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A Review of Asprosin as new Biomarker for diagnosis different Diseases

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***Abstract*—This study was designed to investigate the connections between (Inflammation, Cardiovascular diseases (CVDs),-diabetes mellitus,-Obesity,-polycystic ovary syndrome, thyroid and cancer)-and asprosin hormone. Asprosin is present in high amounts in a variety of diseases that are considerably manifested in several cases and illnesses Asprosin hormone is newly adipokine helps the liver produce glucose. White adipose tissue secretes the novel hormone asprosin, which stimulates the release of hepatic glucose, making protein a possible target for new treatments for obesity and type 2 diabetes mellitus. Exons (65 and 66) of the gene(Fibrillin 1 (FBN1)), which was recently shown to be a new hormone released by white adipose tissues, are the final two exons that code for asprosin. However, further research is needed to fully understand how asprosin affects pancreatic beta-cells, leading to pathologically elevated cellular dysfunction and inflammation. Asprosin hormone is raised in human with metabolic disease. The findings imply that asprosin hormone may be crucial for maintaining insulin and glucose homeostasis as well as acting as a risk factor for a number of diseases, including CVDs, obesity, T2DM, cancer, hypothyroidism, and PCOS. Depleting asprosin or attenuating its activity may potentially offer a novel therapeutic option for the treatment of T2DM and obesity.**

***Keywords*—Asprosin, diabetes mellitus, Cardiovascular diseases, obesity, FBN1.**

I. INTRODUCTION

A new adipokine is called asprosin that is a circulating hormone and mostly released by white adipose tissue (WAT). According to earlier research, asprosin affects insulin resistance, glucose tolerance, and fasting-induced homeostasis [1]. The Fibrillin1 gene (FBN1), the precursor of a recently identified glucogenic hormone, encodes for asprosin [2, 3]. The previous studies verified the greatest expression levels in WAT of mice and humans after analyzing FBN1 mRNA expression, indicating the crucial role of (Fbn1) in adipogenesis [4]. In a study of newborns premature aging (NPS), Romere et al., first discovered asprosin as a novel glucogenic protein adipokine in (2016). Exons (65 and 66) of FBN1 gene, which code for asprosin. Despite having significantly lower plasma insulin levels in the (NPS) patients. whose (FBN1) truncating mutation renders them asprosin-deficient, maintained euglycemia. In addition to eating less and being fairly thin, the (NPS) patients. The probable effects of asprosin on lipid and carbohydrate metabolism are indicated by all of these abnormalities. Asprosin functions intricately in the organs, and central nervous system (CNS). It affects cell apoptosis, insulin resistance, glucose metabolism, and hunger [5].

The disturbance of the regular metabolic processes is primarily responsible for metabolic diseases including obesity, coronary vascular disease, POLY-CYSTIC ovaries syndrome (PCOS), and diabetes. Asprosin has a crucial and intricate function in metabolism and METABOLIC illnesses, according to a recent study. Asprosin has a crucial and essential function in metabolic disorders and metabolism [6]. In order to act in the brain, asprosin can also leave the circulation and pass the blood-brain barrier (Fig. 1). The discovery of asprosin in the cerebrospinal fluid (CSF) of rats at quantities (5- to 10) fold lower than in plasma was the first proof that it was a cerebrospinal fluid (CSF) protein in addition to being a plasma protein. Fasting elevated CSF asprosin levels similar to plasma.

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Additionally, asprosin administered intravenously demonstrated a striking capacity to pass the blood-brain barrier and reach the CSF [7].

II. Asprosin function

Asprosin is released into circulation in mice and human at a nanomolar quantity. In the liver, asprosin induces the release and synthesis of glucose, which activates the Cyclic adenosine-Mono-Phosphate (cAMP) signaling flow through the unidentified (G protein-coupled receptor (GPCR)) and increases hunger in the hypothalamus [8].

III. Mechanism of asprosin action

After being secreted, asprosin travels through the bloodstream before being drawn in by the liver, where it attaches to the surface of hepatocytes and stimulates blood glucose increase, a necessary condition for life and proper brain function [1]. Asprosin enters the liver and the brain after being released from white adipose tissue. Asprosin has a glucogenic action in the liver via activating the olfactory (G-protein-coupled receptor). Asprosin increases hunger in the brain by activatingorexigenic(AgRP) neurons via receptor and subtly suppressinganorexigenic(POMC) neurons [7].

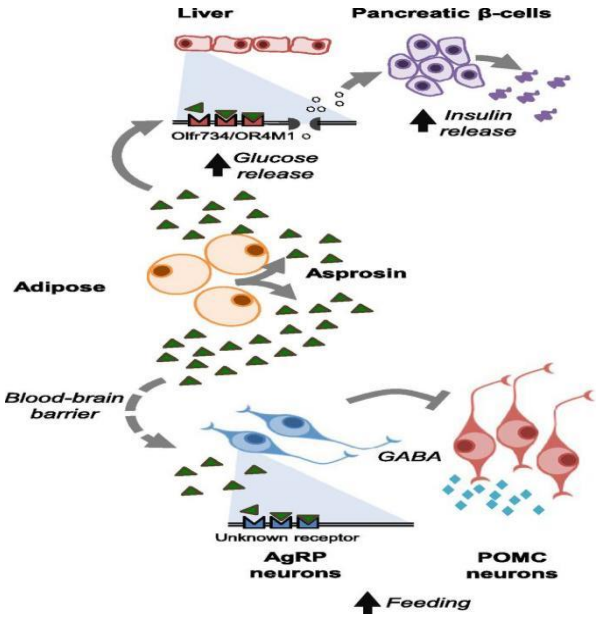

Figure 1: mechanism of asprosin action[7].
Note: Plasma agouti-related protein (AgRP) ;Pro-opiomelanocortin (POMC); Gamma-aminobutyric acid (GABA); olfactory receptor (OLFR734) and olfactory receptor family 4 subfamily M member 1 (OR4M1).

IV. Asprosin and disease

A. *Inflammation:*

Through the development of inflammation, persistently non-esterified fatty acids and elevated blood glucose cause pancreatic β-cells malfunction and apoptosis,[9]. OBESITY-ASSOCIATED with abnormally high blood free fatty acids that result in c-Jun N-terminal kinase and oxidative stress, which lead to promoted inflammation [10]. Therefore, by maintaining pancreatic β-cells , effective inflammation control may be a therapeutic strategy for treating type 2 diabetes. In fact, recent clinical investigations have shown that reducing inflammation reduces type 2 diabetes by increasing insulin production from -cells and improving hyperglycemiaContrarily, circulating pro-inflammatory cytokines such interferon gamma, tumor necrosis factor alpha(TNFα) and interleukin 1 beta (IL-1), decrease β-cell insulin secretion by impairing calcium flow. Additionally, TNFα causes inflammation in β-cell, which leads to β-cell apoptosis through the accumulation of (islet amyloid polypeptide) [8,11].

B. *Cardiovascular diseases (CVDs):*

Over the past 30 years, the number of common cases has doubled, and death rates have been steadily climbing, cardiovascular diseases (CVDs) continue to be the major contributor to the worldwide burden of illnesses [12]. Adipokines, bioactive substances and cytokines derived from adipose tissue can control glucose and lipid metabolism and play a part in the onset and progression of CVDs. Some adipokines have protective effects against CVDs, while others have negative effects. Other adipokines, however, affect CVDs differently depending on the conditions [13]. In cases of CVD, diabetes ,obesity , and metabolic syndrome, asprosin may be used as a means of diagnosis and a treatment. The asprosin receptors, functions , and structure are discussed , along with how they relate to CVDs. Adipocytokines have a significant role in the pathophysiology of CVDs by controlling insulin sensitivity and secretion [14]. The development of CVDs and insulin resistance is aided by the angiopoietin-like 4 (ANGPTL4) and adipokines asprosin. In light of this, we proposed that plasma levels of ANGPTL4 and asprosin are related to atherosclerosis and early stages of insulin resistance [15]. A significant function for asprosin and ANGPTL4 in the development of insulin resistance Inducing cardiac ANGPTL4 gene expression guarded the heart against oxidative stress brought on by fatty acids[16, 17].

C. *diabetes mellitus*

Asprosin hormone is a new protein that secretes WAT and the ability to trigger the release of hepatic glucose [18]. The asprosin level was reported to rise in Three kinds of diabetes mellitus (DM). In patients newly diagnosed DM Following a 24-week course of treatment, a hypoglycemic drug sodium-glucose co-transporter-2 (SGLT2) inhibitors, that specifically inhibits glucose reabsorption, considerably reduce the amount of asprosin in the blood)[19]. Circulating asprosin in healthy adults exhibits diurnal oscillation with an abrupt decline that coincides with the start of eating[20].

The level of asprosin is positively correlated in T2DM patients with homeostasis model assessment for insulin resistance (HOMA-IR) hemoglobin A1c, fasting blood glucose (FBG)[21,22]. Lipid metabolism and serum asprosin are closely related to the fact that TG and concentrations of asprosin were positively associated. In T2DM patients, TG and asprosin were associated independently. Dyslipidemia is a prevalent condition in the insulin-resistant liver, where it is accompanied by increased hepatic glucose production in diabetic patients [18, 23].

D. Obesity

With the improvement in people's living standards and unhealthy lifestyles, obesity and obesity-related illnesses including T2DM are rapidly rising globally [11]. Therefore, insulin resistance and hyperinsulinemia are linked to obesity [24]. The asprosin hormone, which also has a central action, stimulates ultimately, appetite causing weight gain and obesity [3, 25]. Obesity is a pathological condition that increases the risk of several illnesses, includingcardiovascular disease, T2DM, some types of the cancer, and fatty liver disease [26]. Adipose tissue functions as an organ to energy storage and secretespeptides, lipids, adipokines, and cytokines that control the metabolism of the heart, liver, central nervous system, and muscles. Asprosin may have more complicated activities than only controlling hunger and weight, since higher asprosin concentrations in obese persons before bariatric surgery were linked to greater weight loss after surgery [27].

E. Thyroid

Thyroid hormones play crucial roles insignaling processes, energy-regulating mechanisms, and healthy development that have an impact on how much energy is used through both peripheral pathways and central [28]. One of the major signs and symptoms of hypothyroidism is weight gain. This is directly related to a rise in the body's overall mass of fat[29]. Asprosin is increased in patients with hypothyroidism and (T2DM with hypothyroidism)(1). Changes in the thyroid profile can affect asprosin secretion, which can cause further problems when there is too much visceral adipose tissue[30].

F. Polycystic ovary syndrome

Energy turbulence is a gynecological illness known as polycystic ovary syndrome (PCOS). According to the information that is currently available, the etiopathology of PCOS may be influenced by considerably rising asprosin levels in the blood. Asprosin levels is rise, providing fresh insight into PCOS-related alterations in the reproductive endocrinology and maybe giving light on the pathogenesis of PCOS [31].
found that asprosin decreases insulingrowth factor 1(IGF-1) induced cell proliferation and enhances luteinizing hormone(LH) induced cell androstenedione synthesis, indicating that the novel hormone may control ovarian follicle activity[32]. The PCOS-afflicted study ladies showed the typical concurrent endocrine and metabolic changes for this specific illness. Asprosin levels in women of reproductive age with PCOS are considerably higher. Alterations in asprosin production suggest that WAT might play a role in the development and maintenance of PCOS-related metabolic changes and abnormal insulin secretion and steroid hormone [32].

G. Cancer

Despite the fact that FBN1 mutations have been implicated in a number of studies as the root cause of (Marfan syndrome(MFS)), which is also linked to a higher risk of tumorigenesis. About the function of FBN1 mutations in cancer, very little is known[33,34]. Comparing the downregulation of (FBN1) in this cohort of tumors to the upregulation in other malignancies may indicate tissue-specific expression. According to a prior study, the main promoter of (FBN comprises a single(CpG-rich) region and is largely conserved in mammals [35-37].

V. ASPROSIN SIGNALING PATHWAYS IN DIFFERENT ORGANS.

obesity, diabetes, and the metabolic syndrome (MetS) are all directly linked tothe chronic inflammation. A saturated fatty acid called palmitate promotes inflammation and IR in peripheral tissue. Asprosin was significantly expressed in mice insulinomas after palmitate treatment, and cell viability and insulin secretion were also decreased [8]. Tumor necrosis factoralpha (TNF-), monocyte chemoattractant protein-1(MCP-1), nuclear factorkappa-light-chain-enhancer of activated B cells(NF-B) phosphorylation, apoptosis, and decreased insulinproduction were all brought on by this medication[11]. Additionally, apoptosis, islet -cell dysfunction, and asprosin induced inflammation, and through the activation of (toll-like receptor 4 (TLR4)) expression and the phosphorylation [11]. Additionally, asprosin demonstrated the activation in (endoplasmic reticulum (ER)) inflammation /stress pathways linked to (protein kinase C (PKC)) in skeletal muscle, which impairs insulin sensitivity [38].

A. Asprosin and liver :-

Asprosin enhanced glucose synthesis in the liver by activating the (cyclic adenosine monophosphate(cAMP)/protein kinaseA(PKA) pathway through the G-protein coupled receptor (OR4M1) in human [39].

B. Asprosin and pancreas:-

Through the stimulation of toll-like receptor4 (TLR4) expression and(c-Jun N-terminal kinases (JNK)) phosphorylation in the pancreas, asprosin encourages apoptosis, islet -cell malfunction, , and inflammation[40].

C. *Asprosin and skeletal muscle:-*

Through the activation of ER inflammation /stress pathways linked to (protein kinaseC-delta) (PKC-delta), skeletal muscle experienced decreased insulin sensitivity[41].

D. *Asprosin and adipocyte:-*

Inhibiting the (nuclear factor erythroid2-related factor 2) (Nrf2) pathway caused asprosin overexpression in adipocytes and speed up the lipid deposition process[42].

E. *Asprosin and mesenchymal stromal cells:-*

Through the elevation of (superoxide dismutase2) (SOD2)expression and activation of the (extracellular signal-regulated kinas1/2) (ERK1/2)-SOD2pathway, asprosin controls the function of (mesenchymal stromal cells) (MSC) against apoptosis and ROS production[8].

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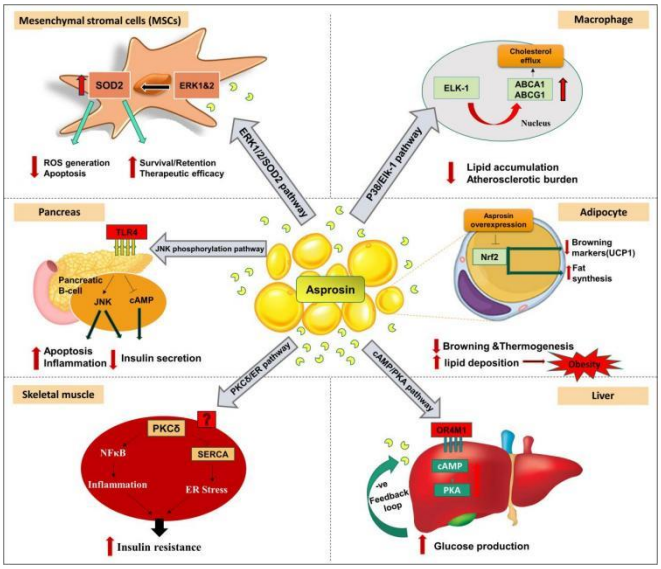

FIGURE2: SIGNALING PATHWAYS OF ASPROSIN IN THE DIFFERENT ORGANS[8].

VI. CONCLUSIONS

Asprosin hormone is raised in human with metabolic disease.The findings imply that asprosin hormone may be crucial for maintaining insulin and glucose homeostasis as well as acting as a risk factor for a number of diseases, including (CVDs, obesity, T2DM, cancer, hypothyroidism, and PCOS). Depleting asprosin or attenuating, its activity may potentially offer a novel therapeutic option for treating T2DM and obesity.

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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