

# A Review of Afamin as Metabolic Novel Marker of Many Diseases

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**ABSTRACT:** Human plasma vitamin E-binding glycoprotein afamin is mostly produced in the liver and released into the circulation. The review in this study related to a glycoprotein afamin marker that is important in many diseases Type 2 diabetes mellitus, cancer, obesity, Gestational diabetes mellitus, oxidative stress, and metabolic syndrome. Although ovarian follicles and human cerebrospinal fluid also contain sizable amounts of AFM, the liver is the main organ that generates it. Though there are minor AFM manifestations have been also reported in the human heart, testis, brain, kidney, and ovary. Afamin is promising metabolic novel marker for gestational diabetes mellitus, metabolic syndrome, cancer and related diseases.

**Keywords:** Afamin, Type2, diabetes mellitus, obesity.

## 1. INTRODUCTION

Afamin (AFM) is an 87 kDa human plasma glycoprotein that shares 55% of albumin's amino acid sequence and contains 15% carbohydrates [1]. Lichtenstein et al. first identified AFM as the fourth gene in the human albumin gene family [2]. The liver is the primary organ that produces AFM, however human cerebrospinal fluid and ovarian follicles also contain significant amounts of this substance [3]. While small expressions of AFM have also been reported in the human heart, testis, brain, kidney, and ovary. Because of Afamin unique ( $\alpha$ - and  $\gamma$ -tocopherol) binding sites, it might be essential for the metabolism of vitamin E [4]. Afamin's circulating levels are not affected by gender, age, prandial state, menstrual cycle, or circadian rhythms. It may be tested in plasma or serum and is rather stable [5]. The liver is where AFM is mostly expressed and secreted. Despite the fact that the physiological role of AFM is mainly unclear, several studies have discovered a strong correlation between AFM and (obesity, type 2 diabetes mellitus T2DM) [6]. The metabolic syndrome (MetS) and body mass index (BMI) the prevalence of have been reported to be positively correlated with serum afamin levels [7][8]. Moreover, transgenic mice that overexpress afamin have higher body weights and (lipoprotein and blood lipid) concentrations [9][10]. Increased afamin levels are linked to pre-eclampsia, T2DM, high blood pressure, elevated blood glucose, dyslipidemia, and obesity, among other important MetS characteristics [3].

### 1.1. AFAMIN STRUCTURE

There are four or five possible (N-glycosylation) sites on afamin [5]. Similar to other albumin multigene family members, afamin has three structural domains that represent (17 Cys-Cys) disulfide bridges. Lichtenstein et al. (1994) identified vitamin-D binding protein family,  $\alpha$ -fetoprotein, and the AFM as the fourth member of the albumin family of the proteins [11]. The cDNA encodes an amino acid sequence that is highly similar to members of the albumin family and has the same pattern of Cys residues that are seen in this family. Furthermore, the gene, like other members of the albumin gene family, maps to chromosome (4). These findings lead us to the conclusion that the 87,000-dalton protein, which we call AFM [12]. The AFM gene produces mature human afamin, which is a single chain of (578) amino acid. It has three sequential albumin domains (aa36-206, 211-403, and 404-599) with five or six intra-chain disulfide links

as their defining feature. The four genes that make up the albumin gene family, which includes the AFM, locate to chromosome [4] in a tandem configuration. It is known that these four genes encode structurally similar serum transport proteins that are connected in terms of evolution [13]. In humans, the glycoprotein afamin is found on chromosomes (4q11–q13). Studies have shown that afamin bind vitamin E, particularly ( $\alpha$ - and  $\gamma$ -tocophero) l, which are two of the most significant forms of the vitamin, both in vivo and in vitro. It also contains several binding sites for both isomers of tocopherol [5]. As shown in fig. 1 [4].

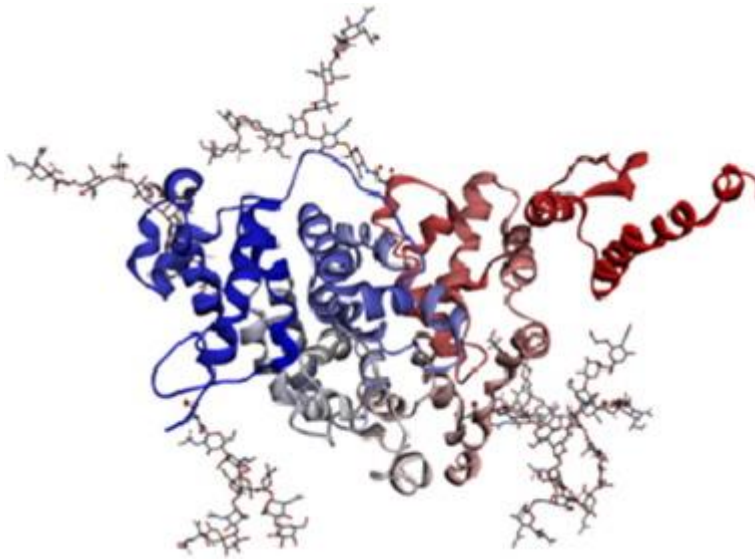


FIGURE1. structure of afamin [4]

## 2. AFAMIN AND DISEASES

### 2.1. TYPE 2 DIABETES MELLITUS AND OBESITY

Afamin is mostly found in the liver, however it is also expressed in the kidneys, testes, brain and ovaries, among other organs. A rise of 20% in the prevalence of type 2 diabetes mellitus when AFM plasma concentrations were raised by 10 mg/L [2]. Additionally, along the course of the disease's follow-up, AFM plasma concentrations were assessed as an independent predictor of the development of T2DM. According to another study, there is a 30% rise in the incidence of T2DM when AFM plasma concentrations are raised by 10 mg/d [3]. Transgenic mice expressing the human AFM gene have been shown to gain weight and have elevated cholesterol and glucose levels. AFM levels are high in MetS and obesity, and they have a strong correlation with glucose, triglycerides (Tg), waist circumference, BMI, and low-density lipoprotein cholesterol in T2DM and obesity [16]. Over 20,000 individuals participated in a big multi-center investigation where strong connections between the incidence and prevalence of T2DM and afamin levels were found [17].

The development of IR that leads to hyperinsulinemia is the vital event in the path mechanism of the metabolic syndrome. Increased fatty acid absorption in the liver is facilitated by elevated insulin levels, which leads to an increase in endogenous (very low-density lipoprotein (VLDL)) synthesis. The enzyme lipoprotein lipase, which breaks down triglyceride-rich lipoproteins, is also less active as a result of the IR [18]. The Tg levels rise even more when there is a combination of increased production and reduced removal. Elevation of Tg is inversely correlated with (high-density lipoprotein (HDL)) [19]. This is caused by the different way that HDL particles mature when lipid components that are produced during Tg breakdown are present. The hepatic lipase's metabolism of these particles quickens when the Tg content of HDL rises [20]. Additionally, the nature of LDL changes: there are more tiny, dense, oxidation-prone LDL particles, which leads to higher amounts of oxidized LDL and faster atherogenesis [21][22]. Endothelial dysfunction and the promotion of atherosclerosis are caused by a combination of low HDL, high small and dense LDL, hyperinsulinemia, hyperglycemia, and hypertriglyceridemia [23]. Previous research has shown that 13% of AFM is attached to lipoproteins in the bloodstream, mostly to tiny, dense HDL particles but also to HDL that contains A1 apolipoprotein. Plasma lipoproteins contain 97% of the lipid-soluble and  $\gamma$ -tocopherol [24][25]. But there are other proteins besides AFM that can also bind these  $\gamma$ -tocopherols selectively. [23]. Through the suppression of lipid peroxidation, tocopherol might

prevent oxidative modifications in LDL, even though the antioxidant ability of ( $\alpha$ - and  $\gamma$ -tocopherol) has not been conclusively demonstrated in clinical research [25].

## 2.2. GESTATIONAL DIABETES MELLITUS (GDM)

Another promising early marker property of afamin with potentially significant implications for therapies of pregnancy complications like GDM was demonstrated by Tramontana who found significantly higher afamin concentrations in the first trimester of pregnant women who went on to develop GDM later in pregnancy[14]. Assessing the exact molecular structure of afamin would facilitate the hunt for physiological ligands and provide light on its physiological function, especially with relation to its involvement in the onset of diabetes mellitus and associated disorders. The IR rises physiologically during pregnancy in order to provide sufficient glucose transport from the mother to the fetus. Pregnancy-onset increased IR is highly correlated with the development of GDM[26][27]Furthermore, low concentrations of sex hormone-binding protein (SHBG) during the first trimester of pregnancy may be a sign of the onset of GDM. Insulin concentrations control the expression of SHBG in the liver. However, there is presently no effective way to test for diabetes during the first trimester of pregnancy. Obesity and IR are closely linked to the OS itself[28][29]. Higher blood AFM concentrations have been linked to both increased glucose concentrations and IR, according to earlier research. The intensity of IR during pregnancy rises as gestational age increases [30][31]. It seems that proper glucose transport from the mother to the fetus has a physiological function in the reduction in insulin sensitivity. Remarkably, IR rises in all women in a similar way regardless of preconception obesity or IR. Therefore, pregnancy-related pathologic glucose metabolism is experienced by women with increased IR concentrations before to conception. This condition leads to pathologic materno-fetal glucose transfer and unfavorable pregnancy outcomes. The placenta produces mediators that contribute to the severity of IR growing[32]. Tumor necrosis factor alpha(TNF- $\alpha$ ) is the primary factor in physiologic IR, as demonstrated by Kirwan et al [33].The pattern of cytokines produced by adipose tissue is almost exactly the same as that of the placenta. The increased risk of GDM in obese women can be explained by this condition. Nevertheless, it is also known that OS conditions raise the amounts of IR mediators like TNF- $\alpha$ . [34]. The TNF- $\alpha$  itself suppresses insulin production [32]. One of the most well-known IR conditions linked to the existence of OS mediators is PCOS. Concerning the relationship between OS and glucose metabolism, AFM concentrations appear to be a good indicator of IR in PCOS patients [34].The blood taken during first trimester screening from women with preeclampsia showed considerably higher median AFM concentrations than did blood from women with simple pregnancy in a pilot trial involving patients diagnosed with pregnancy problems[35].

## 2.3. METABOLIC SYNDROME

The term "insensitivity to insulin-mediated glucose disposal" (IR) describes this condition. One important part of MS is the IR. The IR and MS prevalence is increasing, especially in developing countries with a prevalence estimate range of 20 to 40% depending on the population[36]. Strong risk factors for the onset of cardiovascular disease and T2DM include both IR and MS[37].Afamin concentrations and the prevalence of MS were shown to be correlated in earlier research[3].

The hunt for the primary causes of metabolic syndrome other than overeating and a sedentary lifestyle high in fat and carbohydrates Abdominal obesity may be one of the main causes, since it is thought to be the source of systemic inflammation, which is linked to the onset and progression of IR and T2DM [38].It has been determined that visceral adipose tissue is a significant source of plasminogen activator inhibitor 1, TNF- $\alpha$ , and interleukin-6, which cause systemic inflammation. It's intriguing; the AFM demonstrated robust correlations, especially with waist circumference. There is currently a lack of clarity on the mechanistic and functional understanding of afamin's role in the development of the metabolic syndrome or the pathophysiology of its component parts[39].

## 2.4. CANCER

Researchers have looked into circulating AFM concentrations in a number of additional carcinoma types, such as breast, colorectal, stomach, bladder, thyroid cancer and cervix. Afamin has previously been found to be a possible biomarker for ovarian cancer by comparative proteomics. In contrast to healthy subjects, patients with ovarian cancer had significantly lower plasma concentrations of afamin. More recently, it was reported that there was a significant correlation between afamin plasma concentrations and clinical outcomes, such as survival rates and response to therapy [40].

## 2.5. OXIDATIVE STRESS

Afamin is a different kind of vitamin E carrier plasma glycoprotein, which is produced from the liver and binds to vitamin E. It contributes to oxidative stress (OS) related antiapoptotic cellular mechanisms [41]. The afamin is indicator of OS. The metabolic syndrome and insulin resistance (IR) are linked to elevated AFM levels [42].

### 3. CONCLUSION

Afamin is promising metabolic novel marker for gestational diabetes, type 2 diabetes mellitus cancer, metabolic syndrome, and related disease.

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