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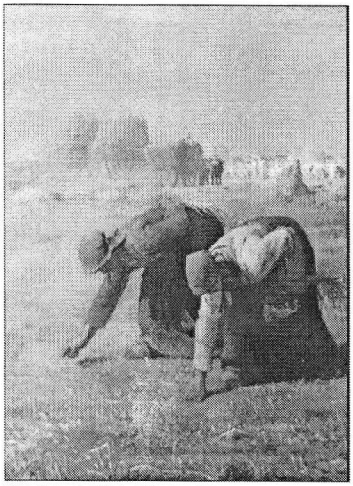

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ASSOCIATION OF THE PRO197LEU POLYMORPHISM OF THE GLUTATHIONE PEROXIDASE 1 GENE AND MARKERS OF THE ENDOTHELIUM FUNCTION IN PATIENTS WITH CHRONIC, DIFFUSE LIVER DISEASES. GENOMIC INFLUENCE ON THE "CLINICAL PHENOTYPE" OF CHRONIC, DIFFUSE LIVER DISEASES.

SKOJARZENIE PRO197LEU POLIMORFIZMU GENU PEROKSYDAZY GLUTATIONU 1 ORAZ MARKERÓW CZYNNOŚCI ŚRÓDBŁONKA U PACJENTÓW Z PRZEWLEKŁYMI, UOGÓLNIONYMI CHOROBAMI WĄTROBY. WPŁYW ZMIENNOŚCI GENÓW NA „KLINICZNY FENOTYP" PRZEWLEKŁYCH, UOGÓLNIONYCH CHORÓB WĄTROBY.

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STRESZCZENIE. *Cele badań. Patogeneza przewlekłych, uogólnionych chorób wątroby (Chronic Diffuse Liver Diseases – CDLD) nie jest wystarczająco wyjaśniona, przedstawia wiele niedostatecznie zbadanych problemów. Stwierdzenia powyższe odnoszą się – wśród innych czynników – do znaczenia zaburzeń czynności śródbłonka szczególnie wynikających z predyspozycji genetycznej. Z tych względów podjęto własne badania tego problemu ujmowanego w nowy sposób.*

Metody. Przeprowadzono kliniczno-doświadczalne badania mające na celu wyjaśnienie mechanizmów uszkodzenia stanu czynnościowego śródbłonka w CDLD. W tym celu oznaczono występowanie genetycznie uwarunkowanego polimorfizmu PRO197LEU - substytucja leucyny przez prolinę w kodonie 197 ludzkiego genu regulującego syntezę i funkcję enzymu – peroksydazy glutathionu (GPX1) to jest enzymu przeciwdziałającego działaniu oksydacyjnego stresu.

Dodatkowo określono stan czynnościowy tarczycy.

Badania dotyczyły 28 pacjentów z CDLD.

W zakresie genetyki 1. oceniono polimorfizm PRO197LEU genu GPX1; 2. oznaczono wybrane markery czynności śródbłonka.

Wyniki. Stwierdzono, że badany polimorfizm genu GPX1 jest istotnie skojarzony ze zwiększonymi poziomami markerów uszkodzenia funkcji śródbłonka u homozygotycznych nosicieli polimorfizmu PRO197LEU.

Wskazuje to na możliwy udział predyspozycji genetycznej do dysfunkcji śródbłonka w patogenezie CDLD.

Słowa kluczowe *– Przewlekłe, uogólnione choroby wątroby (CDLD), zaburzenia czynności tarczycy, cząsteczki adhezyjne – ICAM, czynność śródbłonka, PRO197LEU polimorfizm genu peroksydazy glutationu (GPX1).*

SUMMARY. *The aims of the study. The pathogenesis of the chronic, diffuse liver diseases (CDLD) presents several, non-well elucidated, aspects. This statement refers – among others factors – to the significance of the endothelial cells function and respective genetic background in CDLD. Therefore the studies seeking the explanation of this innovative problem were undertaken. The experiments were directed toward assessing the peculiarities of the endothelial, functional state in patients with CDLD depending on the PRO197LEU polymorphism of the glutathione peroxidase 1 gene (GPX1).*

In addition the possible influence of the thyroid function disorders related to CDLD was assessed.

The studies were performed in the group of 28 patients with CDLD.

Methods. The clinical liver diseases diagnosis was based on typical parameters.

Patient with CDLD frequently present the disturbances of the thyroid homeostasis. Therefore in the group under study this peculiar possibility was also examined. For this reason hormones as TSH, and blood serum level of the free triiodothyronine (fT3), free thyroxine (fT4) were determined.

In this group of patients the following assessments were made.

1. 2. PRO 197LEU polymorphism of the GPX1 gene,

2. Level of soluble intercellular adhesion molecule – 1 type – ICAM-1,

3. Desquamated endothelial cells numbers and the content of the nitrogen monoxide (NO) metabolites in blood serum.

Results. In patients with CDLD the reduction of fT3 and the increase of fT4 and TSH was not found.

PRO197LEU polymorphism of GPX1 gene was associated with the disturbances of the endothelial function as manifested by the higher content of ICAM-1 in the blood serum in homozygotic carriers of the LEU-allele. Perturbations in the endothelial function in patients with CDLD were associated with the polymorphism of PRO197LEU of GPX-1 gene. This phenomenon was also supported by the higher index of the desquamated endothelial cells and lower level of NO in cells of the carriers of LEULEU genotype.

Conclusions. In CDLD the abnormal levels of the endothelial cells functional injury markers were associated with respective gene polymorphism of the PRO197LEU GPX-1 gene.

The results of the study revealed the new, genetically determined, mechanism of the liver injury acting within the complex of different, other pathogenetic factors in CDLD.

Key words *– chronic diffuse liver diseases (CDLD), thyroid disorders, intra- cellular adhesion molecules (ICAM), endothelium function, polymorphism of the PRO197LEU GPX1 gene.*

Editor`s note:

glutathione peroxidase (GPX1) is an enzyme decreasing the oxidative stress (neutralization of free radicals), it is selenium dependent; GPX1 gene is located on chromosome 3p21.3.

PRO197LEU polymorphism is a proline (PRO) leucine (LEU) substitution at codon 197 (PRO197LEU) of the human GPX1 gene. It exerts the functional decrease of the GPX1 enzyme auti-oxidative action, exposes the cells and organs to the damaging effects of the oxidative stress.

STUDY PREMISES

Genetic polymorphism constitutes the base for phenotypic differentiation of the individuals within the general population. It is also the pathophysiological mechanism forming the specific, congenital susceptibility to various diseases and pathogenetic disturbances. Studies of these phenomena draw much interest and attention in the area of gene coding factors involved in the development of variable pathology (2, 12, 15).

The analysis of different gene actions and associations plays an important role in the elucidation of specific genetic factors responsible for the development of polymorphic diseases as – in particular – chronic diffuse liver diseases (CDLD). The differences of the marker allele frequency existing between patients and healthy individuals give chance to assess the probalility of the link of particular allele with the specific pathology (12, 16).

The available information concerning the genetic - phenothypic links in the CDLD pathogenesis points to the range of different gene-candidates; with potential links to this pathology. It is a clinically important problem which needs investigation.

This problem comprise many scientific questions. One of them is the significance of the endothelium function disturbances in the CDLD pathogenesis. This is a new area of studying the CDLD. The endothelium functional state may be assessed by determining its markers like cytokines in blood serum, desquamation of endothelial cells (apoptosis) and NO metabolism.

The endothelial cells secretion of the cytokines is – beyond any doubt – related directly to the genetic control (15).

Therefore the dependence of the such endothelium function markers on the GPX1PRO197LEU GPX1 gene polymorphism in patients with CDLD is particularly interesting and clinically important.

In this paper the specific research results elucidating this pathogenetic problem are described.

AIM OF THE STUDY

The study was aimed at:

1. The determination of the markers of the endothelium function in patients with CDLD with examining also the potential secondary disorders in thyroid hormones blood concentration.

2. Assessing the possible association of the assessed endothelial function markers with the PRO197LEU polymorphism of the GPX1 gene.

It was assumed, that such studies may enlarge the knowledge concerning the CDLD pathogenesis.

MATERIALS AND METHODS

Materials and methods are described in the following 8 sections.

1. 28 patients with CDLD aged from 25 to 74 (an average age – 52,3±6,09) were included into the study. There were 19 men (67,9%) and 9 women (32,1%), an average duration of the disease was 5,9±1,30 years. The control group included 20 practically healthy individuals (an average age - 52,2±12,15), 13 men (65,0%) and 7 women (35%) among them.

2. The diagnosis of chronic hepatitis (CH) was made in 13 individuals (46,4%) with an average age of 49,6±8,59. There were 7 men (53,8%) and 6 women (46,2%) among them, an average duration of the disease was 6,0±2,10 years. A mild form of CH was found in 8 patients (28,6%) and moderate form – in 5 patients (17,8%).

Liver cirrhosis (LC) was diagnosed in 15 patients (53,6%) with an average age of 55,0±7,43. Men constituted 11 patients (73,3%), women – 4 (26,7%), an average duration of the disease was 5,7±1,80 years. A mild form of LC was found in 9 patients (32,2%) and moderate form - in 6 (21,4%).

The diagnosis of CH and LC were made accordingly to the Classification of the World Congress of Gastroenterologists (Los Angeles, 1994, with additions of V. Desmet et al, 1995) and specifications of the International Classification of Diseases (ICD) of the 10th revision [4].

CH and LC were verified on the basis of anamnesis, objective status, common laboratory methods of examination (general blood and urine analyses, biochemical blood tests - bilirubin and its fractions, ionogram, proteinogram, coagulogram). The following enzymes were examined in blood serum: alanine-minotransferase (AlAT), aspartate--aminotransferase (AsAT), gammaglutamyltransferase (GGT), alkaline phosphatase (AP). The levels of urea, creatinine were determined in the blood serum as well as markers of hepatitis B and C viruses. Instrumental examinations were also conducted - USG of the abdominal organs, esophago-gastro-duodenofibroscopy.

The degree of the morbid, activity of CH and LC was assessed on the basis of clinical manifestations and biochemical markers – AlAT, AsAT activity, thymol test turbidity, bilirubin level in the blood (5).

The degree of LC compensation was estimated by the criteria of C.G. Child and J.G. Turcotte (1964) in the modification of K.N.H. Pugh (1973). The levels of albumins and prothrombin were determined in the blood serum, the presence of ascites and encephalopathy was examined in each case (13).

The degree of portal hypertension was assessed on the basis of the varicose dilatations in the lower esophageal section, presence of the dilatation of the subcutaneous veins of the anterior abdominal wall, splenomegaly, ascites and hepatic encephalopathy (7).

3. Using the above described clinical examination the patients were included into the group for further study. The inclusion criteria were: the age from 25 to 76, diagnosed CH and LC (of a mild and moderate activity) as verified by clinical, laboratory and instrumental examinations. Informed, written consent of the patient to participate in the study was taken in each case.

These patients were excluded from the investigation: patients with decompensated LC (III degree of hepatic--cellular failure, hypoalbuminemia less than 30%, III-IV degree of hepatic encephalopathy, resistant ascites, systemic hypotension), chronic hepatitis of a viral etiology, Wilson's disease, congenital α1-antitrypsin insufficiency (α1-inhibitor of proteinases), idiopathic (genetic) hemochromatosis, autoimmune hepatitis, diabetes mellitus, III-IV degree of chronic heart failure with ejection fraction of the left ventricle less than 45%, acute disorders of the cerebral circulation and acute coronary syndrome, psychological disorders, residents of the III-IV zones of radiation contamination, individuals during pregnancy or lactation period or those receiving oral contraceptives, with any acute inflammatory processes, other concomitant decompensated diseases or acute conditions able to affect the results of the study.

4. The status the thyroid homeostasis were studied by the assessment of free thyroxine (fT_4), free triiodothyronine (fT_3) and thyroid stimulating hormone (TSH) by means of immune-enzymatic method using the reagents "ImmuneFa-TTH", "IFA-SvT_3" and "IFA-SvT_4-I" (JSC "Immunotech") on the analyzer of immune-enzymatic reactions "Uniplan" calculating the levels of fT_3/fT_4, fT_4/fT_3.

5. Alleles of PRO197LEU regions in GPX1 gene were studied by means of extraction of the genome DNA from leukocytes of the peripheral blood with further amplification of a polymorphic region by means of polymerase chain reaction (PCR) on the programmed amplificatory "Amply-4L" ("Biocom") with individual temperature program for the parameters of every gene.

Depending on GPX1 gene PRO197LEU polymorphism there were 12 homozygotes by PRO-allele, 8 – by LEU-allele and 8 PROLEU-heterozygotes.

Table 1 presents succession of oligonucleotides in primers and their calculation positions on chromosomes.

Tab. 1. Succession of oligonucleotides in primers used for polymerase chain reaction (PCR) identyfying Pro197Leu polymorphism of GPX1 gene.

Gene name	Gene localization on chromosome	Primer	Succession of oligonucleotides in primers
GPX1	3p21	Direct	5'-TCGAAGCCCTGCTGTCTCA-3'
		Reverse	5'-CGAGACAGCAGCACTGCAA-3'

DNA extraction was conducted by means of "DNA-sorb-B" reagents, variant 100 according to the instruction. Purified DNA was kept under the temperature of 20±2°C. Samples for PCR were prepared by means of "AmplySense – 200 – 1" set.

6. The content of soluble intercellular adhesion molecule – 1 type (ICAM-1) in the blood serum was determined with immunoenzymatic method using the commercial test system "BenderMedSystems".

Functional, endothelial state was also estimated by the content of NO metabolites and the amount of desquamated endothelial cells in the blood. NO content in the blood serum was estimated by the concentration of its final stable metabolite – NO_2 and the content of total final metabolites of NO (nitrates+nitrites). The method determining NO_2 content in the venous blood plasma was based on the photocolorimetric detection of optic density of NO_2 stained complex by Griess test [11]. The amount of desquamated endothelial cells (EC) in the blood was assessed by J.Hladovec method in N.Petrishchev et al. modification (6).

7. The protocol of examination of the patients was approved by the Biomedical Ethics Comission of Bukovinian State Medical University. The document was compiled according to the requirements stipulated by the 6th chapter of CH GCP (1996). While compiling the protocol, the main principles of the Helsinki Declaration on Biomedical Research (1974) adapted during the 41st International Assembly in Hong Kong (September, 1989) were followed. The protocol corresponds to the basic principles of proper medical practical work such as respect of a personality, awareness of the patient, estimation of the risk of harm and benefit (17, 18, 19).

8. All findings of patients' examinations were included into the data base of the system Microsoft Office Excel. All data were further processed by formalization, standardizing of the results and statistical analysis.

Before veryfying statistics of the research hypotheses the analysis was conducted of regular distribution of the values in randomized surveys by means of detecting the asymmetry and excess coefficients with the help of Khan-Shapiro-Wilcky criterion was conducted.

Probability of the difference between the mean values and its errors differentiating the groups study was calculated with double odd Student t-criterion.

For the data with normal distribution with equality of general dispersions of sampling checked by means of the Fisher-criterion, the probable difference was with $p<0,05$ (8).

Mathematical calculation of the results obtained was conducted on IBM PC Pentium III by means of computer program Primer of Biostatistics, Version 4.03 (S.Glantz, USA) and the standard package of statistical programs of Microsoft Office Excel 2007 (1).

RESULTS

The results of the studies performed in the selected, as described in the section "Materials and Methods", group of 28 patients with CDLD can be presented in the following order:

1. Assessment of disturbances of the thyroid homeostasis.

Blood serum levels of free triiodotyronine (fT_3) and free tyroxine (fT_4) as well as of TSH were within the normal range. Therefore in the examined group of CDLD cases the existence of the reduction of fT_3, increase of fT_4 due to failure of peripheral monodeiodination with the increase of TSH as described in the literature was not found.

2. The markers of the endothelial function in patients with CDLD as expressed by the determinations of the cytokine – ICAM1, production of NO metabolites and the number of desquamated endothelial cells found in the blood were abnormal when compared with healthy persons. These markers indicate the endothelial disturbances.

3. This endothelial dysfunction was associated in a statistically significant way with the polymorphism of the GPX1 gene as seen in table 2.

The increase of the ICAM-1 content in the blood serum in all 3 subgroups of CDLD with different GPX1 genes was significant. It was - (a) for the carriers of PROPRO genotype – 19,1% ($p1 < 0,001$), (b) PROLEU genotype – 25,4% ($p_1 < 0,001$) and 49,2% ($p_1 < 0,001$). The last subgroup of the LEULEU genotype carriers presented the value of this endothelial function marker 25,3% higher ($p_1 < 0,001$) that the subgroup of patients withe genotype PROPRO.

Pro-allele homozygotes were characterized by a significant decrease of the stable NO metabolites in the blood compared with the control (healthy) group ($p_1 <$ 0,01, table 2). Such decrease were also observed also

Tab. 2. Indices of the endothelial function in patients with CDLD depending on PRO197LEU polymorphism of GPX1 gene (M±m).

Index	Control group n=20	Genotypes of GPX1 gene, n=28		
		PROPRO, n=12	PROLEU, n=8	LEULEU, n=8
ICAM-1, ng/mL	259.60±10.324	309.23±12.463 $p_1<0.01$	351.38±18.274 $p_1<0.001$ $p_2>0.05$	387.41±20.108 $p_1<0.001$ $p_2<0.01$ $p_3>0.05$
Stable NO metabolites (NO_2, NO_3, mcmol/L)	18.14±0.684	13.45±1.002 $p_1<0.01$	11.45±1.139 $p_1<0.001$ $p_2>0.05$	10.24±1.012 $p_1<0.001$ $p_2<0.05$ $p_3>0.05$
Endothelial cells, x 104/L	3.04±0.204	4.63±0.320 p1<0.001	5.83±0.549 $p_1<0.001$ $p_2>0.05$	6.27±0.625 $p_1<0.001$ $p_2<0.05$ $p_3>0.05$

Notes: n- numbers of obseravtions;
p_1 – probability of changes concerning the control
p_2 – probability of changes concerning the group of patients with ProPro-genotype
p_3 – probability of changes concerning the group of patients with ProLeu-genotype

in the LEU-allele homozygotes ($p_1 < 0,001$) and in the PROLEU-heterozygotes ($p_1 < 0,001$). Lower levels of NO metabolites were also found in the blood of LEULEU genotype carriers compared with patients with PROPRO-genotype ($p_1 < 0,001$).

When comparing the numbers of desquamated endothelial cells in the blood of patients with CDLD and carriers of PRO197LEU GPX1 gene with such numbers in the control (healthy) subjects the folloving differences were found: 1) in the PROPRO-genotype subgroup 1,5 times higher ($p < 0,001$); 2) in the PROLEU-genotype subgroup 1,9 times higher ($p < 0,001$); 3) in the LEULEU-genotype subproup 2,1 times higher ($p < 0,001$). The numbers of the desquamated endothelial cells as the marker of the disearrangement of the endothelium function and apoptosis was signifant higher in LEULEU-genotype carriers – in 34,4% ($p < 0,001$) – than in patients with the PROPRO-genotype.

It means that the homozygotic carrier of the LEU-allele with CDLD shows the significantly higher levels of 1) ICAM-1 in the blood serum, 2) numbers of desquamated endothelial cells and also 3) lower levels of the NO stable metabolites.

DISCUSSION

The results of the presented studies revealed the relation between the variations of the gluthation peroxidase1 gene and the endothelial function in patients with chronic, diffuse liver diseases.

The alterations of genes, which code the enzymes of the glutathione family affects in this way the susceptibility and clinical symptomatology of the CDLD. It was found that the possible causative factor of this pathology is the genetically conditioned impairment of the endothelial function and consecutive disturbances in blood supply (12, 20).

What could be the mechanism of this genetic action? One may point to the possibility of the oxidative stress.

Many researchers have found that certain allelic variants of the gluthatione peroxidase gene may also increase the pathogenetic action of the oxidative stress. The intensification of the intracellular peroxidation processes and the anti-oxidative imbalance may act as the important mechanism of the hepatocytes damage promoting the diffuse, parenhymatons chronic liver diseases – CDLD (2, 10).

In specific studies it was revealed that in patients with CDLD being the homozygotes – carriers of the Leu-allele of the gene GPX1 the markers of the liver damage as for example bilirubin metabolism or the blood serum level of aminotranspherases are significantly high (9, 15).

In patients with PRO197LEU polymorphism of the GPX1 gene the intensification of the oxidation processes is typical (14). Free oxygen radicals may directly disturb the NO metabolism (3). Peroxidation of the lipids within the cell membranes is another way of damaging the cells of the endothelium and of the liver the ability of NO production.

Development of an absolute or relative deficiency of NO, impairs the normal regulation of vascular tone. The weakening of the NO-dependent vasodilatatory reactions, in its turn, leads to increased vascular tone, increased, coagulatory action and as a result, tissue hypoxia. In addition,

the reduced inhibitory effect of NO on platelets aggregation, leukocyte adhesion to the endothelium and the smooth muscle cell proliferation of the vascular wall, creates prerequisites for significant vascular disorders.

Important role in the pathogenesis of endothelial dysfunction plays also disturbed adhesion of the endothelial cells.

The endothelial cells integration is – in an important way – regulated by the intracellular adhesion molecule type 1 – ICAM-1 (12, 14).

Disturbances in the mechanisms of the cells adhesion could be the cause of structural endothelium damage (16). of the endothelial wall which enhance the infiltration by macrophages to the subendothelial space. It also induces the endothelial apoptosis (3, 15). These phenomena lead to the increased desquamation of endothelial cells.

The results of our study – both in the area of the assessment of the endothelium function damage and in the assessment of its association with the specific GPX1 gene variation – are supporting the above presented hypothesis. The specific variations in GPX1 gene are in the significant way associated with the character of the endothelium damage in CDLD.

It means that the genetic background may in a specific way influence the pathogenetic processes and the clinical course of the CDLD. It could be stated more generally, that the genomic type influence the clinical phenotype of the chronic, systematic diseases.

CONCLUSIONS

1. PRO197LEU polymorphism of the GPX1 gene is associated in chronic diffuse liver (CDLD) diseases with the specific damage of the endothelium function.

This is proved by the lower levels of NO metabolites and the higher numbers of desquamated endothelial cells in blood of the carriers of the LEULEU-genotype.

2. In patients with CDLD there is a relation between the expression of PRO197LEU polymorphism of GPX1 gene and indices of cellular adhesion, which is revealed by a reliably higher content of intercellular adhesion molecules of the 1 type (ICAM-1) in the blood serum - of homozygotic carriers of Leu-allele.

Abbreviations:
AIAT – Alanine Aminotransferase
ASAT – Asparagine Aminotransferase
CDLD – chronic, diffuse liver disease
CH - chronic hepatits
CL – cirrhosis of the liver
EC – endothelial cell
fT3 – free triiodothyronine
fT4 – free thyroxine
GGT – gammaglutamyl-transpeptidase
GPX1 – gluthatione peroxidase 1
GPX1 gene – gene located in chromosome 3p21.3
ICAM-1 – intracellular adhesion molecule
NO – nitrous oxide
PRO197LEU – proline to leucine substitution at codon 197 of the GPX1 gene (PRO197LEU).

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PATOFIZJOLOGICZNE RELACJE PRZEWLEKŁYCH CHORÓB WĄTROBY I CUKRZYCY NIE SĄ WYSTARCZAJĄCO WYJAŚNIONE

Występowanie przewlekłych, miąższowych chorób wątroby łączy się w znamienny sposób z powstawaniem i przebiegiem cukrzycy. Przyczyny takiego skojarzenia mogą mieć różny charakter; w niektórych, endogennych chorobach wątroby (np. hemochromatoza) są to predyspozycje genetyczne. W innych chorobach miąższowych wątroby mogą to być różne przyczyny, np. zależne od pierwotnie metabolicznych zaburzeń czynności wątroby powodowanych przez cukrzycę - nie-alkoholowe stłuszczenie lub wpływy toksyczne – marskość wątroby z różnych przyczyn. Przewlekle zwiększenie stężenia niektórych enzymów wątrobowych jak np. aminotransferazy alaninowej lub gamma-glutamylo-transferazy można uznać za predyktor zwiększonego ryzyka cukrzycy typu 2.

Zwiększenie ilości tłuszczu w wątrobie ponad 50% jej masy określa się mianem patologicznego stłuszczenia wątroby. Może ono być spowodowane otyłością, zwłaszcza brzuszną, zaburzeniami metabolizmu lipidów w cukrzycy typu 2 a także egzogennymi czynnikami toksycznymi jak np. nadużywanie etanolu. U ok. 5% osób z tym zespołem można wykazać aktywny proces zapalny i włóknienie, które prowadzą do marskości wątroby. Zaburzenia te stanowią ponadto istotny czynnik ryzyka insulinooporności w cukrzycy typu 2. Interesujący jest fakt, że nie dotyczy to wszystkich osób ze stłuszczeniem wątroby. Jest to okoliczność, która wskazuje na istnienie dodatkowych, dotąd nie wyjaśnionych czynników etiologicznych.

W populacji osób z cukrzycą częściej stwierdza się występowanie marskości wątroby. Cukrzyca pogarsza rokowanie odnoszące się do jej przebiegu. Może to łączyć się z faktem zwiększonej - w populacji osób z cukrzycą - zapadalności na wirusowe zapalenie wątroby, a także z wieloma zależnymi od cukrzycy zaburzeniami uszkadzającymi komórki wątrobowe jak epizody hipoglikemii, ketozy lub terapeutyczna polipragmazja. Z kolei przewlekłe miąższowe uszkodzenie wątroby zmienia przebieg cukrzycy i działania terapeutyczne.

Okazuje się, że w tych patogenetycznych relacjach mogą mieć także znaczenie czynniki genetyczne. Jest to problem do dalszych badań.