J Biochem Technol (2021) 12(3): 59-66
https://doi.org/10.51847/eEhtFAcoMP
ISSN: 0974-2328

Fetuin-A as Metabolic Biomarker in Patients at Higher Risk of Heart Failure

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Received: 12 May 2021 / Received in revised form: 29 August 2021, Accepted: 30 August 2021, Published online: 12 September 2021

Abstract

Heart failure (HF) demonstrates an epidemic-shaped growth worldwide and continues to be a staggering health problem regardless of unprecedented efforts in diagnosis and treatment. Any phenotype of HF is associated with increased mortality and morbidity, and also draws exaggerated expenditures from the health care system. Conventional biological markers, such as natriuretic peptides, cardiac troponins, are recommended to predict, diagnose, and stratify patients at higher risk of HF, but their discriminative potencies appear to be sufficiently distinguished in patients having HF with reduced and preserved (HFpEF) ejection fraction besides in case of metabolic comorbidities including diabetes mellitus and abdominal obesity. The discovery of new biological markers to improve predictive models is considered a promising approach in shaping patient-centered care of HFpEF when conventional stratification models reveal limited efficacy. The narrative review aims to elucidate the discriminative ability of fetuin-A to improve the predictive value of conventional biomarkers models among patients with overt HFpEF. We found that fetuin-A serves multifaceted functions being simultaneously a promoter of cardiac remodeling, vascular calcification, HF, adipose tissue and systemic inflammation, type 2 diabetes mellitus, metabolic syndrome, and abdominal obesity, and also it exerts tissue-protective effects. Fetuin-A was found to be closely associated with cardiovascular disease and HFpEF and revealed an ability to improve conventional biomarkers' model to predict HFpEF occurrence.

Keywords: Heart failure, Biomarkers, Fetuin-A, Prediction, Outcomes

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Introduction

Heart failure is still a leading cause of in-hospital mortality among patients with overt cardiovascular disease (CVD) worldwide (Alzahrani *et al.*, 2019; Groenewegen *et al.*, 2020; Permadi *et al.*, 2020; Virani *et al.*, 2021). Although the estimated prevalence of all HF phenotypes in the general population of developed countries fluctuates around 2.5% (Benjamin *et al.*, 2018; Groenewegen, *et al.*, 2020), these parameters are expected to be substantially higher (about 12%) in older people and those who have two more metabolic comorbidities (Bouthoorn *et al.*, 2018; Del Buono *et al.*, 2020). Despite a steady tendency to declining new cases of HF with reduced ejection fraction (HFrEF) in developed countries as a result of new successful strategies of CVD therapies and wide implementation of current clinical guidelines of HF and CVD treatment and prevention, total incidences of HF demonstrate significant growth due to increase in several occurrences of HF with preserved (HFpEF) and mildly reduced ejection fraction (HFmrEF) especially in women population and patients with type 2 diabetes mellitus and abdominal obesity (Del Buono *et al.*, 2020; Yeo *et al.*, 2021). In developing countries, total incidences of all types of HF showed a continuous increase (Roger, 2013). Nowadays HFrEF and HFpEF affect more than 23 million patients around the world (Orso *et al.*, 2017) 5-year mortality resembles those of many cancers (Bui *et al.*, 2011). Moreover, there is no significant difference in the risk of both 30-day and 1-year readmission rates between patients having HFrEF, HF with mildly reduced ejection fraction (HFmrEF), and HFpEF (Dharmarajan *et al.*, 2015). Minimum half of all discharged patients regardless of HF phenotype were readmitted urgently during one year (Lorenzoni *et al.*, 2018). Finally, the conventional strategy to predict the occurrence of HF and HF-related complications including hospitalization is based on biomarkers' models

predominantly such as natriuretic peptides (NPs) and cardiac troponins (Yancy *et al.*, 2017; Bozkurt *et al.*, 2021).

2017 ACC/AHA/HFSA HF clinical guideline recommends implementing NPs, cardiac troponins, and the next-generation biomarkers of fibrosis and inflammation (soluble suppressor tumorigenicity-2 [sST2], galectin-3) to diagnose, predict, manage and stratify patients with HFrEF / HFpEF (Yancy *et al.*, 2017), whereas current versions of the European Society of Cardiology (ESC) and the UK National Institute for Health and Care Excellence (NICE) guidelines contain strong recommendations to use NPs and cardiac troponins only (Ponikowski *et al.*, 2016; Taylor *et al.*, 2019). However, these conventional biomarkers have revealed serious limitations to predict HFpEF, and also their ability to manage patients with HFpEF especially with metabolic comorbidities was not optimal (Ibrahim & Januzzi, 2018; Roalfe *et al.*, 2021).

Fetuin-A is also known as alpha-2-Heremans-Schmid-glycoprotein is considered a regulatory protein, which plays a pivotal role in bone and adipose tissue metabolism, vascular calcification, metabolic disorders (obesity, insulin resistance, and diabetes mellitus), ischemic stroke, and neurodegenerative diseases (Mori *et al.*, 2011). Fetuin-A has demonstrated an ability to mediate the formation and calciprotein particles stabilization and thereby ensures solubilization of mineral and rapid clearance from circulation by macrophages of the mononuclear phagocyte system preventing pathological ectopic calcification (Herrmann *et al.*, 2012). In addition, there is strong evidence that suggests engagement of fetuin-A in the development of adverse cardiac remodeling, participation in endogenous repair system, endothelial and vascular integrity, and skeletal muscle myopathy (Albert & Tang, 2018). Indeed, fetuin-A emerges locally counteracting macrophage polarization and attenuates inflammation and fibrosis preserving cardiac and kidney function (Rudloff *et al.*, 2021). Although fetuin-A exerts a negative role in the development and progression of insulin resistance, abdominal obesity, and diabetes mellitus, it is considered a cardiac and vascular protective factor having a possible predictive value in HFpEF (Icer & Yıldıran, 2020). The narrative review aims to elucidate the discriminative ability of fetuin-A to improve the predictive value of conventional biomarkers models among patients with overt HFpEF.

Materials and Methods

To satisfy the keywords of this study and for English publications, the bibliographic database of life science and biomedical information MEDLINE, Medline (PubMed), EMBASE, the Cochrane Central, and the Web of Science were searched. We used the following keywords [heart failure]; [HFrEF]; [HFmrEF]; [HFpEF]; [fetuin-A]; [alpha-2-HS-glycoprotein]; [cardiovascular risk], [cardiovascular risk factors], [metabolic comorbidities]; [cardiac biomarkers]; [circulating biomarkers]; [stratification]; [prognosis]. All authors independently selected articles, evaluated the quality of the data, presentation, and interpretation correspondence with the study's main idea, and constructed the final list of the references.

Biological Role and Function of fetuin-A in Physiological and Pathological Conditions

Fetuin-A is a 64-kDa multifunctional glycoprotein that is synthesized in the hepatocytes and adipose tissue (Icer & Yıldıran, 2021). It exists in circulation in cell-free form and also it can be packaged into extracellular vesicles originated from hepatocytes and adipocytes to be transferred from mother cells to target cells. The biological role and function of fetuin-A in physiological and pathological conditions are reported in **Figure 1**.

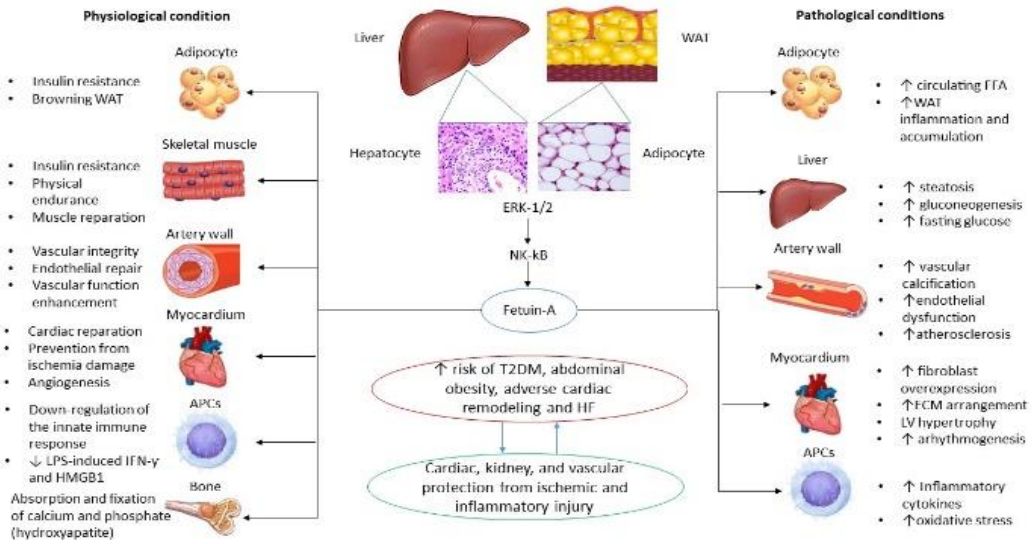

Figure 1. Biological role and function of fetuin-A in physiological and pathological conditions

Abbreviations: APCs, antigen-presenting cells; LPS, lipopolysaccharide; IFN-γ, interferon; FFA, free fatty acids; ERK-1/2, extracellular signal-regulated kinase 1/2; ECM, extracellular matrix; LV, left ventricle; HMGB1, high mobility group box 1 protein; T2DM, type 2 diabetes mellitus; HF, heart failure; WAT, white adipose tissue.

In physiological conditions, fetuin-A acting as an endogamous inhibitor of ectopic calcification supports the absorption and fixation of calcium and phosphate in the form of stable mineral complexes with hydroxyapatite substituting it with carbonate and thereby enhances bone mineralization (Herrmann *et al.*, 2020). In addition, fetuin-A connecting with insulin receptors leading to insulin resistance, glucose tolerance, and an increase in free fatty acids in circulation (Stefan & Häring, 2013). Yet, fetuin-A was found to be a pro-inflammatory mediator that stimulates and potentiates lipopolysaccharide-related response of antigen-presenting cells regarding their production of interferon-gamma and high mobility group box 1 protein, while depending on a type of stimulation fetuin-A can be also an anti-inflammatory mediator. It has been suggested that fetuin-A could be a key player in the enhancement of vascular integrity through mediating vascular reparation and endothelial function that is a result of mobbing and differentiation of endothelial progenitor cells (Zeng *et al.*, 2016; Berezin, 2017). Probably, its protective ability can be explained through potentiation of residence cells' proliferation and enhance angiopoietins' synthesis (Rasul *et al.*, 2012; Tan *et al.*, 2021). Contrary, deficiency of fetuin-A was found to be a profound inductor of pro-fibrotic transforming growth factor-beta and downstream collagen and fibronectin mRNA synthesis in myocardium and kidney parenchyma (Merx *et al.*, 2005). Overall, the biological effects of fetuin-A are translated through three main signal ways **(Figure 2)**. First, fetuin-A exerts an inhibitory signal to the insulin receptor tyrosine kinase which leads to reduced phosphorylation of the insulin receptor (Icer & Yıldıran, 2021). Yet, fetuin-A can significantly suppress basal and insulin-stimulated phosphorylation of E26 transformation-specific like-1 protein signaling, a transcription factor phosphorylated and activated by a mitogen-activated protein kinase, without influencing insulin-stimulated translocation of GLUT-4 or transmembrane glucose transport (Chen *et al.*, 1998). A secondary effect might also be of interest as fetuin-A can aggravate insulin resistance via toll-like receptor 4 subsequently affecting white adipose tissue inflammation and finally decreasing sensitivity to insulin signaling. This pathway might also be influenced by an altered expression of adiponectin with its anti-inflammatory effects and functions on insulin-sensitization. Third, fetuin-A can up-regulate an activity of the ERK 1/2 / NK-kB signaling pathway that leads to an increase in proliferative activity of cells including macrophages, mononuclear, osteoblasts, fibroblasts, and several residence cells, as well as the capability of different cells to release extracellular vesicles (Berezin, 2017; Berezin & Berezin, 2021).

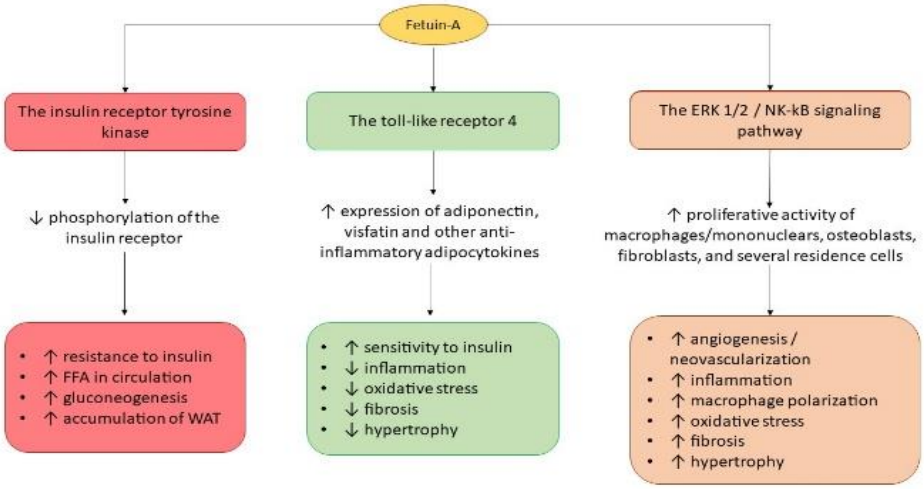

Figure 2. Molecular mechanisms of fetuin-A-related biological effects

Abbreviations: FFA, free fatty acids; NK-kB, ERK-1/2, extracellular signal-regulated kinase 1/2.

In healthy volunteers, the serum levels of fetuin-A are low, although there is individual biological variability of its concentrations depending on age and nutritive status. Because fetuin-A is an essential inhibitor of vascular calcification and a potential promoter of bone mineralization, its level in the general population was found to be positively correlated with bone mineral density regardless of the gender of individuals (Chen *et al.*, 2016). Elevated circulating fetuin-A levels were noticed in several metabolic conditions, including impaired fasting glucose, abdominal obesity, metabolic syndrome, type 2 diabetes mellitus, nonalcoholic fatty liver disease, and HF (Ix *et al.*, 2009; Laughlin *et al.*, 2013; Jirak, *et al.*, 2019; Dogru *et al.*, 2021). The levels of fetuin-A in plasma were associated with its AHSG-T256S gene polymorphisms (Cozzolino *et al.*, 2007; Mohammadi-Noori *et al.*, 2020). Although the high levels of fetuin-A were associated with increased mortality in the general population predominantly related to CVD occurrence, there was not found a significant interrelation between AHSG-T256S gene polymorphism and risk of premature death due to strict similarity in polymorphism distribution of the AHSG gene in patients with CVD compared with the normal population (Cozzolino *et al.*, 2007; Fisher *et al.*, 2009).

Fetuin-A and Ectopic Cardiac and Vascular Calcification

Evidence shows that fetuin-A is a key modulator for minerals absorption by vascular smooth muscle cells, which might then limit ectopic calcification by the reduction cleavage of caspases

and apoptosis, which are considered as crucial elements for vascular calcification (Schoppet *et al.*, 2015; Testuz *et al.*, 2017; Carracedo & Bäck, 2018; Peeters *et al.*, 2018). These findings have increased clinical significance, because vascular calcification may facilitate CVD and HF occurrence independently of other conventional risk factors.

Elevated levels of fetuin-A influenced ectopic calcification including accumulation of calcium in the vascular wall and cardiac valve leaflets and chorda (Carracedo & Bäck, 2018). Schoppet, M., *et al.* (2015) reported that the co-existence of low serum fetuin-A levels and heavy smoking elevated fibroblast growth factor 23 levels or low serum dickkopf-1 levels were associated with a higher risk of abdominal aorta calcification independently of renal function impairment. The meta-analysis of seven clinical studies that enrolled 2283 patients with aortic valve stenosis and 1549 controls, has revealed that aortic valve stenosis patients had significantly lower circulating levels of fetuin-A when compared with control subjects (Di Minno *et al.*, 2017). In the prospective COFRASA/GENERAC cohort serum fetuin-A levels were not corresponded to hemodynamic or anatomic aortic stenosis progression, while its capacity to reduced activity of ectopic calcium deposition was defined (Kubota *et al.*, 2018). Probably, these findings might explain why previous results came from numerous studies did not support the hypothesis that if cardiometabolic risk factors, such as metabolic syndrome and type 2 diabetes mellitus, may play a pivotal role at the early phase of calcific aortic valve stenotic disease (Testuz, *et al.*, 2017; Peeters *et al.*, 2018).

There is strong evidence regarding the fact that patients with chronic kidney disease have a higher risk of ectopic calcification particularly related to elevated fetuin-A levels in patients of different ages (Hamano *et al.*, 2010; Makulska *et al.*, 2019). Makulska, *et al.* (2019) reported that circulating levels of fetuin-A negatively correlated with systolic and diastolic blood pressure, pulse wave velocity indexed to height, intact parathyroid hormone, high sensitivity C-reactive protein, and total levels of cholesterol in children with chronic kidney disease. At the same time, Ossareh *et al.* (2020) did not find any correlation between the levels of fetuin-A and the risk of vascular calcification in hemodialysis patients. In contrast, Mutluay *et al.* (2019) reported that lower concentrations of fetuin-A were associated with higher vascular calcification scores, intima-media thicknesses of the common carotid arteries, high sensitivity C-reactive protein levels, and lower body mass index and albumin. In addition, the investigators suggested that a deficiency of fetuin-A may be a crucial element for the malnutrition-inflammation-atherosclerosis-calcification syndrome (MIAC) in different stages of chronic kidney disease (Mutluay *et al.*, 2019). The FAVORIT (Folic Acid for Vascular Outcome Prevention in Transplantation) trial, which has been enrolled cohort of 685 chronic, stable kidney transplant recipients, increased levels of fetuin-A were found to be a powerful predictor for newly CVD incidences or recurrent CVD events (hazard ratio [HR] 2.25; 95% confidence interval [CI] 1.38-3.69) (Bostom *et al.*, 2018). Finally, it has been suggested that high fetuin-A levels appeared to be a powerful protective factor against vascular calcification in patients with chronic kidney disease including regular hemodialysis individuals (Muzasti & Loesnihari, 2019).

Fetuin-A and Metabolic Conditions at Higher Risk of CVD

Accumulating evidence suggests that elevated fetuin-A level is also caused by impaired fasting glucose and dyslipidemia mainly related to hypertriglyceridemia, which is best fitted to abdominal obesity and type 2 diabetes mellitus. In this context, it is extremely important to notice that fetuin-A can exert skeletal muscle wasting syndrome and accelerate atherosclerosis probably through its pro-inflammatory, pro-atherosclerosis activity and stimulation of macrophage phenotype changes to shape foam cells in the vascular wall (Klöting *et al.*, 2010). Therefore, the putative role of fetuin-A in white adipose tissue inflammation has been recently established (Ix *et al.*, 2009).

Overall, there is uncertainty in predictive values of fetuin-A levels for CAD, and atherosclerosis-related conditions, while numerous studies have shown that plasma fetuin-A levels were independently associated with a higher risk of developing type 2 diabetes mellitus and metabolic syndrome (Jensen *et al.*, 2013; Sun *et al.*, 2013). However, numerous investigators reported that high levels, as well as low levels of fetuin-A, have yielded sufficiently different relations to CVD risk depending on the presentation of overt type 2 diabetes mellitus. For instance, Jensen *et al.* (2013) have established that higher fetuin-A positively correlated to lower CVD risk among persons without type 2 diabetes. Nevertheless, fetuin-A expression and levels were inversely regulated in patients with acute myocardial infarction compared to a control group with excluded CVD (Schernthaner *et al.*, 2017).

Vörös *et al.* (2011) reported that serum levels of fetuin-A did not correlate significantly with adiponectin, leptin, resistin, C-reactive protein, and tumor necrosis factor-α I patients with overt CAD. Yet, investigated noticed that patients having abdominal obesity and type 2 Diabetes Mellitus had higher concentrations of fetuin-A than those who had normal or near-normal body mass index or without type 2 Diabetes Mellitus (Vörös *et al.*, 2011). Finally, the authors concluded that fetuin-A is involved in atherosclerosis more likely through various metabolic pathways, such as insulin resistance, visceral adipose tissue accumulation, and adipocyte dysfunction, than by inflammation in CAD patients with post-myocardial infarction. Interestingly, among 3514 participants who underwent routine echocardiography with the moderate-to-high cardiometabolic risk associated with mild-to-moderate abdominal obesity and who were included in the Framingham Heart Study, there was not found any echocardiographic trait associated with fetuin-A changes in serial measures (von Jeinsen *et al.*, 2018).

Circulating Levels of fetuin-A and Non-Pharmacological / Pharmacological Interventions

Previous observational and clinical studies have yielded that several interventions, such as diet, weight loss, intensive aerobic exercise, metformin, and pioglitazone appeared to be effective for reducing circulating levels of fetuin-A that was closely accosted with improvements in insulin sensitivity and circulating

adiponectin (Mori *et al.*, 2008; Malin *et al.*, 2014; Jirak *et al.*, 2019). In contrast, vitamin D supplementation did not influence the calcification inhibitors fetuin-A and non-phosphorylated non-phosphorylated undercarboxylated matrix gla protein in patients with advanced HF (Zittermann *et al.*, 2019). Thus, the impact of various interventions on circulating levels of fetuin-A is not fully understood and needs large clinical studies to be thoroughly elucidated.

Fetuin-A in Heart Failure

Unlike HFrEF, HFmrEF and HFpEF are more frequently associated with metabolic comorbidities, female gender, older age, and non-ischemic etiology. It has been postulated that some hepatokines, adipocytokines, and myokines, which are synthesized and released in circulation in patients with metabolic comorbidities mainly type 2 diabetes mellitus, metabolic syndrome, and abdominal obesity, can play a crucial role in the occurrence of HFpEF and its transformation into HFmrEF and HFrEF (Berezin *et al.*, 2021). Probably, fetuin-A is a promising biomarker for risk stratification of the patients suspected of incident HFpEF, because fetuin-A is a factor contributing to the pathogenesis of HFpEF in these patients. In addition, previous clinical studies have yielded evidence of the concise predictive ability of fetuin-A for CVD mortality (Cozzolino *et al.*, 2007; Bostom *et al.*, 2018).

There is strong evidence regarding the fact that the serum fetuin-A levels are significantly decreased in the chronic HF patients compared to the healthy volunteers and also they were associated with impaired diastolic and systolic functions of the left ventricle regardless of etiology of HF (Keçebaş *et al.*, 2014). Therefore, fetuin-A has demonstrated a powerful discriminative potency to differentiate HFpEF from HFrEF, because the circulating levels of the biomarker were significantly lower in HFpEF when compared with those who had HFrEF (Keçebaş *et al.*, 2014). Lichtenauer *et al.*, (2018) have established that patients with ischemia-induced HF evidenced lower fetuin-A levels compared to non-ischemic HF patients. Yet, sarcopenic patients with HFrEF had higher levels of fetuin-A in comparison with non-sarcopeninc HFrEF (Chang *et al.*, 2015). In addition, sarcopenic patients with left ventricular hypertrophy and HFpEF had significantly lower fetuin-A levels and higher levels of intact parathyroid hormone (Chang *et al.*, 2017). However, it remains uncertain whether fetuin-A can improve the discriminative potency of NPs and high sensitive cardiac troponins in patients with established HF.

Conclusion

Low levels of circulating fetuin-A are an independent predictor of arterial stiffness, ectopic calcification, cardiac fibrosis, diastolic and systolic dysfunction, impaired tolerance to glucose, adipose tissue accumulation, and insulin resistance that may constitute an underestimated cardiovascular risk factor that contributes to incident CVD and HF failure. Being completely independent of conventional CVD risk factors elevated levels of fetuin-A are considered as adaptive responses to prevent adverse cardiac remodeling, kidney fibrosis, vascular calcification, and accelerating atherosclerosis. The predictive abilities of fetuin-A for HFpEF and cardiovascular mortality require deeper investigation in large clinical studies with simultaneous comparisons of dynamic changes of fetuin-A serum levels with other surrogate biomarkers of HF-related outcomes, such as NPs and high sensitive cardiac troponins.

Acknowledgments: All authors met the authorship criteria according to the latest ICMJE guidelines.

Conflict of interest: None

Financial support: None

Ethics statement: None

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