“OVIDIUS” UNIVERSITY OF CONSTANŢA

DOCTORAL SCHOOL OF MEDICINE

DOCTORAL DOMAIN OF MEDICINE

DIABETES TYPE II RISK FACTOR FOR HEPATOCELLULAR CARCINOMA

ABSTRACT OF DOCTORAL DISSERTATION

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Content

INTRODUCTION

Hepatocellular carcinoma is the 6th neoplasia incidence and the third leading cause of cancer death in the world. Throughout the world are diagnosed each year approximately 630,000 new cases of HCC. Hepatocellular carcinoma mortality index reach 94% [1].

The most common and known risk factor are viral infection, virus B or C, toxic factors - alcohol and aflatoxin, immune diseases like primary biliary cirrhosis plus in recent years metabolic risk factors like diabetes and non-alcoholic hepatic steatosis

A possible explanation for the association of diabetes with hepatocellular carcinoma is that diabetes is often part of the metabolic syndrome characterized by clinical and biochemical changes that include alterations in glucose metabolism and insulin causing hyperglycemia and hyperinsulinemia, dyslipidemia and hypertension. Metabolic disorders associated with metabolic syndrome can cause diabetes and furthermore contribute to the development of NAFLD (non-alchoolic fatty liver disease) and its most severe form non-alcoholic steatohepatitis, so HCC can result from liver cirrhosis caused by NAFLD.

Thus appears to justified an accurate assessment of the risk factors of hepatocellular carcinoma to develop new therapeutic modalities and correct assessment of the evolution and prognosis.

AIM AND OBJECTIVES

- assessment of the main risk factors associated with the development of hepatocellular carcinoma
- description of the clinical features and metabolic patients with type 2 DM and HCC.
- exploring the link between type 2 DM and HCC and establishing a temporal relationship between type 2 DM and HCC occurs
- The impact of oral antidiabetics and insulin therapy in HCC occurrence.
- The impact of diabetes and other risk factors on the development of hepatocellular carcinoma

MATERIAL AND METHODS

It is a retrospective study conducted in Medical Clinic, Oncology and Diabetes and Metabolic Diseases of the Emergency County Hospital "St. Andrei" Constanţa, for a period of four years, from 2009 to 2012 and includes a total of 156 patients diagnosed with hepatocellular carcinoma.

Inclusion criteria:

- aged over 18 years.
- Patients with HCC diagnosed by abdominal ultrasound, CT, MRI, laboratory tests.
- Patients with confirmed type 2 diabetes treated with oral antidiabetic agents and / or insulin.

RESULTS AND DISCUSSION

Demographic characteristics of the batch total

The study included a total of 156 patients diagnosed with HCC, later total group was divided into subgroups according to the study objectives and parameters evaluated.

The distribution of cases according to sex show predominance in men 94 HCC cases (60.3%) vs women 62 cases (39.7%), consistent with the data from the literature indicating the male gender as a risk factor for hepatocellular carcinoma.

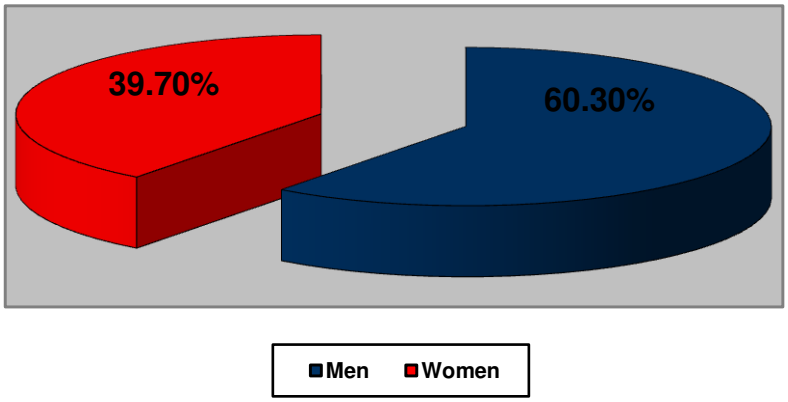

Figure No. 1 Distribution of patients by gender

The average age was 64.39 years for men and 69.53 years for women. (Figure no.2)

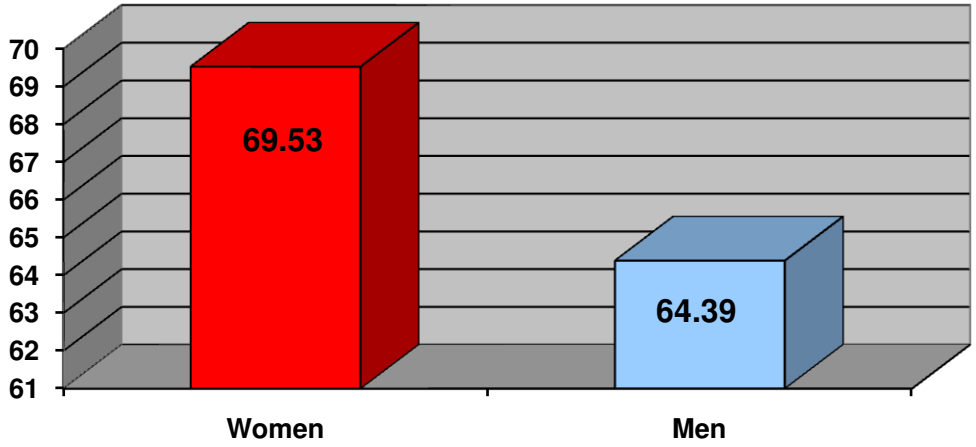

Figure no.2 distribution by age and sex

Analysis of risk factors involved in the occurrence of HCC

Regarding risk factors for HCC occurrence in the studied group distribution was as follows taking into account the most frequent risk factors known: the highest percentage of patients with HCC were associated C virus infection 32.7% of cases, followed by infection with virus B 21.8%, and 14.7% of the associate alcohol. A total of 48 cases (30.76%) were considered unknown origin, patients are B or C virus infection and also deny alcohol.

Also 3.20% of the cases associating mixed etiology viruses B and C infection, HCV infection, among cases with associated 3.84% and alcohol and 2.56% of the cases with HBV associated alcohol consumption.

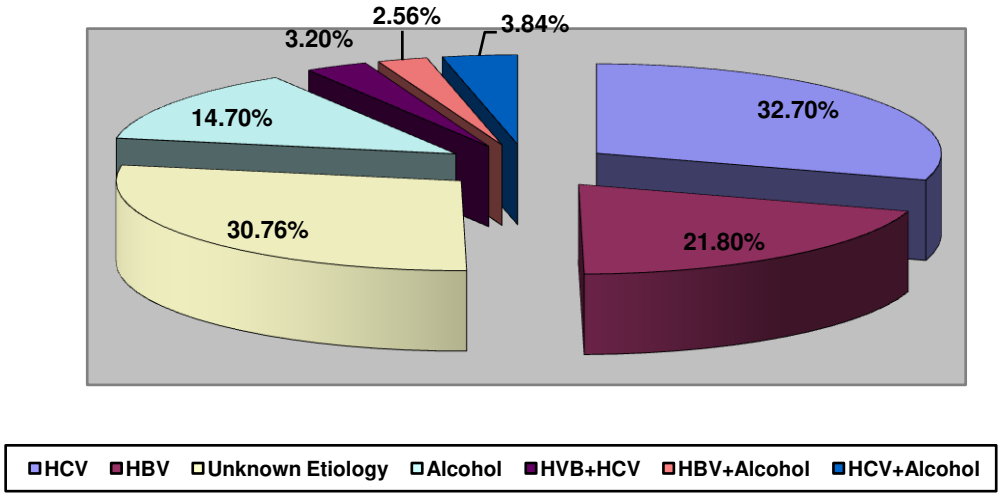

Figure 3. Distribution of of cases according to risk factors for HCC

Liver cirrhosis

Patients with liver cirrhosis regardless of the etiology have an increased risk for developing HCC. Studies have shown that age, male gender and disease severity are predictors for the occurrence of HCC regardless of the the etiology of cirrhosis.

In the study of the 156 total, patients with HCC 94 (60.3%) had cirrhosis at diagnosis of HCC. It notes the predominance of males in the study group. The age of patients in the study varied between 38 and 90 years with a mean age of 65.48 years and found the occurrence of liver cirrhosis in older women, compared to men.

Table 1 Distribution of cases of liver cirrhosis by sex

		Liver cirrhosis	**Total**
Sex	Women	38	38
	Man	56	56
Total		94	94

Study on the impact of diabetes mellitus in patients with HCC

Comparative analysis of patients with HCC diabetics and non-diabetics

Diabetes was associated with HCC development in recent years, trials suggesting involvement in hepatic carcinogenesis of chronic hiperisulinemia and insulin-like growth factor.

In total lot of 156 patients with HCC studied, the presence of diabetes mellitus type II is represented by a total of 37 cases which represents a rate of 23.7%. Data from the literature show an incidence of DM variable, thereby a study in Taiwan show an incidence of 15.8% of cases. [44], while another study by JA Davila United States in 2005 proves the presence of diabetes in patients with HCC in a percentage of 43.3% [45].

1. Distribution of cases according to sex and age

Both groups showed a higher incidence of HCC in men, 61.3% in HCC group respectively 56.8% in the group of patients with HCC and DZ data show no statistically significant difference between the two groups (p> 00.5), the data are comparable with the literature indicates males as risk factor for hepatocellular carcinoma.

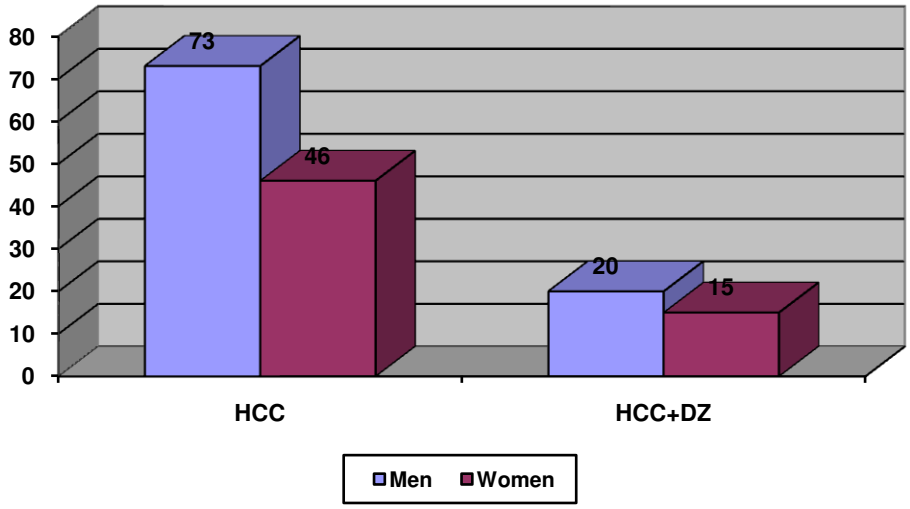

Figure No. 4 Distribution of lots by gender

The average age in the group of HCC was 70.0 years, compared to the group of diabetic patients in which the mean age was of 65.38 years, statistically significant difference p <0.05 (p = 0.03) so the data indicating the occurrence of HCC in younger diabetic patients compared to non-diabetics.

Table no.2 Correlation according to age

			Age	DZplusHHC
Spearman's rho	Age	Correlation coefficient	1,000	,171*
		Sig. (2-tailed)	.	,033
		N	156	156
	DZ-HHC	Correlation coefficient	,171*	1,000
		Sig. (2-tailed)	,033	.
		N	156	156

*. Significant correlation level 0.05 (2-tailed).

2. Distribution of cases according to the presence of other risk factors

In the group of non-diabetic patients with HCC, out of 119 , 42 cases (35.3%) has associated with HCV infection, 30 cases (25.2%) B viral infection and 18 (15.1 %) associated with alcohol consumption.

Of the total 37 cases HCC-DM group, 9 cases (24.3%) presented associated HCV infection, 4 cases (10.8%) were associated with HBV infection and 5 cases (13.5%) associated with alcohol consumption .

It is known that HCV infection has a distinct metabolic profile, associating insulin resistance (IR), hepatic steatosis and cholesterol, thus outlining a particular Metabolic Syndrome. Insulin resistance may thus lead to the emergence of type 2 diabetes.

Table 3. Distribution of lots with the combinations of other risk factors

Lot		Alcohol	VHC	VHB
HCC	Total	119	119	119
	Medie	.15	.35	.25
	Std deviation.	.360	.480	.436
	Minim	0	0	0
	Maxim	1	1	1
HCC-DZ	Total	37	37	37
	Medie	.14	.24	.11
	Std. deviation	.347	.435	.315
	Minim	0	0	0
	Maxim	1	1	1

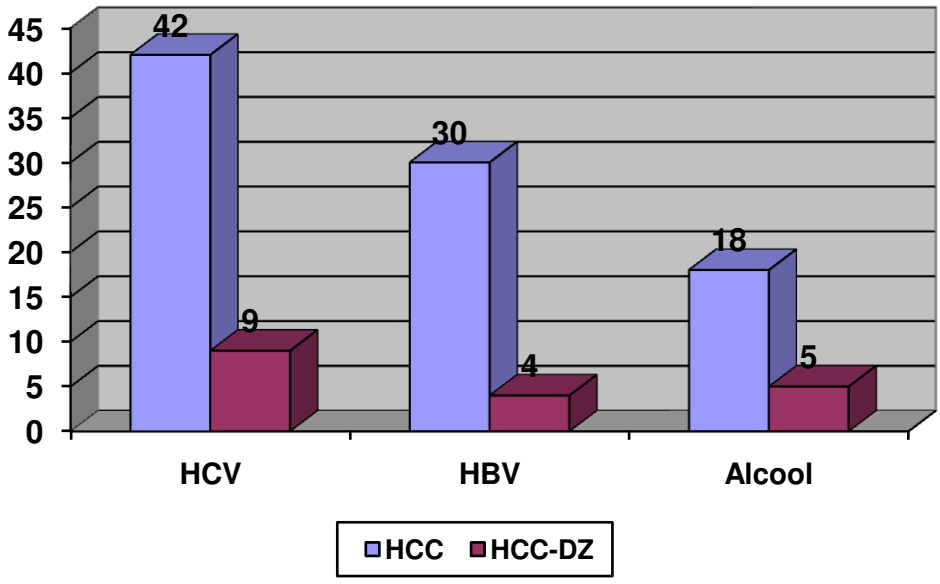

Figure 5. Distribution of cases according to the association of other risk factors

3. Distribution of cases according to the presence of liver cirrhosis

Cirrhosis of the liver in the non-diabetic group was present in a higher percentage compared to the group of diabetic patients, 78 cases (65.5%) and 16 cases (43.2%), which indicates that the hepatocarcinoma in patients with diabetes mellitus occurs in the absence of the hepatic cirrosis, comparison between the two groups is statistically significant (p <0.05).

Table 4. Statistical correlation between diabetes and liver cirrhosis

			DZ-HHC	Ciroza Hepatica
Spearman's rho	DZ-HHC	Correlation coefficient	1,000	-,194*
		Sig. (2-tailed)	.	,015
		N	156	156
	Ciroza Hepatica	Correlation coefficient	-,194*	1,000
		Sig. (2-tailed)	,015	.
		N	156	156

*. Significant correlation level 0.05 (2-tailed).

4. Analysis of cases according to aspect of liver tumor

It is observed in the studied groups a higher percentage of multiple tumors in the group HCC-DM (51.4%) compared with non-diabetic patients group (47.9%) but no statistically significant difference (p> 0.05), data are comparable with data from the literature specialty.

Following data depending on the size of liver tumor seen in both groups studied higher percentage of tumors with diameter greater than 3cm 83.1% for non-diabetic patients group and 54.4% respectively for the group of diabetic patients.

Comparing the two groups based on the size of liver tumors is observed statistically significant difference (p <0.05), so it can be concluded that in non-diabetic patients were observed more advanced HCC.

The data are not consistent with the literature; a study by Deepak N. reveal more advanced HCC patients compared to non-diabetics diabetics tumors larger than 3 cm are present in a higher percentage in this study in diabetic patients [46]

Table No.5 Correlation between tumor size and the presence of diabetes

			Tumor size	DZplusHHC
Spearman's rho	Tumor size	Correlation coefficient	1,000	-,286**
		Sig. (2-tailed)	.	,006
		N	93	93
	DZ-HHC	Correlation coefficient	-,286**	1,000
		Sig. (2-tailed)	,006	.
		N	93	156

**. Significant correlation level 0.01 (2-tailed).

Portal vein thrombosis is present in the group of non-diabetic patients the percentage of 47.1% compared to the group of diabetic patients in which portal vein thrombosis was present in 18.9% of cases studied.

Depending on the presence of portal vein thrombosis is observed that there is statistically significant difference between the two groups studied, which means more advanced forms of HCC as were found in the studied groups in non-diabetic patients (p <00.5).

The data are not consistent with the literature, studies showing the presence of portal vein thrombosis percent higher in diabetic patients.

Table 6 Correlation between the presence of VP thrombosis and diabetes

			Portal vein trhombosis	**DZ-HHC**
Spearman's rho	Tromboza VP	Correlation coefficient	1,000	-,244**
		Sig. (2-tailed)	.	,002
		N	156	156
	DZ-HHC	Correlation coefficient	1,000	1,000
		Sig. (2-tailed)	,002	.
		N	156	156

**. Significant correlation level 0.01 level (2-tailed).

5. Analysis of cases according to laboratory findings

Comparing laboratory findings between the two groups studied are not observed statistically significant differences, except as expected blood glucose values that are statistically significantly higher in the group of diabetic patients. The data are presented in Tables 7

Table 7 Biological parameters in parameters studied groups

Parameters	Diabetes	Non-diabetes	P value
Bilirubin	3.73	3.10	0.582
Hemoglobin	11.76	11.22	0.280
Platelets	133648.65	155705.88	0.435
APTT	75.87	71.94	0.274
Glucose	195.16	113.99	0.00
Total cholesterol	157.14	199.58	0.091
Lipids	146.17	119.00	0.492

6. Analysis of cases according to the AFP

The average values of AFP were higher in the group of non-diabetic patients (AFP = 4386.99ng / ml) compared with diabetic group (AFP = 3329.12ng / ml) but not statistically significant difference was found between groups (p> 0.05). Data are consistent with those in the literature.

There is no significance between sex, age, Child-Pugh class, tumor appearance, tumor size, presence of metastases and AFP.

Comparing the presence of thrombosis AFP and VP statistical significance is observed in the group of non-diabetic patients (p <0.05), in the group of diabetic patients is not observed statistical significance between the presence of VP thrombosis and AFP value (p> 0.05).

Table 8 Correlation between the presence of thrombosis VP and AFP value

	DZ-HHC			AFP	Portal Vein Thrombosis
Spearman's rho	No	AFP	Correlation coefficient	1,000	,200*
			Sig. (2-tailed)	.	,030
			N	118	118
		Portal Vein Thrombosis	Correlation coefficient	,200*	1,000
			Sig. (2-tailed)	,030	.
			N	118	119
	Yes	AFP	Correlation coefficient	1,000	,168
			Sig. (2-tailed)	.	,320
			N	37	37
		Portal Vein Thrombosis	Correlation coefficient	,168	1,000
			Sig. (2-tailed)	,320	.
			N	37	37

*. Significant correlation level 0.05 (2-tailed).

7. Analysis of cases according to metastases

Of the 31 included in the study (19.1%) had metastases at diagnosis. 23 cases in the group of non-diabetic patients, and 8 patients in the group of diabetic patients.

Tabel nr 9 Distribuţia cazurilor în funcţie deprezenţa metastazelor

DZ-HHC			Total	Percent	Valid percent	Cumulativ percent
No	Valid	No	96	80,7	80,7	80,7
		Yes	23	19,3	19,3	100,0
		Total	119	100,0	100,0	
Yes	Valid	No	29	78,4	78,4	78,4
		Yes	8	21,6	21,6	100,0
		Total	37	100,0	100,0	

Analyzing by gender, metastases are observed in males in both groups of patients with no statistically significant difference (p> 0.05). There are also no statistical significance between age and the presence of metastases.

8. Analysis of cases according to CLIP score

CLIP score system is the latest assessment of prognosis for patients with HCC. The score combines data on tumor characteristics (morphology, serum AFP levels, and the presence or absence of portal vein thrombosis with an index of severity of cirrhosis to determine a prognostic score ranges from 0 to 6.

Comparing the two groups was observed in the group of diabetic patients that the most patients have a CLIP score 0 (40.5%) which shows a median survival of 42.5 months compared with non-diabetic group that most patients were 2 score falling by an average of 16.5 spravieţuire months statistically significant difference (p <0.05)

Table no.10 Correlation between the 2 groups according to CLIP score

DZ-HHC			Total	Percent	Valid Percent	Cumulativ percent
No	Valid	0	17	14,3	14,3	14,3
		1	20	16,8	16,8	31,1
		2	36	30,3	30,3	61,3
		3	30	25,2	25,2	86,6
		4	11	9,2	9,2	95,8
		5-6	5	4,2	4,2	100,0
		Total	119	100,0	100,0	
Yes	Valid	0	15	40,5	40,5	40,5
		1	9	24,3	24,3	64,9
		2	10	27,0	27,0	91,9
		3	2	5,4	5,4	97,3
		4	1	2,7	2,7	100,0
		Total	37	100,0	100,0	

Tabel no 11 Correations of CLIP score in DM patients

			DZ-HHC	CLIP scor
Spearman's rho	DZ-HHC	Correlation coefficient	1,000	-,342**
		Sig. (2-tailed)	.	,000
		N	156	156
	CLIP scor	Correlation coefficient	-,342**	1,000
		Sig. (2-tailed)	,000	.
		N	156	156

**. Significant correlation level 0.01 (2-tailed).

Looking at CLIP score according to gender in the two groups is not observed statistically significant association (p> 0.05).

Table No.12 Correlation of CLIP score by gender

	DZ-HHC			CLIP score	Sex
Spearman's rho	No	CLIP score	Correlation coefficient	1,000	,052
			Sig. (2-tailed)	.	,572
			N	119	119
		Sex	Correlation coefficient	,052	1,000
			Sig. (2-tailed)	,572	.
			N	119	119
	Yes	CLIP score	Correlation coefficient	1,000	-,162
			Sig. (2-tailed)	.	,339
			N	37	37
		Sex	Correlation coefficient	-,162	1,000
			Sig. (2-tailed)	,339	.
			N	37	37

Analyzing the CLIP score according to age is observed statistically significant association in the sense the presence of a higher score once with age (p <0.05) in the group of non-diabetic patients. In the group of patients with diabetes there is statistically significant association between CLIP score and age.

Tabel no.13 Correlation of CLIP score by age

	DZ-HHC			CLIP score	Varsta
Spearman's rho	No	CLIP score	Correlation coefficient	1,000	-,219*
			Sig. (2-tailed)	.	,017
			N	119	119
		Age	Correlation coefficient	-,219*	1,000
			Sig. (2-tailed)	,017	.
			N	119	119
	Yes	CLIP score	Correlation coefficient	1,000	-,122
			Sig. (2-tailed)	.	,471
			N	37	37
		Age	Correlation coefficient	-,122	1,000
			Sig. (2-tailed)	,471	.
			N	37	37

The study of patients group with diabetes

The group of diabetic patients is made up of a total of 37 patients, the majority of male 21 cases, 16 female. Descriptive data were presented earlier versus the non-diabetic patients**.**

Treatment of diabetes might affect cancer incidence and mortality [47]. Since the 1960s, metformin (one of the most popular biguanide) has become first-line therapy in diabetic type 2 diabetes worldwide [48]. It has been shown to have a protective potential against cancer as observed in a pilot study on the incidence of Scotland [49] and in a cohort study conducted later [50] in Saskatchewan, Canada [51].

Analyzing according existing antidiabetic notice the following: 21 cases have oral antidiabetic therapy (56.8%), 11 cases insulin (29.7%) and 6 cases have no therapy, only diet 16.2%

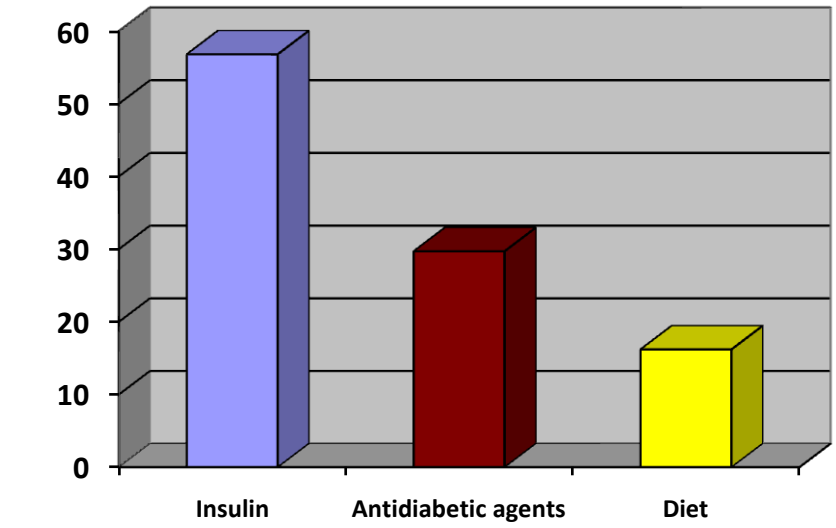

Figure no 6 Distribution of cases according to the type of therapy

According to the oral therapy most cases have as treatment Sulfonylureas 12 cases (32.4%), followed by treatment with metformin in 8 cases (21.6%), and combination of both in 1 patient (2.7%).

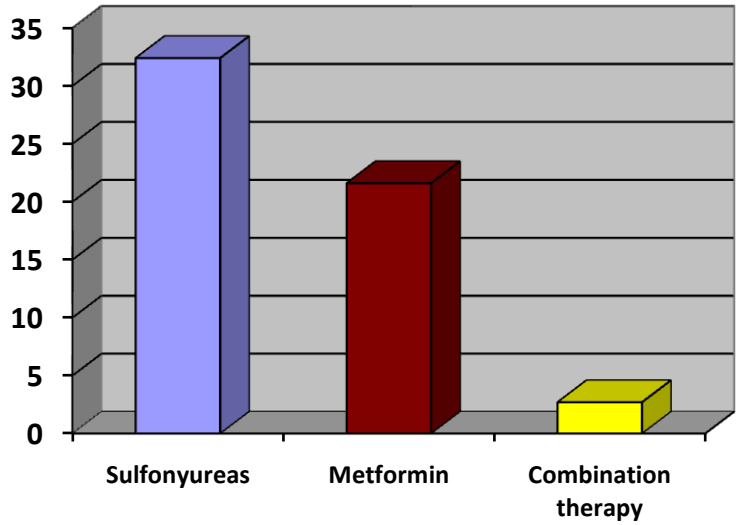

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Figure No. 7 Distribution of cases according to the type oral therapy

The distribution by sex is as follows: oral antidiabetic therapy for most patients are men 14 cases and only 7 women. Regarding insulin therapy most cases were women, 8 cases and only 3 men. (table 14 and 15)

Table no.14 Distribution by oral therapy and gender

DZ-HHC			Oral therapy		Total
			No	Yes	
da	Sex	Women	9	7	16
		Men	7	14	21
	Total		16	21	37

Table no.15 Distribution by insulin therapy and gender

DZ-HHC			Insulin		Total
			No	Yes	
da	Sex	Women	8	8	16
		Men	17	3	20
	Total		25	11	36

There were no statistically significant differences between type of therapy and the AFP value, tumor type or presence of portal vein thrombosis (p> 0.05), but comparative statistical analysis of the type of therapy with tumor size data show statistically significant in patients treated with oral antidiabetic in the sense that these patients have tumor size <3 cm (p <0.05)

Table No.16 Correlation between oral therapy and tumor size

		DZ-HHC		Oral therapy	Tumor size
Spearman's rho	Oral therapy	Yes	Correlation coefficient	1,000	,450*
			Sig. (2-tailed)	.	,036
			N	37	22
	Tumor size (Cm)	yes	Correlation coefficient	,450*	1,000
			Sig. (2-tailed)	,036	.
			N	22	22

*. Significant correlation level 0.05 (2-tailed).

Table No.17 Correlation between insulin therapy and tumor size

		DZ-HHC		Tumor size	Insulin therapy
Spearman's rho	Tumor size (Cm)	Yes	Correlation coefficient	1,000	-,304
			Sig. (2-tailed)	.	,180
			N	22	21
	Insulin therapy	Yes	Correlation coefficient	-,304	1,000
			Sig. (2-tailed)	,180	.
			N	21	36

Regarding glycated hemoglobin values were higher in women with a mean of 8.68 compared with men, with a mean of 8, but with no statistically significant differences (p> 0.05).

In addition was observed no statistically significant associations between type of therapy and glycated hemoglobin values.

Table no.18 Glycated hemoglobin values according to gender

Sex		N	Minim	Maxim	Medie	Std.deviation
Women	Glycated Hb value	16	6,5	11,8	8,688	1,6665
	Valid Nr.	16				
Men	Glycated Hb value	19	5,2	9,8	8,000	1,3988
	Valid Nr.	19				

In respect to the time from the date of diabetes diagnosis and date of diagnosis of HCC, diabetes has been diagnosed with at least 6 months prior to HCC in 34 patients out of 37 cases (91.89%).

The time between the diagnosis of DM and HCC diagnosis was calculated accurately so diabetes was present before the HCC with a mean of 54.43 ± 41.4 months, duration of diabetes was higher in patients treated with insulin (87.42 ± 39.6 months) compared to patients treated with oral antidiabetic agents (53.64 ± 40.5 months), the data being comparable with those in the literature.

Multivariate analysis of risk of developing HCC

Multivariate analysis of risk of developing HCC in patients with diabetes was calculated as compared with a control group of 160 patients number in relation to the data of the the group of HCC patients in terms of age, gender, history of diabetes .

Data show that type 2 diabetes is associated with an increased risk of HCC regardless of the gender, age or other risk factors as association HCV, HBV or alcohol consumption data were comparable to those in the literature.

Tabel no 19 Risck of developing HCC in patients with DM

Cases	**DZ+**	**DZ-**	**OR**	**P value**
Total				
HHC (156)	37 (23.7%)	119 (76.3%)	3.10 (2.1-4.2)	<0.05
CO (160)	21 (13.2%)	139 (86.8%)	2.07 (1.4-2.7)	<0.05
Men				
HHC (94)	21 (56.8%)	73 (61.3%)	3.11 (1.9-4.3)	<0.05
CO (97)	13 (13.41%)	84 (86.59%)	1.96 (1.2-2.7)	<0.05
Women				
HHC (62)	16 (43.2%)	46 (38.7%)	3.08 (1.3-6.9)	<0.05
CO (63)	7 (11.11%)	56 (88.88%)	2.48 (1.2-5.8)	<0.05

Regarding therapy can see that most patients were treated with Sulphonylureas HCC (12 cases), followed closely by patients with insulin therapy and the smallest number of patients in this group have as Metformin treatment versus control group in which most subjects have oral diabetes treatment Metformin in a percentage of 61.9% (13 cases) and treatment with Sulphonylureas in 4 cases (19.04%) and 4 cases have insulin treatment (19.04%)

Table no.20 Statistical comparison of the two treatment groups

	Metformin	Sulphonylurea	Insulin	P value
HCC	8 (21.62%)	12 (32.43%)	11 (29.72%)	<0.05
Control	13 (61.9%)	4 (19.04%)	4 (19.04%)	<0.05

CONCLUSIONS

1. The study included a total of 156 patients diagnosed with HCC (94 men and 62 women). The average age was 64.39 years for men and 69.63 years for women. The highest incidence by age is the age group> 70 years.
2. Type 2 Diabetes was present in 23.7% percent (37 cases), a percentage which fall within the data from the literature showing the incidence of diabetes between 15.8% and 43.3%
3. The average age at diagnosis of HCC within the group of diabetic patients (65.38 years) was significantly lower ($p < 0.05$) compared with the average age of the group of non-diabetic patients (70.0 years).
4. Known risk factors involved in the development of HCC in the group total were HCV 32.7%, HBV 21.8%, 17.7% alcohol. A percentage of 30.76% of the cases (48 cases) were considered of unknown origin, of whom type 2 diabetes showed 19 cases.
5. Liver cirrhosis is one of the most important risk factors for HCC development in total group of patients 94 cases (60.5%) had cirrhosis at diagnosis of HCC. Of these Type 2 Diabetes was present in 16 cases which shows that HCC in patients with type 2 diabetes can occur in the absence of cirrhosis ($p < 0.05$). After Child-Pugh most cases were in class B in both groups with no statistically significant difference ($p > 0.05$).
6. Analysis of groups according to tumor appearance showed a higher percentage of multicentric tumors in diabetic patients without statistical significance ($p > 0.05$)
7. Analysis according to liver tumor size show statistically significant difference between groups ($p < 0.05$) in the studied groups so in non-diabetic patients were observed more advanced HCC. The ***data are not consistent with the literature.***
8. Depending on the presence of portal vein thrombosis is observed that there is statistically significant difference between the two groups studied, which means more advanced forms of HCC as were found in the studied groups in non-diabetic patients ($p < 00.5$). ***The data are not consistent with the literature, studies showing the presence of portal vein thrombosis percent higher in diabetic patients.***

9. The average values of AFP were higher in the group of non-diabetic patients (AFP = 4386.99ng / ml) compared with diabetic group (AFP = 3329.12ng / ml) but not statistically significant difference was found between groups (p> 0.05). ***Data are consistent with those in the literature.***

10. CLIP score analysis compared to the two groups shows that in the group of diabetic patients most have a CLIP score 0 (40.5%) which shows a median survival of 42.5 months compared with non-diabetic group that most patients were classified score 2 with an average survival of 16.5 months statistically significant difference (p <0.05). The presence of liver cirrhosis is an important factor that can influence the survival average and in the group of diabetic patients with advanced liver cirrhosis was significantly smaller percentage compared to non-diabetic patients group.

11. Following Type of therapy most cases have as treatment Sulfonylureas 12 cases (32.4%), followed by treatment with metformin 8 cases (21.6%) and 11 of insulin. ***There were no statistically significant differences between type of therapy and the AFP value, tumor type or presence of portal vein thrombosis (p> 0.05).***

12. The time between the diagnosis of DM and HCC diagnosis was calculated accurately so diabetes was present before the HCC with a mean of 54.43 ± 41.4 months, duration of diabetes was higher in patients treated with insulin (87.42 ± 39.6 months) compared to patients treated with oral antidiabetic agents (53.64 ± 40.5 months), ***the data being comparable with those in the literature.***

13. Multivariate analysis of risk of developing HCC in patients with diabetes was calculated compared to with a control group of 160 patients with data compared to the patients of the the group of HCC in terms of age, gender, history diabetes. ***Data show that type 2 diabetes is associated with an increased risk of HCC regardless of the gender, age or other risk factors as association HCV, HBV or alcohol consumption (p <0.05), the data are comparable with those in literature.***

14. Regarding therapy we can see that most patients in group were treated with Sulphonylureas HCC (12 cases), followed closely by patients with insulin therapy and the smallest number of patients in this group have Metformin as treatment versus control group in which most subjects have oral diabetes treatment with Metformin in a percentage of 61.9% (13 cases) and treatment with Sulphonylureas in 4 cases (19.04%) and 4 cases with insulin treatment (19.04%)

15. In conclusion, this study confirms that diabetes type 2 is an independent risk factor for the occurrence of HCC and long precede the diagnosis of HCC. I showed that diabetes does not influence the clinical characteristics and biological parameters in patients with HCC, AFP levels are also significantly lower in patients with HCC and diabetes, further studies are needed to investigate the role of this marker in the diagnosis of HCC in patients with diabetes . In addition further studies are needed to determine the role of antidiabetic therapy in the prognosis and response to treatment of HCC

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