

Association of Liver Aminotransferases with Lipid Profile in Patients with Type II Diabetes Mellitus

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ABSTRACT

Background and Objectives: Reduced insulin secretion in individuals with type 2 diabetes mellitus (T2DM) results in accumulation of fat in the liver and elevation of liver enzymes. Destruction of hepatocytes due to non-alcoholic fatty liver is associated with increased risk of cardiovascular disease. In this study, we aimed to evaluate association of liver transaminases with lipid profile in patients with T2DM and healthy subjects.

Methods: This case-control study was carried out on 500 subjects with T2DM (250 men and 250 women) and 500 non-diabetic counterparts. Diagnosis of T2DM was confirmed based on the World Health Organization criteria. Fasting blood samples (5 ml) were obtained from all subjects in the morning and serum was extracted for assessment of biochemical parameters. Data were analyzed with SPSS (version 20) and using the Spearman's rank correlation coefficient and Mann-Whitney U test.

Results: Serum levels of total cholesterol (TC), triglyceride, alanine aminotransferase, aspartate transaminase, TC/high-density lipoprotein-cholesterol (HDL-C) ratio and atherogenic index of plasma were significantly higher in subjects with T2DM compared to non-diabetic individuals ($P < 0.005$). Of lipid profile parameters, only risk ratio (TC/HDL-C) was positively correlated with ALT ($P = 0.037$), and no significant correlation was observed for other variables.

Conclusion: Individuals with T2DM have higher lipid profile, atherogenic index of plasma and liver enzymes compared to healthy individuals. Furthermore, TC/HDL-C is significantly correlated with serum level of alanine aminotransferase.

Keywords: Type 2 Diabetes Mellitus, Lipid profile, ALT, AST, Atherogenic index of plasma.

INTRODUCTION

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in insulin production by the pancreas. According to the World Health Organization statistics, 380 million individuals will have diabetes and 418 million individuals will have impaired glucose tolerance by the year 2025 (1). The prevalence of impaired glucose tolerance and diabetes in Iran was reported to be 14.6% and 11.37%, respectively. In addition, the risk of developing diabetes is higher among women, elderly adults and urban residents (2). Type 2 diabetes mellitus (T2DM) is a complex disease associated with reduced high-density lipoprotein-cholesterol (HDL-C) and increased triglyceride (TG) and low-density lipoprotein-cholesterol (LDL-C) levels. These changes are among the main features of insulin resistance syndrome, which is present in majority of patients with T2DM. In addition, high level of cholesterol, TG and LDL-C and low level of HDL-C are common in individuals susceptible to T2DM (3).

The liver plays an important role in regulation of blood glucose and lipids. The level of atherogenic lipoproteins increases in T2DM due to the impaired insulin action. Liver enzymes also increase with the progression of T2DM. The combination of elevated atherogenic lipoproteins and liver enzymes is a risk factor for developing cardiovascular diseases (CVD) (4, 5). Fat accumulation in the liver of patients with T2DM results in non-alcoholic fatty liver disease (NAFLD). At early stages of NAFLD, patients are symptom free until liver enzymes increase due to destruction of hepatocytes. Therefore, follow up of moderate elevations in liver enzymes can predict the risk of NAFLD in patients with T2DM (6). The prevalence of NAFLD is 20-35% in the healthy population and 60-70% among patients with T2DM. Fat accumulation in hepatocytes due to insulin resistance or insulin insufficiency is the underlying cause of NAFLD (7). In a study, 127 of 204 diabetic patients displayed fatty infiltration on ultrasound and 87% of the patients had NAFLD (8). The strong correlation between NAFLD and microvascular complications of diabetes, such as chronic kidney disease is well-demonstrated (9). Aspartate aminotransferase (AST) and alanine transaminase (ALT) are important

aminotransferase enzymes that are elevated individuals. following liver damage or oxidative stress (10). These enzymes may also increase in diabetic patients in the absence of a detectable steatosis on ultrasonography (11). In a study by Chen et al., ALT and AST were elevated in 10.3% and 6.1% of adults with type T2DM, respectively (12). At least one liver enzyme increases in patients with T2DM at early stages of the disease, while other enzymes may increase during disease progression. In people with T2DM, ALT level is usually greater than two fold the upper limit of normal (6). However, some studies reported that liver enzymes are marginally elevated in T2DM and the mean level of ALT and gamma-glutamyl transferase is within the normal range (13). Some reports recommend biannual screening of serum ALT and AST for liver disease in obese people (14). As described previously, dyslipidaemia and a moderate elevation of liver enzymes is common among diabetic patients with NAFLD. The aim of this study was to compare serum level of liver transaminases and lipid profile between patients with T2DM and non-diabetic

MATERIALS AND METHODS

This was a case-control study that was carried out on 500 (250 men) patients with T2DM and 500 (250 men) healthy individuals. Patients were selected via non-probability sampling. Written consent was obtained from all subjects prior to participation in this study. T2DM was defined as fasting blood sugar (FBS) ≥ 126 mg/dl or 2-hour post prandial glucose (2hPG) ≥ 196 mg/dl. Exclusion criteria included a positive history of chronic alcoholism, smoking, hepatic disease (hepatitis, cirrhosis and jaundice) and diabetes complications. Blood sample (5 ml) was taken from each participant after 12 hours of fasting. After separating serum by centrifugation at 1500 g for 10 minutes, level of total cholesterol (TC), TG, LDL-C, HDL-C, ALT and ALP was measured using Pars Azmoon kits and the RA1000 Autoanalyzer (Technicon/Bayer Chemistry Analyser). The LDL-C/HDL-C and risk ratio (TC/HDL-C) as well as atherogenic index of plasma (AIP) [Log (TG/HDL-C)] were calculated based

on the laboratory values. Normal distribution of data was assessed using the Kolmogorov-Smirnov test. Considering the non-normal distribution of data, non-parametric tests were used for data analysis. The Mann-Whitney U test and mean \pm interquartile range (IQR) were used for comparison of study parameters between diabetics and non-diabetic controls. The Spearman's rank correlation coefficient was used to assess linear correlation between study parameters. All statistical analyses were performed using SPSS software (version 20).

RESULTS

The mean age \pm IQR was 51 \pm 16 years in the healthy group and 52.5 \pm 20 years in the T2DM group. There was no significant difference in the mean age of subjects between the groups ($P>0.05$). Serum TC and TG levels were significantly higher in subjects with T2DM compared to non-diabetic individuals ($P<0.05$). The mean level of LDL-C, HDL-C

and LDL/HDL did not differ significantly between the two groups ($P>0.05$). Serum AST and ALT levels were significantly higher in patients with T2DM compared to healthy individuals ($P<0.05$). Moreover, the TC/HDL-C and AIP were significantly higher in subjects with T2DM compared to non-diabetic individuals ($P<0.05$) (Table 1).

The cut-off value of high serum cholesterol and TG level was 200 mg/dl and 160 mg/dl, respectively. The cut-off value for AST and ALT was 40 IU/l. Accordingly, serum TC level was above the normal level in 60% of men with T2DM and 70% of women with T2DM. High TG levels were observed in 87% of men with diabetes and 88% of women with diabetes. Serum AST level was higher than the normal range in 4% of men with diabetes and 10% of women with diabetes. Moreover, high serum ALT level was observed in 22% of men with diabetes and 14% of women with diabetes (Table 2).

Table 1- Comparison of mean age and biochemical parameters between subjects with T2DM and non-diabetic individuals

| Variable | Non-diabetics (mean \pm IQR) | Subjects with T2DM (mean \pm IQR) | Z-value | P-value |
|---------------------------|-----------------------------------|--|---------|---------|
| Age (years) | 51 \pm 16 | 52.5 \pm 20 | -5.25 | 0.1 |
| Total cholesterol (mg/dl) | 165 \pm 25.7 | 241.5 \pm 40.5 | -7.93 | <0.0001 |
| Triglyceride (mg/dl) | 118.5 \pm 68.7 | 242.5 \pm 199 | -9.32 | <0.0001 |
| LDL-C (mg/dl) | 104.5 \pm 36.2 | 115.5 \pm 51 | -1.21 | 0.226 |
| HDL-C (mg/dl) | 38 \pm 16 | 38 \pm 12 | -0.01 | 0.987 |
| AST (IU/l) | 20 \pm 6 | 39 \pm 7 | -2.75 | 0.006 |
| ALT (IU/l) | 20 \pm 8 | 47 \pm 9.7 | -4.99 | <0.0001 |
| LDL/HDL | 3.1 \pm 1.8 | 3 \pm 1.4 | -0.32 | 0.742 |
| TC/HDL-C (Risk ratio) | 4.7 \pm 2 | 5.9 \pm 2 | -5.48 | <0.0001 |
| AIP | 0.5 \pm 0.4 | 0.82 \pm 0.3 | -8 | <0.0001 |

LDL-C= low density lipoprotein cholesterol, HDL-C= High density lipoprotein cholesterol, AST= Aspartate transaminase, ALT= Alanine aminotransferase, TC= Total cholesterol, AIP= atherogenic index of plasma, mg= milligram, dl=decilitre, l= liter, IU= International unit

Table 2- Percentage of subjects with high biochemical values according to gender

| Variable | Non-diabetic men | Diabetic men | Non-diabetic women | Diabetic women |
|--------------------------------|------------------|--------------|--------------------|----------------|
| Total cholesterol (>200 mg/dl) | 24% | 60% | 20% | 70% |
| Triglyceride (>160 mg/dl) | 28% | 82% | 20% | 88% |
| AST (> 40 IU/l) | 0 | 4% | 0 | 10% |
| ALT (>40 IU/l) | 4% | 22% | 2% | 14% |

AST= Aspartate transaminase, ALT= Alanine aminotransferase, mg= milligram, dl=decilitre, l= liter, IU= International unit

No significant relationship was observed between lipid profile and AST ($P>0.05$), while ALT and risk ratio (TC/HDL-C) had a significant positive correlation with lipid

profile ($P<0.05$). Furthermore, a negative correlation was observed between serum HDL-C level and both serum AST and ALT levels ($P>0.05$) (Table 3).

Table 3- Correlation between lipid profile and liver enzymes among subjects with T2DM

| Variable | | AST (IU/l) | ALT (IU/l) |
|---------------------------|---|------------|------------|
| Total cholesterol (mg/dl) | r | 0.115 | 0.110 |
| | P | 0.256 | 0.275 |
| Triglyceride (mg/dl) | r | 0.068 | 0.053 |
| | P | 0.502 | 0.597 |
| LDL-C (mg/dl) | r | 0.092 | 0.006 |
| | P | 0.360 | 0.950 |
| HDL-C (mg/dl) | r | -0.112 | -0.148 |
| | P | 0.267 | 0.141 |
| LDL/HDL | r | 0.154 | 0.086 |
| | P | 0.127 | 0.397 |
| TC/HDL-C (Risk ratio) | r | 0.162 | 0.209 |
| | P | 0.107 | 0.037 |
| AIP | r | 0.126 | 0.139 |
| | P | 0.210 | 0.167 |

DISCUSSION

The aim of this study was to evaluate the relationship between liver transaminases and lipid profile. The findings revealed that the level of TC, TG and liver enzymes (AST and ALT) were significantly higher in patients with T2DM compared to healthy individuals. The risk ratio (TC/HDL-C) and ALP were significantly higher among subjects with T2DM compared to non-diabetic counterparts. Among the lipid profile parameters, only risk ratio had a significant positive correlation with ALT. In addition, HDL-C level did not differ significantly between the two groups. LDL-C was slightly higher in diabetic subjects compared with the controls. These findings are consistent with findings of a study by Al-Jameil et al. (15).

The increase in lipid profile and liver enzymes in patients with T2DM is due to defect in lipogenesis and lipid storage, especially in the liver. Accumulation of fat in the liver results in inflammation and elevation of liver enzymes. Furthermore, TC was higher in men with T2DM than in women with T2DM. This is in line with findings of a study by Ebrahimifar et al. where cholesterol and TG levels were at least 7% higher in men compared to women (3). Marjani et al. also found that serum cholesterol and TG were higher in diabetic

men compared to diabetic women (16). In addition, a study by Ali et al. reported that the level of atherogenic lipoproteins and the risk of developing CVD are higher in diabetic women compared to diabetic men (17). Increased visceral fat is a primary cause of insulin resistance and elevated atherogenic lipid profile. In our study, the higher visceral fat content in women could be related to the high level of atherogenic lipids in women with T2DM (18). In another study on 175 diabetic patients, elevation of one liver enzyme was observed in 57% of the patients, while elevation of at least two liver enzymes was observed in 27% of the patients. In addition, the most common elevated enzyme was ALT, which was less than 2 times higher than the normal range (6). Furthermore, another study reported ALT elevation in 12.5% of patients with T2DM (19). In the present study, serum levels of AST and ALT were significantly higher in subjects with T2DM compared to healthy subjects, but the increase in serum ALT was more notable than AST. Elevation of liver enzymes in patients with T2DM could be due to the absence or reduced production of insulin, which results in hepatic fat accumulation and impaired lipolysis (7). Insulin resistance also affects secretion of inflammatory cytokines, such as tumor

necrosis factor- α . These cytokines in turn increase hepatocyte destruction and ultimately serum levels of liver transaminases. It has been shown that the use of anti-cytokine antibodies could ameliorate destruction of hepatocyte in animal models (20, 21). Increased oxidative stress in diabetic patients could also be involved in the increased serum levels of liver enzymes. The overproduction of reactive oxygen species among diabetic patients results in hepatocyte injury (22). Evidently, administration of statins may also raise serum levels of liver enzymes, which should be noted in interpretation of liver enzymes in diabetic patients (23).

We observed a significant correlation between risk ratio (TC/HDL-C) and ALT. The risk ratio was higher among diabetic subjects. The risk ratio is the best and simplest predicting factor for CVD (24). No significant relationship was observed between ALT and AST or other lipid profile parameters. However, there was a non-significant negative correlation between HDL-C and ALT and AST. Similarly, Balali et al. reported that serum levels of atherogenic parameters and ALT were higher in diabetic patients compared to healthy individuals. In addition, they found a significant positive correlation between ALT and cholesterol, TG and LDL-C as well as a non-significant negative correlation between ALT and HDL-C. In our study, ALT was significantly correlated with risk ratio. In line with our findings, Atiba et al. reported that the level of some atherogenic lipoproteins is significantly higher in diabetic subjects compared to non-diabetic subjects. However, they failed to find

enzymes and lipid profile (25). In another study, serum level of ALT and AST was significantly higher among diabetic patients compared to non-diabetic individuals. Furthermore, the study also revealed a significant positive relationship between ALT, AST, cholesterol, TG, LDL-C and very low-density lipoprotein, and a significant negative correlation between HDL-C and ALT and AST (26).

CONCLUSION

The findings of this study reveal that serum levels of lipid profile and liver enzymes are higher in subjects with T2DM compared to non-diabetic subjects. Furthermore, serum ALT level is correlated with risk ratio.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding publication of this article.

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