

Metabolic Impact of Diabetes Mellitus Type 2 in Hepatitis C Virus Infected Patients

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ABSTRACT: Objective: Patients with chronic hepatitis C are subjected to a greater risk of cardiovascular disease and difficult to control diabetes mellitus type 2 (T2DM) comparatively to people that have never contracted Hepatitis C Virus (HCV). We aimed to investigate the impact of T2DM on HCV patients with the help of Fibromax test results compared to nonT2DM patients, and the metabolic differences between the 2 study groups. Our long term goals are to observe the long term impact of achieving systemic virologic response (SVR) by means of Direct-Acting antivirals (DAA) between the 2 cohorts. Research Design and Methods: We selected a lot of 200 patients with HCV that will undergo interferon-free DAA-based antiviral treatment for HCV and we used the results of the Fibromax Test to compare the biological parameters of T2DM and nonT2DM patients. RESULTS Among patients with T2DM compared to NonT2DM there is a significant correlation on Steatostest, NashTest, GGT, Glycemia, body weight, height and BMI. Test also showed that 15,5% of the test group had elevated glycemia, indicating the probability of developing diabetes in the future. Conclusions: Our results suggest that HCV patients that also have T2DM are subjected to a combined higher risk of accelerated steatosis development, steatohepatitis, added difficulty in controlling glycemic levels. All these previous elements combined with a prevalence for patients to be overweight have a negative metabolic impact. Eradication of HCV with the help of DAA is important in order to help improving the metabolic impact of diabetes on steatosis, steatohepatitis. An added benefit is better management of glycemic control by decreasing insulin use and eliminating one risk factor of T2DM.

KEYWORDS: Hepatitis C Virus, T2DM, Steatosis, Steatohepatitis.

Introduction

Globally there are approximately 71 million individuals infected with hepatitis C virus (HCV) [1], of those infected between 10 and 20% will develop liver complications such as decompensated cirrhosis and hepatocellular carcinoma, complications that were responsible for almost 500.000 deaths in 2015 [2].

In the past treatment for HCV infection consisted of weekly doses of pegylated interferon administered subcutaneously and oral ribavirin [3].

This treatment protocol unfortunately had low success rates and a wide range of side-effects [4].

In recent years, our understanding and knowledge of Hepatitis C virus has expanded.

Since the launch of the first specific direct acting antiviral agents (DAAs) in 2011, now there are several options accessible for HCV treatment such as HCV protease inhibitors, polymerase inhibitors and NS5A inhibitors [5].

The importance of eliminating HCV is not only relevant in the fight against cirrhosis,

hepatocellular Carcinoma (HCC) but also non liver related diseases such as cardiovascular and metabolic diseases [6].

Nowadays, chronic HCV infection is considered to be a systemic disease since it affects not only the liver but also other organs.

Approximately 75% of HCV infected patients also present extrahepatic manifestations, some that can be evident even before the diagnosis of chronic HCV is made [7].

Type 2 diabetes mellitus (T2DM) is among the most common extrahepatic manifestation and can lead to retinopathy, kidney failure, diabetic neuropathy and cardiovascular diseases like hypertension or even stroke [8,9].

Compared to never infected people patients with chronic hepatitis C they are subjected to a higher risk of developing T2DM and studies have shown that up to 1/3 of HCV patients have T2DM [5,10].

The mechanism involved in the association HCV and T2DM is unclear.

It is considered that HCV proteins increase tumor necrosis factor- α , interleukin-2 and other inflammatory cytokines lead to gluconeogenesis,

increased lipid accumulation in the liver and appearance of insulin resistance [11,12].

Studies so far have shown that HCV treatment can lead to an improvement on glycemic control and thus reduce and or prevent future diabetic complications [13,14].

The objective of this study is to evaluate the metabolic differences between T2DM and nonT2DM patients with HCV.

Methods

This study was conducted on 200 patients that have been referred to the “Renasterea”.

Private Clinic and the Department of Internal Medicine of the Emergency County Hospital Craiova between 2017-2021 and accepted in the national plan to eradicate HCV and underwent the Fibromax test to evaluate their liver function prior to DAA administration.

The Fibromax test contains the following results: (fibrosis-FibroTest, activity-ActiTest, steatosis-SteatoTest, non-alcoholic steatohepatitis-NashTest, alcoholic steatohepatitis-AshTest) based on the following 10 biomarkers: Alfa2Macroglobulin, Gamma-glutamyl transferase-GGT, total bilirubin, Apolipoprotein A1, Haptoglobin, alanine aminotransferase (ALT), triglycerides, cholesterol, fasting glucose, Aspartataminotransferase (AST).

Patients were selected among both newly initiated and those that underwent prior interferon based treatment without obtaining SVR.

All patients in our study gave a written informed consent prior to being included in the study and were informed of the procedures that were needed for the study, and of the fact that they could at any point, withdraw their consent.

The protocol for the study was designed to be in accordance with the ethical guidelines specified in the Declaration of Helsinki and approval from the Ethics Committee of the University of Medicine and Pharmacy of Craiova was obtained.

After clinical evaluation, all patients underwent routine blood test including complete

hemoleucogram, determining the viral load of the patient, tests to determine if the patient also has hepatitis B with/without D, HIV coinfection, hepatic carcinoma screening with Alpha-Fetoprotein Tumor Marker, blood coagulation tests, liver enzymes, abdominal echography, colonoscopy, immune profiling and cardiology consults or with other departments depending on associated diseases in order to prevent possible drug interactions.

Patients were admitted into different treatment protocols with Elbasvir 50mg combined with Grazoprevir 100mg (ZEPATIER) 1/day or Ombitasvir 12,5mg combined with Paritaprevir 75mg and Ritonavir 50mg (VIEKIRAX) 2/day+Dasabuvir 250mg (EXVIERA) 2/day based on the Fibromax Scores, prior treatment that failed to obtain SVR, decompensated or compensated cirrhosis.

All data obtained was stored in Microsoft Excel files (Microsoft Corp., Redmond, WA, USA®) with the XLSTAT suit (Addinsoft SARL, Paris, France), and was statistically analyzed in order to investigate the relationship between T2DM and liver function in HCV infected patients.

Numerical data were reported as mean±standard deviation of the values.

The graphical representation and calculation of the regression coefficients were performed with Excel, Pivot tables using the controls, functions, statistics, Figure, and data analysis module.

For complex statistical test we used Mann-Whitney-Wilcoxon test or Kruskal-Wallis test for quantitative data analyzed with the XLSTAT module or with the help of SPSS program.

Results

The study population consists of 200 patients divided in two cohorts, one already diagnosed with T2DM (25%) and one without diabetes (75%).

Of the nonT2DM cohort 15,5% presented elevated glycemic levels, indicating the probability of a prediabetic cohort.

Table 1. Description of study lot.

VARIABLE	CATEGORY	NR	PERCENTIGE
GENDER	FEMININ	141	70.50%
	MASCULIN	59	29.50%
BACKGROUND	RURAL	118	59.00%
	URBAN	82	41.00%
PRIOR TREATMENT	YES	61	30.50%
	NO	139	69.50%
FIBROTEST CLASS	0	7	3.50%
	1	5	2.50%
	2	27	13.50%
	3	76	38.00%
	4	85	42.50%
STEATOTEST CLASS	0	28	14.00%
	1	50	25.00%
	2	77	38.50%
	3	45	22.50%
NASHTEST CLASS	0	74	37.00%
	1	50	25.00%
	2	76	38.00%
ACTITEST CLASS	0	10	5.00%
	1	37	18.50%
	2	55	27.50%
	3	98	49.00%
ASHTEST CLASS	0	189	94.50%
	1	11	5.50%
T2DM	YES	50	25.00%
	NO	150	75.00%
GLYCEMIA	INCREASED	81	40.50%
	NORMAL	119	59.50%
BILIRUBIN	INCREASED	21	10.50%
	NORMAL	179	89.50%
CHOLESTEROL	INCREASED	27	13.50%
	NORMAL	173	86.50%
TRIGLYCERIDES	INCREASED	25	12.50%
	NORMAL	175	87.50%
HYPERTENSIVE	YES	57	28.50%
	NU	143	71.50%
BODY MASS INDEX	NORMAL WEIGHT	71	35.50%
	OVERWEIGHT	80	40.00%
	OBESITY STAGE 1	39	19.50%
	OBESITY STAGE 2	8	4.00%
	OBESITY STAGE 3	2	1.00%

Table 1 provides the baseline characteristics for our study cohort.

The majority of the patients were female (70.50%), came from a rural background 59.00%, 30,5% had previously underwent an interferon based treatment that failed to obtain SVR, about 25% of the sample population presented elevated cholesterol and triglycerides, and 65,5% of the study population was overweight or obese.

Table 2. Specify of Fibromax classes in T2DM patients.

VARIABLE VS. DIABET	p Chi ²	RESULT
FIBROTEST	0.1938	NONSPECIFIC
ACTITEST	0.2992	NONSPECIFIC
STEATOTEST	0.0000	HIGHLY SPECIFIC
NASHTEST	0.0010	HIGHLY SPECIFIC
ASHTEST	0.8579	NONSPECIFIC

As shown in Table 1,2 among the variables evaluated during the Fibromax test with the help of pChi square test formula, only a few of them seem to reveal any correlation between the two study groups.

Thus patients with T2DM show a significant increase in steatosis (SteatoTest) [Figure 1], and steatohepatitis (NashTest) [Figure 2] compared to NonT2DM patients.

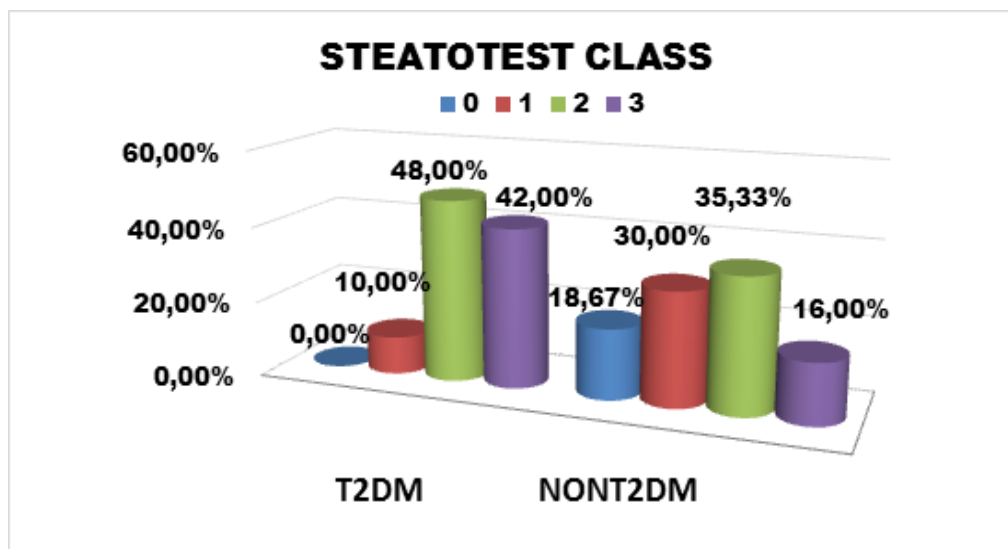


Figure 1. SteatoTest distribution of T2DM VS nonT2DM lot.

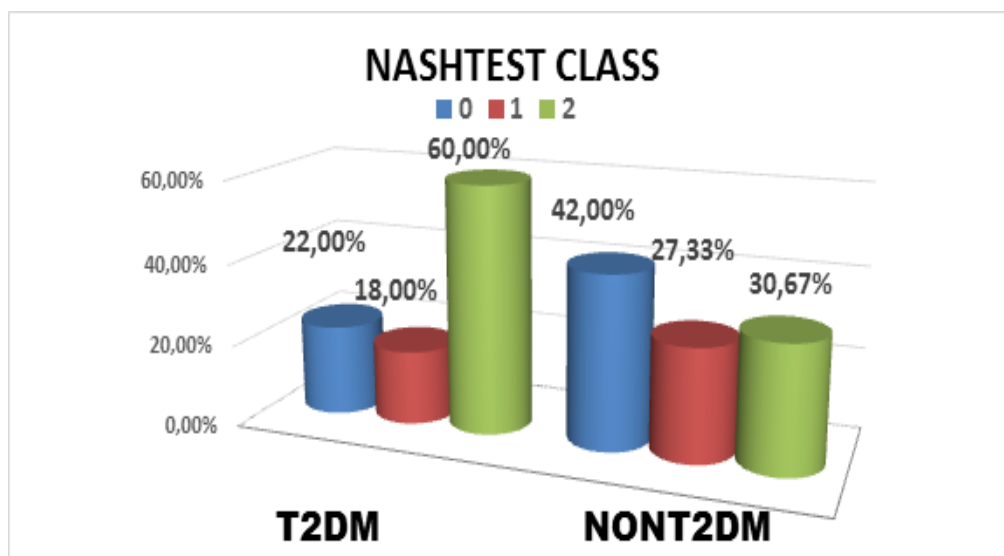


Figure 2. NashTest distribution of T2DM VS nonT2DM lot.

Our study shows that the presence of T2DM is accompanied by a significant increase in the severity of hepatic steatosis and steatohepatitis in regards to central adiposity, compared to nonT2DM patients.

As we can observe in Figure 1, the nonT2DM population has an almost Gaussian distribution as far as the degree of steatosis is concerned.

This distribution shifts completely when we observe the T2DM sample population, we notice

that 90% of its patients are distributed in the 3rd and 4th classes of steatosis, while in the case of the NASH test twice as many patients are distributed in the second class of steatohepatitis.

The presence of significant steatosis, steatohepatitis, insulin resistance coinciding with the tendency of T2DM patients to be overweight or obese indicate the presence of the metabolic syndrome.

Table 3. Blood tests distribution of T2DM VS nonT2DM lot.

Parameter	T2DM	NONT2DM	p Mann-Whitney	RESULT
ALFA2M	3.49±0.77	3.53±0.68	0.4911	NONSPECIFIC
HAP	0.91±0.49	0.85±0.44	0.5601	NONSPECIFIC
APO A1	1.43±0.29	1.43±0.28	0.8567	NONSPECIFIC
TB	0.80±0.74	0.82±0.76	0.0870	NONSPECIFIC
GGT	99.04±88.29	81.95±90.44	0.0051	SPECIFIC
TGP	88.84±49.92	93.27±72.43	0.6486	NONSPECIFIC
TGO	69.26±33.15	72.98±55.64	0.5356	NONSPECIFIC
GLUCOSE	192.36±89.97	101.48±13.44	0.0000	NONSPECIFIC
CHOL	159.80±33.15	161.85±38.70	0.9269	NONSPECIFIC
TRIGL	150.00±138.27	101.84±36.94	0.0565	NONSPECIFIC
WEIGHT	78.06±13.31	70.70±14.07	0.0009	HIGHLY SPECIFIC
HEIGHT	1.67±0.09	1.63±0.09	0.0256	SPECIFIC
BMI	28.10±4.10	26.71±4.48	0.0237	SPECIFIC

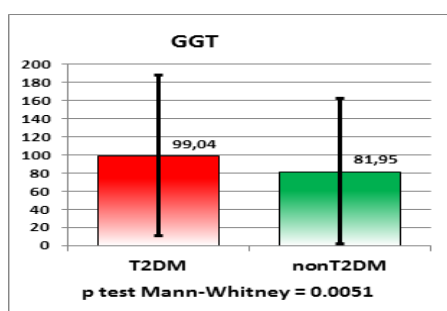


Figure 3. GGT distribution of T2DM VS. nonT2DM lot.

With the help of T Mann-Witney test we prove that there is a significant difference in GGT results among T2DM patients compared to nonT2DM, T2DM lot having a higher GGT average value that the other ($p=0.0051 < 0.05$). [Table 3] and [Figure 3].

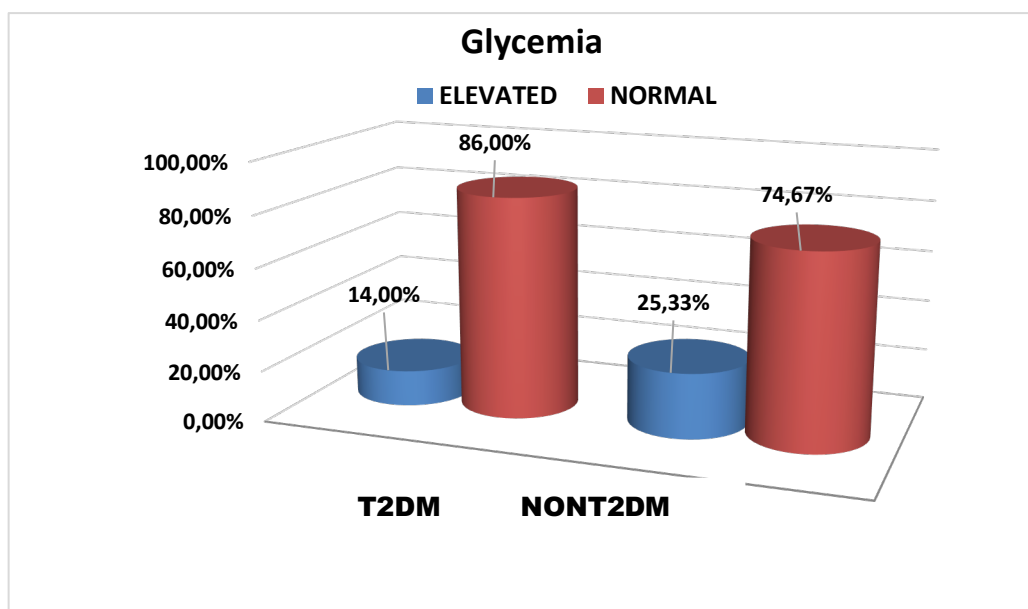


Figure 4. Glycemia levels among T2DM VS nonT2DM lot.

Among the T2DM cohort 14% of the patients present difficulties controlling glycemic levels and 25,33% of nonT2DM patients present elevated glycemic blood levels indicating the probability that they may be at risk of

developing T2DM at some point [Table 1,3 and Figure 4].

Better glycemic control may also improve hepatic steatosis witch frequently accompanies HCV related liver disease.

Discussion

Diabetes is among the leading causes of death in Europe, patients can suffer acute complications such as hypoglycemia or long-term macrovascular complications like stroke or heart disease.

According to recent estimates there were 463 million people have diabetes, in Europe 58 million as of 2019 [15].

Chronic hepatitis C is associated with both the development of insulin resistance and T2DM, thus the effort placed on eradicating HCV with the help of DAA can only be a positive step towards decreasing the incidence and prevalence of T2DM as was already proved during the pegylated interferon era of HCV treatment [16].

In this retrospective cohort study, the metabolic impact of T2DM among the sample population was explored and we did find an important correlation between some of the factors.

Based on our search for similar studies, our results were similar but not to the same extent.

Our study shows that the presence of T2DM is accompanied by a significant increase in the severity of hepatic steatosis and steatohepatitis in regards to central adiposity [17], compared to nonT2DM patients. 33% of HCV patients could have T2DM according to other studies, compared to 25% of HCV patients in our study lot.

These patients are at risk of developing T2DM at some point in the future [18,19].

We also noticed that T2DM patients present much higher GGT levels compared to that of nonT2DM patients.

This result coincides with other 12 studies that have shown that GGT or ALT or AST are significant predictors of T2DM risk, independent of BMI [20].

Researchers believe that HCV is associated with an accelerated development of steatosis [5], others have suggested that proinflammatory cytokines secreted by HCV disrupt insulin signaling [21].

Multiple studies have shown that clearance of HCV can lead to an improvement on insulin resistance and drop fasting glucose levels [22], an aspect we will try to observe in our future study.

Chronic HCV leads to insulin resistance, one of the hallmarks of the metabolic syndrome which includes T2DM, hypertension, hyperlipidemia, insulin resistance, obesity and nonalcoholic fatty liver (NAFL).

Studies have found that NAFL affects 20-30% of HCV patients, with the success of oral DAA and HCV decline, NASH will become the most common cause of cirrhosis [23].

DAA may have an effect in slowing the rate of hepatic steatosis, reducing the secretion rate of proinflammatory cytokines, and improving insulin resistance of patients.

HCV treatment has the potential to impact a large proportion of patients in matters of diabetes control, aspects concerning liver disease and a decrease of cardiovascular risk.

However, the need for more extensive prospective studies that analyzes the long term impact DAA achieved SVR on T2DM compared to nonT2DM patients.

The clinical significance DAA therapy has on controlling fasting glucose and HbA1C, changes in the lipoprotein profile, impact on reducing cardiovascular risk, hypertension control atherosclerotic plaques and more.

Conclusion

Our results suggest that HCV patients that also have T2DM are subjected to a combined higher risk of accelerated steatosis development, steatohepatitis, added difficulty in controlling glycemic levels, combined with a prevalence for patients to be overweight elements that have a negative metabolic impact.

However, the need for more extensive prospective studies that address the longer term impact of DAA achieved on type 2 diabetic patients compared to nonT2DM patients, the clinical significance DAA therapy has on controlling fasting glucose and HbA1C, changes in the lipoprotein profile, impact on reducing cardiovascular risk, hypertension control atherosclerotic plaques and more is significant for a the benefit of future patients.

Conflict of interests

The authors declare that there is no conflict of interest.

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