Research Article

Association of plasma Fetuin-A Levels With Peripheral Arterial Disease in Type 2 Diabetes

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Abstract
Introduction: Fetuin-A is a 64-kDa glycoprotein formed exclusively by liver cells and is secreted into the serum in high concentration. A**ims of the work: The aims of this study are to:** Evaluate the association of plasma fetuin-A and type 2 diabetes mellitus with or without macrovascular complication (as diabetic peripheral arterial disease), also in patients with peripheral arterial disease without diabetes mellitus. Understand the role of Fetuin-A in the pathophysiology of peripheral arterial disease as an inhibitor of calcification. **Patients And Methods:** This is a prospective study which was conducted on 80 subjects (41 males and 39 females) with age range of 22:66 years. The participants were collected from internal medicine clinic, Minia University hospital, Minia governorate, Egypt, during the period from January to June 2016. The study was approved by the faculty of medicine, Minia university ethical committee. The aims of this study are to evaluate the association of plasma fetuin-A and type 2 diabetes mellitus with or without macrovascular complication (as diabetic peripheral arterial disease), also in patients with peripheral arterial disease without diabetes mellitus and understand the role of Fetuin-A in the pathophysiology of peripheral arterial disease as an inhibitor of calcification. **Results:** This study included 80 subjects were classified to three groups as follow: Group (I): DM: Included 30 patients have type 2 diabetes mellitus without peripheral arterial disease. Group (II): DM+PAD: Included 30 patients have type 2 diabetes mellitus with peripheral arterial disease. Group (III): Control: Included 20 healthy control subjects.
Discussion: Peripheral artery disease is a common circulatory problem in which narrowed arteries reduce blood flow to limbs, is a major public health problem (Norgren et al., 2007). The epidemiologic literature shows that patients with PAD have up to three times the risk of all cause mortality. **Conclusion:** From the previous results it can be concluded that: The present results postulate an association between lower plasma fetuin-A level and peripheral vascular disease in type 2 diabetic patients who already suffer from both insulin resistance and vascular calcification and the balance between the two functions of fetuin-A may depend on various ambiguous factors.
Keywords: CBC: Complete blood count, CDC: Centers for Disease Control and Prevention, CKD: Chronic kidney disease

Introduction

Fetuin-A is a 64-kDa glycoprotein formed exclusively by liver cells and is secreted into the serum in high concentration (Celebi et al., 2015). In muscle and fat, fetuin-A leads to insulin resistance because in these tissues it binds to the insulin receptor tyrosine kinase (Barclay and Vega, 2008). Serum concentration of fetuin-A is directly associated with insulin resistance and dyslipidaemia because it inhibits the insulin-stimulated autophosphorylation of the insulin receptor (Mehrotra, 2007). It also acts as a marker of vascular disease in type-2 Diabetes (Roos et al., 2010). Fat accumulation in the liver may be associated with a higher level of fetuin-A (Stefan et al., 2006). Serum fetuin-A concentration is a good indicator of liver cell function and it ranges from approximately 454-644 ng/ml in healthy individuals (Kalabay et al., 2007).

Diabetes mellitus (DM) is one of the most serious diseases and the pathophysiologies of type II DM are reduced insulin sensitivity and increased insulin resistance associated with enhanced hepatic glucose output and impaired insulin secretion due to a progressive decline of b-cell function (DeFronzo et al., 2010). increasingly becoming a major chronic disease burden all over the world specially in Africa. In

2011, about 14 million individuals were estimated to have diabetes in Africa, and this is expected to rise to 28 million by 2030 (Bos and Agyemang, 2011). In 2013, 382 million adults were diagnosed with diabetes worldwide and this number is expected to grow to 592 million in 2035 (International Diabetes Federation, 2015). Also, it is a fast-growing health problem in Egypt with a significant impact on morbidity, mortality, and health care resources. Currently, the prevalence of type 2 diabetes in Egypt is around 15.6% of all adults aged 20 to 79 (Hegazi et al., 2015).

Aims of the Work

The aims of this study are to:

Evaluate the association of plasma fetuin-A and type 2 diabetes mellitus with or without macro-vascular complication (as diabetic peripheral arterial disease), also in patients with peripheral arterial disease without diabetes mellitus.

Understand the role of Fetuin-A in the pathophysiology of peripheral arterial disease as an inhibitor of calcification.

Patients and Methods

This is a prospective study which was conducted on 80 subjects (41 males and 39 females) with age range of 22:66 years. The participants were collected from internal medicine clinic, Minia University hospital, Minia governorate, Egypt, during the period from January to June 2016. The study was approved by the faculty of medicine, Minia university ethical committee. The aims of this study are to evaluate the association of plasma fetuin-A and type 2 diabetes mellitus with or without macrovascular complication (as diabetic peripheral arterial disease), also in patients with peripheral arterial disease without diabetes mellitus and understand the role of Fetuin-A in the pathophysiology of peripheral arterial disease as an inhibitor of calcification.

Participants were classified to three groups:

Group (I): DM: Included 30 patients have type 2 diabetes mellitus without peripheral arterial disease.

Group (II): DM+PAD: Included 30 patients have type 2 diabetes mellitus with peripheral arterial disease.

Group (III): Control: Included 20 healthy control subjects.

Participants were chosen according to the following:

Inclusion criteria:

Patients with type 2 diabetes mellitus in different ages for group I and group II.

Healthy non diabetic persons with different ages (matched with the other two groups) as control group.

Patients with peripheral arterial disease with a history of claudication

Exclusion criteria:

Patients with type 1 diabetes mellitus.

Patients with renal impairment (createnine more than 1.5)

Patients with auto immune disease, bronchial asthma or any patient treated with corticosteroids.

Patients with severe dyslipidemis (triglycerides >600 mg/dl or cholesterol >350 mg/dl).

Pregnant diabetic women.

Patients with liver diseases.

Results

This study included 80 subjects were classified to three groups as follow:

Group (I): DM: Included 30 patients have type 2 diabetes mellitus without peripheral arterial disease.

Group (II): DM+PAD: Included 30 patients have type 2 diabetes mellitus with peripheral arterial disease.

Group (III): Control: Included 20 healthy control subjects.

Table: Kidney function among studied groups.

Variable	Group I DM (n=30)	Group II DM+PAD (n=30)	Group III Control (n=20)	P. value		
Creat. (mg/dl)				0.400 NS		
Range	(0.5-1.3)	(0.5-1.33)	(0.4-1.2)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	0.87 ± 0.23	0.81 ± 0.18	0.80 ± 0.21	0.456 NS	0.510 NS	0.999 NS
Urea (mg/dl)				0.767 NS		
Range	(18-55)	(18.7-68)	(20-60)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	34.4 ±10.7	34.9 ± 10.6	36.7 ± 12.2	0.979 NS	0.755 NS	0.851 NS

One way ANOVA test for parametric quantitative data between the three groups followed by post Hoc Tukey correction for each two groups.
* Significant ($p<0.05$) ** Significant ($p<0.01$). NS. Not significant.

Discussion

Peripheral artery disease is a common circulatory problem in which narrowed arteries reduce blood flow to limbs, is a major public health problem (Norgren et al., 2007). The epidemiologic literature shows that patients with PAD have up to three times the risk of all cause mortality (Krishna et al., 2015). The risks of death from coronary artery disease are up to six times greater for PAD patients in comparison to those without the disease (Grenon et al., 2013). PAD, however, is usually not recognized as a major public health threat and motivation to evaluate patients for PAD is much lower than it is for other cardiovascular conditions (Shah et al., 2008). Peripheral artery disease is a serious health condition that increases an individual's risk for heart attack, stroke, and leg amputation. The reported prevalence is 22–42% (Grenon et al., 2013). Also, PAD is expected to be one of the leading cause of death in developing countries "like Egypt" in the future (Sayed et al., 2016). Also, the overall prevalence of PAD is slightly higher in men than in women, although prevalence rates among women increase later in life (Mozaffarian et al., 2015).

Diabetes mellitus (DM) is a metabolic disorder characterized by increased mortality rates and importantly implicated in the atherogenetic process (Tousoulis et al., 2012).

Hyperglycemia, insulin resistance, hyperinsulinemia, hyperlipidemia, and hyperhomocysteinemia represent important pathophysiological components of DM that result in endothelial/ vascular dysfunction through several underlying processes (Kampoli et al., 2011). Patients with diabetes mellitus often have extensive and severe PAD and a greater propensity for arterial calcification (Aboyans et al., 2006). Also, it is well known that PAD is a state of advanced and systemic atherosclerosis and that in patients with diabetes is often accompanied by vascular calcification of the tunica media of the arterial wall (Mönckeberg sclerosis) (Jude et al., 2010). Also, it has been reported that patients suffering from type 2 diabetes and peripheral artery disease (PAD) (type 2 diabetes–PAD) have a five times higher risk for cardiovascular mortality than patients with one disease alone (Lorant et al., 2011). Also, Giacco et al., (2010) reported that, although the reasons for accelerated vascular disease in T2DM are not yet fully clear, insulin resistance or adipo-cytokines may contribute to the pathogenesis of diabetic microangiopathies and macroangio-pathies by modulating vascular function and affecting inflammatory processes.

Conclusion

From the previous results it can be concluded that: The present results postulate an association between lower plasma fetuin-A level and peripheral vascular disease in type 2 diabetic patients who already suffer from both insulin resistance and vascular calcification and the balance between the two functions of fetuin-A may depend on various ambiguous factors.

Our findings suggest that fetuin-A could play a role in the development of PAD in type 2 diabetes through increased calcification burden. Also, fetuin-A could be used as a marker of PAD in type 2 diabetes patients.

Clearly, future studies, with larger populations, are required to determine the association between PAD in diabetic patients and fetuin-A and also, elucidate the exact mechanism.

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