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ORIGINAL ARTICLE

Insulin Resistance and β Cell Function in Patients with Chronic Hepatitis and Impaired Glucose Tolerance

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HBV and HCV infections play an important role in the pathogenesis of patients with diabetes. The aim of this study was to determine changes in blood glucose, insulin resistance and β cell function in IGT patients with chronic hepatitis B and C.

Materials and Methods: A group of 560 patients with IGT, chosen from among participants of the Tehran Glucose and Lipid Study, were enrolled in this survey; their sera were examined in stage I for hepatitis B and C. FBS, HOMA-IR, β cell function in the three groups (hepatitis B, C and seronegative) were studied, and these evaluations were repeated after 3 years. The changes over three years were quantitatively calculated by means of T tests paired T test. X2 and the MC Nemar test ANOVA variance analysis were used for qualitative variables (for determination of variable effects). Spearman and Pearson correlation coefficients were used to find relationship between variables.

Results: Of participants, 64.9% were female and 35.1% male; their average age was 50.8±12.7 years at the beginning of the study. There was no significant difference for FBS, HOMA-IR, β cell function between the 3 groups. After three years, six of them were HCV positive and six were HBV positive. There was no significant difference between their FBS, HOMA-IR and βCF after 3 years. Blood glucose changes and β cell function in persons that were positive for HBV or HCV in the first and second stages of the study showed no significant statistical change after three years, whereas HOMA-IR showed significant reduction compared to the beginning of study (from 4±2 to 3.1±2.2, p<0.05). In general, in persons that were seronegative for HBV or HCV in both stages of this study, significant changes were observed in different degrees of insulin resistance after three years; 22.5% of persons sensitive to insulin became resistant, while 49.6% of them became sensitive (p<0.001), changes that were not observed in seropositive patients.

Conclusion: There was no significant statistical difference between the seropositive group for changes in blood glucose, HOMA IR, and β cell function after 3 years whereas in the seronegative patients, blood glucose increased and β cell function and HOMA-IR decreased.

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Introduction

Diabetes is a highly prevalent disease affecting over 150 million people worldwide and three million people in Iran, with numerous cases yet unidentified.[1] Researches conducted in Iran show a prevalence of 1.4-14.7

percent in cities and 4.3-7.3 percent in rural regions. In addition, the IGT prevalence in cities was 8.2-22 and 2.3-7.2 percent in cities and rural regions respectively.[2] Genetic and environmental factors are effective in causing diabetes, and hence investigating especially the environmental factors can perhaps reduce its prevalence; the timely diagnosis and treatment can decrease use its consequences considerably.[2]

Hepatitis B and C are prevalent viral infections; in one study conducted in Iran, on 39841 persons, the average prevalence of HBV carriers was 1.7 percent, its prevalence being 0.59% among 7879 blood donors.[3] A positive relationship between chronic hepatitis B and C and diabetes mellitus has been confirmed in young and old people, males and females and different races.[4,5] The cause of higher prevalence of IGT in chronic hepatitis B and C are not clear yet but glucose metabolism changes in patient with chronic liver disease have been demonstrated; HBV and HCV infections play an important role in the pathogenesis of DM in these patients.[6] Considering the role of environmental factors in diabetes, controlling the above mentioned factors is effective in reducing DM and its consequences.[1] In most studies an increasing IGT prevalence in HCV has been documented, but HBV, IGT and DM prevalences were less than HCV and some studies reported similar IGT prevalences in general populations.[5,7] In Iran, one survey showed no relationship between IGT prevalence and HCV infections, in contrast to findings of other studies.[8] Therefore this study was conducted with the aim of evaluating HBV and HCV infection, insulin resistance and β cell function in people, aged over 20 years, that had IGT; The population was studied before (stage one) and after three years, (stage two), for changes of glucose intolerance, insulin resistance and β cell function in seropositive and seronegative individuals, and changes found in these variables between two groups were compared.

Materials and Methods

In this observational study, the population was selected for among participants of the Tehran Lipid and Glucose Study (TLGS), a research being conducted for determining atherosclerosis risk factors among Tehran's urban population and changing lifestyles to prevent the increasing trend of diabetes mellitus and dislipidemia. The design of this research has two main parts; the first phase, a cross–sectional study for the prevalence, determining CVD risk factors and the second phase, the prospective intervening cohort study designed for the next for 20 years. Of the 15005 people that participated in this study in 1998 (first phase), 9472 people aged over 20, underwent GTT tests and 607 of this group were found to have IGT, of which 560 ultimately people entered the study. Three years (2001: second phase) after the first phase, participants were assessed again. At both stages of this study, questionnaires were completed, anthropometric parameters measured and blood samples were taken; GTT was performed.

Anthropometric findings: Subject's weight without shoes and garment was measured by a digital scale (Germany, SEGA, accuracy of ±100 gr. This scale was standardized after every 10 measurings; subject's height was measured to an accuracy of one millimeter while standing without shoes by a ruler placed directly over their head. BMI was computed by weight per kilogram divided by height square per kg/m^2.

GTT: Using glucose kit (Iran, pars Azmoon company), blood glucose was measured by enzymatic colorimetry.

Laboratory methods: The blood samples were centrifuged at 3000 rpm for 10 minutes, autoanalysis was conducted by Selecta 1-2 apparatus (Vital scientific, Spankeren, Netherlands). Blood glucose measurement was done using the Pars Azmoon company Kit-Tehran-Iran with normal range of 75-110 and coefficient variation of <3%.

HBS Ag was performed using the ELISA screening test (ELISA Neutralization Kit,

Dia. Pro Diagnostic Bioprobes s.r.l. Milano-Italy) and the positive results were confirmed by Hbs Ag Screening test: (ELISA, SRB ELISA Kit, Shanghai Rongsheng Biotech co., Ltd Shanghi, China) by the Neutralization Method. HCV Antibody (Anti-HCV) was surveyed by the ELISA screening method (inno LIA HCV III, innogenetoics biotechnology, Gent, Belgium) and the positive findings were confirmed by confirmatory ELISA test with HCV Ab test: ELISA, SRB (ELISA Kit, Shanghai Rongsheng Biotech co, Ltd. Shanghai, China) with the western blot method. Since all the above mentioned tests are qualitative, all positive and borderline results were double checked; for qualitative tests however, such as RIBA, repeating of results and calculation of coefficient variation for accuracy is not necessary.

HOMA-IR: Insulin resistance after measuring FBS (Enzymatic Colorimetry) and serum fasting insulin by insulin test: (ELISA insulin Accubind, monobin inc, costa Mesas co, USA Kit), by the IRMA method were calculated by the formula.[19]

$$\text{Insulin resistance} = \frac{\text{Fasting insulin (ml/L)} \times \text{FBS (mmol/L)}}{22.5}$$

Insulin resistance was grouped as follows: Group 1, HOMA-IR=2.24 as insulin sensitive, group 2 HOMA-IR= 2.24-3.59 as an intermediate, and group 3 HOMA-IR>3.59 as the insulin resistant group.

The above mentioned variables were studied twice, once at the beginning of the TLGS (stage 1) and again 3 years later (stage 2) and the changes related to baseline data were compared. In this study, the information was gathered using interviews, observation and questionnaires. The data collected were analyzed by SPSS software. Average, standard deviation, percentage and mode were used for describing variable positions. T test and paired T test were used in quantitative variables and X2 and McNemar tests were applied in examining qualitative variables and ANOVA was used for determining variable effects. For assessing the relationship between variables, the Spearman, and Pearson correlation coefficient were used.

Results

Of the population, 64.9% were female, while 35.1% were male; average age was 50.8±12.7 years, the youngest patient being 20, and the oldest one, 82 years old. After 3 years, 27 had normal blood glucose, 212 patients still had IGT and 91 became diabetic. The serologies were studied at stage I for HBV and HCV; 2 persons were HCV positive and eight were HBV positive. In the second assessment, six persons were HCV positive and six persons were HBV positive. At baseline, the only significant difference between seropositive and seronegative was higher HDL levels in the seropositive group.

At baseline, there were no significant differences using ANOVA by post-hoc test type Bonferroni, between three groups for FBS, HOMA-IR and β cell function. It should be mentioned that after three years, one HCV and two HBV patients, positive at baseline, were seronegative for HCV and HBV.

Seronegative and seropositive patients at baseline and after 3 years were compared and the only difference observed was reduced levels of cholesterol in the seropositive group. FBS, HOMA-IR and βCF in three groups were compared and showed no significant difference in variance analysis by post-hoc test type Bonferroni. In both assessments, seven people were HCV or HBV positive and 545 persons were seronegative. Changes in all variables such as BMI, cholesterol, triglycerides, HDL, LDL, FBS, systolic and diastolic blood pressure between two evaluations in seronegative people were statistically significant, except BMI and blood glucose, which showed a descending trend compared to baseline values. In the seropositive group, however no significant differences in changes were seen (Table 1).

Table 1. Epidemiologic and clinical features of seronegative and seropositive patients at baseline and 3 years later

Variable	Baseline	Seropositive Three years later	P Value	Baseline	Seronegative Three years later	P Value
BMI (kg/m^2)	26 ± 4	26±4	0.7	28.8±4.3	29.1±4.9	0.002
Cholesterol (mg/dL)	224±74	178±35	0.1	260±48	207±40	0.001
Triglycerides (mg/dL)	132±81	133±72	0.9	224±158	197±118	0.001
HDL (mg/dL)	49±17	43±18	0.1	42±10	38±10	0.001
LDL (mg/dL)	138±64	113±20	0.3	146±39	131±33	0.001
FBS (mg/dL)	104±33	111±46	0.3	99±12	101±20	0.009
Systolic blood pressure (mmHg)	136±32	122±8	0.3	129±20	116±19	0.001
Diastolic blood pressure (mmHg)	88±269	76±9	0.1	81±10	78±10	0.001

* Mean ± SD

Three years later, 5 patients that were seronegative in phase I, were HCV positive (recently infected with HCV). The changes in cardiovascular risk factors during these three years were studied, and changes in waist, cholesterol and LDL showed significant differences; cholesterol and LDL had reduced, whereas waist increased. There was no significant difference in other cardiovascular risk factors (Table 2).

Table 2. Comparison of cardiovascular risk factors in seronegative patients who were HCV or HBV seropositive at study outset

Variable	Baseline	Three years later	Difference	P Value
BMI (kg/m^2)	27±4*	28±4	-0.4±0.8	0.3
Waist size (cm)	92±12	97±11	-5±3	0.02
Cholesterol (mg/dL)	260±53	185±23	75±50	0.02
Triglycerides (mg/dL)	315±207	166±63	149±239	0.2
HDL (mg/dL)	36±8	35±6	1.4±8.0	0.7
LDL (mg/dL)	171±39	110±14	60±36	0.04
Systolic blood pressure (mmHg)	116±5	122±19	-6±15	0.3
Diastolic blood pressure (mmHg)	73±4	71±7	2±5	0.5

* Mean ± SD

Blood glucose, insulin resistance and βCF changes in these people were compared after three years, showing no significant difference. In general, six persons at both evaluations, were HBV positive, with no significant differences in blood glucose, insulin resistance and βCF; only one patient with HCV had remained positive; three years later, blood glucose, insulin resistance and βCF changes in this person showed that her blood glucose and HOMA-IR increased in comparison with baseline assessments but because of a lack of similar patients, statistical comparison was impossible. Results after three years, of comparison of variables studied in six persons who had been HCV positive at baseline

in comparison are not shown; of these six persons, one was HCV positive in both assessments but 5 of them were HCV negative at baseline, with no significant difference for blood glucose, HOMA-IR, βCF during three years in this group. Table 3 shows that of 560 patients, 545 were HCV and HBV negative in both assessments. In this group, blood glucose, β-cell function, and HOMA-IR were studied during these three years. Significant increase was found in blood glucose, while HOMA-IR and βCF were reduced. Of the patients, 15 persons were HBV or HCV positive at baseline. Blood glucose, insulin resistance and βCF changes in these patients were again assessed after three years and compared. Blood glucose and βCF had no significant differences in either assessment, whereas HOMA-IR with p=0.04 showed significant reduction in comparison to baseline values (Table 4).

Insulin resistance was studied for patients with hepatitis B, before and after 3 years; out of 6 HBV positive patients in this study, one was insulin sensitive, while another was intermediate HOMA-IR in both assessments. One patient was in the insulin resistance stage becoming insulin sensitive HOMA-IR after 3 years; three patients were insulin resistant in both assessments (Table 5).

Table 3. Comparison of blood glucose changes, insulin resistance and β cell function in seronegative patients with IGT at baseline and three years later

Variable	Baseline	Three years later	Difference	P Value
Serum glucose (mg/dL)	99±12*	101±20	2±18	0.009
Insulin resistance (HOMA-IR)	4±3	3±4	-1.0±4.2	0.02
β cell function	199±231	167±310	-32±303	0.01

* Mean ± SD

Table 4. Comparison of blood glucose changes, insulin resistance and β cell function in B or C seropositive patients at baseline and 3 years later

Variable	Baseline	Three years later	Difference	P Value
Serum glucose (mg/dL)	101±25*	108±35	-6.6	0.1
Insulin resistance (HOMA-IR)	4±2	3±2	0.9	0.04
β cell function	235±168	135±118	100	0.1

* Mean ± SD

Table 5. The number and percentage of individuals with different HOMA-IR index cut-offs among persons with chronic hepatitis type B in population with IGT at baseline and 3 years later

Study outset	Three years after outset (HOMA-IR)			Total
(HOMA-IR)	<2.24	<2.24-3.5/3	>3.59	
<2.24	100%	0	0	100%
2.24-3/59	0	100%	0	100%
>3.59	25%	0	75%	100%
Total	33.3%	16.6%	50%	100%

* Lack of statistical significant difference with MC Nemar test

Among people who were seronegative, different HOMA-IR cut-offs were studied. At baseline, 187 patients were HOMA-IR=2.24; three years later, 145 of them remained the same, whereas 29 patients in phase two reached HOMA-IR=intermediate and 13 patients reached the insulin resistant stage. At baseline, 133 patients were HOMA-IR=224-3.59, and after three years, 66 persons of them reached the insulin sensitive stage; 33 patients reached the insulin resistant stage and 34 remained at the intermediate stage. Ultimately, of 548 patients, 222 were in the HOMA-IR insulin resistant stage, and three years later, 65 patients reached an insulin sensitive stage; 48 patients reached the intermediate stage and 115 patients remained in the previous stage. In general, in both assessments, 50% of seronegative patients were in an insulin sensitive stage and 20% and 29.4% were in intermediate and insulin resistance stages of HOMA-IR cut offs respectively. (Table 6); the above mentioned differences were significant by Mc Nemar test (p<001).

Table 6. The number and percentage of persons with different HOMA-IR index cut offs in seronegative population with IGT at baseline and 3 years later

Beginning of study	Three years after study outset ((HOMA-IR))		
(HOMA-IR)	<2.24	<2.24-3.59	<3.59
<2.24	145 (77.5)*	29 (15.5)†	13 (7)
2.24-3/59	66 (49.6)	34 (25.6)	33 (24.8)
>3.59	65 (28.5)	48 (21.1)	(50.4)
Total	276 (50.4)	111 (20.3)	161 (29.4)

* P<0.001 with McNemar test; † Numbers in parentthesis denote percentage

Discussion

Blood glucose, HOMA-IR and βCF in the three groups showed no significant difference (seronegative, hepatitis B, C). After three years, six patients were HCV positive and six were HBV positive. People who were seronegative, showed significant differences after three years of insulin resistance, while this was not so in seropositive patients. Data related to the relationship between glucose metabolism disorders and viral hepatitis or chronic liver disease was contradictory because of differences in sampling methods and definitions. In epidemiologic studies, the relationship between chronic hepatitis C and diabetes has been observed, but some other factors like age, obesity and liver fibrosis prevent confirmation of this relationship.[9] It seems that insulin resistance with IGT are associated with intensity of liver injury in patients with hepatitis C.[10] Body mass index, lack of response to previous antiviral treatment and degree of portal inflammation are among factors of the hemostasis model of insulin resistance. This study showed that hepatitis C is associated with increased diabetes prevalence. Their hypothesis is that the insulin resistant effect resulted from a virus, and its function is associated with the fibrogenic mechanism in hepatitis C. Insulin resistance induction by the hepatitis C virus could have no relationship with liver disease intensity and this effect may be related to virus genotype; the relationship between IGT and viral hepatitis however was considered less than other cases. Literature available shows there is a relationship between insulin resistance and IGT. For example, in the Mexico City study[11] the rate of insulin resistance in 1449 people of Mexico City with GTT was studied by HOMA. There was a relationship between insulin resistance and IGT, whereas a relationship between hepatitis C and insulin resistance in the absence of diabetes was

seen, suggesting that insulin resistance may intensify fibrosis; it seems that there is a strong association between glucose tolerance disorders and hepatitis C from the pathophysiologic point of view.

In a study by Castro et al[12] of 227 patients with hepatitis, 40% of patients (versus 11.7% of normal population) were infected with IGT. There was no relationship between specific types of viral hepatitis and IGT or DM in their study, one of the first follow up studies, that showed no relationship between IGT and a specific type of hepatitis. Alison[13] who surveyed retrospectively the data from patients with severe liver cirrhosis, candidates for liver transplantation found a relationship between hepatitis C and glucose metabolism disorders. Hepatitis C is a major factor in severe hepatitis, often resulting in transplantation; since patients with hepatitis C are older than patients with other chronic liver disorders, this factor affected the relationship observed. Freyzer et al[14] reported that the average ages of patients with Hepatitis C are higher than patients with chronic liver diseases from hepatitis B, showing the relationship between age and diabetes in this study. Emanuel Manesis et al[15] conducted a prospective study on glucose intolerance in patients with chronic hepatitis B and C. A hundred patients with chronic viral hepatitis were hospitalized for liver biopsy (57 patients with chronic hepatitis C and 43 patients with hepatitis B) and compared with 100 people as a control group that were matched for age, sex and BMI. The prevalences seen among the chronic hepatitis C, B, and control group (12.5%, 4.5%, 10%) showed no statistically significant difference; abnormal glucose tolerance (glucose intolerance or diabetes by OGTT) was however higher in the hepatitis C than in the control group, with no difference seen between the chronic hepatitis B and control groups (14% versus 14%). Ultimately, the prevalence of IGT and the new cases of diabetes by OGTT, were 4.2 times higher in chronic hepatitis C, but for hepatitis B in comparison to the general population, no difference was observed.

In Iran, only one study performed on IGT prevalence in HCV infections, showed no relationship, contrary to results of other studies.[8] In a study conducted by Alavian and et al,[16] on 185 patients with chronic liver diseases and cirrhosis (hepatitis type B and C), somewhat different results were obtained; they found some relationship between diabetes and IGT with liver disease. In their study, the liver disease intensity was related to the change of glucose metabolism disorders.

It seems that the mechanism of the relationship between liver disease intensity and glucose metabolism disorder is similar to the relationship between liver disease and the disorders of insulin resistance. In addition liver sensitivity to glucose is reduced in cirrhosis. An interesting point in the Petit study[4] is that it shows insulin resistance in the initial stage of liver disease, and even in patients with chronic hepatitis without glucose tolerance disorder, there is a strong relationship between insulin sensitivity and fibrosis.[17] In spite of this, there is another hypothesis that chronic liver disease is the result of diabetes. According to this theory, insulin resistance, facilitates lipolysis, increasing free fatty acids gathering in liver. Free fatty acid oxidation cause poisonous free radicals and lipid reoxidation. When the liver capacity of antioxidant is insufficient, mitochondrial disorder and TNF-α cause inflammation and fibrosis.[18]

Endothelial cell activation by inflammatory adipokinesis (TNF-α or interlokin-6) prevents insulin marking and increases profibrogenic cytokine production. These factors increase matrix by mesenchymal cells around endothelial cells (e.g. liver stellate cells) and lead to fibrosis.[19] It is not clear whether HCV infection causes diabetes and glucose metabolism disorders or whether diabetes increases the chances of being infected with HCV. Overall reviews show that there are no documents confirming that hepatitis C infec-

tion causes diabetes it seems that insulin resistance is a result of hepatitis C. The mechanism of this relationship is not completely clear, but increasing iron storage, liver steatosis or TNF-α play an important role in this relationship; autoimmunity is however rejected in this problem.[20] This study could not show a meaningful relationship between viral hepatitis and glucose tolerance disorders, a relationship not seen in all studies; its absence in this study shows the study volume and power insufficiency. In this study, the number of seropositive individuals was 10 at baseline, and three years later was 12; on the other hand, changes observed in seronegative groups that had acceptable sample volume increased cardiovascular risk factors and FBS. An increasing prevalence of obesity has been documented in different societies.[21] While the relationship between insulin resistance and obesity has been confirmed, insulin resistance increased. in a society with increased obesity prevalence.

In this study, considering the time between the two assessments (baseline & 3 years later) of the study, it can be said that there is a relationship between increasing risk factors in seronegative groups and increasing obesity and insulin resistance in a population. The low level of patients with hepatitis is one of disadvantages of this study, which does not permit us to state our opinions about the existence or lack of a relationship between insulin resistance and viral hepatitis in IGT patients. It is therefore recommended that further studies on larger numbers of patients be conducted.

It is concluded that changes in FBS, insulin resistance, and beta cell function do not differ statistically between hepatitis B and C seropositive and seronegative subjects, followed for three years.

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