Review

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Interaction of fetuin-A with obesity related insulin resistance and diabetes mellitus

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Abstract: Fetuin-A (FetA) is a glycoprotein primarily synthesized in hepatocytes, but recent studies have demonstrated that it is also synthesized in adipose tissue, classifying it as both a hepatokine and an adipokine. FetA has been shown to play a role in the regulation of glucose and lipid metabolism, thereby controlling overall body homeostasis. Elevated serum FetA levels have been reported in obesity, and this increase has been associated with insulin resistance (IR) and type 2 diabetes mellitus (T2DM). Therefore, investigating the molecular mechanisms underlying the variations of FetA in obesity and obesity-related metabolic diseases is crucial for the development of preventive strategies. Studies examining the molecular pathways involved in the relationship between FetA, adipose tissue, IR, and T2DM have shown that deviations in the expression of transcription factors such as nuclear factor erythroid-related factor 2 (Nrf2), nuclear factor kappa B (NF-κB), and peroxisome proliferator-activated receptor γ (PPARγ) in pancreatic, adipose, and liver cells contribute to the increase in FetA and the development of IR and/or T2DM. Consequently, future studies aimed at suppressing transcription factors in the signaling pathways that increase FetA expression, and identifying new agents that can regulate FetA secretion, could be therapeutically beneficial in treating obesity and obesity-related complications.

Keywords: fetuin-A; obesity; insulin resistance; adipose tissue; type 2 diabetes mellitus

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Introduction

Fetuin-A (FetA), also known as α2-Heremans-Schmid glycoprotein (AHSG), is a multifunctional protein [1]. Although this protein was first identified in 1944, its structure was elucidated and named by Heremans, Schmid, and Bürgi in 1961 [2–5]. However, its physiological importance has only become increasingly discussed in the last two decades.

FetA is considered a hepatokine because it is primarily synthesized by hepatocytes and secreted into the bloodstream to exert its metabolic effects [6]. Recent studies suggest that the liver plays a role in regulating glucose and lipid metabolism through FetA and may control overall physiological energy homeostasis [7, 8]. It has been shown that FetA is also secreted by various tissues other than the liver, including adipose tissue. Following the identification of FetA secretion from adipose tissue along with the liver, FetA has been recognized as both a hepatokine and an adipokine [9, 10]. FetA has been reported to mediate the recruitment of macrophages to adipose tissue [11] and to increase the expression of pro-inflammatory cytokines such as IL-6 and TNF-α while decreasing adiponectin expression [12].

Previous studies have highlighted that FetA is involved in several significant metabolic pathways, including inflammation, cell growth, energy homeostasis, and adipocyte metabolism [13–15]. It has been proposed that FetA plays a crucial role in various physiological and pathological processes, including insulin resistance, inflammation, vascular calcification, lipid metabolism, cell growth, and bone metabolism [9, 16–20]. Some studies have reported that FetA acts as a chaperone to prevent systemic calcification and to reduce the risk of coronary artery disease and kidney stone formation [21, 22]. Increased serum FetA concentrations have been associated with obesity, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, type 2 diabetes mellitus (T2DM), and polycystic ovary syndrome, indicating its relevance to metabolic processes [23].

As evidenced by recent studies, understanding the molecular mechanisms and metabolic pathways associated with obesity, insulin resistance (IR), and T2DM has become increasingly important, particularly given the rising prevalence of these conditions in developed societies. Identifying

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these pathophysiological processes is crucial for early detection and the development of preventive strategies. The aim of this review is to comprehensively examine the role of FetA in the development of obesity and insulin resistance/type 2 diabetes mellitus and to explore potential preventive mechanisms.

Structure and adipose tissue release of fetuin-A

FetA is a glycoprotein of approximately 64 kDa, consisting of a 282-amino-acid A chain, a 182-amino-acid B chain, and a 40-amino-acid phosphorylation site along with a binding peptide chain [9, 23]. In human circulation, FetA exists in both phosphorylated (approximately 20 %) and dephosphorylated (approximately 80 %) forms [24, 25]. Haglund et al. reported using mass spectrometry that FetA in circulation is phosphorylated at Ser120 and Ser312, with a predominant phosphorylation at Ser312, approximately 20 % [25]. Additionally, FetA contains two N-linked glycosylation sites (Asp138 and Asp158) and two O-linked glycosylation sites (Thr238 and Thr252), which are thought to be important for explaining FetA's heterogeneity observed in humans [19].

Adipose tissue is one of the key tissues, along with the liver, that determines circulating FetA concentrations [26–29]. Both visceral and subcutaneous adipose tissues have the capacity to express and secrete FetA [11, 26]. However, visceral adipose tissue secretes more FetA compared to subcutaneous adipose tissue and is reported to be more sensitive to nutritional and physiological changes. FetA secreted from adipose tissue has been shown to increase macrophage infiltration and stimulate pro-inflammatory responses [11, 26]. A study conducted in individuals with metabolic syndrome reported that as the proportion of adipose tissue increased, FetA secretion also increased, correlating with HOMA levels [30]. A recent study indicated that FetA regulates the activation of silent information regulator 1 (SIRT) and AMP-activated protein kinase (AMPK) [15]. Another study demonstrated the significant role of toll-like receptor 4 (TLR4) in age-related adipose tissue inflammation [31]. In a clinical study conducted by Stefan et al. in 2006, it was reported that plasma levels of FetA are associated with insulin resistance and that FetA levels increase with hepatic fat accumulation. They also indicated a direct relationship between FetA, fatty liver, and insulin resistance, highlighting its pathological role [32]. Epidemiological studies have shown that high serum FetA levels are associated with obesity, T2DM, and metabolic syndrome [33–37].

Fetuin-A and obesity

One of the topics investigated in studies exploring the increasing global prevalence of obesity and its metabolic consequences is the relationship between FetA and obesity. The primary aim of researching the relationship between FetA and obesity is to identify the molecular pathways involved in the development of obesity and to uncover methods for preventing obesity [38–40].

Studies exploring the connection between FetA and obesity have centered on adipose tissue lipid storage, inflammation, and insulin resistance. Experimental human studies, animal models, and cell culture studies have examined the expression of FetA, its serum levels, and its responses to various treatments and medications. Elevated circulating levels of FetA have been consistently observed in conditions such as obesity, metabolic syndrome, T2DM, and cardiovascular events [41–44]. Some studies have indicated that increased serum FetA levels contribute to hepatic insulin resistance and heighten the risk of obesity [45]. Recent studies have suggested that FetA may induce insulin resistance by inhibiting endogenous insulin receptor tyrosine kinase activity, thereby promoting obesity [46, 47]. One research on phosphorylated FetA has shown that its presence can hinder glucose transport protein 4 (GLUT-4) translocation, glucose uptake into cells, and glycogen synthesis in skeletal muscle, further increasing obesity risk [19, 48].

Ren et al. demonstrated that obese individuals with a body mass index (BMI) >30 kg/m^2 experienced a statistically significant decrease in serum FetA levels following an 8–10 % reduction in body weight [19]. Similarly, Ix et al. found a positive correlation between serum FetA levels and visceral adipose tissue in relation to body fat percentage [49]. Studies on fetuin knockout (KO) mice have shown these animals to be resistant to weight gain and exhibit lower body fat percentages [50].

Effects of physical exercise and weight control on FetA levels

The results regarding the effects of physical exercise on circulating FetA are unclear. Variations in the content and duration of exercise programs might significantly contribute to this uncertainty. Malin et al. (2014) examined physical exercise therapies frequently recommended for obesity treatment and reported that exercise-induced reductions in serum FetA levels improved hepatic insulin sensitivity [45]. Another study demonstrated that three months of aerobic

exercise led to a decrease in serum FetA levels [51]. Khadir et al. evaluated the relationship between physical exercise and FetA levels and showed that physical exercise reduced plasma FetA levels [27]. It was also reported that an eight-week regimen of garlic extract and aerobic exercise reduced FetA levels and inflammation in rats fed a high-fat diet (HFD), with the combination being more effective [52]. Previous studies have shown that chronic exercise programs reduce serum FetA levels and induce adiponectin expression in humans [15], leading to increased weight loss and improved metabolic control due to decreased inflammatory cytokines in the liver and muscle [53]. This effect is suggested to occur through the suppression of FetA expression via AMPK and nuclear factor kappa B (NF-κB) [8]. It has been reported that FetA can modulate the expression of SIRT1 and AMPK, which play significant roles in adipocyte metabolism, thereby reducing the expression of peroxisome proliferator-activated receptor γ (PPARγ) and adiponectin, which regulate energy homeostasis [15]. Studies investigating the effects of dietary interventions such as low-calorie diets on serum FetA levels have yielded mixed results. While most studies suggest that calorie restriction leads to decreased FetA levels [54, 55], some studies have not found a significant relationship between dietary calorie restriction and FetA levels [56].

FetA and metabolic syndrome

Serum FetA levels have been shown to be associated with metabolic syndrome [57]. In a study involving obese individuals with metabolic syndrome, niacin treatment was reported to reduce serum FetA levels [58]. Additionally, a study conducted in 2018 demonstrated that FetA levels are elevated in obesity and are associated with metabolic diseases [59]. Hüttl et al. highlighted the beneficial effects of empagliflozin on hepatic lipid metabolism and lipid accumulation, independent of obesity. The study reported reductions in lipogenesis, changes in cytochrome P450 proteins, and decreased FetA levels [60]. High serum FetA levels in overweight/obese individuals, along with low adiponectin and free leptin levels, have been found to particularly increase the risk of myelodysplastic syndromes (MDS) [61].

Effects of curcumin and/or capsaicin treatment on FetA levels

In our recent study, we observed for the first time in the literature that an 8-week administration of curcumin (100 and 400 mg/kg bw/day) in rats fed with a HFD (5.1 kcal/g diet) resulted in a decrease in the elevated serum FetA levels due to the antilipidemic effect of curcumin (100 and 400 mg/kg bw/day) [62]. In a clinical study, we identified elevated serum levels of FetA, arginase-1, and leptin in obese individuals, while adiponectin levels were decreased. Additionally, FetA was found to be positively correlated with HOMA-IR in this study [63]. In another study using a different animal model, we found that increased liver FetA expression in rats fed HFD and curcumin/capsaicin was particularly reduced in the livers of rats treated with curcumin [64].

All these studies demonstrate that FetA is closely associated with obesity-related weight gain and body fat percentage and is influenced by dietary, physical, or interventional treatments aimed at weight management.

Fetuin-A and insulin resistance

Despite incomplete understanding the pathway of FetA synthesis is regulated in the organism, mounting evidence suggests its significant association with metabolic diseases, prompting extensive investigation into its relationship with insulin sensitivity, glucose tolerance, and circulating lipid levels. Numerous studies highlight the pivotal role of FetA, a hepato-adipokine, in obesity-induced insulin resistance [65]. Serum FetA levels have been identified as a biomarker of obesity and a crucial determinant of insulin resistance [66, 67]. Increasing evidence links elevated circulating FetA levels with heightened insulin resistance [68–71]. FetA acts as an endogenous inhibitor of tyrosine kinases, binding to the extracellular domain of insulin receptors and impeding receptor autophosphorylation, thereby diminishing insulin sensitivity, glucose utilization, and ultimately increasing the risk of type 2 diabetes [69–71].

Trepanowski et al. reported that FetA plays a role in regulating the insulin signaling pathway and acts as an inhibitor of insulin resistance in muscle, liver, and adipose tissue [65]. In conditions of hyperlipidemia, elevated FetA levels have been shown to shift macrophage polarization from an anti-inflammatory to a pro-inflammatory subtype, exacerbating adipose tissue inflammation and promoting insulin resistance [11]. Additionally, FetA is implicated in altering the functional effects of key metabolic regulators, Sirtuin 1 and AMPK, in the adipocytes of HFD-fed mice [15]. FetA has been shown to directly induce insulin resistance [72], suppress the secretion of adiponectin from adipocytes [13], and cause damage to pancreatic β-cells [73]. Supporting evidence comes from a study where serum FetA levels in older individuals were examined over a 5-year period and found to be associated with increased fat mass [74]. Numerous experimental studies in humans have reported

that elevated circulating FetA levels are associated with fatty liver and insulin resistance [75]. Consistent with these findings, *in vitro* studies and animal models have demonstrated that increased plasma FetA levels are related to insulin resistance when circulating free fatty acids are elevated [76, 77].

Studies elucidating the molecular mechanisms linking FetA to insulin resistance have focused on pancreatic, adipose and liver tissues, proposing various hypotheses for the development of insulin resistance:

Pancreas

FetA has been demonstrated to suppress insulin secretion through c-Jun N-terminal kinase and Ca^{2+}-dependent signaling pathways in pancreatic β-cells responsible for insulin secretion [78, 79]. It has been demonstrated that obese mice exhibit elevated levels of free fatty acids (FFA) and FetA in circulation, and studies suggest that these two factors collaborate to impair pancreatic β-cell function [66, 80–82]. FFA and FetA have been identified as critical contributors to pancreatic β-cell dysfunction, with FetA, whose serum levels increase due to obesity, shown to reduce glucose sensitivity in pancreatic β-cells and promote low-grade inflammation [73, 78, 81, 82]. It has been reported that this mechanism occurs in pancreatic β cells as a result of lipid accumulation within the cells and the stimulation of transcription factors such as FFA and FetA, as well as nuclear factor erythroid 2-related factor 2 (Nrf2) and cluster of differentiation 36 (CD36). The study also stated that insulin secretion could be induced by suppressing Nrf2 [66]. The development of FFA and FetA-mediated IR in pancreatic β cells is summarized in Figure 1.

In a different study, Mukhuty et al. suggested that islet cytokine release and macrophage accumulation increased in HFD-fed mice, leading to polarization and decreased β-cell function. They demonstrated the relationship between islet inflammation and FetA (Figure 2). This study was supported by an *in vitro* study using MIN6 cells, which showed that palmitate-mediated FetA secretion stimulates the polarization and migration of RAW 264.7 cells. This, in turn, suppresses insulin secretion, negatively affecting MIN6 cell function [82].

Adipose tissue

Obesity-induced insulin resistance is considered the main cause of type 2 diabetes. Increased fat accumulation in adipose tissue and signaling pathways that suppress the use of excess stored lipids for energy reduce insulin sensitivity.

Studies have shown that TLR4 can induce inflammatory signaling and insulin resistance in adipose cells and macrophages. It has been reported that FetA activates this receptor by forming a complex with fatty acids [67, 83]. *In vitro* studies have demonstrated that in adipocytes, FetA acts as an adapter protein for saturated fatty acids (SFA) and may explain the contribution of SFA to TLR4 signaling activation and insulin receptor tyrosine kinase inhibition [84–86]. It has been shown that in adipose tissue, FetA stimulates adipocytes, accelerating the entry of macrophages, which in turn stimulates the secretion of proinflammatory cytokines [87]. This situation leads to the development of insulin resistance. At this point, it is crucial that PPARγ, an important transcription factor that regulates energy production and lipid utilization, also regulates many genes involved in lipid and carbohydrate metabolism [88, 89]. Phosphorylation of PPARγ at residue Ser273 inactivates this transcription factor, disrupting the regulation of energy homeostasis. This mechanism was described by Choi et al. and Banks et al. [90, 91]. When activated via the MEK-ERK-Cdk5 signal transduction pathway, PPARγSer273 becomes phosphorylated, and this phosphorylation is linked to insulin

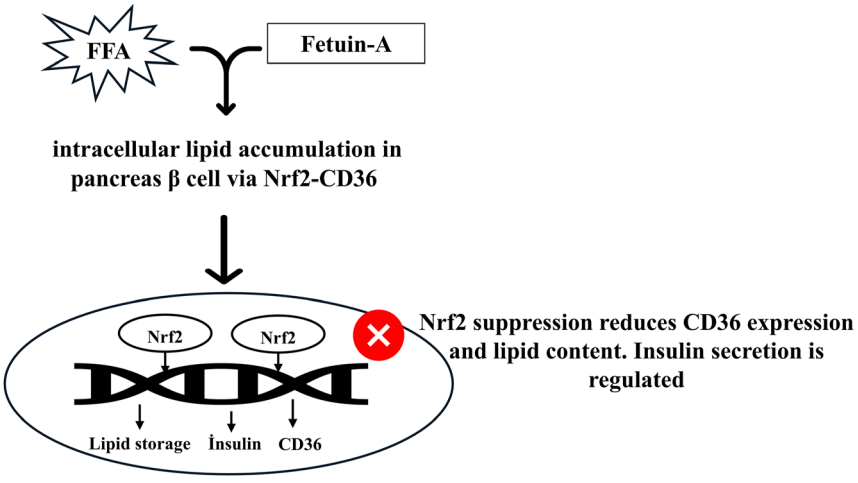

Figure 1: Elevated levels of free fatty acids (FFAs) and fetuin-A (FetA), along with the nuclear factor erythroid 2-related factor 2 (Nrf2) and cluster of differentiation 36 (CD36), are present in the circulation and lead to lipid accumulation in pancreatic β cells, impairing insulin secretion. Suppression of Nrf2 can help reverse this condition.

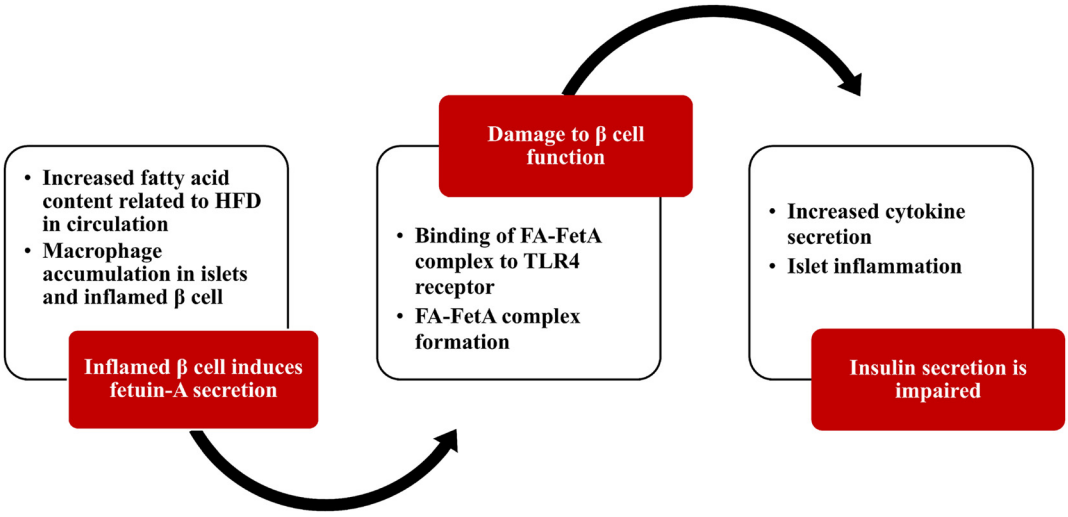

Figure 2: A high-fat diet and elevated levels of fetuin-A (FetA) lead to macrophage polarization and inflammation in pancreatic β cells, resulting in impaired insulin secretion.

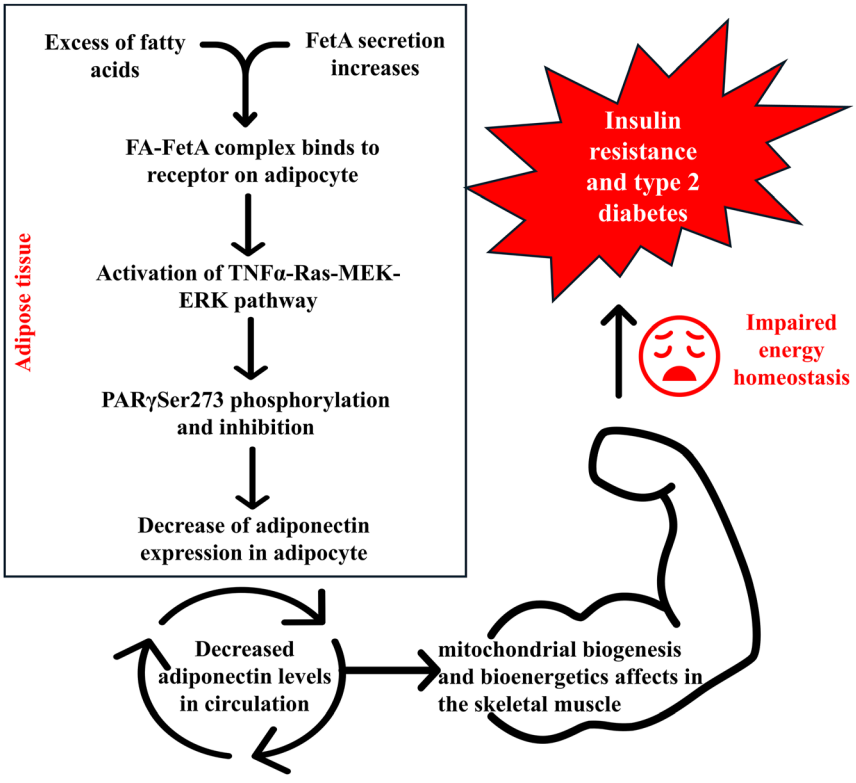

Figure 3: Elevated levels of fatty acids and fetuin-A (FetA) in adipose tissue lead to phosphorylation and inhibition of PPARγSer273 through the MEK-ERK-Cdk5 signaling pathway. This results in decreased circulating adiponectin levels and may contribute to insulin resistance and type 2 diabetes by disrupting the mitochondrial energy mechanism in skeletal muscle.

resistance. It has also been shown that suppression of this phosphorylation leads to an increase in insulin sensitivity (Figure 3) [91].

Liver

FetA has been reported to inhibit insulin receptor tyrosine kinase in the liver and skeletal muscle [92]. FetA is similar in amino acid sequence to insulin receptor tyrosine kinase and type II transforming growth factor-β (TGF-β) receptor, and therefore may have an inhibitory effect on the insulin signaling pathway. It has an antagonistic effect with TGF-β [46, 93]. In their study, Zhao et al. reported that F-box and WD repeat domain-containing 7 (FBXW7), an E3 ubiquitin protein ligase, is an important regulator of FetA expression in the liver. They showed that FBXW7 stimulates insulin

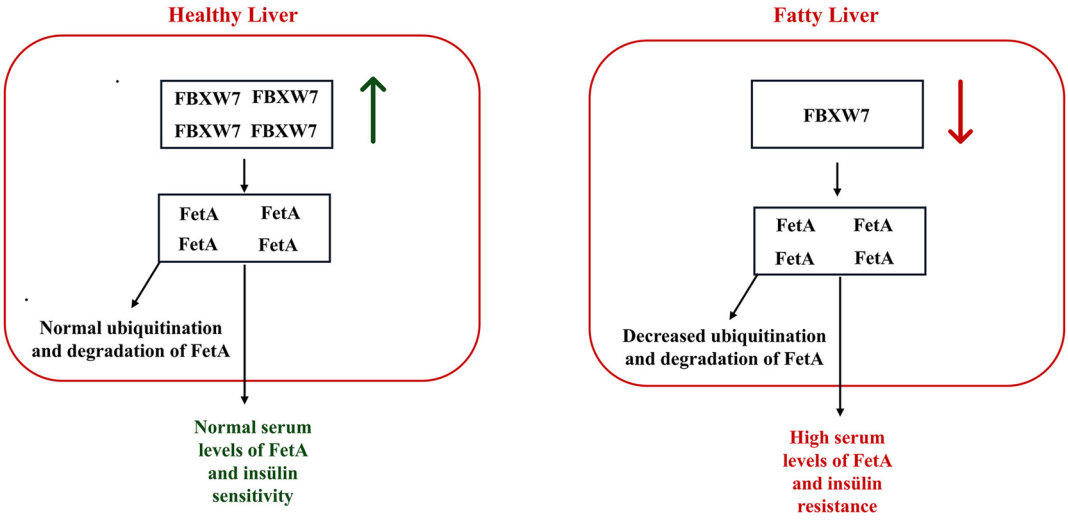

Figure 4: In a healthy liver, F-box and WD repeat domain containing 7 (FBXW7) regulates fetuin-A (FetA) expression and insulin sensitivity. A reduction in FBXW7 levels in fatty liver leads to increased fetuin-A expression and the development of insulin resistance.

resistance and hyperglycemia [94]. Increased FBXW7 expression in the liver of obese individuals has been shown to have beneficial metabolic effects, protecting against hyperglycemia, insulin resistance, and glucose intolerance [94]. This mechanism is summarized in Figure 4.

Ou et al. showed that FetA levels increased in patients with NAFLD and type 2 diabetes. In this study, endoplasmic reticulum (ER) stress increased *in vitro* with high glucose and palmitate application, stimulating FetA expression. This situation resulted in the development of insulin resistance. As a possible mechanism, it has been reported that hyperlipidemia and hyperglycemia increase ER stress and cause protein misfolding. Phosphorylation of PERK, eIF2α, and MAPK (as shown in Figure 5) indicates that FetA protein expression increases in hepatic cells with ERK1/2 activation. The increase in FetA is associated with the development of insulin resistance [95].

Recent studies show that the phosphorylation of FetA plays an important role in its inhibitory effect on insulin signaling [19, 48]. It has been reported that phosphorylated FetA (pFetA) is the physiologically active form of the inhibitor and is primarily secreted by hepatocytes under conditions of insulin resistance or hyperglycemia [5]. Kothari V et al. examined the difference between serum FetA and pFetA and demonstrated that elevated serum glucose levels increased the secretion of pFetA but not FetA [5]. In their

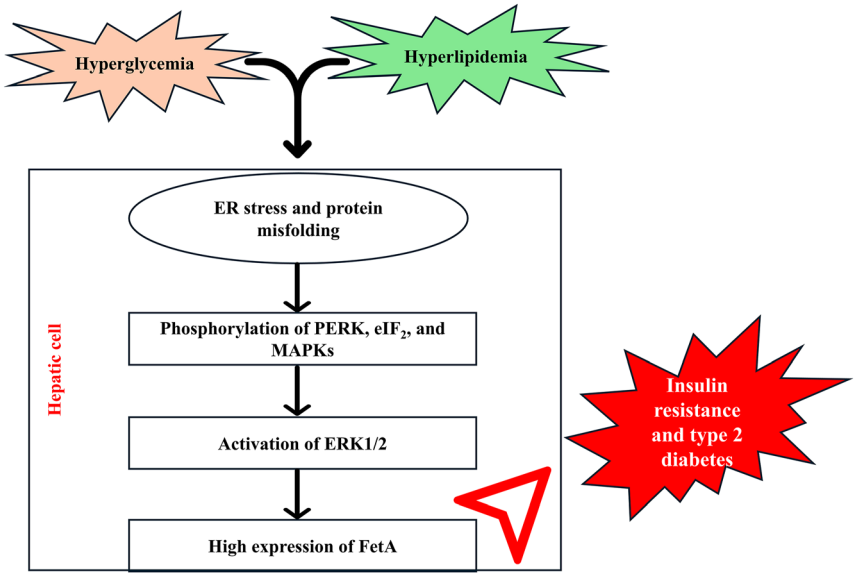

Figure 5: Elevated glucose and lipid levels increase endoplasmic reticulum (ER) stress by inducing protein misfolding in hepatocytes. This results in the activation of PERK, phosphorylation of eIF2α and MAPK, activation of ERK1/2, and subsequent increase in fetuin-A (FetA) expression. Higher fetuin-A levels are associated with insulin resistance and type 2 diabetes.

study, Ren et al. showed that the phosphorylation status of FetA at Ser312 is associated with obesity and insulin resistance, suggesting that FetA phosphorylation may play a role in regulating insulin activity. Additionally, they found that an 8–10 % weight loss increased insulin sensitivity by significantly reducing serum pFetA and the pFetA:FetA ratio [19]. In a 2020 study, Ren et al. reported that moderate-intensity exercise decreases serum FetA, which may lead to increased insulin sensitivity [48]. A recent study also reported that pFetA inhibited glucose uptake and glycogen synthesis, while dephosphorylated FetA had no such effect. Kovářová M et al. observed that FetA exists in various glycosylation forms in human plasma, but the degree of Ser312 phosphorylation does not correlate with glycosylation [96].

The association of FetA with insulin resistance has prompted the investigation of interventions or chemical agents to inhibit this mechanism. One such agent is apigenin, a flavonoid found in many vegetables and fruits. Studies have reported that apigenin has protective effects against obesity, diabetes, and related complications [97, 98]. In their study, Hsu et al. demonstrated in cell culture and mice that apigenin prevented the palmitate-induced increase in FetA expression and the formation of the FetA-insulin receptor complex, thereby preventing palmitate-induced impairments in insulin signaling and glucose uptake in hepatocytes. Similar results were observed in mice fed a HFD; in these mice, apigenin reduced oxidative stress in the liver, prevented the increase in circulating FetA levels caused by a HFD, and consequently protected them from hyperglycemia and insulin resistance [99]. It has been shown that apigenin suppresses FetA mRNA expression by reducing NF-κB activation, an important transcriptional factor involved in the regulation of insulin resistance and required for palmitate-induced FetA expression in hepatocytes [12, 100]. Additionally, Haukeland and colleagues showed that six months of metformin treatment reduced serum FetA levels in individuals with fatty liver [33]. These results suggest that AMPK activation may reduce elevated FetA and possibly pFetA levels. Heo et al. reported that melatonin improved hepatic insulin resistance and steatosis by suppressing FetA expression [101]. Ghadimi et al. conducted a clinical study showing that ellagic acid supplementation reduces inflammation and insulin resistance in diabetic patients [102].

Regarding physical exercise, a recent meta-analysis found that in adult subjects, exercise programs of varying frequency and duration (e.g., 3–5 sessions of 40–70 min per week for 1–12 weeks) and intensity (e.g., 60–85 % of maximum heart rate) showed a decrease in FetA levels after completion of aerobic exercise programs. However, it was reported that this was partly due to pre-existing metabolic status [103]. A 12-week aerobic exercise program of treadmill walking at 85 % of maximum heart rate for 60 min per session reduced FetA levels in obese and insulin-resistant individuals, leading to decreased hepatic insulin resistance, total body fat percentage, and fasting insulin levels [45]. Lee et al. showed that long-term exercise can increase insulin sensitivity by decreasing fat content and plasma levels of FetA [77]. In this study demonstrating the protective effects of physical exercise on insulin sensitivity, it was reported that this effect could be explained by changes in circulating FetA and free fatty acids, with a decrease in macrophage entry into adipose tissue leading to a decrease in TLR4 signaling [77]. A study by Malin et al. showed that FetA was directly linked to decreased hepatic insulin resistance and systemic inflammation after exercise in older, obese, pre-diabetic adults [45]. This finding suggests that physical exercise is an important mechanism for reducing the risk of type 2 diabetes by lowering FetA levels, as weight gain has been shown to increase FetA and impair systemic insulin sensitivity [50, 104].

It has been reported that FetA-deficient rodents can be protected from diet-induced insulin resistance [105]. Previous studies have found that genetic deletion of FetA in obese mice improves insulin sensitivity and resistance [50, 106]. In their study, Mathews et al. reported that the increased insulin sensitivity observed in aged FetA-null mice might be due to increased receptor phosphorylation in the absence of the physiological inhibitor FetA [105]. It has been reported that mice with FetA knockout have increased insulin sensitivity and are resistant to diet-induced weight gain [105]. FetA knockout mice have also been reported to be sensitive to glucose and insulin and resistant to HFD-induced weight gain [107].

One study reported that FetA is a reliable marker of NAFLD and is positively associated with IR. The important finding in this study is that increased serum FetA levels not only indicate the risk of insulin resistance in patients with NAFLD but also reflect liver tissue damage [108]. High FetA levels have also been shown to be associated with insulin resistance in women with polycystic ovary syndrome and pre-adolescent children [109, 110]. In a study conducted in prepubertal children, it was reported that FetA levels and HOMA-IR levels increased in obese children, these two parameters were correlated, and FetA could be an alternative indicator for IR [110].

Fetuin-A and diabetes mellitus

The most important reasons for the development of T2DM in humans are obesity, a sedentary lifestyle, and improper

nutrition. In people who develop insulin resistance due to obesity, lifestyle changes and, if necessary, drug supplements can reduce the incidence of T2DM in the future. Since T2DM significantly reduces people's quality of life and can cause metabolic complications over the years, it is crucial in preventive medicine to detect this disease in advance and, if possible, prevent it. Therefore, identifying potential biomarkers affected by obesity and IR, such as FetA, may also be effective in taking precautions against T2DM.

Many studies have aimed to examine the relationship between FetA and T2DM. Obesity is the major precipitating factor of IR-associated diabetes. The release of stimulatory agents from adipose tissue, including pro-inflammatory cytokines, is triggered by obesity [111]. IR and obesity are integral factors in the development of T2DM, and previous clinical studies have shown that the simultaneous presence of these factors leads to significantly higher FetA levels in people with diabetes than in people without diabetes [1]. Studies have shown that FetA inhibits insulin receptor tyrosine kinase activity and reduces Akt activity in skeletal muscle. It has been suggested that this situation is also associated with the risk of T2DM [41], ultimately causing a decrease in peripheral glucose uptake [50]. A previous study suggested that FetA plays a role in the pathogenesis of T2DM by stimulating adipose tissue inflammation and insulin resistance [112].

Insulin signaling in muscles and the liver has been shown to be suppressed by FetA through the autophosphorylation of insulin receptors, leading to hyperinsulinemia [113]. Previous studies have revealed that increased FetA levels are associated with heightened metabolic risks, including T2DM, NAFLD, polycystic ovary syndrome, and excessive fetal growth [34, 113–115]. It was found that FetA was negatively associated with adiponectin levels. Furthermore, adiponectin levels decreased in the adipocytes of HFD-fed diabetic mice due to the effects of FetA via Wnt3a and PPARγ [116]. A different study reported that FetA release reduces insulin sensitivity by suppressing adiponectin expression in adipose tissue [38]. In humans, the genes encoding FetA and adiponectin are located side by side on chromosome 3q27, which is associated with T2DM and metabolic syndrome (MetS); however, they act in opposite directions [13]. The FetA-adiponectin ratio (FAR) was first introduced by Ju et al. in 2017, and its relationship with MetS in adults was shown to be more significant when calculated as a ratio [117]. In their study, Ahn et al. reported that the FAR level was higher in obese+T2DM children compared to non-obese children. FAR demonstrated a stronger association with BMI than FetA and adiponectin individually, and this association was more pronounced in diabetic children than in controls [118]. In a study conducted by Pathak et al. in 2023, it was suggested that FetA levels are associated with diabetes biomarkers and obesity. FetA was found to play a significant role in the pathogenesis of T2DM, which is often associated with obesity. Cu, Mg, and Mn were reported to be influential in the development of obesity-related T2DM. Zn, along with FetA, was noted to play a role in the pathogenesis and complications of obesity due to its effects on insulin sensitivity and insulin resistance, whereas Mg was identified as an independent biomarker for diabetes [119].

In a different study, FetA levels were found to increase in obesity, particularly in relation to NAFLD, and it was suggested that this may serve as a warning biomarker for the development of T2DM [65, 120]. A multicenter cohort study published in 2014 by Stefan et al. reported that both adiponectin and FetA are factors that can predict T2DM and insulin resistance. Adiponectin, secreted from fat tissue, has a significant impact on metabolism, while the increase in FetA levels is largely attributed to NAFLD. They also suggested that FetA might play a role in the pathogenesis of T2DM by affecting insulin secretion [120]. In their study, Zhou et al. found that higher serum FetA levels were observed in obese T2DM patients compared to normal weight T2DM patients and obese individuals with normal glucose tolerance. This study indicated that high FetA levels in obese and obese+T2DM individuals are associated with obesity [121]. Another study reported increased FetA levels in obese individuals with T2DM in association with elevated pro-inflammatory cytokine levels [67, 122]. Reinehr et al. found that FetA levels were higher in obese adolescents with T2DM compared to obese adolescents without T2DM [34]. Previous studies have also reported that FetA is positively associated with fasting blood glucose and HbA1c, identifying it as an independent risk factor for diabetes [32, 36]. However, a recent study highlighted a strong association between FetA and diabetes risk that is not related to fatty liver [123]. It was noted that glucose and hyperglycemia increase FetA gene promoter activity and liver expression [124]. Khadir et al. showed that FetA functions as a hepatokine that stimulates metabolic dysfunction due to obesity and diabetes [27].

In a different study, higher levels of FetA and matrix metalloproteinase-7 (MMP-7) were observed in obese+T2DM patients compared to the healthy group. It was reported that FetA levels decreased after Roux-en-Y gastric bypass (RYGB), mini gastric bypass (MGB), and sleeve gastrectomy (SG) operations, while MMP-7 levels remained unchanged [125]. Kacka et al. examined FetA levels in children with Type 1 diabetes (T1DM) and found that FetA levels in obese children without diabetes were higher than in obese children with T1DM. This finding suggests a potential protective role of FetA against coronary artery disease and acute cardiovascular events in healthy individuals, possibly due to its effect

in preventing mineral accumulation in the vessels [126–129]. The study also indicated that FetA levels in obese diabetic patients correlated with obesity, high daily insulin requirement, and insulin resistance. The researchers proposed that these findings could be used to predict cardiovascular complications of T1DM and monitor poor glycemic control [126].

Several studies have suggested differing findings regarding serum FetA levels in diabetes. Noureldein et al. showed that fenofibrate and pioglitazone, either alone or in combination, increased SIRT1 levels and decreased FetA levels in obese and obese+diabetic individuals [130]. A recent study reported that plasma FetA levels in obese individuals with T2DM and gastric bypass did not change after surgery but showed a positive correlation with BMI for 12 months [131]. Almarashda et al. found no association between FetA or Fetuin-B levels and T2DM in serum but noted that FetA may affect insulin resistance in the general adult Saudi population. Additionally, serum FetA was found to independently affect serum triglyceride levels [132]. Gündüz et al. reported that serum FetA levels were significantly lower in patients with T2DM compared to the control group [133]. Mori et al. reported that pioglitazone and six months of metformin treatment reduced serum FetA in patients with T2DM [134]. This study also indicated that pioglitazone, unlike metformin, suppressed FetA expression in Fao rat hepatoma cells [135]. In a study involving postmenopausal diabetic women using metformin or pioglitazone, no changes in FetA and adiponectin levels were observed, which was attributed to the antidiabetic drugs used [136]. Another study suggested that FetA is important for the development of insulin resistance in the early phase of weight gain, but there is no evidence showing that FetA affects T2DM-related insulin resistance that progresses with increasing weight and obesity [137]. Choi et al. reported that calorie restriction significantly reduced hepatic expression and circulating levels of FetA and regulated cardiovascular risk factors in obese rats and patients with T2DM [54]. Mancuso et al. suggested that FetA plays an important role in psychiatric symptoms and cognitive performance in prediabetic and diabetic individuals, with serum FetA levels being an independent risk factor for the development of anxiety disorders and depression, alongside insulin resistance [138].

Conclusions

FetA is a significant glycoprotein secreted by various tissues in the body, primarily the liver. Research indicates that FetA plays a crucial role in the development of obesity and related complications, such as IR and T2DM. FetA exerts its effects related to obesity through its secretion from the liver and adipose tissue. Elevated serum levels of FetA are observed in obese individuals. FetA derived from adipose tissue forms a complex with free fatty acids, which stimulates inflammation in adipose tissue, disrupts energy homeostasis, and may contribute to the development of insulin resistance and T2DM over time.

Studies investigating the molecular mechanisms linking FetA to insulin resistance have focused on the pancreas, adipose tissue, and liver. Hypotheses suggest that FetA secretion may increase due to stimulation of the Nrf2 transcription factor in the pancreas, PPARγS273 phosphorylation via the MEK-ERK-Cdk5 signaling pathway in adipose tissue, and a decrease in FBXW7 in the liver, with subsequent signaling stimulated by increased ER stress. Increased FetA levels have been consistently associated with IR and T2DM in recent clinical, animal, and cell culture studies.

In conclusion, FetA is considered a risk factor for obesity, IR and diabetes. Future large-scale experimental studies measuring serum FetA levels may facilitate its use as a diagnostic biomarker for obesity and related risk factors. Additionally, research aimed at suppressing transcription factors involved in FetA expression and developing new agents to inhibit FetA secretion could offer therapeutic potential for treating obesity and its associated complications.

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