

Fetuin a (AHSG) in Metabolic and Inflammatory Diseases: A Foe or A Friend

Sindhu S*, Nadeem A and Rasheed A

Immunology & Innovative Cell Therapy Unit, Dasman Diabetes Institute (DDI), Kuwait

***Corresponding author:** Sardar Sindhu Immunology & Innovative Cell Therapy Unit, Dasman Diabetes Institute (DDI), P.O. Box 1180, Dasman 15462, Kuwait, Tel: +965 2224 2999; E-mail: sardar.sindhu@dasmaninstitute.org

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Abstract

Fetuin A/AHSG was first isolated by Pedersen in 1944 from the fetal bovine serum. In adult humans, fetuin A is mainly secreted by the liver and the adipose tissue and it acts as an inhibitor of ectopic calcification. Fetuin A is also related to critical aspects of cardiometabolic health in humans such as insulin sensitivity, glucose tolerance, non-alcoholic fatty liver disease, atherosclerosis, and cardiovascular disease. The emerging evidence supports fetuin A as a pleiotropic glycoprotein with both inflammatory and anti-inflammatory attributes. In this paper, we briefly review the available literature that supports the diverse role of fetuin A as a positive acute phase reactant (its pathologic role) as well as a negative acute phase protein (its protective role). This functional paradox of fetuin A seems to be inherent in its unique ability to interact with multiple receptors that can regulate key activities related to both human health and disease.

Keywords: Fetuin-A; α 2-HS-glycoprotein; Inflammatory; Anti inflammatory; Metabolic Disease

Background

Fetuin A or α 2 Heremans-Schmid glycoprotein (AHSG) is a 64kDa glycoprotein that is found in high concentrations ranging from 300-1000 μ g/mL in human serum [1]. It was first isolated by Pedersen in 1944 as a glycoprotein found in high concentrations in fetal bovine serum and hence named as Fetuin, designating a link with 'fetus' wherein it was originally discovered. During the fetal development, it is expressed in most organs including liver, kidney, gastrointestinal tract, brain, and skin [2]. In adult humans, Fetuin A is mainly expressed and secreted by the liver and adipose tissue [3]. The circulating Fetuin A has been reported to be elevated in metabolic disorders including obesity, type-2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), and metabolic syndrome [4-7]. Fetuin A is a systemically-

acting inhibitor of ectopic calcification[8] which is also related to critical parameters of metabolic health including insulin sensitivity, glucose tolerance, circulatory lipids as well as both pro- and anti-inflammatory proteins [1,6,7,9]. Macrophages use Fetuin A as an opsonin for endogenous cationic-deactivating molecules such as spermine which may have implications for the innate immune response modulation and endocytosis [10]. Despite its relative abundance in the circulation, the dynamic role of Fetuin A during various disease conditions remains poorly understood. The following summarizes the accumulating evidence pointing to the dual-faceted nature of Fetuin A as a pleiotropic molecule having both inflammatory and anti inflammatory attributes.

Fetuin A as an Inflammatory Molecule or a Positive Acute Phase Reactant

Toll-like receptor (TLR)-4 plays a key role in the innate immunity and metabolic inflammation. The circulatory free fatty acids (FFAs) that are found at high levels in obesity and T2D trigger the adipose tissue inflammation through the TLR4-dependent pathway, leading to the induction of insulin resistance. Of note, FFAs do not directly bind to TLR4 [11] and Pal et al. reported that Fetuin A acted as an endogenous ligand for TLR4 and also demonstrated that the FFA-induced proinflammatory cytokine expression in adipocytes occurred only in the presence of both Fetuin A and TLR4 [12]. This group further showed that FFAs did not induce inflammatory signaling and insulin resistance in adipocytes with mutated TLR4 or galactoside-cleaved Fetuin A. Fetuin A was shown to directly bind with the Leu100-Gly123 and Thr493-Thr596 residues of TLR4 through its terminal galactoside moiety to cause a lipid-induced insulin resistance [12]. The inflammatory role of fetuin A is further supported by the reports that circulatory Fetuin A could inhibit insulin receptor autophosphorylation as well as downstream signaling *in vitro* [13,14]. Consistent with these observations, Fetuin A-deficient mice showed enhanced insulin sensitivity [15], implying that Fetuin A might be a negative regulator of insulin signaling. Accordingly, the circulating Fetuin A was found to be elevated in insulin-resistant as compared with insulin-sensitive obesity [16]. Notwithstanding, another study found no significant difference of serum Fetuin A levels between T2D and non-diabetic individuals while the Fetuin A levels in non-diabetics correlated with insulin resistance index called homeostatic model assessment of insulin resistance (HOMA-IR) which shows the independent effect of Fetuin A on insulin resistance in non-diabetic subjects [17]. The authors speculated that the lack of a correlation between Fetuin A levels and HOMA-IR in diabetics was due to the presence of diabetes-related morbid factors such as glucose toxicity and/or non-enzymatic glycation that could dominate and mask the effect of Fetuin A on insulin resistance, although the precise mechanism(s) remain unclear. Further in this regard, levels of non-esterified fatty acids and systemic Fetuin A were shown to interact to predict the degree of insulin resistance [18]. We suggest that it may also be of interest to analyze the relationship between levels of phosphorylated Fetuin A and insulin resistance since the phosphorylated Fetuin A is a more potent inhibitor of insulin signaling as compared with non-phosphorylated Fetuin A in affecting the insulin receptor autophosphorylation [13]. A direct mechanistic link between Fetuin A and insulin resistance is further

supported by the evidence that human Fetuin A interferes with insulin receptor signaling by modifying tyrosine kinase phosphorylation [19].

Interestingly, *Fetuin A/AHSG* gene is located on chromosome 3q27 which is also recognized as a metabolic syndrome susceptibility locus [20]. The relationship between Fetuin A and metabolic syndrome is further highlighted by a positive association of the systemic Fetuin A levels with the parameters of metabolic syndrome such as waist circumference, blood pressure, fasting plasma glucose, fasting insulin, HOMA-IR, oral glucose tolerance test (OGTT)-derived 2h glucose and insulin, low-density lipoprotein cholesterol, total cholesterol, and triacylglycerol levels [3]. The elevated circulatory levels of saturated fatty acid palmitate have been reported in obesity/T2D and palmitate-induced Fetuin A was shown to stimulate triacylglycerol accumulation in hepatocytes through the mechanism involving mammalian target of rapamycin-sterol and regulatory element binding protein-1c pathway [21]. Some studies have reported the elevated circulatory levels of Fetuin A in obesity and related disorders including T2D, NAFLD, and metabolic syndrome [3,22,23] which may be due to the presence of hyperglycemia and/or hyperlipidemia which are important clinical features of insulin resistance and metabolic syndrome. Takata et al. demonstrated that the incubation of human hepatoma HepG2 cells with glucose enhanced the expression of Fetuin A via the ERK1/2 signaling pathway [24]. In agreement with this, Ou et al. also showed that Fetuin A expression induced by both glucose and lipids involved the endoplasmic reticulum stress and ERK 1/2 signaling pathway [25]. As a proinflammatory molecule or a positive acute phase reactant, Fetuin A has been associated with metabolic syndrome, NAFLD, carotid intima media thickness, arterial stiffness, atherosclerosis, coronary artery disease, and cardiovascular events/morbidity in diabetes [26,27].

Fetuin A as an Anti-Inflammatory Molecule or a Negative Acute Phase Reactant

On the contrary to afore-mentioned, Fetuin A also acts as an anti-inflammatory protein or a negative acute phase reactant during various disease conditions. The recognition of pathogen- or damage-associated molecular patterns by TLRs on the innate immune cells leads to the release of early-phase proinflammatory cytokines, such as TNF- α , IFN- γ , and IL-6 which suppress the hepatic Fetuin A synthesis mediating a negative acute phase response during the first 24-48 hrs following endotoxemia or sepsis [28]. In a clinical study involving 53 T2D and 72 age- and

sex-matched non-diabetic individuals, we recently found that the circulatory Fetuin A levels in T2D patients were associated negatively with a wide range of inflammatory cytokines/chemokines and activation biomarkers including TNF- α , IFN- γ , IL-1 β , IL-15, CCL-2, CCL-4, CCL-11, CCL-22, CXCL-8, CX3CL-1, GRO, and VEGF which clearly suggests that plasma Fetuin-A may have the predictive significance as a negative acute phase reactant in metabolic disease. We further investigated this negative association between Fetuin A and proinflammatory cytokines by using HepG2 cell culture model and found that the proinflammatory cytokines including IFN- γ and TNF- α down modulated while the anti-inflammatory IL-10 up regulated Fetuin A expression in HepG2 cells at 24h and 48h. Notably, TNF- α -mediated suppression of Fetuin A was observed even as early as 12h (our unpublished data). These observations suggest that different cytokines can divergently regulate hepatic Fetuin A expression. Besides, Wang *et al.* also showed the late-phase inflammatory mediators, such as HMGB1, promoted the expression of hepatic Fetuin A which explains the restoration of circulatory Fetuin A levels back to normal limits at or beyond 72h following endotoxemia and sepsis [29]. This negative regulatory effect of TNF- α , IFN- γ , and IL-6 on Fetuin A synthesis also explains the lower Fetuin A levels found in various inflammatory disease conditions including chronic kidney disease, pancreatitis, and rheumatoid arthritis [30]. As a negative acute phase reactant, increased Fetuin A levels could be able to counteract the inflammatory response and confer protection. Accordingly, the lower Fetuin A levels in inflammatory bowel disease, Crohn's disease, ulcerative colitis, and chronic obstructive pulmonary disease were found to be predictor of a poor disease outcome [31, 32]. Similarly, low Fetuin A levels were found to be associated with increased cardiovascular mortality in patients on dialysis [33]. Ma and Feng showed that the administration of Fetuin A conferred dose-dependent protection against lethal endotoxemia and enhanced long-term survival in animals by its inhibitory effects on the release of inflammatory cytokines [31]. Another study also showed that Fetuin A was able to suppress the expression of proinflammatory cytokines in LPS-stimulated macrophages [34]. In further agreement with anti-inflammatory attributes of Fetuin A, it was also found to be neuroprotective and low Fetuin A concentrations were associated with more severe cognitive decline in Alzheimer's disease patients [35].

Concluding remarks

As opposed to the initial understanding of Fetuin A as a circulatory inhibitor of vascular calcification and a predictor of vascular disease, the accumulating evidence rather supports its role as a pleiotropic glycoprotein with diverse effects *viz.* both inflammatory and anti-inflammatory attributes. These paradoxical functions of Fetuin A may relate to its ability to bind with multiple receptors including insulin receptor, TGF- β receptor, and the innate immune TLRs. Therefore, on one hand, Fetuin A as a positive acute phase reactant or an inflammatory molecule plays a pathologic role in the development of insulin resistance. On the other hand, Fetuin A as a negative acute phase reactant or an anti-inflammatory protein may play a protective role during several inflammatory disease conditions such as inflammatory bowel disease, chronic kidney disease, rheumatoid arthritis, pancreatitis, Crohn's disease, Alzheimer's disease, ischemia, cardiovascular disease, chronic obstructive pulmonary disease, endotoxemia, and sepsis. Notably, our recent unpublished data show that Fetuin A may also act as a negative acute phase reactant in obesity/T2D which is a novel aspect of this hepatokine considering the existing paradigm of its role in metabolic disease and this interesting aspect of Fetuin A warrant further studies. The future studies may also investigate whether the Fetuin A expressed by expanding adipose tissue in obesity/T2D has similar interactions or associations with other proteins of pathobiological significance as does the hepatic Fetuin A which is often the predominant form found in the circulation of adult humans. Overall, Fetuin A not only has a predictive significance for disease outcome, but can also serve as a target for therapeutic intervention.

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