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ROLE OF ASPROSIN IN OBESITY, DIABETES, AND METABOLIC SYNDROME

Dr. Mohamad Y. Rezk[1&2]*

[1]Basic Medical Sciences Department, Unaizah College of Medicine and Medical Sciences, Qassim University, KSA.
[1]Physiology Department- Faculty of Medicine- Zagazig University, Egypt.

***Corresponding Author: Dr. Mohamad Y. Rezk**

Basic Medical Sciences Department, Unaizah College of Medicine and Medical Sciences, Qassim University, KSA.

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ABSTRACT

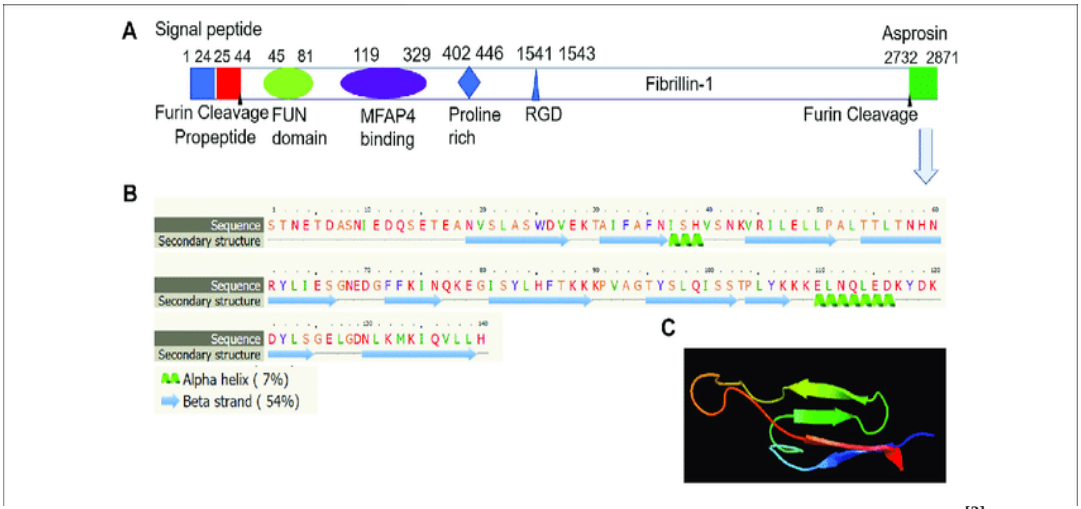
Asprosin is an adipokine secreted by white adipose tissue. Asprosin has a glucogenic and orexigenic actions and has wide effects on different body tissues. Its role in obesity, diabetes and metabolic syndrome is controversial and deserve a lot of work to elucidate its exact effect. Many studies investigated the role of asprosin in obesity and they documented contradictory findings. Reviewing these studies took a lot of time to explain the contradiction so we Explained in this literature review the causes of contradiction to reach the exact role of asprosin in obesity, diabetes, and metabolic syndrome.

KEYWORDS: Asprosin, Obesity, Diabetes, Glucose, Insulin, Metabolic syndrome.

Contents

INTRODUCTION

Asprosin - a 30 kDa and 140 amino acids- is a novel adipokine synthesized by cleaving the C-terminus of profibrillin-1 protein by furin (a proteolytic enzyme).[1] Asprosin was named after the Greek word for white (ασπροσ), because the white adipose tissue appears to be the main source of plasma asprosin.[2]



*** Figure 1: Molecular structure of human asprosin protein (Liu et al., 2022).[3]**

(A) Asprosin is derived from the C-terminal region of prefibrillin-1.

(B) Asprosin is predicted to consist of two alpha helixes and several beta strands.

(C) Tertiary structure analysis showing human asprosin protein that mimics crystal structure of cadherin8 ec1 domain.

Synthesis and mechanism of action of asprosin

Asprosin was first discovered by Romere et al. 2016, who identified the fasting-induced protein hormone that modulates hepatic glucose release and named it asprosin. They also detected *Fibrillin-1* (FBN1) mRNA in white adipose tissue in higher concentrations and suggested

that white adipose tissue is the dominant producer of asprosin.

A preclinical study showed low plasma asprosin levels in mice exposed to genetic resection of adipose tissue (≈ 65% adipose tissue reduction).[4] Furthermore, asprosin may have a regulatory role in the browning process of primary adipocytes.[5] Asprosin overexpression in subcutaneous white adipose tissue enhanced browning-specific markers UCP1 (Uncoupling Protein 1; is a Protein Coding gene) and accelerate lipid deposition by inhibiting the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway in high-fat diet mice.[6]

Asprosin is also produced by the heart, liver, pancreas, stomach, skeletal muscles, lungs, and brain.[7] Measurable amounts of asprosin were found in different body fluids like saliva, breast milk, urine, serum, and plasma.[8-10] Asprosin was also expressed in the ovaries, placenta, and cartilage.[11-12]

Asprosin is secreted by white adipose tissue then circulates at nanomolar levels, and is recruited to the liver activating the G protein-cAMP-PKA pathway and releasing glucose into the circulation which in turn inhibits asprosin secretion *via* a negative feedback loop.[2]

Mechanism of action of asprosin

Asprosin exerts peripheral and central effects.[13] **Its peripheral effect** is a glucogenic through binding with the olfactory receptor 4M1 (OR4M1 rhodopsin family member) and its central effect is an appetite stimulant hormone by binding with a cell surface receptor termed protein tyrosine phosphatase receptor δ (Ptprd).[4&13] OR4M1 is considered the primary asprosin receptor in humans, while OLFR734 is the mouse ortholog. OLFR734 is markedly distributed in the testis, liver, kidney, olfactory epithelium tissue, and olfactory bulb (**Li et al., 2019) Figure 2**.

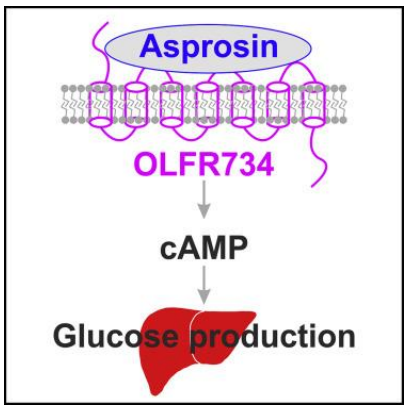


Figure 2: (Li et al., 2019)[4]; shows the peripheral effects of asprosin on hepatocytes.

Circulating asprosin binds to the OLFR734 on the surface of hepatocytes promoting glucose production by activating the cAMP-dependent-protein kinase A (PKA) pathway.[14]

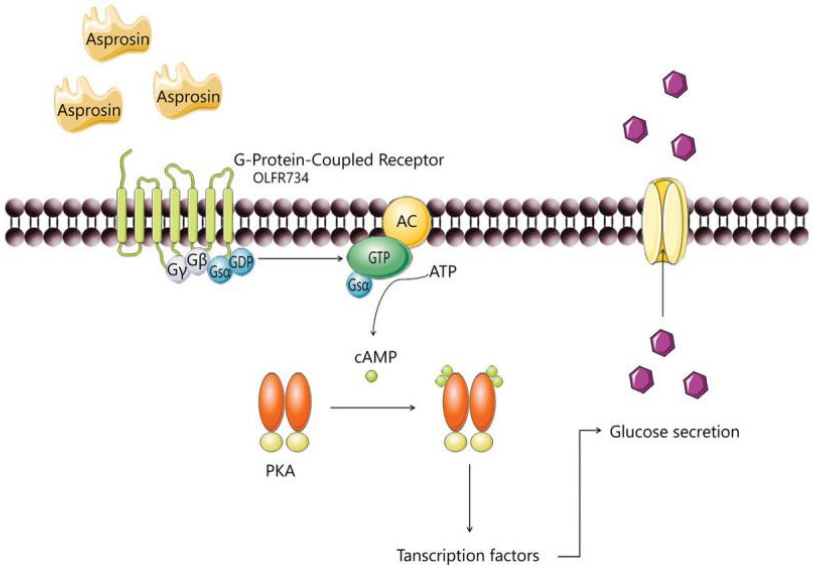


Figure 3: Mechanism of asprosin action on liver cells; Asprosin activates G-protein-coupled receptors (GPCR) and adenylyl cyclase (AC) synthesizes cAMP from ATP. cAMP activates protein kinase K (PKA) resulting in formation of transcription factors leading to glucose release. (Luís et al., 2020).[14]

Asprosin central effect (Figure 4) is mediated by stimulating the hypothalamic feeding center. In the hypothalamic arcuate nucleus (ARH), asprosin acts directly on hunger-stimulating neurons known as agouti-related peptide neurons (AgRP) *via* the G protein-cAMP-PKA pathway[15] and inhibits pro-opiomelanocortin (POMC) neurons through γ-Aminobutyric acid (GABA).[16]

Asprosin has a high binding affinity to the protein tyrosine phosphatase receptor δ (Ptprd) in the hypothalamic AgRP neurons.[17] This is confirmed by **Mishra et al.,**[13] who found a significant reduction of appetite, blood glucose levels, and leanness after the genetic excision of Ptprd receptors from AgRP neurons. Asprosin mRNA and protein are highly expressed in the hypothalamus's paraventricular nucleus (PVN) where asprosin stimulates the sympathetic outflow.[18]

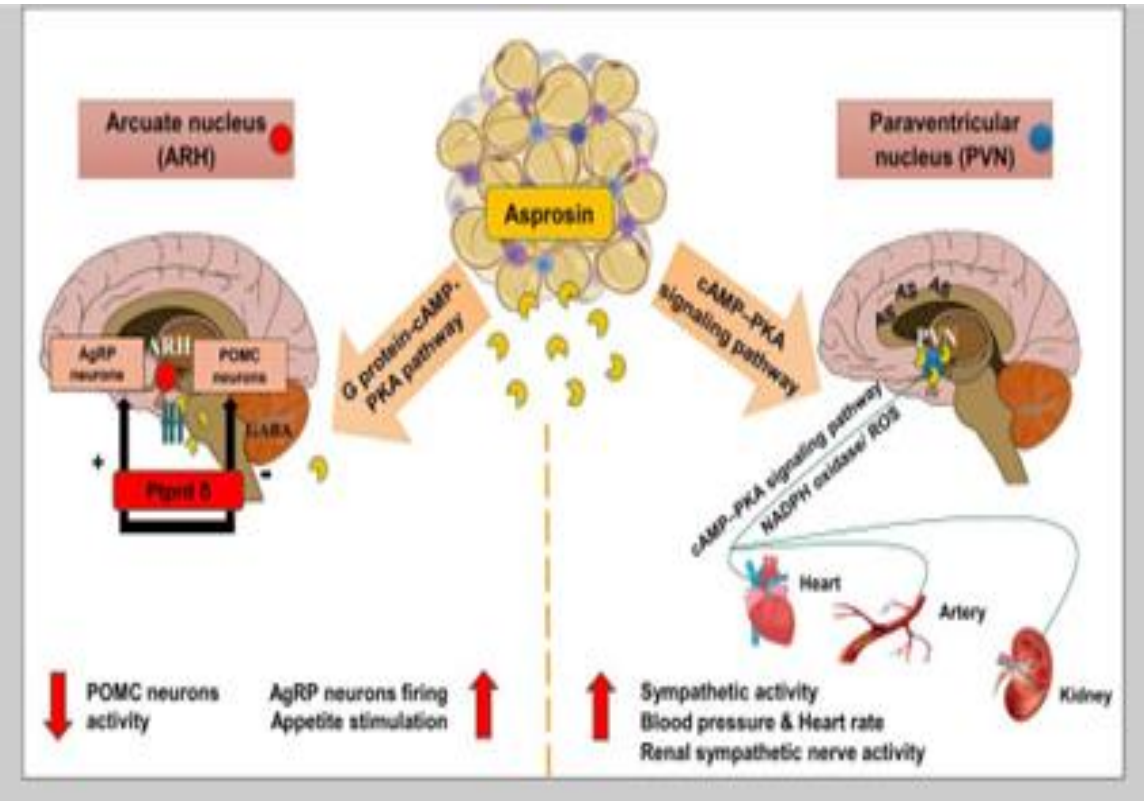


Figure 4: Shows the Central Effects of Asprosin.

- Asprosin exerts its appetite-stimulating effect by acting mainly *via* Protein tyrosine phosphatase receptor δ (Ptprd) in; **Hypothalamic arcuate nucleus (ARH) →**
- ↑ agouti-related protein neurons (AgRP) +
- ↓ Pro-opiomelanocortin neurons (POMC).
- **In the paraventricular nucleus (PVN)**
- Asprosin →↑Sympathetic outflow, blood pressure, and heart rate *by* promoting the cyclic adenosine monophosphate (cAMP) level, adenylyl cyclase (AC), and protein kinase A (PKA) activity mediated by nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) activity and superoxide production (Reactive Oxygen Species; ROS).[5]

Obesity

Obesity is a serious medical condition which becomes an increasing public health problem worldwide. Obesity is the excessive accumulation or abnormal body fat distribution, affecting health.[19]

Obesity is complicated by other diseases such as type 2 diabetes mellitus (T2DM), hepatic steatosis, cardiovascular diseases, stroke, dyslipidemia, hypertension, gallbladder problems, osteoarthritis, sleep apnoea, other breathing problems, certain types of cancer, all of which can lead to an increased risk of mortality.[19]

According to the **Centers for Disease Control and Prevention (2022)**[20]; Overweight is considered when the Body mass index (BMI) is from 25.0 to < 29.9 kg/m² and after that obesity starts and classified into 3 types:

- **Class I obesity:** BMI 30 to <35 kg/m².
- **Class II obesity:** BMI 35 to <40 kg/m².
- **Class III obesity (morbid obesity):** BMI 40+ kg/m².

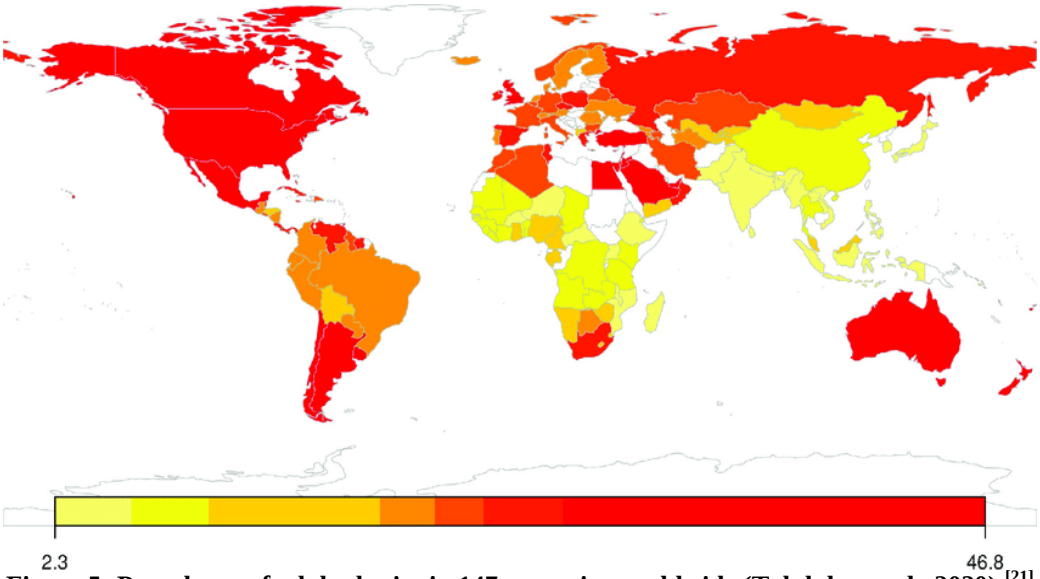


Figure 5; Prevalence of adult obesity in 147 countries worldwide (Talukdar et al., 2020).[21]

Color scales represent the proportion of obese adults in countries.

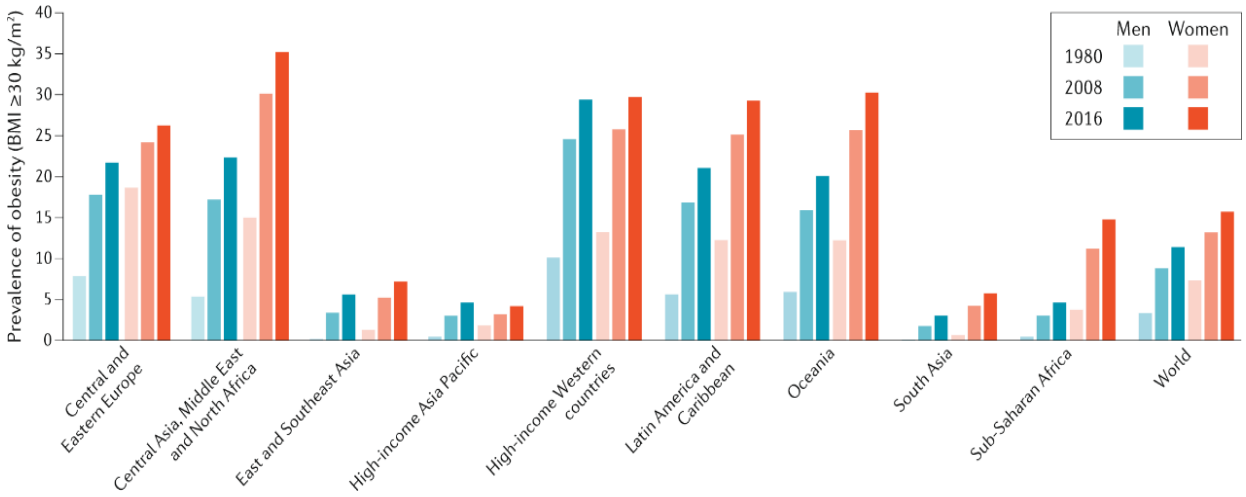


Figure 6: The global prevalence of obesity in men and women in 1980, 2008, and 2016 from selected regions of the world shows an increase in obesity worldwide (Malik et al., 2020).[22]

Complications of obesity (Figure 7); (Kyrou et al., 2018)[23]

Role of asprosin in obesity

Ugur and Aydin 2019[8], found that the levels of asprosin were the lowest in the underweight and highest in the obese and they concluded that the asprosin level is related to obesity as the concentration increases with increased body mass index (BMI) and decreases with decreased BMI. They also suggested that asprosin antagonists could be used in the treatment of obesity. This suggestion is confirmed by **Duerrschmid et al.,[16]** who reported that treatment with specific asprosin antibodies significantly reduced the pathologically elevated asprosin levels in humans with insulin resistance (IR) and high-fat diet mice models. In addition, these studies were consistent with **Romere et al.,[2]** who reported that adult insulin-resistant obese mice have pathologically enhanced levels of asprosin during fasting, and injection of asprosin in mice increased blood glucose and insulin levels.

Wang et al., investigated the potential role of asprosin and its relationship to various obesity-related markers in obese children. They found a significant increase in serum asprosin in obese children in comparison with the controls. They also found that asprosin is significantly increased in children with insulin resistance (IR) compared with the control group. They found a positive correlation between asprosin and waist-to-hip ratio (WHR), diastolic blood pressure, HOMA-IR, leptin-to-adiponectin ratio, and TNF-α.[18]

In another study conducted on 117 obese patients (BMI>35) who underwent bariatric surgery and 57 non-obese subjects, **Wang et al.,**[18] found a significant increase in asprosin levels in obese patients compared with the non-obese subjects (2360 ± 5094 vs. 307 ± 832 ng/ml, $p < 0.0001$). They also found a significant reduction in asprosin levels 6 months after bariatric surgery (162.2 ± 169.1 ng/ml).

On the other hand, **Long et al., (2019)[24]** found a significant reduction in fasting asprosin in obese children (9.24 ± 4.11 ng/mL) compared with the normal-weight controls (12.33 ± 4.18 ng/mL, $p < 0.001$) and a significant reduction in boys compared with girls in the obese but not in the control group. They also found a negative correlation between asprosin and BMI, HOMA-IR, insulin, and HDL.

In addition, **Corica et al., (2021)[25]** conducted a cross-sectional study on 43 obese and 24 lean children and they found a significant reduction in asprosin levels in the obese group in comparison with the control group. They also found a negative correlation between fasting asprosin and BMI. This controversy between the studies reporting higher asprosin levels in obesity and those reporting lower levels might be attributed to gender differences however this suggestion is contradicted by the findings of **Sünnetçi Silistre and Hatipoğl (2020)[26]** who reported a significant increase in asprosin levels in obese children without any significant sex differences.

After reviewing the detailed methodology of all these studies, we suggested that the controversy might be attributed to the type of study and racial factors where **Wang et al., (2019)[18]** conducted a cross-sectional study on 79 obese Chinese children and 40 lean controls and the study of **Long et al., (2020)[24]** conducted on 47 obese children and 40 healthy normal-weight. In the latter study, the control group was normal weight and the former was lean children.

In the corresponding table, a summary of the differences in the mentioned studies;

Table 1: Modified after Farrag et al., 2023).[5]

The study	Methodology	Results
Ugur and Aydin (2019)	Adult obese patients; 116 volunteers Low weight (8) Normal weight (44) Overweight (19) Obese (45).	Significant increase in serum asprosin in the obese group compared with the other groups
Wang et al., (2019)	Cross-sectional study; Obese (79) Lean control (40)	Increased Serum asprosin in obese groups compared with the control groups without any gender differences
Long et al., (2019)	87 Obese Chinese children (49 boys, 38 girls): A. Obese (40) B. Normal weight (47)	• Significant reduction in asprosin in obese compared with the normal controls. • Significant reduction in asprosin in boys compared to girls.
Wang et al., (2020)	Adult Obese underwent bariatric surgery (36-47 y): • 117 Obese • 57 Non obese	Significant increase in serum asprosin in the obese group compared with the control.
Sünnetçi Silistre and Hatipoğl (2020)	A cross-sectional study conducted on 158 Turkish children:	Significant increase in serum asprosin in the obese compared to the normal

	• 44 Obese. • 54 Overweight. • 60 Normal Weight	weight group without sex differences.
Corica et al., (2021)	A cross-sectional, case-controlled study on: 67 subjects: • 43 Obese Caucasian children. (21 m - 22 f). • 24 Normal weight controls.	Significant reduction in the fasting serum asprosin in obese children compared with the controls and boys compared with girls. A negative correlation between serum asprosin and BMI without correlation with IR.

The role of asprosin in weight reduction

The role of asprosin in weight reduction was confirmed by **Wang et al.,**[27] and **Cantay et al., (2022)**[28], both studies found a significant reduction in asprosin levels 6 months after bariatric surgery and sleeve gastrectomy associated with weight loss.

In addition, **Ceylan et al., (2020)**[29] found a significant reduction in plasma asprosin and insulin levels after aerobic exercise in overweight, obese, and normal-weight subjects. The same findings were reported by **Kantorowicz et al., 2021)**[30] who found a significant reduction in asprosin levels and waist-hip ratio in obese women after a training program for two months.

In consistent with the previous studies, we suggested that asprosin has a potential role in weight reduction and we hypothesized that asprosin might be increased during pregnancy and gestational diabetes (GD) suggesting a potential role in food intake stimulation during pregnancy and suggesting a role in the prediction of GD. Our suggestion is confirmed by our finding that asprosin has a positive correlation with body weight ($r=0.821$, $p<0.05$), body mass index ($p<0.05$) and food intake **(Rezk et al., 2020).**[31]

Diabetes mellitus

Diabetes mellitus is the collective term for heterogeneous metabolic disorders whose main finding is chronic hyperglycemia. The cause is either a disturbed insulin secretion, a disturbed insulin effect, or usually both (**Petersmann et al., 2019).**[32]

According to Diabetes Care (2015)[33], **Diabetes is classified into:**

1. Type 1 (beta-cell destruction) congenital diabetes
2. Type 2 (progressive insulin deficiency with insulin resistance)
3. Gestational diabetes (GDM) (diabetes occurs during pregnancy)
4. Specific types of diabetes due to other causes, e.g., Maturity-onset diabetes of the young [MODY])
   Secondary diabetes due to endocrinal causes like acromegaly and Cushing syndrome.

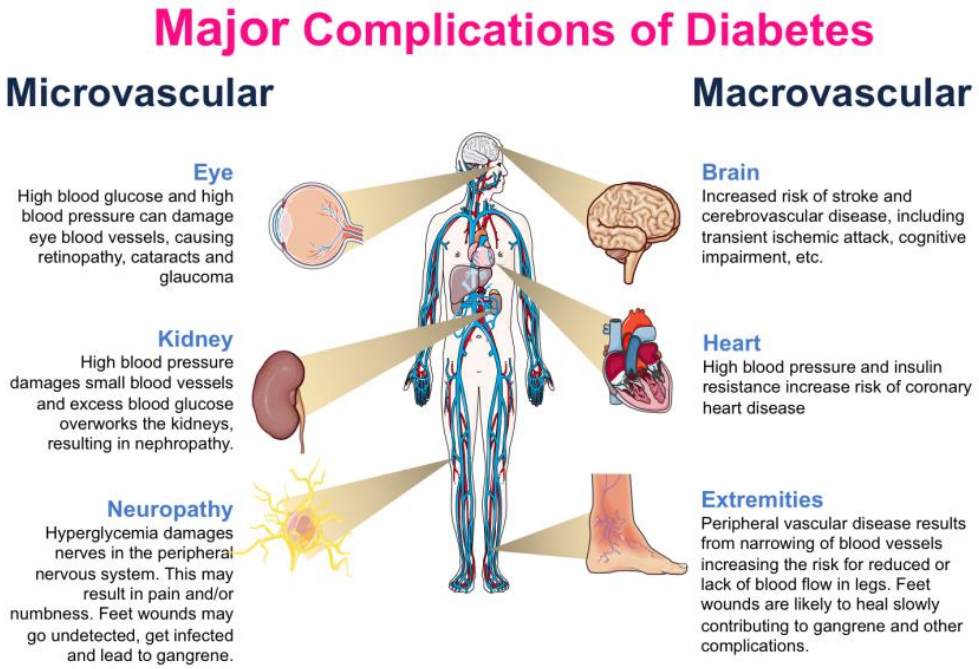


Figure 9: Major microvascular and macrovascular complications associated with diabetes mellitus. (**Jiang et al., 2017).**[34]

Pathophysiology of diabetes; Various mechanisms are activated by hyperglycemia inducing the diabetic complications associated with DM like retinopathy, nephropathy, neuropathy, and cardiovascular complications.

1st mechanism (figure 10) through activation of protein kinase C (PKC) β

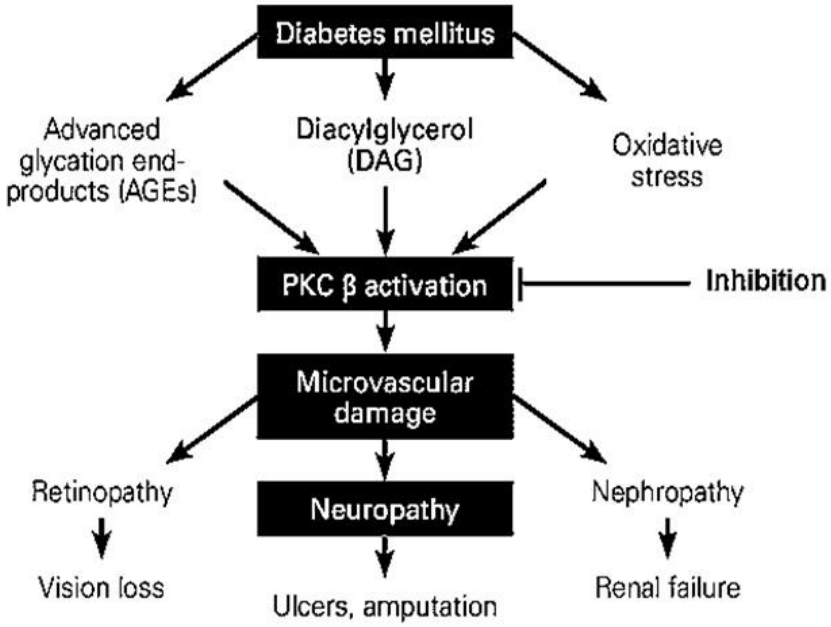


Figure 10: Diabetic complications arising from the activation of PKC β (Ohiagu et al., 2021).[35]

2nd mechanism

The polyol pathway is linked with the generation of oxidative stress, leading to the emergence of diabetic complications as observed clinically **(Figure 11)**

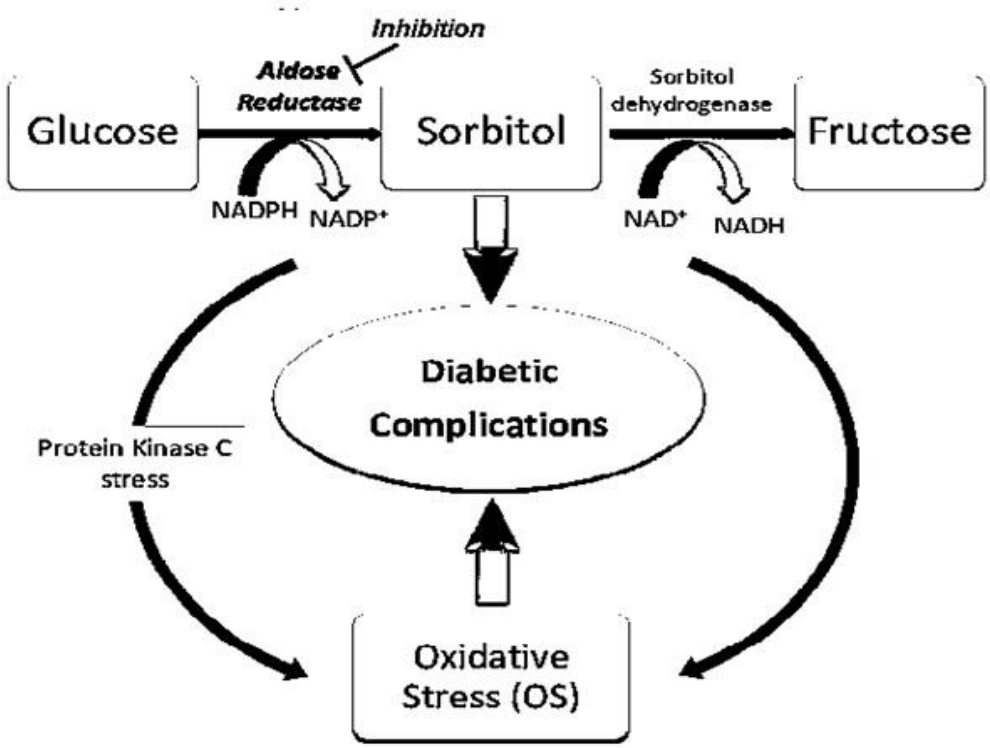


Figure 11: The Polyol pathway in glucose metabolism (Sharavana et al., 2017).[36]

3rd mechanism; (Figure 12)

Increased synthesis of advanced glycation end-products (AGEs) results from the reaction between glucose and the amino group of amino acids in the absence of enzymes. In addition to other mechanisms like increased glucose oxidation result in the formation of harmful reactive species and ketoaldehyde compounds like peroxide (H2O2) and malondialdehyde.[37& 38]

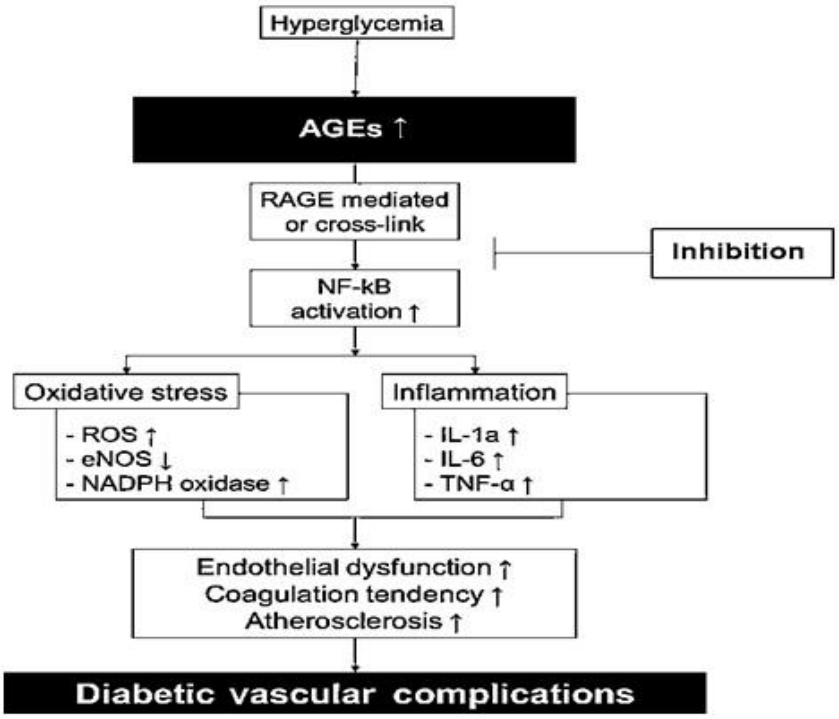


Figure 12: Advanced glycation end-products (AGEs) mechanism in diabetic vascular complications (Modified From Rhee and Kim 2018).[37]

RAGE: advanced glycation end-product receptor; **NF-kB**: nuclear factor kB; **IL**: interleukin; **TNF**-a: tumor necrosis factor a; **ROS**: reactive oxygen species; **eNOS**: endothelial nitric oxide synthase; **NADPH**: nicotinamide adenine dinucleotide phosphate. **(Ohiagu et al., 2021).[35]**

Role of asprosin in diabetes mellitus

Many studies investigated the role of asprosin in diabetes type-2 like the study conducted by **Zhang et al., (2019)[39]** who found a significant increase in asprosin levels in diabetic adults with (Diabetes mellites Type-2) T2DM. These findings are supported by **Farrag et al., (2023)[5]** who reported that asprosin acts as an orexigenic and glucogenic hormone.

Another study by Timurkaan and Timurkaan[40] found a significant increase in serum asprosin levels in the diabetic compared with the control group. They also found that asprosin correlates positively with HOMA-IR, insulin, BMI, and triglyceride levels in the diabetic group.

In an older study by **Wang et al., (2018)[41]** 143 participants were chosen and categorized into 3 groups, the 1st group was the normal control (n; 52) and the 2nd group was impaired glucose regulation (IGR) (n; 40), the 3rd group was T2DM (N; 51). They found a significant increase in plasma asprosin levels in IGR and nT2DM compared with the control group.

Wang et al.,[41] also found a significant positive correlation between asprosin levels and fasting plasma glucose (FPG), post-challenge plasma glucose (2hPG), HbA1c, and HOMA-IR and negatively correlated with HOMA-β.

This was also confirmed by **Zhang et al., (2020)[42]** who found a significant increase in asprosin levels in T2DM patients compared with the normal control subjects. In addition, **Gozel and Kilinc, (2021)[43]** found a significant increase in serum and saliva asprosin in the newly diagnosed T2DM. They suggested that asprosin could represent a risk factor for T2DM and concluded that asprosin could be a potential therapeutic target in the treatment of diabetes.

In consistent with the previous studies, our study **(Rezk et al., 2020)[31]** found that asprosin increased significantly in pregnant, gestational and insulin-treated groups in comparison with the control group. In addition, asprosin increased significantly in the gestational diabetic group on day 7 and day 20 in comparison with pregnant group day 7 and day 20 respectively. Also,

asprosin decreased significantly in insulin treated group day 7 and day 20 in comparison with gestational diabetic group day 7 and 20 respectively. All these findings confirmed the role of asprosin in diabetes and its potential therapeutic role in diabetes mellitus type 2.

In addition, asprosin was found to have a role in diabetes type-1. This was confirmed by **Ko et al., (2019)**[44] who found that lowering blood glucose in exercise is mediated through the reduction of asprosin level which reduces the hepatic release of glucose in diabetes type-1. They also found that induction of type-1 diabetes in rats by injection of a single dose streptozotocin (STZ) 65 mg/kg. i.p. resulted in asprosin reduction.

Metabolic syndrome (Ms)

Metabolic syndrome is a complex pathology characterized by a cluster of biochemical, clinical, and metabolic factors that raise the risk of cardiovascular diseases, type 2 diabetes mellitus, and all-cause mortality **(Luís et al., 2020).**[14] These features include obesity, inflammation, hypertension, insulin resistance, atherosclerotic dyslipidemias, endothelial dysfunction, and inflammation.

Clinical picture (Mendrick et al., 2018)[45]

1. Central obesity; adipose tissue accumulation around the waist and trunk.
2. Hypertension
3. Low HDL cholesterol
4. High triglycerides level
5. High blood glucose
6. Insulin resistance.
7. Associated conditions;

A. Hyperuricemia
B. Fatty liver
C. PCOS in women.
D. Erectile dysfunction in men

Pathophysiology of metabolic syndrome

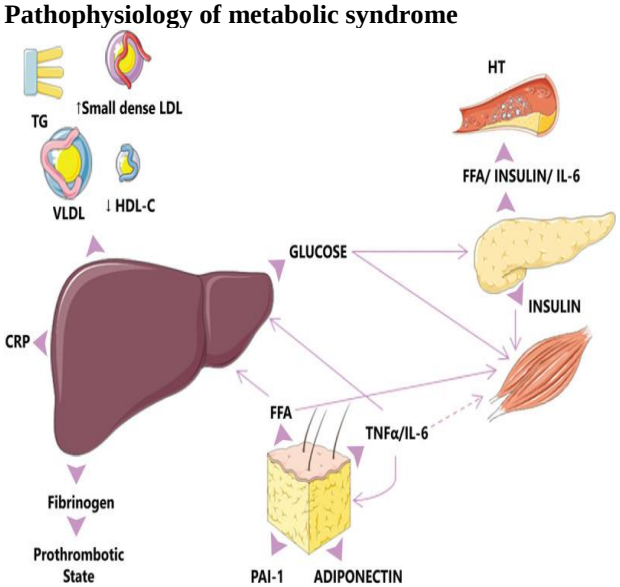


Figure 13: Luís et al., 2020).

↑ FFA by the adipose tissue → ↑ cytokines such as IL-6 and TNFα among others → ↑ insulin resistance. Cytokines may → ↑ hepatic glucose production, VLDL, and insulin resistance in muscle.

- CRP=C-reactive protein
- FFA=free fatty acids
- HDL=high-density lipoproteins;
- HT=hypertension
- IL-6=interleukin 6
- LDL=low-density lipoproteins; PAI1=plasminogen activator inhibitor-1
- TG=triglycerides
- TNFα=tumor necrosis factor α
- VLDL=very low-density lipoproteins.

Role of asprosin in metabolic syndrome

Many studies investigated the role of asprosin in metabolic syndrome and its associated diseases. Some of these studies are discussed above in demonstrating the role of asprosin in diabetes type-2 and obesity. In addition, **Wang et al., 2018)**[41] found a significant positive correlation between plasma asprosin and waist circumference (Wc), triglyceride (TG), and homeostasis model assessment for insulin resistance (HOMA-IR) and negatively correlated with homeostasis model assessment for β-cell function (HOMA-β). In addition, **Luís et al., (2020)**[14] suggested that asprosin might be a potential biomarker in T2DM and metabolic syndrome.

In another study conducted by **Zhang et al., (2019)**[42], they found a significant increase in serum asprosin levels in T2DM adults ($P<0.001$). Also, asprosin neutralization decreased food intake and body weight in a mouse model of metabolic syndrome **(Mishra et al., 2021).**[46] In addition, **Kantorowicz et al., (2021)**[47] reported a significant reduction in the blood asprosin and waist-hip ratio in obese women with metabolic syndrome after two months of the training program.

The role of asprosin in the disorders associated with metabolic syndrome is investigated in many studies, one of which was conducted by **Liu et al., (2021)**[48] who found a significant increase in asprosin levels in obese Chinese children with non-alcoholic fatty liver disease (NAFLD).

We also found that asprosin has a negative correlation with insulin and HOMA-B and a positive correlation with HOMA-IR. Our findings were supported by **Ke et al., (2020)**[49] who found a significant increase in asprosin levels in NAFLD adults with a positive correlation to HOMA-IR, and triglycerides (TG).

In addition, the role of asprosin in Poly Cystic Ovary Syndrome (PCOs) is reported by **Yuan et al., 2020)**[50] who mentioned that 2 studies found a link between asprosin and PCOs. The 1st study by **Li X., et al. (2018)**[51] found a significant increase in plasma asprosin in PCO patients compared to the control. They also found that asprosin was positively correlated with

Apolipoprotein B (ApoB) and Low-density Lipoprotein-Cholesterol (LDL-C). The second study was conducted by **Alan et al. 2019)**[52] and found the same results. However, **Chang et al., (2019)**[53] did not find any correlation between asprosin and PCOS and its metabolic abnormalities.

CONCLUSION

Asprosin has a definite role in obesity and its effect in adult is confirmed to be a pathogenic factor predisposing to obesity so anti-asprosin medications could be potential therapeutic agents in obesity. Contradictory reports about the role of asprosin in childhood obesity is due to racial as well as methodological factors. Asprosin levels were significantly elevated during normal pregnancy, suggesting that asprosin may have a physiological role during pregnancy as it may stimulate appetite and food intake commonly occurring during pregnancy. Gestational diabetic rats were found to have significantly higher asprosin levels compared with the pregnant group. Asprosin may be a potential factor in predicting diabetes mellitus during pregnancy. Asprosin has a potential role in diabetes especially T2DM. Asprosin may act as a biomarker for the diagnosis of diabetes. Asprosin has a promising role in obesity, diabetes mellitus, and metabolic syndrome.

Recommendations

- The confirmed role of asprosin in obesity puts it as a priority in future management protocols.
- The link between asprosin and polycystic ovary syndrome is controversial and requires further research.
- Asprosin is a molecule with broad-spectrum research benefits so it should be investigated in humans on a large-scale population.
- Asprosin could be a therapeutic target for treating diabetes, obesity, and cardiovascular disorders.
- As the molecule is newly discovered, it necessitates further research on other organs and elucidate its relationship with the endocrinal system especially pancreatic islets.
- We recommend using anti-asprosin medications for the treatment of obesity, diabetes and metabolic syndrome but the application should be on animal models before application in human.
- Investigating the role of asprosin in gastrointestinal tract function and using in vitro as well as in vivo models.

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