

## Evaluation of Immunoglobulin A in Diabetic Patients and its Relation with Oral Complications

Sodابه Farahnak<sup>1</sup>, Robab Sheikhpour<sup>2,3</sup>, Foad Iranmanesh<sup>4</sup>

1- Department of endodontics, School of Dentistry, Shahid Sadoughi University of Medical Science, Yazd, Iran  
 2- Department of Physical Education, Taft Branch, Islamic Azad University, Taft, Iran  
 3- Hematology and oncology research center, Shahid Sadoughi University of Medical Science, Yazd, Iran  
 4- Department of endodontics, Dental School, Rafsanjan University of Medical Science, Rafsanjan, Iran  
 5- Diabetes and Obesity center, Shahid Sadoughi University of Medical Science, Yazd, Iran

### \*Correspondence:

Robab Sheikhpour, Department of Physical Education, Taft Branch, Islamic Azad University, Taft, Iran  
 3- Hematology and oncology research center, Shahid Sadoughi University of Medical Science, Yazd, Iran  
 Email: robab.sheikhpour@iauyazd.ac.ir  
 Tel: (98) 913 152 2462

**Received:** 15 May 2015

**Accepted:** 05 Jun 2016

**Published in August 2016**

### Abstract

Diabetes mellitus is a group of metabolic diseases caused by a combination of insulin resistance and impaired insulin secretion by pancreatic  $\beta$  cell. In 2007, 246 million people (roughly 6%) were affected by diabetes worldwide and it is estimated that this will increase to 380 million in 2025. Diabetes is associated with several long-term complications such as cardiovascular disease, nephropathy, retinopathy, neuropathy and some oral complications. In addition, Diabetes mellitus causes an increased risk of morbidity because of infection disease. It seems that, the increased frequency of infections associated with Immunoglobulin-A (IgA) deficiency in these patients. Therefore a low IgA secretion rate is suspected to be one of these mechanisms. Moreover, it shows a main antiviral activity by neutralizing toxins and viruses. It by inhibiting the attachment and replication of pathogenic microorganisms prevents colonization of these pathogens. Therefore, it acts as a first line of defense against pathogens and early detection of immunoglobulin A deficiency in diabetic patients can prevent the vicious cycle of recurrent infections and reduces risk for morbidity and metabolic decompensation. Moreover, the Salivary-IgA is the widespread immunoglobulin in mixed saliva and is assumed to be an important factor for adaptive immunity in the oral cavity. Therefore, according to these studies, Immunoglobulin A, its mechanism, IgA deficiency and diabetes and its relation with oral complications are explained in this paper.

**Keywords:** Immunoglobulin A, Diabetic patients, Immunodeficiency, Oral complications

### Introduction

**F**etuin-A, alpha-2- Heremans Schmid glycoprotein (1), (AHSG) (2-6) is a phosphorylated glycoprotein (2) with molecular weight of 60 KDa (7) produced

primarily by liver (2,8-11) and secreted to plasma (12). It as member of the Fetuin group is comprised of three O-linked and two N-linked oligosaccharide chains (2). Fetuin-A

can form complexes with calcium and phosphorous in the circulation and prevents the sedimentation of these minerals in serum (7). Therefore, Fetuin-A by binding to calcium ion inhibits ectopic calcium deposition and protects vascular calcification (13).

Also it acts as cysteine protease inhibitor (14) known cystatin superfamily protein member with two cystatin domains and a proline and glycine domain as third domain (15). Fetuin-A is a multifactorial protein and its role is documented from brain development to bone remodeling and immune function (16) regulation of insulin activity, hepatocyte growth factor activity and inhibition lymphocyte blastic transformation (17). Also the role of Fetuin-A is linked to tissue regeneration, including heart, lung, kidney, nervous system and liver (15). Fetuin-A be as a negative acute phase reactant and its level correlates with liver function (18), but its concentration is not associated with the level of inflammatory cytokine (18). Fetuin-A has an important role in apoptosis (15). Apoptosis is a complex network of biochemical and molecular pathways with fine regulatory mechanisms that control the death event in a cell, but the mechanism of apoptosis by Fetuin is unknown (19,20). Studies showed that high level of Fetuin-A is associated with obesity and weight gain in individuals (21). Liang et al. reported that Fetuin-A is a promising candidate biomarker for the risk of diabetes (13). Fetuin-A via inhibiting insulin receptor autophosphorylation impels insulin resistance (13,22).

### **Fetuin-A and type 2 diabetes mellitus**

Diabetes is the most common metabolic disorder (23,24). The Fetuin-A gene is placed on chromosome 3q27, the chromosomal area that was formerly mapped as a type 2 diabetes (T2DM) and metabolic syndrome susceptibility locus (25). Genetics studies showed that single nucleotide polymorphism in Fetuin-A gene causes T2DM in cross-sectional studies. However the role of Fetuin-A in T2DM still remains unclear (25). Fetuin-

A inhibits phosphorylation of the insulin receptors (21) in liver and muscle resulted to decreased insulin signaling resulted insulin resistance (21), therefore, the high level of Fetuin-A is associated with insulin resistance and incidence of T2DM (21). Insulin resistance is a path physiological mechanism of T2DM may contribute to the development of T2DM and associated vascular complications. Also insulin resistance is associated with dyslipidemia and hypertensive diseases (13). Another studies on animals showed that Fetuin-A suppresses tyrosine kinase activity in muscle and liver via inhibiting the autophosphorylation of this enzyme and insulin receptor substrate proteins (IRS-1) (26). However, despite strong associations of Fetuin-A with insulin resistance in non-diabetic subjects, Mori et al. did not observe any correlation between Fetuin-A and insulin resistance among T2DM (21).

Studies reported that Fetuin-A can play an important role in both obesity and fatty liver with insulin resistance, T2DM and vascular complications (21). There is negative correlation between fatty liver and increased Fetuin-A levels associated with the metabolic syndrome with the level of adiponectin and positive correlation with the level of CRP (21). Thomas et al. reported that relation between Fetuin-A and metabolic syndrome may be the result of Fetuin-A induced suppression of Adiponectin production (27). Adiponectin as adipokine is associated to insulin resistance and inversely related to TNF- $\alpha$  (21). Also this study reported that Fetuin-A suppresses the production of adiponectin in animals and humans. Also Fetuin-A induced inflammation associated with the metabolic syndrome and an atherogenic lipid profile (27). Ismael et al. showed that relation between the level of serum Fetuin-A and features of the metabolic syndrome is likely involved in the pathogenesis of insulin resistance and metabolic syndrome in human, but prior studies about relation of Fetuin-A to insulin resistance suggested that Fetuin-A interferes

with insulin action at peripheral tissues by its interaction with insulin receptor (28).

### **Fetuin-A and Obesity**

Obesity as a risk factor of metabolic syndrome is associated with increased waist circumference, impaired glucose metabolism, hypertension, and etc (28). It causes increased vascular dysfunctions and vascular disease (21). The mechanism of this function may be due to hypertension, dyslipidemia, fatty liver, inflammation, and insulin resistance (21). Also obesity is associated with elevated pre-inflammatory mediators and reduced adiponectin levels (21). Thus, the level of adiponectin is higher in lean than in obese individuals and are highly associated with reduced incidence of vascular diseases (21). Ismail et al. in another study reported that high level of inflammatory cytokines was observed in obese individual than lean which plays a role in causing insulin resistance. The significant source of proinflammatory cytokines in obesity is the adipose tissue (28). Thomas and Christian showed that decreased level of Fetuin-A is associated with decrease of insulin resistance in obese children who reduced their overweight substantially due to a lifestyle modification in contrast to obese children(28).

Lin et al. evaluated the relation between Fetuin-A and obesity in rats. They observed that obesity increases Fetuin-A gene expression, indicating an important role of Fetuin-A in predisposing to obesity (21). Another study showed that increased Fetuin-A and plasma levels of proteins expression are associated with fat accumulation in liver (25). Studies evaluated whether this effect is mediated through tissue-specific actions of the inhibitory effect of FetuinA on the insulin receptor tyrosine kinase or through alternative pathways in humans could yield novel insights into the regulatory mechanisms of dyslipidemia, hypertension, and disturbed glucose metabolism. Unfortunately, there are limited data available on the role of FetuinA as a regulator of insulin sensitivity in humans.

Mori et al. did not find a significant association between FetuinA and insulin resistance (28).

Another study showed that obese children with metabolic syndrome have higher Fetuin-A concentration than obese children without metabolic syndrome and healthy control. Stepien et al. in another study evaluated the relation between anthropometric obesity parameters, serum concentrations of ghrelin, resistin, leptin, adiponectin and homeostasis model assessment (HOMA-IR) in obese non-diabetic insulin-sensitive and insulin-resistant patients. They reported that waist circumference, adiponectin, leptin and ghrelin are related to insulin resistance and can be prognosticator of this pathology (28).

### **FetuinA, lipids and cardiovascular disease**

Obesity as the most common nutritional disorder causes increased mortality and morbidity of cardiovascular disease (29). Liang et al. in another study reported that the level of visceral obesity is associated with dyslipidemia (13). Also damaging of normal function of endothelium and platelets is associated with Hyperglycemia and insulin resistance led to inflammation, vasoconstriction and thrombosis. All these conditions enhance the risk of atherosclerosis (7). So far, little is known about the relations of FetuinA with cardiovascular disease (CVD) in human populations (30). One study showed that Fetuin-A is involved in cardiovascular disease and metabolic disease risk (31). Fetuin-A levels have been positively associated with diabetes risk in middle-aged and older individuals, incident diabetes in older men and women, carotid artery intima-media thickness in middle-aged adults, and risk of myocardial infarction and stroke (31). Many features of metabolic syndrome like blood pressure, waist circumference and HDL- cholesterol are related to Fetuin-A (27). Ayman et al. in another study reported that the level of FetuinA do not correlate with some clinical and metabolic parameters like BMI,

blood pressure, total cholesterol, HDL and triglyceride in type 2 diabetic patients with early diabetic nephropathy with or without hyperglycemia (25). Anna et al. showed that Fetuin-A was positively correlated with LDL-cholesterol and triglycerides levels, but no association between Fetuin-A with HDL-cholesterol, waist circumference, blood pressure and BMI. They reported that Fetuin-A can be used as a marker and play some role in pathogenesis of metabolic syndrome, type 2 diabetes and higher risk of cardiovascular disease (26). Ayman et al. reported that Fetuin-A could play a role in the development

of early microvascular disease (especially nephropathy) in type 2 diabetes, but possible mechanisms remain unclear(25).

## Conclusion

These findings support the hypothesis that high plasma Fetuin-A level is significantly associated with an increased risk of developing type 2 diabetes and obesity. It seems that Fetuin-A is probably involved in the pathogenesis of insulin resistance and Metabolic Syndrome in humans.

## References

- Hendig D, Schulz V, Arndt M, Szliska Ch. Role of Serum Fetuin-A, a Major Inhibitor of Systemic Calcification, in Pseudoxanthoma Elasticum. *Clinical Chemistry*. 2006;52(2):227-34.
- Sun Q, Cornelis MC, Manson JA, B.Hu F. Plasma Levels of Fetuin-A and Hepatic Enzymes and Risk of Type 2 Diabetes in Women in the U.S. *Diabetes*. 2013;62:49-56.
- Mori K, Emoto M, Inaba M. Fetuin-A: a multifunctional protein. *Recent Pat EndocrMetab Immune Drug Discov* 2011;5(2):124-46.
- Mori K, Emoto M, Inaba M. Fetuin-A and the cardiovascular system. *AdvClin Chem* 2012;56:175-95.
- Vörös K, Cseh K, Kalabay L. The role of fetuin-A in cardiovascular diseases. *Orv Hetil* 2014;5;155(1):16-23.
- Stefan N, Hennige AM, Staiger H, Machann J, Schick F, Kröber SM, et al. Alpha2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans. *Diabetes Care* 2006;29(4):853-7.
- Shidfar F, Zarrati M, Khamseh MB. Relationship between serum levels of fetuin-A with apo-A1, apo- B100, body composition and insulin resistance in patients with type 2 diabetes. *Medical Journal of the Islamic Republic of Iran* 2014;28(100):1-7.
- Singh M, Sharma PK, Garg VK, Mondal SC, Singh AK, Kumar N. Role of fetuin-A in atherosclerosis associated with diabetic patients. *J Pharm Pharmacol* 2012;64(12):1703-8.
- Herrmann M, Schäfer C, Heiss A, Gräber S, Kinkeldey A, Büscher A, et al. Clearance of fetuin-A-containing calciprotein particles is mediated by scavenger receptor-A. *Circ Res* 2012 17;111(5):575-84.
- Erdmann J, Salmhofer H, Knauß A, Mayr M, Wagenpfeil S, Sypchenko O, et al. Relationship of fetuin-A levels to weight-dependent insulin resistance and type 2 diabetes mellitus. *RegulPept* 2012;178(1-3):6-10
- Celebi G, Genc H, Sertoglu E, Kara M, Tapan S, et al. The Relationship of Circulating Fetuin-A With Liver Histology and Biomarkers of Systemic Inflammation in Nondiabetic Subjects with Nonalcoholic Fatty Liver Disease. *Saudi J Gastroenterol*. 2015;21(3):139-45.
- Watson K, Koumangoye R, Thompson P, Sakwe AM, Patel T. Fetuin-A triggers the secretion of a novel set of exosomes in detached tumor cells that mediate their adhesion and spreading. *FEBS Lett*. 2012;586(19):3458-63.
- Yin L, Cai W, Zhu L-Y, Li J, -Hui Su X, Wang X-L, Chang X-, Sun K. Association of plasma Fetuin-A and clinical characteristics in patients with new-onset type 2 diabetes mellitus. *Biomedical Reports. Medical Journal of the Islamic Republic of Iran (MJIRI)* 2014;2:839-42.
- Guillory B, Sakwe AM, Saria M, Thompson P, Adhiambo Ch. Lack of Fetuin-A (2-HS-Glycoprotein) Reduces Mammary Tumor Incidence and Prolongs Tumor Latency via the Transforming Growth Factor- Signaling Pathway in a Mouse Model of Breast Cancer. *Am J Pathol*. 2010;177(5):2635-44.
- Yu Ch-Li, Tsai M-H. Fetal fetuin selectively induces apoptosis in cancer cell lines and shows anti-cancer activity in tumor animal models. *Cancer Letters* 2001;166:173-84.
- Kundranda MN, Ray S, Saria M, Friedman D, Matrisian LM. Annexins expressed on the cell surface serve as receptors for adhesion to immobilized fetuin-A. *Biochimica et Biophysica Acta* 2004;1693:111-23.
- Kalabay L, Gráf L, Vörös K, Jakab L, Benkő Z. Human serum fetuin-A/ $\alpha$ 2HS- glycoprotein level is

- associated with long-term survival in patients with alcoholic liver cirrhosis, comparison with the Child-Pugh and MELD scores. *BMC Gastroenterology* 2007;7:15.
18. Krisztián Szabolcs Vörös. The role and interactions of fetuin-A in hepatic and fetuin-A in hepatic and cardiovascular disease. 2014.
  19. Sheikhpour R, Chinisaz M, Jabbari S. New Perspectives on the Role of Hyperglycemia, Free Fatty Acid and Oxidative Stress in b-Cell Apoptosis. *IJDO* 2014;6(3):51-57.
  20. Chandra J, Zhivotovsky B, Zaitsev S, Juntti-Berggren L. Role of Apoptosis in Pancreatic beta-Cell death in Diabetes. *Diabetes* 2001;50(1):44-8.
  21. Rasul S, Wagner L, Kautzky-Willer A. Fetuin-A and angiotensin in obesity and type 2 diabetes mellitus. *Endocrine* 2012;42:496-505.
  22. Yin L, Cai W-J, Chang X-Y, Li J, Su X-H. Association between fetuin-A levels with insulin resistance and carotid intima-media thickness in patients with new-onset type 2 diabetes mellitus. *Biomedical Reports*. 2014;2:839-42.
  23. Sheikhpour R. Glucagon-like peptide 1 and type 2 diabetes: Targets and new therapies. *Indian J Sci Technol* 2012;5(6):2891-8.
  24. Sheikhpour R. Diabetes and Oxidative Stress: The Mechanism and Action. *IJDO* 2013;5(1):40-6.
  25. Ramadan A, Shoukry A, Ismail MI, Borai M. Serum Fetuin-A Levels in Type 2 Diabetes Patients with Early Diabetic Nephropathy: It's Relation to Diabetes Control. *Journal of American Science*, 2011;7(5):759-66.
  26. Dabrowska AM, Tarach JS, Wojtysika B. Current Issues in Pharmacy and Medical Sciences. *Curr. Issues Pharm. Med. Sci.* 2013;26(3):305-8.
  27. Reinehr Th, Roth Ch L. Fetuin-A and Its Relation to Metabolic Syndrome and Fatty Liver Disease in Obese Children Before and After Weight Loss. *ClinEndocrinolMetab*, 2008;93(11):4479-85.
  28. Ismail NA, Ragab Sh, Nour A. Effect of Oral Curcumin Administration on Insulin Resistance, Serum Resistin and Fetuin-A in Obese Children: Randomized Placebo-Controlled Study. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*. 2014;5(1):887-97.
  29. Wang Zh, Nakayama T. Inflammation, a Link between Obesity and Cardiovascular Disease. *Hindawi Publishing Corporation*. 2010;1-18.
  30. Jenesen MJ, Bartz TM, Mukamal KJ. Fetuin-A, Type 2 Diabetes, and Risk of Cardiovascular Disease in Older Adults. *Diabetes care* 2012;18.
  31. Jenkins NT, McKenzie JA, Hagberg JM, Witkowski S. Plasma fetuin-A concentrations in young and older high- and low-active men. *Metabolism*. 2011;60(2):265-71.