International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

Relationship between Zinc-Alpha-2-Glycoprotein, Obesity, And Metabolic Syndrome

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Abstract:

Zinc-alpha-2-glycoprotein (ZAG) is a 40–43 kDa soluble glycoprotein first identified in human plasma and secreted by various tissues, particularly adipose tissue. It plays a significant role in lipid mobilization, energy homeostasis, and regulation of metabolic processes. ZAG acts as an adipokine—a cytokine secreted by fat tissue—implicated in the modulation of body fat and insulin sensitivity. Obesity is characterized by excess adipose tissue and is often accompanied by metabolic disturbances. Numerous studies have shown that ZAG expression is downregulated in obese individuals compared to lean individuals. Lower levels of ZAG in adipose tissue and circulation are associated with increased fat accumulation, reduced lipolytic activity, and impaired energy metabolism. Experimental models have demonstrated that ZAG overexpression or administration can reduce fat mass and enhance glucose tolerance, suggesting a protective role against obesity and insulin resistance. Metabolic syndrome is a cluster of conditions—including central obesity, insulin resistance, hypertension, and dyslipidemia—that increase the risk of cardiovascular disease and type 2 diabetes. ZAG has been proposed as a potential biomarker for metabolic syndrome, due to its inverse correlation with several metabolic syndrome components such as waist circumference, triglycerides, and insulin resistance markers.

Keywords: Zinc-Alpha-2-Glycoprotein, obesity, metabolic syndrome.

Introduction:

Metabolic syndrome is a cluster of risk factors, including central (abdominal) obesity, increased blood pressure, elevated glucose and triglycerides, and low high-density lipoprotein cholesterol (HDL-C) levels. Metabolic syndrome increases the risk of developing type 2 diabetes mellitus (T2DM), cardiovascular diseases, nonalcoholic fatty liver disease (NAFLD), chronic kidney disease, cancer and other diseases **(1).**

Obviously, metabolic syndrome severely endangers public health and puts a substantial economic burden on the whole society. Unfortunately, due to the global epidemic of obesity and T2DM, the number of people with metabolic syndrome has increased sharply in recent years **(2).**

The diagnosis of metabolic syndrome can be made when at least 3 factors of the following 5 are present: abdominal obesity—abdominal circumference that exceeds 102 cm in men and 88 cm in women indicates excess

abdominal fat, triglycerides equal to or >150 mg/dl, HDL cholesterol equal to or <40 mg/dl in men and 50 mg/dl in women, blood pressure equal to or >135/85 mm Hg, and fasting blood glucose equal to or >100 mg/dl **(3).**

The pathogenic mechanisms associated with metabolic syndrome are complex and need to be fully explained. The large geographic variation in the prevalence of metabolic syndrome emphasizes the importance of environmental and lifestyle factors, such as excess dietary calories and physical inactivity, as major contributors to the disease. Adipose tissue secretes cytokines that contribute to insulin resistance and endothelial dysfunction, which cause the development of metabolic syndrome. Studies show that abdominal obesity is a key trigger for most of the pathways associated with metabolic syndrome, emphasizing the importance of excess caloric intake as a major initiating factor **(4).**

Of all the proposed mechanisms, insulin resistance, neurohormonal activation, and chronic inflammation appear to be the main factors leading to the development of metabolic syndrome and cardiovascular disease **(5).**

Zinc-alpha-2-glycoprotein (ZAG) is assigned to the major histocompatibility complex (MHC) class I family of proteins. ZAG is present in a variety of epithelia and is secreted into many body fluids. It was demonstrated that, in contrast to class I MHC proteins, ZAG does not bind peptides or beta2-microglobulin and its functions are diverged from the functions of MHC class I molecules **(6).**

Growing evidence suggests that altered production of adipose-derived protein factors, such as ZAG plays an important role in the pathophysiology of obesity and its associated complications, such as metabolic syndrome. ZAG gene expression in adipocytes is primarily controlled by androgens, progestins, and Glucocorticoids **(7).**

Overexpression of ZAG in cultured hepatocytes significantly inhibits lipogenesis by decreasing metabolic nuclear receptors sterol regulatory element-binding protein (SREBP-1c), liver X receptor (LXR), and lipogenic enzymes in the liver, also lipolysis and fatty acid β-oxidation were stimulated. On the other hand, the knocking down of ZAG resulted in inhibition of fatty acid β-oxidation, increased lipogenesis, and lipid accumulation **(8).**

Up to now, the mechanisms underlying the close link of ZAG and obesity involve the regulation of lipogenesis- and lipolysis-related enzymes, the browning of white adipose tissue, and the paracrine manner to stimulate adiponectin production. Furthermore, ZAG also plays an important role in modulating adipose tissue insulin sensitivity. Silencing ZAG resulted in reduced insulin receptor substrate-1 (IRS-1) and glucose transporter-4 (GLUT4) gene expression in primary human adipocytes **(9).**

Numerous studies indicate that zinc and the new zinc-related adipokine, zinc-α2-glycoprotein (ZAG), are involved in lipid metabolism. Excess body fat lowers blood concentrations of Zn and ZAG, leading not only to the development of obesity but also to other components of the metabolic syndrome. Zinc homeostasis disorders in the body negatively affect the lipid profile and cytokine secretion **(10).**

Zinc appears to be a very important ZAG homeostasis regulator. The physiological effects of ZAG are related to lipid metabolism, but studies show that ZAG also affects glucose metabolism and is linked to insulin resistance. ZAG has a zinc binding site in its structure, which may indicate that ZAG mediates the effect of zinc on lipid metabolism **(11).**

Numerous studies have found that zinc supplementation in overweight individuals significantly reduced blood levels of total cholesterol, LDL (Low-density lipoprotein)cholesterol and triglycerides, potentially reducing cardiovascular morbidity and mortality. Some results also indicate that it increases HDL-C (High-density lipoprotein) cholesterol levels **(12).**

ZAG has been shown to play a significant role in reducing obesity and improving insulin sensitivity, both in experimental animal model studies and in human studies. Furthermore, ZAG at physiologically relevant concentrations increases the release of adiponectin from human adipocytes. In addition, ZAG has been shown to inhibit in vitro leptin production **(9).**

Zinc (Zn) is currently one of the most important micronutrients in the human body. It is also an essential part of life processes, bone development, and body growth. Zinc plays a major role in the metabolism of carbohydrates, fats, and proteins. It is a component of more than three hundred metalloenzymes and exhibits antioxidant activity, thus participating in the reduction of oxidative stress **(13).**

Zinc is also involved in the synthesis, storage and transport of insulin. Zinc deficiency in the body means that the energy production process is disrupted. This is due to the abnormal behaviour of metalloenzymes that include zinc, such as carbonic anhydrase. It is involved in energy production reactions in the body **(10).**

When this process is disrupted, fat tissue is formed instead of energy, which promotes the development of overweight and obesity. Studies also show that at low blood levels of this element, lipid management is disrupted, leading to an increase in total cholesterol, triglycerides and LDL cholesterol. Zinc is a very important regulator of ZAG homeostasis, which plays a role in lipid metabolism and glucose homeostasis **(13).**

Correct blood zinc concentrations are also essential to maintain adequate ZAG activity, as Zn facilitates the binding of adipokine to substrates. In vitro research has shown zinc binding to play a key role as it induces oligomerization of the zinc-α2 glycoprotein, allowing ZAG to bind to fatty acids **(11).**

In addition, zinc metabolism changes in obese individuals may result in an impaired ZAG function. ZAG contains trace elements such as zinc. ZAG has been shown to have 2 strong and 15 weak zinc binding sites, and the attachment of zinc at these sites enables ZAG to bind to fatty acids and β-adrenergic receptors **(12).**

ZAG and obesity:

The ZAG impact mechanism on lipid metabolism has not yet been clearly defined, but the overwhelming majority of studies indicate that ZAG may affect this process in multiple ways. ZAG increases lipolysis in white adipose tissue (WAT) by acting through the classical cyclic AMP pathway **(9).**

ZAG stimulates the expression of peroxisome proliferator-activated receptor γ (PPARγ) and early B cell factor 2 (EBCF), resulting in increased binding of these molecules to Prdm16 and UCP-1. Prdm16 and UCP-1 promotes white adipose tissue browning and energy consumption, which increases lipolysis **(12).**

Furthermore, ZAG, through mediating PKA and p38 mitogen-activated protein kinase (MAPK) signalling, can increase the expression of lipolysis-related molecules (UCP-1, PRDM16, CIDEA—cell death activator, PGC-1α—peroxisome proliferator-activated receptor gamma coactivator 1-alpha, NRF-1/2—nuclear respiratory factor 1/2, mtTFA—human mitochondrial transcription factor A, ATGL—adipose triglyceride lipase, HSL, CPT1-A—carnitine palmitoyltransferase I and p-acyl-CoA carboxylase) **(13).**

The ZAG-induced increase in body temperature and decrease in body weight and body fat can be partly attributed to its effect on UCP-1 in brown adipose tissue, leading to the use of released lipid for heat generation and increased energy expenditure. The lipolytic effects of ZAG have also been attributed to the up-regulation of thermogenin that results from β3-adrenergic receptor activation **(12).**

In addition, it stores triglycerides, which are energy substrates for the body. Fat cells produce and secrete proteins called adipokines. It is believed that the adipose tissue of slim people secretes mainly anti-inflammatory cytokines, including adiponectin, ZAG, TGF-β and IL-4 **(10).**

The adipose tissue of obese people, due to the accompanying inflammation, mainly secretes pro-inflammatory cytokines such as: TNF-α, IL-1β, and IL-6. They act in an autocrine/paracrine manner, affecting nutrient metabolism, modulating appetite, insulin sensitivity and inflammation. Impaired adipokine secretion can lead to obesity, metabolic syndrome and cardiovascular disease **(9).**

The expression of ZAG in adipose tissue changes depending on various factors. Increased expression is influenced by PPARγ, glucocorticoids, some β3-adrenergic receptor agonists, thyroid hormones and growth hormone (GH), among others. On the other hand, chronic inflammation and increased serum leptin levels may reduce ZAG secretion in the adipose tissue **(13).**

Several studies showed that people with excessive body fat have reduced levels of zinc and ZAG in their blood, and its deficiency is a factor in the development of obesity and diabetes. Zinc stimulates lipogenesis and glucose uptake in isolated adipocytes, and zinc ions in the body act as insulin mimetics, affecting the insulin signalling pathway **(12).**

Many studies indicated that impaired Zn homeostasis in obese individuals also affects circulating lipid concentrations in the blood. Numerous other studies have found that zinc supplementation significantly reduced blood levels of total cholesterol, LDL cholesterol and triglycerides, potentially reducing cardiovascular morbidity and mortality **(10).**

ZAG and metabolic syndrome:

Zinc is also involved in regulating the expression of pro-inflammatory cytokines produced by adipocytes. Zinc administration has been shown to positively reduce inflammation in obese individuals with metabolic syndrome **(11).**

Many authors evaluated the correlation of zinc and inflammatory markers. They found a significant relationship between serum zinc concentrations and levels of IL-6, TNF-α and c-reactive protein (CRP) in women and between zinc and IL-6 levels in men **(14).**

Several studies demonstrated that serum zinc levels were negatively correlated with inflammatory markers. According to many analyses, an increase in blood zinc concentration is negatively correlated with the change in inflammatory markers (hs-CRP, MCP-1, VCAM-1 and MDA + HAE) after a supplementation period of zinc **(7).**

ZAG plays a huge role in the regulation of adipose tissue mass. It acts multidirectionally, playing a role in stimulating lipolysis, inhibiting lipid accumulation in adipose tissue, regulating serum lipid values and influencing the secretion of other adipokines **(9).**

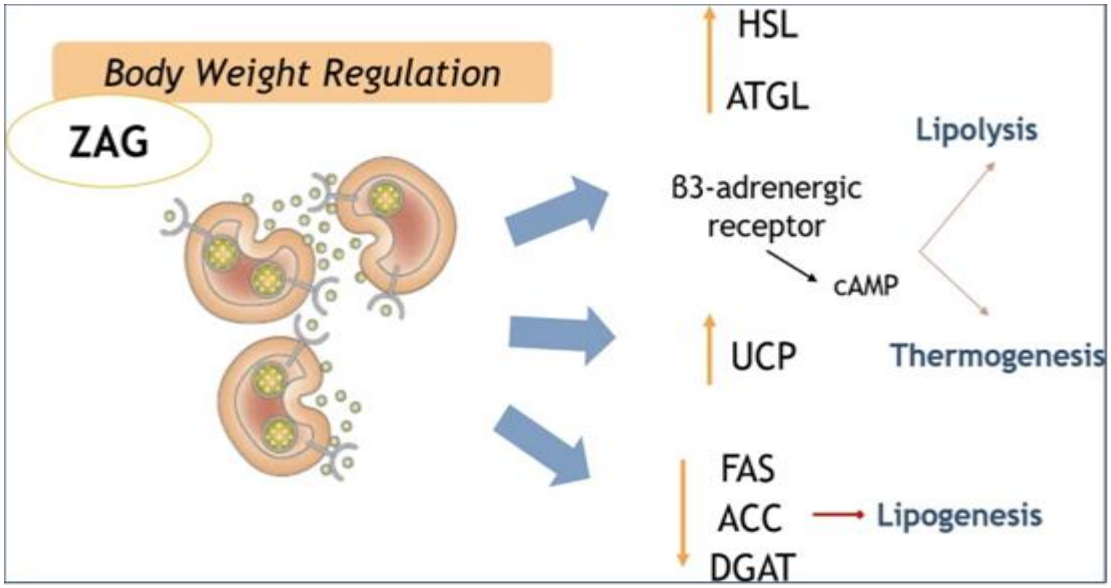

Figure (1): ZAG functions in body weight regulation **(9).**

The effect of ZAG is correlated with decreased levels of lipogenic enzymes (FAS, ACC1, DGAT) and increased expression of lipolytic enzymes (HSL) in adipose tissue. In addition, in vitro tests showed that incubation of ZAG with adipocytes isolated from mouse adipose tissue stimulates lipolysis to a concentration-dependent extent. This may suggest that ZAG has a direct lipolytic effect **(15).**

ZAG expression in human adipose tissue is positively associated with adiponectin expression. Adiponectin has been shown to have anti-inflammatory properties and to increase tissue sensitivity to insulin, which is associated with its decreasing levels in obesity. Adiponectin, through activation of AMP kinase, promotes glucose uptake and fatty acid oxidation in skeletal muscle and reduces vascular inflammation **(16).**

It was initially suggested that the association between ZAG and adiponectin is due to the fact that overexpression of ZAG in 3T3-L1 adipocytes leads to an increase in adiponectin transcripts. ZAG at physiologically relevant concentrations, increases the release of adiponectin from human adipocytes **(14).**

ZAG can stimulate the tissue sensitizing effects of insulin and the anti-inflammatory effects of adiponectin. It was also found that there is a negative correlation between ZAG and leptin mRNA levels in visceral and subcutaneous fat in humans **(16).**

In addition, ZAG mRNA levels are negatively correlated with BMI, fat mass, plasma insulin levels, HOMA-IR model and C-reactive protein. ZAG has been shown to inhibit in vitro leptin production and treatment with recombinant ZAG was found to lead to a reduction in leptin secretion by SGBS cells **(7).**

White adipose tissue is found in excess in obese and overweight people. Studies indicate that ZAG has the potential to induce WAT browning in 3T3-L1 adipocytes. Many authors observed increased expression of brown adipose tissue-specific genes, such as PRDM16, CIDEA, UCP-1, in adipocytes with ZAG overexpression **(15).**

Furthermore, ZAG stimulated mitochondrial biogenesis, which is characteristic of adipose tissue browning. ZAG could induce lipolysis and inhibit lipogenesis in white adipose tissue as it increased the expression levels of

ATGL, HSL, p-HSL and p-ACC lipases. These findings may be used in the future to address obesity and related metabolic disorders **(11).**

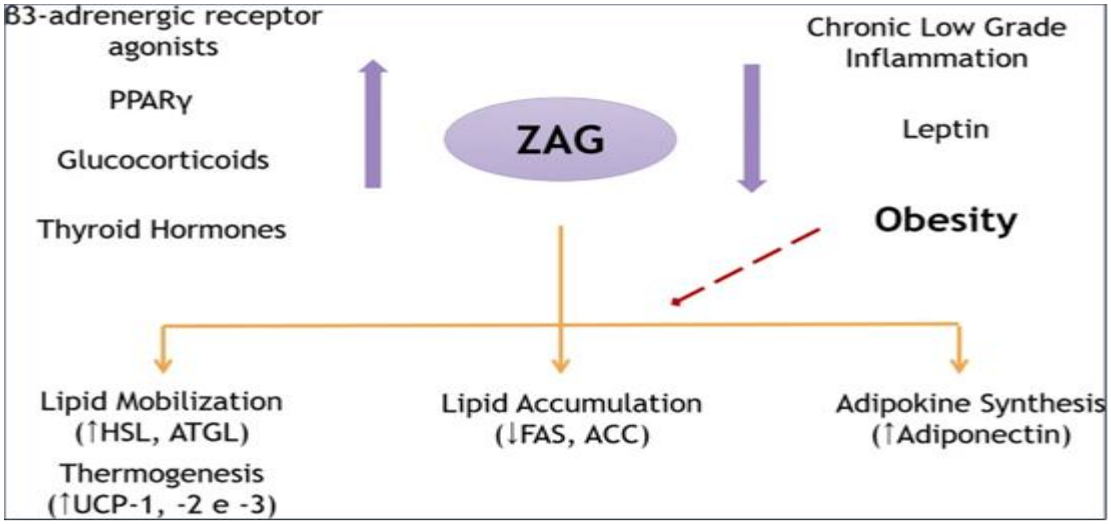

Figure (2): Factors that affect the secretion of ZAG and these influence on obesity pathogenesis. β3-adrenergic receptor agonists, PPAR, glucocorticoids, and thyroid hormones may stimulate secretion of ZAG by adipose tissue. On the other hand, chronic low-grade inflammation, leptin, and obesity are factors that reduce protein secretion. In the context of obesity, a reduction in ZAG secretion can inhibit ZAG-mediated processes, such as lipolysis, lipogenesis reduction, and adipokine production as adiponectin. ACC acetyl-CoA carboxylase, ATGL adipose tissue triglyceride lipase, HSL hormone-sensitive lipase, FAS fatty acid synthase, PPARγ peroxisome proliferator-activated receptor γ, UCP-1, mitochondrial uncoupling protein 1, UCP-2 mitochondrial uncoupling protein 2, UCP-3 mitochondrial uncoupling protein 3, ZAG zinc-α2-glycoprotein **(9).**

It turns out that ZAG is also found in cord blood and influences the development of body fat as early as infancy. ZAG in cord blood is positively correlated with fat-free mass, birth weight, and gestational age at delivery **(16).**

Elevated ZAG levels may also indicate ZAG resistance, similar in mechanism to hyperinsulinemia and hyperleptinaemia caused by the body's resistance to insulin or leptin. The serum ZAG concentration value can be considered a circulating biomarker of obesity and metabolic syndrome. However, further research is needed to determine whether the theses are correct and to fully understand the pathophysiological functions of ZAG **(9).**

Reduced ZAG levels are also associated with an increased risk of developing metabolic syndrome (those with the lowest ZAG levels had almost two times the risk of metabolic syndrome compared to those with the highest ZAG levels). This suggests that the ratio of serum ZAG to fat mass may be a future diagnostic biomarker for the diagnosis of metabolic syndrome **(14).**

Overweight and obesity accompany many metabolic diseases, including the polycystic ovary syndrome (PCOS). Studies indicate that ZAG levels are significantly lower in women with PCOS than in healthy women and prove the effect of ZAG on obesity and the development of insulin resistance in the course of PCOS. Women with excessive body weight and women with elevated blood glucose levels also exhibited lower blood ZAG levels **(7).**

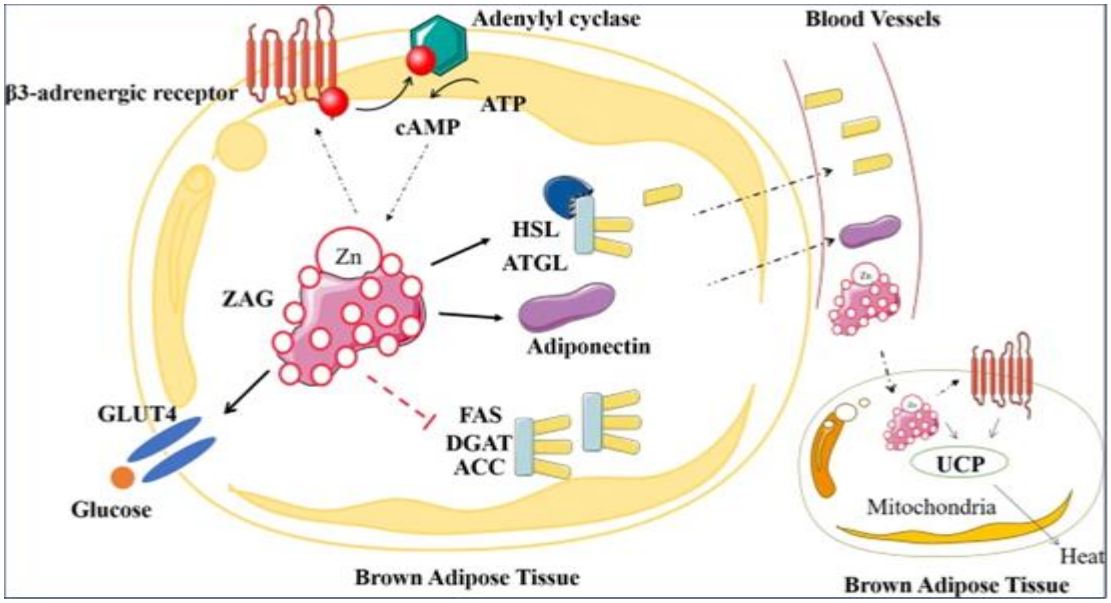

Figure (3): Role of zinc and zinc-α2-glycoprotein in lipid metabolism. Zinc participates in the structure of zinc-α2-glycoprotein and is important for its binding to fatty acids and β3-adrenergic receptors. Thus, this adipokine performs its functions in the induction of lipolysis, through the regulation of key enzymes, inhibits lipogenesis, promotes the translocation of glucose receptors, increases the secretion of adiponectin, and favors thermogenesis in brown adipose tissue and other peripherals tissues. ACC acetyl-CoA carboxylase, ATGL adipose tissue triglyceride lipase, cAMP cyclic adenosine monophosphate, ATP adenosine triphosphate, DGAT diglyceride: glycerol acyltransferase, FAS fatty acid synthase, GLUT4 glucose transporter type 4, MCP mitochondrial decoupling protein **(9).**

Using genetic profiling, it was found that ZAG transcripts in adipose tissue are reduced in obese women. It has also been observed that in obese men and women, ZAG gene and protein expression is down-regulated compared to slim individuals. Reduced ZAG expression in adipocytes during obesity may be associated with impaired adipose tissue metabolism in obesity **(11).**

ZAG also potentially affects cholesterol metabolism. The ZAG gene was associated with circulating blood cholesterol levels, which may indicate that ZAG plays a role in its metabolism. This correlation may be due to the role ZAG plays in the body, namely in lipolysis. The researchers suggest that the correlation between ZAG and total cholesterol is the result of increased TG lipolysis, caused by the effects of ZAG **(10).**

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