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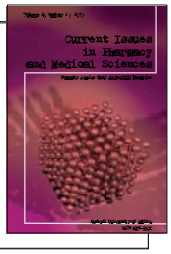

Fetuin-A in patients with metabolic syndrome

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ABSTRACT

Metabolic syndrome is a common disorder the prevalence of which is estimated to be about 20% in Polish adult population. Abdominal obesity and insulin resistance are important pathogenetic factors. Metabolic syndrome plays a role as a risk factor for type 2 diabetes and cardiovascular disease. Fetuin-A is a multifunctional plasma glycoprotein. It is a physiological inhibitor of insulin receptor tyrosine kinase and thus associated with insulin resistance, metabolic syndrome and an increased risk for type 2 diabetes. The study was conducted in 62 patients with metabolic syndrome (34F and 28M) aged 35-83. In 47 persons type 2 diabetes was a component of metabolic syndrome, 62% of diabetics had coronary artery disease as a macrovascular complication. Determinations of biochemical parameters and anthropometric measurements were performed in the studied group. We analysed a relationship between serum fetuin-A concentration and components of metabolic syndrome and total cholesterol, LDL-cholesterol, HbA1C, BMI as well. Diabetics had lower fetuin-A concentrations than patients without diabetes (0.550 g/l vs 0.600 g/l). Fetuin-A levels in patients with diabetes and coronary artery disease were significantly lower (0.535 g/l) than in those without macrovascular complications (0.590 g/l) (Z=1.969; p=0.048). Furthermore the correlation between fetuin-A serum concentration and fasting plasma glucose, LDL-cholesterol and triglycerides levels were observed. Patients with higher fasting glucose had lower fetuin-A levels. However, fetuin-A concentration was positive correlated with LDL-cholesterol and triglycerides levels. No association between fetuin-A and waist circumference, blood pressure, HDL-cholesterol, HbA1C and BMI were found. In summary, serum fetuin-A level has a correlation with some components of metabolic syndrome. We concluded that fetuin-A could be used not only as a marker, but also plays some role in pathogenesis of metabolic syndrome, type 2 diabetes and higher risk of cardiovascular disease.

Keywords: fetuin-A, metabolic syndrome, type 2 diabetes

INTRODUCTION

Metabolic syndrome (MetS) is a common disorder the prevalence of which is estimated to be about 20% in Polish adult population, currently affecting over 5.7 million people [9]. MetS is a clustering of increased waist cirumference, dyslipidemia, impaired glucose metabolism and hypertension [8]. Abdominal obesity and insulin resistance are important pathogenetic factors [9]. MetS plays a role as a risk factor for type 2 diabetes and cardiovascular disease [7].

Fetuin-A, also known as Alpha 2-Heremans Schmid Glycoprotein (AHSG), is a multifunctional plasma agent with a molecular weight of approximately 60 kDa and half-life of several days [14]. AHSG was first discovered in 1944 by Kai O. Pedersen in calf serum [15]. Several years later, J.F. Heremans (in 1960) and K. Schmid with W. Burgi (in 1961), in the independent studies, isolated it in humans [6]. During fetal development fetuin-A is abundantly synthetized by multiple tissues. In adults it is secreted predominantly by the liver (>95%) [12,14]. Fetuin-A is a physiological inhibitor of insulin receptor tyrosine kinase and thus associated with insulin resistance, MetS and an increased risk for type 2 diabetes [7,14].

The aim of this study was to analyse in humans relationships between serum fetuin-A concentrations and the components of metabolic syndrome and total cholesterol, LDL-cholesterol, HbA1c, BMI as well.

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MATERIAL AND METHODS

The study was conducted in 62 patients, 34 women (55%) and 28 men (45%), with metabolic syndrome aged 35-83. They were treated at the Endocrinology Department and in the Outpatient Clinic of the Independent Public Clinical Hospital No.4 in Lublin. In 47 subjects diabetes type 2 was a component of MetS. The duration of diabetes mellitus was estimated to be from newly diagnosed disease to about 30 years. Sixty-two percent of diabetics had coronary artery disease as a macrovascular complication. In the studied group determinations of biochemical parameters and anthropometric measurements were performed. Correlations between serum fetuin-A concentrations and components of MetS such as: waist circumference (WC), blood pressure, triglycerides and HDL-cholesterol levels, fasting glucose and total cholesterol, LDL-cholesterol, HbA1C, BMI levels as well have been analysed. The material was the peripheral blood obtained from the ulnar vein (10 ml). Serum was separated from the collected blood samples by centrifugation for 10 min. at 1000 rpm, aliquoted and stored frozen at –20°C until analysis. Serum fetuin-A concentration was determined with the use of Human Fetuin-A ELISA Kit (antibodies specific for the human fetuin-A protein) with an assay sensitivity of 3.5µg/ml. For statistical analysis of the obtained results, Statistica 8.0 StatSoft was used. Distribution of the studied variables were tested using the W Shapiro-Wilk test, the Kolmogorov-Smirnov test and the Lilliefors test. The Brown-Forsythe test was applied to check the equality of group variances. Lack of the normal distribution and/or the equality of variances were noted. For a comparison of the obtained results, the non-parametric tests: U Mann-Whitney or Kruskal-Wallis were used. Correlations between variables were investigated by Spearman's test. A p value <0.05 was considered as statistically significant in all analyses.

RESULTS

The results of serum fetuin-A concentration (g/l) and selected parameters the analysed group have been shown in Table 1.

In the serum of diabetics the median fetuin-A concentration was 0.550g/l and the result was lower compared to the level in patients without diabetes mellitus (median= 0.600 g/l). However, it was no statistically significant (Fig.1). Patients with type 2 diabetes and coronary artery disease had significantly lower level of fetuin-A than those without macrovascular complications, median: 0.535 g/l and 0.590 g/l (Z=1.969; p=0.048) respectively (Fig.2). Furthermore, the statistically significant correlations between fetuin-A serum concentration and fasting plasma glucose, LDL-cholesterol and triglycerides levels have been observed. These correlations have been summarized in Table 2.

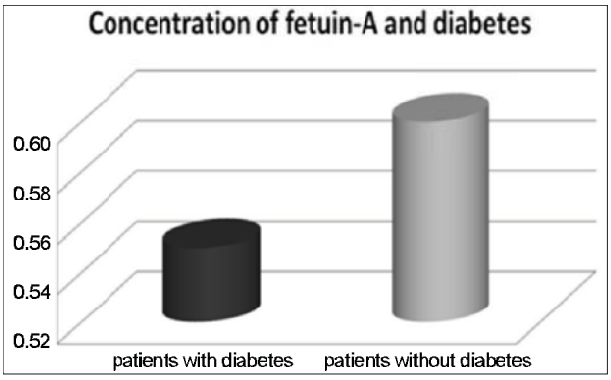

Fig. 1. The concentration of fetuin-A in diabetics and in patients without diabetes mellitus

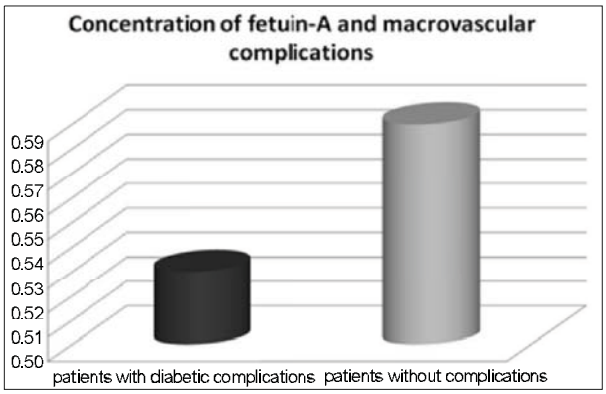

Fig. 2. The concentration of fetuin-A in diabetics with coronary artery disease and in patients without macrovascular complications

Table 1. Serum levels of fetuin-A (g/l) and selected parameters in analysed patients (n=62)

PARAMETERS	X ± SD	MEDIAN	MINIMUM	MAXIMUM
Fetuin – A (g/l)	0.578 ± 0.114	0.585	0.300	0.960
BMI (kg/m2)	33.821 ± 5.481	32.420	19.500	47.00
Waist circumference (cm)	F: 109.940 ± 12.340 M: 110.270 ± 9.210	F: 110.000 M: 109.500	F: 83.000 M: 100.000	F: 136.000 M: 13.000
HbA1C (%)	7.728 ± 2.153	6.755	5.400	14.000
Fasting plasma glucose (mg/dl)	132.855 ± 41.747	123.500	86.000	300.00
Systolic blood pressure (mmHg)	135.710 ± 17.209	130.000	110.000	180.000
Diastolic blood pressure (mmHg)	84.081 ± 11.409	80.5000	60.000	110.000
Triglycerides (mg/dl)	145.145 ± 90.252	119.500	47.000	532.000
HDL – cholesterol (mg/dl)	F: 56.410 ± 14.940 M: 45.290 ± 10.190	F: 52.500 M: 43.500	F: 36.000 M: 28.000	F: 97.000 M: 68.000
LDL – cholesterol (mg/dl)	118.677 ± 41.031	114.000	52.000	213.000
Total cholesterol (mg/dl)	198.823 ± 50.82	191.000	120.000	330.000

Table 2. The correlations between fetuin-A level and fasting plasma glucose, LDL-cholesterol, triglycerides concentrations in the studied group

VARIABLES	R Spearman	t (N-2)	p
Fasting plasma glucose	-0.275	-2.218	0.030
LDL – cholesterol	0.263	2.108	0.039
Triglycerides	0.252	2.018	0.048

Subjects with higher fasting glucose had lower fetuin-A levels (Fig. 3). On the contrary, fetuin-A concentration was positive correlated with LDL-cholesterol and triglycerides levels (Fig. 4 and Fig. 5). Based on statistical analysis, no associations between fetuin-A and WC, blood pressure, HDL-cholesterol, HbA1C and BMI have been found in our patients with MetS.

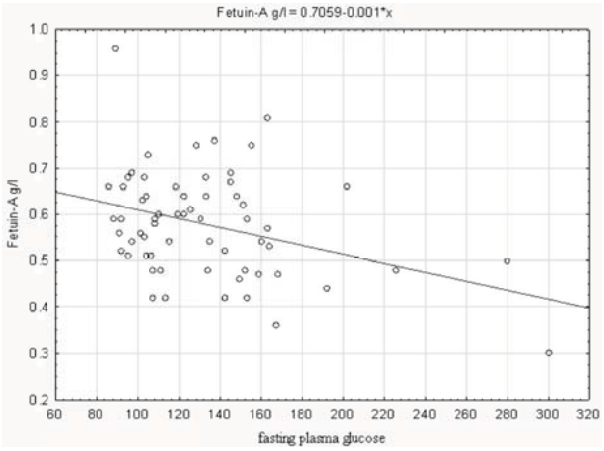

Fig. 3. The correlation between fetuin-A serum concentration and fasting plasma glucose in patients with MetS

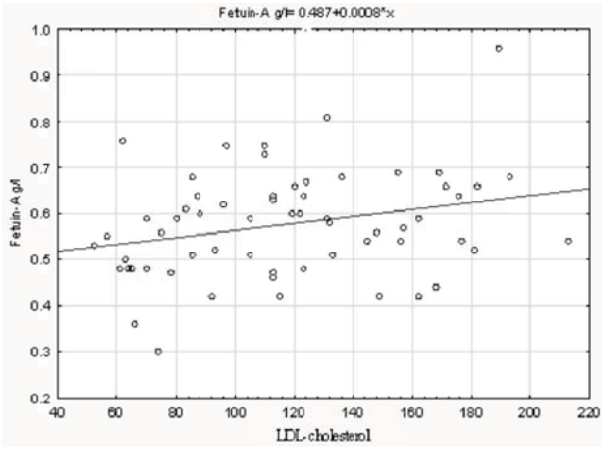

Fig. 4. The correlation between fetuin-A serum concentration and LDL-cholesterol in patients with MetS

DISCUSSION

Fetuin-A belongs to the cystatin family of the proteinase inhibitors and natural inhibitors of insulin receptor [6,10]. Animal studies in rats have shown that it supresses tyrosine kinase activity in muscles and in the liver by inhibiting the autophosphorylation of this enzyme and

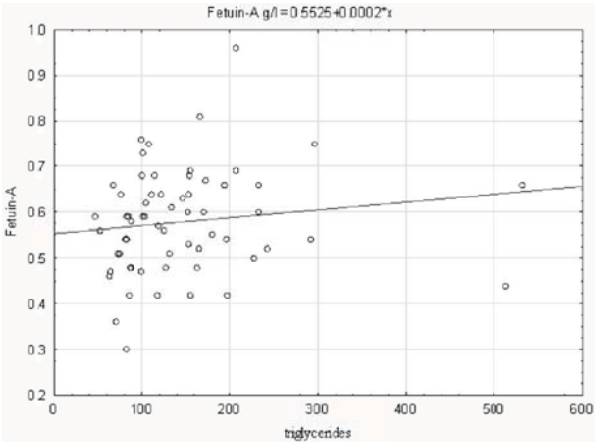

Fig. 5. The correlation between fetuin-A serum concentration and triglycerides in patients with MetS

insulin receptor substrate proteins (IRS-1) as well [8,10, 12]. Thus fetuin-A is found to be involved in the development of insulin resistence [13]. It is well known that fetuin-A knockout mice demonstrate improved insulin sesitivity, resistance to weigt gain when challenged with a high-fat diet, lower serum free fatty acid and triglyceride levels [5,8,12]. In humans, the gene for fetuin-A is localized on chromosome 3q27, which has been mapped as a susceptibility locus for MetS and type 2 diabetes mellitus. Several single nucleotide polimorphisms of the fetuin-A gene were found to be associated with adipocyte insulin action, dyslipidemia and type 2 diabetes [7,8].

A close association between fetuin-A levels and the metabolic syndrome has been shown in cross sectional studies [2,4]. Moreover in longitudinal analyses fetuin-A has been correlated to many components of MetS such as blood pressure, waist circumference, HDL-cholesterol [3,8]. Some reports suggested that the relationship between fetuin-A and MetS may be also a result of fetuin-A induced supression of adiponectin- adipocytokine which represents an important determinant of the whole body sensitivity and cardiovascular disease- production. What's more, fetuin-A induces low-grade inflammation, which is also associated with MetS and atherogenic lipid profile [8]. In our study we analysed correlations between fetuin-A and BMI, WC, blood pressure, lipid profile, fasting plasma glucose and HbA1C level in patients with MetS.

Some clinical studies confirm that low serum fetuin-A concentrations are found in diabetics [7]. Another studies indicate that patients with impaired glucose tolerance but not impaired fasting glucose have higher fetuin-A levels than normal subjects [2]. Wojtysiak-Duma et al. [14] in their study demonstrated that in the patients with type 2 diabetes serum concentration of fetuin-A was significantly lower as compared with healthy participants. It has been thought that decrease in fetuin-A is associated with the presence of peripheral artery disease in patients with type 2 diabetes, besides traditional cardiovascular risk factors [13,15]. Ix et al. [5] and Stefan et al. [11] suggested

that fetuin-A may be an independent risk factor for type 2 diabetes. These reports are consistent with our results because in our subjects with type 2 diabetes fetuin-A concentration was lower than in those without this disease. What's more, persons with coexistence of coronary artery disease had also significantly lower level of fetuin-A than patients without macrovascular complications. However, in contrast to our and some authors findings, there are authors who suggest that an elevated serum fetuin-A level has positive correlation with blood glucose concentration [10,15]. It is known that the drugs such as metformin, pioglitazone and niacin may affect the level of fetuin-A in serum [2,7]. In our subjects, metformin and niacin have been used.

The relationship between BMI and fetuin-A is not clear. Stefan et al. [12] reported no association between fetuin-A and the percentage of body fat. On the other hand, data from the Heart and Soul Study [4] as well as reports by Ismail et al. [3], Singh et al. [10] and Ix et al. [4] demonstrate that elevated fetuin-A concentrations were connected with BMI and waist circumference. In our study we observed no association between BMI, WC and fetuin-A. Erdmann et al. [2] suggested that fetuin-A level may not have similar connection to BMI when the entire range of obesity and morbid obesity is considered and the link between these parameters is rather non- linear.

Insulin resistance and MetS are known to be conditions which increase the chances of cardiovascular diseases [10]. Some authors supported the idea that elevated serum fetuin-A concentration is connected with atherogenic lipid profile and may contribute to the development of atherosclerosis [4,10,13]. These statements are similar to our results. In the analysed group of patients, fetuin-A was positively correlated with LDL-cholesterol and triglycerides levels. We didn't find any association between fetuin-A and HDL-cholesterol, which is consistent with report of Brix et al. [1].

Reinehr and Roth [8] described that in obese children with MetS fetuin-A has been correlated significantly to the systolic and diastolic blood pressure. Similar results in adult obese patients have been reported by many authors [3,7,15]. In contrast to them, Brix et al. [1] did not find any connection of fetuin-A to blood pressure. No any association between fetuin-A and blood pressure has been shown in our study as well.

CONCLUSIONS

In summary, serum fetuin-A concentration is correlated with some components of metabolic syndrome. There has been observed a decrease in fetuin-A in patients with higher fasting glucose and in diabetics. Higher fetuin-A concentrations have been connected with atherogenic lipid profile. Lower fetuin-A levels in serum have been associated with the occurence of macrovascular complications in patients with type 2 diabetes. We concluded that fetuin-A could be used not only as a marker, but also plays some role in pathogenesis of MetS, type 2 diabetes and higher risk of cardiovascular disease. The limitations of this study is a small analysed group of patients and the lack of a control group, however our results are similar to the findings of some authors. Additional studies are required to confirm and generalise these statements of the larger population of individuals with MetS.

REFERENCES

1. Brix J.M., Stingl H., Hollerl F. et al. Elevated Fetuin-A concentrations in morbid obesity decrease after dramatic weight loss. *J. Clin. Endocrinol. Metab.*, 95, 4877, 2010.
2. Erdmann J., Salmhofer H., Knauß A. et al. Relationship of fetuin-A levels to weight-dependent insulin resistence and type 2 diabetes mellitus. *Regul. Pept.*, 178, 6, 2012.
3. Ismail N.A., Ragab S., Abd El Dayem S.M. et al. Fetuin A levels in obesity: differences in relation to metabolic syndrome and correlation with clinical and laboratory variables. *Arch. Med. Sci.*, 5, 826, 2012.
4. Ix J.H., Shlipak M.G., Brandenburg V.M. et al. Association between human fetuin-A and the metabolic syndrome: data from the Heart and Soul Study. *Circulation*, 113, 1760, 2006.
5. Ix J.H., Wassel C.L., Kanaya A.M. et al. *Fetuin-A and incident diabetes mellitus in older persons.* JAMA, 300, 182, 2008.
6. Jahnen-Dechent W., Heiss A., Schäfer C. et al. Fetuin-A regulation of calcified matrix metabolism. *Circ. Res.*, 108, 1494, 2011.
7. Kaushik S.V., Plaisance E.P., Kim T. et al. Extended-release niacin decreases serum fetuin-A concentrations in indivuduals with metabolic syndrome. *Diabetes. Metab. Res. Rev.*, 25, 427, 2009.
8. Reinehr T., Roth C.L. Fetuin-A and its relation to metabolit syndrome and fatty liver disease in obese children before and after weight loss. *J. Clin. Endocrinol. Metab.,* 93, 4479, 2008.
9. Sieradzki J. (2010). *Cukrzyca i zespół metaboliczny*. In: Choroby wewnętrzne. Stan wiedzy na rok 2010. Szczeklik A. (editor). Kraków: Medycyna Praktyczna; p. 1283.
10. Singh M., Sharma P.K., Garg V.K. et al. Role of fetuin-A in atherosclerosis associated with diabetic patients. *J. Pharm. Pharmacol.*, 64, 1703, 2012.
11. Stefan N., Fritsche A., Weikert C. et al. Plasma fetuin-A levels and the risk of type 2 diabetes. *Diabetes*, 57, 2762, 2008.
12. Stefan N., Hennige A.M., Steiger H. et al. á2-Heremans-Schmid Glycoprotein/Fetuin-A is associated with insulin resistence and fat accumulation in the liver in humans. *Diabetes Care,* 29, 853, 2006.
13. Vörös K., Gráf L. Jr., Prohászka Z. et al. Serum fetuin-A in-metabolic and inflammatory pathways in patients with myocardial infarction. *Eur. J. Clin. Invest.*, 41, 703, 2011.
14. Wojtysiak-Duma B., Malecha Jędraszek A., Burska A. et al. Serum fetuiny-A levels in patients with type 2 diabetes mellitus. *Ann. UMCS Sect. DDD*, 2, 93, 2010.
15. Xu Y., Xu M., Bi Y. et al. Serum fetuin-a is corretaled with metabolic syndrome in middle-aged and elderly Chinese. *Atherosclerosis*, 216, 180, 2011.