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MYONECTIN, IRISIN, APELIN-13 AND ELABELA HORMONES LEVELS AS BIOMARKERS FOR TYPE 2 DIABETES MELLITUS : A SYSTEMATIC REVIEW

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Insulin resistance is thought to be a key pathophysiologic indicator underlying type 2 diabetes mellitus. Nevertheless, its pathophysiology is complex and remains uncertain. Myokines such as myonectin and irisin produced by muscle tissue were shown to impact the sensitivity to insulin and could play an essential role in the etiology of insulin resistance. Apelin and Elabela are endogenous peptide ligands of the angiotensin II protein J receptor (APJ) that are actively involved in the control of lipid and glucose metabolism, implying a vital role in the management of metabolic conditions like type 2 diabetes. In this review, the data on the level of myonectin, irisin, apelin-13 and Elabela in patients with type 2 diabetes mellitus were analyzed.

K e y w o r d s: myonectin, irisin, apelin-13, Elabela, insulin resistance, type 2 diabetes mellitus.

Type 2 diabetes mellitus (T2DM) is a chronic endocrine and metabolic disease that is becoming increasingly common worldwide. It poses a major threat to human health and can result in a number of acute and chronic problems [1]. It is among the major global issues pertaining to public health. The primary risk factors for type 2 diabetes are believed to be overweight, resistance to insulin, dyslipidemia, and inactivity [2, 3]. Type 2 diabetes develops as a result of a combination of a pair of factors: tissues' inability to respond to insulin and pancreatic β-cells' decreased ability to produce insulin [4]. The outcome of obesity may appear to be a relatively straightforward excessive accumulation of body weight. Progressively increasing body weight serves as a trigger for subsequent metabolic diseases, with T2DM unquestionably closely associated with obesity [5]. The result of metabolism-related T2DM is straightforward: high blood glucose levels caused by decreased sensitivity to insulin or due to a decrease in the number of functional β-cells. Obesity plays a significant role in the development and progression of T2DM, contributing to increased genetic and epigenetic susceptibility, changes in the microenvironment that impair insulin signaling, impaired β-cell function, and dysregulation of the microbiome-gut-brain axis. However, in certain individuals with innate insulin resistance, type 2 diabetes can arise before obesity [6]. Excessive body fat buildup can lead to the development of type 2 diabetes, and the risk of type 2 diabetes rises proportionally with an increase in body mass index. The connection between obesity and type 2 diabetes involves intricate cellular and physiological mechanisms. This link is characterized by changes in β cell function, adipose tissue biology, and insulin resistance in multiple organs, all of which are induced by excess body fat. However, these alterations can be improved and even returned to normal levels through effective weight loss [7]. T2DM develops gradually as a result of β-cell stress, apoptosis, and an increase in macrophages. Type 2 diabetes mellitus (T2DM) advances at a slower pace because there is a longer duration of decline in the remaining β-cell function and mass [8].

This review, which updates and summarizes the most recent information on insulin resistance markers in patients with type 2 diabetes mellitus, is meant to serve as a narrative review. Our study terms for these potential markers were "insulin resistance", "Type 2 Diabetes Mellitus", and "Type 2 Diabetes Mellitus and markers" in the PubMed and

Google Scholar databases. The study included agents that, in the past twenty years, have been linked to insulin resistance in the course of type 2 diabetes mellitus; to our knowledge, no recent thorough review has been published regarding their relationship to type 2 diabetes mellitus. This study qualified certain markers, such as myonectin, irisin, apelin-13, and Elabela. Publications written only in English were included, such as review articles, observational studies, and case-control trials. There was no restriction based on the year of publication. The year 2024 was the end of the search.

Myonectin hormone

Patients with type 2 diabetes have an increased risk of developing cardiovascular disease, and the risk of cardiovascular problems is further increased if coexisting hypertension is present [9]. It has been suggested that the pathophysiologic common component underlying both hypertension and type 2 diabetes is insulin resistance (IR). Its pathophysiology is complicated and still unknown. Muscle tissue is a key target tissue for insulin resistance (IR) and is known to be an active endocrine organ that produces myokines such as fibroblast growth factor 21, irisin, and IL-6 that affect insulin sensitivity and may thus be involved in the IR pathophysiology [10]. One of the pathophysiologic reasons why T2DM occurs is insulin resistance. Because obesity increases visceral fat, it increases the risk of developing insulin resistance by 80%. Insulin signaling is hampered when extra visceral fat builds up in the abdominal region because it increases the body's vulnerability to inflammation, the generation of cytokines, and adipokine dysregulation. Increased insulin sensitivity has been linked to the positive effects of physical activity [11]. The metabolism of fats and carbohydrates by the entire body is significantly influenced by skeletal muscle. However, muscle also secretes growth factors and cytokines, which are referred to as myokines. These substances have the ability to influence metabolic processes, inflammatory processes, and additional systems in a paracrine, endocrine, or autocrine manner. Skeletal muscle absorbs a significant amount of glucose from food in reaction to insulin, and any extra glucose is stored as glycogen in the muscle until it is needed. Furthermore, in response to energy needs, muscle uses mitochondrial β-oxidation to burn a significant quantity of fat. It has long been known that skeletal muscle insulin resistance plays a significant role in the underlying mechanisms of type 2 diabetes. Skeletal muscle's function as an organelle secreting hormones and cytokines that are polypeptides with physiological activity collectively referred to as myokines that are responsible for modulating metabolic, inflammatory, and other physiological processes in nonmusical tissue has only recently been recognized, despite the muscle's well-established role in regulating the body's metabolism of glucose and fat. The hormone myonectin/erythroferrone, sometimes referred to as CTRP15, is released. The protein has not been thoroughly characterized biochemically despite its significance in physiological activities [12]. Myonectin was just recently identified, and preliminary research suggested that it plays a part in the absorption and oxidation of fatty acids in the liver and adipose tissue. The methods by which exercise regulates them, however, are still being worked out. Insulin resistance may be facilitated by impaired myokine secretion and function, including myonectin and irisin [13]. Myonectin levels in obese individuals were lower than in lean individuals, according to preclinical study focusing on the connection between myonectin and metabolic disorders. Subjects with type 2 diabetes did not exhibit an increase or decrease in circulating myonectin [10]. The aforementioned findings show that myocintin is linked to several metabolic and endocrine disorders; nevertheless, it is unclear if myocintin contributes to the pathophysiology of PCOS. The researcher Zhu Li et al. conducted a study on type 2 diabetes, the levels of circulating myonectin were notably lower than those of the controls. Compared to lean non-diabetic controls, obese non-diabetic controls had noticeably lower serum myonectin levels. Visceral fat area, subcutaneous fat area, hemoglobin A1c (HbA1c), serum myonectin concentrations in diabetic patients were significantly negatively correlated with low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), total cholesterol (TC), triglyceride (TG), body mass index (BMI), and the homeostatic model assessment of insulin resistance (HOMA-IR). A multivariate stepwise regression study, after controlling for variables, showed that the primary independent indicators of low blood myonectin concentrations were visceral fat, LDL-C, TG, BMI, and HOMA-IR[14]. Al-Regaiey K.A. and et al. [15]. He studied the effect of one new myokine that has a big impact on diabetes is myonectin. This study looked at the connection between body composition and plasma myonectin levels, lipid profiles, and glycemic

indices in individuals with T2DM. It was found that T2DM patients had lower plasma myonectin levels than healthy, non-diabetic Saudi adult individuals. The following variables showed a significant negative correlation with plasma myonectin levels: waist, triglycerides, HbA1c, insulin, and the HOMA-IR index by Li et al. had reported similar results, showing that circulating myonectin levels had a significant negative association with BMI, lipid, and glycemic parameters (including total and LDL cholesterol, triglyceride, HbA1c, fasting insulin, and HOMA-IR index) and were reduced in diabetic patients compared to the control subjects [14]. In a different investigation, myonectin levels were found to be inversely linked with HbA1c and to be considerably lower in diabetes patients with peripheral arterial disease (PAD) than in non-diabetic PAD patients [16]. Huibo Sun and et al. recently identified that myonectin reduces the levels of free fatty acids in the bloodstream in mice while improving the uptake of fatty acids in cultured adipocytes and hepatocytes. A sample of 228 individuals suffering from T2DM and 72 normal people participated in this study. Next, three categories of diabetic individuals were identified: T2DM patients without diabetic retinopathy, non-invasive diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR). The case group's myonectin concentrations in serum and aqueous humor were considerably lower than those of the control group. Compared to the other two T2DM patients, PDR patients had much lower serum and liquid humor myonectin concentrations [17].

Irisin hormone

In 2012, irisin was shown to be a hormone released by the skeletal muscle during exercise. The irisin structure is made up of around 112 amino acids, and it helps mice develop brown adipocyte-like cells [18]. People with diabetic kidney disease who have T2DM are linked to multifactorial faulty energy metabolism. It has recently been shown that skeletal muscles secrete the hormone irisin, which is triggered by exercise. Patients with chronic renal illness are thought to typically have aberrant irisin levels. The precise function of irisin in type 2 diabetes and prediabetes is still unknown, and its relationship to glycemic indices and lipid profiles is contentious [19]. When compared to healthy controls, T2DM patients and prediabetics had reduced levels of circulating serum irisin, according to research by Ibrahim Hasan Ibrahim and his team [20]. Najlaa Abed Jassim study of irisin hormone concentration in patients with T2DM by the search significance that irisin levels play in the etiology of numerous disorders, most notably diabetes mellitus, is a topic of intense attention [21]. Vanessa Lopes Mathia et al. study the function of irisin in type 2 diabetes mellitus and how it is linked to fat and changes in metabolism. Patients with T2DM were found to have significantly higher levels of glycated hemoglobin and plasma glucose. Patients with T2DM had decreased levels of irisin gene expression compared to the control group. In type 2 diabetes mellitus, irisin expression and body mass index were found to be positively correlated by correlation analysis, but plasma irisin and body mass index were found to be negatively correlated [22]. There were no discernible relationships between irisin expression and either plasma glucose or glycated hemoglobin levels, this means the information implies that the control of irisin expression of genes and plasma irisin levels are directly influenced by body weight, potentially connecting irisin to changes in adiposity seen in T2DM related to obesity [23].

Apelin-13 and Elabela hormones

The APJ receptor (angiotensin II protein J receptor) is present in acinar cells and pancreatic ductal cells, while apelin is mostly found in the beta and alpha cells of pancreatic islets. Apelin production and release are stimulated by insulin, which is thought to be the primary regulator of apelin. Hypoxia and obesity also have an impact on apelin. An apelin-mediated increase in peripheral glucose absorption has been observed in both normal and insulin-resistant mice. It was discovered that administering apelin exogenously improved glucose metabolism. Additionally, apelin-induced glucose absorption was found in type 2 diabetic adipocytes as well as separate normal adipocytes. These findings suggest that, in cases of high insulinemia, apelin may function as an exogenous insulin sensitizer. Nevertheless, apelin was found to be increased in the beta cells of type 2 diabetes in mice. Insulin secretion triggered by glucose can be inhibited by an apelin-36 injection. Apelin is reported to limit insulin secretion via activating phosphodiesterase 3B activity, which in turn stimulates cAMP breakdown and impairs glucose clearance. Insulin stimulates apelin production via binding to its receptor on adipocytes, it gives insulin secretion negative feedback. Conversely, apelin-13 treatment has been shown to

drastically lower blood glucose and raise serum insulin levels [24]. In addition to this, chronic apelin administration raises insulin levels and pancreatic islet mass in diabetics considerably. These outcomes were linked to the inactivation of AKT, ERK, and AMPK in the pancreas of diabetic mice and the increase of PERK-IRE1a-CHOP signaling [25]. Apelin is a peptide that serves as a natural ligand for the G-protein in humans. Apelin can influence glucose levels, insulin secretion, and insulin sensitivity. Apelin-13 is a widely studied subtype of apelin that has been demonstrated to be useful in treating both obesity and T2DM. It has been recommended as a therapeutic target for metabolic conditions. Apelin-13 has been found to affect a number of physiological processes and is strongly linked with diabetes, obesity, cardiovascular diseases, and hypertension. Apelin-13 may be a viable novel therapy for diabetic kidney disease by regulating the process of acetylation of histone in the body. Additionally, apelin-13 can lower the stress of the endoplasmic reticulum in the pancreas, and this is connected to diabetes. These findings suggest that apelin-13 has an important role in managing diabetes-related issues. As a result, we hypothesized that there could be a link between apelin-13 levels in the blood and the development of osteoporosis in people with T2DM. Nevertheless, the relationship between apelin-13 and BMD has not been investigated at present [26]. The lack of long-term effectiveness of pharmaceuticals with clinical approval has increased interest in the creation of innovative, effective antidiabetic alternatives. Apelin, a peptide that functions as an endogenous ligand of the APJ receptor, is one possible choice in this context. Apelin comes in a variety of molecular forms and was first investigated for its potential cardiovascular advantages and it may also be important for glycemic management [27]. Human chromosome xq25-26.1 has the APLN gene, which codes for the 77-amino acid precursor of apelin. After Gly22 in the Gly22-Gly23 sequence, a 22-amino acid segment at the N-terminus is cleaved by proteases to generate apelin-55, also known as proapelin. At first, apelin-55 was thought to be a proprotein and apelin-36 to be a precursor of the more physiologically active isoforms of apelin-17 and apelin-13. This resulted from apelin-36 having Arg-Arg residues, which are characteristic of endopeptidase cleavage sites similar to trypsin [28]. Recent research, however, indicates that apelin processing is more intricate than first thought. Apeline-55 can therefore activate the APJ receptor and is not a physiologically inert proprotein, but less effectively than its shorter isoforms produced from its C-terminus [27]. Moreover, the mechanisms behind the formation of apelin-13 from apelin-36 remain incompletely understood (pGlu) apelin-13 denoting the spontaneous N-terminal cyclization of the Gln1 residue in apelin-13 [29]. Study indicates that apelin, which is raised in the blood due to its presence in the central nervous system, plays a major role in the etiology of neuropathy and can be utilized as an indicator of the extent of peripheral nerve injury. In addition, a progressive role in diabetic neuropathy and DM, as well as nerve damage and the development of comorbidities, has been associated with a longer disease course, a high BMI, and excessive lipid consumption [30].

Elabela (ELA), also known as Toddler and Apela, is a 54 amino acid peptide that has a mature structure of 32 amino acids and a secretion signal, based on two study groups that recently identified it. The kidney is one of the organs that secretes ELA, a naturally occurring ligand of the APJ receptor and a G-protein-coupled receptor. It releases a hormone peptide that is active throughout embryogenesis and circulates in adults [31]. There are three exons in the zebrafish ELA gene, which is found on chromosome 1. ELA is expressed from the middle of the blastocyst until three days following fertilization in the zebrafish embryo. On chromosome 4, the human gene AK092578, which codes for ELA, is composed of 3 exons and a non-coding RNA transcript gene. The 54 amino acid precursor protein that the ELA mRNA encodes has a conserved open reading frame (ORF). There are 22 amino acid residues in the ELA N-terminal signal sequence, and the mature peptide ELA-32 also has 22 amino acid residues, of which 13 amino acids in the C-terminal are shared by all vertebrates. In response to the Golgi apparatus and endoplasmic reticulum actions, subsequently, ELA-32 breaks down into smaller molecular isoforms, like ELA-21 and ELA-11 [32]. Previous research has demonstrated that the hormone ELA, which increases insulin sensitivity and glucose intake, is activated by the APJ receptor and contributes to glucose homeostasis. Patients with T2DM have lower amounts of this hormone in their blood due to their diabetes. In zebrafish embryos, it was demonstrated that this hormone was an APJ ligand. It was later discovered in the placenta, heart endothelium, blood vessels, hepatic cells, and renal and hepatic cells [33]. It is anticipated that the rise in triglycerides and nitric oxide

may be linked to elevated glucose levels in GDM. Apelins are thought to decrease glucose transport to erythrocytes by blocking the sodium-dependent glucose transporter (SGLT). Therefore, we think that the aforementioned substances may trigger one another to develop GDM pathology [34].

The Table presents biomarkers of insulin resistance in type 2 diabetes mellitus. In patients with T2DM, changes in myonectin levels may serve as a helpful indicator of their insulin sensitivity. In addition to being a potential therapeutic target for type 2 diabetes and its complications, myonectin also has the potential to be a novel biomarker for diagnosis [10, 14, 15]. A study done by Andreas Leiherer et al. [16] showed no correlation of myonectin with age among patients, where 219 were aged 65 and higher, with an average age of 74 years, and 191 were under 65, with an average age of 57 years. In the older age group, the prevalence of T2DM was 40.6%, but in the younger age group, it was 42.4%. Myonectin concentrations were shown to be considerably lower in older T2DM patients as compared to non-diabetic subjects; however, in younger individuals, concentrations were not significantly lower. Regression analysis showed that the connection between myonectin and T2DM in older individuals was consistent with an unmodified odds ratio, yet not with younger patients. After controlling for sex, BMI, LDL and HDL cholesterol, current smoking, and statin intake, the relationship between myonectin and T2DM persisted in the elderly, however, not in younger individuals [16]. The study findings were in line with other research findings and indicated that individuals with T2DM had considerably lower circulating irisin levels than those of the control group [35, 36]. The observation that the ELA levels in healthy individuals are higher than those in diabetic patients without microalbuminuria, and that the ELA levels in diabetic patients without microalbuminuria are higher than those in patients with kidney damage and advanced albuminuria [37]. In type 2 diabetic rat models, apelin-13 administered over an extended period of time can prevent pancreatic beta cell loss or dysfunction and decrease the uptake and oxidation of myocardial fatty acids by inhibiting the PPAR-α receptor [38]. This study shows that the increase in apelin levels is not primarily caused by obesity. There is evidence that apelin-13 may be involved in the pathophysiology of diabetes due to the correlation between apelin-13 levels and glucose concentrations as well as insulin sensitivity. Irisin, a peptide hormone, is potentially implicated in lipid metabolism, insulin resistance, and obesity. Nevertheless, its contribution to the development of T2DM is still unclear. A study revealed that the levels of irisin in the blood serum of patients with T2DM were considerably elevated compared to the control groups. Irisin had a strong inverse correlation with body mass index, fasting blood glucose, glycated hemoglobin, insulin, and insulin resistance. Elevated plasma irisin levels in individuals with T2DM are associated with measures of body fatness, indicating that irisin may have potential as a therapeutic intervention [22].

Conclusions. The study concludes that plasma myonectin levels are significantly associated with T2DM, particularly in elderly vascular-risk patients. Our study demonstrates reduced myonectin levels in T2DM patients with poor glycemic control and

T a b l e. Predictors biomarkers of insulin resistance in patients with type 2 diabetes mellitus

Age (years)	Sex	BMI	Levels	References
		Myonectin		
45-60	Female and male	High	Myonectin levels were decreased	[14]
45-65	Female	–	Myonectin levels were decreased	[15]
54-69	Female and male	23.5 ± 3.1	Myonectin levels were decreased	[10]
		Irisin		
40-50	Female and male	–	Irisin levels were decreased	[35, 36]
		Elabela		
45-65	Female and male	–	Elabela levels were decreased	[37]
		Apelin-13		
45-65	Female and male	–	Apelin-13 levels were increased	[38]

an inverse association with glycemic indices. Thus, myonectin may be a useful biomarker and may have a role in the pathophysiology of T2DM.

Patients with persistent problems from T2DM showed decreased circulation irisin levels compared to those without such issues. Furthermore, there was a negative correlation found between the degree of chronic problems and irisin levels.

The ELA level is higher in healthy individuals in comparison to diabetic patients without microalbuminuria, as well as in diabetic people without microalbuminuria compared with those who have advanced albuminuria and kidney damage, suggesting that it could be an important clinical prognostic factor and possibly an appealing therapy for patients with diabetic nephropathy.

This study has demonstrated that the hormone ELA, which increases insulin sensitivity and glucose intake, is activated by the APJ receptor and contributes to glucose homeostasis. Patients with T2DM have lower amounts of this hormone in their blood due to their diabetes. In zebrafish embryos, it was demonstrated that this hormone was an APJ ligand. It was later discovered in the placenta, heart endothelium, blood vessels, hepatic cells, and renal and hepatic cells.

The beta and alpha cells of pancreatic islets contain the majority of apelin. Insulin is regarded to be the main regulator of apelin, as it stimulates the creation and release of apelin. Apelin is similarly affected by obesity and hypoxia. Both normal and insulin-resistant mice have shown an increase in peripheral glucose absorption mediated by apelin. It was found that exogenously administered apelin enhanced the metabolism of glucose.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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РІВНІ ГОРМОНІВ МІОНЕКТИНУ, ІРИЗИНУ, АПЕЛІНУ-13 ТА ЕЛАБЕЛИ ЯК БІОМАРКЕРІВ ЦУКРОВОГО ДІАБЕТУ 2 ТИПУ: СИСТЕМАТИЧНИЙ ОГЛЯД

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Резистентність до інсуліну вважається ключовим патофізіологічним показником, що лежить в основі цукрового діабету 2 типу. Проте, його патофізіологія залишається складною і недостатньо зрозумілою. Було показано, що міокіни, такі як міонектин та іризин, вироблені м'язовою тканиною, впливають на чутливість до інсуліну та можуть відігравати істотну роль в етіології резистентності до інсуліну. Апелін і Елабела, ендогенні пептидні ліганди рецептора протеїну J ангіотензину II (APJ), активно беруть участь у контролі метаболізму ліпідів і глюкози, що вказує на їхню важливу роль у лікуванні метаболічних станів, таких як діабет 2 типу. У цьому огляді проаналізовано дані щодо рівня маркерів резистентності до інсуліну – міонектину, іризину, апеліну-13 та Елабели – у пацієнтів із цукровим діабетом 2 типу.

Ключові слова: міонектин, іризин, апелін-13, Елабела, інсулінорезистентність, цукровий діабет 2 типу.

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