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Zinc alpha 2 glycoprotein (ZAG): A potential novel pharmacological target in diabetic retinopathy

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Abstract: Zinc alpha 2 glycoprotein (ZAG) is a 41 KDa secretory soluble glycoprotein found in different body fluids like the serum, saliva, sweat, breast milk, and urine. It is also found in tissues like the testis, epididymis, kidney, spleen, liver, lungs, heart, and brain. ZAG is an adipokine with multiple roles, including lipid mobilization, modulating glucose metabolisms, improving insulin sensitivity, inhibiting tumor proliferation through RNAse activity, and suppressing inflammation. Low levels of zinc and ZAG are linked to metabolic syndrome and are also reported as potential biomarkers for diabetic nephropathy. Interestingly zinc has been found to regulate the binding of ZAG to fatty acids. Based on very few reports on the vitreous ZAG and based on its known functions, we speculate that ZAG has a potential role in diabetic retinopathy. In this article, we discuss the structural component of the protein, its secretion from various tissues, and its distribution in multiple tissues in normal and disease conditions, especially in diabetes and its complications.

Introduction

Zinc is an essential trace element engaged in the body's growth and development, as well as the metabolism of lipids, proteins, and carbohydrates. It controls the activation and expression of over 300 metalloenzymes. Zinc deficiency leads to impaired growth, reproduction, and immunity in humans and animals (Hara *et al.*, 2017; Huang *et al.*, 2017; Olechnowicz *et al.*, 2018; McCall *et al.*, 2000). Zinc is a regulator of zinc alpha 2 glycoprotein (ZAG), a multifunctional glycoprotein (Severo *et al.*, 2020). ZAG has two strong and 15 weak sites for zinc binding. The attachment of zinc to ZAG enables fatty acids and β-adrenergic receptors to bind (Kumar *et al.*, 2013; Zahid *et al.*, 2016; Wei *et al.*, 2019; Severo *et al.*, 2020). Recently ZAG protein has been reported to have a role in the development of many systemic diseases, including diabetes and diabetic nephropathy. This review discusses the structure, function, and role of ZAG in several diseases. We have also speculated the possible role of this protein as a therapeutic target in diabetic retinopathy.

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Structure of Human Zinc Alpha 2 Glycoprotein

ZAG is a 41 kDa glycoprotein named after it tended to precipitate with zinc and its electrophoretic migration is similar to that of α2-globulins (Schmitt *et al.*, 2008). ZAG resembles the major histocompatibility complex (MHC) class I protein and shares 30% to 40% of amino acids sequence identity with the MHC complex heavy chain. It contains three domains, α1, α2, and α3 domains, and is not anchored to plasma membranes, being a soluble protein and does not associate with α2-microglobulin (Sánchez *et al.*, 1999). ZAG's ligand binding site is predominately occupied by polar amino acid side chains, except for a prominent arginine (Arg-73) that protrudes from the side of the groove and acts as a strut to hold the groove open (McDermott *et al.*, 2006). ZAG has two different fatty acid binding sites similar to those seen in the cluster of differentiation-1e (CD1e) (Blumberg *et al.*, 1995). ZAG groove binds hydrophobic ligands such as polyunsaturated fatty acids (Kennedy *et al.*, 2001; Delker *et al.*, 2004). The first crystal structure of ZAG, bound to Dancy amino undecanoic acid (DAUDA), has identified that the ZAG α1-α2 groove was flexible and able to accommodate DAUDA in two different positions as in Fig. 1 (Zahid *et al.*, 2016; Lau *et al.*, 2019). Further, Zahid *et al.* (2022) also revealed that the whole ZAG groove is dynamic in lipid binding and can lodge a

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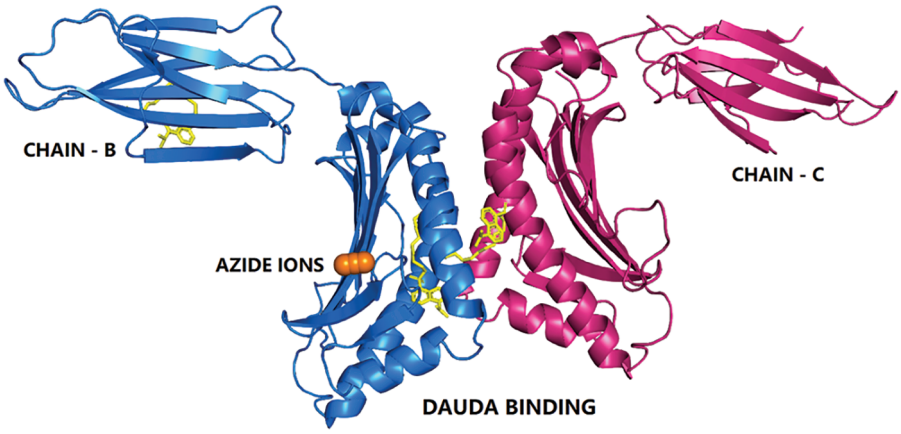

FIGURE 1. The cartoon representation of human zinc-alpha 2-glycoprotein bound to fatty acid.

broader range of signaling lipids, and its function is dictated by its bound lipids.

The 11-{[5-(dimethylamino) naphthalen-1-yl] sulfonyl} amino undecanoic acid (11D) in complex with Chain B (blue color), chain C (pink color) shown as sticks in yellow color, and the azide ion (AZI) is shown as orange spheres.

Site of Zinc Alpha 2 Glycoprotein Expression

ZAG was first identified in 1961 in human blood (Burgi and Schmid, 1961). Epithelial cells in the liver synthesize and secrete ZAG. Jirka and Blanický (1980) identified three isoforms of ZAG in normal human serum in 1980 through crossed starch gel immune electrophoresis. Other than serum, it is reported in various body fluids like sweat, saliva, cerebrospinal fluids, milk (Bundred *et al.*, 1987), urine (Jain *et al.*, 2005), and amniotic fluid (Ding *et al.*, 1990). It is expressed in several human tissues like the kidney, spleen, and liver (Table 1). Its level increases from lowest to highest from children to adults (Jirka and Blanický, 1980). ZAG plasma levels range from 8–12 mg/dL in young people to 18–30 mg/dL in healthy adults (Cabassi and Tedeschi, 2013). ZAG is reported to act in both autocrine and paracrine modes (Mracek *et al.*, 2010).

TABLE 1

Zinc alpha 2 glycoprotein (ZAG) concentration in human tissues

S. No.	Tissue	Concentration (µg/g)	References
1	Hyperplastic prostate	1176 ± 199	Frenette *et al.* (1987), Gerhard and Haupt (1981), Tada *et al.* (1991)
2	Adenocarcinomatous prostate	156 ± 70	
3	Testis	35 ± 5	Frenette *et al.* (1987)
4	Epididymis	41 ± 3	
5	Kidney	74	
6	Spleen	16	
7	Liver	13	
8	Lungs	10	
9	Heart	9	
10	Brain cortex	0.5	
11	Subcutaneous and visceral adipocytes	0.008	Mracek *et al.* (2010)

The Role of Zinc Alpha 2 Glycoprotein in Energy Metabolism

ZAG expression is induced by glucocorticoids, adrenergic receptor agonists, thyroid hormones, and growth hormone in adipocytes. ZAG stimulates the expression of peroxisome proliferator-activated receptor (PPAR) and early B cell factor 2, which binds to PR SET Domain 16 (PRDM16) and uncoupling protein-1 (UCP-1) initiates browning of adipocytes (Elattar *et al.*, 2018). The ZAG-induced increase in UCP-1 in brown adipose tissue helps modulate the body temperature and decreases body weight and fat (Sanders and Tisdale, 2004; Tisdale, 2009; Russell and Tisdale, 2011a; Xiao *et al.*, 2018). ZAG also helps in the up-regulation of thermogenin through adrenergic receptor activation (Bao *et al.*, 2005; Stejskal *et al.*, 2008). Other than this, adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), carnitine palmitoyl transferase I (CPT1-A), and p-acyl-CoA carboxylase are modulated by ZAG, which leads to browning of adipocytes and increases energy expenditure (Xiao *et al.*, 2018). ZAG activates various proteins such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1), nuclear respiratory factor 1 and 2 (NRF-1/2), human mitochondrial transcription factor A, which modulates the mitochondrial energetics (Scarpulla *et al.*, 2012). These entire factors ultimately lead to increased lipolysis (Fig. 2).

Zinc Alpha 2 Glycoprotein as A Regulator of Lipid Metabolism

ZAG plays a significant role in multiple ways to regulate the fat mass of adipose tissue. It stimulates lipolysis, inhibits lipid accumulation in adipocytes, and regulates serum lipids by influencing adipokines. Zinc and ZAG levels are reduced in the blood of people with excessive body fat (Marreiro *et al.*, 2006; de Luis *et al.*, 2013; Suliburska *et al.*, 2013; Yerlikaya *et al.*, 2013; Severo *et al.*, 2020) and are thought to play a role in the development of diabetes and obesity (Fukunaka and Fujitani, 2018). Human recombinant ZAG administration to ob/ob mice has shown reduced body

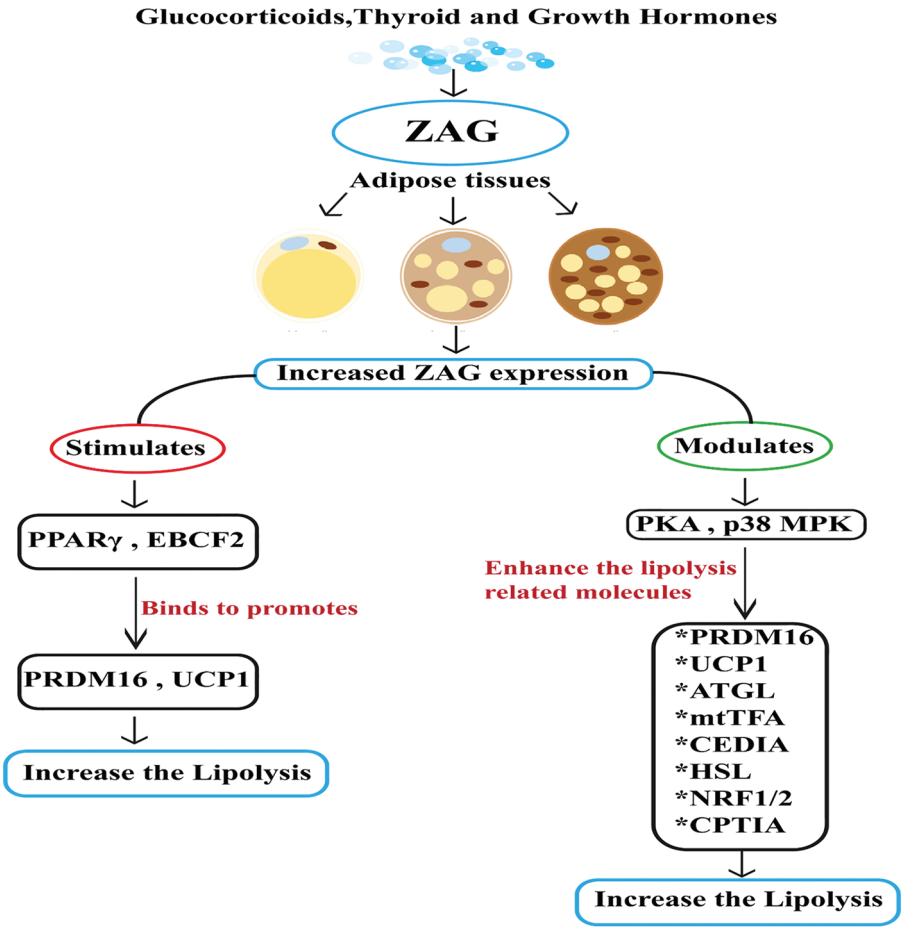

FIGURE 2. Stimulation of zinc alpha 2 glycoprotein (ZAG) expression in the physiological state. In the physiological state glucocorticoids, thyroid and growth hormones stimulate zinc alpha 2 glycoprotein (ZAG). The secreted ZAG is the main player in converting white adipose tissue (WAT) into brown adipose tissue (BAT). Conversion of WAT into BAT increases ZAG leve; increased ZAG stimulates the expression of PPARγ and early B cell factor 2 (EBCF2), which binds to the promoter region of PRDM16 and UCP1 and converts WAT into BAT and increases the lipolysis activity. Increased ZAG also modulates protein kinase A and p38/MAPK signaling pathways and enhances lipolysis-related molecules like PRDM16, UCP1, ATGL, mtTFA, CIDEA, HSL, NRF-1/2, and CPT1A and increases the lipolysis activity.

weight and fat content and a 30% reduction in adipose mass (Hirai *et al.*, 1998; Russell and Tisdale, 2010, 2011b). Further, mice deficient in ZAG showed reduced lipolysis even after treatment with FK-forskolin, IBMX-isobutyl methylxanthine, and isoprenaline (Banaszak *et al.*, 2021).

ZAG regulates the metabolism of free fatty acids released during lipolysis (Marrades *et al.*, 2008) by stimulating fatty acid oxidation (Russell and Tisdale, 2002, 2010) Hepatocytes overexpressed with ZAG show augmented lipolysis and β oxidation of fatty acids and inhibit the palmitic acid-induced lipogenesis and lipid accumulation in hepatocytes (Xiao *et al.*, 2017). Low ZAG level is reported as a risk factor for metabolic syndrome. A potential future diagnostic biomarker for metabolic syndrome is the serum ZAG to fat mass ratio. Further, ZAG in adipose tissue and skeletal muscle activates the AMPK pathway by up-regulating the GLUT-4 and UCP isoforms (Eckardt *et al.*, 2011). When the body is in a catabolic condition, ZAG is activated, inducing lipolysis to increase the amount of free fatty acids that are accessible as an energy source for cancer, cachexia, or inadequate dietary intake. On the other hand, it is reported that increased serum leptin levels and chronic inflammation levels reduce ZAG secretion in the adipose tissue (Fig. 3).

The Role of Zinc Alpha 2 Glycoprotein in Systemic Diseases

ZAG is modified in various pathologies like coronary artery disease, brain disorders, liver disorders, cancers, and in diabetes (Liu *et al.*, 2019, 2020). Huang *et al.* (2019) suggested that ZAG exerts an anti-inflammatory effect by regulating the c-Jun N-terminal kinase/activator protein-1 signaling pathway and could be used as a therapeutic target for cardiovascular disease.

Krabbe's disease is an autosomal recessive disorder primarily affecting infants, and epilepsy seen in Krabbe's disease is associated with ZAG (Maślińska *et al.*, 2013). Its expression is also decreased in temporal epilepsy of rats and humans (Liu *et al.*, 2017). These studies indicate that ZAG has the potential to cross the blood-retinal barrier.

In liver tissues of non-alcoholic fatty liver disease (NAFLD), ZAG level increased in males compared to females and correlated with metabolic syndrome (Yilmaz *et al.*, 2011). Another study found that ZAG protects against NAFLD by ameliorating hepatic steatosis, insulin resistance, and inflammation. Overexpression of ZAG inhibits lipogenesis and fatty acid β-oxidation and attenuates palmitic acid-induced fat accumulation. It is proposed to have the potential to alleviate hepatosteatosis (Xiao *et al.*, 2017).

The concentration of ZAG has been reported to increase in carcinomas (Hirai *et al.*, 1998) and is considered a promising biomarker for prostate (Henshall *et al.*, 2006) and breast (Sánchez *et al.*, 1992) carcinomas. It stimulates lipid degradation in adipocytes and causes extensive fat loss in advance stage cancers. *In vivo*, ZAG decreased tumor cell growth and melanin synthesis more than *in vitro*.

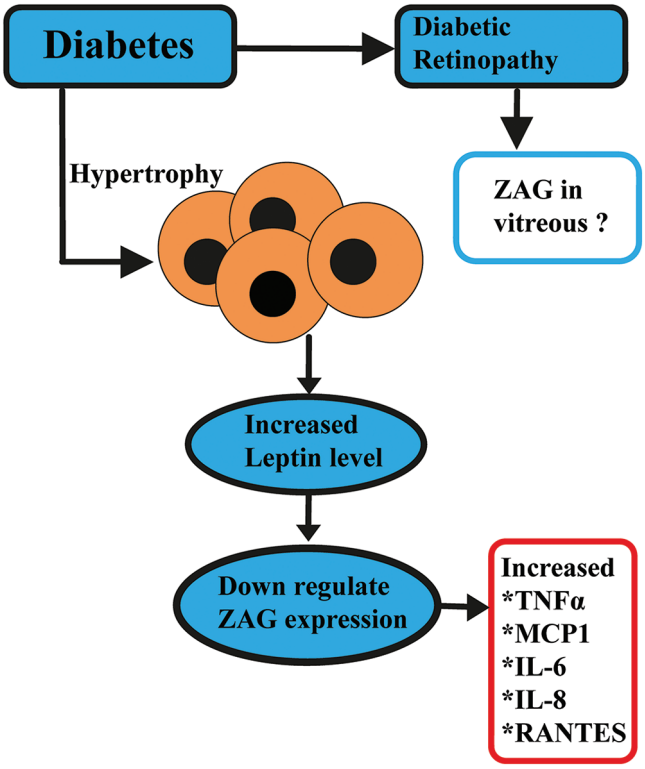

FIGURE 3. Speculated role of ZAG in diabetic retinopathy. In a chronic Inflammation state, adipose tissue hypertrophy leads to increased levels of adiponectin (APN), interleukin (IL)6, IL8, monocyte chemoattractant protein-1 (MCP1), Regulated upon Activation, Normal T cell Expressed, and Secreted (RANTES), and leptin level to down-regulates the zinc alpha 2 glycoprotein (ZAG).

Cyclin-dependent kinases are necessary rate-limiting enzymes in the cell cycle downregulated by ZAG, indicating the role of ZAG in hindering tumor progression (He *et al.*, 2001).

The Role of Zinc Alpha 2 Glycoprotein in Diabetes

Intravenous administration of ZAG in mice has been shown to reduce blood glucose and improve glucose tolerance (Wargent *et al.*, 2013). In oral glucose tolerance tests in mice, ZAG could increase urinary glucose excretion and decrease plasma glucose and insulin (Russell and Tisdale, 2012). ZAG also increases glucose uptake into adipocytes and augments glucose transporter 4 (GLUT4) via β1-adrenergic receptors (Ceperuelo-Mallafré *et al.*, 2015). β-adrenergic receptors are proposed to play an essential role in ZAG-regulated glucose metabolism, but the specific mechanism is still under investigation. Studies on the relationship between ZAG and insulin resistance have shown controversial results (Yeung *et al.*, 2009; Liao *et al.*, 2016; Qu *et al.*, 2016; Tian *et al.*, 2016) with most of them being negative relationships. Silencing ZAG in adipocytes decreases adiponectin, insulin receptor substrate 1, GLUT4, and PGC1α expression (Balaz *et al.*, 2014). Treatment with dapagliflozin, an antagonist of sodium-dependent glucose transporter 2, in type 2 diabetes mellitus (T2DM) patients has been shown to increase serum ZAG and alleviate IR (Selva *et al.*, 2009; Wei *et al.*, 2019). Further, whether the alterations in ZAG occur before the onset of dysglycemia or vice versa is still uncertain. Additionally, more work is required to understand if adiposity is the leading player in ZAG and dysglycemia (Pearsey *et al.*, 2020). Interestingly, ZAG level is reported to decrease in gestational diabetic mellitus patients as well (Näf *et al.*, 2012).

The Role of Zinc Alpha 2 Glycoprotein in Diabetic Nephropathy

ZAG has been proposed as an early diagnostic marker of diabetic nephropathy (Wang *et al.*, 2016). In T2DM, Urine ZAG was higher than in serum due to secretion by tubular epithelial cells (Vallon and Thomson, 2012). However, a few other studies suggest that urine ZAG levels gradually increase in diabetic patients with standard micro and macroalbuminuria, indicating its relationship with the development of diabetes nephropathy (Nielsen *et al.*, 2011). Additionally, according to other research, ZAG was first found in albumin-negative urine samples before the appearance of albumin in patients with T2DM from South Asia. This finding suggests that ZAG may be an early novel urinary biomarker for screening non-albuminuric diabetic nephropathy (Levey *et al.*, 1999). Further, a positive correlation was observed between urinary and serum ZAG with the duration of diabetes mellitus. Further, compared to T2DM patients with normal estimated glomerular filtration rate (eGFR), patients with T2DM who had greater eGFR had significantly higher ZAG urine concentration (Elsheikh *et al.*, 2019).

There are various reports on the levels of ZAG in the serum, plasma, and urine. In different disease conditions, the ZAG levels vary from 500 ng/mL–200 μg/mL in serum, plasma, and urine (Table 2). In diabetes mellitus, its range varies from 1 to 150 μg/mL in serum and 21 to 47 mg/L in plasma samples. In obesity, the range is 100 ng to 134 μg/mL in serum, whereas in chronic kidney disease, its range is 12 to 200 μg/mL; in the case of metabolic syndrome, it varies from 24 to 41 μg/mL. The variation in the serum ZAG level in the disease cases shows that the quantification of ZAG has to be further standardized in relevance to sensitivity and specificity. This is crucial to decipher the specific range indicating the disease progression. To our knowledge, there are no reports of ZAG in the serum of diabetic retinopathy patients.

Possible Role of Zinc Alpha 2 Glycoprotein in Diabetic Retinopathy

In DR, there is vascular leakage due to endothelial permeability induced by signaling pathways like p38, mitogen-activated protein kinase (MAPK), and nuclear factor-κB, which contribute to this by regulating claudin-5 expression (Adachi *et al.*, 2012). Further, Sorrentino *et al.* (2007) showed that *in vivo* re-endothelialization capacity of endothelial progenitor cells derived from individuals with diabetes mellitus is severely impaired and is restored by peroxisome proliferator-activated receptor gamma (PPARγ)

TABLE 2

Zinc alpha 2 glycoprotein (ZAG) levels in human serum and plasma samples

S. No.	Sample	ZAG level in control	ZAG level in disease state	No. of samples (N)	Country	Year of publication	Diseases	Age group
1	Serum µg/mL	———————	74.7 ± 20.9	148	China	2022	CKD (Chan *et al.*, 2022)	58.4 ± 11.3
2	Serum µg/mL	———————	116 ± 34.4	113	Germany	2021	D (Kraemer *et al.*, 2021)	51.1 ± 14.7
3	Serum mg/L	38.73 ± 3.29	58.89 ± 4.17	56 Controls and 55 diseases	China	2021	D (He *et al.*, 2021)	48.2 ± 6.5
4	Serum mg/L	62.57 ± 19.05	43.94 ± 14.51	80 Controls and 80 diseases	China	2021	GD (Xu *et al.*, 2021)	30.08 ± 3.88
5	Serum µg/mL	8.78 ± 1.66	8.37 ± 1.52 7.98 ± 0.94	70 Controls 84 obesities and 151 mets	China	2020	O and METS (Wang *et al.*, 2020)	47.56 ± 10.36
6	Serum µg/mL	8.02 ± 0.98 7.95 ± 0.74	8.44 ± 1.14 7.55 ± 0.85	32 Controls 40 obesities and 104 controls 49 D & O	China	2020	O (Liu *et al.*, 2020)	45.19 ± 8.50 45.60 ± 7.91 47.80 ± 9.38 49.24 ± 6.56
7	Serum µg/mL	107 ± 30.5	100.9 ± 37.1	29 Controls 30 obesities	Iran	2020	O (Alipoor *et al.*, 2020)	59.41 ± 12.44 55.47 ± 9.89
8	Urinary ZAG mg/g Serum ZAG mg/L	26.91 ± 2.41 20.27 ± 1.52	36.86 ± 3.76 46.09 ± 2.31 56.73 ± 2.62 24.55 ± 1.68 32.23 ± 2.11 40.82 ± 1.89	22 C 22 G1 22 G2 22 G3	China	2019	C—control T2DM group G1-normal albuminuria G2-microalbuminuria G3-macroalbuminuria (Elsheikh *et al.*, 2019)	51 ± 6.62 51 ± 6.91 51 ± 6.29 51 ± 5.76
9	Serum µg/mL	1.53 ± 0.30	1.37 ± 0.31	40 Controls 76 obese	China	2018	O (Zhu *et al.*, 2018)	———————
10	Serum µg/mL	50.1 ± 9.0	38.3 ± 11.4	40 Controls 40 obese	China	2018	O (Liu *et al.*, 2018)	44.6 ± 8.3
11	Serum µg/mL	———————	1.46 (1.13–1.60)	438	China	2017	T2DM (Xu *et al.*, 2017)	61.3 ± 4.0
12	Serum mg/L	46.1 ± 18.6	35.0 ± 11.8	234 Controls 255 METS	China	2017	METS (Lei *et al.*, 2017)	37–82
13	Serum ng/mL	106 ± 31	100 ± 34	44 Controls 44 obese	Iran	2017	O (Hosseinzadeh-Attar *et al.*, 2017)	57 ± 10
14	Plasma mg/L	59.4 ± 16.2	35.6 ± 9.1	100 Controls 162 T2DM	China	2016	T2DM (Liao *et al.*, 2016)	53 ± 11
15	Plasma mg/L	58.93 ± 16.53	34.48 ± 13.47	100 Controls 97 T2DM	China	2016	T2DM (Qu *et al.*, 2016)	58 ± 10
16	Serum µg/mL	78.3 ± 42.0	61.4 ± 32.2	42 Controls 32 HBP	China	2014	HBP (Zhu *et al.*, 2014)	53.1 ± 9.2
17	Plasma µg/mL	75.6 ± 25.1	129.1 ± 58.8	9 Controls 7 CKD	France	2014	CKD patients (Pelletier *et al.*, 2013)	61.6 ± 4.1 65.0 ± 4.3
18	Serum mg/L	59.36 ± 16.20	37.14 ± 13.25		China	2013	NGT T2DM (Yang *et al.*, 2013)	53 ± 11 54 ± 9

(Continued)

Table 2 (continued)

S. No.	Sample	ZAG level in control	ZAG level in disease state	No. of samples (N)	Country	Year of publication	Diseases	Age group
				100 Controls 100 T2DM				
19	Serum µg/mL	121.87	113.69	20 Controls 21 AKI & CKD	Germany	2013	CKD & AKI (Sörensen-Zender *et al.*, 2013)	40–70
20	Serum µg/mL	———————	36.21 ± 10.33 37.62 ± 9.64	L-IR-11 H-IR-14	Spain	2012	O (Garrido-Sánchez *et al.*, 2012)	40.9 ± 10.6 38.3 ± 7.9
21	Plasma mg/L	54.6 ± 23.0	151.5 ± 50.1	20 Controls 43 HD	Brazil	2012	Leal *et al.* (2012)	———————————
22	Serum mg/L	48.3 ± 35.5	94.4 ± 29.4	60 Controls 60 CHD	Germany	2011	CHD (Philipp *et al.*, 2011)	———————————
23	Serum µg/mL	63.26 ± 16.4	40.87 ± 10.45	10 Controls 20 obese	Spain	2009	O (Selva *et al.*, 2009)	53.60 ± 11.45 49 ± 7.7
24	Serum mg/L	9.8	19.2	152 Controls 106 T2DM	China	2009	T2DM (Yeung *et al.*, 2009)	55.17 ± 12.5
25	Serum mg/L	16.1	12.3	109 Controls 149 obese	China	2009	O (Yeung *et al.*, 2009)	55.17 ± 12.5

Note: METS: Metabolic Syndrome; O: Obesity; D: Diabetes; GD: Gestational diabetes; NGT: Normal glucose tolerance; T2DM: Type 2 Diabetes Mellitus; CKD: Chronic kidney disease; AKI: Acute Kidney Injury; L-IR: low Insulin Resistance; H-IR: High Insulin Resistance; HD: Hemodialysis: CHD: Chronic hemodialysis; HBP: High blood pressure; NGT: Normal Glucose tolerance.

ligand rosiglitazone. ZAG has been shown to regulate PPARγ. The role of ZAG in diabetic retinopathy is not yet inferred. Proteomics studies in vitreous of cases proliferative diabetic retinopathy have reported altered ZAG expression (García-Ramírez *et al.*, 2007; Zou *et al.*, 2020). In our earlier study in retinal cells, we found ZAG downregulation with high glucose treatment (Vidhya *et al.*, 2018). Zinc regulates ZAG, and the dyshomeostasis of zinc is reported in DR. Zinc is identified to prevent neovascularization by inhibiting VEGF expression in DR (Deniro and Al-Mohanna, 2012). Ischemia in diabetic retinopathy is a crucial component. Studies have shown zinc transporter 8 is reduced in ischemic insults. Therefore, zinc supplementation might have an adjuvant role in ischemia in proliferative diabetic retinopathy. The mechanism may be through ZAG, which needs further studies.

Conclusion

ZAG is a multifaceted glycoprotein and has been reported to decrease in diabetes and diabetic nephropathy. Few proteomic studies showed altered ZAG levels in the vitreous of diabetic retinopathy patients. Its definite mechanism and role in diabetic retinopathy are yet to be explored. ZAG is a metabolic regulator and lipolytic agent and modulates inflammatory genes further; it regulates PPARγ. PPARγ agonists are gaining importance as anti-diabetic drugs; therefore, we hypothesize that ZAG could be an essential player in the pathophysiology of diabetic retinopathy, and further studies are required to understand its mechanism in the disease progress. With all the gathered evidence, there are still lacunae on the role of ZAG in diabetic retinopathy. Further studies are required to unravel the possibility of ZAG as an independent or adjuvant pharmacological modulator for the treatment of diabetic retinopathy.

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