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A review on the role of novel adipokine Isthmin-1 and Subfatin in human type 2 diabetes mellitus

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Abstract*—Adipokines are essential for maintaining cardiovascular and metabolic balance. The term "adipokines" refers to peptides in the pancreas, brain, vascular system, liver, immune system and muscle. adipokines regulate numbers of factors, such as energy expenditure, hunger, satiety, insulin sensitivity, and blood pressure, insulin secretion, adipogenesis and fat distribution, and that might make them play a role in future pharmacological treatment strategies for obesity and metabolic diseases. Isthmin-1 (Ism-1) is a recently discovered insulin-like adipokine that suppresses hepatic lipids. According to recent research, Ism-1 can enhance lipid metabolism and treat metabolic disorders linked to type 2 diabetic mellitus (T2DM). The primary source of the protein subfatin (SUB) is white adipose tissue. Subfatin (SUB) is expressed in these following tissues: adipose tissue, brain tissue, thymus gland, liver, activated human monocytes, spleen, omental adipose tissue, muscle, salivary glands and heart tissues. The SUB lowers insulin resistance to control glucose metabolism. Isthmian-1 is a novel biomarker for early management and diagnosis of T2DM and has a beneficial effect in glucose homeostasis and might be therapeutic for diabetes. Subfatin also plays a role in glucose metabolism and insulin sensitivity, so it has significant effect in pathogenesis and complication of diabetes.

Keywords*—Isthmin-1, diabetes mellitus, Subfatin, adipokine, insulin resistance.

I. INTRODUCTION

Recent epidemiological research reveals a concerning rise in obesity incidence in modern societies. Increased body weight is unquestionably caused by subcutaneous and visceral adipose tissue buildup, which is mostly the result of bad dietary habits and is strongly linked to inactivity. This, in turn, raises the risk of cardiovascular complications and diabetes [1]. Adipose tissue produces numerous hormones and molecules, namely cytokines or adipokines, the metabolism of body glucose and lipids were effected by obese disorders in production process of cytokines and adipokines; these hormones associated with lipid and carbohydrates metabolism, which may lead to insulin resistance and type 2 diabetes [2]. Accumulation of lipids and fats increased dysfunction and stress in tissues; development of obesity was lead to many comorbidities such as hypertension, cardiovascular, type 2 diabetes (T2D) disease, liver dysfunction and cancer [3]. In addition to storing fat, the adipose tissue is endocrine organ secretes a variety of physiologically active molecules, including chemokines, hormones, adipokines, and cytokines that control the body's metabolic processes, influence inflammation, and have an impact on endocrine activities [4]. Adipose tissue secretes physiologically active chemicals called adipokines, which function similarly to traditional hormones. These signaling proteins are present in cells and regulate or alter a variety of biological processes in the target organs, including the heart, blood vessels, muscles, brain, liver, and immune system [5]. Adipokines have diverse roles and can impact numerous processes, such as appetite and regulating energy, metabolizing lipids and glucose, endothelial cell function, enhancing insulin sensitivity, causing inflammation, blood pressure, angiogenesis, hemostasis, metabolic syndrome and development of atherosclerosis [6,7]. More than (600) adipokines with various biological functions have been identified so far. Obesity associated

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with development of persistent low-grade inflammation and the activation of pro-inflammatory adipokines. Therefore, in people who are suffering from obesity, the release of adipokines that reduce inflammation is inhibited [8,9].

II. ISTHMIN- 1

Recently, it was discovered that isthmin 1 (ISM1) is an adipokine released by adipose tissue. It increases adipose tissue's absorption of glucose while inhibiting hepatic lipid production [10]. It is part of the ISM1 and ISM2 gene families of isthmins. The gene of ISM1 is found on chromosome (20) and encodes a (~60kDa) protein and containing (499) amino acids [11]. Isthmin-1 signaling depends on PI3K and combines phosphorylation targets with the insulin signaling. These are not mediated by the insulin-like growth factor1 receptor or insulin receptor , but rather by an as-yet-unidentified receptor tyrosine kinase [12]. Research has demonstrated that ISM1 has anti-inflammatory properties, most likely by inhibiting NF-κB activation and inflammatory cytokine/chemokine synthesis. Additionally, it has been discovered that ISM inhibits angiogenesis and induces death in endothelial cells [13]. The ISM1 expression can be found in numerous adult animal tissues, such as the kidneys, heart, lung, and lymphocytes [14]. Recently ,Jiang et al. demonstrated that mature adipocytes release ISM1 and initiate a cascade of insulin-like signaling [10]. Furthermore, ISM1 binds to two membrane receptors, (integrin αvβ5 and GRP78), which causes tumor and endothelial cells to undergo apoptosis. Remarkably, glomerular disorders have been associated with both receptors' expression in glomeruli. [15]. According to recent research, the protein ISM1 released by adipocytes functions as an adipokine by phosphorylating (AktS473) in healthy humans to enhance insulin resistance and glucose tolerance [12,16]. By using a cross-sectional design, cohort of Spanish youngsters found out that serum levels of the new insulin-like adipokine ISM1 are certainly linked to obesity in pubertal males but not in females [17,18]. People who have diabetes have a ten-fold higher chance of developing cardiovascular disease (CVD). Three major risk factors for CVD are endothelial damage, albuminuria, and mitochondrial dysfunction. According to a recent study, individuals with albuminuria had a positive correlation with serum ISM1. Studies showed that lowering albuminuria improved cardiovascular case for patients with diabetes[19,20]. Interestingly, despite the fact that insulin and ISM1 regulate glucose in a similar fashion, ISM1 does not operate on the insulin receptor; instead, it binds to a specific receptor to activate the (PI3K-AKT) pathway, which in turn promotes adipocytes' absorption of glucose [21,22]. In skeletal and adipose cells, glucose transporter 4 (GLUT4) is glucose transporter protein that is primarily controlled by insulin or adenosine triphosphate (ATP) [23]. Research conducted in vitro has shown that ISM1 facilitates the translocation of GLUT4 from the cytoplasm to the plasma membrane, whereas glucose absorption is enhanced by endogenous phosphorylation of the energy metabolism component AKTS473. Skeletal muscle cells and mature adipocytes of human showed that ISM1 was able to induce (pAKTS473) phosphorylation levels. phosphatidylinositol 3-kinase (PI3K) inhibitors showed that ISM1induced glucose uptake was completely blocked, indicating that ISM1 requires (PI3K)to induce glucose uptake in the adipocytes [10,24]. Insulin stimulates the mammalian target of rapamycin(mTOR) and its complexes (mTORC1) and (mTORC2) which controls insulin sensitivity[25]. ISM1 may be involved in the induction of the PI3K-AKT signaling pathway and glucose uptake through mTORC2 because mTORC2 inhibitors blocked ISM1-induced AKT signaling while mTORC1 inhibitors did not. This was demonstrated in cells treated with mTORC1, 2 inhibitors and then stimulated with ISM1 or insulin [10]. Interestingly, despite the fact that insulin and ISM1 regulate glucose in a similar fashion, ISM1 does not operate on the insulin receptor; instead, it binds to a specific receptor to activate the PI3K-AKT pathway, which in turn promotes adipocytes' absorption of glucose [21] as shown in figure 1. [10].

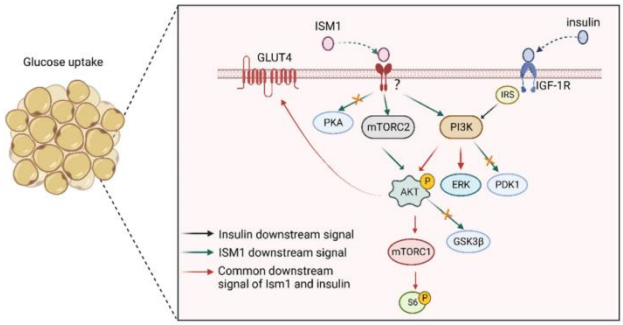

Figure 1 :mechanism of ISM1[10].

III. FUNCTIONS OF THE ISTHMIN-1

The ISM1 is responsible for several essential tasks since its first discovery in 2002. The ISM1 is an adipokine that is essential for several pathologic processes, such as immunity, cancer, cell proliferation, endothelial cell permeability, and physiogenesis. It is also involved in metabolism [21]. The body's regulation of protein, lipid, and glucose metabolism is significantly influenced by the ISM1.Also, ISM1 controls cellular autophagy, angiogenesis, and the immunological milieu, which influences the development of cancer [21].

IV. SUBFATIN

A disease that is known as an obesity is defined by an excessive build-up of fat in the subcutaneous and visceral areas of the body as well as overweight gained as a result of energy expenditure. Adipose tissue, which is made up of adipocytes, or adipose cells, has the amazing ability to store excess energy in the form of lipids. This is where the extra weight is kept [26]. Subfatin, also known as cometin, is a tiny cytokine (about 27 kDa) released by a protein that is encoded by the METRNL gene (simeler of meteorin). It's highly expressed in the activated macrophages and mucosal tissues of the skin. It has also been suggested that subfatin functions as a hormone in a number of illnesses, including type 2 diabetes mellitus T2DM, obesity, and metabolic disorders [27]. Skeletal

muscle and Adipose tissue release subfatin, a recently identified adipokine with anti-inflammatory and insulin properties. Exercise enhances energy expenditure, improves glucose tolerance, and causes white adipose tissue (WAT) browning via activating the WAT via pathway on skeletal muscle and cold exposure [28,29]. The subfatin gene is found on human chromosome (17q25.3) and mouse chromosome (11qE2). The subfatin protein, which has 311 amino acids, is encoded in human genomes, according to bioinformatic study [30]. Adipose tissue, which is made up of adipocytes, or adipose cells, has the amazing ability to store excess energy in the form of lipids. This is where the extra fat is stored[26]. Subfatin, also known as cometin, is a tiny (about 27 kDa) cytokine released by a protein that is encoded by the METRNL gene (simeler of meteorin). It's highly expressed in the activated macrophages and mucosal tissues of the skin. It has also been suggested that subfatin functions as a hormone in a number of illnesses, including type 2 diabetes mellitus T2DM, obesity, and metabolic disorders [27].

V. Functions of the Subfatin

According to current research, subfatin may enhance insulin sensitivity, boost energy expenditure, regulate lipid metabolism, causing change of white adipose to brown colour, and support anti-inflammatory gene [31,32]. Exercise is known to facilitate the release of proteins associated to metabolism by repeatedly contracting and relaxing the skeletal muscle. This results in a variety of phenotypic changes in the skeletal muscle and assists in relieving metabolic problems [31]. Following exercise, particularly after exposing to cold, subfatin is stimulated into circulation in adipose tissue. Elevated subfatin increases the expression of genes linked to beige anti-inflammatory cytokines and fat thermogenesis , enhances glucose tolerance, and increases energy expenditure [33]. The level of insulin resistance is independently related to serum subfatin [34].

VI. Isthmin-1 and Type 2 Diabetes Mellitus

Hyperglycemia is an indicator of type 2 diabetes mellitus (T2DM), a chronic metabolic disease. Microvascular problems such as diabetic retinopathy, diabetic nephropathy(DN) ,and neuropathy can arise from persistent hyperglycemia [35,36]. Jiang *et al.,* identified ISM1 as an adipokine expressed in mature adipocytes with a significant function in the metabolism of fats and carbohydrates. According to recent research, ISM-1has a variety of advantageous metabolic benefits, such as enhancing insulin resistance, preventing hepatic steatosis, and increasing glucose absorption [10]. o\Overexpression of the ISM-1 by viral vector transduction may suppress endogenous hepatic glucose synthesis, improve insulin sensitivity, and decrease hepatic fat [37]. It is now believed that adipokines and adipose tissue regulate inflammation, lipid metabolism , glucose homeostasis, and immunity in addition to being involved in energy storage [38]. Recent studies showed that ISM-1 might raise glucose absorption in mouse and human adipocytes by causing glucose transporter 4GLUT4 translocation to the plasma membrane [39]. According to earlier research, adiponectin seems to raise serum HDL-C levels, and HDL can raise adiponectin levels in turn [40]. The adipokine ISM1plays a crucial function in lipid metabolism, yet prior research on its association with HDL-C has ISM1not been entirely apparent [10]. It has been documented that ISM1accelerated the shift from prediabetes to T2DM by indirectly promoting the islet(β- cell) dysfunction [41]. Additionally, it has been demonstrated that therapeutic dosages of recombinant ISM1can cure fatty liver and diabetes in obese rats (22). It inhibits liver lipogenesis and lowers blood glucose by stimulating a shared intracellular signaling pathway with insulin through a unique receptor [42,43]. Therefore, more research on the relationship between T2DM and ISM1is required. It has been shown that there is a positive link between albuminuria and serum ISM1 levels in individuals with T2DM [37,44]. There are many studies showed the relationship between isthmin-1 and T2DM . The first one was by by Jiang et al. In this study, recombinant ISM1 was administered to skeletal muscle cells of human adipocytes. They found that there was a non-insulin-dependent pathway for ISM1-mediated glucose absorption. It was demonstrated that various cell types have varying capacities for ISM1-mediated glucose absorption. There have been indications that this might be connected to glucose transporter proteins or unique receptors to different cell types. Research conducted in vitro has demonstrated that ISM1 facilitates the translocation of the GLUT4 from the cytoplasm to plasma membrane in skeletal and adipose muscle cells. Consequently, it was discovered that ISM1 binds to an as-yet-unidentified receptor to mediate its impact rather than the insulin receptor [10]. Just a year later, Wang et al. examined the levels of ISM1 in the blood of people who had just received a T2DM diagnosis and compared them with those healthy people who did not have the disease. They discovered that, in comparison to normal glycemic controls, those with T2DM had much decreasing in serum ISM1 concentrations. Furthermore, serum ISM1 concentration has been demonstrated to be an independent protective factor against type 2 diabetes using logistic regression analysis. Consequently, they proposed that models to forecast the population's risk of developing diabetes may be developed using serum ISM1 [16]. Another study that was published in 2022 looked at the connection between severity of the albuminuria in people with T2DM and serum ISM1 concentrations. Compared to the groups with microalbuminuria and normal albuminuria , the group with macroalbuminuria had considerably higher serum ISM1 concentrations [21]. Serum ISM1 was known to be protective against the onset of type 2 diabetes in the earlier investigation. On the other hand, this study demonstrated a correlation between high serum ISMI1 concentrations and macro albuminuria, a measure of the severity of DN. These contradicting findings lead us to believe that ISM1 may have distinct functions in the development and onset ofT2DM [37]. Liao et al. looked at relationship between diabetic neuropathy and serum ISM1 levels in diabetic patients in different research that was published in 2023. In contrast to Wang et al.'s previously stated work, the authors of this study discovered significantly greater serum ISM1

concentrations in T2DM patients than in healthy controls. While the authors did not detect a significant association with HbA1c , HOMA-IR, or BMI , they did find a positive relationship with age and gender in the correlation study between baseline characteristics in serum ISM1 andT2DM . Analogous to this investigation, found that there was a statistically significant difference in the serum ISM1 concentration between the GDM group and the non-DMG group [19].

VII. Type 2 diabetes mellitus and subfatin

Obesity raises the risk of CAD (coronary artery disorders)and T2DM is linked to dysregulation of the adipokine production and chronic inflammation [45]. The body's biggest endocrine organ, adipose tissue, regulates homeostasis through the release of adipokines, which are involved in a number of signaling pathways. Adipokines are thought to be promising possibilities for explaining how systemic lipid and glucose metabolism and adipose tissue interact [46,47]. Patients with type 2 diabetes have low levels of subfatin, which is critical for the etiology (development of disease problems) and increases insulin resistance. Elevated levels of subfatin have been shown to improve glucose tolerance and the intercellular insulin signal, as well as to limit the release of inflammatory mediators, which are chemicals produced by inflammatory cells and responsible for all changes associated with inflammation[27]. Subfatin raises insulin sensitivity and energy expenditure, according to studies [33]. There was conflicting research in the past on the connection between subfatin and obesity. It was noted in the literature that obese people had reduced subfatin level [28]. In a different research, children with obesity expressed more subfatin than healthy children, whereas in another study, it was found that there is no difference in the subfatin levels between obese and non-obese people [27]. It has been demonstrated in a total of three studies published that T2DM patients had reduced subfatin levels when compared to the control group [48,49]. According to these investigations, there is a negative association between subfatin level and both HOMA index and insulin level. Low subfatin level may be linked to deteriorating glucose tolerance. Insulin resistance and Insulin sensitivity may be impacted by changes in subfatin expression, particularly when such changes are brought on by increasing body adiposity from obesity[50]. The information on the subfatin levels in diabetes individuals' circulation is concerning. Lee *et al.,* [51] found the level of subfatin are lower in T2DM, but studies by Chung [31], and Wang [52], found increased subfatin levels in T2DM. Skeletal muscle and adipose tissue both express the adipokine subfatin. Subfatin is believed to be effective in glucose metabolism because it enhances insulin sensitivity in the adipose tissue by upregulating (PPAR-γ) expression [53]. According to certain theories, over-expression of subfatin may result in decreased lipogenesis and insulin resistance by inhibiting the expression of PPAR-γ in adipocytes [28,54] .

VIII. Conclusions

Isthmian-1 is a novel biomarker for early management and diagnosis of T2DM. I have a beneficial effect on glucose homeostasis and might be therapeutic for diabetes. Subfatin also plays a role in glucose metabolism and insulin sensitivity, so it has significant effect in pathogenesis and complication of diabetes.

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Conflict of interest

Authors declare that they have no conflict of interest.

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