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# TYPE 2 DIABETES MELLITUS IN PATIENTS WITH CHRONIC VIRAL HEPATITIS C AND B

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ABSTRACT

**Summary.** A number of clinical and population-based studies have shown a link between the development of insulin resistance and type 2 diabetes mellitus and hepatitis C.

**Purpose of research:** to study the frequency of type 2 diabetes mellitus and its course in patients with chronic viral hepatitis C and B during antiviral therapy.

**Material and methods:** 213 patients (164 with CVH C, 34 with CVH B and 15 with CVH B + C) were examined before and in the course of treatment. All patients received standard antiviral therapy. In patients with type 2 diabetes, the level of fasting glycemia was determined daily in the first 8-12 weeks of treatment. The level of glycemia was determined at the laboratory at least once every 2 weeks. Glycated hemoglobin was determined every 3 months during treatment and another 6 months after completion of the antiviral therapy.

**Results:** In the group of patients with CVH C, type 2 diabetes mellitus occurred 2 times more often (13.4%) than in groups with CVH B (6.1%) with a reliability of p <0.01. With HCV genotype 3 is 2.5 times more often than with genotype 1 (p <0.001). Among patients, type 2 diabetes is 2.5 times more often men than women (p <0.01). Upon reaching an early virological response in 77.3% of patients, the level of glycemia returned to normal. The correlation coefficient between the achievement of a full virological response (negative PCR results on HCV RNA) and the normalization of the level of glycemia was 0.75. Glycemia control was maintained for 6 months after the completion of the antiviral therapy in the background of a persistent virological response.

**Conclusions:** The presence of diabetes is the basis for screening for HCV, regardless of other factors. 75-77% of type 2 diabetes mellitus in the cohort of patients with CVH C is possibly virus-associated. Treatment of HCV infection can lead to a cure for type 2 diabetes mellitus in this category of patients.

**Key words:** viral hepatitis C, genotype 3, type 2 diabetes mellitus.

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## INTRODUCTION

Hepatitis C virus (HCV) is a common cause of acute and chronic hepatitis, and can lead to serious consequences like liver cirrhosis and hepatocellular carcinoma (HCC). The development of liver cirrhosis and HCC in the outcome of chronic hepatitis C depends on several, mainly related to the host cofactors, such as age, gender, level of alcohol consumption, overweight, immune status and concomitant infections like viral hepatitis B. One of these cofactors is type 2 diabetes mellitus, even at the stage of insulin resistance (IR) [1, 2].

Although IR can develop independently of HCV, a significant amount of clinical and experimental studies suggest that HCV plays a role in its pathogenesis. This aspect is important because IR can not only accelerate the development of cirrhosis and HCC in the outcome of chronic viral hepatitis C, but can also reduce the response to antiviral therapy [3, 4].

According to WHO (2011), 3% of the world's population is infected with viral hepatitis C (HCV) and more than 170,000 are chronic carriers [3]. In addition, 40-76% of patients with HCV show at least one extrahepatic manifestation of HCV infection. Extrahepatic manifestations can often be the first and only clinical sign of chronic viral hepatitis C [5,6].

Today the prevalence of diabetes mellitus is also a global problem. In fact, almost 6% of the world's population suffers from diabetes mellitus, including the prevalence of type 2 diabetes mellitus from 2.0% to 9.4% [4], increasing to 12.3% in adults aged 40-74 years. A doubling of this number is expected by 2030 and a predominance is predicted among young people, especially in developing countries [7, 8].

The assumption that HCV could be the cause of diabetes mellitus was first made by Allison et al. in 1994. Since then, several dozen scientific papers have been published on the relationship between HCV and type 2 diabetes mellitus. Several studies conducted in various parts of the world have found that 13% to 33% of patients with chronic HCV have diabetes mellitus, more often type 2 [6, 7, 8,9].

## PURPOSE OF RESEARCH

To study the frequency of type 2 diabetes mellitus and its course in patients with chronic viral hepatitis C and B during antiviral therapy.

## MATERIAL AND METHODS

The work was carried out in the hepatological center in Shymkent from 2014 to 2016. Patients with CVH were sent for examination from medical institutions in Turkestan, Kentau, Taraz, and Shymkent. Examination and treatment of patients was carried out mainly on an outpatient basis. The data of 213 patients with chronic viral hepatitis B and C were analyzed. The number of examined men were 50% (107), women - 50% (106). The number of patients with CVH C and B at the age of 20-29 was 32 (15%) patients, in 30-39years - 68 (32%) patients, in 40-49years 76 (36%) patients, in 50-59 years 28 (13%) of patients and at the age of 60-69 years the number of patients was 9 (4%).

The diagnosis of HBV infection was confirmed by the detection of ELISA HBsAg, HBeAg. Upon detection of antiHBe, antiHbcor IgM and IgG, the diagnosis was verified by HBV DNA PCR. The diagnosis of HCV infection was made based on the detection of total anti-HCV and the detection of RNA HCV. When hepatitis B was detected, patients were tested for HDV infection by ELISA (anti-HDV) and PCR (HDV DNA). ELIZA diagnostics was carried out using test systems of Vector-Best CJSC / Koltsovo, Russian Federation. Polymerase chain reaction was performed using test systems and equipment for PCR diagnostics (Litech / Moscow). All patients with CVH C were genotyped by PCR.

Studies by PCR and ELISA were performed in the Olymp CDL Ltd of South Kazakhstan branch (head of laboratory. A. Gramotikopulo laboratory), in the diagnostic center of INVIVO Ltd (head of laboratory. M. A. Popova).

Among 213 examined patients, CVH C accounts for 77% (164) of patients, CVH B was detected in 33% (49) of patients, among which only 9% (19) were patients with co-infection: CVH B + C - 7% ( 15 patients), CVH B + D- 2% (4 patients) (Fig. 1).

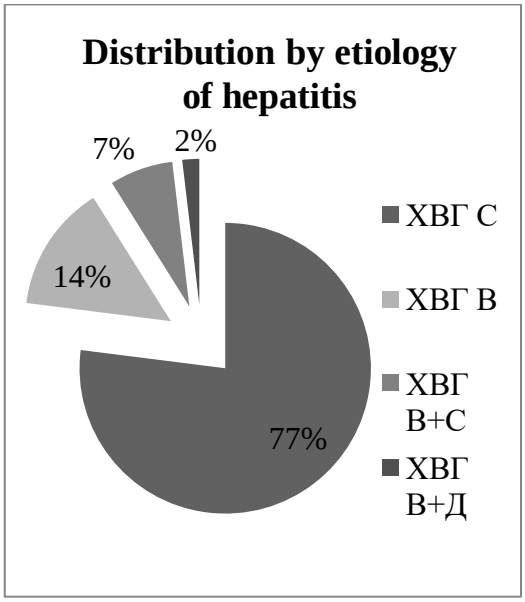


**Figure 1**

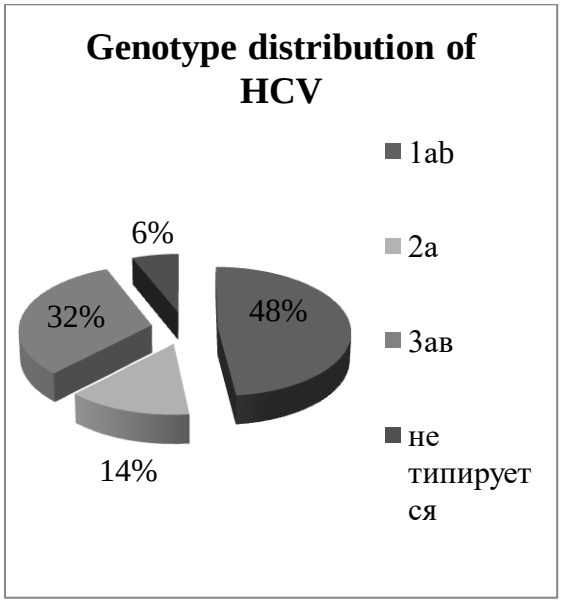


**Figure 2**

When HCV genotyping, it was found: 1ab genotype in 79 (48%) patients, 2a genotype in 23 (14%) patients, 3ab genotype in 52 (32%) patients and 10 (6%) patients in which the genotype is not typed (Fig. 2).

To determine the level of fibrosis, patients underwent liver elastometry using the FibroScan apparatus. All patients underwent liver elastometry at the Regional Clinical Hospital. Among 213 examined patients, F-0-1 was observed in 48 patients, which corresponded to 23% of patients, F-2 in 71 (33%) patients, F-3 in 66 (31%) patients and in 28 (13%) patients F-4, which corresponds to cirrhosis of the liver.

Table 1 shows that among the examined, 30 patients suffered from monoinfection of CVH B, 164 patients with CVH C, and the rest are mixed hepatitis. The average age of patients with CVH B is 35,9 ± 7,5 years; in patients with CVH C, the average age ranges from 36,3 ± 8,9 years. Among the examined patients with CVH B, men suffer more often (59%) than women (41%), and with CVH C, on the contrary, women suffer more often (53%) than men (47%). According to the activity of the infectious process among patients with CVH B, the minimum degree of activity was observed in 25 (51%) patients, low in 13 (27%) patients, and moderate in 11 (22%) patients. Among patients with CVH C, 101 (62%) patients had a minimal degree, 46 (28%) had a low degree, and 17 (10%) had a moderate degree of activity.

Among the examined patients there were persons who had a history of drug addiction and alcoholism. In the group of patients with CVH C, 6 patients had a history of drug addiction and 7 patients had alcoholism. The same results were in the group of patients with CVH B: 7 patients with drug addiction and 5 patients with a history of alcoholism.

**Table 1 - Characterization of groups of patients with CVH**

| | CVH B | CVH C | Total |
|---|---|---|---|
| mono infection | 30 | 164 | 194 |
| B+D | 4 | | 4 |
| C+B | | 15 | 15 |
| average age, years | 35,9 ± 7,5 | 36,3 ± 8,9 | 36,1 ± 8,2 |
| men | 29 | 78 | 107 |
| women | 20 | 86 | 106 |
| minimal activity | 25 | 101 | 126 |
| low activity | 13 | 46 | 59 |
| moderate activity | 11 | 17 | 28 |
| drug addiction | 7 | 6 | 13 |
| alcoholism | 5 | 7 | 12 |

Among patients with CVH, 25 patients with type 2 diabetes mellitus were identified. Type 1 diabetes mellitus was not detected in the examined patients. All patients before examination for markers of hepatitis C and B for 4-5 years were under medical supervision at the endocrinologist for type 2 diabetes mellitus. At the initial visit to the endocrinologist, patients complained of weakness, sweating, thirst, weight loss and polyuria, and these patients were referred for screening for diabetes mellitus. Type 2 diabetes mellitus was diagnosed based on the detection of hyperglycemia and determination of the level of C-peptide. After verification of the diagnosis, all patients started taking drugs to lower blood sugar (Diabeton, Glucofage, Metformin). The diagnosis of chronic viral hepatitis was suspected after ALT and AST levels began to rise in blood tests. After positive results of screening for viral hepatitis and verification of the diagnosis by PCR, a diagnosis of chronic viral hepatitis was made and patients were referred to a hepatology center for antiviral therapy.

All patients with CVH C and B were divided into 2 groups: main and control. Of 25 patients with type 2 diabetes mellitus, 9 were in the main group and 16 patients belonged to the control group.

Patients in the control group, according to the protocol for the diagnosis and treatment of chronic viral hepatitis B and C, received antiviral therapy (Pegintron / Pegasis + ribavirin). Patients of the main group received a Betaleukin (recombinant interleukin 1β) 10 injections under skin every other day at a dose of 5-8 ng / kg of body weight.

Patients with type 2 diabetes mellitus the level of fasting glycemia was determined daily in the first 8-12 weeks of treatment. The level of glycemia was determined in the laboratory at least once every 2 weeks. Glycated hemoglobin was determined every 3 months during treatment and another 6 months after completion of the antiviral therapy.

Statistical processing of the obtained research results was carried out using t Student criterion. The differences between the compared groups and numbers were considered significant at p <0.05-0.01-0.001.

## THE RESULTS OF THE STUDY

The study found that the incidence of type 2 diabetes mellitus was different in patients depending on the etiology of viral hepatitis. In the group of patients with CVH C, type 2 diabetes mellitus occurred 2 times more often than in groups with CVH B with a reliability of p <0.01 (Table 2). In 13.4% (22 patients) cases in patients with HCV infection and 6.1% (3 patients) cases in patients with CVH B.

Among patients with CVH, type 2 diabetes mellitus is more common in individuals with genotype 3. 2.5 times more often than with genotype 1 with a reliability of p <0.001 (Table 3). The correlation coefficient between the 3 HCV genotype and the presence of type 2 diabetes mellitus was 0.77.

**Table 2 - Frequency of type 2 diabetes mellitus depending on the etiology of viral hepatitis**

| n=213 | CVH C n=164 | | CVH B n=49 | | P |
|---|---|---|---|---|---|
| | abs | M ± m | abs | M ± m | |
| Type 2 diabetes mellitus | 22 | 13,4 ± 2,7 | 3 | 6,1 ± 3,4 | <0,01 |

**Table 3 - Frequency of type 2 diabetes mellitus depending on the CVH C genotype**

| n=164 | 1 genotype n=79 | | 3 genotype n=52 | | P |
|---|---|---|---|---|---|
| Endocrine system diseases | abs | M ± m | abs | M ± m | |
| Type 2 diabetes mellitus | 6 | 7,6 ± 3,0 | 16 | 30,8 ± 6,4 | <0,001 |

Among patients, type 2 diabetes mellitus was 2.5 times more common in men than in women with a reliability of p <0.01 (Table 4).

**Table 4 - Frequency of type 2 diabetes mellitus depending on gender.**

| n=213 | men n=107 | | women n=106 | | P |
|---|---|---|---|---|---|
| | abs | M ± m | abs | M ± m | |
| Type 2 diabetes mellitus | 18 | 16,8 ± 3,6 | 7 | 6,6 ± 2,4 | <0,01 |

## ANTIVIRAL THERAPY RESULTS

During treatment, it was found that when an early virological response was achieved in 17 of 22 (77.3%) patients with CVH C, glycemia levels returned to normal within 2-3 weeks without taking any anti-diabetic medications. Due to the achievement of complete control over the level of glycemia, anti-diabetic medications in patients were canceled. Patients continued to follow a diet (table 5 with limited intake of fast-digesting carbohydrates). In 5 patients, glycemic control was not observed when a virologic response was achieved.

The correlation coefficient between the achievement of a full virological response (negative PCR results on HCV RNA) and the normalization of glycemia was 0.75. That is, in these patients, type 2 diabetes mellitus turned out to be HCV-associated.

In patients with CVH, there were no significant differences in the control of glycemia and the level of viral load.

There was no difference between the groups with CVH C receiving betaleukin before receiving antiviral therapy and not receiving diabetes relief. That is, the use of betaleukin did not worsen the course of diabetes mellitus and / or did not contribute to the manifestation of impaired glucose tolerance.

**Table 5 – Frequency of type 2 diabetes mellitus in patients with CVH C and B**

| n=213 | CVH C n=164 | | CVH B n=49 | | P |
|---|---|---|---|---|---|
| Endocrine system diseases | abs | M ± m | abs | M ± m | |
| Type 2 diabetes | 22 | 13,4 ± 2,7 | 3 | 6,1±3,4 | <0,05 |
| Virus-associated type 2 diabetes | 17 | 10,4 ± 2,4 | 0 | 0,0 ± 0,0 | <0,001 |
| Diabetes as a Concomitant Pathology | 5 | 3,0 ± 1,3 | 3 | 6,1 ± 3,4 | -0,836 |

When analyzing the long-term results of treatment, it was found that for 6 months after completion of treatment in all patients whose glycemic level was achieved with early virological response, the level of glycated hemoglobin remained below 7.0% - on average 5,60±0,552 %. Thus, glycemic level control was maintained for 6 months after completion of the antiviral therapy against the background of achieving a stable virologic response.

## THE DISCUSSION OF THE RESULTS

Among the systemic manifestations of chronic hepatitis, pathology of the endocrine system plays an important role [10, 11]. A number of clinical studies (Allison et al (1994), Lecube et al (2004), Cacoub et al (2000)) and general population-based (NANHES-III) studies have concluded that there is a causal relationship between HCV and type 2 diabetes mellitus [12,13,14].

Recent studies in the United States have shown that among patients with a virological response to treatment, there is a significant decrease in glycated hemoglobin (HbA1c). The study was conducted in 2435 patients with type 2 diabetes mellitus and chronic viral hepatitis. All patients received treatment with interferon-free regimens using different direct-acting antiviral agents DAAs. A significant difference was obtained in the level of glycemia (in terms of gliked hemoglobin), depending on

the achievement of a stable virologic response (SVR) and treatment failure - 0.98% versus 0.68% (reliability 0.34, P = 0.02). The use of anti-diabetic medications, including insulin among patients with SVR decreased from 41.3% to 38%, while in the group of non-responders it even increased from 49.8% to 51% [15, 16, 17].

Achieving normalization of glycemia with a simultaneous reduction and complete rejection of anti-diabetic medications in 77.3% of patients with SVR is a strong argument in favor of the fact that the hepatitis C virus, especially genotype 3, plays a significant role in the pathogenesis of type 2 diabetes mellitus, and successful eradication of the virus can lead to the relief of insulin resistance. However, this effect was not obtained in all patients [18, 19]. Either the remaining 22.7% have diabetes mellitus, independent of the presence of viral hepatitis C, or the eradication of the virus has not eliminated all the pathogenetic mechanisms of diabetes [20, 21, 22, 23].

The practical significance of the work is recommendations for improving the diagnosis of HCV infection: the presence of diabetes mellitus is the basis for screening for HCV, regardless of other factors. 75-77% of type 2 diabetes mellitus in the cohort of patients with CVH C is possibly virus-associated. Treatment of HCV infection can lead to a cure for type 2 diabetes mellitus in this category of patients.

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