Future Biochemistry and Bioscience
Yenilikçi Biyokimya ve Biyobilim

FBB 2024;6(2):61-71
http://doi.org/10.48086/ASD0066

Derleme Makalesi /Review Article

Asprosin ve Neuregulin-4: Tip 2 Diabetes Mellitus'un Glisemik Düzenlemesinde Rol Alan Adipokinlere Bir Bakış

Asprosin and Neuregulin-4: A Focus on Novel Adipokines for The Glycaemic Regulation in Type 2 Diabetes Mellitus

Musa Latif ÇÖLLÜOĞLU [1,2*], Neslihan BUKAN[3]

[1]Gazi Üniversitesi Sağlık Bilimleri Enstitüsü Tıbbi Biyokimya Ana Bilim Dalı, Ankara, Türkiye

[2]Lokman Hekim Üniversitesi Tıp Fakültesi Tıbbi Biyokimya Ana Bilim Dalı, Ankara, Türkiye

[3]Gazi Üniversitesi Tıp Fakültesi Tıbbi Biyokimya Ana Bilim Dalı, Ankara, Türkiye

Öz

Asprosin ve neuregulin-4 iki farklı yağ dokudan sentezlenen ve metabolik hastalıklar üzerindeki etkileri sayesinde son zamanlarda dikkat çeken iki endokrin salgı olarak görülmektedir. Sırasıyla beyaz yağ dokudan ve kahverengi yağ dokudan salgılanan asprosin ve neuregulin-4'ün glisemik regülasyon ile bağlantılı olmaları obezite ve insülin direnci gibi tedavi edilmezse sonunda tip 2 diabetes mellitus'a yol açan metabolik bozukluklar ile de yakından ilişkili olduklarını düşündürtmektedir. Diğer yandan asprosin ve neuregulin-4'ün soğuğa maruz kalma gibi çevresel etkiler sonucunda beyaz yağ dokunun metabolizmasını değiştirip kahverengi yağ doku benzeri bir metabolizmaya geçiş yapması olarak bilinen "kahverengileşme" sürecine etki ettikleri görülmektedir. Asprosin ve neuregulin-4 metabolizma üzerindeki etkileri sayesinde çeşitli hastalıkların hem gelişiminde hem de tedavisinde rol oynayabilme potansiyeline sahip moleküller olarak görülmektedirler. Bu derleme, asprosin ve neuregulin-4'ün temel görevleri, obezite ve insülin direnci üzerine etkileri, beyaz yağ dokunun kahverengileşme sürecine nasıl dahil oldukları ve tip 2 diabetes mellitus ile ilişkisi üzerine bir fikir sağlamak amacı ile ele alınmıştır.

Anahtar Kelimeler: Asprosin, Neuregulin-4, Glisemik regülasyon, Tip 2 Diabetes Mellitus, Obezite, İnsülin direnci, Kahverengileşme

Abstract

Asprosin and neuregulin-4 are two endocrine secretions synthesized by two different types of adipose tissue that have recently attracted attention for their effects on metabolic diseases. The fact that asprosin and neuregulin-4, which are secreted from white and brown adipose tissue respectively, are associated with glycaemic regulation suggests that they are closely related to metabolic disorders such as obesity and insulin resistance, which, if left untreated, eventually lead to type 2 diabetes mellitus. On the other hand, asprosin and neuregulin-4 appear to affect the 'browning' process, known as the transition of white adipose tissue, to brown adipose tissue-like metabolism, by altering its metabolism as a result of environmental influences such as exposure to cold. Asprosin and neuregulin-4 appear to have the potential to play a role in both disease development and treatment through these different effects on metabolism. This review aims to provide insight into the basic functions of asprosin and neuregulin-4, their effects on obesity and insulin resistance, their involvement in the browning process of white adipose tissue, and their relationship with type 2 diabetes mellitus.

Key Words: Asprosin, Neuregulin-4, Glycaemic regulation, Type 2 diabetes mellitus, Obesity, Insulin resistance, Browning

İletişim adresi/Address for Correspondence:
Musa Latif Çöllüoğlu https://orcid.org/0009-0004-1094-3309, Neslihan Bukan https://orcid.org/0000-0003-1691-618X
Adres: Söğütözü Mh. 2179 Cd. No: 6 06510 Çankaya/Ankara
E-mail: mlatifcolluoglu@gmail.com
Telefon: +905415258958
Geliş Tarihi/Received:08 Ağustos 2024. Kabul Tarihi/Accepted:20 Ağustos 2024. Çevrimiçi Yayın/Published Online:31 Ağustos 2024.

INTRODUCTION

With the development of science and technology, rapid changes have occurred in all areas of daily life, from urbanization to agriculture, and living standards have improved. However, these changes have led people to adopt faster, more sedentary, and more stressful lifestyles. As a result, most people are developing unhealthy eating habits, particularly fast food and packaged products. These eating habits can predispose people to many diseases such as type 2 diabetes mellitus (T2DM) and obesity, which are the most common diet-related diseases and are on the rise worldwide.

Type 2 DM, also known as adult-onset diabetes or insulin-independent diabetes, is a heterogeneous and progressive disease that affects β-cell function and insulin utilization. It is characterized by hyperglycemia. Elevated blood glucose levels in T2DM patients can be attributed to two reasons: insulin resistance and pancreatic B-cell dysfunction[1].

The International Diabetic Federation (IDF) reports approximately 536 million diabetics worldwide. The prevalence of the disease, which spans a broad spectrum from children to the elderly, is predicted to increase in the future[2]. Although T2DM may have a genetic basis, environmental factors such as age, physical activity, pregnancy, and diet especially obesity may also lead to T2DM[3].

Obesity is a medical condition that is characterized by the accumulation of excessive amounts of fat in different parts of the body. It is generally measured by using the body mass index (BMI) which is a widely used anthropometric measurement that correlates mass and height to classify the amount of an individual's body fat. BMI is calculated in a way that an individual's body mass (in kilograms) is divided by the square of their height (in meters), expressed in units of kg/m². World Health Organization (WHO) classifies BMI lower than 18.5 kg/m² as underweighted, BMI between 18.5 kg/m² and 24.9 kg/m² as normal weighted, BMI between 25 kg/m² and 29.9 kg/m² as overweighted and BMI higher than 30 kg/m² as obese [4].

Adipose tissue (AT) - also known as body fat – is described as an organ that can be involved in various metabolic actions – energy storage, heat production, immune function, and mechanical and thermal insulation[5]. AT is specialized in different parts of the body to fulfill these functions.

Even though different forms of AT are found in the body, it can be divided into white adipose tissue (WAT) and brown adipose tissue (BAT). The main function of WAT is being body's energy store. In WAT, the continuous cycle of anabolism and catabolism of the lipids occurs according to the external stimulus. When nutrients are plentiful, feeding stimulates the storage of excess energy in the form of triacylglycerol (TAG) through an activation of the lipogenic pathway. The size of WAT is an increase in this positive energy balance period. On the other hand, in the absence of sufficient nutrients and energy deficiency, fasting induces the lipolytic pathway to break down those stored TAG depots into fatty acids and glycerol for energy production. Thus, the size of the WAT declines in a period when energy expenditure is more than the intake[6]. For the lipogenic pathway, a peptide hormone insulin acts as a stimulant to the uptake of glucose into adipocytes and initiates the de novo fatty acid synthesis by providing expression of required genes such as sterol regulatory element-binding protein 1 (SREBP1) that controls the expression of genes required for cholesterol, fatty acids, TAG and phospholipid synthesis[6-8]. For the lipolytic pathway, fasting decreases the circulating insulin levels which suppress the lipogenic pathway and provides the elevation in the levels of glucagon in the blood which promotes lipolysis in adipocytes[6,9]. The breakdown of TAGs reveals the glycerol which is used as a substrate for the gluconeogenic pathway and fatty acids that are further broken down to a group of substances that provide energy to the brain called ketone bodies unless carbohydrate depots are available[6,10]. In addition to the main function, WAT also takes part in thermal insulation and absorption of mechanical shock[11]. Organisms living in cold areas tend to increase their AT to maintain their core body temperature. The WAT placed under the skin works as an insulator and prevents the heat from getting lost[12]. On the other hand, BAT is known for its ability to produce heat through non-shivering thermogenesis. The main feature of BAT is to contain a large number of mitochondria. In addition to its role in the production of energy in the form of adenosine triphosphate (ATP) with oxidative phosphorylation, mitochondria in BAT generate heat with oxidizing fat. For that purpose, brown adipocytes uniquely express uncoupling protein (*Ucp*) genes, especially the *Ucp1* gene.

The protein product of *Ucp1* is placed in the inner membrane of the mitochondrion[13]. In the normal process of oxidative phosphorylation, the electron transport chain (ETC) pumps protons to intermembrane space and ATP-synthase provides a channel for electrons to dissipate the electrochemical proton gradient. During the passage of protons through ATP synthase, a phenomenon called "Proton Motive Force" produces energy for the synthesis of ATP molecules from ADP and Pi. However, in BAT, the presence of UCP1 in the inner mitochondrial membrane provides an alternative route for dissipation of the electrochemical proton gradient. The passage of protons through UCP1 uncouples the oxidative phosphorylation from ATP synthesis. The energy generated by the concentration gradient is released as heat instead of the synthesis of ATP. The heat production of the mitochondria in BAT with the above-mentioned mechanism is involved in the thermoregulation of mammals[13].

In addition to the different types, AT also includes adipocyte-like and non-adipocyte types of cells such as pre-adipocytes - the precursor cells for adipocytes, endothelial cells, immune cells, and extracellular matrix components[14]. The presence of different cell types makes AT a dynamic organ that can adapt and respond to internal and external stimuli through structural, metabolic, and phenotypic remodeling called AT plasticity. Temperature, presence of certain metabolites and macromolecules, hormones drugs, and physical activity affect the status and working of AT[15].

To the major roles in energy storage, WAT is also considered one of the major endocrine organs of the body that affect distanced organs and tissues to regulate metabolism and have an impact on inflammation through secretions of bioactive peptides and proteins called "adipokine" [16-17]. These adipokines are involved in the regulation of a wide range of metabolic actions, including food intake, energy expenditure, reproduction, gene regulation, insulin secretion and sensitivity, inflammation, and immune response[6]. Similarly, BAT is not only a site for non-shivering thermogenesis but also acts as a secretory organ. The secretions released from BAT are called “brown adipose tissue adipokines” or “batokines” and take part in crosstalk with several different organs through autocrine, paracrine, and endocrine effects[18-19].

As mentioned before, the pathogenesis of T2DM is mainly based on the progressive loss of β-cells by the actions of inflammatory components and insulin resistance[20-21]. Being overweight and obese is considered one of the significant driving forces and accelerators of the development of T2DM[22]. Accumulation and expansion of the WAT in the ectopic sites such as the liver, muscle, pancreas, and heart due to intake of excess amount of energy is mostly the reason behind the co-occurrence of obesity and T2DM[23]. This ectopic expansion of WAT is achieved through either the formation of new adipocytes (hyperplasia), enlargement of present adipocytes (hypertrophy), or both[24]. Hypertrophy and hyperplasia of WAT cause the alteration in the size, functioning, inflammatory state, and body distribution[25]. These alternations are manifested by abnormalities in the size and amount, extracellular matrix composition, oxidative stress, immune cell filtration, and adipokine secretion of adipocytes[26]. Unusual expansion of the WAT makes the cells unresponsive to insulin because of the disrupted surface-to-cell ratio[27]. Exorbitantly expansion and accumulation also cause remodeling of the microenvironment which can be characterized by aberrant inflammation, disrupted mitochondrial function, and dysregulated secretion of adipokines that result in impaired insulin signaling, reduced insulin-stimulated glucose-transport, β-cell dysfunction, insulin resistance, and ultimately T2DM[26, 28-29].

In this review, we will focus on two novel adipokines, asprosin and neuregulin-4 (Nrg-4). First, we will focus on asprosin. It’s metabolic roles, relationship with obesity and insulin resistance, and how it affects the browning of WAT. Then, we intensify on Nrg-4 to discuss the same topics as in the article. Finally, we will summarize how both asprosin and Nrg-4 are involved in the glycemic regulation of T2DM.

ASPROSIN

Asprosin is a 140 amino acid long, C-terminal cleavage product of FBN-1 gene encoded by exons 65 and 66. The higher expression of asprosin mRNA levels has been detected in WAT which is described as a main site of secretion of asprosin[30]. Asprosin is an adipokine that has a quite important effect on regulating glucose metabolism in several organs. Two major roles of

asprosin in the body are stimulating food intake and inducing hepatic glucose production, however, it can be also included in obesity, insulin resistance, and inhibition of browning of WAT.

Food Intake and Hepatic Glucose Production

The hypothalamus, as one of its duty, act as a feeding control center that regulates appetite with the orexigenic agouti-related peptide (AgRP) neurons and the anorexigenic pro-opiomelanocortin (POMC) neurons. Asprosin can be classified as one of the orexigenic hormones that induce appetite stimulation in the hypothalamus on AgRP neurons. Asprosin induces its receptors on the hypothalamus and activates a G protein-coupled receptors and cyclic AMP (cAMP) second messenger pathway. After that, AgRP neurons have fired which stimulates food intake. At the same time, asprosin inhibits POMC neurons- the appetite-suppressing neurons that indirectly stimulate appetite[31-33].

As one of the main sites in the regulation of metabolism, asprosin acts on the liver. Li. et. al[34] proposed that asprosin possesses its effect on the liver through an olfactory receptor 734 (OLFR734) receptor. Its activation further activates the adenylyl cyclase-PKA-cAMP responsive element binding (CREB) pathway and ultimately stimulates hepatic glucose production. In their study, Romere et. al.[30] showed with in vivo and in vitro experiments in hepatocytes that dose-dependent exposure to asprosin causes an increase in the cAMP concentration and the activity of protein kinase A (PKA). They also demonstrated that G-protein inhibitor- suramin, and competitive agonist of cAMP binding to PKA - cAMPS-Rp, sequester the effects of asprosin and hepatic glucose release.

Obesity and Asprosin

As mentioned before, in obesity, the amount of and distribution of adipose tissue is increased through hyperplasia and hypertrophy. With this increase, it is expected that the synthesis and secretion of asprosin increase as well. It is reported in the study of Wang et.al.[35] with 174 obese and non-obese female patients, serum asprosin levels in the obese patients had significantly high compared to non-obese patients. Similarly, in the study of Cantay et. al.[36] with 74 subjects, asprosin levels in the adipose tissue were significantly high. Asprosin levels are high not only in obese adults but also in obese children. In the study of Silistre et. al. [37], with 158 Turkish children, they found that serum asprosin levels were significantly higher in the obese group compared to the normal weight group with no gender difference. Likewise, Wang et. al. [38] found in their study with 119 Chinese children that serum asprosin levels were increased in the mild to moderate and severe obese group compared to the control group. Thus, it can be hypothesized that regardless of age, gender, and ethnicity, asprosin release in obese individuals is significantly higher compared to non-obese ones.

Insulin Resistance and Asprosin

Obesity, by itself, is a disease, however, it is also the underlying cause of most of the metabolic impairment. The accumulation of excess fat due to a sedentary lifestyle and overnutrition can both cause hyperlipidaemic conditions and chronic low-grade inflammation[39].

The relation of asprosin with insulin resistance can be shown through its effects on skeletal muscles and pancreatic β-cells[40]. The study of Jung et. al.[41] to understand how high-fat diet-induced asprosin affects skeletal muscle revealed that asprosin induces the Protein kinase C d (PKC d) which inhibits the sarcoplasmic reticulum Ca^{2+} ATPase 2 (SERCA2) and causes ER stress. They also stated that PKC d promotes the secretion of inflammatory markers through the NFkB-mediated pathway. Both of this condition attenuates the response of skeletal muscle to the insulin and ultimately cause insulin resistance.

In their study, Lee et. al.[42] investigating the effects of asprosin on pancreatic b-cells observed that toll-like receptor 4 (TLR-4) expression is significantly increased with fatty acid-induced asprosin treatment. TLR-4 activates c-Jun N-terminal kinase (JNK) which further ceases insulin secretion, induces apoptosis, and attracts inflammation-related cells. They also showed that siRNA-mediated suppression of TLR-4 is associated with reduced inflammation which is related to asprosin response, decreased glucose-stimulated insulin secretion, and low apoptosis rate. Their results suggest that the asprosin-induced TLR-4/JNK signaling pathway can cause impairment in insulin secretion, cellular dysfunction in b-cells, and finally insulin resistance.

Either way, uptake in the skeletal muscle and secretion from the pancreas, secretion of excess amount of asprosin due to increased levels of fat impair the metabolism, and homeostasis and take part in inflammation and cellular stress which may cause impairment of the binding and secretion of insulin consequently insulin resistance [43].

Inhibition of browning of WAT

Browning is a capacity of WAT to modify its metabolism to a BAT-like profile[44]. WAT to enter the browning process requires a specific stimulus. Chronic cold exposure, exercise, thyroid hormones, and dietary components such as cinnamon oil, fish oil, curcumin, capsaicin, genistein, and berberine can induce shifting WAT metabolism into BAT metabolism to become a brite (BRown In whITE)/beige adipose tissue (BeAT)[45]. During the process, increased mitochondrial number, increased expenditure in the energy, multilocularities of lipid droplets, activation of thermogenic genes such as peroxisome proliferator-activated receptor α (PPARα), bone morphogenetic protein 7 (BMP7) and UCP1 can be observed in WAT[46-48]. However, some molecules, like asprosin can inhibit the browning of WAT. Miao et. al.[49] found in their study that overexpression of asprosin causes a significant decrease in the browning genes including PPARα and UCP1. They also hypothesize that asprosin may interfere with the browning of WAT through nuclear factor erythroid 2–related factor 2 (Nrf2) known for its effects on oxidative stress as an antioxidant[50]. Another study, conducted by Yin et. al.[51] demonstrated that asprosin-knockout promotes angiogenesis of WAT. They suggested that angiogenesis changes the microenvironment of WAT and stimulates the browning of WAT. From these studies, it can be understood that asprosin negatively affects the browning of WAT. However, understanding the underlying mechanism of how the asprosin is involved in this pathway requires further investigations.

NEUREGULIN-4

Nrg-4 is one of the members of neuregulins which are polypeptides belonging to the epidermal growth factor (EGF) family. They can bind and act through the ErbB family of receptor tyrosine kinase. Until now, with Nrg-4, four of them have been identified. The first identified member, Neuregulin-1 (Nrg-1) has some roles in cardiovascular diseases, neurodevelopmental diseases, and cancer[52-54]. The second and third identified members of neuregulins, Neuregulin-2 (Nrg-2) and Neuregulin-3 (Nrg-3), found in the neural tissue in excess[55-56]. The fourth identified member of neuregulins, Nrg-4, has major effects on energy metabolism and homeostasis. Nrg-4 exhibits binding specificity for only ErbB-4[18]. Nrg-4 can be expressed and secreted from different organs such as the pancreas; however, the main expression and secretion site for Nrg-4 is BAT[57]. Nrg-4 is one of the important batokines that have several effects on different metabolic processes such as thermogenesis, insulin resistance, obesity, and browning of WAT – similar metabolic pathways to the asprosin but with different effects.

Thermogenesis

Thermogenesis is quite important for the human body because the proper functioning of metabolism requires a certain temperature[58]. BAT is the main site for thermogenesis and Nrg-4 is one of the molecules that can take part in thermogenesis. Wang et. al. demonstrated in their study that the expression of Nrg-4 was elevated with acute cold exposure[59]. However, Nrg-4 is involved in thermogenesis indirectly. Thermoregulation is ensured and dependent on the central nervous system (CNS) and sympathetic nervous system (SNS) respectively[60]. A proper connection between BAT and the nervous system through a neuronal circuit is quite important for the adjustment of homeostatic body temperature regulation[61]. Nrg-4 provides interconnection of CNS and BAT by supporting and regulating the growth and elaboration of neuronal dendrites[62-63]. Comparing the morphological and functional differences between Nrg-4 absence and presence in mice, Paramo et. al found that Nrg-4 null mice show defects in neuronal development, appearance, and function[64]. In addition to adipocyte-nerve signaling, Nrg-4 also promotes BAT innervation [57].

Obesity and Neuregulin-4

In addition to the classical definition of obesity, it can also be defined from the inflammatory

perspective[65]. State of obesity may be identified as a malnutrition by excess and closely related to the immune dysfunctions[66]. It has been found that the immune response and antibody production are lower in obese people than in lean people, and therefore the incidence and severity of infectious diseases are higher[67]. Wang et. al.[59] demonstrated in their study that there was an inverse relation between Nrg-4 expression and inflammation. As obesity causes inflammation, Nrg-4 expression tends to reduce in adipose tissue. On the other hand, Chen et. al.[68] showed that increased expression of Nrg-4 contributes to the increase in energy expenditure, fuel oxidation, and secretion of several adipokines that are involved in the amelioration of metabolic dysregulation in obesity.

Obesity is not only reducing Nrg-4 levels transcriptionally but also lowering the circulating Nrg-4 levels. Cai et. al.[69] showed in their research that increasing body mass index (BMI) and waist circumference were negatively correlated with circulating Nrg-4. Additionally, studies by Nugroho et. al.[70-71] hypothesized that to cope with obesity and related metabolic disorders, Nrg-4 acts as a pro-angiogenic factor to increase the vascularity of adipose tissue. The positive effects of lifestyle changes in terms of physical activity on obesity are known[72]. In addition to those positive effects, Alizadeh et. al.[73] and Saeidi et. al.[74] showed in their studies that different intensity levels of exercise provide an increase in the serum Nrg-4 levels and improvement in the obesity-related markers.

Insulin Resistance and Neuregulin-4

It is known that inflammation is one of the major causes and contributors to insulin resistance. Obesity-related low-grade inflammation in AT causes interference in insulin signaling and makes AT unresponsive to insulin acts[75-76]. Wang et. al.[59] reveal in their

study that the close relationship between inflammation and insulin resistance causes the downregulation of Nrg-4 expression. On the other hand, Chen et. al. [68] demonstrated in their research that increased expression of Nrg-4 provides an improvement in insulin sensitivity and enhancement in glucose metabolism.

Insulin resistance also affects the functioning of the pancreatic β-cells – the production site of insulin. Failing the reduction of blood glucose constantly stimulates β-cells to continue insulin secretion[77]. Exhaustion causes islet cells to not secrete insulin. Nrg-4 signaling is also important for pancreatic islet cells to produce insulin. South et. al.[78] proposed the potent role of Nrg-4 in the growth and regulation of islet cells. Their study showed that binding of Nrg-4 to the human epidermal growth factor receptor 4 (HER4) in the pancreas stimulates the secretion of insulin. Reduced expression, secretion, and binding of Nrg-4 causes the pancreas not to secrete insulin and further contributes to the progression of insulin resistance.

Browning of WAT

As mentioned before, AT is a dynamic organ that internal and external stimuli and can adjust its metabolism. Cold exposure acts as a stimulant for the browning of the WAT[79]. Christian[57] mentions that cold exposure to WAT, especially in subcutaneous WATs, triggers the expression of BAT-related genes such as Ucp1 and PPARa. In their study, Rosell et al. proposed that Nrg-4 may be one of the five molecules associated with the browning process[80]. Wang and Seale[79] emphasize the neuromodulator effects of Nrg-4 on AT which is considered a responsible process from the browning. Christian[57] and Henriques et. al.[81] proposed that upon cold exposure, the increased Nrg-4 secretion from BAT can increase the innervation of WATs. This could be the stimulation for browning and transmitted through a norepinephrine-cAMP-PKA pathway which is also used in the thermoregulation in BAT. Additionally, Pellegrinelli et. al.[82] suggests an alternative route that Nrg-4 may act interdependently with BMP8b to regulate angiogenesis and neuromodulation and facilitate the browning process of WAT.

RELATIONSHIP OF ASPROSIN AND NEUREGULIN-4 WITH TYPE 2 DIABETES MELLITUS

In normal functioning, the β-cells increase their mass and secretion in response to increased demand for insulin to compensate for elevation in the blood glucose and maintain blood sugar in the normal range[83]. However, in T2DM, the body fails to produce enough amount of insulin from β-cells, thus, insulin demand is high and utilization is low by peripheral cells and tissues[84].

Hence, blood glucose levels cannot be kept in the normal range. Obesity and insulin resistance are two factors causing the body does not sustain normal blood glucose levels and contributing factors for the development of T2DM[83]. Asprosin and Nrg-4 are two molecules secreted by different adipose tissues and act in an antagonistic manner. They have a potential role in the development and prevention of T2DM, respectively.

Asprosin is classified as a contributing adipokine in the development of T2DM owing to its role in the formation of insulin resistance and obesity. Jung et. al. [41] describe asprosin as a "Novel adipokine, has been suggested as a diabetogenic factor." In accordance, Wang et. al.[85], demonstrated in their study that the asprosin levels of the impaired glucose regulation group and newly diagnosed T2DM group are significantly increased compared to the normal glucose regulation group. They also showed that asprosin levels were associated positively with the homeostasis model assessment for insulin resistance (HOMA-IR), and negatively related to the homeostasis model assessment for β-cell function (HOMA-β). Similarly, Zhang et. al. and Groener et. al. showed in their study that the response of serum asprosin levels to fluctuation in the blood glucose levels is impaired or blunted in type 1 diabetes mellitus (T1DM) and T2DM patients [86-87]. Furthermore, asprosin is mentioned as a potential marker for early diagnosis of diabetes[43].

On the other hand, Nrg-4's impeding role on T2DM is known through its regulatory effects on glucose metabolism. Kang et al. [88] in their study with newly diagnosed T2DM patients and a control group found that serum Nrg-4 levels were significantly higher in T2DM patients compared to the control group and positively correlated with fasting plasma glucose level and insulin resistance. Similarly, Chen et al. [89] stated in their study of prediabetes and diabetes patients that serum Nrg-4 levels of prediabetes and diabetes patients were elevated compared to controls. Likewise, in their study with 100 T2DM patients and 50 controls, Kocak et al.[90] demonstrated a significant difference in serum Nrg-4 levels between poorly controlled T2DM, well-controlled T2DM, and the controls. They also stated that Nrg-4 was significantly correlated with fasting plasma glucose. Oppose to those findings, Zhang et al.[91] show in their study that the serum Nrg-4 level of newly diagnosed T2DM patients is significantly low compared to controls.

CONCLUSION

In conclusion, it can be understood that asprosin and Nrg-4 are two antagonistic adipokines that are secreted from distinct adipose tissues. Asprosin is a hormone secreted by WAT that is sensitive to the energy status of the body. It has an orexigenic and glucogenic effect when the body is in a fasting state. In pathological conditions such as obesity, insulin resistance, and as a result T2DM, an abnormal increase in asprosin is observed. Nrg-4 is a BAT-secreted hormone closely associated with BAT thermogenesis by modulating sympathetic innervation of adipose tissue. Nrg-4 also acts as a novel hormone that exerts protective effects to cope with metabolic diseases like insulin resistance, obesity, and T2DM. It is also considered that there is Nrg-4's partial involvement in lifestyle changes including training, bariatric surgery, and medications use for the improvement of those metabolic diseases is also known. Thus, a pharmacological interference of asprosin and promising positive effects of Nrg-4 may be considered as a potential therapeutic approach for the treatment of metabolic diseases.

Etik Onay: Etik onay gerekmemektedir.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemektedir.
Finansal Destek:-
Ethical Approval: Not applicable
Conflict of Interest: Authors declared no conflict of interest.
Financial Support: None

REFERENCES

1. Robertson, R. P., Harmon, J., Tran, P. O., Tanaka, Y., & Takahashi, H. Glucose toxicity in beta-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. Diabetes, 2003;52(3):581-587. https://doi.org/10.2337/diabetes.52.3.581
2. International Diabetes Federation. *IDF Diabetes Atlas*. 2021 Retrieved 08.07.2024 from https://www.diabetesatlas.org
3. Cantley, J., & Ashcroft, F. M. Q&A: insulin secretion and type 2 diabetes: why do β-cells fail? BMC Biol, 2015;13:33. https://doi.org/10.1186/s12915-015-0140-6
4. World Heath Organistion. *Obesity and overweight*. 2024. Retrieved 08.07.2024 from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

5. Iacobini, C., Vitale, M., Haxhi, J., Menini, S., & Pugliese, G. Impaired Remodeling of White Adipose Tissue in Obesity and Aging: From Defective Adipogenesis to Adipose Organ Dysfunction. Cells, 2024;13(9):763. https://www.mdpi.com/2073-4409/13/9/763
6. Luo, L., & Liu, M. Adipose tissue in control of metabolism. Journal of Endocrinology, 2016;231(3):R77-R99. https://doi.org/10.1530/JOE-16-0211
7. Assimacopoulos-Jeannet, F., Brichard, S., Rencurel, F., Cusin, I., & Jeanrenaud, B. (1995). In vivo effects of hyperinsulinemia on lipogenic enzymes and glucose transporter expression in rat liver and adipose tissues. Metabolism, 1995;44(2):228-233. https://doi.org/https://doi.org/10.1016/0026-0495(95)90270-8
8. Ferré, P., & Foufelle, F. SREBP-1c Transcription Factor and Lipid Homeostasis: Clinical Perspective. Hormone Research, 2007;68(2):72-82. https://doi.org/10.1159/000100426
9. Carmen, G.-Y., & Víctor, S.-M. Signalling mechanisms regulating lipolysis. Cellular Signalling, 2006;18(4):401-408. https://doi.org/https://doi.org/10.1016/j.cellsig.2005.08.009
10. Langin, D.Adipose tissue lipolysis as a metabolic pathway to define pharmacological strategies against obesity and the metabolic syndrome. Pharmacological Research, 2006;53(6):482-491. https://doi.org/https://doi.org/10.1016/j.phrs.2006.03.009
11. Blüher, M. Adipose tissue dysfunction contributes to obesity related metabolic diseases. Best Practice & Research Clinical Endocrinology & Metabolism, 2013;27(2),:163-177. https://doi.org/https://doi.org/10.1016/j.beem.2013.02.005
12. MacCannell, A. D. V., Sinclair, K. J., McKenzie, C. A., & Staples, J. F. Environmental temperature effects on adipose tissue growth in a hibernator. Journal of Experimental Biology, 2019;222(3). https://doi.org/10.1242/jeb.194548
13. Kozak, L. P., & Harper, M. E. (2000). Mitochondrial uncoupling proteins in energy expenditure. Annu Rev Nutr, 20, 339-363. https://doi.org/10.1146/annurev.nutr.20.1.339
14. Corvera, S. Cellular Heterogeneity in Adipose Tissues. Annual Review of Physiology, 2021;83: 257-278. https://doi.org/https://doi.org/10.1146/annurev-physiol-031620-095446
15. Sakers, A., De Siqueira, M. K., Seale, P., & Villanueva, C. J. Adipose-tissue plasticity in health and disease. Cell, 2022;185(3): 419-446. https://doi.org/https://doi.org/10.1016/j.cell.2021.12.016
16. Maury, E., & Brichard, S. M. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Molecular and Cellular Endocrinology, 2010;314(1):1-16. https://doi.org/https://doi.org/10.1016/j.mce.2009.07.031
17. Fasshauer, M., & Blüher, M. Adipokines in health and disease. Trends in Pharmacological Sciences, 2015;36(7): 461-470. https://doi.org/https://doi.org/10.1016/j.tips.2015.04.014
18. Gavaldà-Navarro, A., Villarroya, J., Cereijo, R., Giralt, M., & Villarroya, F. The endocrine role of brown adipose tissue: An update on actors and actions. Rev Endocr Metab Disord, 2022;23(1): 31-41. https://doi.org/10.1007/s11154-021-09640-6
19. Villarroya, F., Cereijo, R., Villarroya, J., & Giralt, M. Brown adipose tissue as a secretory organ. Nature Reviews Endocrinology, 2017;13(1): 26-35. https://doi.org/10.1038/nrendo.2016.136
20. Association, A. D. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2019. Diabetes Care, 2018;42(1): S13-S28. https://doi.org/10.2337/dc19-S002
21. Mandrup-Poulsen, T. Type 2 diabetes mellitus: a metabolic autoinflammatory disease. Dermatol Clin, 2013;31(3):495-506. https://doi.org/10.1016/j.det.2013.04.006
22. Versini, M., Jeandel, P. Y., Rosenthal, E., & Shoenfeld, Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev, 2014,13(9): 981-1000. https://doi.org/10.1016/j.autrev.2014.07.001
23. Ruze, R., Liu, T., Zou, X., Song, J., Chen, Y., Xu, R., Yin, X., & Xu, Q. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments [Review]. Frontiers in Endocrinology, 2023;14. https://doi.org/10.3389/fendo.2023.1161521
24. Hamdy, O., Porramatikul, S., & Al-Ozairi, E. Metabolic obesity: the paradox between visceral and subcutaneous fat. Curr Diabetes Rev, 2006;2(4): 367-373. https://doi.org/10.2174/157339981060204036725. Kusminski, C. M., Bickel, P. E., & Scherer, P. E. Targeting adipose tissue in the treatment of obesity-associated diabetes. Nature Reviews Drug Discovery, 2016;15(9): 639-660. https://doi.org/10.1038/nrd.2016.75
26. Sun, K., Kusminski, C. M., & Scherer, P. E. Adipose tissue remodeling and obesity. The Journal of Clinical Investigation, 2011;121(6): 2094-2101. https://doi.org/10.1172/JCI45887
27. Czech, M. P. Mechanisms of insulin resistance related to white, beige, and brown adipocytes. Molecular Metabolism, 2020;34: 27-42. https://doi.org/https://doi.org/10.1016/j.molmet.2019.12.014
28. Kusminski, C. M., & Scherer, P. E. Mitochondrial dysfunction in white adipose tissue. Trends in Endocrinology & Metabolism, 2012;23(9): 435-443. https://doi.org/10.1016/j.tem.2012.06.004
29. Tuomi, T., Santoro, N., Caprio, S., Cai, M., Weng, J., & Groop, L. The many faces of diabetes: a disease with increasing heterogeneity. The Lancet, 2014;383(9922):1084-1094. https://doi.org/10.1016/S0140-6736(13)62219-9
30. Romere, C., Duerrschmid, C., Bournat, J., Constable, P., Jain, M., Xia, F., Saha, Pradip K., Del Solar, M., Zhu, B., York, B., Sarkar, P., Rendon, David A., Gaber, M. W., LeMaire, Scott A., Coselli, Joseph S., Milewicz, Dianna M., Sutton, V. R., Butte, Nancy F., Moore, David D., & Chopra, Atul R. Asprosin, a Fasting-Induced Glucogenic Protein Hormone. Cell, 2016;165(3):566-579. https://doi.org/10.1016/j.cell.2016.02.063

31. Keser, M. G., & Ünüsan, N. Asprosin ve Glikoz Metabolizması Üzerine Etkileri [Asprosin and Effects on Glucose Metabolism]. Türkiye Diyabet ve Obezite Dergisi, 2021;5(1): 89-95. https://doi.org/10.25048/tudod.840549
32. Duerrschmid, C., He, Y., Wang, C., Li, C., Bournat, J. C., Romere, C., Saha, P. K., Lee, M. E., Phillips, K. J., Jain, M., Jia, P., Zhao, Z., Farias, M., Wu, Q., Milewicz, D. M., Sutton, V. R., Moore, D. D., Butte, N. F., Krashes, M. J., . . . Chopra, A. R. Asprosin is a centrally acting orexigenic hormone. Nat Med, 2017;23(12):1444-1453. https://doi.org/10.1038/nm.4432
33. Sohn, J. W. Network of hypothalamic neurons that control appetite. BMB Rep, 2015;48(4): 229-233. https://doi.org/10.5483/bmbrep.2015.48.4.272
34. Li, E., Shan, H., Chen, L., Long, A., Zhang, Y., Liu, Y., Jia, L., Wei, F., Han, J., Li, T., Liu, X., Deng, H., & Wang, Y. OLFR734 Mediates Glucose Metabolism as a Receptor of Asprosin. Cell Metabolism, 2019;30(2):319-328.e318. https://doi.org/10.1016/j.cmet.2019.05.022
35. Wang, C.-Y., Lin, T.-A., Liu, K.-H., Liao, C.-H., Liu, Y.-Y., Wu, V. C.-C., Wen, M.-S., & Yeh, T.-S. Serum asprosin levels and bariatric surgery outcomes in obese adults. International Journal of Obesity, 2019;43(5):1019-1025. https://doi.org/10.1038/s41366-018-0248-1
36. Cantay, H., Binnetoglu, K., Gul, H. F., & Bingol, S. A. Investigation of serum and adipose tissue levels of asprosin in patients with severe obesity undergoing sleeve gastrectomy. Obesity, 2022;30(8): 1639-1646. https://doi.org/https://doi.org/10.1002/oby.23471
37. Sünnetçi Silistre, E., & Hatipoğl, H. U. Increased serum circulating asprosin levels in children with obesity. Pediatrics International, 2020;62(4): 467-476. https://doi.org/https://doi.org/10.1111/ped.14176
38. Wang, M., Yin, C., Wang, L., Liu, Y., Li, H., Li, M., Yi, X., & Xiao, Y. Serum Asprosin Concentrations Are Increased and Associated with Insulin Resistance in Children with Obesity. Annals of Nutrition and Metabolism, 2019;75(4): 205-212. https://doi.org/10.1159/000503808
39. Grosso, G., Laudisio, D., Frias-Toral, E., Barrea, L., Muscogiuri, G., Savastano, S., & Colao, A. Anti-Inflammatory Nutrients and Obesity-Associated Metabolic-Inflammation: State of the Art and Future Direction. Nutrients, 2022;14(6): 1137. https://www.mdpi.com/2072-6643/14/6/1137
40. Farrag, M., Ait Eldjoudi, D., González-Rodríguez, M., Cordero-Barreal, A., Ruiz-Fernández, C., Capuozzo, M., González-Gay, M. A., Mera, A., Lago, F., Soffar, A., Essawy, A., Pino, J., Farrag, Y., & Gualillo, O. Asprosin in health and disease, a new glucose sensor with central and peripheral metabolic effects. Front Endocrinol (Lausanne), 2022;13: 1101091. https://doi.org/10.3389/fendo.2022.1101091
41. Jung, T. W., Kim, H.-C., Kim, H. U., Park, T., Park, J., Kim, U., Kim, M. K., & Jeong, J. H. Asprosin attenuates insulin signaling pathway through PKCδ-activated ER stress and inflammation in skeletal muscle. Journal of Cellular Physiology, 2019;234(11):20888-20899. https://doi.org/https://doi.org/10.1002/jcp.28694
42. Lee, T., Yun, S., Jeong, J. H., & Jung, T. W. Asprosin impairs insulin secretion in response to glucose and viability through TLR4/JNK-mediated inflammation. Molecular and Cellular Endocrinology, 2019;486: 96-104. https://doi.org/https://doi.org/10.1016/j.mce.2019.03.001
43. Yuan, M., Li, W., Zhu, Y., Yu, B., & Wu, J. Asprosin: A Novel Player in Metabolic Diseases [Mini Review]. Frontiers in Endocrinology, 2020; 11. https://doi.org/10.3389/fendo.2020.00064
44. Barbatelli, G., Murano, I., Madsen, L., Hao, Q., Jimenez, M., Kristiansen, K., Giacobino, J. P., De Matteis, R., & Cinti, S. The emergence of cold-induced brown adipocytes in mouse white fat depots is determined predominantly by white to brown adipocyte transdifferentiation. Am J Physiol Endocrinol Metab, 2010;298(6): E1244-1253. https://doi.org/10.1152/ajpendo.00600.2009
45. Machado, S. A., Pasquarelli-do-Nascimento, G., da Silva, Debora S., Farias, G. R., de Oliveira Santos, I., Baptista, L. B., & Magalhães, K. G. Browning of the white adipose tissue regulation: new insights into nutritional and metabolic relevance in health and diseases. Nutrition & Metabolism,2022;19(1):61. https://doi.org/10.1186/s12986-022-00694-0
46. Barberá, M. J., Schlüter, A., Pedraza, N., Iglesias, R., Villarroya, F., & Giralt, M. Peroxisome Proliferator-activated Receptor α Activates Transcription of the Brown Fat Uncoupling Protein-1 Gene: A LINK BETWEEN REGULATION OF THE THERMOGENIC AND LIPID OXIDATION PATHWAYS IN THE BROWN FAT CELL*. Journal of Biological Chemistry, 2001;276(2): 1486-1493. https://doi.org/https://doi.org/10.1074/jbc.M006246200
47. Schulz, T. J., Huang, T. L., Tran, T. T., Zhang, H., Townsend, K. L., Shadrach, J. L., Cerletti, M., McDougall, L. E., Giorgadze, N., Tchkonia, T., Schrier, D., Falb, D., Kirkland, J. L., Wagers, A. J., & Tseng, Y.-H. Identification of inducible brown adipocyte progenitors residing in skeletal muscle and white fat. Proceedings of the National Academy of Sciences, 2011;108(1): 143-148. https://doi.org/doi:10.1073/pnas.1010929108
48. Villarroya, F., Peyrou, M., & Giralt, M. Transcriptional regulation of the uncoupling protein-1 gene. Biochimie, 25017;134:86-92. https://doi.org/https://doi.org/10.1016/j.biochi.2016.09.017
49. Miao, Y., Qin, H., Zhong, Y., Huang, K., & Rao, C. Novel adipokine asprosin modulates browning and adipogenesis in white adipose tissue. Journal of Endocrinology, 2021;249(2): 83-93. https://doi.org/10.1530/joe-20-0503
50. Schneider, K. S., & Chan, J. Y. Emerging Role of Nrf2 in Adipocytes and Adipose Biology. Advances in Nutrition, 2013;4(1):62-66. https://doi.org/https://doi.org/10.3945/an.112.003103
51. Yin, T., Chen, S., Zeng, G., Yuan, W., Lu, Y., Zhang, Y., Huang, Q., Xiong, X., Xu, B., & Huang, Q. Angiogenesis–Browning Interplay Mediated by Asprosin-Knockout Contributes to Weight Loss in Mice with Obesity. International Journal of Molecular Sciences,

2022;23(24),:16166. https://www.mdpi.com/1422-0067/23/24/16166
52. Odiete, O., Hill, M. F., & Sawyer, D. B. Neuregulin in cardiovascular development and disease. Circ Res, 2012;111(10):1376-1385. https://doi.org/10.1161/circresaha.112.267286
53. Shi, L., & Bergson, C. M. (2020). Neuregulin 1: an intriguing therapeutic target for neurodevelopmental disorders. Transl Psychiatry, 10(1), 190. https://doi.org/10.1038/s41398-020-00868-5
54. Zhang, C., Mei, W., & Zeng, C. (2022). Oncogenic Neuregulin 1 gene (NRG1) fusions in cancer: A potential new therapeutic opportunities. Biochim Biophys Acta Rev Cancer, 2022;1877(3):188707. https://doi.org/10.1016/j.bbcan.2022.188707
55. Carraway, K. L., 3rd, Weber, J. L., Unger, M. J., Ledesma, J., Yu, N., Gassmann, M., & Lai, C. Neuregulin-2, a new ligand of ErbB3/ErbB4-receptor tyrosine kinases. Nature, 1997;387(6632):512-516. https://doi.org/10.1038/387512a0
56. Zhang, D., Sliwkowski, M. X., Mark, M., Frantz, G., Akita, R., Sun, Y., Hillan, K., Crowley, C., Brush, J., & Godowski, P. J. (1997). Neuregulin-3 (NRG3): a novel neural tissue-enriched protein that binds and activates ErbB4. Proc Natl Acad Sci U S A, 1979;94(18):9562-9567. https://doi.org/10.1073/pnas.94.18.9562
57. Christian, M. (2015). Transcriptional fingerprinting of "browning" white fat identifies NRG4 as a novel adipokine. Adipocyte, 2015; 4(1):50-54. https://doi.org/10.4161/adip.29853
58. Guslisty, A. A., Malomuzh, N. P., & Fisenko, A. I. Optimal Temperature for Human Life Activity. Ukrainian Journal of Physics, 2018;63(9):809. https://doi.org/10.15407/ujpe63.9.809
59. Wang, G. X., Zhao, X. Y., Meng, Z. X., Kern, M., Dietrich, A., Chen, Z., Cozacov, Z., Zhou, D., Okunade, A. L., Su, X., Li, S., Blüher, M., & Lin, J. D. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. Nat Med, 2014;20(12): 1436-1443. https://doi.org/10.1038/nm.3713
60. Labbé, S. M., Caron, A., Lanfray, D., Monge-Rofarello, B., Bartness, T. J., & Richard, D. Hypothalamic control of brown adipose tissue thermogenesis. Front Syst Neurosci, 2015;9: 150. https://doi.org/10.3389/fnsys.2015.00150
61. Tabuchi, C., & Sul, H. S. Signaling Pathways Regulating Thermogenesis. Front Endocrinol (Lausanne), 2021;12: 595020. https://doi.org/10.3389/fendo.2021.595020
62. Villarroya, F., Cereijo, R., Gavaldà-Navarro, A., Villarroya, J., & Giralt, M. Inflammation of brown/beige adipose tissues in obesity and metabolic disease. J Intern Med, 2018; 284(5): 492-504. https://doi.org/10.1111/joim.12803
63. Villarroya, J., Cereijo, R., Gavaldà-Navarro, A., Peyrou, M., Giralt, M., & Villarroya, F. New insights into the secretory functions of brown adipose tissue. J Endocrinol, 2019;243(2): R19-r27. https://doi.org/10.1530/joe-19-0295
64. Paramo, B., Bachmann, S. O., Baudouin, S. J., Martinez-Garay, I., & Davies, A. M.. Neuregulin-4 Is Required for Maintaining Soma Size of Pyramidal Neurons in the Motor Cortex. eNeuro, 2021; 8(1). https://doi.org/10.1523/eneuro.0288-20.2021
65. Bray, G. A., Heisel, W. E., Afshin, A., Jensen, M. D., Dietz, W. H., Long, M., Kushner, R. F., Daniels, S. R., Wadden, T. A., Tsai, A. G., Hu, F. B., Jakicic, J. M., Ryan, D. H., Wolfe, B. M., & Inge, T. H. The Science of Obesity Management: An Endocrine Society Scientific Statement. Endocrine Reviews, 2018;39(2),:79-132. https://doi.org/10.1210/er.2017-00253
66. de Heredia, F. P., Gómez-Martínez, S., & Marcos, A. Obesity, inflammation and the immune system. Proceedings of the Nutrition Society, 2012;71(2): 332-338. https://doi.org/10.1017/S0029665112000092
67. Martí, A., Marcos, A., & Martínez, J. A. Obesity and immune function relationships. Obes Rev, 2001;2(2): 131-140. https://doi.org/10.1046/j.1467-789x.2001.00025.x
68. Chen, Z., Wang, G. X., Ma, S. L., Jung, D. Y., Ha, H., Altamimi, T., Zhao, X. Y., Guo, L., Zhang, P., Hu, C. R., Cheng, J. X., Lopaschuk, G. D., Kim, J. K., & Lin, J. D. Nrg4 promotes fuel oxidation and a healthy adipokine profile to ameliorate diet-induced metabolic disorders. Mol Metab, 2017;6(8): 863-872. https://doi.org/10.1016/j.molmet.2017.03.016
69. Cai, C., Lin, M., Xu, Y., Li, X., Yang, S., & Zhang, H. Association of circulating neuregulin 4 with metabolic syndrome in obese adults: a cross-sectional study. BMC Med, 2016;14(1): 165. https://doi.org/10.1186/s12916-016-0703-6
70. Nugroho, D. B., Ikeda, K., Barinda, A. J., Wardhana, D. A., Yagi, K., Miyata, K., Oike, Y., Hirata, K. I., & Emoto, N. Neuregulin-4 is an angiogenic factor that is critically involved in the maintenance of adipose tissue vasculature. Biochem Biophys Res Commun, 2018;503(1):378-384. https://doi.org/10.1016/j.bbrc.2018.06.043
71. Nugroho, D. B., Ikeda, K., Kajimoto, K., Hirata, K. I., & Emoto, N. Activation of neuregulin-4 in adipocytes improves metabolic health by enhancing adipose tissue angiogenesis. Biochem Biophys Res Commun, 2018;504(2):427-433. https://doi.org/10.1016/j.bbrc.2018.08.197
72. Oppert, J. M., Bellicha, A., & Ciangura, C. Physical activity in management of persons with obesity. Eur J Intern Med, 2021;93:8-12. https://doi.org/10.1016/j.ejim.2021.04.028
73. Alizadeh, M., Shahrbanian, S., & Hackney, A. C. Comparison of the effects of 12 weeks of three types of resistance training (traditional, circular and interval) on the levels of neuregulin 4, adiponectin and leptin in non-athletic men with obesity. Arch Med Deporte, 2021;38(6):389-396. https://doi.org/10.18176/archmeddeporte.00066
74. Saeidi, A., Shishvan, S. R., Soltani, M., Tarazi, F., Doyle-Baker, P. K., Shahrbanian, S., Mollabashi, S. S., Khosravi, N., Laher, I., Moriarty, T. A., Johnson, K. E., VanDusseldorp, T. A., & Zouhal, H. Differential Effects of Exercise Programs on Neuregulin 4, Body Composition and Cardiometabolic Risk Factors in Men With Obesity. Front Physiol, 2021;12:797574. https://doi.org/10.3389/fphys.2021.797574
75. Zatterale, F., Longo, M., Naderi, J., Raciti, G. A., Desiderio, A., Miele, C., & Beguinot, F. Chronic Adipose Tissue Inflammation Linking Obesity to

Insulin Resistance and Type 2 Diabetes [Review]. Frontiers in Physiology, 2020;10. https://doi.org/10.3389/fphys.2019.01607

76. Makki, K., Froguel, P., & Wolowczuk, I. Adipose Tissue in Obesity-Related Inflammation and Insulin Resistance: Cells, Cytokines, and Chemokines. International Scholarly Research Notices, 2013;(1):139239. https://doi.org/https://doi.org/10.1155/2013/139239
77. Kahn, S. E. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia, 2003;46(1): 3-19. https://doi.org/10.1007/s00125-002-1009-0
78. South, J. C. M., Blackburn, E., Brown, I. R., & Gullick, W. J.The Neuregulin System of Ligands and Their Receptors in Rat Islets of Langerhans. Endocrinology, 2013;154(7): 2385-2392. https://doi.org/10.1210/en.2012-2133
79. Wang, W., & Seale, P. Control of brown and beige fat development. Nature Reviews Molecular Cell Biology, 2016;17(11):691-702. https://doi.org/10.1038/nrm.2016.96
80. Rosell, M., Kaforou, M., Frontini, A., Okolo, A., Chan, Y. W., Nikolopoulou, E., Millership, S., Fenech, M. E., MacIntyre, D., Turner, J. O., Moore, J. D., Blackburn, E., Gullick, W. J., Cinti, S., Montana, G., Parker, M. G., & Christian, M. Brown and white adipose tissues: intrinsic differences in gene expression and response to cold exposure in mice. Am J Physiol Endocrinol Metab, 2014;306(8):E945-964. https://doi.org/10.1152/ajpendo.00473.2013
81. Henriques, F., Bedard, A. H., Guilherme, A., Kelly, M., Chi, J., Zhang, P., Lifshitz, L. M., Bellvé, K., Rowland, L. A., Yenilmez, B., Kumar, S., Wang, Y., Luban, J., Weinstein, L. S., Lin, J. D., Cohen, P., & Czech, M. P. Single-Cell RNA Profiling Reveals Adipocyte to Macrophage Signaling Sufficient to Enhance Thermogenesis. Cell Rep, 2020;32(5): 107998. https://doi.org/10.1016/j.celrep.2020.107998
82. Pellegrinelli, V., Peirce, V. J., Howard, L., Virtue, S., Türei, D., Senzacqua, M., Frontini, A., Dalley, J. W., Horton, A. R., Bidault, G., Severi, I., Whittle, A., Rahmouni, K., Saez-Rodriguez, J., Cinti, S., Davies, A. M., & Vidal-Puig, A. Adipocyte-secreted BMP8b mediates adrenergic-induced remodeling of the neuro-vascular network in adipose tissue. Nat Commun, 2018;9(1): 4974. https://doi.org/10.1038/s41467-018-07453-x
83. Kahn, S. E., Hull, R. L., & Utzschneider, K. M. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature, 2006;444(7121): 840-846. https://doi.org/10.1038/nature05482
84. Chandrasekaran, P., & Weiskirchen, R. (2024). The Role of Obesity in Type 2 Diabetes Mellitus-An Overview. Int J Mol Sci, 25(3). https://doi.org/10.3390/ijms25031882
85. Wang, Y., Qu, H., Xiong, X., Qiu, Y., Liao, Y., Chen, Y., Zheng, Y., & Zheng, H. Plasma Asprosin Concentrations Are Increased in Individuals with Glucose Dysregulation and Correlated with Insulin Resistance and First-Phase Insulin Secretion. Mediators of Inflammation, 2018;(1): 9471583. https://doi.org/https://doi.org/10.1155/2018/9471583
86. Zhang, X., Jiang, H., Ma, X., & Wu, H. Increased serum level and impaired response to glucose fluctuation of asprosin is associated with type 2 diabetes mellitus. Journal of Diabetes Investigation, 2020;11(2): 349-355. https://doi.org/https://doi.org/10.1111/jdi.13148
87. Groener, J. B., Valkanou, A., Kender, Z., Pfeiffenberger, J., Kihm, L., Fleming, T., Nawroth, P. P., & Kopf, S. Asprosin response in hypoglycemia is not related to hypoglycemia unawareness but rather to insulin resistance in type 1 diabetes. PLOS ONE, 2019;14(9): e0222771. https://doi.org/10.1371/journal.pone.0222771
88. Kang, Y. E., Kim, J. M., Choung, S., Joung, K. H., Lee, J. H., Kim, H. J., & Ku, B. J. Comparison of serum Neuregulin 4 (Nrg4) levels in adults with newly diagnosed type 2 diabetes mellitus and controls without diabetes. Diabetes Research and Clinical Practice, 2016;117: 1-3. https://doi.org/https://doi.org/10.1016/j.diabres.2016.04.007
89. Chen, L.-L., Peng, M.-M., Zhang, J.-Y., Hu, X., Min, J., Huang, Q.-L., & Wan, L.-M. Elevated circulating Neuregulin4 level in patients with diabetes. Diabetes/Metabolism Research and Reviews, 2017;33(4): e2870. https://doi.org/https://doi.org/10.1002/dmrr.2870
90. Kocak, M. Z., Aktas, G., Erkus, E., Yis, O. M., Duman, T. T., Atak, B. M., & Savli, H. Neuregulin-4 is associated with plasma glucose and increased risk of type 2 diabetes mellitus. Swiss Medical Weekly, 2019;149(4344): w20139. https://doi.org/10.4414/smw.2019.20139
91. Zhang, L., Fu, Y., Zhou, N., Cheng, X., & Chen, C. Circulating neuregulin 4 concentrations in patients with newly diagnosed type 2 diabetes: a cross-sectional study. Endocrine, 2017;57(3): 535-538. https://doi.org/10.1007/s12020-017-1324-3