

Can Adipokine FAM19A5 Be a Biomarker of Metabolic Disorders?

Agnieszka Wesołek-Leszczynska ^{1,2}, Katarzyna Pastusiak ¹, Paweł Bogdański^{1,*}, Monika Szulińska^{1,*}

¹Department of Treatment of Obesity, Metabolic Disorders and Clinical Dietetics, Poznan University of Medical Sciences, Poznań, Poland; ²Doctoral School, Poznan University Of Medical Sciences, Poznań, Poland

*These authors contributed equally to this work

Correspondence: Agnieszka Wesołek-Leszczynska, Department of Treatment of Obesity, Metabolic Disorders and Clinical Dietetics, Poznan University of Medical Sciences, 82/84 Szamarzewskiego Street, Poznań, 60-569, Poland, Tel +48 721 947 738, Email aa.wesolek@gmail.com; 76871@student.ump.edu.pl

Aim: One of the most critical functions of adipose tissue is the production of adipokines, ie, numerous active substances that regulate metabolism. One is the newly discovered FAM19A5, whose older name is Tafa-5.

Purpose: The study aimed to review the literature on the FAM19A5 protein.

Methods: The review was conducted in December 2023 using the PubMed (Medline) search engine. Sixty-four papers were included in the review.

Results: This protein exhibits the characteristics of an adipokine with positive features for maintaining homeostasis. The results showed that FAM19A5 was highly expressed in adipose tissue, with mild to moderate expression in the brain and ovary. FAM19A5 may also inhibit vascular smooth muscle cell proliferation and migration through the perivascular adipose tissue paracrine pathway. Serum levels of FAM19A5 were decreased in obese children compared with healthy controls. There are negative correlations between FAM19A5, body mass index, and fasting insulin. Serum FAM19A5 level is correlated with type 2 diabetes, waist circumference, waist-to-hip ratio, glutamic pyruvic transferase, fasting plasma glucose, HbA1c, and mean shoulder pulse wave velocity. FAM19A5 expression was reduced in mice with obesity. However, the data available needs to be clarified or contradictory.

Conclusion: Considering today's knowledge about FAM19A5, we cannot consider this protein as a biomarker of the metabolic syndrome. According to current knowledge, FAM19A5 cannot be considered a marker of metabolic disorders because the results of studies conducted in this area are unclear.

Keywords: fat tissue, metabolic syndrome, adipokines, adipocytes, obesity

Visceral Adipose Tissue

Adipose tissue, in addition to its energy storage function, is a vital endocrine organ. It also protects against heat loss and mechanical injuries. One of the most critical functions of adipose tissue is the production of adipokines, ie, numerous active substances that regulate metabolism. Both excess and deficiency of adipose tissue negatively affect health. Overall mortality, cardiovascular diseases, metabolic diseases, and obesity are related to body fat content. Visceral fat tissue is particularly metabolically active.¹

The essential component of adipose tissue is adipocytes, scattered within the skeleton formed by collagen fibers. There is a subpopulation in adipose tissue stem cells called stromal vascular fraction cells (SVF) and preadipocytes, fibroblasts, leukocytes, macrophages, and endothelial cells. All these elements influence the metabolic function of adipose tissue, regardless of its morphological type. White adipose tissue (WAT) is the largest body store of energy, accumulated in triglycerides (TG), and is the largest endocrine gland—brown adipose tissue (BAT) functions to generate thermal energy, mainly in children. Pink adipose tissue is involved in milk production in women during pregnancy and lactation. Depending on the location of fat tissue in the body, it is divided into subcutaneous and visceral. Subcutaneous adipocytes are large and less metabolically active, while visceral adipocytes are small and more active. Visceral tissue is

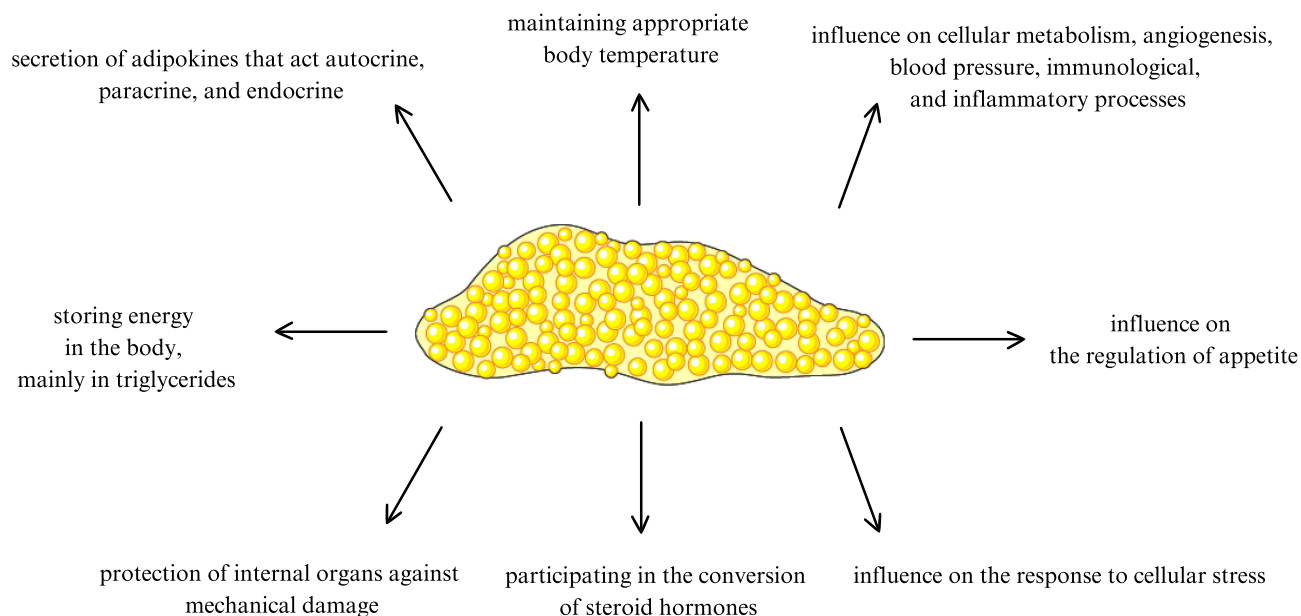


Figure 1 Function of fat tissue in the human body.⁸

more metabolically active and secretes more hormone-like substances. Its increased content in obesity significantly increases the risk of cardiovascular diseases.^{2,3} The summary of fat tissue's function is presented in [Figure 1](#).

Malnutrition and, consequently, too low body fat content may result in improper functioning of organs and, in children, growth retardation.⁵ Obesity is a significant problem for the public health worldwide, because it has become an epidemic. According to the World Health Organization (WHO), more than 1 billion people worldwide have obesity — 650 million adults, 340 million adolescents, and 39 million children.^{6,7}

Assessing the concentration of body fat makes it possible to assess a person's nutritional status and plan an appropriate nutrition plan, and in the case of obesity - to plan appropriate treatment. The simplest method of estimating overweight and obesity is to measure waist circumference (WC) and calculate the waist-hip ratio (WHR). These indicators are more effective in estimating the risk of cardiovascular diseases than assessing body weight based on body mass index (BMI). The most popular method of estimating body fat content is to perform a body composition analysis using the bioelectrical impedance method. The result is given in kilograms and %. The correct body fat percentage in women is 20–30%, while in men, it is 10–20% of the total body weight. Values exceeding 32% and 26% in women and men indicate obesity. More accurate methods for assessing body fat are computed tomography (CT), magnetic resonance imaging (MRI), and double-beam X-ray absorptiometry (DXA).^{1,8}

Improper nutrition, lack of physical activity, increased stress, certain medications, and psychological and social factors may increase the risk of obesity. Obesity treatment includes permanent changes in eating habits and lifestyle, increasing physical activity, and health and nutrition education. Pharmacological treatment should be tailored to the patient's capabilities and comorbidities. Available substances approved for treating obesity include tetrahydrolipstatin, bupropion hydrochloride, naltrexone hydrochloride, and liraglutide. Obesity treatment can also be supported by individual physiotherapy and psychological support.^{9–11}

Obesity causes several health consequences. It increases the risk of, among others, stroke, cataracts, coronary heart disease, diabetes, dyslipidemia, hypertension, pancreatitis, non-alcoholic fatty liver disease, liver cirrhosis, infertility, osteoarthritis, and cancer.¹² All of these conditions are mainly related to chronic inflammation induced by excess fat tissue.

Inflammation is a protective response to tissue damage or destruction. Short-term treatment destroys or dilutes both the damaging agent and the damaged tissues. However, long-term inflammation has a destructive effect on human health. This condition occurs in people with obesity. It is characterized by lymphocytes and macrophages as well as proliferation of blood vessels and connective tissue. Chronic inflammation is caused by excess fat tissue in these people. The induction

and continuation of inflammation are influenced by the secretion of pro-inflammatory adipokines by adipose tissue. These include interleukin-6 (IL-6) and tumor necrosis factor α (TNF- α). IL-6 stimulates hepatocytes to synthesize and secrete c-reactive protein (CRP). Moreover, the accumulation of free fatty acids in obesity activates pro-inflammatory serine kinase cascades. These include I κ B kinase (IKK) and c-Jun N-terminal kinase (JNKs), which stimulate adipose tissue to release IL-6. Elevated CRP may be an independent risk factor for cardiovascular diseases, including acute myocardial infarction. Increasing the concentration of IL-6 and TNF- α inhibits and reduces the synthesis and secretion of adiponectin. Reducing the adiponectin concentration increases the risk of cardiovascular diseases. Persistent inflammation is a decisive risk factor for developing metabolic syndrome, diabetes, and cancer. Increased adipose tissue content regulates the secretion of adipokines.^{13–15}

New adipokines that may be the best biomarkers in metabolic disorders are still being sought.

Adipokines in Obesity

Adipokines are proteins secreted by adipose tissue. These proteins influence glucose and lipid metabolism. They regulate the feeling of hunger and satiety and maintain metabolic homeostasis. Their concentrations influence the concentrations of other substances, including hormones. They influence neuroendocrine and immune functions. WAT secretes, among others, leptin, omentin, adiponectin, resistin, visfatin, apelin, vaspin, hepcidin, chemerin, TNF- α , monocytes chemoattractant protein-1 (MCP-1), IL-6, retinol-binding protein 4 (RBP-4) and plasminogen.¹⁶ Adipsin was discovered as the first adipokine in 1987.¹⁷ However, the discovery of leptin produced by mature adipocytes in 1994 increased interest in the presence of adipokines and their functions in metabolism.¹⁸

The functions of selected adipokines in the human body are presented in [Table 1](#).

The role of many adipokines still needs to be clarified, or the results of studies are contradictory. Such adipokines include the newly discovered Family With Sequence Similarity 19 Member A5 protein (FAM19A5), which another, older name is TAFA-5.

Metabolic Syndrome

Metabolic syndrome (MetS) is a group of comorbidities that include obesity, hypertension, and disorders of carbohydrate and lipid metabolism. However, the latest definition of MetS from 2022 suggests that it should be diagnosed as obesity comorbid with two of the following criteria - high blood pressure, impaired glucose metabolism, and increased cholesterol concentration in lipoproteins other than high-density lipoprotein (HDL) (atherogenic dyslipidemia). Obesity can be diagnosed based on Body Mass Index (BMI) or waist circumference. The population of MetS patients is not homogeneous. This is due to two or three of the above disorders accompanying obesity, which generate various combinations of pathologies occurring in each person.²⁶

MetS is a major clinical problem, and its incidence is increasing in Poland. According to the Multi-centre National Population Health Examination Study (WOBASZ), 2014, MetS was 33% and 39% in women and men aged 20–74, respectively. This result increased by almost 3% and 9% in women and men, respectively, compared to the WOBASZ study 2003.^{6,27} Globally, almost 25% have MetS. Epidemiological studies highlight the problem of the increasing number of people with MetS worldwide. The increase is particularly noticeable among children and adolescents, which coincides with the increase in the number of children with obesity.²⁸

Obesity is considered a core element of MetS. Excessive accumulation of fat tissue and the resulting activity of visceral fat tissue causes over 200 complications. MetS consequently causes impaired kidney function, metabolic-associated fatty liver disease, obstructive sleep apnea, polycystic ovary syndrome, and hyperuricemia. MetS also increases the risk of cardiovascular disease and vascular disease and increases the risk of death from cardiovascular disease. Obesity and MetS are associated with increased oxidative stress, essential in the pathogenesis of comorbidities that may develop during MetS. Furthermore, the component of the MetS that contributes most to the relationship between metabolic syndrome and oxidative stress is the component related to obesity and insulin resistance. The essential treatment for MetS is lifestyle change, increasing physical activity, stopping smoking, and changing eating habits, along with pharmacological treatment. These changes consequently cause weight loss, visceral fat tissue reduction, and reduction in the concentration of pro-inflammatory adipokines, especially from visceral adipose tissue.²⁸

Table 1 The Functions of Selected Adipokines in the Human Body

Adipokine	Function in the human body
Leptin	<ul style="list-style-type: none"> Plays a role in diet-related hormone regulation interacts with receptors in the hypothalamus, suppressing hunger and stimulating the feeling of satiety affects women's fertility high leptin levels may be a key pathological feature of hyperandrogenic PCOS in women takes part in immunity, promoting the activation, proliferation, and cytokine production of T lymphocytes may play a role in the occurrence and development of breast cancer¹⁹
Visfatin	<ul style="list-style-type: none"> Increases glucose uptake in peripheral tissues, reduces both gluconeogenesis and glucose release, reduces stimulation of the insulin signaling cascade inhibits macrophage apoptosis crucial function for NAD biosynthesis increased visfatin levels result in increased levels of inflammatory markers such as IL-6, IL-8, CRP, and MCP-1, endothelial dysfunction, and an increase in oxidative stress²⁰
Resistin	<ul style="list-style-type: none"> Binds to the isoform decorin on the surface of fat progenitor cells and modulates the expansion of white adipose tissue can modulate adipogenesis and carbohydrate metabolism probably passing on some of his pro-inflammatory functions by binding to CAP-1 causes the development insulin resistance and activation of pro-inflammatory cytokines²¹
Apelin	<ul style="list-style-type: none"> Acts as a potent activator of cardiac contraction, controls systemic perfusion, affects both the heart and the vascular system in the vascular system, NO affects the action of apelin as a vasodilator causes peripheral and coronary vessels to dilate and increases heart function regulates the homeostasis of body fluids influences the regulation of the hypothalamic-pituitary-adrenal axis is necessary for insulin sensitivity²²
Chemerin	<ul style="list-style-type: none"> Takes part in inflammatory processes, stimulating the innate and adaptive immune response stimulates digenesis, binds to metabotropic receptors with a serpentine structure CMKLR1 and CCRL2, affecting the cellular level of calcium ions, cAMP and kinase activity serum chemerin concentration correlates with inflammatory markers such as CRP and cytotoxic pro-inflammatory kinases (TNF-α, IL-6)^{23,24}
Tumor necrosis factor α (TNF- α)	<ul style="list-style-type: none"> Pleiotropic pro-inflammatory cytokine regulates cell differentiation and growth affects the release of prostaglandins and leukotrienes, platelet-activating factors, NO, and reactive oxygen species, plays an essential role in regulating the immune response takes an active part in apoptosis plays a crucial role in the inflammatory response takes part in the process of clot formation and fibrinolysis²⁸

Abbreviations: CAMP, cyclic adenosine monophosphate; CAP-1, adenyl cyclase-associated protein 1; CCRL2, chemokine receptor-like 2; CMKLR1, chemerin chemokine-like receptor 1; CRP, c-reactive protein; IL-6, interleukin 6; IL-8, interleukin 8; MCP-1, monocytes chemoattractant protein-1; NAD, nicotinamide adenine dinucleotide; NO, nitric oxide; PCOS, polycystic ovary syndrome; TNF- α , tumor necrosis factor- α .

FAM19A5 Original Direction of Research

Family With Sequence Similarity 19 Member A5 protein (FAM19A5), another older name is Tafa-5, and it is one of five proteins encoded by the Tafa1-Tafa5 genes. FAM19A5 is less related to other Tafa family proteins. This protein exhibits the characteristics of an adipokine with positive features for maintaining homeostasis.²⁹ Wang et al in 2018 showed that FAM19A5 is an adipokine. The authors analyzed the expression profile of a panel of human cDNAs from multiple tissues. The results showed that FAM19A5 was highly expressed in adipose tissue, with mild to moderate expression in the brain and ovary, and was barely detectable in other tissues. Detailed results also showed FAM19A5 expression in humans in subcutaneous, perirenal adipose tissue. FAM19A5 was also detected in the epididymal adipose tissue of mice. The secretion of this protein by fat cells of various origins was also compared in humans and mice.

According to the authors, FAM19A5 was primarily secreted by rat epididymal adipocytes compared to other cell types, including the vascular fraction of adipose tissue, primary rat adventitial aortic fibroblasts, human umbilical vein endothelial cells, rat and human vascular smooth muscle cells (VSMCs), as well as primary mouse peritoneal macrophages. The same project also demonstrated the protective effect of FAM19A5. Adipose tissue-derived FAM19A5 inhibited neointimal formation after in vivo injury in mice, and circulating FAM19A5 levels negatively correlated with neointimal formation. Moreover, the authors suggest that FAM19A5 may also inhibit VSMC proliferation and migration through the perivascular adipose tissue paracrine pathway.²⁹ FAM19A5 contributes to the wound healing process after brain injury,³⁰ and also participates in receptor activator for nuclear factor κ B ligand (RANKL) induced differentiation of osteoclast precursor cells through interactions with the N-formyl peptide receptor 2 (FPR2).³¹ In humans, serum levels of FAM19A5 were decreased in obese children compared with healthy controls. Moreover, there are negative correlations between FAM19A5 and BMI and fasting insulin. These results suggest an association of the FAM19A5 protein with metabolic disorders and emphasize its suggested positive effects on the body.³²

The first data on FAM19A5 genes comes from 2004. Y. Tom Tang et al then discovered a family of small secreted proteins in *Homo sapiens* and *Mus musculus*. The family consisted of five highly homologous genes. They were referred to as Tafa-1 to -5. This study used a method of identifying new gene families, which was new in 2004, encoding proteins secreted non-transmembranely. The authors showed that the Tafa genes 1 to 4 are more closely related to each other than to Tafa-5. This was demonstrated by comparing nucleotide and amino acid sequences. The study looked for the proteins encoded by these genes, but the state of knowledge still needed to be improved. Tafa-2 expression level was low. Tafa-1, Tafa-3, Tafa-4, and Tafa-5 proteins were detected in culture supernatants. The expression of these genes was also studied by quantitative real-time polymerase chain reaction (PCR). Expression has been studied in the brain, colon, heart, kidney, liver, lungs, spleen, and thymus. All Tafa genes are expressed at different levels in the brain and deficient levels in other tissues. According to the authors, genes from the Tafa family are expressed mainly in the central nervous system.³³ The Tafa-5 protein discovered in 2004 will, in the future, be called the FAM19A5 protein.

A year later, in 2005, genes from the Tafa family became the object of interest of Teresita Díaz de Ståhl et al. The team identified areas of loss or gain on chromosome 22, either constitutional or cancer-derived deoxyribonucleic acid (DNA), which could indicate the position of putative genes involved in glioblastoma development. A high-resolution tiling-path chromosome 22 array to a series of 50 glioblastoma samples to investigate the underlying abnormalities in both constitutional and tumor-derived DNA. Analysis of the amplified regions revealed the presence of two interesting candidate genes: TOP3B and Tafa-5. It was shown that this gene encodes a protein, which was then named Tafa-5 - like the gene's name. According to the authors, the Tafa family proteins are distantly related and contain conserved cysteine residues at fixed positions. They belong to chemokines. According to the authors, the TOP3B and Tafa-5 genes may be involved in the genesis of glioblastoma.³⁴

Until 2018, the topic of Tafa genes was not discussed. At that time, links between the Tafa-5 (FAM19A5) protein and disorders, including metabolic disorders, were sought.

In 2018, Anna A. Kashevarova et al checked the genetic analysis of a 4-year-old girl with a terminal deletion at 22q13. The girl showed developmental delays, hyperactivity, mood swings, and sleep disturbances. The array comparative genomic hybridization (aCGH) results were confirmed by real-time PCR in three tissues: lymphocytes, skin fibroblasts, and oral epithelium. Fluorescence in situ hybridization (FISH) analysis was used to confirm the ring form of chromosome 22 and to determine the level of cells with monosomy 22 among skin lymphocytes and fibroblasts. Real-time PCR confirmed the presence of microdeletions with primers for the FAM19A5 (Tafa-5) gene, SHANK3, and ACR genes. According to single nucleotide polymorphism (SNP) analysis, the 22q13.32-q13.33 microdeletion occurred de novo on the mother's chromosome. The above results suggest a link between the FAM19A5 gene and the Phelan-McDermid syndrome described in girl.³⁵

After the discovery of Tafa genes in 2004, interest in FAM19A5 (Tafa-5) functions has been most noticeable in neurology, neurological and psychiatric diseases.

FAM19A5 – Central Nervous System

Referring to a 2004 paper where only limited information was available on FAM19A5 function in the brain,³³ Anu Shahapal et al wished to determine the expression pattern of FAM19A5 during embryogenesis and in the adult brain and to identify the types of brain cells that express FAM19A5 in FAM19A5-LacZ knock-in (KI) mice. In the results, FAM19A5-LacZ KI homozygous mice showed more vital X-gal staining than heterozygous mice. Moreover, global X-gal staining in embryonic stages showed dominant expression of FAM19A5 in the brain and spinal cord. In adult mice, FAM19A5 was widely expressed in multiple brain regions. Interestingly, increased FAM19A5 expression was shown in response to traumatic brain injury. The authors concluded that FAM19A5 is a crucial regulator of central nervous system (CNS) development and the brain's response to injury.³⁰ Already a year earlier, in 2018, Can Zheng showed that FAM19A5 protein expression levels correlate with brain development. The FAM19A5 protein has been shown to function during embryonic brain development by promoting neuronal differentiation and suppressing astrocyte differentiation. Despite this, the full function of the FAM19A5 protein in the brain needed clarification to the authors.³⁶

Research on the effect of FAM19A5 in the CNS was continued. A case report from 2019, which presented a female fetus with schizencephaly accompanied by cerebro-occipital hernia, polymicrogyria, agenesis of the corpus callosum, facial dysmorphia, and ventricular septal defect in the myocardium, showed a deletion of chromosome 22q13.32, including the FAM19A5 gene. The authors suggested that the presence of the FAM19A5 gene could be associated with the development of schizencephaly.³⁷

In the same year, Anna J Khalaj's team demonstrated that FAM19A functions as cell type-specific regulators of neurexin modification in the nervous system. FAM19A1-A4 binds to the cysteine loop domain of neurotoxins, forming intermolecular disulfide bonds during transport through the secretory pathway. According to the authors, FAM19A serves as cell type-specific regulators of neurexin modification, which is associated with disorders such as autism spectrum disorder (ASD), schizophrenia, and mental retardation.³⁸

Moreover, FAM19A5 protein deficiency in mice showed hyperactive locomotor behavior, long-term memory deficits, and failure to acquire fear. These results suggest that FAM19A5 influences the nervous system's development and the mature brain's proper functioning.³⁹

It was also checked whether the concentration of FAM19A5 protein correlated with the severity of vascular dementia. The study included 136 patients with vascular dementia and 81 healthy controls. The results showed that serum FAM19A5 concentration was significantly higher than the control group ($p < 0.001$). Moreover, Spearman correlation analysis showed that serum FAM19A5 levels significantly correlate negatively in patients with vascular dementia ($r = -0.414, <0.001$). Based on the results, the authors suggest that FAM19A5 protein concentration may be a biomarker for predicting cognitive function in patients with vascular dementia.⁴⁰

Hye Lim Lee et al checked whether FAM19A5 concentrations correlate with the optic neuritis spectrum disorder. The study included blood sera from 199 patients from 11 hospitals over 21 months. Patients were divided into neuromyelitis optica spectrum disorders with positive aquaporin-4 antibody (NMOSD-AQP4), other CNS demyelinating diseases, and healthy controls. In the results, serum FAM19A5 concentration was higher in patients with NMOSD-AQP4 and correlated with clinical characteristics. According to the authors, serum FAM19A5 may be a new clinical biomarker for NMOSD-AQP4.⁴¹

In 2020, it was shown for the first time that FAM19A5 concentrations are associated with depressive states in mice. Genetic deletion of FAM19A5 resulted in increased depressive behavior and impaired hippocampus-dependent spatial memory in mice. FAM19A5 levels in the plasma and hippocampus of chronic stress-treated mice were significantly reduced, whereas overexpression of human FAM19A5 selectively in the hippocampus may attenuate chronic stress-induced depressive behavior. This study provided a new mechanism for chronic stress-induced depression. It has been shown that FAM19A5 may be a new biomarker for the diagnosis and treatment strategy of depression.⁴² Kyu-Man Han et al in 2020 confirmed that serum FAM19A5 may be a potential biomarker of neurodegenerative changes in major depressive disorder (MDD) in humans. The study included 52 previously untreated patients with MDD and 60 healthy controls. Serum FAM19A5 levels were significantly higher in MDD patients than in the healthy controls group.

According to the authors, serum FAM19A5 levels may reflect reactive astrogliosis and associated neuroinflammation in MDD.⁴³

Another study from 2021 checked whether the concentration of FAM19A5 protein changed after administration of cilostazol (phosphodiesterase-3 inhibitor as an adjunctive to antidepressants) (CLS) in patients with MDD. Cilostazol is a phosphodiesterase type 3 (PDE3) inhibitor. Inhibition of PDE3 activity leads to an increase in cAMP concentration in blood platelets and smooth muscles of blood vessels, inhibiting platelet aggregation and dilating blood vessels. The study included 80 participants with MDD. They were given cilostazol 50 mg or placebo twice daily plus escitalopram (selective serotonin reuptake inhibitors) (ESC) 20 mg once daily for six weeks. Serum FAM19A5 concentrations were statistically significantly lower in the CLS group compared to the placebo group after the end of drug administration. According to the authors, FAM19A5 may be clinically helpful in assessing antidepressant response.⁴⁴

Also, in 2021, FAM19A5 was investigated to be associated with Parkinson's disease (PD) and Parkinson's disease with depression (PDD). Plasma FAM19A5 levels (2.456 ± 0.517) were shown to be significantly higher in the PD group compared to the control group (2.23 ± 0.457) ($P < 0.001$). Importantly, plasma FAM19A5 concentration was also significantly higher in the PDD subgroup (2.577 ± 0.408) compared with the nondepressed subgroup (2.406 ± 0.549) ($P = 0.045 < 0.05$). The authors suggest that plasma FAM19A5 may serve as potential tools for early prediction of PD and PDD in clinical settings.⁴⁵

The use of FAM19A5 in preventing, diagnosing, or treating central nervous system injuries, degenerative brain diseases, or central nervous system diseases seems promising.

FAM19A5 in Oncological Diseases

The discovery of FAM19A5 increased interest in the function of this protein in oncology. Tavan Janvilisri et al in 2015 tested new serum biomarkers for differentiating cholangiocarcinoma from benign biliary tract diseases. Using a proteomic approach, Tavan Janvilisri et al tested new serum biomarkers for differentiating cholangiocarcinoma (CCA) from benign biliary tract disease (BBTD). At that time, the available tumor markers, including CA19-9 and CEA, were ineffective and had limited use due to low sensitivity and specificity. Serum samples from 19 CCA and 17 BBTD patients were used. Five of the most essential proteins were found that showed the maximum fold change between CCA and BBTD. It included MAGED4B, KIAA0321, RBAK, and UPF3B, as well as the TAF5 protein, which was first named as FAM19A5. According to the authors, these proteins, including FAM19A5, will be clinically helpful in preventing misdiagnosis between CCA and BBTD as they have similar clinical manifestations.⁴⁶

In the same year, the study by Zhiqing Hu et al evaluated the clinical and prognostic significance of TAF5 in 90 human gastric cancer (GC) samples and the *in vitro* activity of TAF5 in cultured gastric cancer cells. TAF5 was upregulated in GC compared to adjacent normal tissues. Moreover, TAF5 overexpression in GCs was associated with poor differentiation and poorer tumor, lymph node, and metastasis stages. In addition, high TAF5 expression was correlated with poor patient outcomes. The authors suggest that TAF5 has a significant effect on GC progression.⁴⁷

The study by Yan-Fang Wang et al from 2020 included 25 patients with mantle cell lymphoma (MCL), one of modern oncology's significant challenges. The mean serum FAM19A5 concentration in MCL patients was significantly higher than in the control group ($P=0.0461$). FAM19A5 expression in serum and lymph nodes showed a significant correlation ($r=0.8683$, $P=0.001$). Moreover, the mean recurrence/death-free survival of MCL patients with high, intermediate, and low FAM19A5 expression was 17, 27, and 37.5 months, respectively, which showed a significant statistical difference ($P=0.0360$). The conclusions suggest that FAM19A5 expression levels are increased in MCL patients, and patients with high FAM19A5 expression are at increased risk of disease relapse or death. According to the authors, FAM19A5 may be a new prognostic marker and potential therapeutic target for MCL.⁴⁸

The 2022 study by Shoujing Luan et al aimed to investigate whether FAM19A5 could be a new target in diagnostics and prognostic in patients with thyroid cancer. It was observed that FAM19A5 levels were increased in thyroid cancer. FAM19A5 was an independent predictor of poor prognosis in thyroid cancer patients. According to the authors, FAM19A5 may serve as a potential biomarker in the diagnosis and prognosis of thyroid cancer.⁴⁹

Although the concentration of FAM19A5 is higher in patients with selected oncological diseases, there is still no information on the importance of this protein as a tumor marker.

FAM19 – Other Research Directions

In addition to research on the association of the FAM19A5 protein with nervous system disorders and cancer, its other functions in the pathophysiology of diseases were also searched for. In 2017, MinYoung Park et al demonstrated that FAM19A5 strongly stimulates murine bone marrow-derived macrophages (BMDM), causing chemotactic migration and inhibiting osteoclastogenesis induced by the receptor activator for nuclear factor κ B ligand (RANKL) gene. The authors suggest that FAM19A5 and its target N-formyl peptide receptor 2 (FPR2) may act as a novel endogenous ligand/receptor negatively regulating osteoclastogenesis.³¹

In the same year, in nephron progenitor cells, a DNA region in intron 2 of the Wnt9b FAM19A5 target gene was identified and shown to be physically related to β -catenin. Whether this element could act as a cell type-specific enhancer in mice and humans was tested. Although in multiple contexts, Myc is a target of β -catenin, authors' characterization of a cell type-specific enhancer for the Wnt9b/ β -catenin target gene Fam19a5 shows that Myc and β -catenin cooperate to activate gene expression controlled by this element.⁵⁰

Moreover, Yanfang Wang et al demonstrated that the FAM19A5/S1PR1 signaling pathway regulates mantle cell lymphoma viability and proliferation.⁵¹

N Sevane et al looked for reasons for the rapid livestock adaptation to extreme climatic conditions. They compared the methylomes of two Creole cattle breeds living in tropical environments with their putative Spanish ancestors. They wanted to understand the epigenetic mechanisms underlying the rapid adaptation of a domestic species to a new and more physiologically challenging environment. Candidate genes involved in adaptation processes in tropical areas have been revealed, including genes variously hyper- or hypomethylated above 80% in Creole samples showing biological features and functions related to the immune response, including the FAM19A5 gene. These data suggested the need for further research on the influence of this gene in disease resistance and the improvement of cattle productivity and welfare.⁵²

In 2022, it was checked whether there is a link between FAM19A5 and cerebral small vessel disease (cSVD). A total of 344 patients with recent small subcortical infarction (RSSI) and 265 healthy controls were included in the study. FAM19A5 was highly expressed in the RSSI group ($P = 0.023$), showing a positive correlation with cerebral infarct volume ($P < 0.01$). Furthermore, higher FAM19A5 levels reflect better outcomes in patients with RSSI. According to the authors, increased FAM19A5 levels are associated with cerebral small vessel disease and lead to better treatment outcomes.⁵³

Data on the association of FAM19A5 with physiology and other disorders still need to be made more explicit. There needs to be more information. A summary of data on the importance of FAM19A5 in physiology and metabolic disorders is presented in [Table 2](#).

Research on the relationship between FAM19A5 concentration and CNS functions or disorders has increased interest in the influence of FAM19A5 protein and energy homeostasis and metabolic disorders.

FAM19A5 - Metabolic Disorders

The role of different type of adipokines in metabolic disturbances for eg MetS is in the great interest among researchers all around the world. Each passing year brings about a deepening understanding of the mechanism underlying the function of adipokines such as leptin, visfatin, resistin and apelin ([Table 1](#)). Currently the search for a cause and effect relationship between FAM expression and the occurrence of metabolic disorders is still ongoing. The functions of this protein are still unclear and have been the subject of interest in several works. Undoubtedly, the influence of the tested protein on the centers responsible for maintaining energy homeostasis in the CNS, mainly the hypothalamus, probably plays an important role. In the meantime, clinical studies began to appear looking for a connection between FAM19A5 and metabolic disorders.

For the first time this relationship in 2008, Sarah Juel Paulsen et al showed that neuropeptide TFAFA5 is expressed in the hypothalamic paraventricular nucleus and is regulated by dehydration. New genes involved in the hypothalamic

Table 2 A Summary of Data on the Importance of FAM19A5 in Other Disorders

Data	Study group / tissues / genes	Results / functions
Sarah Juel Paulsen et al, 2008 ⁵⁴	Cells from the rat brain, 379 units	<ul style="list-style-type: none"> • Neuropeptide TAF5 is expressed in the hypothalamic paraventricular nucleus • TAF5 is expressed in the hypothalamic paraventricular nucleus and is regulated by dehydration • TAF5 mRNA is highly expressed in the hypothalamic PVN, which binds vasopressin and oxytocin in magno- and paracellular neurons
MinYoung Park et al, 2017 ³¹	Bone marrow cells from wild-type C57BL/6 mice of five to seven weeks of age	<ul style="list-style-type: none"> • FAM19A5 strongly stimulates murine BMDM, causing chemotactic migration and inhibiting osteoclastogenesis induced by the RANKL gene • FAM19A5 and its target FPR2 may act as a novel endogenous ligand/receptor negatively regulating osteoclastogenesis
Pan X. et al, 2017 ⁵⁰	Wnt9b, Six2-eGFPcre BAC, catnb flox, c-Myc i N-Myc mice	<ul style="list-style-type: none"> • Nephron progenitor cells, a DNA region in intron 2 of the Wnt9b FAM19A5 target gene was identified and shown to be physically related to β-catenin • Myc is a target of β-catenin, authors' characterization of a cell type-specific enhancer for the Wnt9b/β-catenin target gene FAM19A5 shows that Myc and β-catenin cooperate to activate gene expression controlled by this element
N Sevane et al, 2019 ⁵²	Colombian cattle (n=6)	<ul style="list-style-type: none"> • Genes involved in adaptation processes in tropical areas have been revealed, including genes variously hyper- or hypomethylated above 80% in Creole samples showing biological features and functions related to the immune response, including the FAM19A5 gene
You-Bin Lee et al, 2019 ⁵⁵	223 individuals (45 without diabetes and 178 with type 2 diabetes) from the Korea Guro Diabetes Programme in Korea, Asia.	<ul style="list-style-type: none"> • Serum FAM19A5 concentrations (pg/mL) were higher in patients with type 2 diabetes [median (interquartile range), 172.70 (116.19, 286.42)] compared to those without diabetes [92.09 (70.32, 147.24)] ($p < 0.001$). • Increases in the serum FAM19A5 tertile were associated with trends in waist-to-hip ratio, fasting plasma glucose, glycated hemoglobin, and mean shoulder pulse wave velocity. • FAM19A5 serum was positively correlated with WC, WHR, ALT, fasting plasma glucose, HbA1c, and mean shoulder pulse wave velocity.
Xia Lei et al, 2019 ⁵⁶	Cells from Eight-week-old C57BL/6J male mice	<ul style="list-style-type: none"> • Expression of FAM19A5 in various areas of the mouse brain is induced or suppressed by undernutrition and nutritional states. • In male mice, FAM19A5 deficiency altered food intake patterns during the light-dark cycle
Fatemeh Ali Yari et al, 2021 ⁵⁷	Total of 69 subjects including 37 NAFLD and 32 control subjects	<ul style="list-style-type: none"> • The plasma FAM19A5 concentration in NAFLD patients was significantly lower in NAFLD patients compared with the control group. • significant negative correlations were observed between plasma FAM19A5 levels and BMI, visceral fat, ALT, AST, LS, and cIMT

(Continued)

Table 2 (Continued).

Data	Study group / tissues / genes	Results / functions
Wesołek A. et al, 2022 ⁵⁸	45 people with MetS, 35 healthy people without MetS	<ul style="list-style-type: none"> • There were no differences in the blood levels of FAM19A5 between the groups. • The level of FAM19A5 was 163.16±55.11 pg/mL and 197.57 ±112.89 pg/mL (p=0.1341) in subjects with and without MetS, respectively. • In group A, there was a correlation between FAM19A5 and DBP (R= -0.40) and HDL levels (R= -0.37). • In patients with MetS, elevated FAM19A5 serum levels may indicate dyslipidemia development
Hoyun Kwak et al, 2020 ⁵⁹	C57BL/6J mice's central and peripheral nervous system and peripheral tissues	<ul style="list-style-type: none"> • Total FAM19A5 levels in the central and peripheral nervous system were higher than in any peripheral tissues

Abbreviations: ALT, glutamic pyruvic transferase; AST, aspartate transaminase; BMDM, bone marrow-derived macrophages; cIMT, carotid intima media thickness; DBP, diastolic blood pressure; DNA, deoxyribonucleic acid; FAM19A5, TFA Chemokine Like Family Member 5; FPR2, N-formyl peptide receptor 2; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LS, liver stiffness; MetS, metabolic syndrome; mRNA, messenger RNA; NAFLD, nonalcoholic fatty liver disease; PVN, paraventricular nucleus; RANKL, receptor activator for nuclear factor κ B ligand; TFA5, TFA Chemokine Like Family Member 5; WVC, waist circumference; WHR, waist to hip ratio.

control of energy homeostasis in rats were sought. The distribution of TFA5 mRNA expression was analyzed using quantitative PCR on a rat cDNA tissue library. Previous reports confirmed that TFA5 is mainly expressed in the central nervous system. Additionally, TFA5 mRNA is highly expressed in the hypothalamic paraventricular nucleus (PVN), which binds vasopressin and oxytocin in magno- and paracellular neurons. It was also checked whether fasting or dehydration can affect TFA5 mRNA levels. The results showed that TFA5 mRNA was explicitly down-regulated in the PVN following water deprivation. The authors showed the need for further research because the significance of the TFA5 protein remained unclear and unconfirmed.⁵⁴

In the same year, the team of Jana Bundzikova et al cited previous results on the TFA5 gene and protein in a review where reports on the response of substances co-expressed in hypothalamic magnocellular neurons to osmotic challenges in normal and Brattleboro rats.⁶⁰ Knowledge about the function and function of the TFA5 gene and protein remained unclear in 2008.⁶⁰

The functions of FAM19A5 were further searched. Dasol Kang et al in 2020 showed that FAM19A5 was expressed in mouse hypothalamic cells expressing proopiomelanocortin (POMC) and neuropeptide Y (NPY)/agouti-related peptide (AgRP) and in microglia. Moreover, TNF- α , which induces inflammatory responses in the disease, significantly increases FAM19A5 expression in the hypothalamus. Additionally, inhibition of FAM19A5 expression reduced TNF- α -induced anorexia, body weight loss, and TNF- α -induced inflammatory factor expression in mice. The authors concluded that FAM19A5 plays an essential role in hypothalamic inflammatory responses. This suggested the connection of the FAM19A5 protein with the feeling of hunger and satiety also.⁶¹

Hoyun Kwak et al 2020 examined FAM19A5 protein levels and their gene expression in mice's central and peripheral nervous system and peripheral tissues. In the results, total FAM19A5 levels in the central and peripheral nervous system were higher than in any peripheral tissues. They were also higher than the levels in adipose tissue. These results also emphasize the need to understand the detailed functions of the FAM19A5 protein in the nervous system and adipose tissue.⁵⁹

In 2019, B. An et al wanted to identify candidate genes for the organism measurement features of beef cattle 463 Wagyu (n = 463 animals). In addition to FAM19A5, 11 genes have been discovered. From this, the FAM19A5 gene was considered a novel candidate gene associated with body dimensional characteristics in the beef cattle studied. The FAM19A5 gene was associated with animals' hip height, height and body length.⁶² This is the first time this protein has been linked to the dimensional features of the animal body.

You-Bin Lee et al in 2019 showed that serum FAM19A5 concentrations (pg/mL) were higher in patients with type 2 diabetes mellitus [median (interquartile range), 172.70 (116.19, 286.42)] compared to those without diabetes [92.09 (70.32, 147.24)] ($p < 0.001$). The association of FAM19A5 with other metabolic parameters was also checked, as well as with anthropometric measurements. Increases in the serum FAM19A5 tertile were associated with trends in waist-to-hip ratio, fasting plasma glucose, glycated hemoglobin, and mean shoulder pulse wave velocity. The authors' novel results showed that FAM19A5 serum was positively correlated with waist circumference, waist-to-hip ratio, alanine aminotransferase, fasting plasma glucose, glycated hemoglobin, and mean shoulder pulse wave velocity. This was the first study to link FAM19A5 to selected inflammation parameters in people with type 2 diabetes.⁵⁵

Xia Lei, in 2019, showed that the expression of FAM19A5 in various areas of the mouse brain is induced or suppressed by undernutrition and nutritional states. In male mice, FAM19A5 deficiency altered food intake patterns during the light-dark cycle. The authors highlighted for the first time the potential role of the FAM19A5 protein in modulating physiology and links to appetite.⁵⁶

Fatemeh Ali Yari et al wanted to test whether FAM19A5 is associated with non-alcoholic fatty liver disease (NAFLD). Sixty-nine patients were included in the study, including 37 with NAFLD and 32 from the control group. In the results, the plasma FAM19A5 concentration in NAFLD patients was significantly lower in NAFLD patients compared with the control group. Moreover, significant negative correlations were observed between plasma FAM19A5 levels and BMI, visceral fat, alanine aminotransferase (ALT), aspartate aminotransferase (AST), liver stiffness (LS), and carotid intima media thickness (cIMT). This is the first time circulating FAM19A5 levels have been reported to be associated with NAFLD. The authors suggested continuing research to link FAM19A5 with liver disorders.⁵⁷

It was also checked whether the concentration of FAM19A5 protein differs in people with MetS compared to healthy people. This was our study, the aim of which was to look for a relationship between FAM19A5 and MetS exponents for the first time. The concentration of FAM19A5 was determined in 45 people with MetS (group A) and 35 healthy people without MetS (group B). There were no differences in the blood levels of FAM19A5 between the groups. The level of FAM19A5 was 163.16 ± 55.11 pg/mL and 197.57 ± 112.89 pg/mL ($p = 0.1341$) in subjects with and without MetS, respectively. In group A, there was a correlation between FAM19A5 and diastolic blood pressure (DBP) ($R = -0.40$) and high-density lipoprotein (HDL) levels ($R = -0.37$). In patients with MetS, elevated FAM19A5 serum levels may indicate dyslipidemia development.⁵⁸

The FAM19A5 protein has also been shown to be associated with cardiovascular diseases. In 2018, Yingbao Wang et al examined whether adipose tissue-derived FAM19A5 regulates vascular pathology following trauma in rats. It was shown that the FAM19A5 protein was abundantly expressed in adipose tissue. Interestingly, FAM19A5 expression was decreased in obese mice. FAM19A5 overexpression significantly inhibited vascular smooth muscle cell proliferation, migration, and neointima formation in injured rat carotid arteries. The information from the 2018 project by Yingbao Wang et al was a breakthrough in the reports on the importance of FAM19A5. The FAM19A5 protein was first identified as an adipokine.²⁹

Fei Ma et al 2022 checked whether there are clinical associations between FAM19A5 levels and the presence and severity of coronary artery disease (CAD). The study included 186 patients with CAD and 58 without CAD who underwent coronary angiography (CAG). Serum FAM19A5 levels in the CAD group were significantly lower than in the non-CAD group [1.53 (1.13 – 2.27) ng/mL vs 2.33 (1.69 – 3.51) ng/mL; $P = 0.013$]. Logistic regression analysis showed that reduced serum FAM19A5 concentration was a risk factor for coronary heart disease (OR: 0.563, 95% CI: 0.409–0.776, $p < 0.001$). According to the authors, serum FAM19A5 concentration has been negatively associated with the presence and severity of coronary artery disease and may represent a new biomarker for diagnosing and determining the severity of coronary artery disease.⁶³

Chen Weia et al 2022 checked whether FAM19A5 is associated with acute coronary syndrome (ACS). The study included 168 consecutive hospitalized patients with suspected ACS. After adjusting for confounding factors, serum FAM19A5 levels were independently associated with ACS ($p < 0.05$). Moreover, serum FAM19A5 levels correlated with ACS severity. FAM19A5 is, therefore, a new potential clinical biomarker of ACS.⁶⁴

The summary of data about connections between FAM19A5 and metabolic disorders is presented in Table 3.

Table 3 A Summary of Data on the Importance of FAM19A5 in Metabolic Disorders

Data	Study group / tissues / genes	Results / functions
Sarah Juel Paulsen et al, 2008 ⁵⁴	Tissues from mice	<ul style="list-style-type: none"> • TAFAS is expressed in the hypothalamic paraventricular nucleus and is regulated by dehydration, • TAFAS mRNA is highly expressed in the hypothalamic PVN, which binds vasopressin and oxytocin in magno- and paracellular neurons, • TAFAS mRNA was explicitly down-regulated in the PVN following water deprivation
Dasol Kang et al, 2020 ⁶¹	Eight-week-old male C57BL/6 mice	<ul style="list-style-type: none"> • FAM19A5 was expressed in mouse hypothalamic POMC and NPY/ AgRP and in microglia, • TNF-α, which induces inflammatory responses in the disease, significantly \uparrow FAM19A5 expression in the hypothalamus, inhibition of FAM19A5 expression reduced TNF-α-induced anorexia, body weight loss, and TNF-α-induced inflammatory factor expression
Hoyun Kwak et al, 2020 ⁵⁹	C57BL/6J mice	<ul style="list-style-type: none"> • Total FAM19A5 levels in the central and peripheral nervous system were \uparrow than in any peripheral tissues, • They were also \uparrow than the levels in adipose tissue
B. An et al, 2019 ⁶²	Beef cattle Wagyu (n = 463 animals)	<ul style="list-style-type: none"> • FAM19A5, 11 genes have been discovered, • The FAM19A5 gene was considered a novel candidate gene associated with body dimensional characteristics in the beef cattle, • The FAM19A5 gene was associated with animals' hip height, height and body length
You-Bin Lee et al, 2019 ⁵⁵	223 individuals (45 without diabetes and 178 with type 2 diabetes)	<ul style="list-style-type: none"> • That serum FAM19A5 concentrations (pg/mL) were \uparrow in patients with type 2 diabetes mellitus [median (interquartile range), 172.70 (116.19, 286.42)] compared to those without diabetes [92.09 (70.32, 147.24)] ($p < 0.001$), • Increases in the serum FAM19A5 tertile were associated with trends in waist-to-hip ratio, fasting plasma glucose, glycated hemoglobin, and mean shoulder pulse wave velocity, • FAM19A5 serum was positively correlated with waist circumference, waist-to-hip ratio, alanine aminotransferase, fasting plasma glucose, glycated hemoglobin, and mean shoulder pulse wave velocity
Xia Lei, 2019 ⁵⁶	Eight-week-old C57BL/6J mice	<ul style="list-style-type: none"> • The expression of FAM19A5 in various areas of the mouse brain is induced or suppressed by undernutrition and nutritional states, • In male mice, FAM19A5 deficiency altered food intake patterns during the light-dark cycle
Fatemeh Ali Yari et al, 2021 ⁵⁷	69 patients (37 with NAFLD and 32 from the control group)	<ul style="list-style-type: none"> • The plasma FAM19A5 concentration in NAFLD patients was significantly \downarrow in NAFLD patients compared with the control group, • Significant negative correlations were observed between plasma FAM19A5 levels and BMI, visceral fat, ALT, AST, LS, and cIMT
Wesołek et al, 2022 ⁵⁸	45 people with MetS (group A) and 35 healthy people without MetS (group B)	<ul style="list-style-type: none"> • There were no differences in the blood levels of FAM19A5 between the groups, • The level of FAM19A5 was 163.16 ± 55.11 pg/mL and 197.57 ± 112.89 pg/mL ($p = 0.1341$) in subjects with and without MetS, respectively, • In group A, there was a correlation between FAM19A5 and DBP ($R = -0.40$) and HDL levels ($R = -0.37$), • In patients with MetS, elevated FAM19A5 serum levels may indicate dyslipidemia development
Yingbao Wang et al, 2018 ²⁹	Male C57BL/6J mice	<ul style="list-style-type: none"> • FAM19A5 protein was abundantly expressed in adipose tissue, • FAM19A5 expression was \downarrow in obese mice, • FAM19A5 overexpression significantly inhibited vascular smooth muscle cell proliferation, migration, and neointima formation in injured rat carotid arteries

(Continued)

Table 3 (Continued).

Data	Study group / tissues / genes	Results / functions
Fei Ma et al, 2022 ⁶³	186 patients with of CAD and 58 without CAD who underwent CAG	<ul style="list-style-type: none"> • Serum FAM19A5 levels in the CAD group were significantly ↓ than in the non-CAD group [1.53 (1.13–2.27) ng/mL vs 2.33 (1.69–3.51) ng/mL; P = 0.013], • Logistic regression analysis showed that reduced serum FAM19A5 concentration was a risk factor for coronary heart disease (OR: 0.563, 95% CI: 0.409–0.776, p < 0.001), • Serum FAM19A5 concentration has been negatively associated with the presence and severity of coronary artery disease and may represent a new biomarker for diagnosing and determining the severity of coronary artery disease
Chen Weia et al, 2022 ⁶⁴	ACS (n = 121) and Non-ACS (n = 47) groups	<ul style="list-style-type: none"> • FAM19A5 levels were independently associated with ACS (p < 0.05), • Serum FAM19A5 levels correlated with ACS severity, • FAM19A5 is a new potential clinical biomarker of ACS

Abbreviations: ACS, acute coronary syndrome; AgRP, agouti-related peptide; ALT, glutamic pyruvic transferase; AST, aspartate transaminase; BMI, body mass index; CAD, coronary artery disease; CAG, coronary angiography; cIMT, carotid intima media thickness; DBP, diastolic blood pressure; FAM19A5, Tafa Chemokine Like Family Member 5; HDL, high-density lipoprotein; LS, liver stiffness; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NPY, neuropeptide Y; POMC, cells expressing proopiomelanocortin; PVN, paraventricular nucleus; TAFAS, Tafa Chemokine Like Family Member 5; TNF- α , tumor necrosis factor α .

Considering that the growing obesity epidemic increases the number of diagnoses of cardiovascular diseases, it seems necessary to look for further links of the FAM19A5 protein with heart and blood vessel diseases and metabolic diseases. Some of the above results are contradictory and require further extension.

Abbreviations

MCP-1, monocytes chemoattractant protein-1; aCGH, array comparative genomic hybridization; ACS, acute coronary syndrome; AgRP, agouti-related peptide; ALT, glutamic pyruvic transferase; AST, aspartate transaminase; BAT, brown adipose tissue; BBTD, benign biliary tract disease; BMDM, bone marrow-derived macrophages; BMI, body mass index; CAD, coronary artery disease; CAG, coronary angiography; CAP-1, adenylyl cyclase-associated protein 1; CCA, cholangiocarcinoma; Cimt, carotid intima media thickness; CMKLR1, chemerin chemokine-like receptor 1; CNS, central nervous system; CRP, c-reactive protein; cSVD, cerebral small vessel disease; CT, computed tomography; DBP, diastolic blood pressure; DNA, deoxyribonucleic acid; DXA, double-beam X-ray absorptiometry; ESC, selective serotonin reuptake inhibitors; FAM19A5, Tafa Chemokine Like Family Member 5; FISH, fluorescence in situ hybridization; FPR2, N-formyl peptide receptor 2; GC, gastric cancer; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IKK, I κ B kinase; IL-6, interleukin-6; JNKs, c-Jun N-terminal kinase; KI, knock-in; LS, liver stiffness; MCL, mantle cell lymphoma; MDD, major depressive disorder; MetS, metabolic syndrome; MRI, magnetic resonance imaging; mRNA, messenger RNA; NAD, nicotinamide adenine dinucleotide; NAFLD, nonalcoholic fatty liver disease; NMOSD-AQP4, neuromyelitis optica spectrum disorders with positive aquaporin-4 antibody; NPY, neuropeptide Y; PCOS, polycystic ovary syndrome; PCR, polymerase chain reaction; PD, Parkinson's disease; PDD, Parkinson's disease with depression; POMC, proopiomelanocortin; PVN, paraventricular nucleus; RANKL, receptor activator for nuclear factor κ B ligand; RBP-4, retinol-binding protein 4; RSSI, recent small subcortical infarction; SNP, single nucleotide polymorphism; SVF, stromal vascular fraction cells; TAFAS, Tafa Chemokine Like Family Member 5; TG, triglycerides; TNF- α , tumor necrosis factor α ; VSMCs, vascular smooth muscle cells; WAT, white adipose tissue; WC, waist circumference; WHO, World Health Organization; WHR, waist to hip ratio; WOBASZ, Multi-centre National Population Health Examination Study.

Summary

Serum FAM19A5 level is correlated with type 2 diabetes, NAFLD, waist circumference, waist-to-hip ratio, glutamic pyruvic transferase, fasting plasma glucose, HbA1c, and mean shoulder pulse wave velocity. However, considering today's knowledge about FAM19A5, we cannot consider this protein a metabolic syndrome biomarker. The main reason for this answer to the question in the title is the divergent results of the studies presented above. It should be emphasized,

however, that the importance of this adipocytokine in the pathogenesis of many diseases affecting various systems proves the excellent research potential of FAM19A5. It will also allow us to understand the importance of metabolic disorders in the entire body's functioning. More information is needed on the association of the FAM19A5 protein with other substances, such as insulin. Like other adipokines, the FAM19A5 protein seems to be an essential substance in the human body.

Disclosure

Paweł Bogdański and Monika Szulińska are co-last authors for this study. The authors report no conflicts of interest in this work.

References

1. Thomas E, Fitzpatrick J, Etl AI MS, Taylor-Robinson SD, Bell JD. Whole body fat: content and distribution. *Prog Nucl Magnet Res Spect.* 2013;73:56–80. doi:10.1016/j.pnmrs.2013.04.001
2. Kuryszko J, Sławuta P, Sapikowski G. Secretory function of adipose tissue. *Pol J Veterin Sci.* 2016;19:441–446. doi:10.1515/pjvs-2016-0056
3. Colaianni G, Colucci S, Grano M. Anatomy and physiology of adipose tissue. In: Lenzi A, Migliaccio S, Donini L, editors. *Multidisciplinary Approach to Obesity.* Springer International Publishing; 2015:3–12.
4. Buczkowska M, Buczkowski K, Głogowska-Gruszka A, et al. Adipose tissue – the structure and its functions, with particular emphasis on the characteristics of selected adipokines and their effects on the organism. *Med Og Nauk Zdr.* 2019;25:162–169. doi:10.26444/monz/110429
5. Budzulak J, Majewska KA, Kędzia A. Malnutrition as the cause of growth retardation among children in developed countries. *Ann Agric Environ Med.* 2022;29:336–341. doi:10.26444/aaem/148010
6. Drygas W, Niklas AA, Piwońska A, et al. Multi-centre national population health examination survey (WOBASZ II study): assumptions, methods, and implementation. *Kardiologia Polska (Polish Heart Journal).* 2016;74:681–690. doi:10.5603/KP.a2015.0235
7. World Health Organisation. *WHO EUROPEAN REGIONAL OBESITY REPORT 2022.* Denmark; 2022.
8. Placzkowska S, Pawlik-Sobiecka L, Kokot I, et al. Wykorzystanie bezpośrednich i pośrednich metod oceny profilu składu ciała u młodych osób – badanie pilotażowe. *Fam Med Prim Care Rev.* 2015;1:33–38.
9. Tchang BG, Saunders KH, Igel LI. Best practices in the management of overweight and obesity. *Med Clin North Am.* 2021;105:149–174. doi:10.1016/j.mcna.2020.08.018
10. Luniewski M, Matyjaszek-Matuszek B, Lenart-Lipińska M. Diagnosis and non-invasive treatment of obesity in adults with type 2 diabetes mellitus: a review of guidelines. *J Clin Med.* 2023;12:4431. doi:10.3390/jcm12134431
11. Gaesser GA, Angadi SS. Obesity treatment: weight loss versus increasing fitness and physical activity for reducing health risks. *iScience.* 2021;24:102995. doi:10.1016/j.isci.2021.102995
12. Bogdański P, Filipiak KJ, Kowalska I, et al. Interdyscyplinarne stanowisko w sprawie rozpoznawania i leczenia otyłości. *Forum Zaburzen Metabolicznych.* 2020;11:47–54.
13. Ellulu MS, Patimah I, Khaza'ai H, et al. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci.* 2017;4:851–863. doi:10.5114/aoms.2016.58928
14. Khanna D, Khanna S, Khanna P, et al. Obesity: a Chronic Low-Grade Inflammation and Its Markers. *Cureus.* 2022;14(2):e22711. doi:10.7759/cureus.22711
15. Kolb H. Obese visceral fat tissue inflammation: from protective to detrimental? *BMC Med.* 2022;20:494. doi:10.1186/s12916-022-02672-y
16. Chwalba A, Machura E, Ziora K, Ziora D. The role of adipokines in the pathogenesis and course of selected respiratory diseases. *Endokrynol Pol.* 2019;70:504–510. doi:10.5603/EP.a2019.0051
17. Cook KS, Min HY, Johnson D, et al. Adipsin: a circulating serine protease homolog secreted by adipose tissue and sciatic nerve. *Science.* 1987;237(4813):402–405. doi:10.1126/science.3299705
18. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. *Nature.* 1994;1(372):6505.
19. Al-Hussaini HA, Alburghaif AH, Naji MA. Leptin hormone and its effectiveness in reproduction, metabolism, immunity, diabetes, hopes and ambitions. *J Med Life.* 2021;14(5):600–605. doi:10.25122/jml-2021-0153
20. Abdalla MMI. Role of visfatin in obesity-induced insulin resistance. *World J Clin Cases.* 2022;10:10840–10851. doi:10.12998/wjcc.v10.i30.10840
21. Borsuk A, Biernat W, Zięba D, et al. Wielokierunkowe działanie rezystyny w organizmie. *Postępy Higieny i Medycyny Doświadczalnej.* 2018;72:327–338. doi:10.5604/01.3001.0011.8252
22. Gandham R, Sumathi M, Dayanand C, et al. Apelin and its Receptor: an Overview. *JCDR.* 2019;13(6):BE01- BE06.
23. Stojek M. The role of chemerin in human disease. *Postępy Hig Med Dosw.* 2017;71:110–117. doi:10.5604/01.3001.0010.3795
24. Roguska J, Zubkiewicz-Kucharska A. Chemerin as an early marker of metabolic syndrome. *Pediatr Endocrinol Diabetes Me.* 2018;24:45–51. doi:10.18544/PEDM-24.01.0102
25. Badowska-Kozakiewicz AM. Biologiczna rola czynnika martwicy nowotworów α w fizjologii i patofizjologii. *Przegląd Menopauzalny.* 2013;14:1:12.
26. Dobrowolski P, Dudek D, Dyrbuś K, et al.; A joint position paper by the Polish Society of Hypertension, Polish Society for the Treatment of Obesity, Polish Lipid Association, Polish Association for Study of Liver, Polish Society of Family Medicine, Polish Society of Lifestyle Medicine, Division of Prevention and Epidemiology Polish Cardiac Society, “Club 30” Polish Cardiac Society, and Division of Metabolic and Bariatric Surgery Society of Polish Surgeons. Metabolic syndrome – a new definition and management guidelines. *Arch Med Sci.* 2022;18:1133–1156.
27. Wyrzykowski B. Epidemiologia zespołu metabolicznego w Polsce. Wyniki programu WOBASZ. *Kardiologia Polska.* 2005;63(6).
28. Mohamed SM, Shalaby MA, El-Shiekh RA, et al. Metabolic syndrome: risk factors, pathogenesis, and management with natural approaches. *Food Chem Advan.* 2023;3:100335. doi:10.1016/j.focha.2023.100335

29. Wang Y, Chen D, Zhang Y, et al. Novel adipokine, FAM19A5, inhibits neointima formation after injury through sphingosine-1-phosphate receptor 2. *Circulation*. 2018;138:48–63. doi:10.1161/CIRCULATIONAHA.117.032398
30. Shahapal A, Cho EB, Yong HJ, et al. FAM19A5 expression during embryogenesis and in the adult traumatic brain of FAM19A5-lacZ knock-in mice. *Front Neurosci*. 2019;13:917. doi:10.3389/fnins.2019.00917
31. Park M, Kim HS, Lee M, et al. FAM19A5, a brain-specific chemokine, inhibits RANKL-induced osteoclast formation through formyl peptide receptor 2. *Sci Rep*. 2017;7. doi:10.1038/s41598-017-15586-0
32. Xie K, Liu L, Yin C, et al. Follistatin-Like 1 and family with sequence similarity to 19 member a5 levels are decreased in obese children and associated with glucose metabolism. *Ann Nutr Metab*. 2022;78:213–221. doi:10.1159/000524624
33. Tom Tang Y, Emtage P, Funk WD, et al. TFAFA: a novel secreted family with conserved cysteine residues and restricted expression in the brain. *Genomics*. 2004;83:727–734. doi:10.1016/j.ygeno.2003.10.006
34. de Ståhl T D, Hartmann C, de Bustos C, et al. Chromosome 22 tiling-path array-CGH analysis identifies germ-line- and tumor-specific aberrations in patients with glioblastoma multiforme. *Gen Chromos Can*. 2005;44:161–169. doi:10.1002/gcc.20226
35. Kashevarova AA, Belyaeva EO, Nikonov AM, et al. Compound phenotype in a girl with r(22), concomitant microdeletion 22q13.32-q13.33 and mosaic monosomy 22. *Mol Cytogenet*. 2018;11:26. doi:10.1186/s13039-018-0375-3
36. Zheng C, Chen D, Zhang Y, et al. FAM19A1 is a new ligand for GPR1 that modulates neural stem-cell proliferation and differentiation. *FASEB J*. 2018;fj201800020RRR. doi:10.1096/fj.201800020RRR
37. Inan C, Sayin NC, Gurkan H, et al. Schizencephaly accompanied by occipital encephalocele and deletion of chromosome 22q13.32: a case report. *Fetal Pediatr Pathol*. 2019;38:496–502. doi:10.1080/15513815.2019.1604921
38. Khalaj AJ, Sterky FH, Sclip A, et al. Deorphanizing FAM19A proteins as pan-neurexin ligands with an unusual biosynthetic binding mechanism. *J Cell Biol*. 2020;219:e202004164. doi:10.1083/jcb.202004164
39. Yong HJ, Ha N, Cho EB, et al. The unique expression profile of FAM19A1 in the mouse brain and its association with hyperactivity, long-term memory and fear acquisition. *Sci Rep*. 2020;10:3969. doi:10.1038/s41598-020-60266-1
40. Li J, Li S, Song Y, et al. Association of serum FAM19A5 with cognitive impairment in vascular dementia. *Dis Markers*. 2020;2020:8895900. doi:10.1155/2020/8895900
41. Lee HL, Seok HY, Ryu H-W, et al. Serum FAM19A5 in neuromyelitis optica spectrum disorders: can it be a new biomarker representing clinical status? *Mult Scler*. 2020;26:1700–1707. doi:10.1177/1352458519885489
42. Huang S, Zheng C, Xie G, et al. FAM19A5/TFAFA5, a novel neurokinin, plays a crucial role in depressive-like and spatial memory-related behaviors in mice. *Mol Psychiatry*. 2021;26:2363–2379. doi:10.1038/s41380-020-0720-x
43. Han KM, Tae W-S, Kim A, et al. Serum FAM19A5 levels: a novel biomarker for neuroinflammation and neurodegeneration in major depressive disorder. *Brain Behav Immun*. 2020;87:852–859. doi:10.1016/j.bbi.2020.03.021
44. Abdallah MS, Ramadan AN, Omara-Reda H, et al. Double-blind, randomized, placebo-controlled pilot study of the phosphodiesterase-3 inhibitor cilostazol as an adjunctive to antidepressants in patients with major depressive disorder. *CNS Neurosci Ther*. 2021;27:1540–1548. doi:10.1111/cns.13731
45. Li XN, Hao D-P, Qu M-J, et al. Development and validation of a plasma FAM19A5 and MRI-based radiomics model for prediction of parkinson's disease and parkinson's disease with depression. *Front Neurosci*. 2021;15:795539. doi:10.3389/fnins.2021.795539
46. Janvilisri T, Leelawat K, Roytrakul S, et al. Novel Serum Biomarkers to Differentiate Cholangiocarcinoma from Benign Biliary Tract Diseases Using a Proteomic Approach. *Dis Markers*. 2015;2015:105358. doi:10.1155/2015/105358
47. Hu Z, Niu G, Ren J, et al. TFAFA5 promotes proliferation and migration in gastric cancer. *Mol Med Rep*. 2019;20:4477–4488. doi:10.3892/mmr.2019.10724
48. Wang YF, Huang S-Y, Zhang Z-H, et al. Clinical efficacy of allo-HSCT on FLT3-ITD positive AML patients. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2020;28(4):1183–1188. doi:10.19746/j.cnki.issn.1009-2137.2020.04.017
49. Luan S, Li J, Qin S, et al. FAM19A5 is an independent prognostic biomarker in thyroid cancer. *Res Square*. 2022. doi:10.21203/rs.3.rs-1712708/v1
50. Pan X, Karner CM, Carroll TJ. Myc cooperates with β -catenin to drive gene expression in nephron progenitor cells. *Development*. 2017;144:4173–4182. doi:10.1242/dev.153700
51. Wang Y, Zhang Z, Wan W, et al. FAM19A5/S1PR1 signaling pathway regulates the viability and proliferation of mantle cell lymphoma. *J Recept Signal Transduction Res*. 2022;42:225–229. doi:10.1080/10799893.2021.1895220
52. Sevane N, Martínez R, Bruford MW. Genome-wide differential DNA methylation in tropically adapted Creole cattle and their Iberian ancestors. *Anim Genet*. 2019;50:15–26. doi:10.1111/age.12731
53. Hao Z, Yang S, Yin R, et al. Increased level of FAM19A5 is associated with cerebral small vessel disease and leads to a better outcome. *PeerJ*. 2022;10:e13101. doi:10.7717/peerj.13101
54. Paulsen SJ, Christensen MT, Vrang N, et al. The putative neuropeptide TFAFA5 is expressed in the hypothalamic paraventricular nucleus and is regulated by dehydration. *Brain Research*. 2008;1199:1–9. doi:10.1016/j.brainres.2007.12.074
55. Lee YB, Hwang H-J, Kim JA, et al. Association of serum FAM19A5 with metabolic and vascular risk factors in human subjects with or without type 2 diabetes. *Diab Vasc Dis Res*. 2019;16:530–538. doi:10.1177/1479164119860746
56. Lei X, Liu L, Terrillion CE, et al. FAM19A1, a brain-enriched and metabolically responsive neurokinin, regulates food intake patterns and mouse behaviors. *THE FASEB Journal*. 2019;33:14734–14747. doi:10.1096/fj.201901232RR
57. Yari FA, Shabani P, Karami S, et al. Circulating levels of FAM19A5 are inversely associated with subclinical atherosclerosis in non-alcoholic fatty liver disease. *BMC Endocr Disord*. 2021;21:153. doi:10.1186/s12902-021-00820-8
58. Wesolek A, Skoracka K, Skrypnik K, et al. Assessment of progranulin and FAM19A5 protein blood levels in patients with metabolic syndrome. *J Physiol Pharmacol*. 2022;73.
59. Kwak H, Cho EH, Lee YN, et al. Is FAM19A5 an adipokine? Peripheral FAM19A5 in wild-type, FAM19A5 knock-out, and LacZ knock-in mice. *bioRxiv*. 2020. doi:10.1101/2020.02.19.955351
60. Bundzikova J, Pirnik Z, Zelena D, et al. Response of substances co-expressed in hypothalamic magnocellular neurons to osmotic challenges in normal and brattleboro rats. *Cell Mol Neurobiol*. 2008;28:1033–1047. doi:10.1007/s10571-008-9306-x
61. Kang D, Kim HR, Kim KK, et al. Brain-specific chemokine FAM19A5 induces hypothalamic inflammation. *Biochem Biophys Res Commun*. 2020;523:829–834. doi:10.1016/j.bbrc.2019.12.119

62. An B, Xia J, Chang T, et al. Genome-wide association study reveals candidate genes associated with body measurement traits in Chinese wagu beef cattle. *Anim Genet.* 2019;50:386–390. doi:10.1111/age.12805
63. Ma F, Hao J, Zhao J, et al. Circulating FAM19A5 level is associated with the presence and severity of coronary artery disease. *Int J Cardiol.* 2022;354:50–55. doi:10.1016/j.ijcard.2022.03.011
64. Wei C, Liu Y, Xing E, et al. Association between novel pro- and anti- inflammatory adipocytokines in patients with acute coronary syndrome. *Clin Appl Thromb Hemost.* 2022;28:10760296221128020. doi:10.1177/10760296221128021

Diabetes, Metabolic Syndrome and Obesity

Dovepress

Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-journal>