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Fetuin-A levels determine cardiovascular risk in young diabetic patients.

Müge Keskin[1*], Cavit Çulha[1], Neşe Ersöz Gülçelik[1], Esranur Ademoğlu[1], Ahmet Keskin[2], Yalçın Aral[1]

[1]Department of Endocrinology and Metabolism, Ankara Training and Research Hospital, Ankara, Turkey

[2]Department of Family Medicine, Yıldırım Beyazıt University, Ankara, Turkey

Abstract

Objective: Young adults with type 2 diabetes were demonstrated to have increased cardiovascular disease risk. Fetuin-A levels are associated with insulin resistance, impaired glucose tolerance, hepatosteatosis, subclinical inflammation and increased cardiovascular risk. Apolipoprotein (Apo) B/Apo A1 ratio is a well-defined cardiovascular risk assessment marker. In this study, we aimed to investigate the potential role of Fetuin-A in demonstrating cardiovascular disease risk in young adults with type 2 diabetes.

Material and methods: We performed a prospective study on 18 controls, 18 diabetic and 19 prediabetic patients (aged 20-40 y). History, physical examination and anthropometric measurements were done for each subject. Fasting serum samples were obtained from all subjects and glucose, insulin, Fetuin-A, LDL, triglyceride, HDL, VLDL, apoB, apoA1, lipo A, HSCRP levels were measured. Serum Fetuin-A levels were determined by ELISA.

Results: Fetuin-A levels were significantly lower in control patients than diabetic and prediabetic patients (33.46 ± 22.10 *vs.* 51.68 ± 17.10 ng/ml, p<0.05 and 33.46 ± 22.10 *vs.* 47.70 ± 10.47 ng/ml, p<0.05, respectively). Fetuin-A levels did not differ between diabetic and prediabetic patients (51.68 ± 17.10 *vs.* 47.70 ± 10.47 ng/ml, p>0.05). BMI adjusted correlations revealed a positive correlation between Fetuin-A levels and glucose, Apo B levels and Apo B/Apo A1 ratio.

Conclusions: Studies showed that Fetuin-A levels may play a role in the pathophysiology of cardiovascular diseases. In our study, we found a significant increase in Fetuin-A levels in young type 2 diabetic and prediabetic patients. Thus, Fetuin-A may be a useful marker in determining cardiovascular risk of young patients with diabetes or at risk for diabetes.

Keywords: Type 2 diabetes mellitus, Fetuin-A, ApoB/ApoA1 ratio.

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Introduction

Type 2 Diabetes Mellitus (T2DM) is characterized by Insulin Resistance (IR) and impaired insulin secretion, development of which obesity is important factor [1,2]. The prevalence of T2DM is increasing in the young population worldwide [3]. In fact that is more common than type 1 diabetes in some ethnic groups. Prediabetes increases the risk of diabetes 34% in 7.5 y and the risk of Cardiovascular Disease (CVD) 11% in 10 y. With effective treatment including diet, exercise can decrease 28%-59% diabetes incidence [4]. Recent evidences show that T2DM progression is rapid because of complications such as heart, renal, nerve injury, retinopathy, developing in early stages of the disease [5,6].

Fetuin-A is known as natural inhibitor of insulin receptor tyrosine kinase. So that prevents Insulin Receptor Substrate 1(IRS) protein production. IRS-1 protein have significant role in regulating insulin signalling pathway and several cellular functions including glucose storage transport, protein-fat metabolism, differentiation and growth of cell. Metabolic pathway of the relationship between high fetuin-A levels and developing atherosclerosis including obesity, adipocyte dysfunction and IR [7]. Fetuin-A can play a role in development of CVD by several mechanisms. The most important one induces metabolic disorders such as insulin resistance, hyperglycaemia and dyslipidaemia which disrupt the endothelium and platelets, resulting inflammation, vasoconstriction, thrombosis. Thus contributes to formation and maintenance of atherosclerosis [8,9].

Fetuin-A is a part of the cystatin super family of cysteine protease inhibitors [8]. Fetuin-A also called as Alpha 2-Heremans Schmid Glycoprotein (AHSG), is an abundant and a multifunctional plasma protein [10]. Fetuin-A serves as significant role in normal and pathological conditions such as physiological calcification inhibitor in osteogenesis, inhibitor of ectopic calcification of the vascular system, inhibitor of insulin signalling and induces adipocyte dysfunction, proangiogenic and proinflammatory effect [8,11]. Fetuin-A is the first hepatokin which proved to have a major pathogenic role in metabolic diseases have a direct effect on the glucose

and lipid metabolism. Pro-inflammatory mediators secreted from adipose tissue and play a role in vascular damage, IR, atherogenesis. Fetuin-A is a strong promoter for inflammatory cytokine expression in monocytes and adipocytes, and suppresses the production of adiponectin [12]. Fetuin-A functions as an adaptor between the FFA and TLR4 signals that activation of NFKB and AP1 in lipid-induced inflammation. Transcription of inflammatory genes increases, leading to production of inflammatory cytokines and ultimately to insulin resistance [13].

The relationship between fetuin-A and T2DM may be genetic origin because of *fetuin-A* gene is localized on chromosome 3q27 which related with susceptibility locus of T2DM and metabolic syndrome. In addition recent studies showed that chromosome 3q27-qter associated with early-onset T2DM in French families [14]. Furthermore, *adiponectin* gene is located beside fetuin-A and both of them are important for IR and CVD. Hennige et al. suggested that fetuin- A induces subclinical inflammation through affecting cytokines expressions. This effect causes suppression of the atheroprotective hormone adiponectin [15].

Ishibashi et al. suggested that significantly high fetuin-A levels associated with IR and atherogenic lipid profiles in Japanese men [1]. On the other hand, Ketteler et al. reported that low fetuin-A levels is associated with cardiovascular mortality in patients on haemodialysis. In these patients, AHSG deficiency might be related with vascular calcification [16].

Inflammation plays an important role in all phases of atherosclerosis. HSCRP level is easy to measure and reliable biomarker of inflammatory state. The ApoB/ApoA1 ratio represents the cholesterol balance between the atherogenic and anti-atherogenic lipoproteins [17]. The ApoB/ApoA1 ratio has been shown to be a strong predictor for cardiovascular risk among lipid parameters [18].

The objective of this study was to investigate the potential significance of fetuin-A for cardiovascular risk in young patients with T2DM and prediabetics. To support this hypothesis, evaluate its relationship with the cardiovascular risk marker ApoB/ApoA1 ratio.

Materials and Methods

The present study was performed in Ankara Educational and Research Hospital with 18 diabetic and 19 prediabetic patients, 18 healthy controls, aged 20-40 y. All subjects were in good general health based on medical history, physical examination and anthropometric measurements. Exclusion criteria included history of CVD, pancreatitis, abnormal liver (>2 times upper limits of normal). All individuals who enrolled in this study have normal renal function tests and had no CVD.

Fasting serum samples were obtained from all subjects and glucose, insulin, Fetuin-A, LDL, triglyceride, HDL, VLDL, apoB, apoA1, lipo A, HSCRP levels were measured. Serum levels of glucose, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides (TG) were assayed on the day of collection by using spectrophotometric methods by Beckman Coulter AU 2700 analyzer. ApoB, apoA1, lipo A, HSCRP were performed on the Siemens Nephelometer BN II (Siemens Healthcare Diagnostics Inc., Newark, DE) using Siemens reagents. Fetuin- A was determined using an enzyme-linked immunosorbent assay kit (The AssayMax Human alpha-2-HS-Glycoprotein ELISA, US). Serum insulin was measured by ELISA kit (DRG Instruments GmbH, Germany). Insulin resistance was estimated using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) by dividing the product of fasting insulin (uIU/mL) and glucose (mg/dl) by 405. Body Mass Index (BMI) was calculated as body weight/ $(\text{body height})^2$.(kg/m^2).

Fasting blood samples were collected and a 75 g OGTT was performed. Diagnosis of T2DM, Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) were based on the American Diabetes Association criteria. All healthy control subjects were without family history of diabetes, and had normal glucose tolerance according to a 75 g OGTT performed before inclusion in the study.

This study was conducted in accordance with the guidelines in The Declaration of Helsinki and approved by the ethical committee at Ankara Education and Training Hospital. The study was approved by the ethics committee of our hospital.

Statistics

Statistical analyses were carried out using SPSS (version 14.0). Data is expressed as mean ± Standard Deviation (SD). The differences among subgroup were estimated by one-way Analysis of Variance (ANOVA). Spearman correlations were performed to examine the associations between fetuin-A and other variables. Partial correlation was performed between fetuin A and IR, ApoB, ApoA1, ApoB/A1 ratio controlling for BMI.

Results

Baseline characteristics of the study population are summarized in Table 1. The mean serum level of fetuin-A was 33.46 ± 22.108 ng/ml in control groups, 51.69 ± 17.093 ng/ml in diabetic groups and 47.70 ± 10.478 ng/ml in prediabetic groups. Significant differences in circulating fetuin-A concentrations between the control and diabetics, control and prediabetics ($p<0.007$, $p<0.038$, respectively) was observed. Diabetic and prediabetic patients had similar fetuin-A levels. APOB/A1 ratio was statistically differences between the controls and diabetics, and diabetic and prediabetic patients ($p<0.00$, $p<0.002$, respectively). There were differences between groups with respect to fetuin-A, IR, BMI, glucose, ApoB, HSCRP, ApoB/A1 ratio. Fetuin-A levels were positively correlated with IR, glucose *vs.* ApoB levels

($p<0.009$, $p<0.008$, $p<0.002$ respectively). After adjusting for BMI, fetuin-A was correlated with ApoB and ApoB/A1 ratio.

Table 1. *Clinical and biochemical characteristics.*

	Control	T2DM	Prediabetics	p
Fetuin-A (ng/ml)	33.46 ± 22.108	51.69 ± 17.093	47.70 ± 10.478	0.006
HOMA-IR	2.38 ± 0.838	7.63 ± 6.431	4.32 ± 1.923	0.001
BMI (kg/m^2)	26.74 ± 4.503	34.75 ± 9.250	31.09 ± 5.517	0.003
Glucose (mg/dl)	87.06 ± 4.734	152.06 ± 64.819	104.37 ± 9.352	0.000
HDL (mg/dl)	53.11 ± 13.181	41.33 ± 9.917	50.84 ± 10.511	0.007
LDL (mg/dl)	114.17 ± 26.01	131.61 ± 30.42	117.79 ± 29.83	0.169
Triglycerides (mg/dl)	118.44 ± 68.70	176.94 ± 76.19	119.95 ± 51.95	0.005
T Cholesterol (mg/dl)	183.28 ± 25.98	203.56 ± 37.84	192.42 ± 32.41	0.198
Creatinine (mg/dl)	0.85 ± 0.13	0.83 ± 0.11	0.82 ± 0.07	0.984
APOB (mg/L)	796.56 ± 140.220	1087.28 ± 221.299	950.63 ± 181.983	0.000
APOA1 (mg/L)	1461.89 ± 273.038	1280.94 ± 131.961	1356.37 ± 172.789	0.032
APOB/A1 (mg/L)	0.5651 ± 0.1559	0.8530 ± 0.17568	0.7101 ± 0.15916	0.000
HSCRP (mg/L)	1.98 ± 2.144	6.49 ± 4.080	4.17 ± 4.189	0.002

Discussion

T2DM is the most common type of diabetes mellitus with a rate of 90%-95% in the world. Its prevalence is expected to increase more rapidly in future due to increase in obesity [19]. Currently, T2DM is also common in the young population, which brings the risk for Cardiovascular Disease (CVD). This study is the first to evaluate the fetuin-A level, both cardiovascular risk factors and as factors that play a role in pathogenesis of diabetes in young adults at the age of 20-40 y with new diagnosed T2DM and prediabetic patients.

Classical diagnose age of metabolic disease pulled down further today. So we have to be more careful for diagnosis of diabetes in young people which have risk factor and obesity. We can protect young population from microvascular and macrovascular complications of diabetes with early detection. Wilmot et al. found that high prevalence of T2DM and impaired glucose regulation in obese younger adults in STAND study supported our work [3]. Wilmot et al. demonstrated diastolic dysfunction in younger adults with T2DM. Diastolic dysfunction has been known as predicting heart failure and mortality, but might be reversible with early diagnosis and treatment [5].

We demonstrated that fetuin-A level is increased in young prediabetic patients similar to the diabetic patients. The contribution of hepatokin-mediated mechanism, a new notion in pathogenesis of metabolic diseases will lead to two important advancements in future. First, it will pave the way for subgrouping of patients as very high and very low risk for development of such diseases. Second, they can be a new target for the prevention and treatment of major metabolic disorder such as T2DM and CVD [12]. Fetuin-A value begins to increase in prediabetic period likewise diabetic period, as indicated in our study. In that way, it predicts both developments of diabetes mellitus and the risk for CVD. Dutta et al. investigated the effect of fetuin-A in prediabetic population in India and found that fetuin-A is important predictor for progression prediabetes to diabetes [20]. Similarly our study, Yin et al. evaluated fetuin-A levels in new-onset T2DM for preventing diabetic vascular complication and found that fetuin-A was positively correlated with carotid intima media thickness, TG, LDL, HOMA-IR, fasting plasma glucose [10]. Naito et al. clearly demonstrated that fetuin-A play a role directly pathogenesis of atherosclerosis with detecting high level of fetuin-A within atheromatous plaques in human coronary arteries [21]. Rasul et al. concluded that high fetuin-A levels are associated with pathogenesis of T2DM, fatty liver and their vascular damages, while low fetuin-A levels are associated with raised vascular calcification [12].

In our study, IR was correlated with the ApoB level when fetuin-A levels of patients were evaluated by their BMI. Obesity-related T2DM poses a risk for early development of CVD. Shah et al. identified increased incidence in deterioration of cardiac structure, increased systolic function and reduced diastolic function in adolescent and young adult patients with obesity-related T2DM as compared to the control. They suggested that this was a risk for premature heart failure and this risk could be very higher in the young population [22]. A variety of studies have showed that prediabetes had a subclinical inflammation, procoagulation and endothelial dysfunction. Chakarova et al. found increased serum lipid and HSCRP level in patients with IGF and IGT when they

evaluated of the cardiovascular risk [23]. TODAY study group reported that dyslipidaemia and chronic inflammation developed very often and became worse over time in young patients with T2DM, and indicated the importance of treatment [24]. Ou et al. suggested that fetuin-A exacerbates arterial stiffness in diabetes and considered risk factors of CVD [25].

Most of study is evaluated fetuin-A level in adult or older adult population with diabetes. Similarly, Song et al. in their study associated the high fetuin-A concentration with T2DM and IR in adults at the age of 40 or over [26]. Additionally, lots of study has been shown that association of fetuin-A and diabetes. Sun et al. showed an independent relationship between the high fetuin-A levels and the high risk of developing diabetes [27]. Gunduz et al. reported that fetuin-A could have a role in pathogenesis of T2DM [28]. Stefan et al. found that high plasma level of AHSG was related to the insulin resistance [29]. In their recent study, Stefan et al. suggested that fetuin-A could play a role in pathogenesis of T2DM by affecting insulin secretion [30]. Erdmann et al. suggested that fetuin-A is related to development of IR in early stage of weight gain [31].

In the current study, we demonstrate that fetuin-A serum levels are positively associated with glucose, insulin resistance, Apo B levels. These results contribute that fetuin-A may be a useful marker in determining cardiovascular risk of young patients with diabetes or at risk for diabetes.

Cardiovascular diseases are the major cause of mortality and morbidity in patients with T2DM. Zhao et al. confirmed fetuin-A levels are greatly higher in diabetic patients and they showed for the first time that fetuin-A was higher among patients with T2DM, and have coroner disease than those without T2DM. They deduced that fetuin-A could be a potential biomarker for illustrating the formation and growth of Coronary Artery Disease (CAD) in diabetic patients [32]. The link between metabolic disorders, formation and progression of atherosclerosis is known well. Fetuin-A is known to induce insulin resistance and adipocyte dysfunction, and fetuin-A is therefore considered to induce early atherosclerosis [33]. Fiore et al. was the first to show the relationship between the fetuin-A and atherosclerosis of peripheral vessels by measuring the arterial intima-media thickness. They reported the fetuin-A levels were significantly higher in patients with carotid or femoral atherosclerosis [34]. Weikert et al. provided evidence for the idea that there was a link between the high plasma levels of fetuin-A, and the increased the risk of Myocardial Infarction (MI) and ischemic stroke, in their large prospective cohort study [35]. Akin et al. demonstrated that fetuin-A levels were higher in CAD and it was confirmed using coronary computed tomography angiography [36]. Aroner et al. assessed the relationship between fetuin-A, arterial calcification and glycaemic status in the development of CVD which was the first study in an ethnically diverse population. This study found a positive association between fetuin-A and CVD with IFG and an inverse association between fetuin-A and arterial calcification without diabetes. Fetuin-A hypothesize in normoglycemic patients, play role inhibition of arterial calcification and reducing risk of CVD [37]. Some previous studies have been reported that inverse association with fetuin-A and CVD. Stenvinkel et al. found low fetuin-A related to cardiovascular death in End-Stage Renal Disease (ESRD) patients by reason of inflammation, accelerated atherosclerosis, ectopic calcifications [38]. In another study, Bilgir et al. showed that low fetuin-A significantly decreased in patients with MI and they thought low fetuin-A might play role development of CAD [39]. Laughlin et al. suggest that low plasma fetuin-A levels are independently associated with increased risk of CVD without diabetes but reduced risk cardiovascular mortality with diabetes in older community-dwelling adults. Their results relationship between fetuin-A and cardiovascular health is rather complex process [40]. Singh et al. has clearly explained that relevance of several levels fetuin-A with atherosclerosis seconder to diabetes. Increased levels of fetuin-A in bloodstream might be caused by IR that disrupts endothelium and thus, revealed inflammation, vasoconstriction, thrombosis. Probability of atherosclerosis is increased with this condition. Whereas, decreased levels of fetuin-A, results vascular calcification and exacerbates atherogenesis [7].

In our study, we detected fetuin-A was correlated with ApoB and ApoB/A1 ratio, when we divided subjects to BMI. Many studies have indicated the association of the ApoB/ApoA1 ratio with ischemic and atherosclerotic cardiac disease, and it is considered to be a good cardiovascular risk marker. Some studies revealed that Apo B/A1 ratio more useful than conventional lipids for risk predicting of cardiovascular events as non-fatal and fatal MI [41]. We also evaluated dyslipidaemia and we found that TG levels were significantly higher in diabetic patients in this study. Lipid parameters are specified in detail in Table 1.

Fetuin-A is an enigmatic protein because of important for lots of pathways in mammalian, but its level is influenced by several factors including aging, high fat diets, calorie restriction, medication such as thiazolidinedione, niacin, omega-3 polyunsaturated fatty acids [42]. It is currently known that the risk for cardiovascular disease is increased same level in prediabetic patients with type 2 diabetic patients. So that appropriate treatment must be given to prediabetic patients for preventing progression to diabetes [43].

Consequently, fetuin-A contributes to pathogenesis of diabetes mellitus and cardiovascular disease through its effects impairing the metabolism with the development of insulin resistance and dyslipidaemia. Therefore, it will make it possible to consider a new target in the treatment. This risk ratio of transition prediabetes to diabetes may be taken to further down or disease may not occur with the development of new treatment strategies. Apart from the effectiveness of a new treatment modality can be investigated by looking at the level of the fetuin-A. Limitation of this study is small sample size. So that there is need for a larger-scale studies with long term follow-up on this topic.

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*Correspondence to

Müge Keskin

Department of Endocrinology and Metabolism

Ankara Training and Research Hospital

Turkey