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Serum Fetuin A Level, Liver Enzymes Activities and Insulin Resistance in Patients with Type 2 Diabetes

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Some studies have indicated that increased levels of liver enzymes may associate with development of diabetes in future. The association between liver enzymes and type 2 diabetes are inconsistent and may depend on the ethnic difference among different populations. The aim of present study was to assess serum Fetuin A level, liver enzymes activities and insulin resistance in patients with type 2 diabetes in Gorgan. The study groups consisted of 75 type 2 diabetic patients and 75 control subjects. Both subjects were matched for age and sex. Different parameters were in the Metabolic Disorders Research Center. There were significant differences in the mean value of glucose, triglyceride, Low Density Lipoprotein (LDL), Alanine Transaminase (ALT), γ-glutamyltransferase (GGT), insulin, HOMA-IR and fetuin A when type 2 diabetic patients compared with control groups. There were significant negative correlation between fetuin A and age in subjects with type 2 diabetic patients and control groups ($p<0.05$). The present study showed that serum fetuin-A levels are significantly increased in type 2 diabetes mellitus. Our findings show that studied liver enzymes were higher in type 2 diabetic patients than control groups. The relationship of liver aminotransferase levels and risk of type 2 diabetes development seems to be complex. Increased levels of fetuin-A and studied enzymes in subjects should be an alert for further clinical evaluation and screening.

Key words: Fetuin A, liver enzymes, insulin resistance, type 2 diabetes

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is one of chronic diseases which are characterized by insulin resistance and impaired insulin secretion. The disease may be acquired or inherited. High prevalence and incidence of type 2 diabetes make it an important disease (Koster *et al*., 2012). Prevalence of type 2 diabetes mellitus is raising worldwide (Gadsby, 2002; De Lusignan *et al*., 2005; Passa, 2002). It has reported that 190 million people around the world tolerate diabetes mellitus. It is predicted that prevalence of T2DM may change from 330-366 million in the years 2025-2030. The 77.6% of all diabetic patients in the world will take place in the developing countries by the year 2030 (Azizi *et al*., 2003a; Hussain *et al*., 2007) and it affect 6% of the world's population (Adeghate *et al*., 2006). Some studies have shown that the prevalence of T2DM changes from 1.2-14.6%, 4.6-40% and 1.3-14.5% in Asia, the Middle East and Iran, respectively (Azizi *et al*., 2003a, b). Many studies showed that prevalence of type 2 diabetes changes in different ethnic and age groups and postmenopausal women (Marjani *et al*., 2012a, b; Marjani and Shahini, 2013; Marjani and Moghasemi, 2012; Shahini *et al*., 2013; Marjani and Mojerloo, 2011; Marjani *et al*., 2007). Studies have indicated that the liver enzymes, such as γ-glutamyltransferase, the aminotransferases and alkaline phosphatase, have shown an association with elevated risk of type 2 diabetes. Many findings revealed that γ-glutamyltransferase is the strongest risk indicator for type 2 diabetes when compared with other liver enzymes (Fraser *et al*., 2009; Perry *et al*., 1998; Andre *et al*., 2005; Nannipieri *et al*., 2005; Wannamethee *et al*., 2005; Nakanishi *et al*., 2004). The importance of the associations of liver aminotransferases with type 2 diabetes is not exactly clear. The enzyme alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are found in the liver, in serum and in different tissues. These enzymes are used to screen for liver diseases (Kim *et al*., 2005).There are an association between liver injury and increased level of ALT in serum (Ruhl and Everhart, 2009). Alanine aminotransferase may be an important marker for fatty liver (Andre *et al*., 2005; Westerbacka *et al*., 2004), which has significant role in the development of type 2 diabetes (Vozarova *et al*., 2002). Some other studies have indicated that increased levels of liver enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyltranspeptidase (GGT) are associated with development of diabetes in future (Andre *et al*., 2005; Nannipieri *et al*., 2005; Nakanishi *et al*., 2004; Vozarova *et al*., 2002; Sattar *et al*., 2007; Schindhelm *et al*., 2007; Wannamethee *et al*., 2005; Lee *et al*., 2004; Satter *et al*., 2004). The association between these liver enzymes and type 2 diabetes are inconsistent as it has shown in different studies (Nannipieri *et al*., 2005; Schindhelm *et al*., 2005). This may depend on the ethnic difference among different populations. A glycoprotein, fetuin-A is secreted by the liver. It is revealed as a biomarker for risk of type 2 diabetes (Sun *et al*., 2013; Ix *et al*., 2008, 2012; Stefan *et al*., 2008; Laughlin *et al*., 2013; Rasul *et al*., 2012). Increased levels of fetuin-A seem to be associated with insulin resistance (Song *et al*., 2011). Studies have shown that there are association between many circulating proteins and the regulation of insulin sensitivity. The important circulating proteins are adiponectin (Spranger *et al*., 2003; Lindsay *et al*., 2002) retinol binding protein (Yang *et al*., 2005; Graham *et al*., 2006) and fetuin-A (as an endogenous inhibitor of the insulin-stimulated insulin receptor tyrosine kinase) (Auberger *et al*., 1989; Mathews *et al*., 2000; Rauth *et al*., 1992). Fetuin-A administration to rodents showed that insulin-stimulated tyrosine phosphorylation of the insulin receptor inhibited and fetuin-A administration to rat inhibited insulin receptor substrate in liver and skeletal muscle (Auberger *et al*., 1989). It has revealed that increased level of fetuin-A are associated with insulin resistance in humans (Stefan *et al*., 2006; Mori *et al*., 2006). This can be suggesting that fetuin-A may has an important role in the pathophysiology of type 2 diabetes. In the present study, we assessed serum Fetuin A level, liver enzymes activities and insulin resistance in patients with type 2 diabetes in Gorgan.

MATERIALS AND METHODS

The study groups consisted of 75 type 2 diabetic patients and 75 control groups. The control groups had no hepatic, renal or any other diseases. Both groups were matched for age and sex. Blood samples were collected from two groups after a 12 h fasting. Serum glucose (Glu), Total Cholesterol (TC) and High Density Lipoprotein Cholesterol (HDLC), Low Density Lipoprotein Cholesterol (LDLC), triglycerides (TG) and liver enzymes (γ-glutamyltransferase (GGT), alanine transaminase (ALT) and aspartate transaminase (AST)) were determined using commercial kits and spectrophotometer technique in the Metabolic Disorders Research Center, Gorgan Faculty of Medicine. Serum fetuin-A and insulin were determined by ELISA kit. The fetuin-A kit was bought from Bioassay Technology Laboratory (CAT.NO: E1386Hu, Shanghai Crystal Day Biotech Co., LTD, China). Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was determined using the following formula: HOMA-IR = FPG (mg dL^{-1})×fasting IRI (μU mL^{-1})/405. SPSS- 18 version software was used to determine statistical analysis (as means and standard deviations). Comparison of different parameters between two groups was done by independent sample t test. The association between serum fetuin-A level and liver enzymes, insulin resistance and other parameters was determined by using Pearson's correlation test. The p-value lower than 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of type 2 diabetic patients and control groups are indicated in Table 1. The mean age of type 2 diabetic patients and control groups were 55.50±8.80 and 53.18±10.70 years, respectively. There were significant

Table 1: Clinical characteristic of type 2 diabetic patients and control groups

Parameters	Diabetic subjects	Control groups	p-value
Age (years)	55.50±8.88	53.18±10.70	0.15
Fasting blood glucose (mg dL^{-1})	133.10±4.04	100.37±7.87	<0.001
Cholesterol (mg dL^{-1})	192.48±45.63	187.77±39.47	0.50
Triglyceride (mg dL^{-1})	174.50±83.80	115.89±46.42	<0.001
HDL-Cholesterol (mg dL^{-1})	45.13±11.59	45.72±12.49	0.76
LDL-Cholesterol (mg dL^{-1})	116.28±30.64	99.38±33.64	0.001
Aspartate transaminase (U L^{-1})	20.40±5.37	20.33±4.08	0.93
Alanine transaminase (U L^{-1})	21.41±6.90	17.17±4.93	<0.001
γ-glutamyltransferase (U L^{-1})	31.10±7.21	15.92±3.75	<0.001
Insulin (U L^{-1})	11.78±0.48	6.91±0.98	<0.001
HOMA-IR	3.86±0.10	1.70±0.19	<0.001
Fetuin A	2261.34±1215.31	1476.93±440.47	<0.001

HDL: High density lipoprotein, LDL: Low density lipoprotein, HOMA-IR: Homeostatic model assessment of insulin resistance

Table 2: Fetuin A correlated with different parameters of control group and type 2 diabetic subjects

	Groups	
Parameters	Control	Diabetic
Age (years)	p = 0.0001 r = -0.648	p = 0.0001 r = -0.408
Glu (mg dL^{-1})	p = 0.929 r = 0.011	p = 0.689 r = -0.047
TC (mg dL^{-1})	p = 0.331 r = 0.113	p = 0.067 r = -0.213
TG (mg dL^{-1})	p = 0.057 r = 0.221	p = 0.374 r = -0.104
HDL-C (mg dL^{-1})	p = 0.052 r = -0.225	p = 0.161 r = -0.164
LDL-C (mg dL^{-1})	p = 0.089 r = 0.198	p = 0.083 r = -0.201
AST (U L^{-1})	p = 0.625 r = 0.094	p = 0.226 r = 0.142
ALT (U L^{-1})	p = 0.086 r = 0.200	p = 0.101 r = 0.191
GGT (U L^{-1})	p = 0.345 r = 0.111	p = 0.265 r = 0.130
Insulin (U L^{-1})	p = 0.564 r = -0.068	p = 0.575 r = 0.066
HOMA-IR (μU L^{-1})	p = 0.382 r = -0.103	p = 0.691 r = 0.047

GLU: Glutamic acid, TC: Total cholesterol, HDLC: High density lipoprotein cholesterol, LDLC: Low density lipoprotein cholesterol, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: γ-glutamyl transferase, HOMA-IR: Homeostatic model assessment of insulin resistance, TG: Triglyceride

increases in the mean value of glucose, triglyceride, Low Density Lipoprotein (LDL), alanine transaminase (ALT), γ-glutamyltransferase (GGT), insulin, HOMA-IR and fetuin A of type 2 diabetic patients in comparison to control groups. No significant differences were considered in other parameters among both groups. Correlation between different parameters in type 2 diabetic patients and control groups are summarized in Table 2. There were significant correlation between fetuin A and age in type 2 diabetic patients and control groups ($p<0.05$). There were no significant correlation between fetuin-A and other parameters in both groups.

DISCUSSION

Fetuin-A is a glycoprotein which secret by liver (Denecke *et al*., 2003). Some studies have indicated that fetuin-A has exhibited as a biomarker for risk of type 2 Diabetes Mellitus (T2DM) (Laughlin *et al*., 2013; Rasul *et al*., 2012; Song *et al*., 2011; Lindsay *et al*., 2002; Stefan *et al*., 2008). It has reported that there is an association between fetuin-A and Insulin Resistance (IR) (Graham *et al*., 2006; Mathews *et al*., 2002). Studies on animal and human showed that fetuin-A cause insulin resistance and may play an important role in occurrence of type 2 diabetes. Our study shows that high serum fetuin-A levels were seen in type 2 diabetes in comparison to control groups. Some studies have revealed that type 2 diabetes cases had higher levels of fetuin-A compared to subjects without diabetes (the difference was not statistically significant) (Stefan *et al*., 2008). This finding is in agreement with our study result. Studies have shown that high levels of fetuin-A are associated with insulin resistance in humans (Mathews *et al*., 2002). This means that fetuin-A may have a role in the pathophysiology of type 2 diabetes which is not in agreement with our findings. In our study, the serum fetuin-A levels were significantly correlated with age. Our results revealed that fetuin-A may have a role in T2DM patients with aging. Some studies have revealed that physiological aging may lead to a decrease in insulin sensitivity and increase insulin level. It has reported that there are a relationship between the age-related impairment of insulin action and defects in the insulin signaling mechanism when subjects have insulin resistance. Aging may cause a change in phosphorylation of receptor (Fulop *et al*., 2003). Different findings indicate an association between fetuin-A and insulin resistance. Fetuin-A has also been shown to correlate with liver fat in patients at risk of T2DM (Kantartzis *et al*., 2010). It has reported that there are a correlation between the fetuin-A gene expression and key enzymes in lipid and glucose metabolism (Haukeland *et al*., 2012). In our studies, γ-glutamyltransferase, ALT and AST levels were higher in type 2 diabetes when compared with control groups. In disagreement with other studies, we showed that serum fetuin-A levels in our study were not correlated with the serum γ-glutamyltransferase level, which may consider as a marker of fatty liver (Angulo, 2002).

Liver injury or liver diseases may depend on ALT and AST transaminases levels which are known as important indicators for liver damage (Pratt and Kaplan, 2000). In a study on a Korean adolescent, it has been indicated that ALT levels are significantly associated with AST levels (Lee and Yang, 2013). Studies have shown that increased liver fat is linked to hepatic insulin resistance (Goto *et al*., 1995). This may lead to an elevation in hepatic glucose production (Marchesini *et al*., 2001) which may cause the development of T2D. Many studies reported that AST is also associated with fatty liver, but its extent is lesser than ALT. Kim *et al*. (2009) indicated there are significant association between serum levels of liver enzymes (ALT and γ-glutamyltransferase) and risk of type 2 diabetes. In general, there are a relationship between serum γ-glutamyltransferase level and serum ALT or AST level. The association of GGT, ALT and AST may be show the possible role of these enzymes in liver damage and incidence of diabetes. It has indicated that normal and abnormal levels of ALT and AST enzymes showed low and high risk for diabetes, respectively (Mehta *et al*., 2000; Custro *et al*., 2001). Some findings have demonstrated that there are an association between fatty liver and insulin resistance syndrome and type 2 diabetes mellitus (Chitturi *et al*., 2002). It is also revealed that the association between an abnormal level of ALT or AST enzymes and diabetes may indicate a relation between fatty liver and insulin resistance syndrome. It has also suggested that chronic inflammation caused by increased levels of liver enzyme may reveal impair insulin signaling in the liver (Ruhl and Everhart, 2009; Lee and Jacobs Jr, 2005). There are many controversial results in aminotransferase levels, in relation to type 2 diabetes development.

CONCLUSION

The present study showed that serum fetuin-A levels are significantly increased in type 2 diabetes mellitus. Our findings show that studied liver enzymes were higher in type 2 diabetic patients than control groups. The relationship of liver aminotransferase levels and risk of type 2 diabetes development seems to be complex. Increased levels of fetuin-A and studied enzymes in subjects should be an alert for further clinical evaluation and screening.

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