WEB OF SCIENTIST: INTERNATIONAL SCIENTIFIC RESEARCH JOURNAL
ISSN: 2776-0979, Volume 4, Issue 1, Jan., 2023

CLINICAL AND BIOCHEMICAL PARALLELS OF INSULIN RESISTANCE IN PATIENTS WITH CHRONIC HEPATITIS C

Shagazatova B. Kh.
Akhmedova F. Sh.
Akhmedov Sh.M.
Tashkent Medical Academy

Resume:
The literature provides data on extrahepatic manifestations of the hepatitis C virus (HCV), its possible direct or immuno-mediated effects on pancreatic β-cells and its role in the etiology and pathogenesis of diabetes. There are also reports of a high prevalence of HCV in type 2 diabetes mellitus.Purpose of study to evaluate the clinical significance of insulin resistance on indicators of carbohydrate-lipid metabolism in patients with chronic hepatitis C.
Insulin resistance was detected in 31.7% of patients with chronic hepatitis C and characterized by the severity of the clinical picture with a predominance of asthenic syndrome, enlargement and densification of the liver compared with patients without IR insulin resistance. In 2/3 of patients with chronic hepatitis C with insulin resistance, abdominal obesity and a decrease in high-density lipoprotein cholesterol were found, which is significantly more often compared to patients without insulin resistance.

Keywords: chronic hepatitis, insulin resistance, metabolic syndrome, diabetes mellitus, HOMA-IR index, abdominal obesity

Introduction

Viral hepatitis C is part of a large group of viral hepatitis with parenteral transmission, which has become available for study since the end of the 80s, when a virus-specific protein was isolated which allows identifying this disease [4]. The literature of the 90s is characterized by a rapid flow of information regarding the HCV problem, which is associated with its widespread prevalence[1]. According to recent data, 3% of the world's population are infected with HCV, and this figure will increase 5-10 times in the next 10 years. In many ways, such an increase can be explained by an improve in the quality of diagnosis of this disease, however, there are enough evidence of true increase in the number of patients who fell sick with HCV [11].
Information on the spread of HCV in the Republic of Uzbekistan appeared in the second half of the 90s. Studies by A.I. Ivanova showed that HCV markers are present

in the blood of 5.2% of patients examined at the clinic with a diagnosis of hepatitis. In Tashkent, among adult populations, the number of patients with HCV was 9% (10).

A feature of HCV is a wide range of extrahepatic lesions [12]. Extrahepatic manifestations are often they are ahead of the clinical picture of the hepatic process, masquerading as another disease, and sometimes for many years they prevail over a moderate or weakly expressed hepatic process [16].

The literature provides data on extrahepatic manifestations of the hepatitis C virus (HCV), its possible direct or immuno-mediated effects on pancreatic β-cells and its role in the etiology and pathogenesis of diabetes. There are also reports of a high prevalence of HCV in type 2 diabetes mellitus [14]. In type 2 diabetes, markers of HBV infection seroconversion are more often found than with type 1 diabetes.

Diabetes Mellitus type 2 characterized a group of heterogeneous disorders of carbohydrate metabolism. This largely explains the lack of generally accepted theories of the etiology and pathogenesis of this disease. It is known that with type 2 diabetes there are two main defects at the same time: insulin resistance (IR) and impaired β-cell function [1]. In most patients with type 2 diabetes, the deterioration of tissue sensitivity to insulin is the primary (inherited) defect. If β-cells are not able to maintain a sufficiently high level of insulin secretion to overcome IR, hyperglycemia develops. Such a sequence of events is characteristic both for patients with metabolic syndrome and for people with normal body weight [9]. But in some patients with type 2 diabetes, a primary defect can occur at the level of b-cells and manifest as a violation of insulin secretion. IR in such individuals is formed combined or following a violation of insulin secretion. The severity of metabolic disorders in patients with diabetes depends, according to some authors, on the functional status of the liver [15]. There is no doubt the fact of a possible liver damage directly due to chronic hyperglycemia [11].

There are reports of a high prevalence of chronic viral hepatitis (HCV) in type 2 diabetes mellitus (type 2 diabetes). In type 2 diabetes, markers of HBV infection seroconversion are more often found than with type 1 diabetes. Researchers linked the high frequency of viral hepatitis among patients with diabetes with an increased risk of getting an infection, which is determined by: significant parenteral loading, the presence of an immunosuppressive state due to the main disease; a significant number of asymptomatic virus carriers among this category of patients. Diabetes patients are at increased risk of infection with viruses that cause hepatitis B, C and D [2,5,6].

The value of HBV and HCV infection in the initiation of autoimmune processes directed to the β-cell of the pancreas, accompanied by a decrease in insulin secretion,

is shown. In this case, a more rapid decrease in insulin secretion occurs compared to uninfected ones. It is proved that infection with HBV and HCV patients with diabetes is one of the leading risk factors for the development of slowly progressive autoimmune diabetes. HCV infection is associated with a higher risk of progression of the clinical stages of diabetic nephropathy and "diabetic foot syndrome" of a neuroischemic form [11].

Viral hepatitis has an adverse effect on the course of diabetes, which manifests with an increase in polyuria, hyperglycemia, glucosuria and polydipsia and contribute to the transition of latent forms to clinically obvious form, as well as the transition of mild form of diabetes to moderate severity and into severe form [7,13]. It should be noted that the risk of diabetes is increased in patients with HCV, especially in the presence of risk factors such as an increased body mass index and advanced age. HCV proteins can disrupt insulin signaling, which leads to a decrease in insulin sensitivity and impaired glycemic control even at the stages preceding cirrhosis [26].

There are few studies on the characteristics of the clinic course, the outcome of viral hepatitis combined with insulin resistance, performed in the Republic of Uzbekistan. Taking into account the inconsistency of the literature data regarding the clinic and therapeutic tactics, it seems interesting to analyze the clinical course of viral hepatitis C from the position of insulin resistance. The study is devoted to these issues.

The aim of the study was to evaluate the clinical significance of insulin resistance on indicators of carbohydrate-lipid metabolism in patients with chronic hepatitis C.

Material and Methods

The study included 41 patients with chronic hepatitis C, who examined in the clinic Republican specialized scientific-practical medical centre of virology of the Ministry of Health of the Republic of Uzbekistan. The diagnosis of chronic hepatitis C was made on the basis of detection of virus markers in the blood: HCV-Ab, RNA-HCV by the method of passive agglutination of gelatinous particles (Serodia, Japan) and polymerase chain reaction (PCR), as well as by the combination of clinical and medical history, epidemiological, biochemical, instrumental data, according to the classification of chronic hepatitis.

Laboratory examination of patients included a standard set of clinical and biochemical parameters for chronic hepatitis. The lipid profile of the serum of venous blood was determined by the enzymatic colorimetric method using kits (Roche, Germany). The content of immunoreactive insulin in blood serum was determined by the method of solid-phase enzyme-linked immunosorbent assay (ELISA) using a set

of reagents. To assess insulin resistance (IR), the Homeostatic model assessment (HOMA)-IR Insulin Resistance Index (Matthews D., 1985) was used: (fasting glucose, mmol / l x fasting insulin, mcU / ml / 22.5). The presence of IR was confirmed with a HOMA-IR index of equal to or more than 2.77. In order to assess carbohydrate metabolic disturbances, we determined the values of fasting plasma glucose (GPN) and glycated hemoglobin in venous blood.

All examined patients underwent ultrasound examination of the abdominal organs using the ALOKA D - 630 apparatus (Germany) with linear (5 MHz) and convex (3.5 MHz) probes, in which the thickness of the right, vertical size and thickness of the left lobe of the liver, and the total diameter of the hepatic veins in 1st order, portal vein diameter, echogenicity of the liver parenchyma, size of the spleen, diameter of the splenic vein, were examined.

The obtained data were processed using a software package using parametric and nonparametric methods of comparison and studying the correlation dependence between the features. The differences were considered significant at $p < 0.05$.

Results and Discussion

In the vast majority (68.2%) of patients, hepatitis C was detected during screening and only 1/3 of the patients were examined purposefully due to the presence of clinical and laboratory abnormalities. In almost half of the patients (47.6%), the duration of hepatitis was more than 8 years, in 28.6% from 3 to 8 years, 14.9 to 3 years, and in 8.9% the duration of the disease could not be established. 75.6% of patients had minimal clinical manifestation of hepatitis. Most often, patients noted inconsistent severity, discomfort in the right hypochondrium, complained of an asthenovegetative nature. In 56.9% of patients, an objective examination revealed hepatomegaly.

Insulin resistance was detected in 31.7% of patients with chronic hepatitis C. No gender differences were found in the groups of patients with chronic hepatitis C with and without IR ($p > 0.05$), as well as the age of the patients (35.2 ± 9.9 and 32.8 ± 8.7 years, $p > 0.05$) However among patients with IR, people older than 40 years were more occured (45.5% and 24.8%, respectively, $p < 0.05$). A direct correlation was revealed between the weak strength of the HOMA-IR index and age (r-0.0186; $p < 0.05$). Despite the literature data on an increase in the frequency of IR and associated metabolic disorders in carbohydrate metabolism with a longer history of chronic hepatitis C, in our study patients with chronic hepatitis C with and without IR did not differ in duration of infection ($p > 0.05$)

Patients with IR more often had asthenic complaints compared with patients without IR (66.7% and 50.0, respectively, $p < 0.05$). In patients with chronic hepatitis C, with

IR, hepatomegaly (64%) and increased echogenicity of liver tissue (84.5%) were detected more often according to ultrasound data compared with patients without IR (31.3% and 52.6%, respectively, p <0.05))

In patients with IR, the activity of alanine aminotransferase(AlAT), aspartate aminotransferase(AsAT), gammaglutamyltranspeptidase (GGTP) is significantly higher, the level of thymol test, y-globulins, the level of blood albumin is lower. The vast majority of patients with chronic hepatitis C with IR (95%) had increased AlAT activity, while among patients without IR, an increased enzyme level was observed in 73.8% (p <0.05). Patients with IR are 2 times more likely to have an increased level of thymol test (42.9%), hypergammaglobulinemia (33.2%), compared with those without IR (23.9% and 15.3%, respectively, p <0.05) .

In patients with chronic hepatitis C with IR, the components of the metabolic syndrome were significantly more often detected compared with patients without IR.

Table 1 Indicators of carbohydrate metabolism in patients with chronic hepatitis C with insulin resistance

Indicators	Patients with chronic hepatitis C		P
	With IR (n-13)	Without IR (n-28)	
Fasting glycemia mmol / l	14,5±0,92	5,8±0,87	<0,001
HbA1c %	13,3±0,76	9,6±0,56	<0,01
HOMA IR	10,8±4,9	2,8±3,78	<0,05

According to the results of our study, indicators of carbohydrate metabolism also significantly differed in the compared groups. As can be seen from the table. 1, of 13 patients with chronic hepatitis C with IR, 11 patients (84.6%) showed an increase in fasting glucose, while in the group of patients without IR, an increase in morning glucose was not observed. An increase in the level of glycated hemoglobin was almost 2 times more common in patients with IR (69.2%), compared with patients without IR (35.7%).

WEB OF SCIENTIST: INTERNATIONAL SCIENTIFIC RESEARCH JOURNAL
ISSN: 2776-0979, Volume 4, Issue 1, Jan., 2023

Table 2 Indicators of lipid metabolism in patients with chronic hepatitis C

Indicators	Patients with chronic hepatitis C		P
	With IR (n- 13)	Without IR(n-28)	
Total cholesterol (mmol / L) M ± m	4,57±0,34	4,62±0,28	>0,05
Triglycerides (mmol / L) M ± m	1,67±0,32	0,75±0,45	<0,05
VLDL-C (mmol / L) M ± m	0,87±0,23	0,67±0,17	<0,05
LDL-C (mmol / L) M±m	2,13±0,21	2,05±0,43	>0,05
HDL-C (mmol / L) M ± m	1,00±0,34	1,32±0,48	<0,05
Frequency of decrease in the level of HDL-C (%)	64, 6	43,6	<0,05
Frequency of hypertriglyceridemia (%)	20,7	4,2	<0, 001
AO frequency (%)	64,5	36,4	<0,01
Waist circumference (cm) M±m	90,8±11.7	81,8±9.8	<0.01
BMI (kg / m2) M± m	26,8±3.7	22,4±3.2	<0.01

As can be seen from the table. 2, if abdominal obesity, as the main causative factor of IR and metabolic syndrome, was found in 48.2% of patients with chronic hepatitis C, then in cases with IR almost 2 times more often than without it. According to the results of our study, the most common component of MS detected in 52.8% of patients with chronic hepatitis C was a decrease in the level of high density lipoprotein cholesterol (HDL-C). Moreover, in patients with IR, the level of HDL-C was significantly lower than in its absence. A decrease in the level of HDL-C was detected in the majority (64.6%) of patients with chronic hepatitis C with IR, while in patients without IR, less than half of the cases (43.6%, p <0.05). It should be noted that the frequency of decrease in the level of HDL-C was not depended on presence or absence abdominal obesity (52.6% and 50.4%, respectively, p> 0.05). Hypertriglyceridemia was detected in 9.4% of cases, and much more often in patients with IR (21.7%) than in patients without IR (3.7%). In patients with IR, the level of triglycerides (TG) was significantly higher (p <0.05) in comparing with patients without IR.

Metabolic syndrome was diagnosed in 6 patients with chronic hepatitis C (15%) and significantly more often in cases with IR than without it (30.2% and 5.8%, respectively, p <0.001). Most patients with chronic hepatitis C with IR had overweight or obesity (70.4%), while among patients without IR, increased BMI was detected in 38.2% (p <0.001).

Conclusions

1. Insulin resistance was detected in 31.7% of patients with chronic hepatitis C and is characterized by the severity of the clinical picture with a predominance of asthenic syndrome, enlargement and compaction of the liver compared with patients without IR.
2. In 2/3 of patients with chronic hepatitis C with insulin resistance, abdominal obesity and a decrease in the level of high density lipoprotein cholesterol were found, which is significantly more often compared to patients without insulin resistance.
3. The presence of insulin resistance, metabolic syndrome and its components in patients with chronic hepatitis C is accompanied by greater biochemical activity of hepatitis (in terms of AlAT)

References

1. Alieva A.V., Rahimova G.N., Ismailov S.I. Epidemiologiya saharnogo diabeta i prediabeta v Uzbekistane: rezul'taty skrininga // ZHurnal klinicheskoj i teoreticheskoj klinicheskoj mediciny. -2017.-№ 2 C.58-61
2. Bajzhanova, ZH.ZH. Metabolicheskij sindrom u pacientov s hronicheskim gepatitom S // Klin. gepatologiya.- 2010. - №1.- S.17-23.
3. Bogomolov, P.O. Nealkogol'naya zhirovaya bolezn' pecheni: steatozi nealkogol'nyj steatogepatit. Klin. perspektivy gastroenterologii, gepatologii. - 2004.- №3. - S.20-27.
4. Gulinskaya, O.V. CyrkunovV.M. Insulinorezistentnost' u pacientov s hronicheskim gepatitom S. //Sovremennye problemy infekcionnoj patologii cheloveka -Minsk.- 2012.- S.175-178.
5. Dedov I.I., Mel'nichenko G.A., Fadeev V.V. / Endokrinologiya. – M: Medicina, 2000. - S.631-638.
6. Ignatova, T. M.,AprosinaZ.G., SerovV.V. Vnepechenochnye proyavleniya hronicheskoj HCV-infekcii//Ros.med. zhurnal.- 2001.- №2.- S.13-18.
7. Musabaev I.K., Musabaev E.I. Differencial'naya diagnostika gepatitov A, V, S, D, E, G.- Tashkent,1999.-C 86-89.
8. Musabaev E.I. Kan M.V., Mustafaeva E., Bondarenko I. G.. Virusnyj gepatit S i ego rol' v patologii pecheni Hronicheskiezabolevaniya pecheni- ot virusnogo gepatita do cirroza s portal'noj gipertenziej.– Tashkent,1996.- S. 28-29.
9. Priven V.Z., Pogorelov M.E. Klinicheskaya harakteristikaepidemicheskogo gepatita u bol'nyh saharnym diabetom // Ostryjvirusnyj gepatit i ego posledstviya: Voprosy epidemiologii,patogeneza, kliniki i profilaktiki.- Habarovsk,-1996- S.92-97

10. Rahimova G.N. Standarty po vedeniyu i lecheniyu saharnogo diabeta 2 tipa (rukovodstvo dlya vrachej) Tashkent - 2018 - Str 4-5
11. Hafisova O.O. [i dr.] Vliyanie Metformina na formirovanie ustojchivogo virusologicheskogo otveta.Vestnik RUDN.- 2011.- №2.- S.48-57
12. Bortoletto, G. Insulin resistance (IR) defined by the homeostasis model of assessment insulin resistance (HOMA-IR) index has a direct effect on early viral kinetics during pegylated-interferon therapy for chronic hepatitis C. // Hepatology.- 2007.- Vol.46.- P.361.
13. CammaC. [et al.] Insulin resistance is associated with steatosis in non-diabeticpatients with genotype 1 chronic hepatitis Hepatology. - 2006. - Vol.43. - P.64-71.
14. Harrison, S.A. Correlation between insulin resistance and hepatitis C viral load. // Hepatology. - 2006. - Vol.43. - P.1168.
15. Huang [et al.] Hepatitis C viremia increases the association with type 2diabetes mellitus in a hepatitis B and C endemic area: an epidemiological link with virologicalimplication.J. Gastroenterol. - 2007. - Vol.102. - P.1237-1243.
16. Hadziyannis [et al.]Peginterferon alfa-2a and ribavirin combination therapyinchronic hepatitis C. A randomized study of treatment duration and ribavirin dose Ann. Intern. Med. - 2004. -Vol.140. - P.346 -355.
17. RomeroGomez M. [et al.]Insulin resistance impairs sustained response ratetopeginterferon plus ribavirin in chronic hepatitis C patients// Gastroenterology.-2006.-Vol.128.-№3.-P.636-641.
18. Kawaguchi, T. Causal relationship between hepatitis C virus core and the development of type 2 diabetes mellitus in a hepatitis C virus hyperendemic area: a pilot study.// Int. J. Mol. Med. - 2005. - Vol.16. - P.109-114.
19. Khalili M., Lim J.W., Bass N. et al. New onset diabetes mellitus after liver transplantation: the critical role of hepatitis C infection. / Liver Transplant. - 2004. - №10. - P.349-355.
20. Mehta, S.H. Hepatitis C virus infection and incident type 2 diabet. // Hepatology. -2003. - Vol.38. - P.50-56.
21. Petit, J-M. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C.// J. Hepatol. - 2001. - Vol.35. - P.279-283.
22. Siagris D., Vafíadis G., Michalaki M. et al Serum adiponectin in chronic hepatitis C and B //J Viral Hepat. 2007. - Vol. 14, № 8. - P. 577-583.

23. Souza A.F., Pace F.H., Chebli J.M., Ferreira L.E. Insulin resistance in non-diabetic patients with chronic hepatitis C: what does it mean? //Arq Bras Endocrinol Metabol. -2011. Vol. 55, №6. P. 412-418.
24. Tachi Y., Katano Y., Honda T. Impact of amino acid substitutions in the hepatitis C virus genotype lb core region on liver steatosis and hepatic oxidative stress in patients with chronic hepatitis C. //Liver Int. 2010. - Vol. 30, №4.-P. 554-559.