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REVIEW ARTICLE

An investigation of the relationship between new fasting hormone asprosin, obesity and acute–chronic exercise: current systematic review

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ABSTRACT

The purpose of this study was to reveal the relationship between new fasting hormone asprosin, obesity, and acute–chronic exercise. The prisma guidelines were followed in forming the methodological model of this review. The articles between 2016 and 2020 (including March) were identified by scanning Google Scholar, Pub Med, and Science Direct databases. Thirty-five articles were defined from 188 articles. Three cross-sectional, and 1 prospective cohort design studies in adults, and 3 cross-sectional studies in children were found. Three randomised-control group designed studies which examined the effect of acute exercise on serum asprosin levels in obese individuals. Asprosin may be a new therapeutic biomarker to be considered in the development, but long-term and deep-rooted researches are needed, and increasing the number of studies examining the effect of exercise on asprosin in the future might help us to identify the mechanisms underlying the decrease or increase in asprosin after exercise.

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Introduction

Obesity is a global public health problem, and ranked 5th with 4.8% of deaths worldwide (Wilson *et al*. 2019). It is closely related to the risk factors of various diseases such as type-2 diabetes, insulin resistance, hypertension, glucose intolerance, increased visceral adipose tissue, and some types of cancer (Katch *et al*. 2011, p(0).560). The World Cancer Research Fund has shown that about 14 cancer types are linked to overweight and obesity (Wilson *et al*. 2019). According to the report published by the World Health Organisation, the prevalence of obesity nearly tripled between 1975 and 2016, and approximately 13% of the world's adult population over 650 million adults (11% of men and 15% of women) were obese (World Health Organization 2018). It was also predicted that by 2030 60% of the world's population, i.e. 3.3 billion people, could be overweight (2.2 billion) or obese (1.1 billion) if recent trends continue (Kelly *et al*. 2008). Therefore, it is extremely important to conduct more research to understand the pathophysiology of the increase in obesity, and to develop various treatment methods (Oussaada *et al*. 2019).

Obesity is a chronic multi-dimensional disease accompanied by genetic, behavioural, environmental conditions (excessive energy intake and physical inactivity), appetite regulation disorders, dysregulation of metabolism, and hormonal balance, that causes energy imbalance, and supports excessive fat accumulation (McCafferty *et al*. 2020, Wallis *et al*. 2020). In order to identify the mechanisms underlying obesity, it is necessary to understand especially how appetite/nutritional behaviours are regulated in the control of body weight, and this also helps to develop new strategies to combat obesity. The functional disorders in appetite or nutritional signals of the brain cause disruptions in energy balance or metabolism, promoting an increase in body weight, resulting in obesity. The regulation of energy balance, appetite, or nutritional behaviour involves a process resulting from the interaction between very complex events. The main coordinator of this process is the Arcuate Nucleus, located in the hypothalamus in the brain. This nucleus and brainstem (nucleus tractus solitaris) areas integrate various behavioural, endocrine, neural and autonomic responses from the brainstem and peripheral organs through afferent and efferent pathways (Miller 2019). In recent years, the studies showed that neuron groups, especially in the Arcuate Nucleus, played an active role in appetite regulation and energy metabolism. There are two different groups of neurons in the arcuate nucleus. The anabolic NPY (neuropeptide Y) and AgRP (Agouti-related protein) neurons located in the arcuate nucleus are orexigenic i.e. trigger food intake, and creating a feeling of hunger. In contrast, the catabolic Pro-opiomelanocortin (POMC) and Cocaine and Amphetamine Regulated Transcript (CART) neurons are anorexigenic, meaning they inhibit food intake, and generating a feeling of satiety (Dulloo 2010, p. 71–72, Suzuki *et al*. 2010, Miller 2019). In addition to the hypothalamus, vagal afferent neurons, and hormones released from various peripheral organs such as the gastro-intestinal tract (ghrelin, cholecystokinin, glucagon-

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like peptide-1, peptide Y), pancreas, liver, and adipose tissue (leptin, insülin, adiponectin, resistin) send a continuous signal to the hypothalamus about the level of stored, and currently available fuel, and play an extremely important role in energy homeostasis. Thus, human energy metabolism is managed through a process involving complex cross-talk between the hypothalamus, and the peripheral tissues mentioned above (Hellstrom *et al*. 2004, Miller 2019). Especially in these peripheral tissues, adipose tissue is very important in terms of providing information about possible pathological mechanisms underlying obesity.

Adipose tissue, commonly referred to as "fat", is a type of loose connective tissue consisting of collagen fibres, blood vessels, fibroblasts, and lipid-filled cells surrounded by a matrix of immune cells (Ahima and Flier 2000). Adipose tissue was previously considered only as an energy store, but this concept was revised after the discovery of the leptin hormone, the first adipocyte-derived cytokine, by the Friedman group in 1990 (Choe *et al*. 2016). In response to changes in nutritional status, the discovery of the hormone leptin opened a door to understand how adipose tissue communicates with the central nervous system and, showed that the adipose tissue acts as an endocrine organ in modulating energy homeostasis (Choe *et al*. 2016, Miller 2019). There are two different types of adipose tissue; brown and white adipose texture. These two adipose tissues have antagonistic functions and play a central role in systemic energy homeostasis (Chouchani and Kajimura 2019). Brown adipose tissue has the ability to oxidise fatty acids to produce heat, a process called thermogenesis, and plays a role in energy expenditure. In humans, 1–2% of adipose tissue consists of this tissue. The thermogenetic properties of this tissue are mainly controlled by Mitochondrial Uncoupling Protein-1, which is mainly expressed from this tissue. Activated brown adipose tissue is thought to be very useful in combating obesity due to its energy expenditure feature, and also people with higher body weight, and body mass index value has less active brown adipose tissue. The dominant type of adipose tissue, commonly referred to as "fat" in mammals, is white adipose tissue (WAT). WAT is surrounded by loose connective tissue that is mostly vascularised and innervated, and this tissue consists of macrophages, fibroblasts, adipocyte precursors, and mostly adipocytes, including various cell types. The largest WAT stores are located in the subcutaneous region, and around the viscera. WAT, which contributes more than 95% of adipose tissue in humans, controls lipid mobilisation and distribution in the body, and also provides unlimited capacity for triglyceride, and energy storage, which is the vital for survival (Ahima 2006, Van den Beukel and Grefhorst 2014, Luo and Liu 2016, Chouchani and Kajimura 2019, Kahn *et al*. 2019). The simultaneous increase in insulin, glucose, and lipids during meals stimulates the formation of triglycerides and storage in liver and WAT. Conversely, lowering of insulin during fasting triggers glycogen breakdown with the activation of the sympathetic nervous system, and the release of fatty acids (lipolysis) for use by various tissues such as muscle, liver, and kidney. This transition from carbohydrates to fat-based metabolism occurs with a decrease in insulin, and an increase in "counter-regulatory" hormones, such as epinephrine, growth hormone, and glucocorticoids. Second, WAT maintains glucose supply to the brain and vital organs. Fatty acids released from adipose tissue during fasting are partially oxidised by muscle and liver, producing ketones that act as alternative fuels for the brain and peripheral organs. In contrast, postprandial increase in glucose, and lipids results in adipose fatty acid transport, and lipogenesis under the influence of insulin (Ahima and Flier 2000, Ahima 2006).

In recent studies, it was emphasised that WAT is a metabolically active endocrine organ that secretes more than 100 adipocyte-derived peptide hormones (more than 50 adipokines, cytokines, chemokines, hormone-like factors), inflammatory mediators, bioactive lipids, and packaged miRNA molecules with having hormonal, autocrine and paracrine properties that play an important role in the regulation of both central, and peripheral energy metabolism, and this endocrine organ also has a close communication network with other tissues, including the hypothalamus, pancreas, liver, skeletal muscle, kidneys, endothelium, and immune system (Balistreri *et al*. 2010, Coelho *et al*. 2013, Kahn *et al*. 2019). The production and secretion of adipokines and lipokines depends on the energy state of the adipose tissue, and these factors contribute to systemic energy metabolism by specifically regulating appetite, satiety, thermogenesis, inflammation, tissue repair, immune functions, blood pressure, glucose, and lipid metabolism. Many peptides, initially described as adipokines or hormones, are secreted by endothelial and immune cells, and other organs found in adipose tissue, which means that adipocyte contribution can be difficult to detect (Balistreri *et al*. 2010, Scheja and Heeren 2019). The most known of these hormones are Leptin, Adiponectin, Resistin, Retinol Binding Protein-4, Adipsin, Apelin, Visfatin, Vaspin, Tumour Necrosis Factor-α (TNF-α), İnterleukin-6 (IL-6), Plasminogen Activator Inhibitör-1 (PAI-1), Angiotensinogen P, Free Fatty Acids (FFA), Acylation Stimulating Protein (ASP), Vascular Endothelial Growth Factor-I (VEGF-I), Adipsin, Glycerol, and Insulin-Like Growth Factor-1 (IGF-I) (Balistreri *et al*. 2010, Galic *et al*. 2010, Coelho *et al*. 2013) (Table 1).

Obesity induces adipose tissue dysfunction which manifests as ectopic fat distribution, adipocyte hypertrophy, changes in the cellular composition and intracellular matrix in addition to its endocrine function, and also closely related to the development of insulin resistance in peripheral tissues such as skeletal muscle and liver (Galic *et al*. 2010, Blüher 2019). The increase in WAT mass in obesity is associated with characteristic deep histological and biochemical changes of inflammation (Ahima and Flier 2000). According to the results obtained from the studies, obesity has been found to be associated with chronic low-grade inflammation as well as, being a metabolic disease (Itoh *et al*. 2011). The adipose tissue that expands during obesity releases several chemotactic factors which migrate and leak into the adipose tissue through the process of adhesion to endothelial cells to induce macrophage infiltration and inflammation. The macrophages increase the production of pro-inflammatory cytokines such as TNF-α and IL-6 by cross-talk with parenchymal

Table 1. The hormones secreted into the bloodstream by adipose tissue and their functions.

Leptin	It signals the hypothalamus about triacylglyceride storage levels in white adipose tissue. It stimulates energy consumption, adn creates a feeling of satiety by changing the balance of anorexogenic and orrogenic hypothalamic peptides. It stimulates lipolysis, inhibits lipogenesis, and increases insulin sensitivity, glucose metabolism. It provides recovery of euglycemia, and plays a deep role in the regulation of whole body metabolism. In obesity, the leptin concentration is high due to the overfeeding, which causes leptin resistance. This limits the biological activity.
Adiponectin	Unlike leptin, adiponectin secretion often decreases in obesity. It increases insulin sensitivity, fatty acid oxidation, energy consumption, and reduces glucose production by the liver. It is a polypeptide hormone with having anti-inflammatory, antioxidant, antiatherogenic, antidiabetic and anticancer properties with TNF-α-mediated inhibition of the NF-κB pathway.
Resistin and Retinol binding protein-4	It is positively associated with adiposity. It plays a role in insulin resistance. It has an adverse effect compared to adiponectin, and its physiological role is to maintain fasting glycaemia. In rats, it triggers the glucose production rate that causes an increase in severe liver insulin resistance (In dietary obese mice, plasma resistin concentrations increase, mRNA levels decrease in the white adipose tissue of obese rodents, stimulates lipolysis)
Adipsin	It stimulates triglyceride storage, and prevents lipolysis.
Apelin	It increases insulin sensitivity of the tissues, and has a role in reducing food intake. It inhibits glucose-induced insulin secretion.
Visfatin	It stimulates insulin secretion, and shows hypoglycaemic effect by increasing insulin sensitivity, and glucose uptake by muscle cells, and adipocytes. It also has a pro-adipogenic, and lipogenic effect.
Vaspin	It increases insulin sensitivity of tissues. It suppresses the production of resistin, leptin and TNF-α.
TNF-α IL-6	Recently, macrophages were recognised as an important part of the secretion function of adipose tissue. The main inflammatory stokin source is TNF-α, and IL-6. An increase in the circulation levels of these macrophage-derived factors lead to a chronic low-grade inflammatory condition associated with the development of insulin resistance, and diabetes in obesity.
PAI-1	It controls the inhibition of the activation of the plasminogen, and the inhibitor of the fibrinolytic system.
Anjiyotensinojen	The precursor of angiotensin II; it is the regulator of blood pressure, and electrolyte homeostasis.
FFA	It is oxidised in the tissues to produce local energy. It acts as a substrate for triglyceride, and structural molecular synthesis. It causes the development of insulin resistance
ASP	It affects the speed of triacylglycerol synthesis in adipose tissue.
VEGF	It stimulates angiogenesis.
Gliserol	It is the structural component of the biological lipids, and gluconeogenic precursor
IGF-1	It triggers the proliferation of a wide variety of cells, and mediates the effects of growth hormone and many cells.

adipocytes. For example, TNF-α derived from macrophage induces the release of saturated fatty acids from adipocytes through the lipolysis, causing inflammatory changes in macrophages through Toll-like receptor 4 (TLR4). This is accompanied by increased release of free fatty acids, and irregular secretion of leptin, adiponectin, resistin, and retinol binding protein-4 (RBP4). These adipocyte-derived hormones and macrophage-derived molecules act together in a paracrine or autocrine style to worsen the inflammation of the adipose tissue. The paracrine cycle mentioned above between adipocytes and macrophages causes the vicious cycle to occur, thereby further accelerating adipose tissue inflammation. The systemically changing adipokine secretion through actions in the hypothalamus leads to increased food intake, reduced energy consumption, and decreased insulin sensitivity of muscle and liver through enhanced ectopic lipid accumulation and inflammation. As a result, the development of obesity and insulin resistance due to disruptions in adipokine secretion is observed (Galic *et al*. 2010, Itoh *et al*. 2011). The interest in the biology, physiology, and pathology of adipose tissue, which consists of cells specialised in fat storage, increased significantly due to the rise in obesity prevalence worldwide. The disruptions in the secretion of adipokines play an important role in the development of diseases associated with obesity, such as insulin resistance, chronic inflammation, mitochondrial dysfunction, depression, cancer, hypertension, cardiovascular diseases, and metabolic disorders (De Oliveira Leal and Mafra 2013, Luo and Liu 2016, Chouchani and Kajimura 2019, Derosa *et al*. 2020). Thus, understanding the adipose tissue biology and pathology makes an additional contribution to existing therapeutic methods for the prevention and treatment of obesity-related diseases. In addition to the adipokines specified in Table 1, recent studies emphasised that a new hormone is secreted from adipose tissue, and plays a key role in regulating glucose metabolism and appetite regulation, and may be a therapeutic target for the prevention of diseases such as obesity, type-2 diabetes, insulin resistance. This is the current hormone Asprosin, which is described as a new adipokine.

Asprosin discovered in 2016 in a study on Neonatal Premature Aging patients (patients with asprosin deficiency due to a truncated mutation in FBN1) by Romero and colleagues. In this study, these patients maintained eucleacemia, consumed very little food and were extremely weak,

although their plasma insulin levels were significantly lower. All these abnormalities showed the possible effects of asprosin on carbohydrate and lipid metabolism. Asprosin is derived from the word "aspros", meaning "white" (because white adipose tissue is the source of plasma asprosin) in Greek. Asprosin is the C-terminal cleavage product of Profibrillin, and is encoded by two exons FBN1. Exon 65 encodes 11 amino acids, and exon 66 codes 129 amino acids. The releasing liver glucose into the circulation, maintaining brain function, and survival in starvation is extremely important (Romero *et al*. 2016). Liver glucose is regulated by a series of hormones that precisely regulate plasma glucose levels. One of these hormones is asprosin, a hunger-induced glycogenic protein hormone that controls hepatic glucose production, and insulin sensitivity, consisting of 140-amino acids. It is found at the nanomolar level in circulation in humans, mice, and rats (in the fasting state: 5–10 nM levels) (Romero *et al*. 2016). The function of this hormone is to activate the G-protein-cAMP-PKA pathway by the Olfactory Receptor (OLFR734) to trigger the release of liver glucose stores by increasing intracellular cAMP levels, and causes rapid release of glucose into the circulation (Romero *et al*. 2016, Li *et al*. 2019). Li *et al*. (2019) stated that OLFR734, the protein of asprosin, played a critical role in maintaining glucose homeostasis in obesity and starvation condition. The studies showed that a single recombinant asprosin injection into wild-type rats caused a serious increase in blood glucose level, and hyperinsulinemia within 30 min. In 60 min after the injection, the blood glucose level of rats returned to normal. Therefore, the reducing asprosin, the new adipokine hormone, has a suppressive or restraining role in lowering blood sugar, and excessive secretion of insulin hormone (hyperinsulinemia) (Greenhill 2016, Kajimura 2017). The level of circulating asprosin increases in the state of hunger (basal glucose), and decreases after eating (high glucose). The blood glucose has a suppressive role on plasma asprosin level in the negative feedback loop. It was determined that asprosin had a circadian rhythm in humans, mice, and rats, and an overnight hunger caused a rise in circulating asprosin level (Romero *et al*. 2016, Kajimura 2017).

Methods

This study is a systematic review study designed to examine the relationship between new fasting hormone asprosin, obesity–obesity-related diseases, and acute–chronic exercise. This current systematic review study was carried out utilising the results from previous studies (studies with having ethical approval) by related original researchers. Therefore, this study is exempted from ethical approval. The instructions in Prisma were followed in order to create this systematic review. The prisma consists of a 27-point checklist and a four-phase flow diagram. According to the Prisma, it was suggested that the first 11 items are sufficient, and that the items in the first 11 items should be followed in the creation of this systematic review. In the Prisma directive, the first 1–4 items are included in the title, abstract, and introduction section, respectively. The items between 5 and 11 in the Prisma directive were taken into account in the contribution of the methodological model of this review (Liberati *et al*. 2009).

Prisma-Item 5: Protocol and registration

The current systematic review was not registered.

Prisma-Item 6: Eligibility criteria

The eligibility criteria for this study were determined as follows: (1) Cross-sectional studies involving the comparison of basal asprosin level between overweight/obese, type-2 diabetes, individuals and normal healthy individuals. (2) Prospective-cohort-designed and systematic review studies that provide information on the underlying mechanisms of the relationship between obesity, type-2 diabetes, and asprosin or exercise and asprosin level. (3) The studies with randomised control groups examining the effect of acute or chronic aerobic/anaerobic exercise on asprosin level, pretest–posttest studies. (4) Articles published between 2016 and 2020 years. (5) Abstract text or poster presentation, and English articles published in full-text. (6) Studies in humans and rats/mice. (7) Studies in which the sample group is adults or children.

Prisma-Item 7. Information sources

Pubmed, Google Academic, and Science Direct electronic databases were scanned between March and April 2020 to identify articles that meet the purpose of the study and the eligibility criteria.

Prisma-Item 8. Literature search

The articles suitable for the purpose of the study were determined by using words such as "asprosin", "asprosin and obesity", "asprosin and Type-2 diabetes", "asprosin and acute exercise", "asprosin and chronic exercise" in Pubmed, Google Scholar, and Science Direct electronic databases.

Prisma-Item 9. Study selection

Considering the inclusion criteria mentioned above, the titles and full texts of the studies in the specified databases were independently scanned by 2 people (HIC and OS) in a non-blind forma. Two researchers recorded the search results by creating a table in a word environment. The two authors independently determined which articles were appropriate for the purpose of the study. The selected articles were compared, and a new list was created. The disputes between the researchers were resolved in consensus, and articles were classified as excluded, verified, and included. For articles in the verification category, the full text was reached to make a final decision. The excluded studies after the full text review were listed in the excluded studies category by specifying the reasons for exclusion (studies written in different languages and carried out in different fields were excluded).

Prisma-Item 10. Data collection process

The first author of this review made data collection and extraction. The appropriate articles determined in the Pub Med database were sent to the researcher's e-mail address using the "E-mail" section in the database, and the articles were recorded in the Word format. In the Science Direct and Google Scholar database, the articles were transferred to the Word format as the author, title, abstract, reference, and doi number of the articles by looking at the content of the studies. In addition, full text of all articles and abstract texts of poster presentations were stored in the computer environment.

Item 11. Data items

The information elements identified from each article that meet the eligibility criteria, and included in the study are as follows:

1. In studies examining the relationship between asprosin, obesity and obesity-related diseases (Table 2): (a) authors and publication year of the article, sample group (mean age, gender, and disease types = obese, type-2 diabetes or insulin resistance). (b) Comparison of basal asprosin level scores of normal weight or normal glucose tolerance groups and groups with obesity, type-2 diabetes and insulin resistance. (c) the relationship between parameters of adiposity (body mass index and blood lipids) and glucose metabolism (glucose, insulin resistance) and asprosin hormone.
2. In studies investigating the effect of exercise on asprosin level (Table 3); (a) authors and year of the article. (b) sample group (mean age, gender). (c) exercise protocol (content of the exercise, duration, type and intensity). (d) effect of exercise on asprosin (scores, comparison with healthy people).

Results

A flow diagram of the process used to identify articles relevant to the purpose of this review was shown in Figure 1. A total of 229 studies were reached as a result of scanning databases such as Google Scholar, Pubmed, and Science Direct. Thirty-seven similar articles in this database were excluded, and 188 articles were determined to be scanned. After reviewing the abstract and content of 188 articles, it was determined that these articles did not meet the eligibility criteria of this review, and 110 of them were removed. Forty-three of the remaining 78 articles were excluded because they were written in different languages (Chinese, Russian, etc.) or the relationship of asprosin with different diseases (drug-naive anorexia nervosa, chronic hepatitis and staging of fibrosis, malignant mesothelioma, Oxytocin Treatment, cardiomyocytes, etc.) in other medical fields A total of 35 studies were included in the systematic review by meeting the inclusion criteria (Figure 1).

As a result of the screening, 3 cross-sectional, and 1 prospective cohort design studies in adults, and 3 cross-sectional studies in children comparing the basal asprosin level of the overweight/obese group and normal weight group were found. In addition, 7 cross-sectional studies were determined in disease groups associated with asprosin and glucose metabolism diseases, such as type-2 diabetes, insulin resistance, impaired glucose tolerance, and polycystic ovary syndrome. In these studies, basal asprosin scores of this type of diseased groups and groups with normal glucose metabolism were compared (Table 2).

Two randomised-control group-designed studies, which examined the effect of acute exercise on serum asprosin levels in overweight and obese individuals, were detected. One of these studies was published as a summary text in the conference report. Apart from these, a one pre-test–post-test design study investigating the effect of acute anaerobic exercise on asprosin level in terms of exercise metabolism in young normal healthy individuals was found. As a result of the screening, there are no studies examining the effect of chronic exercise on asprosin in humans, and especially overweight/obese individuals. The effects of aerobic exercise on asprosin levels in type-1 diabetic rats were investigated chronically in 3 pretest–post-designed randomised control group studies (one of them is abstract text), and the potential role of asprosin was revealed in the treatment of type-2 diabetes in these studies. From the remaining 15 studies, 1 study was the discovery of asprosin hormone, 1 study was the determination the orexigenic effect of asprosin, and the other systematic review studies that reviewed the role and importance of asprosin in metabolic diseases such as obesity, type-2 diabetes (Table 3).

Discussion

Obesity and obesity-related diseases

Recent studies showed that asprosin plays an important and complex role in metabolic diseases such as obesity, type-2 diabetes, insulin resistance (Yuan *et al*. 2020). Greenhill (2016) propounded that the determination of the oxygenic and glucogenic functions of the asprosin might be the potential pharmacological tool in the treatment of obesity and type-2 diabetes. It was explained by the research on 20 albino rats conducted by Edrees and Morgan (2018) that asprosin caused obesity development, and metabolic disruption. The rats were divided into two groups as control and asprosin treated. Asprosin-treated group received 30 μg of subcutaneous asprosin daily for 10 days. As a result, they reported that the body weight, body mass index, food intake, serum glucose level, serum insulin level, insulin resistance, liver glucose output, and triglyceride level increased significantly in the group that was injected with asprosin after 10 days. According to the studies conducted on adults people, and mice in the literature, asprosin hormone was found to be closely related to obesity and obesity-related diseases, and this hormone was high in individuals with these diseases (Yuan *et al*. 2020) (Table 2).

Table 2. The studies showing the relationship between asprosin, obesity, and obesity related diseases.

Researchers	Sample group	Asprosin level (Results)
Ugur and Aydın (2019)	Adults underweight, normal weight, overweight, and obese group (class I, class II, and class III) (mean age: 37.00 ± 4.75 years)	Asprosin was ∼2 times higher in class I and II obese group, and ∼4 times higher in III obese group compared to other groups.
Alan *et al.* (2019)	Control group and polycystic ovary syndrome group (mean age: ∼30 years)	Polycystic ovary syndrome group (6.41 ± 1.89 ng/mL) > control group (3.69 ± 1.22 ng/mL)
Wang *et al.* (2019a)	Normal weight (mean age: 47 years), and obese group (mean age: 36 years)	Obese group (2360 ± 5094 ng/mL) > normal weight group (307 ± 833 ng/mL) The cut-off value for asprosin level predicting the presence of obesity: >144 ng /mL, The sensitivity and specificity rates for asprosin level in predicting obesity were 71% and 71%, respectively.
Wang *et al.* (2018)	Group with having normal glucose regulation (mean age: ∼54 years), group with impaired glucose regulation, Type-2 diabetes group.	Impaired glucose regulation group (82.40 ± 91.06 ng/mL) > type-2 diabetes group (73.25 ± 91.69 ng/mL) > having normal glucose regulation group (16.22 ± 9.27 ng/mL). Asprosin, insulin resistance, and BMI were positively correlated.
Zhang *et al.* (2019a)	Control group (mean age: 47.60 ± 7.95 years), and type-2 diabetes group (mean age: 49.93 ± 10.99 years)	Type-2 diabetes > control group. Asprosin level was positively associated with fasting glucose and triglyceride
Li *et al.* (2018)	Healthy group, type-2 diabetes group and polycystic ovary syndrome group (Adult women)	Type-2 diabetes group > polycystic ovary syndrome group > healthy group
Schumann *et al.* (2017)	Adult obese women (mean age: 47.1 ± 14.2 years) and men group (mean age: 53.7 ± 7.5 years), control groups for women (46.1 ± 13.6 years), and male group (52.3 ± 5.0 years)	Obese women group = 19.9 ± 36.7 ng/mL, obese men group = 7.1 ± 7.5 ng/mL Non-obese women group = 9.2 ± 9.5 ng/mL, non-obese men group = 12.4 ± 10.4 ng/mL **(Not Significant)**
Acara and Guler (2019)	Normal glucose tolerance group (51.41 ± 8.88 years), and type-2 diabetes group (50.61 ± 8.77 years),	Type-2 diabetes group (6.75 ± 1.54 ng/mL) > control group (4.05 ± 1.28 ng/mL). A positive relationship was found between asprosin, insulin resistance, and unfavourable lipid profile.
Chang *et al.* (2019)	Control group (27.42 ± 0.37 years), and polycystic ovary syndrome group (25 ± 0.22 years).	Polycystic ovary syndrome group = 65.72 ± 5.24 ng/mL, control group = 50.01 ± 7.47 (ng/mL) **(Not Significant).** Overweight/obese group = 65.63 ± 7.48 ng/mL)>normal weight group = 58.49 ± 5.26 ng/mL) **(Significant)**
Long *et al.* (2019)	Normal weight and obese group (6–14 years children)	Normal weight (12.33 ± 4.18 ng/mL) > obese group (9.24 ± 4.11 ng/mL) **(Significant).** Negative relationship between asprosin and body mass index was found.
Sunnetci and Hatipoglu (2020)	44 children with obesity, 54 overweight children and 60 normal weight children (mean age: 12.58 ± 2.42)	Obese (106.293 ± 122.69 ng/mL) > overweight (79.744 ± 29.54 ng/mL) > normal weight (70.903 ± 17.49 ng/mL) (**Significant**).
Wang *et al.* (2019b)	40 normal weight children (mean age: 10.94 ± 2.19 years), 79 obese children (mean age: 10.82 ± 2.12 years.	Children with obese and insulin resistance (1.56 ± 0.07 ng/mL) > obese children (1.51 ± 0.44 ng/mL) > obese children without insulin resistance (1.18 ± 0.06 ng/mL) > normal weight children (0.96 ± 0.48 ng/mL) **(Significant).** Asprosin hormone was found to have a positive correlation with waist–hip ratio, diastolic blood pressure, leptin/adiponectin ratio, insulin resistance, and TNF-α.

The studies demonstrated that the asprosin was found to be high in adult obese individuals as compared with the normal weight individuals (except one study). However, contradictory results were seen in studies in children, and these results showed that asprosin had a complex role in obesity (Table 2). Long *et al.* (2019) suggested that the detection of low asprosin levels in obese children compared to normal weight children might result from the obese children being still in the compensatory phase of the metabolic balance. The mechanism that causes the formation of asprosin obesity has not been fully clarified. In studies, high asprosin in adult obese individuals was based on various mechanisms. Romero *et al.* (2016) indicated that FBN1 mRNA expression was expressed not only from adipose tissue but also from organs such as lungs, heart, and gastro-intestinal tract. Therefore, Wang *et al.* (2019a) asserted that obese individuals having higher levels of asprosin than normal individuals might be possible by releasing asprosin not only from adipose tissue but also from other organ systems. Duerrschmid *et al.* (2017) found out that obese people and mice had pathologically circulating high asprosin concentration, and the pathophysiological roles of this high asprosin level were uncertain, and that neutralising the level of plasma asprosin using a monoclonal antibody caused decreased appetite, body weight and improvements in the glycemic profile. According to Romero *et al.* (2016), Duerrschmid *et al.* (2017), Chopra and Moore (2019), and asprosin is an orexigenic hormone that acts centrally and triggers appetite, as well as the glycogenic

Table 3. The effect of acute and chronic exercise on asprosin hormone.

Researchers	Sample group	Exercise protocol (Content of the exercise, duration, type and intensity)	Results
Schumann *et al.* (2017) (conference report)	Adult obese women (mean age: 47.1 ± 14.2 years) and men group (mean age: 53.7 ± 7.5 years), control groups for women (46.1 ± 13.6 years), and male group (52.3 ± 5.0 years)	**Acute Anaerobic Exercise (Exhaustive Exercise)** A treadmill running test at speeds ranging from 2 to 4.9 km/h (individually adjusted) with increasing inclines were implemented to obese participants. The test on the treadmill was completed when the participants' maximum age-related heart rate was >85%. The treadmill running test at a starting speed of 6 km/h with 2 km/h increments every 3 min accompanied was applied to the ormal weight recreational athletes.	It was reported that acute exercise did not affect asprosin levels in both obese individuals and women, and in normal weight recreational athletes (men and women).
Wiecek *et al.* (2018)	10 healty women (mean age: 22.64 ± 1.49 years) 10 healthy men (mean age: 21.64 ± 1.22 years)	**Acute Anaerobic Exercise** Anaerobic exercise protocol was applied for 20 sec spint (pedal load: 5.79 ± 0.64 kg for men, pedal load: 3.88 ± 0.42 kg for women) on the bicycle ergometer. The participants were asked to pedal for 3 minutes at 60 rpm after 20 seconds of sprinting.	**For men;** acute anaerobic exercise did not have an impact on asprosin level. **For women;** The asprosin level was found to be before exercise: 4.02 ± 0.49 nmol/L, 3 minutes after exercise: 3.70 ± 0.70 nmol/L, 15 minutes after exercise: 4.05 ± 0.70 nmol/L, 30 minutes after exercise: 4.71 ± 1.70 nmol/L, 60 minutes after exercise: 4.39 ± 0.83 nmol/L, 24 hours after exercise: 4.11 ± 0.98 nmol/L. It was observed that asprosin level declined 3 minutes after exercise, but augmented within 60 minutes after exercise.
Ceylan *et al.* (2020)	10 normal weight adult men (mean age: 37.70 ± 4.66 years) 10 Overweight/obese adult male group (mean age: 37.10 ± 4.33 years)	**Acute Aerobic Exercise** A 30-minute aerobic exercise protocol was applied to adults and obese individuals at the intensity of exercise (55–59 intensity of heart rate reserve) recommended by ACSM.	Asprosin level decreased after acute aerobic exercise both morning and evening (Evening exercise > Morning Exercise) Compared to the normal weight group, overweight and obese individuals showed more decrease in the level of asprosin after exercise.
Ko *et al.* (2019)	Rats with type 1 diabetes were divided into three groups as control (6), diabetic rats from streptozotocin (6), and diabetic rats from streptozotocin + aerobic exercise (6).	**Chronic Aerobic Exercise** Type-1 diabetes mellitus was induced with a single dose of streptozotocin (intraperitoneally 65 mg/kg). Aerobic exercise protocol was applied to the exercise group for 8 weeks, 4 days a week, for 60 minutes on the treadmill at a speed of 20 m/min.	It was reported that hepatic asprosin levels played an important role in the effective regulation of plasma glucose levels, increased liver asprosin level resulted in disruptions in hepatic glucose metabolism, and regular aerobic exercise suppressed blood glucose level by decreasing hepatic asprosin levels in diabetic rats caused by streptozotocin.
Nakhaei *et al.* (2019)	54 male Wistar rats were divided into standard diet and the high-fat diet group. these mice received a diet for 12 weeks (without exercise stimuli).	**Chronic Aerobic Exercise** After diet programme, these mice were divided to 4 groups such as normal control standard diet, control, continuous swimming training (load 0–3% body mass, 5 d/wk, for 8 weeks), interval swimming training (load 5–16% body mass, 5d/wk, for 8 weeks).	The asprosin concentration 29.50% and 33.71% decreased in continuous swimming training and interval swimming training groups compared to control group, respectively. In addition, it was claimed that a decrease in asprosin after exercise led to a reduction in the appetite of mice with metabolic syndrome. .
Seo *et al.* (2020) Abstract text	5 week old male Sprague–Dawley rats were divided into two groups. 1. streptozotocin-induced diabetes group 2. streptozotocin with aerobic exercise training	**Chronic Aerobic Exercise** Type-1 diabetes mellitus was induced with a single dose of streptozotocin (intraperitoneally 65 mg/kg). Aerobic exercise protocol was applied to the exercise group for 8 weeks, 4 days a week, for 60 minutes on the treadmill at a speed of 20 m/min.	Aerobic exercise led to a significant reduction in asprosin, protein kinase A, Transforming growth factor beta. Aerobic exercise caused an improvement in hepatic asprosin-dependent PKA/TGF-β and AMPK downstream pathways of mice with type-2 diabetes

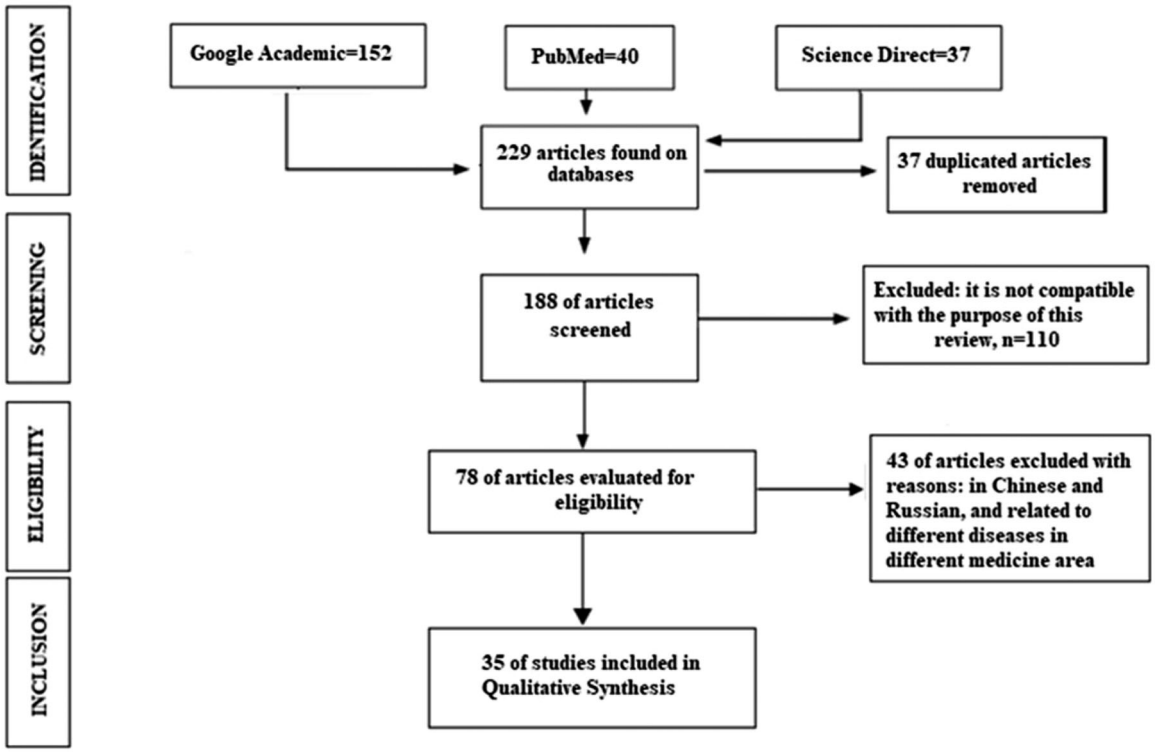

Figure 1. Prisma flow diagram of review with number of articles included, and excluded during the literature search, and selection process.

function of the asprosin. It can be said that the high level of asprosin in obese individuals might creates a feeling of hunger, and triggers more food intake, and as a result, obesity might develop due to an increase in body weight and body fat percentage in these individuals. Wang *et al*. (2019a), in their prospective cohort designed study, they observed that obese individuals had high levels of asprosin hormone, and excessive weight loss after bariatric surgery significantly reduced circulating asprosin levels. In addition, they claimed that asprosin was less secreted from adipocytes due to decreased adipose tissue mass after bariatric surgery, and changes in appetite, glucose homeostasis, and gastro-intestinal hormones might be possible mechanisms causing decreased circulating asprosin. As a result, they suggested that asprosin had more complex functions than appetite control, and glucose regulation. According to the results of Wang *et al*. (2019a) research, we can comment as follows; the basal value of asprosin levels may decrease due to loss of body weight or fat mass after long-term applications such as food restriction or food restriction + regular exercise in overweight/obese individuals. In a review study, asprosin might be a biomarker indicating adipose tissue mass or was a target in the treatment of obesity; however, observational studies could not fully confirm the cause-effect relationship between asprosin and obesity. In order to explain this relationship more clearly, *in vitro* and in vivo researches are required (Yuan *et al*. 2020).

Table 2 also showed that asprosin hormone was detected to be high in patient groups such as, type-2 diabetes, insulin resistance, impaired glucose regulation, and polycystic ovary syndrome, as well as obesity. Uncontrolled hepatic production of glucose undoubtedly causes hyperglycaemia. However, glucose homeostasis is very tightly controlled to eliminate the damage caused by excessive, and insufficient glucose in biological systems. In other words, no matter how much asprosin causes glucose formation in the liver; it should try to keep blood sugar levels within physiological limits by producing insulin in pancreatic beta cells. However, insulin not being produced, the development of insulin resistance, and the contribution of asprosin to excessive glucose formation, or the inclusion of glucagon in the increase in glucose release, lead to pathological conditions such as type-2 diabetes (Ugur *et al*. 2018). Also, asprosin secretion may increase during fasting as a mechanism to prevent or compensate for hypoglycaemia. In a study, it was found that asprosin did not increase in response to hypoglycaemia status, and was associated with insulin resistance and alterations in liver structure, most likely early stages of non-alcoholic fatty liver disease (Groener *et al*. 2019). In another study, it was stated that β cells play a role as an asprosin source under hyperlipidemic conditions, palmitate-derived asprosin secretion induced β cell inflammation, dysfunction and apoptosis by TLR4/NK mediated signalling. As a result, the asprosin-mediated activation of the TLR4/JNK-dependent pathway was detected to be a potential therapeutic target for the treatment of type-2 diabetes due to its maintenance of β-cell function (Lee *et al*. 2019). Romero *et al*. (2016) indicated that obese humans and mice were pathologically high in circulating asprosin levels, a single asprosin injection promoted hepatic gluconeogenesis by increasing cellular cAMP levels, resulting in a significantly rise in blood glucose level, and hyperinsulinemia within 30 min. After 60 min of injection, blood sugar returned to the normal condition. High glucose production from the liver caused by asprosin may increase

glucose toxicity in the blood. Increased glucose toxicity, i.e. hyperglycaemia, impairs the function of insulin-secreting beta cells of the pancreas, causing more insulin secretion, and as a results, hyperinsulinemia, type-2 diabetes or insulin resistance occurs (Ugur and Aydin 2019). It was demonstrated that blocking the effect of asprosin with a neutralising antibody or genetically deletion of Fbn1 reduced plasma insulin, and hepatic glucose production in the living organism (*in vivo*) (Kajimura 2017). The mechanisms for why basal asprosin levels are high in individuals with impaired glucose metabolism remain uncertain (Elnagar *et al*. 2018). Kajimura (2017) and Ko *et al*. (2019) stated that blocking or regulating the downstream pathways of asprosin such as a pathway related to AMP-activated protein kinase/transforming growth factor beta, and parallel mitochondria along Protein Kinase A may be useful in the treatment of type-2 diabetes. In addition, circulating asprosin showed circadian oscillation, with an acute drop that coincides with the onset of eating in healthy people (Romero *et al*. 2016). In a study, both fasting and postprandial asprosin levels were found to be significantly higher in patients with type-2 diabetes. While serum asprosin level coincides with the onset of the oral glucose tolerance test in individuals with normal glucose tolerance, this circadian oscillation was impaired in patients with type 2 diabetes mellitus. It was suggested that the impaired response of the asprosin to the glucose fluctuation may be one of the reasons for the onset of type 2 diabetes (Zhang *et al*. 2019b). As a result, the studies brought forward that the anti-asprosin or asprosin hormone may be a powerful potential therapeutic biomarker for the early diagnosis or treatment of type-2 diabetes (Elnagar *et al*. 2018, Wang *et al*. 2018, Chopra and Moore 2019, El Kattawy and Ashour 2019, Lee *et al*. 2019).

Discussion 2. The relationship appetite, asprosin, and acute–chronic exercise

In Figure 2 was shown that asprosin is a hormone that stimulates appetite or hunger (Duerrschmid *et al*. 2017). According to this study in humans and animals, it was stated that plasma asprosin crossed the blood–brain barrier, and activated orexigenic AgRP neurons via a path connected to cAMP, and this signal also caused downstream anorexigenic POMC neurons to be inhibited in a GABA-dependent manner, as a result, it triggered the sensation of appetite, causing an increase in adiposity, and body weight. It was also observed that neutralising the level of plasma asprosin using a monoclonal antibody led to a decrease in appetite and body weight, as well as improving the glycemic profile. As a result, asprosin hormone is both a glycogenic and orexigenic hormone.

The signal systems underlying appetite control are quite complex. At the physiological level, it is well known that the hypothalamus region of the brain plays a key role in the central regulation of eating behaviours in humans. In the hypothalamus, especially the arcuate nucleus (orexigenic and aneroxigenic neuropeptides) constantly receives neural, metabolic and endocrine signals from the periphery, and also ensures the maintenance of energy homoeostasis by adjusting not only energy intake but also energy consumption. Although most of the peripheral signals are produced by the gastro-intestinal tract, the pancreas and adipose tissue play an active role in this process (Hellstrom *et al*. 2004, Martins *et al*. 2008). In a research, it was asserted that appetite control was based on a network of interactions that form part of the psycho-biological system. The system consisted of three levels. These levels of psychological events (perception of hunger, desire and hedonic, i.e. delusional sensations), behavioural processes (meals, snacks, energy, and macronutrient intake), level of peripheral physiology, and metabolic events, that is, the level of neurotransmitter, and metabolic interactions in the brain. The appetite reflected the simultaneous operation of the events and processes on three levels. As with some eating disorders, when appetite was impaired, these three levels were negatively affected. In this system, neural events triggered and directed behaviour, each behaviour contained a response in the peripheral physiological system, and then these physiological events were translated into brain neurochemical activity, respectively (Hopkins *et al*. 2006).

Exercise or physical activity affects the energy balance equation by creating an energy deficit through energy consumption. However, energy consumption also has an impact on appetite control (i.e. physiological and psychological regulatory processes that stimulate food intake), and energy intake. This dynamic interaction means a shift in the energy balance. Exercise stimulates biological mechanisms that control appetite, while changing energy intake. The main effects of exercise on the expression of appetite are due to the lean and fat mass, resting metabolic rate, gastric adjustment to ingested food, and the changes in episodic peptides such as insulin, ghrelin, cholecystokinin, and glucagon-like peptide, as well as tonic peptides such as leptin. There is evidence in the literature that exercise affects all these components. In addition, exercise adjusts eating drive (a conscious feeling that reflects the mental impulse of eating) through modulation of hunger, and postprandial satiety corrections through interaction with the nutritional composition. The effects of exercise on each physiological component vary from person to person (depend on individual physiological characteristics), exercise duration and intensity. Therefore, individual responses to exercise are highly variable and difficult to predict (Blundell *et al*. 2015). The studies were shown that moderate to severe acute exercise has an appetite suppressing feature. This condition was defined as "exercise-related anorexia" (Stensel 2010, Hazell *et al*. 2016). The exercise-induced anorexia was observed to occur especially after $MaxVO_2 > 60$ intensity exercises, and the suppression of hunger was short-lived. The studies were shown that acute exercise induced a decrease in ghrelin level (King *et al*. 2010, Douglas *et al*. 2017, Goltz *et al*. 2018, Ueda *et al*. 2018), a rise in hormones such as cholecystokinin, glucagon-like peptide-1, peptide Y that create a feeling of satiety (Holmstrup *et al*. 2013, Douglas *et al*. 2017, Goltz *et al*. 2018, Ueda *et al*. 2018), a decline subjective sensation of hunger (Matos *et al*. 2018, Khalaj and Mirzaei 2020, Linoby *et al*. 2020), and energy

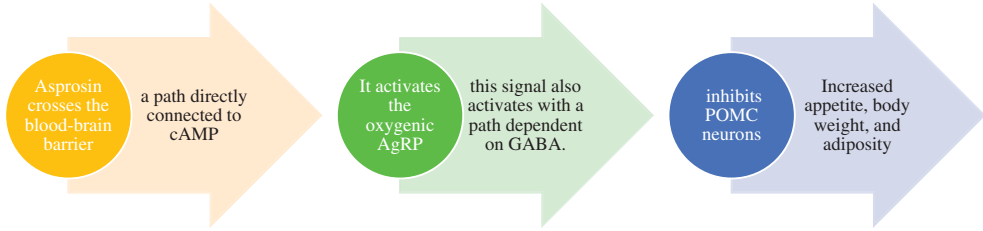

Figure 2. The relationship between asprosin and appetite.

intake (Khalaj and Mirzaei 2020, Linoby *et al*. 2020) in overweight/obese women and men. Although there is no clarity about the mechanisms that cause acute exercise to decrease in appetite, it was suggested that there were certain mechanisms that led to decline in appetite after exercise. These mechanisms were blood re-distribution, sympathetic nervous system activity, gastro-intestinal motility, cytokine release, free fatty acid concentrations, lactate production, changes in plasma glucose, and insulin concentrations. The redistribution of blood during exercise was important for suppressing ghrelin, which triggers the feeling of hunger, other mechanisms such as changes in plasma glucose and insulin levels, sympathetic nervous system activity, cytokine release, and muscle metabolism mediated changes in anorexigenic signals that create a feeling of satiety, namely Peptide YY, pancreatic polypeptide GLP-1 (Hopkins *et al*. 2006).

In literature, the most studied orexigenic hormone in studies examining the effect of exercise on appetite-related hormones is ghrelin. It was showed that the plasma level of ghrelin rised before meals, and decreased rapidly after food intake. In addition, peripheral administration of ghrelin increased food intake, and activated fasting-AgRP neuron populations in the arcuate nucleus in the hypothalamus. Asprosin is an orexigenic hormone that has a central effect similar to the ghrelin hormone, also defined as a new adipokine (Romero *et al*. 2016, Duerrschmid *et al*. 2017, Beutler and Knight 2018). As explained earlier, it was ascertained that stimulated AgRP neurons that increase the appetite, reduced the excitation frequency of POMC neurons that suppress appetite or create a feeling of satiety (Duerrschmid *et al*. 2017). In the literature, the studies examining the effect of acute exercise on asprosin level are quite limited, and 3 studies were encountered (Table 3). Two of these studies (one is conference paper and the other is an international book) were performed on overweight/obese individuals. The third study was conducted on healthy women and men with normal weight.

Table 3 showed six studies (3 acute and 3 chronic) examining the effect of exercise on asprosin level. In the studies, 3 were performed on humans, and the other 3 were conducted on rats. In studies, the decrease in asprosin level after exercise was depended on certain mechanisms. Wiecek *et al*. (2018) examined the importance of asprosin for energy metabolism during exercise, and they proposed that a decrease in asprosin level measured at 3 min after acute anaerobic exercise in women might be related to blood glucose level. Considering that asprosin caused glucose to be released from liver cells and exclusion of asprosin was a major disorder of this process (Romero *et al*. 2016), blood sugar level after anaerobic exercise might be a factor that induced asprosin release. They also stated that the asprosin level was low in the third minute after the exercise, that is, when the blood sugar was high, and that the asprosin level was the highest in the 30th minute after the exercise, that is, when the blood sugar was the lowest (Wiecek *et al*. 2018). The reason for this is the dominant energy source glucose in high intensity exercise. Therefore, when glucose in the blood or muscles decreases after high-intensity exercise, the blood glucose level is optimised by converting it into glucose in the liver. Therefore, asprosin may have played an active role in this process. In addition, Romero *et al*. (2016) indicated that FBN1 mRNA expression was secreted from other tissues other than adipose tissue. One of these tissues was skeletal muscle. This might indicate its potential role in releasing glucose from muscle glycogen during high intensity anaerobic exercise (dominant energy source glucose) (Wiecek *et al*. 2018). Therefore, there is no such study in the literature. In the following years, it is recommended to conduct studies examining the relationship between energy metabolism during anaerobic exercise, and asprosin level. Ko *et al*. (2019) emphasised the need to focus on insulin and glucagon related pathways, and changes in cAMP to identify possible mechanisms that caused a decrease in asprosin levels of exercise in obese and type-2 diabetics patients in future studies. Ceylan *et al*. (2020) found a higher decrease in serum asprosin levels in overweight/obese adult individuals especially after evening aerobic exercise compared to normal weight individuals. The reason for this was attributed to the amount of energy consumed during exercise, and the diet restriction made by the participants due to their psychological perceptions about the importance of the study, although no restriction was imposed on them during the study. They argued that negative energy balance triggered orexigenic signals more, and caused a further decline in serum asprosin level, which is important for appetite control of overweight/obese individuals. The finding different results in studies examining the effect of exercise on asprosin may be linked to the type, duration, and intensity of exercise, gender, chronic or acute, experimental design, characteristics of the participants, and parameters evaluated.

Conclusion

Asprosin is a new hormone found in 2016. The most of the studies demonstrated that this hormone is high especially in diseases, such as obesity and type-2 diabetes. This shows that asprosin may be a new therapeutic biomarker to be considered in the development, and treatment of obesity,

type-2 diabetes, but the necessary receptor, and the mechanism of action of asprosin have not yet been determined, and the factors regulating its secretion are unclear, a long-term and deep-rooted research is needed. The reason why this hormone is high especially in obesity, and obesity-related diseases such as type-2 diabetes, is supported by researches, and researches should be increased to detect the underlying mechanisms. There is only one study examining the effect of acute or chronic exercise on asprosin, especially in overweight/obese individuals, and type-2 diabetes patients (except rats). Therefore, it is thought that increasing the studies by examining the effect of exercise on asprosin might contribute to the regulation of glucose metabolism in type-2 diabetes, and appetite control in obesity, and also help to the understanding of the mechanisms that cause a decrease/increase in asprosin after exercise. In future studies, the effects of different types and intensities of exercise on asprosin levels in individuals with obesity and metabolic diseases can be examined. Asprosin is also a hormone that triggers appetite, and it was seen in the literature that exercise suppressed the feeling of appetite for a short time, and created a feeling of satiety. Therefore, it is recommended to be supported with parameters related to appetite, such as measuring the blood glucose levels, determining the subjective appetite perceptions with a 100 mm visual analog scale, or detecting the energy intakes of the participants (before and after exercise) in the further studies to be carried out for a clear idea whether the exercise really suppresses the appetite through a decrease in asprosin. Besides, the research on the support of asprosin hormone for glucose metabolism during exercise is not available in the literature. It is extremely important to investigate this issue in the future studies.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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