females than males.[41] Alexander et al found a mean value for NLR was 2.8 (reference range, 1.2−4.4), PLR was 137 (reference range, 75−199) in a healthy Nigerian population[41]. In a study on 8711 participants, Fest et al found a mean NLR value of 1.76 (0.83−3.92), and for PLR of 120 (61−239).[43]

Table 2. Studies Evaluating PLR in Patients with DFU.

Study, country, year	Type of study, period	No of patients, type	PLR cut-off value/ mean value	Mean PLR values	Associated correlations of PLR	Measured Outcomes with statistical significances ($p < 0.05$)
Chen W,[17] 2021	non-randomized, retrospective	348 T2 DM with DFU undergoing amputation	postop PLR 160.05 (sensitivity of 73.1% and specificity of 47%)	189.96 ± 87.10 (postoperative values)	Wagner grade fibrinogen,	survival in 1,2, 5 years: low PLR: 95.7%, 83.9% and 74.8% high PLR ratio: 88.6%, 64.5% and 47.6%
Eren MA,[18] 2019	non-randomized, retrospective, 2016 to 2017	78 DFI patients 18 (Wagner 2 group) 44 (Wagner 3 group) 16 (Wagner 4 group)	No info	140.8 ± 42.6 (Wagner 2 group) 185.7 ± 90.2 (Wagner 3 group) 222.1 ± 95.5 (Wagner 4 group)	Wagner grade	prediction of length and cost of hospital stay in patients with DFI both length and cost of stay were positively correlated with PLT count; cost of stay correlates with PLR
Demirdal T,[19] 2018	non-randomized, prospective, 2010 to 2016	280 patients with DM and DFI (96.4% T2DM)	187.3 (67.9% sensitivity; 59.1% specificity in predicting osteomyelitis			predicting peripheral arterial disease, peripheral neuropathy, osteomyelitis
			337.8 [35.8 sensitivity and 89.8% specificity for amputation]	310.9 ± 200.9 in the amputation group 232.5 ± 86.2 in debridement/ drainage group		predicting the need for amputation in DFI
Mineoka Y,[27] 2019	non-randomized, prospective, 2012 to 2014	295 [IWGDF group 0] 141 [IWGDF group 1 to 3] 17 [DFU group]	not calculated	107 ± 31 [IWGDF group 0] 117 ± 40 [IWGDF group 1 to 3] 148 ± 65 [DFU group]	duration of diabetes, TG	correlation with DF severity [IWGDF] and DFU risk
Zhang K,[29] 2021	randomized, prospective, 2018 to 2019	104 [DFU group] 102 [T2DM only group] 90 [healthy controls]	147.6 [sensitivity 65.4%; specificity 80.4%]	DFU: 171.19 ± 60.73 T2DM: 119.35 ± 33.84 HC: 99.98 ± 20.36 [$p < .05$]	PLR useful for prediction of: 94. DFU in T2DM patients; 95. severity of DFU [Wagner classification]	
Gocer H,[30] 2017	non-randomized, retrospective, 2006 to 2012	258 DFU admitted for amputations	not calculated	247.7 [12.6 to 776.9]- deaths within 6 months 222.3 [55.9 to 677.1] – deaths 6 months-1 year 229.4 [129.8 to 816.9] – deaths 1 to 3 years 195.0 [0.8 to 1185.2] - survivors	NLR	high preoperative PLR correlates with mortality, but not statistically significant

Azab et al's study in 2014 reported the mean NLR value of 2.15, among 9427 samples in the "U.S. National Health and Nutrition Examination Survey".[44] In Lee et al's study, the mean value was 1.65 for NLR and 132.4 for PLR and in Kweon et al study, was 1.53 for NLR and 121.07 for PLR.[45,46] Age, sex, and race distribution in the subjects enrolled in the study groups may have impacted the final results.[41] Trtica Majnarićet al described a different age-related dynamic of NLR in men versus women.[47] Premenopausal women have higher values of NLR than men, possibly due to estrogen-related neutrophilia. After 50 years of age, a significant drop in NLR values occurs in women.[47,48] Howard et al found that multiple other demographic and lifestyle factors may impact the value of NLR, such as body mass index, physical activity, smoking history, and alcohol consumption.[49]

Prognostic Value of NLR and PLR in Patients with Diabetic Mellitus

Changes in total blood count were signaled to be associated with micro and macrovascular changes in patients with diabetes mellitus.[50] However, NLR is less influenced by physiological processes like dehydration or physical exercise and is expected to better characterize the pathological changes.[31,47]

Low-grade inflammation was suggested to be a link between obesity, metabolic syndrome, and diabetes.[51–53] Both PLR and PLR were correlated with insulin resistance and pro-inflammatory status.[54–56] Constant hypersecretion of cytokines such as CRP, IL-6, TNF-α, and MCP-1, induces a chronic elevated neutrophilic granulocyte count.[57–59]

There is well-documented clinical evidence that NLR and PLR are increased in metabolic syndrome when compared to healthy subjects.[60,61] Surendar et al found a significant statistical correlation between NLR and each component of metabolic syndrome: hyperglycemia, hypertriglyceridemia, abdominal obesity, hypertension, and low HDL cholesterol.[61] NLR mean values were: 1.68 ± 0.63 and 2.10 ± 0.70 ($P < .001$) in the MS (negative) and MS (positive) subjects, respectively.[61]

As reflecting a continuum of inflammatory and prothrombotic changes, mean higher values are encountered inT2DM, with even more elevated values in diabetic patients with micro and macrovascular complications.[62–69] Sefil and Hussain showed that NLR is a reliable biological marker for diabetes monitoring and glycemic control, being well correlated with fasting plasma glucose and HbA1c.[62–63] Other studies showed that high NLR and PLR value is an independent risk factor for microvascular changes, such as diabetic retinopathy, neuropathy, and nephropathy, and may be useful as a clinical tool for early diagnosis.[70–73] In the study of Fawwad et al, NLR was 1.14 times higher in diabetic subjects with at least one microvascular complication than in diabetic patients without any complications (4.34 ± 3.32 vs 3.36 ± 2.67, P < .0001).[71]

In a study by Liu et al, both PLR and NLR were found to be correlated with lower extremity arterial disease and its severity in diabetic patients, PLR being superior as a predictive factor.[65] Both biomarkers were positively correlated with age, duration of T2DM, HbA1c, total triglycerides, total cholesterol, and LDL- cholesterol.

However, one should take into account that the limits of variations of NLR and PLR are wide, and a certain value cannot discriminate between specific groups (metabolic syndrome vs DM vs DM with complications). Both NLR and PLR are regulated by multiple physiological and pathological factors. Though extremely sensitive biomarkers that reflect the functionality of multiple processes, such as inflammation, infection, atherosclerosis, metabolic disorders, or neuroendocrine stress, their signification should be carefully judged in the clinical context.[10]

The Roles of Neutrophils, Lymphocytes, and Platelets in Diabetic Micro and Macroangiopathy Associated with DFU

Multiple pathological mechanisms lead to NLR and PLR elevation in patients with DF: the underlying DM, the chronic hypoxia, and atherosclerosis caused by peripheric arterial disease, trauma, and superposed infection. Hyperlipemia, hyperglycemia, and insulin resistance have as metabolic effects a low-grade chronic inflammation, increased oxidative stress, and accumulation of advanced glycation end products (AGEs), with multiple effects on blood cells.

In T2DM, platelets are affected by the non-enzymatic glycation of membrane proteins, which makes them less deformable and more prone to aggregation and thrombus formation.[73] High levels of reactive oxygen species (ROS) increase the intracellular influx of Ca^{++}, with mitochondrial disfunction, platelets activation, and degranulation, secreting a large array of pro-inflammatory biomarkers, such as Il8, PF4, serotonin, thromboxane A2, beta-thromboglobulin, with secondary recruitment of the neutrophils, thrombocytosis, and accelerated atherosclerosis.[75,76] On the other hand, platelets are regulated by serum insulin, via insulin receptors, blocking platelet aggregation and collagen adherence.[77,78] Low-grade hemorrhages associated with microvascular disease and atherosclerosis induce increased platelet productions, with a significant number of younger platelets in the peripheric blood.[79] Those younger platelets are larger, with higher levels of mediators of inflammation in their intracytoplasmic granules.[36,79]

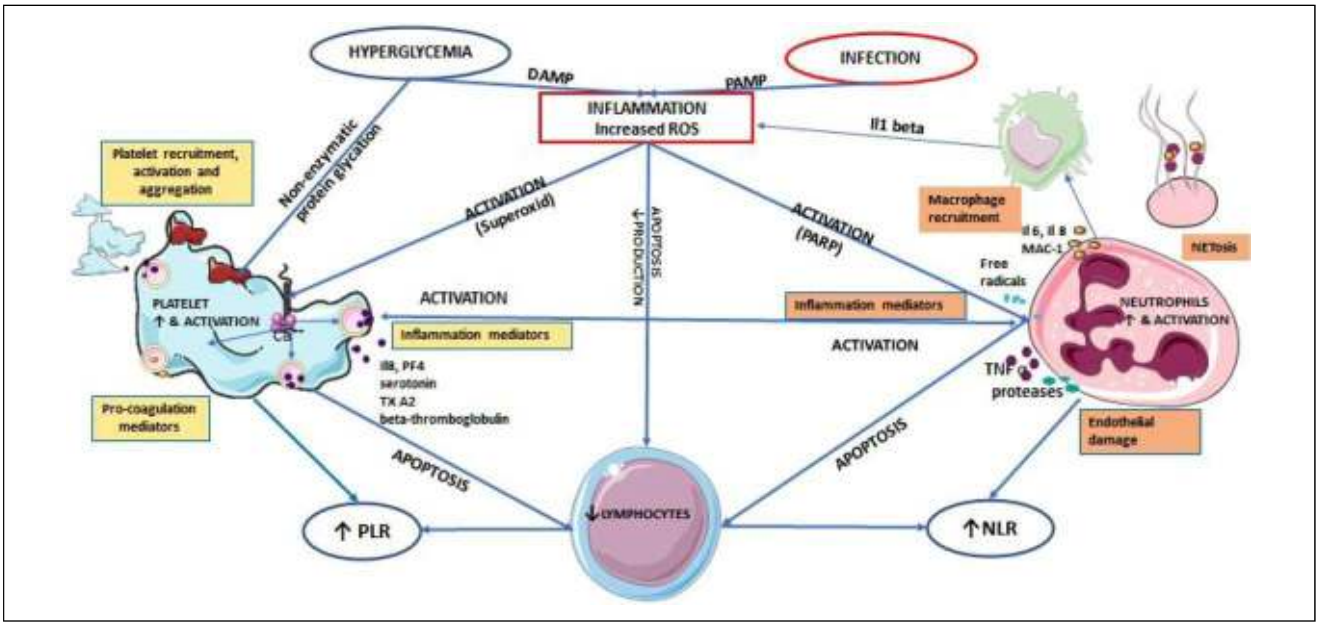

Figure 1. NLR and PLR – biomarkers of inflammation in DFU (some elements from the picture are courtesy of https://smart.servier.com/).

The lymphocytes have a protective, modulating role during inflammation, promoting tissue repair, Il-10 expression, and an anti-atherosclerotic activity.[52] Prolonged inflammation induces decreased levels of blood lymphocytes by multiple mechanisms: depressed bone marrow synthesis induced by chronic stress reaction, mediators of inflammations produced by activated cells, or by competitive stimulation of neutrophil production. Another mechanism is apoptosis triggered by increased levels of ROS related to hyperglycemia and activated neutrophils, by promoting DNA damage.[39,67,80] (Figure 1).

Neutrophils are activated by low-grade inflammation and increased oxidative status via poly (ADP ribose) polymerase (PARP) and release proteases, superoxide radicals, and cytokine leading to endothelial damage and dysfunction, platelet activation, and recruitment of macrophages.[37,38,67]

The tissular consequences are activation of the neutrophils' extracellular traps (NET) with NETosis, increased levels of pro-inflammatory cytokines, proteolytical enzymes, superoxide radicals, and endothelial damage.[81–83] NADPH oxidase (NOX) dependent and NOX independent mechanisms were described for NETosis. High reactive oxygen species, NADPH oxidase (NOX), and mitochondrial enzymes stimulate chromatin decondensation and nuclear localization of the enzymes. Common pathogens encountered in DFU, like Staphylococcus aureus also may trigger NETosis by NOX independent mechanisms, involving SK3 calcium ionophores and mitochondrial activation.[82–84]

Subjects with T2DM exhibited elevated NETosis products, including neutrophil elastase, mono- and oligonucleosomes, and cell-free double-stranded DNA (dsDNA), as compared to the control subjects, evidence for an increased basal NETosis related to the hyperglycemic environment.[84,85] These products may induce harm in the epithelial cells and other cells in the wound bed, and prevent healing. In patients with DFU, Fadini et al found that neutrophils isolated from patients with DFU possessed increased spontaneous NETosis but impaired inducible NETosis, one of the mechanisms of the impaired response to pathogens in DFU.[83]

Novel approaches to wound healing in diabetic foot ulcers (DFUs) include targeting NETs at different levels. Experimental NETosis inhibition by (PAD)4 inactivation promotes wound healing.[84] In a prospective study by Menegazzo et al, T2DM patients treated with metformin exhibit significantly decreased concentrations of neutrophil elastase, PR3, histones, and dsDNA, whereas insulin or dapagliflozin had no significant effect, independent of the glycemic level.[84] The mechanism was proved to be the inhibition of membrane translocation of protein kinase C-beta II isoform, which is a mediator of hyperglycemia-induced chronic complications, and activation of NADPH oxidase in neutrophils, thus decreasing NETosis.[85]

Questions to Answer in the Near Future and Practical Implications

While the detrimental effect of NLR and PLR on outcomes is continuous, the clinically significant "cut-off" value is not known. Although all studies led to similar conclusions,

important limitations must not be overlooked. Findings in the majority of studies have not been replicated or validated in prospective studies.

In the reviewed studies, the cut-off value of NLR used to predict the outcomes varied significantly, from 3.5 for predicting infection to <4.19 to 4.3 for wound healing and conservatively manageable DFU and >6.73 to 9.2 for predicting amputation.[19,20,23,24,26] NLR value of >6.5 was found to be an indicator of peripheral arterial disease in DFU and could be a useful tool to select patients that can benefit from revascularization procedures.[19]

On the other hand, NLR is a more accurate prognostic marker when serial measurements are obtained. Altay et al found that NLR on day 14 was higher in patients who underwent vascular intervention (5.1 vs 2.9; p = .007).[26] Metineren et al showed that decreased postoperative values suggest favorable outcomes.[21] In a systematic review and meta-analysis regarding the significance of NLR in infectious diseases, Russell et al founded that longitudinal measuring of this biomarker gives information about the resolution or continuation of the septic process, and could be a useful tool in clinical decision making.[90]

In studies evaluating the predictive role of PLR, a cut-off value of 147.6 was found to be predictive for DFU in T2DM patients, 187.3 for osteomyelitis, and 337.8 for amputation.[19,30]

PLR was found to be an important biomarker for atherosclerosis and critical limb ischemia, independently of the glycemic status. Several studies found that PLR > 111 indicates a risk of severe atherosclerosis and CAD and should be managed more carefully, while PLT > 150 was associated with critical limb ischemia.[91–93]

The reviewed studies differed in design (retrospective vs prospective), time of follow-up (short vs mid-and long-term survival), classification criteria used for DFUs, and structure of study group, such as the severity of DFU and association of infection. Hence, additional longitudinal data is needed to investigate the role of NLR and PLR as predictor factors for DFU and to establish reference values that could be used in clinical practice.

In evaluating whether DFI, NLR, and PLR correlate with other non-specific inflammatory biomarkers, the white blood cell count, erythrocyte sedimentation rate, and C reactive protein (CRP) were examined. Their contribution as predictors appeared to be stronger when more than one parameter was taken into account.

Conclusions

Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are easily applicable blood tests, which are well correlated with the risk for DFU, the severity of lesions, the risk for amputation, and short and midterm mortality. The significance of the elevated value of these biomarkers in DFU is related to chronic hyperglycemia and low-grade systemic inflammation, atherosclerotic and vascular complications, and also the associated septic factor. Serial, dynamic follow-up can provide useful information in planning and monitoring DFU treatment, as well as in risk stratification of these vulnerable patients, with multiple comorbidities. Further randomized studies are needed to set the cut-off values with clinical significance.

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Conflicts of Interest

The authors declare that the present article was written independently. APS is currently Vice President of the Romanian National Diabetes Committee and she has given lectures, received honoraria and research support, and participated in conferences, advisory boards and clinical trials sponsored by many companies including AstraZeneca, Boehringer Ingelheim, Coca-Cola, Medtronic, Eli Lilly, Merck, Novo Nordisk, Novartis, Roche Diagnostics, Sanofi. MR is full-time Professor of Internal Medicine at University of Palermo, Italy and currently Medical Director, Novo Nordisk Eastern Europe; he has given lectures, received honoraria and research support, and participated in conferences, advisory boards and clinical trials sponsored by many pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, Kowa, Eli Lilly, Meda, Mylan, Merck Sharp & Dohme, Novo Nordisk, Novartis, Roche Diagnostics, Sanofi and Servier. None of the above-mentioned companies had any role in this article, which has been written independently, without any financial or professional help, and reflects only the opinion of the authors, without any role of the industry.

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I. Lucrări relevante

9. Bjørklund G, Peana M, Pivina L, Dosa A, Aaseth J, Semenova Y, Chirumbolo S, Medici S, Dadar M, **Costea DO**. Iron Deficiency in Obesity and after Bariatric Surgery. *Biomolecules* 2021, 11(5), 613. doi: 10.3390/biom11050613. PMID: 33918997; PMCID: PMC8142987. (IF din 2021=6.064). 15 PAGINI

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Review

Iron Deficiency in Obesity and after Bariatric Surgery

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Abstract: Iron deficiency (ID) is particularly frequent in obese patients due to increased circulating levels of acute-phase reactant hepcidin and adiposity-associated inflammation. Inflammation in obese subjects is closely related to ID. It induces reduced iron absorption correlated to the inhibition of duodenal ferroportin expression, parallel to the increased concentrations of hepcidin. Obese subjects often get decreased inflammatory response after bariatric surgery, accompanied by decreased serum hepcidin and therefore improved iron absorption. Bariatric surgery can induce the mitigation or resolution of obesity-associated complications, such as hypertension, insulin resistance, diabetes mellitus, and hyperlipidemia, adjusting many parameters in the metabolism. However, gastric bypass surgery and sleeve gastrectomy can induce malabsorption and may accentuate ID. The present review explores the burden and characteristics of ID and anemia in obese patients after bariatric surgery, accounting for gastric bypass technique (Roux-en-Y gastric bypass—RYGB) and sleeve gastrectomy (SG). After bariatric surgery, obese subjects' iron status should be monitored, and they should be motivated to use adequate and recommended iron supplementation.

Keywords: obesity; iron deficiency; iron metabolism; bariatric surgery; iron supplement

1. Introduction

Iron (Fe) is one of about 20 essential trace elements bearing crucial functions in the human organism and almost all living systems [1–3]. Fe is a redox-active element highly widespread in the majority of human tissues, particularly, as it is well known, in muscle cells (myoglobin) and erythrocytes (hemoglobin) [4]. The human genome codes about 500 iron-containing proteins. Iron proteins, as ferritin (Ft) and hemosiderin, work as Fe storage proteins, whereas transferrin (Tf) acts as a Fe transporter in plasma. Furthermore, Fe is involved in several enzymatic processes and physiological reactions. Therefore, Fe is a fundamental trace element with well-controlled homeostasis [3]. Both iron deficiency (ID) and overload (IO) are related to common human diseases with different clinical symptoms, including anemia and siderosis, obesity, and even neurodegenerative disorders [5–8]. ID is known as the most common nutritional disorder globally. Between four and five billion people might suffer from ID and, because an estimated two billion are anemic, several hundred million manifest ID anemia [9–12]. ID is also associated with decreased

work capacity in adults and impaired mental development in children. The latent ID without anemia can be severe, and specific laboratory tests are required for its detection, management, and diagnosis [13]. Commonly, ID and anemia can be induced by many factors such as helminthic infections, nutritional deficiencies, and irregular menstrual cycles in women. However, an inflammatory component is a critical factor in the different stages of uptake, storage, and transportation of Fe in anemia, which also is frequently observed in many inflammatory disorders [14].

This problem has a multifactorial nature, and the upregulation of hepcidin plays a key role. Hepcidin (Hep) is an inducer of innate immunity and an important component of inflammatory anemia. Hep can control the amount of bioavailable iron in acute inflammation; this limits inflammation and reduces erythropoiesis [15]. Inflammatory anemia is characterized by the fact that, with sufficient iron in the macrophages, the return of iron to serum is blocked by Hep. Interleukin-6 (IL-6) as a pro-inflammatory cytokine promotes Hep overproduction by activating the Janus kinase signal transducer and transcriptional activator 3. This leads to a degradation of ferroportin in lysosomes, slowing down iron transport into serum, its accumulation in macrophages, and decreasing iron transfer from enterocytes [16]. The inflammatory component of obesity leading to excessive production of Hep (and lipocalin 2) is considered one of the potential mechanisms of hypoferremia in obesity. The overproduction of these proteins is associated with the sequestration of iron in the cells of the reticuloendothelial system. In this case, iron accumulates in adipose tissue, causing oxidative stress and endocrine dysfunction of adipose tissue and inflammation of the endoplasmic reticulum. Iron-mediated mechanisms of toxicity can contribute to obesity aggravation. Thus, it is possible to explain the mutual influence of impaired iron status and the pathogenesis of obesity [10].

Cytokines IL-6, IL-1β, and IL-22 have been connected with the elevated Hep expression secondary to inflammation. In contrast, tumor necrosis factor α (TNFα), a key mediator of different inflammatory disorders, including inflammatory bowel disease (IBD), can inhibit Hep expression, and treatment with anti-TNFα antibodies improved anemia status in patients with IBD. Other "signals" that regulate Hep expression in the context of inflammation include endoplasmic reticulum stress and gastrointestinal microbiota composition [17].

Apart from Hep, inflammatory mediators can also influence iron homeostasis, and the sample of such mediators could be made of TNFα, which can act directly on intestinal epithelial cells to inhibit iron transport. Besides, a combination of lipopolysaccharide and pro-inflammatory cytokine interferon γ can result in intracellular sequestration of iron and decreased ferroportin levels [18].

Low-grade chronic inflammation is common in obesity, and recent research offered some insights into the intracellular pathways of obesity-associated inflammation. Such overfeeding is the starting point of inflammation, which originates from cells and tissues involved in metabolism, i.e., adipocytes and hepatic macrophages that trigger the inflammatory response. Liver tissues of obese individuals are characterized by increased activation of certain kinases (c-jun N-terminal kinase), with simultaneous inhibition of other kinases (k kinase) that can stimulate the expression of inflammatory cytokines. The upregulation of inflammatory mediator gene expression occurs due to downstream transcriptional programs, and the transcription factors involved are nuclear factor κB, activator protein-1, and interferon regulatory factor. Inhibitory signaling of metabolic pathways develops secondarily to increasing cytokines' levels and exacerbating receptor activation [19]. The puzzling issue of ID associated with obesity is still under the spotlight, and the physiopathology of ID during obesity is not well defined. A relationship between obesity and the prevalence of ID has been recently investigated in adolescent people, showing that normal-weight individuals did not differ greatly from obese subjects (29.5% vs. 22.6%, $p = 0.3$) [20].

Consistent with several findings, obesity is significantly associated with ID [21–25], and according to some evidence, diet-induced weight loss could improve iron homeostasis and help obese people correct and resolve ID [26]. ID and its related symptoms (including

pallor, fatigue, dry skin, brittle hair/nails, and loss of appetite) can occur not only if the Fe level is insufficient but also from its limited intestinal absorption or prolonged blood loss. Bariatric surgery in obese persons and individuals with Type 2 Diabetes (T2D) may cause ID [27].

ID in the human body after bariatric surgery occurs due to the following mechanisms:

- decrease in iron intake due to its low absorption
- poor tolerance to iron reach foods
- low adherence of patients to iron-containing drugs
- decreased hydrochloric acid secretion due to the presence of a shunt or resection of the greater curvature of the stomach
- decrease in the absorbing surface due to a duodenal shunt or damage to the intestinal villi.

Depending on the volume of surgery, further monitoring, dietary characteristics, in the long-term postoperative period, the prevalence of iron deficiency is detected in 18.0–53.3% of patients, and iron deficiency anemia reaches 52–54% [28]. Gastric bypass (Roux-en-Y gastric bypass—RYGB), sleeve gastrectomy (SG), adjustable gastric band (LAGB), and biliopancreatic diversion with duodenal switch (BPD/DS) are the most common surgical procedures used to cause weight loss in severely obese subjects and TD2 individuals. RYGB and SG are surgical procedures that induce a more rapid and significant long-term weight loss but could lead to vitamin and mineral deficiencies. ID and anemia resulting from Fe starvation have been reported in the range of 6–22% in obese patients referred to bariatric surgery, representing an elevated prevalence compared to 6–7% in the general population [29–31]. Furthermore, the anemia prevalence increases significantly after bariatric surgery, to about 10–63%, mostly attributed to iron deficiency [31–34]. However, iron deficiency is not synonymous with anemia, as vitamin B_{12} and B_9 deficiencies can also provoke anemia. Apart from nutrient deficiencies, there are other potential causes of anemia, including inherited blood disorders, imbalances of certain hormones, hemolysis, and blood loss. The present review explores the burden and characteristics of ID and iron-deficiency anemia in obese patients and after bariatric surgery (especially RYGB and SG).

2. Iron Metabolism

Before addressing the role of obesity and bariatric surgery in causing or promoting ID, a brief introduction of iron physiology mechanisms is helpful. In addition to its well-known role in hemoglobin biosynthesis, Fe displays its function as a component of various proteins, explaining the variety of symptoms characterizing ID. Thus, Fe has an essential role in several metabolic, immunological, and central nervous functions [1,4,35–37].

Fatigue, weakness, depressed mood, and retardation of cognitive development in children can result from the altered metabolism of Fe [38–41]. The crucial proteins related to Fe metabolism are Hep, transferrin (Tf), and ferroportin-1 (Fpn-1) [42]. Genetic variations of these proteins have been closely associated with impaired iron metabolism, chronic anemia, and motor neuron disorder [41].

Hep and Fpn are two molecules mainly responsible for the regulation of systemic iron homeostasis. Balancing each other, they control the cellular iron export. Hep is an antimicrobial peptide of 25 amino acids, formerly known as LEAP-1 (liver-expressed antimicrobial peptide) [43]. Fpn, which exhibits 8-12 putative transmembrane domains, acts as a cellular iron exporter, while Hep reduces iron export by binding to Fpn, causing its subsequent degradation [44]. Hep inhibits the intestinal absorption and transfer of Fe from the duodenal enterocytes into blood plasma by inducing a change in the Hep receptor Fpn-1. The Hep-Fpn-1 complex is located in cells that have an essential role in degrading and internalizing the Fpn-1, and thus, the complex represses the Fe efflux from enterocytes, macrophages, and hepatocytes, reducing the Fe released into the circulation [42]. Thus, Hep is an inhibitor of the Fe uptake from the gut and the recycling of Fe from the reticuloendothelial system (RES).

Duodenal enterocytes regulate the levels of circulating Fe through dietary absorption. After absorption in the duodenum and proximal jejunum (Figure 1), iron is transported

across enterocytes, reaching the basolateral membrane. Fpn helps irons to cross the basolateral membrane and to enter the systemic circulation. In addition to iron release from enterocytes, Fpn is also responsible for iron export from other cells, including hepatocytes and macrophages [45]. Iron demand also acts as a signal that influences iron absorption from the intestine and/or releases from the reticuloendothelial system since iron deficiency can lead to restricted erythropoiesis and anemia. Increased iron absorption is regulated via enterocytes that synthesize more Fpn, duodenal cytochrome B (Dcytb), and divalent metal transporter 1 (DMT1). Dcytb is needed to reduce ferric Fe^{3+} to Fe^{2+}, while DMT1 transports iron into enterocytes, and Fpn releases it into the systemic circulation [46–48].

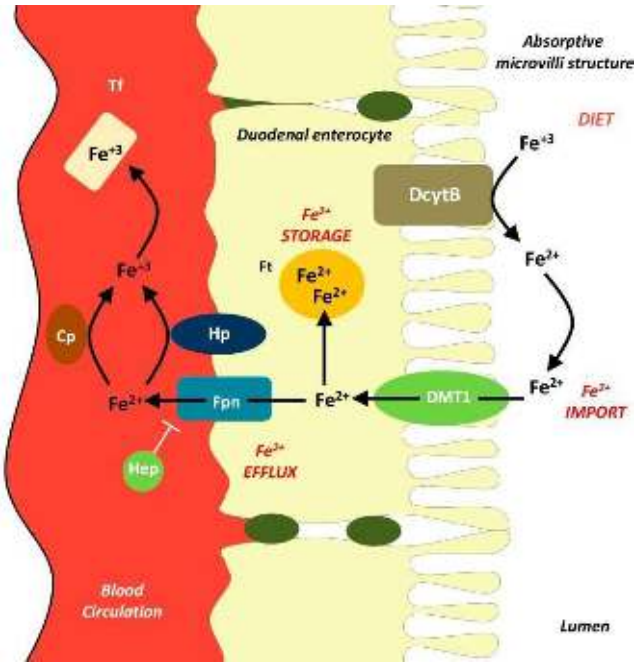

Figure 1. Dietary iron absorption and transport across duodenal enterocytes.

Dietary ferric iron (Fe^{3+}) is converted to ferrous iron (Fe^{2+}) by the apical ferric reductase duodenal cytochrome b (DcytB). After Fe reduction to the ferrous form (Fe^{2+}), it could cross into the cytoplasm by an apical Fe transporting divalent metal transporter-1 (DMT1, also known as DCT1, SLC11a2, and Nramp2). Both DcytB and DMT1 are localized to the microvilli-covered surface of simple columnar and simple cuboidal epithelium, known as the brush border. Iron is either stored or moved from the enterocyte into the circulation through the sole basolateral transporter ferroportin (Fpn, also named SLC40A1). The ferroxidase hephaestin (Hp), aided by ceruloplasmin (Cp), oxidizes Fe^{2+} to Fe^{3+} to enable loading onto the plasma carrier protein transferrin (Tf). Hepcidin (Hep) decreases serum iron levels by inhibiting iron release by Fpn.

Erythroferrone is a Fam132b protein secreted by maturing erythroblasts and functions as a biologically active substance that links erythropoiesis and iron metabolism. There is evidence for the role of erythroferrone as a Hep suppressor in anemias due to blood loss, hemolysis, and hereditary anemias with ineffective erythropoiesis. This ability may be useful for treating anemias with increased hepcidin expression, including anemias in inflammatory diseases, chronic kidney diseases, and iron-deficiency anemias resistant to treatment with iron medications [49]. Erythroferrone deficiency also contributes to the development of insulin resistance in a high-fat diet (HFD), a significant increase in the number of adipocytes, and adipose tissue accumulation, which is associated with an increase in lipoprotein lipase activity [50].

Metabolic syndrome may be associated with elevated transferrin and ferritin levels in about 30% of patients with non-alcoholic fatty liver disease. This phenomenon has been termed “Dysmetabolic Iron Overload Syndrome (DIOS)”. This iron overload can

negatively impact metabolic processes and be a risk factor for diabetes mellitus. However, in the process of progression of obesity in such patients, iron deficiency is observed. The development of DIOS is based on an increase in Hep and decreased duodenal Fpn [51].

3. Biomarkers of Iron Status

The status and turn-over of Fe are evaluated by numerous characteristics, such as its metabolism, absorption, and interactions with other nutrients. Different methods or biomarkers have been established to determine the supply and status of Fe. Low hemoglobin (anemia) is an ID indicator, although reduced ferritin is considered the best indicator [52]. Serum ferritin is a protein that plays a critical role in Fe storage. The regulation of ferritin synthesis occurs on the post-transcriptional level by binding cytoplasmic iron regulatory protein to an iron-responsive element in the 5′ untranslated region of ferritin mRNA [53]. Ferritin is composed of two subunits: light (L) and heavy (H), having a molecular weight of 19 kDa and 21 kDa, respectively, and homologous sequences. The ratio of L- and H-subunits depends on the tissue type and may impact inflammation or infection. Tissue ferritins might be H-subunit rich, predominately found in the heart and kidney, and L-subunit rich, mostly found in the liver and spleen. Serum ferritin is not the same as tissue ferritin (a heteropolymer of H- and L-subunits). Although serum ferritin is an important clinical marker of iron status, its precise source remains undetermined [54]. Depending upon the Fe content, it contains a molecular weight of ≥ 440,000 Dalton. It consists of a protein shell (apoferritin) composed of 24 subunits and a Fe core with an average of approximately 2500 Fe^{3+} ions. The ferritin level determination is relevant in diagnosing anemias and in monitoring Fe therapy [55,56]. However, the serum ferritin level is influenced by a series of physiological and pathological factors, such as inflammation, infection, and malignancy [57]. Elevated serum ferritin levels are the key acute-phase reactants and are of great importance to clinicians since they indicate the need for therapeutic interventions to control inflammatory responses in high-risk patients. Although serum ferritin serves as an inflammatory marker, it is unclear whether it reflects or causes inflammation or is involved in an inflammatory cycle. Hyperferritinemia may play a protective role in inflammation because it limits the production of free radicals and mediates immunomodulation [58]. As a key modulator of Fe homeostasis, Hep is considered a promising new biomarker for Fe status, e.g., in chronic kidney disease (CKD) [59]. Reduced values of Hep induce IO in renal disease with ineffective erythropoiesis and also in hereditary hemochromatosis. Due to decreased renal clearance, serum Hep levels increase in CKD. This leads to inhibition of duodenal iron absorption and contributes to systemic iron deficiency, iron deficiency for erythropoiesis, and resistance to endogenous exogenous erythropoietin. As soon as CKD is characterized by impaired renal production of erythropoietin, hepcidin-mediated iron restriction plays a role in CKD patients with anemia [60]. Fnp, Hep and their modulators are proved to be promising targets for diagnosing and treating Fe disorders and anemias [61].

Dysregulation of Hep causes Fe homeostasis modification and the development of pathological disorders, such as Fe restrictive and Fe loading anemias and hemochromatosis [62]. Fe can also be transported in the plasma by transferrin, which donates Fe to cells via the interplay with a specific membrane receptor, named the transferrin receptor (TfR). Although soluble TfR is rarely used clinically, this marker has recently been of interest as a substitute for ferritin in inflammatory processes [63–66]. Elevated TfR values indicate a depot Fe shortage and functional ID, a condition defined by tissue iron deficiency, despite sufficient iron stores. Combining the biochemical marker ferritin with the soluble TfR, Hep, complemented by other parameters such as transferrin saturation and reticulocyte's hemoglobin, represents the current measure of repertory in ID and anemia.

4. Iron Deficiency and Anemia in Obesity

ID is a common finding of metabolic alterations occurring in obesity [11,67]. A primary underlying pathophysiological mechanism is a decreased ability for duodenal Fe absorption, reported in several studies [21,68,69]. Thus, Mujica-Coopman et al. identified the

significantly decreased absorption of isotope-labeled Fe in obese women of childbearing age compared with normal-weight counterparts [70]. The prevalence of IDA among all women studied was approximately 7%, and iron deficiency was observed in 9%. Iron status was normal in 66% of women, with no differences in BMI categories. Although the percentage of Fe absorption was lower in obese women, this did not affect their Fe status. Zimmermann et al. came to a similar conclusion when reporting that a higher body mass index (BMI) is associated with decreased Fe absorption [71]. Among the women included in the study, about 20% had an iron deficiency; this figure among the studied children reached 42%. Iron absorption rates were independent of iron status. Benotti et al. have recently addressed the disturbance in iron metabolism during metabolic surgery in obese subjects [72]. The International Diabetes Federation (IDF) position statement on bariatric surgery has been recommended for treating and preventing T2D in obese people [73–75]. The American Diabetes Association talks about "metabolic surgery" to indicate the bariatric approach to prevent and solve T2D in obese subjects [76]. The terminology may be misleading, but the goal is to address a metabolic syndrome with surgery. A meta-analysis by Cheng et al. on iron status in obese populations reported that obese individuals have higher concentrations of ferritin than normal-weight subjects [77], which might result from the low-grade inflammation characterizing obese subjects. The authors of a recent meta-analysis concluded that obese individuals have lower concentrations of serum Fe and decreased transferrin saturation percentages than non-overweight individuals. This meta-analysis also helped to conclude that obese subjects have a considerably higher risk of ID than the controls (OR: 1.31; 95% CI: 1.01–1.68) [22].

The serum Fe reduction phenomenon may be due, in part, to the low-grade or chronic inflammation provoked by the progression of obesity via a chain of pathological mechanisms. Compared to normal-weight subjects, adipose tissue of the obese subjects is characterized by excessive quantities of macrophages and producers of pro-inflammatory cytokines [78]. Moreover, obesity is associated with increased adipokines production in the fat cells that play a central role in regulating insulin resistance and many aspects of inflammation, immunity, and susceptibility to viral infection [79,80]. Dysregulation of adipocytokines production is involved in developing obesity-related diseases, such as diabetes mellitus, hypertension, cardiovascular disease, and hyperlipidemia. Adipocytokines and pro-inflammatory cytokines, together with free fatty acids abundant in obesity, trigger a cascade of harmful adipose tissue reactions to other body systems and organs. Concomitantly, the liver undergoes lipid accumulation (non-alcoholic fatty liver disease, NAFLD), which further disrupts the Fe balance due to an increase in the production of cytokines and insulin resistance [81].

In obese patients, reduced BMI leads to decreased Hep levels, which improves iron absorption and metabolism. After a six-month weight-loss program, these results were observed [82], while inflammatory markers and Fe status were improved after the intervention, which resulted in decreased BMI [83]. Only those weight loss programs based on a well-balanced, healthy approach improved functional Fe status due to increased dietary Fe absorption, decreased expression of inflammatory cytokines, and diminished insulin resistance [21,26,84].

It also has to be pointed out that the treatment of ID might improve obesity status. According to Aktas et al., intake of iron supplements at iron-deficiency anemia significantly reduces BMI, improves waist circumference, and decreases triglyceride after treatment compared to the pre-treatment period [85]. On the contrary, iron deficiency anemia aggravates obesity since it is associated with a greater state of fatigue, which results in a further decrease in physical activity [86]. There is no doubt that ID must be identified and adequately controlled in all individuals suffering from overweight and obesity.

5. Iron Deficiency, Inflammation, and Obesity

There is a close relationship between Fe status change and inflammatory activity. For example, it has been shown that pro-inflammatory cytokines such as interleukin-6 (IL-6)

can increase the contents of Hep in liver cells. IL-6 stimulates Hepcidin Antimicrobial Peptide (HAMP) expression, and this effect is mediated via a signal transducer and a transcription activator binding site on the Hep promoter [87]. Increased inflammatory activity with reduced intestinal absorption of Fe, with stronger sequestration of Fe in macrophages and lowered Fe, are reflected in the serum, which, at the same time, shows an increase in serum ferritin levels [88–90].

The subsequent decrease in hemoglobin and Fe levels of plasma induces the anemia referred to as anemia of inflammation. These Fe metabolism modifications likely play a critical role in host defense by restricting the Fe availability for invading microorganisms [91]. This relationship between inflammatory activity and ID is known to be of global importance because of the prevalence and incidence of some situations, such as overweight, obesity, and conditions with chronically elevated inflammatory activity [24]. In the case of overweight, increased levels of circulating IL-6 are also found [92].

Chronic inflammation is considered one of the processes linked to obesity and obesity-associated diseases, including insulin resistance [93]. Obesity is accompanied by inflammation of body fat, which proceeds with adipose tissue infiltration by immune-competent cells. This process is associated with hypersecretion of TNFα and IL-6 and the development of insulin resistance, activated inflammation of colon macrophages, and their recruitment into adipose tissue [94].

One recently launched point of view states that several activators of the immune system, including smoking, a surplus of saturated trans-fats, omega-6 fatty acids, and carbohydrates with a high glycemic index, together with a sedentary lifestyle, promote the development of obesity. The result may be a cascade leading to insulin resistance and atherosclerosis [95–97]. Acute-phase proteins, including coagulation proteins (fibrinogen, prothrombin) and transport proteins (including ceruloplasmin, haptoglobin, ferritin, and C-reactive protein), act as mediators of the immune response. Interleukins increase the synthesis of acute-phase proteins and components of the complement system in the liver, and their elevated level in the serum is a sign of systemic inflammatory response [92].

Triggering factors for the synthesis of acute-phase reactants are adipokines, among which the most studied are tumor necrosis factor-alpha (TNFα) and IL-6. TNFα is synthesized not only by macrophages but also by adipocytes and stromal cells. Its concentration in tissues is hundreds of times higher than in blood; the local effects include stimulation of lipogenesis and adipocyte growth. TNFα has systemic effects by activating fatty acids' synthesis and increasing their concentration in the blood [98–100].

About 30% of circulating IL-6 is synthesized by fat cells. The study included 22 women and 17 men: median age, 36 years (interquartile range, 26–48 years); body mass index, 31.8 kg/m^2 (range, 22.3–38.7 kg/m^2); percent body fat, 28.7% (range, 17.6–50.7%). IL-6 has been released from the adipose tissue bed of all subjects. However arterial plasma concentrations of IL-6 were correlated significantly with body mass index (Spearman's r = 0.48; $p < 0.01$) and percentage of body fat (Spearman's r = 0.49; $p < 0.01$) [101].

A positive relationship between various anthropometric parameters of obesity and plasma levels of IL-6 has been described for men and postmenopausal women (estrogens are known to inhibit IL-6 secretion) [102–104].

In individuals with severe obesity, elevated blood leptin levels and leptin resistance are usually observed [105]. Recent studies have shown that increased leptin levels contribute to oxidative stress by enhancing macrophages' phagocytic activity and inducing the synthesis of pro-inflammatory cytokines (TNFα, IL-6, IL-2, and interferon-gamma) and secondarily increased level of endothelial cell dysfunction markers [106,107].

Another adipokine, visfatin, is synthesized by bone marrow and blood lymphocytes and is also present in fat tissue [108,109]. Visfatin has prooxidant and pro-inflammatory effects [110]. The inflammation in obese subjects is closely related to ID, and it induces impaired Fe absorption in the duodenum with inhibition of duodenal ferroportin expression and increased Hep concentrations [21]. In obese people, biomarkers such as ferritin, soluble TfR, and Hep are more susceptible to oxidative damage, directly related to BMI,

fat percentage, and triglyceride levels [111]. Antioxidant protection markers are significantly reduced, along with the development of obesity, particularly in the central type, characterized by significant fat deposition in the abdomen [112].

6. Bariatric Surgery and Postoperative Iron Status

Bariatric surgery is the most effective treatment for weight loss and long-term weight maintenance. It improves life quality by reducing obesity-related comorbid conditions such as cardio- and cerebrovascular diseases, respiratory diseases, T2D, degenerative joint disease, and even cancer [113]. The bariatric procedures comprise gastric banding, sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion (BPD), with or without duodenal switch (DS). Of these methods, SG is the most common surgical weight-loss procedure. As discussed above, ID and anemia are frequent in obese patients.

Consequently, monitoring the Fe status before bariatric surgery is of crucial importance [28,114]. Bariatric patients with anemia generally stay longer in hospital than nonanemic patients (2.7 vs. 1.9) [115]. Iron loss following bariatric surgery is also expected to enhance absorption unless absorptive capacity is concomitantly reduced, resulting from bariatric surgery. Thus, after bariatric surgery, anemia often becomes a significant concern [114,115]. Some bariatric surgery methods, such as biliopancreatic diversion, duodenal switch, and RYGB, have been associated with a malabsorption procedure, which leads to impaired absorption of Fe. Patients after surgery are characterized by a decrease in the transition of Fe^{3+} to Fe^{2+} due to hydrochloric acid deficiency leading to anemia [116]. Together with decreased secretion of hydrochloric acid, different factors of anemia and ID are attributed to the reduced food intake and frequent occurrence of meat intolerance [28,117,118]. The American Society for Metabolic and Bariatric Surgery (ASMBS) recommended guidelines to recover iron levels following bariatric surgery [28,119,120]. A study in a group of 32 women who underwent bariatric surgery and post-bariatric abdominoplasty showed that, two days after surgery, the average hemoglobin level decreased from 12.98 to 10.8 g/dL. Seven days later, it increased to 11.53 g/dL, but there was no further increase in hemoglobin. The same trend is found for serum Fe and transferrin. The average ferritin level decreased within 56 days after surgery from 29.8 to 16.4 µg/L. Iron and hemoglobin deficiency were observed in 45% of the patients [121].

Moreover, ID anemia may increase over time in patients after bariatric surgery, even if they take Fe supplements. A ten-year follow-up of a group of 151 patients after gastric bypass surgery, conducted in Brazil, showed that anemia persisted in 37.5% of the patients when the ferritin level was lower than 15 µg/L, and in 45.0% when the ferritin was lower than 30 µg/L [122]. In a Portuguese retrospective cohort study involving 1999 patients with a follow-up period of 4 years, post-bariatric surgery anemia was diagnosed in 24.4% of the patients. The variables associated with a higher prevalence of anemia were sex and the type of bariatric surgery. Females and RYGB procedures present a two-fold increased risk of developing anemia compared to males and gastric sleeve and gastric band surgery [123]. Of the studied patients, 84.8% were female, with a median age of 42.3 years. These findings are consistent with the results of another study that showed similar results: the risk of developing anemia was three-fold higher in women than men [124].

On the other hand, given that obese patients have elevated serum Hep levels and signs of inflammation associated with obesity, it can be expected that a decrease in the amount of adipose tissue after bariatric surgery can activate Fe absorption [125]. This assumption was demonstrated by the results of a six-month prospective study in 38 patients who underwent laparoscopic sleeve gastrectomy (LSG). Patients consumed iron sulfate (6 mg ^{57}Fe) and intravenous iron citrate (100 µg ^{58}Fe). Six months later, a decrease in body fat, interleukin IL-6, and Hep was found ($p < 0.005$ for all indicators). Iron absorption increased by 30% in patients with ID (from 9.7% to 12.4%, $p = 0.03$), while, in individuals with normal Fe content, absorption remained unchanged. The results allowed the authors to conclude that loss of adipose tissue leads to improved absorption of Fe [126]. However, gastric bypass

surgery, especially RYGB and sleeve gastrectomy, induces iron malabsorption that could accentuate ID [127,128].

7. Iron Supplementation after Bariatric Surgery

In general, in symptoms including performance weakness from fatigue, irritability, and apathy, the ID diagnosis should always be considered, even if there is no anemia. Increasing public awareness exists to improve nutrition and use food supplements when needed, such as Fe supplements [12]. Simultaneous consumption of vitamins and minerals, abundant in fruits or fruit juices, improves the Fe absorption. If these measures are not sufficient, ID can be cured through food supplements, medication, and intravenous drug therapy [129,130]. Given new findings concerning Fe metabolism regulation and the analytical availability of the corresponding biomarkers (Ft, soluble TfR, Hep), it is possible to detect an insufficient supply or a disturbed balance in Fe metabolism at an early stage. This is particularly important among women of reproductive age to optimize the maternal nutritional status before pregnancy and during the prenatal course [131]. Drug therapy can be performed orally or, in some cases, parenterally. If possible, iron should be administered orally, and intravenous administration should be considered when oral iron is insufficient or not well tolerated [132]. However, there is high variability in iron supplementation strategies among clinicians. In the systematic review of Enani et al., the iron supplementation dosage varied from 7 to 80 mg daily across the studies evaluated [127]. After bariatric surgery at Innlandet Hospital, Norway, patients are routinely recommended daily supplementation with Fe (100 mg), usually in the form of sulfate. In a cross-sectional study of 36 women with an average age of 45 years who underwent bariatric surgery, ID was found in 42% of participants. The additional administration of non-heme Fe at a dose of 45 mg/day had a positive association with serum ferritin ($\beta = 0.964$; $p = 0.029$). Most recent studies demonstrate that bariatric surgery effectively normalizes menstrual regularity in 74–85% of obese women of reproductive age, correlated with weight loss [133–135]. The intake of vitamin C from food also contributed to an increase in Fe levels [136]. The Obesity Society and American Society for Metabolic and Bariatric Surgery recommend a dose of 195 mg non-heme iron (sulfate, fumarate, or gluconate) per day for bariatric surgery patients [137]. A recent RCT (NCT 02404012) indicated that this dose of non-heme iron is effective for normalization of Fe status following RYGB, whereas a commercial heme iron supplementation (in a polypeptide form and in a recommended dose of 31.5 mg/day) proved ineffective in this regard [138]. Interestingly the bioavailability of such an oral formulation was greater in healthy subjects compared to ferrous sulfate. However, even in patients with chronic kidney disease, its efficacy was not superior [138].

Further studies are needed to find new heme iron formulations with greater water solubility and efficacy in improving iron status biomarkers, even in RYGB patients. Ferrous sulfate is the gold standard in oral iron supplements for treating ID in bariatric surgery patients, but it is not always well-tolerated. Gastrointestinal complaints and nausea are not uncommon. These can be mitigated by using fortified foods. For patients with severe oral iron intolerance or severe ID due to iron malabsorption, intravenous iron infusion (dextran, ferric gluconate, or sucrose) is necessary [137]. A recommended form of Fe is a sustained-release preparation. A slow-release formulation based on Fe-Kojic acid complexes is better absorbed in patients with sleeve gastrectomy but not in those with gastric bypass [139]. Chewable supplements with multivitamins and minerals are available. They should contain at least 18 mg of iron. Vitamin B_{12} and fat-soluble vitamins A, D, E, and K are included, together with microelements such as selenium, copper, and zinc. Calcium decreases iron absorption and should be taken separately (as citrate [140]) two hours apart from iron. The dose to be taken (1, 2, or 3 tablets/day) is related to the type of bariatric surgery (SG, RYGB, or DS, respectively). Close monitoring and tailored Fe supplementation pre-and post-bariatric surgery is required, and lifelong monitoring performed under appropriate laboratory supervision is recommended [141,142].

8. Concluding Remarks and Future Perspectives

Iron deficiency is the most crucial micronutrient deficiency known in children, and it has received growing attention as a global public health issue. Such a deficiency is commonly related to low Fe intake or increased physiological demands, as seen in pregnancy, chronic inflammatory diseases, including morbid obesity, or after bariatric surgery. Different studies have shown that the determination of several biomarkers is necessary to evaluate individual Fe status. The current data reveal multiple forms of interactions between Fe and the immune system. These interactions may critically impact the Fe status in ID, which is frequently observed in obese individuals. This review has summarized the role of pro-inflammatory cytokines, such as interleukin-6, which can increase Hep synthesis in liver cells and inhibit Fe absorption.

Moreover, we explored the burden and characteristics of ID and anemia in obese patients and after bariatric surgery. In cases of morbid obesity remitted for bariatric surgery, it is mandatory to evaluate Fe status, both pre- and postoperatively, with long-life proper monitoring in an appropriate clinical context. Furthermore, monitoring the effect of supplementation is also needed to avoid Fe excess. Aside from the fundamental role of Fe in anemia, a less focused issue regards the role of Fe as a micronutrient in many other biological activities of the organism. The present report summarizes the outcomes of different analyses, which reveal that Fe deficiency remains a primary global health objective.

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Abbreviations

BMI: body mass index, BPD: biliopancreatic diversion, DMT1: divalent metal transporter-1, DS: duodenal switch, Fpn-1: ferroportin-1, Ft: ferritin, Hep: hepcidin, Hp: hephaestin, ID: iron deficiency, IL-n: interleukin-n, IO: iron overload, LSG: laparoscopic sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass, SG: sleeve gastrectomy, T2D: Type 2 Diabetes, Tf: transferrin, TNFα: tumor necrosis factor-alpha.

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Review

Follow-up after bariatric surgery: A review

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ABSTRACT

Bariatric surgery is becoming increasingly popular in the treatment of severely obese patients who failed to lose weight with the help of non-surgical interventions. Such patients are at increased risk for premature death, type 2 diabetes, high blood pressure, gallstones, coronary heart disease, dyslipidemia, some cancers, anxiety, depression, and degenerative joint disorders. Although bariatric surgery appears to be the most effective and durable treatment option for obesity, it is associated with a number of surgical and medical complications. These include a range of conditions, of which dumping syndrome and malnutrition due to malabsorption of vitamins and minerals are the most common. To achieve better surgery outcomes, a number of postsurgical strategies must be considered. The aim of this review was to describe possible complications, ailments, and important moments in the follow-up after bariatric surgery. Adequate lifelong monitoring is crucial for the achievement of long-lasting goals and reduction of post-bariatric complications.

Introduction

Bariatric surgery can be a treatment option for sickly obese patients who have not succeeded with the medical treatment of obesity [1]. Such patients are at increased risk for premature death, type 2 diabetes, high blood pressure, gallstones, coronary heart disease, dyslipidemia, some cancers, anxiety, depression, and degenerative joint disorders [2]. However, patients with additional diseases, such as severe respiratory failure, heart failure, or kidney failure, may not be approved for surgical treatment if the risk for complications is considered high. Also, patients with severe mental illness, intoxication, or mental retardation may be unsuitable candidates for obesity surgery [3].

Patients who are severely obese may benefit from non-surgical management that induces cardiometabolic effects. The currently recommended weight loss goal is 5% to 10% of the patient's initial weight in 6 mo [4]. However, bariatric surgery presents the most effective and durable treatment option for obesity. These procedures provide significant and lasting weight reduction, improve somatic and mental obesity-related diseases and quality of life (QoL), and reduce long-term mortality. In conjunction with dietary, behavioral, and lifestyle changes, bariatric surgery could become an effective tool in obtaining an optimal body weight [5].

Currently, bariatric surgery is recommended for severely obese patients with a body mass index (BMI) >40 kg/m^2, who failed to benefit from previous dietary modifications and non-surgical treatment options. Alternatively, bariatric surgery may be suggested for individuals presenting with a BMI 3≥5 kg/m^2 but with obesity-related comorbid conditions [6]. Moreover, the International Diabetes Federation proposed to recommend bariatric surgery to patients with type 2 diabetes mellitus (T2DM) having suboptimal blood glucose control on a background of adequate medical therapy even though their BMI might be 30 kg/m^2 [7]. Thus, the term *metabolic surgery* has recently evolved to describe interventions targeted to control T2DM and cardiometabolic risk factors [8].

Historically, metabolic surgery appeared in the mid-20th century, and jejunoileal bypass was the first surgical approach [9]. The appearance of the laparoscopic technique helped to improve the

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postoperative course, and the risk for death and severe complications after surgery is now low [10]. However, bariatric surgery can still cause serious complications and several ailments. As there is an emerging pool of data regarding special considerations on post-bariatric care, this review focuses on complications, ailments, and important moments in the follow-up after bariatric surgery.

Surgical methods

In general, bariatric surgery includes three types of procedures: blocking, restrictive, and mixed. In modern reality, the preference is given to laparoscopic interventions as opposed to open-type procedures [11]. Biliopancreatic diversion, jejunoileal bypass, and endoluminal sleeve constitute the group of blocking procedures, which lead to the blockage of food absorption [12]. In biliopancreatic diversion that is now replaced by the duodenal switch, a part of the stomach is resected, and a smaller stomach is formed [13]. Although jejunoileal bypass is no longer practiced, endoluminal sleeve gained little popularity [8].

Restrictive procedures form another group of bariatric surgical interventions and are targeted to shrinking the stomach size. Several procedures constitute the group of restrictive interventions: vertical banded gastroplasty, adjustable gastric band, sleeve gastrectomy, intragastric balloon, and stomach plication. In an adjustable gastric band, a special silicone band is used to create a small gastric pouch, and the addition or removal of saline helps to adjust its size [14]. In sleeve gastrectomy, surgical removal of the larger portion of the stomach takes place with suturing or stapling of the open edges to permanently reduce the stomach size [15]. Intragastric balloons are placed inside the stomach to decrease the intragastric space and could be left for $\leq$6 mo [16]. Stomach plication is, in fact, a type of gastric sleeve except that a sleeve is formed by suturing of the stomach, which helps to preserve its absorption capability [17].

So-called mixed procedures embrace both blockage and restriction of the stomach. This group of surgeries constitutes gastric bypass, sleeve gastrectomy with duodenal switch, and implantable gastric stimulation. Gastric bypass alone constitutes not less than 50% of all obesity operations. This procedure possesses hormonal properties in addition to the restriction of the stomach size [18]. Biliopancreatic diversion with duodenal switching involves resection of stomach with subsequent tubulization to a volume of around 150 mL. As a next stage of the surgery, the stomach is disconnected from the duodenum and connected to the small intestine. Like in the case with gastric bypass, weight loss occurs due to hormonal changes in addition to the restriction of stomach size [19]. Implantable gastric stimulator represents a special device that enables electrical stimulation of the external surface of the stomach. This stimulation is believed to alter the activity of the enteric nervous system with the subsequent feeling of satiety [20].

Early postoperative period

It is a common practice to place a patient undergoing bariatric surgery in the post-anesthesia care unit after surgery. Following the gastrografin leak test in patients having a nasogastric tube, oral therapy in liquid form is started. Otherwise, the patient gets therapy in tablets or crushed tablets. There is a need to obtain a basic metabolic profile every 12 h within the first 2 d postoperatively and every 24 h within the other 3 d postoperatively [21]. As respiratory problems present a frequent complication within the first few days after bariatric surgery, oxygen is administered by nasal cannula. Patients with serious associated health disorders are at a higher risk for respiratory problems [22].

At the end of the early postoperative period, which normally lasts for the first 2 or 3 d, the patient could be transferred to the inpatient surgical postoperative unit, where he or she is monitored for the presence of an anastomotic leak following gastric bypass or sleeve gastrectomy. If no leaks are present, a clear liquid diet can be started. Such a diet includes clear broth, sugar-free drinks, diluted fruit juices, and/or gelatin desserts. After the gastrointestinal (GI) tract has recovered from the surgery, mashed food is taken for 1 to 2 wk. Such food commonly consists of high-protein, protein shakes, dairy products, and soft meats. Furthermore, it is recommended that patients consume a diet consisting of crispbread, lean dairy products, eggs, fish, chicken, lean and minced meat, and lightly cooked vegetables before returning to a normal diet [23].

At the inpatient surgical postoperative unit, the following care is commonly provided: pain control, wound care, blood pressure monitoring, intravenous infusions to monitor a basic metabolic profile, and pulmonary hygiene. As post-bariatric nausea and vomiting present a frequent complication and are more common in females and non-smokers, certain measures of prophylaxis must be applied. In general, the patients have commonly undergone volume depletion and dehydration as they experience problems with drinking the appropriate amount of fluids due to adaptation to a new gastric volume [24].

Recommendations after hospital discharge

Typically, at the time of discharge, it is recommended that patients follow a full liquid diet and monitor their hydration and urine production. During the first month postsurgery, the recommended daily calorie intake ranges from 400 to 800 kcal, which are mostly achieved by the reduction of daily glycemic load. Also, there is a need to consider the intake of multivitamins as reduced absorption of essential nutrients is very common after bariatric surgery [25]. As both epigastric pain and vomiting may follow every food intake, patients are given instructions on food practices, such as to eat slowly, to stop eating immediately after reaching satiety, and to avoid simultaneous consumption of food and drinks.

Other instructions include maintaining a healthy diet and visiting the dietitian regularly for $\geq$1 y after surgery [26]. Additionally, patients are instructed to change their environment as it largely shapes their food habits. If patients become intolerant to certain foods, they are advised to follow a more vegetarian-based diet, as vegetables and fruits are commonly tolerated. In general, it is not rational to recommend a fully vegetarian diet to this category of patients. For example, if the patient is intolerant to meat, there are different alternatives regarding how to cook it in order to make it more tolerable [27]. Also, zero alcohol consumption is recommended within $\geq$12 mo [28]. Commonly, the recommended daily protein intake ranges from 1 to 1.5 g/kg of ideal body weight (IBW) [29]. However, those patients who undergo sleeve gastrectomy or gastric bypass require higher daily protein intake in an amount of 1.5 to 2.0 g/kg of IBW [30].

Body weight and blood pressure (BP) monitoring is recommended weekly during the stage of rapid weight loss after bariatric surgery, which commonly lasts for 4 to 6 mo. As the stage of rapid weight loss slows down, BP and body weight should be monitored at 8, 10, and 12 mo postsurgery. Because diabetes mellitus appears to be a frequent comorbidity of obesity, blood glucose levels must be monitored daily in patients with diabetes. Still, it should be noted that glycemic control commonly normalizes very quickly after bariatric surgery. For this reason, the dosage of antihypertensive and diabetic medications need to be adjusted to prevent hypotension and hypoglycemia [23]. However, patients who have achieved normal blood sugar levels and BP postsurgery may have a

recurrence of diabetes and hypertension later. As a result, monitoring of blood sugar levels and BP is necessary both in the weeks after surgery and in subsequent years [31].

After obesity surgery, the uptake and metabolism of several drugs may be altered, and both reduced and increased levels of serum medications may occur [32]. Dose adjustment of medications may, therefore, be necessary. In particular, this applies to pharmaceuticals with a narrow therapeutic window such as warfarin, lithium, and some antiepileptic drugs [33]. Patients suffering from chronic vomiting may be prescribed proton pump inhibitors or prokinetic therapy [34].

Postoperative ailments

Newly occurring GI disorders may occur ≥50% of patients during the first year post-gastric bypass [3]. The most common complaints are nausea, vomiting, postprandial regurgitation, dumping syndrome, air pain, gastroesophageal reflux, and diarrhea [35]. Some vomiting and postprandial regurgitation in the months after surgery are common and are usually due to the patient eating too much or too fast. This can be described as the food "stopping." Dumping syndrome is common and is likely due to hyperosmolar food, especially sugary drinks and foods, drawing fluid into the small intestine lumen. This leads to a vagal reaction with palpitations, nausea, abdominal pain, lethargy, cold sweating, dizziness, vomiting, and diarrhea that occur within 30 min of food intake.

To prevent GI symptoms after obesity, patients are advised to consume frequent and small protein- and fiber-rich meals, chew their food well, eat slowly, and drink ample meals. Often, yeast baking, pasta, rice, and non-milled meats are poorly tolerated. Most patients eventually adjust to these eating patterns and to the limitations of obesity surgery, and the ailments will often disappear.

Postprandial hypoglycemia, also called late dumping, can occur in ≥7 % of patients after gastric bypass and is likely due to insulin hypersecretion. The condition occurs 1 to 3 h after food intake and is characterized by symptoms of low blood sugar. The symptoms may be reminiscent of dumping syndrome. In some patients, this condition could be very severe associated with neuroglycopenia that manifests as altered cognition, loss of consciousness, or even seizures. The main principle of prevention is to eat relatively small and frequent fiber-rich meals and to avoid quickly absorbable carbohydrates [36]. As for the episodes of symptomatic hypoglycemia, oral intake of carbohydrates (10—15 g) could be recommended to relieve the symptoms. When severe neuroglycopenia develops and the patient is unable to consume carbohydrates due to loss of consciousness, a family member may administer glucagon [37].

Other typical postoperative ailments are loss of hair, neuropathies, anemia (and related cold sensation), and poor wound healing. This is most pronounced during the weight reduction phase and usually normalizes as the weight stabilizes. The most common reason for this is micronutrient deficiency, which could be more profound after malabsorptive procedures. Intake of vitamins and minerals could lead to a speedy recovery [38].

Adjuvant weight loss medications

Although most patients gain from advances in bariatric surgery in terms of weight loss, some patients may experience weight recidivism [39]. The causation of this phenomenon is multifactorial and includes poor compliance with the proposed diet, impaired food behaviors like binge eating or grazing, inadequate physical activity and sedentary lifestyle, physiologic compensatory mechanisms, metabolic imbalances, and even postoperative complications [40]. It should be noted that obesity is a chronic condition, and thus it might be refractory to treatment in a subset of patients as a result of environmental influences or genetic predisposition. Several options were proposed to solve the issue of weight recidivism, and they cover the whole spectrum of interventions beginning with lifestyle modifications and ending with medical therapy and revisional surgical procedures [5].

In cases when anatomic causes are responsible for weight regain after bariatric surgery, revisional procedures are the best solution [41]. Still, it is worth remembering that they have an increased rate of complications compared with the primary procedures. This is why medical therapy may be proposed to those patients who carry a higher risk for undergoing revisional surgery or are less compliant with lifestyle changes. Phentermine is an appetite suppressant with a good safety profile, and its use started in 1959. Phentermine is prescribed alone or in combination with topiramate, and it results in 12.8 % excess weight loss in patients who have undergone bariatric surgery [42].

Although other weight loss medications like lorcaserin, naltrexone/bupropion, and liraglutide have recently appeared, phentermine is still most commonly prescribed in the United States, perhaps because it is the least expensive [43]. Since 2012, lorcaserin has been marketed under the brand name Belviq on the U.S. market. However, the FDA recently asked its manufacturer to voluntarily withdraw it owing to the potential risk for cancer [44].

There is a significant positive correlation between BMI before bariatric surgery and total weight loss after the use of weight loss medications [45]. Still, many questions regarding a protocol for adjuvant weight loss therapy after bariatric surgery remain unanswered. The range of these questions includes an optimal time for initiation of adjuvant pharmacotherapy, an adequate drug choice, and dosages. Additionally, there is a need to tailor adjuvant pharmacotherapy to the needs of the individual patient and to practice it in conjunction with dietary education and behavioral changes to prevent weight recidivism.

Vitamin and mineral deficiencies

Obese patients often have low serum vitamin levels even before surgery [46]. Postsurgically decreased absorptive surface area of the GI tract causes micronutrient deficiencies that are more obvious in patients who have undergone gastric bypass, duodenal switch, or sleeve gastrectomy. Moreover, some patients may develop an aversion to specific foods, which further deteriorates their micronutrient status [47]. The following micronutrient deficiencies are most frequently observed: vitamins B_1 (thiamin), B_9 (folate), and B_{12} (cobalamin), and D; and trace elements iron, copper, and zinc [48].

Although it is recommended that take vitamin and mineral supplements, micronutrient deficiency is rather common and may even induce clinically significant morbidity [49]. As such, after gastric bypass, 60% to 80% of patients taking only one multivitamin tablet daily become deficient in vitamin B_{12}, iron, and vitamin D [50]. As is the case with other major surgical interventions, anemia secondary to iron or vitamin B_{12} deficiency is common [51]. The bone density in the hip and thigh is reduced, but it is unclear whether this is a physiologic adaptation to lower body weight or a pathophysiologic process [52]. There is no reliable evidence that obesity surgery increases the risk for fractures [53]. In rare cases, severe thiamine deficiency in the months after obesity surgery can lead to Wernicke encephalopathy [54].

For all these reasons, there is a need to understand which vitamins and micronutrients should be monitored and at which intervals after different types of bariatric interventions. This may help to identify deficiencies at a subclinical stage before they become clinically evident and cause associated health problems. However,

a number of financial issues arise as vitamin assays are not cheap, and interpretation of their results may be rather misleading. Thus, the use of health care resources needs to be balanced in relation to the expected outcomes [55].

Given the dangers of vitamin and mineral deficiencies after surgery, it is recommended that all patients take prophylactic vitamin and mineral supplements. Although a number of guidelines for post-surgical monitoring of patients exist, their recommendations for prophylactic supplementation vary [21,56,57], primarily because of the scarcity of solid evidence in this field. Still, it is quite obvious that patients with several micronutrient deficiencies require more comprehensive follow-up and aggressive case management.

After malabsorptive bariatric interventions, a slow process of adaptation to intestinal malabsorption occurs and is accompanied by an increase of the absorptive surface area of the GI tract [58]. Being responsible for micronutrient absorption, channel proteins, and carrier proteins are produced in higher amounts that may decrease the need for micronutrient supplementation over time [59]. To our knowledge, however, is a lack of long-term studies investigating an increase in micronutrient absorption after post-surgical GI adaptation.

Physical activity

In those patients who are not considered suitable candidates for bariatric surgery, routine physical exercise is an integral part of a long-term weight reduction program. However, physical activity alone does not result in substantial body weight loss and needs to be supported by food restriction [60]. As for patients who have undergone bariatric interventions, little is known as to whether physical exercise can provide any benefits in terms of additional weight loss, prevention of weight recidivism, and improved health outcomes.

According to different estimates, suboptimal weight loss is observed in 10% to 30% of bariatric surgery patients and high preoperative BMI, older age, T2DM, impairment of cognitive functions, and mental health are the strongest predictors [61,62]. It might be hypothesized that in such a category of patients, physical exercise is an important adjunctive therapy for weight loss. However, a number of intervention studies failed to establish any additional effects of exercise on weight loss in post-bariatric patients [63,64]. Similarly, one study reported an improvement of excess weight loss at 12, but not 36 mo after surgery [65]. This lack of effect on weight loss might be attributed to the strong influence produced by the surgery itself. However, these findings do not exclude the possibility that additional weight loss might be induced by a higher dose/intensity of exercise.

As for the prevention of weight recidivism after bariatric surgery, physical activity has been shown to produce beneficial effects on long-term normalization of body weight subsequent to dietary restrictions [66]. Although the data obtained from National Weight Control Registry demonstrate that moderate-intensity exercise plays a significant role in the maintenance of weight loss [67], there is no evidence to support these findings in the context of bariatric surgery. That is why the question of the importance of physical exercise for weight loss maintenance after obesity surgery remains unanswered.

In addition to depletion of adipose tissue, 31.3% of weight loss after gastric bypass is due to the loss of fat-free mass (FFM) that is composed of skeletal muscles, body organs, and bones [68]. Although clinical effects produced by that loss are not fully understood yet, FFM significantly affects the resting energy expenditure and regulates the core body temperature [69]. For this reason, a loss of FFM may induce weight recidivism in the long term [70]. It was reported that regular physical exercise (30 min of exercise per session, more than three sessions a week) in post-bariatric patients induced 28% excess loss of adipose tissue and 8% excess gain in skeletal muscle [71].

As for senile post-bariatric patients, a decrease of bone density and depletion of skeletal muscle might significantly deteriorate physical functioning, cause the progression of sarcopenia, and reduce QoL [72]. It has been demonstrated that physical exercise might be particularly effective in the preservation of skeletal muscle in older adults [73] and thus, might prove to be useful in senile post-bariatric patients.

Apart from weight loss, bariatric surgery facilitates a number of positive metabolic changes, including improved glycemic control and insulin sensitivity [74]. Although bariatric surgery enables significant loss of adipose tissue, lean metabolically healthy individuals have better insulin sensitivity [75]. Because lean mass is primarily responsible for glucose utilization after meals, physical activity may play a role in the improvement of peripheral insulin sensitivity after bariatric surgery. This is confirmed by the findings of a randomized controlled trial that demonstrated the potential of moderate aerobic exercise in additional improvements in insulin sensitivity in a cohort of patients who had undergone gastric bypass [64].

Mental illnesses

Many postbariatric patients present with the symptoms of mental distress before the surgery. For instance, it has been reported that the prevalence of depression and anxiety at the time of preoperative evaluation is around 20% to 60% and 30% to 50%, respectively [76,77]. In general, 16% of patients are considered to be inappropriate candidates for bariatric surgery and are thus referred to psychological counseling. Psychotropic medications are commonly prescribed to candidates for bariatric surgery, and nearly 50% of them receive at least one medication [78]. Antidepressants are being prescribed most frequently, followed by anxiolytics and mood stabilizers [79].

Mental symptoms, eating disorders, and QoL generally improve after obesity surgery, and this change is proportional to weight loss [80]. At the time of a 1-y follow-up, 50% of bariatric patients are no longer taking any psychotropic medication, however, 4% are newly prescribed some antidepressant medication [79]. This implies that few patients free from depression at preoperative evaluation develop it at the time of a 1-y follow-up. This may be due to underdiagnosed and undertreated psychopathology presenting before and after bariatric surgery.

Prescription of antidepressants and psychotropic medication to a patient after bariatric surgery causes special considerations related to intestinal drug absorption and metabolism. This is predisposed by a number of physiologic and pathologic factors induced by surgery, alterations in electrolyte balance, and nutritional status. Also, these patients may have altered drug elimination compared with their preoperative status because of changes in enterohepatic circulation [81].

It is important to be aware that positive psychological effects are often most pronounced in the weight reduction phase and that they can be transient [82]. Inadequate weight loss, failure to lose weight, or early weight loss plateau may predispose bariatric patients to depression and anxiety. In turn, this may provoke the impairment of food behavior and binge eating disorder [83]. Increased incidence of suicide after obesity surgery has been reported [84], and the rates of suicide are 58% higher than those in the control groups. Expressed in terms of per 10 000 persons per year, the postsurgical incidence of suicide ranges from 4.1 to 11.1

[85,86]. Of interest is the fact that around 30% of suicides are observed during the first year of follow-up, and the remaining 70% occur during the 3 y after bariatric surgery [87]. Thus, patients with serious mental illness may need close postoperative follow-up from local obesity centers, physicians, and psychiatric specialist health services.

Pregnancy

Women of childbearing potential undergoing obesity surgery are advised to avoid pregnancy before surgery and for the first 12 to 18 mo postoperatively. Because fertility is affected by obesity due to oligo-anovulation and irregular menstrual cycle [88], women should be informed that fertility may increase as a result of weight loss. Apart from preconception, obesity is associated with an increased risk for miscarriage before 20 wk of gestation [89]. Excess body weight also carries elevated risks for maternal, fetal, and neonatal complications, including gestational hypertension, gestational diabetes mellitus, and pre-eclampsia [90], large-for-gestational-age newborn, birth injuries and premature delivery, and neonatal hypoglycemia and hyperbilirubinemia [91].

There are publications that addressed the issue of pregnancy after bariatric surgery in terms of maternal and neonatal outcomes. Although obesity surgery can substantially reduce the incidence of the irregular menstrual cycle by nearly 50% and of polycystic ovary syndrome by close to 40% [92], it is important to maintain an optimal lifelong BMI to preserve fertility. According to a meta-analysis conducted by Milone et al., women with higher presurgical BMIs had lower rates of postsurgical spontaneous pregnancies and the number of kilograms lost did not significantly improve it [93]. As for gestational diabetes mellitus, its rates decrease significantly in post-bariatric pregnant women compared with obese women with no previous bariatric surgery. Also, the rates of pregnancy-related hypertensive disorders and pre-eclampsia decrease significantly in women who have undergone bariatric surgery compared with their obese counterparts [94,95].

There is ample literature reporting neonatal outcomes in post-bariatric pregnancies. The most recent meta-analysis published by Kwong et al. reported significantly reduced rates of large-for-gestational-age infants (odds ratio [OR], 0.31) in post-bariatric women [96]. However, there was a significant increase in small-for-gestational-age infants (OR, 2.16), intrauterine growth restriction (OR, 2.16), and preterm deliveries (OR,35) compared with women who did not have bariatric surgery. The same meta-analysis failed to establish the differences in rates of stillbirths, admissions to neonatal intensive care unit, congenital malformations, and neonatal death [96]. A significant risk for preterm birth in pregnancies after bariatric surgery was also confirmed by two other meta-analyses [94,95]. Nevertheless, an earlier published large study identified a trend toward a higher combined risk for neonatal mortality and stillbirth in post-bariatric women [97].

Although it is commonly recommended that women should avoid conception during a phase of active weight loss that usually lasts for the first 12 mo postsurgery due to the risks for impaired fetal growth, little is known about those who conceive within this period. Still, no differences in neonatal birth weight, small-for-gestational-age and large-for-gestational-age newborns, prematurity, congenital anomalies, and neonatal intensive care unit admission were reported for women who conceived before and after 12 mo [98]. Nevertheless, a recommendation to ensure a proper follow-up and monitoring for those women who become pregnant after bariatric surgery appears to be reasonable.

Plastic surgery

Being a common consequence of bariatric surgery, massive weight loss is characterized $\geq$50% loss of excess weight [99]. Post-bariatric patients frequently present with excess skin and loss of skin elasticity that causes many cosmetic issues. Post-bariatric patients may have breast ptosis, upper and mid-back rolls, "deflated" arms, and abdominal "apron." The newly appeared skin folds lead to intertrigo and skin irritation that often are resistant to medical therapy. This is why these patients represent a challenge to plastic surgeons.

The most suitable candidates for post-bariatric plastic surgery are those who maintain a stable weight for$\geq$3 to 6 mo 1 y after the surgery. Although postbariatric patients have a BMI of 25 to 35 kg/m^2, the commonly used indications for body contouring are BMI $<$30 kg/m^2, absence of comorbidities or very few health problems, non-smoking, and realistic expectations considering the possible outcomes [100]. As for realistic expectations after postbariatric contouring procedures, the patients need to realize that they will require a number of surgeries over a period of time and that there will be scars in the places of skinfolds. However, many patients readily accept those limitations in exchange for improved body contours [101].

The abdomen is an area of most common interventions. Liposuction is often done on patients with BMI $>$30 kg/m^2 as patients presenting with lower BMI may only need skin excision. Apart from the abdominal area, liposuction could be applied to the back, thighs, arms, and neck. As many post-bariatric patients present with abdominal pannus, a panniculectomy is one of the frequently performed contouring procedures. Because this procedure does not address flanks, abdominoplasty helps to remodel the entire abdomen, and it could be combined with circumferential procedures if back deformities are also present [102].

Breast ptosis is another consequence of massive weight loss, and mastopexy or breast lift surgery may be performed. Although those patients who preserve excess BMI may benefit from breast reduction, decreased breast volume could be corrected by augmentation with autologous fat or breast implants. In contrast with women, post-bariatric men may benefit from the rejuvenation of the breast as other breast surgeries could be feminizing for them [103]. Because many postbariatric patients present with "wings," brachioplasty is done to enable an appropriate arm contouring [104]. Perhaps, the most challenging task for a plastic surgeon is to address the remaining adiposity in thighs. Although lateral thigh may be reached during lower body lifting, medial thigh requires a different approach, which resembles brachioplasty [105].

Provision of post-bariatric services

Several clinical practice guidelines consider the issue of the provision of medical services to post-bariatric patients. A minimum of 2 y of follow-up should be provided at regular intervals by a team of qualified professionals consisting of a surgeon, a dietician, and a nurse. Access to other health care professionals, such as a clinical psychologist, should be provided if needed. Hematologic parameters must be evaluated at each follow-up, in addition to biochemical and nutritional evaluations. The tests must be repeated promptly if any unexpected symptoms are demonstrated [106].

At every visit, a patient's weight should be checked and recorded, and evaluation of weight-related health problems must be made with a subsequent adaptation of a dosage of previously prescribed medications. Commonly, a surgeon is invited when postsurgical complications, such as a stricture, are suspected [107]. Still, several patient groups require more frequent follow-up. The sample of these could be made of pregnant and breastfeeding

Table 1
Summary of key recommendations after bariatric surgery

Patient care domain	Intervention	Expected outcome
Early postoperative period		
Diet	Clear liquid diet for a short time period	Prevention of postoperative anastomosis leakage
	Full liquid diet and pureed foods for first 1—2 wk	Early return to normal bowel functioning
Medical therapy	Provision of multimodal analgesics	Pain control
	Oral therapy in liquid form or crushed tablet	Prevention of postoperative anastomosis leakage
	Oxygen administration via nasal cannula	Prevention of respiratory problems
Medical evaluation	Evaluation of basic metabolic profile every 12—24 h within the first 5—7 postoperative days	Early identification of any related health problems for timely management
Ambulation	Encouragement of early ambulation	Prevention of venous thromboembolism
Late postoperative period		
Diet and eating behavior	A well-balanced diet with limited intake of carbohydrates and an emphasis on protein sources	Preservation of optimal body weight and bowel functioning. Prevention of obesity recidivism
	Monitoring with a qualified dietitian	
	Promotion of healthy eating behavior	
Micronutrient supplementation	A supplement of vitamins, minerals, and essential trace elements	Prevention and management of deficiency states, and decrease the load of comorbidity
Medical evaluation	Monitoring of physiologic parameters with dosage adjustments of medication	Prevention of associated morbidity and mortality
	Regular checkups by a team of qualified professionals	
Ambulation	Encouragement of routine physical exercise	Preservation of optimal body weight, prevention of sarcopenia
Psychological support	Provision of psychology services	Prevention of mental distress

women, patients receiving proton pump inhibitors or thyroxine, patients who underwent to duodenal switch surgery, patients with preexisting intestinal disorders, patients with chronic kidney disease or cardiovascular disease, immobile patients or wheelchair users, and patients with mental health problems [21]. Because other medical professionals commonly follow such categories of patients, there is a need to establish good communication with them to enable a prompt exchange of information.

Patient support groups are becoming increasingly popular, and post-bariatric peer support is not an exception. Apart from offline meetings, many patients could benefit from visiting online forums and specialized websites [108]. Those patients who are lost from follow-up present a big challenge as the timely evaluation of their health status is jeopardized. Thus, professionals providing post-bariatric services have to make every effort to contact such patients either personally or via a general practitioner.

Many countries established specialized bariatric centers to provide a comprehensive postsurgical follow-up. However, usually after 2 y postsurgery, the patients are discharged to primary care facilities where they receive lifelong monitoring with at least annual checks of their nutritional status and evaluation of obesity-related problems. Both post-bariatric patients and their general practitioners have to be informed about a list of symptoms that would require referral to a specialized bariatric center as they are indicative of late surgical complications [109].

In general, maintaining close contact with a patient is a key aspect of improving patient satisfaction with the quality of medical care provided [110]. In turn, this leads to strengthening the provider—patient relationship and increased adherence to treatment recommendations [111]. Thus, a number of international guidelines were published over the past decade in order to improve the quality of medical services available to post-bariatric patients [1,112—114]. In many ways, these guidelines share similar approaches in specifying different aspects of follow-up after bariatric surgery. Table 1 presents an overview of key recommendations on immediate and long-term postoperative care for bariatric patients.

Conclusions

At present, bariatric surgery is becoming increasingly popular in the management of patients with severe obesity. Although generally bariatric surgery is safe and effective, certain clinical problems may arise postsurgically and will require special knowledge and skills from the side of medical professionals involved. This covers a range of preventive, diagnostic, and treatment strategies designed to deliver appropriate care to the post-bariatric patient. A comprehensive post-bariatric follow-up should be provided to all patients regularly as an integral part of their clinical pathway. Perhaps the best approach to the provision of such care is to establish specialized bariatric centers. Still, taking into account the growing number of bariatric patients, the concept of shared care could also be considered. Under this concept, immediately after the early surgical period, a part of post-bariatric care is transferred to general practitioners who, along with obesity specialists and dieticians, monitor a patient's health status. Regardless of the model of care, it is crucial to provide a long-term follow-up and monitoring to all bariatric patients, which will improve surgery outcomes and safety.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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