Original Article

Zinc Alpha 2-Glycoprotein as a Biomarker in Children and Adolescents with Newly Diagnosed Type 1 Diabetes Mellitus

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Abstract

Aims: Zinc alpha 2-glycoprotein (ZAG), a protein similar to major histocompatibility complex-I molecules, fulfills significant functions in lipid metabolism and immune system regulation. This study aimed to examine the ZAG level and its relationship with metabolic parameters in individuals with type 1 diabetes mellitus (T1DM). **Materials and Methods:** The study enrolled 77 subjects: 39 children with early-diagnosed T1DM and 38 healthy individuals (mean age: 10.4 years). Fasting plasma glucose (FPG), total cholesterol (TC), triglyceride, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were assessed using enzymatic methods. The concentration of hemoglobin A1c was measured by high-performance liquid chromatography. ZAG levels were detected using an enzyme-linked immunosorbent assay. **Results:** ZAG levels were significantly higher in patients with T1DM compared to controls and could differentiate substantially between subjects with T1DM and healthy controls based on logistic regression analysis. ZAG levels revealed an appropriate specificity of 92.1% and sensitivity of 64.1%, which were significant for discriminating T1DM. It exhibited a remarkable positive correlation with body mass index, FPG, and LDL/HDL ratio while displaying an inverse correlation with TC and HDL-C. **Conclusion:** ZAG upregulation is an early alteration in T1DM and therefore may contribute to the pathogenesis of T1DM and early-onset dyslipidemia, making it a potential marker for T1DM. Long-term prospective research is suggested to establish the association between ZAG and the development and progression of T1DM.

Keywords: Dyslipidemia, type 1 diabetes mellitus, zinc alpha 2-glycoprotein

Key Message: Zinc alpha 2-glycoprotein (ZAG) is upregulated in the early stages of type 1 diabetes mellitus and can be considered an early biomarker in this disease.

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease, characterized by immune system dysregulation, leading to the progressive destruction of β cells.[1] T cells with destructive capabilities and infiltration of immune cells into the islets of the pancreas result in the loss of pancreatic β cells, diminished insulin secretion, and subsequent hyperglycemia.[2] Insulin plays a crucial role in inhibiting hormone-sensitive lipase in adipose tissue, thereby exerting an antilipolytic effect. It also regulates lipoprotein metabolism by activating lipoprotein lipase

Received: 03-Feb-2025, **Revised:** 24-Apr-2025, **Accepted:** 25-Apr-2025, **Published:** 10-Jul-2025

Access this article online

Quick Response Code:

Website: https://journals.lww.com/JODB

DOI: 10.4103/jod.jod_17_25

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How to cite this article: Golpour P, Nourbakhsh M, Momeni H, Azar MR, Nourbakhsh M. Zinc alpha 2-glycoprotein as a biomarker in children and adolescents with newly diagnosed type 1 diabetes mellitus. J Diabetol 2025;16:240-6.

activity. Consequently, the absence of insulin disrupts lipid metabolism regulation. Poor glycemic control and hyperglycemia further contribute to abnormal plasma lipid and lipoprotein levels.[3-5] The risk of cardiovascular diseases is particularly high in patients with T1DM, partly due to lipid abnormalities and other related factors.[6]

Bioactive mediators, such as adipokines, play a significant role in carbohydrate and lipid metabolism regulation and are involved in the promotion of inflammatory responses.[7] Adipokines can impact insulin secretion and function, energy metabolism, adipogenesis, inflammation, and immune system modulation.[8,9] Zinc alpha 2-glycoprotein (ZAG), with a molecular weight of 41-kDa, is primarily secreted by mature adipocytes but is also produced in other tissues such as skeletal muscle, liver, kidney, and brain, and is released into the body fluids.[10] ZAG expression is principally regulated by peroxisome proliferator-activated receptor γ and tumor necrosis factor α (TNF-α).[11] Although ZAG is similar to the major histocompatibility complex (MHC) class I family of proteins, its functions diverge from those of this protein family, yet it appears to have a role in immune regulation.[12,13] ZAG has been associated with various disease states, including prostate, breast, and bladder cancer, as well as cachexia, obesity, and type 2 diabetes.[11,14-17] Increased levels of ZAG have also been reported in certain autoimmune diseases, such as autoimmune retinopathy and multiple sclerosis.[18,19]

ZAG has been proposed to have various biological functions, with its primary role being the modulation of lipid and glucose metabolism.[20] The precise mechanism by which ZAG affects the metabolism of lipids is not yet fully understood; however, numerous studies have demonstrated that ZAG regulates lipid metabolism through several mechanisms. It stimulates lipolysis and increases energy expenditure by activating the β3 adrenergic receptor, leading to the upregulation of uncoupling protein.[21] ZAG enhances the browning process of white adipose tissue,[22] upregulates lipolytic genes such as adipose triglyceride (TG) lipase, hormone-sensitive lipase, and carnitine palmitoyltransferase 1A,[23] and downregulates acetyl-CoA carboxylase, fatty acid synthase, and acyl-coenzyme A: diacylglycerol transferase, enzymes with lipogenic properties.[24]

Furthermore, ZAG has been implicated in glucose uptake and insulin action.[25] It enhances basal glucose uptake by adipocytes through the upregulation of glucose transporter 4 (GLUT4).[26,27] Silencing ZAG gene expression in adipocytes reduces the expression of adiponectin, insulin receptor substrate 1, and GLUT4, confirming its role in the regulation of glucose metabolism.[28]

Considering the significant impact of ZAG on lipid and glucose metabolism, as well as its involvement in immune regulation and inflammation, this study aimed to inspect the levels of ZAG in patients with early-diagnosed T1DM and examine its relationship with metabolic parameters.

Materials and Methods

Subjects

This case–control study enrolled a total of 77 children, aged between 2 and 16 years, including 46 patients with newly diagnosed T1DM. Thirty-eight control subjects were enrolled and selected based on age and gender to match the patient group. The required sample size for this study was determined based on the mean and standard deviation values for ZAG from a previous study.[29] With a significance level of 0.05 (two-tailed) and a power of 80%, a power analysis for an independent *t*-test determined that a minimum of 24 participants per group was required, making a total sample size of 48 participants for the study.

Following clinical examination and routine medical history acquisition, anthropometric parameters, such as weight, height, waist circumference, and hip circumference, were measured for all participants. The formula: weight (kg)/height^2 (m^2) was utilized to calculate the body mass index (BMI). BMI percentiles and z-scores were determined based on the sex and age of each subject. Z-scores for weight and height were also calculated. The z-scores were determined using the online calculator provided by the Children's Nutrition Research Center at Baylor College of Medicine for the age range of 2–20 years, utilizing data from the National Health and Nutrition Examination Survey directed by the Centers for Disease Control and Prevention, USA, (https://www.bcm.edu/bodycomplab/BMIapp/BMI-calculator-kids.html).

All patients included in the study were recently diagnosed with T1DM. They first presented with symptoms of diabetes mellitus and diabetic ketoacidosis, including polyuria, polydipsia, weight loss, fatigue, and high anion gap metabolic acidosis. The diagnosis was confirmed by measuring T1DM-related antibodies, including anti-GAD65, anti-IA-2, and anti-insulin antibodies. The samples were drawn after the stabilization of patients, and none of the patients were in the state of diabetic ketoacidosis at the time of sample collection or exhibited any complications related to diabetes. The inclusion criteria for the study were as follows: (a) recent diagnosis of type 1 diabetes and (b) glycated hemoglobin (HbA1c) levels ≥7%. The exclusion criteria were as follows: (a) the presence of any current chronic or acute illness, (b) a history of hepatic, kidney, or bone metabolism disorders, (c) the presence of any accompanying autoimmune disease, (d) anemia or any hematological disease, (e) presence of other types of diabetes, and (f) endocrinopathies. The patients were receiving insulin treatment (glargine or detemir) following the initial diagnosis. Control subjects were completely healthy and were selected among children who were admitted for

routine growth or puberty checkups. Neither the patients nor the control subjects were taking any medication or specific supplements.

Sample collection and biochemical measurements

Fasting venous blood samples were obtained from the participants immediately after initial confirmation of T1DM and collected in both plain and tubes containing ethylenediaminetetraacetic acid (EDTA). Serum samples were separated and analyzed for routine laboratory parameters. The EDTA-containing blood specimens were immediately centrifuged at 4°C, and the resulting plasma was frozen at −70°C. Another portion of the blood was used as whole blood for the measurement of HbA1c utilizing a high-performance liquid chromatography method.

Fasting plasma glucose (FPG), TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and creatinine levels were determined using colorimetric kits (Pars Azmoon, Iran) by enzymatic methods. The concentration of ZAG in plasma samples was measured by means of an enzyme-linked immunosorbent assay (ELISA) kit (AdipoGen, Switzerland), and intra- and inter-assay coefficients of variation were 6% and 8%, respectively. Leptin levels were also measured using an ELISA kit (Cusabio, China), following the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using MedCalc version 18.9.10 (Ostend, Belgium) and SPSS software version 16.0 (SPSS, Inc., Chicago, IL, USA). The normal distribution of data was assessed using the Kolmogorov–Smirnov test. To assess the disparities between variables in the two study groups, the Mann–Whitney test was employed for non-parametric variables, while the independent samples *t*-test was used for parametric variables. The chi-square test was utilized to evaluate the distribution of gender. Furthermore, the relationship between different variables was analyzed using Pearson's and Spearman's correlation tests for parametric and non-parametric variables, respectively.

Logistic regression analysis was conducted to evaluate the predictive value of ZAG in T1DM. Receiver operating characteristic (ROC) curve analysis with the area under the curve (AUC) calculation was carried out for the estimation of the discriminative capability of ZAG for T1DM. A significance level of $P < 0.05$ was considered statistically significant.

Results

This study represents the first investigation of ZAG concentrations in children and adolescents with T1DM. Table 1 provides an overview of the experimental characteristics and demographic data of the study groups. The patients exhibited significantly lower weight z-score and BMI z-score compared to the control subjects, while there was not any significant difference in height z-score between the two groups. Regarding the biochemical parameters, patients had higher levels of FPG and HbA1c compared to the control subjects. Additionally, patients demonstrated significantly lower HDL-C levels and a

Table 1: The baseline experimental characteristics and demographic variables

Characteristics	Control group	T1DM group	*P* value
Sex (female/male)	21/17	26/20	0.541
Age (years)	11.42 ± 3.2	9.61 ± 4.1	0.056
Height (cm)	146.3 ± 15.9	133.1 ± 19.4	0.000
Height z-score	0.02 (−0.30 to 0.53)	0.01 (−1.01 to 0.48)	0.492
Weight (kg)	50.27 ± 16.6	32.61 ± 15.2	0.000
Weight z-score	1.21 (0.36–1.78)	−0.12 (−0.83 to 0.73)	0.000
BMI (kg/m^2)	22.92 (18.89–26.07)	16.10 (14.93–19.57)	0.000
BMI z-score	1.47 (0.80–1.89)	−0.18 (−0.77 to 0.85)	0.000
FPG (mg/dL)	88.5 (84–95.25)	148.5 (116.5–221.5)	0.000
TG (mg/dL)	96.50 (61.75–153.5)	114.50 (85.5–160)	0.356
TC (mg/dL)	176 (147–189.5)	150.5 (134.25–188)	0.085
LDL-C (mg/dL)	84.50 (71.25–101)	92.50 (76–112)	0.416
HDL-C (mg/dL)	47 (44–52.25)	37 (31–50.25)	0.000
LDL/HDL ratio	1.700 ± 0.67	2.69 ± 1.06	0.000
HbA1c (%)	4.60 (4.1–5.1)	10.20 (8.35–12)	0.000
HbA1c (mmol/mol)	28.0 (21.0–32.0)	89.0 (67.5–108.7)	
Creatinine (mg/dL)	0.9 ± 0.1	0.9 ± 0.2	0.899
Leptin	1.38 (0.95–2.58)	0.98 (0.86–1.24)	0.008

BMI = body mass index, FPG = fasting plasma glucose, TG = triglyceride, TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol

Data are presented as the mean ± SD for parametric variables and median (interquartile range) for non-parametric variables

greater LDL/HDL ratio compared to the control subjects. However, there were no significant differences in TG, TC, and LDL-C levels between the studied groups.

ZAG levels exhibited a significant increase in T1DM subjects compared to normal subjects, with values of 5.30 (2.52–7.56) ng/mL versus 1.47 (0.95–2.46) ng/mL, respectively [$P = 0.000$; Figure 1]. In the correlation analysis, ZAG displayed a negative correlation with both weight z-score and BMI z-score. Among the biochemical parameters, ZAG demonstrated a strong positive correlation with FPG, while its association with HbA1c did not reach statistical significance. Furthermore, partial correlation was used to investigate the relationship between ZAG and FPG while adjusting for BMI as a confounding factor, which showed a significant positive correlation ($r = 0.3340$, $P = 0.002$). ZAG levels showed a negative correlation with both TC and HDL-C, which remained significant for HDL-C after adjusting for BMI ($r = -0.2600$, $P = 0.017$). These correlations were not significant while adjusting for FPG. However, there was no significant correlation observed between ZAG and TG or LDL-C. Notably, ZAG exhibited a significantly positive correlation with the LDL/HDL ratio [Table 2]. As an adipokine, the relationship between ZAG and leptin levels was also investigated; however, no significant correlation was found ($r = 0.027$, $P = 0.88$). The levels of ZAG were not significantly different in male and female individuals.

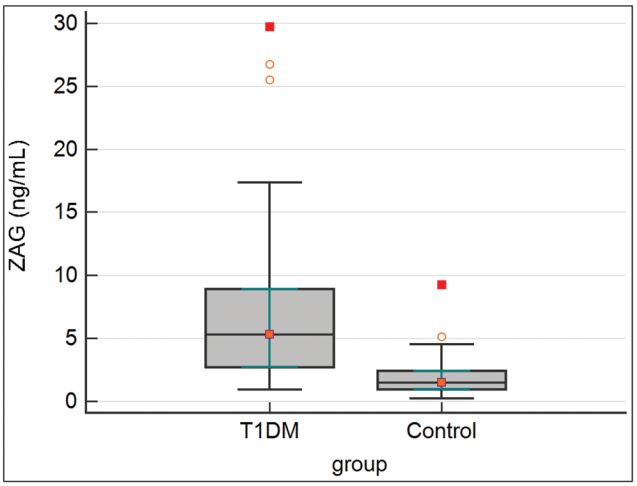

Figure 1: The comparison of zinc alpha 2-glycoprotein between patients with type 1 diabetes mellitus and control group

Table 2: Correlations between zinc alpha 2-glycoprotein (ZAG) and studied parameters

Variables	ZAG All subjects	
	r	*P*
Weight z-score	−0.277	0.011
Height z-score	−0.056	0.611
BMI z-score	−0.292	0.007
TG (mg/dL)	0.056	0.617
TC (mg/dL)	−0.270	0.014
LDL-C (mg/dL)	0.042	0.707
HDL-C (mg/dL)	−0.301	0.005
LDL/HDL ratio	0.234	0.036
FPG (mg/dL)	0.525	0.000
HbA1c (%)	0.529	0.000

BMI = body mass index, TG = triglyceride, TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c

A direct logistic regression analysis was conducted to assess the impact of ZAG on the likelihood of T1DM. The model demonstrated statistical significance, χ^2 (1, $N = 84$) = 35.39, $P < 0.001$, indicating that ZAG levels could differentiate between subjects with T1DM and healthy controls [Table 3]. ZAG levels correctly classified 78.6% of patients. Based on the analysis, the positive predictive value was calculated to be 85%, and the negative predictive value was 72%.

To evaluate the discriminatory potential of ZAG as a marker for T1DM, a ROC curve analysis was performed [Figure 2]. The results revealed that a cutoff value of more than 3.49 ng/mL had an appropriate specificity of 86.84% and sensitivity of 71.74% for distinguishing T1DM, with an AUC of 0.843 (95% confidence interval = 0.742–0.916), $P < 0.001$ [Figure 2].

Discussion

This study represents the first investigation on ZAG levels in children and adolescents diagnosed with T1DM. Our findings demonstrate that patients with T1DM exhibit significantly higher serum concentrations of ZAG compared to healthy children and adolescents. Regression and ROC analyses support the potential of ZAG as a suitable marker for distinguishing T1DM. T1DM, an autoimmune disease, arises from the destruction of

Table 3: Logistic regression parameters

	B	SE	Wald	*df*	*P*	Odds ratio	95% ratio CI for odds	
							Upper	Lower
Zinc alpha 2-glycoprotein	−0.621	0.157	15.686	1	<0.001	0.538	0.395	0.731

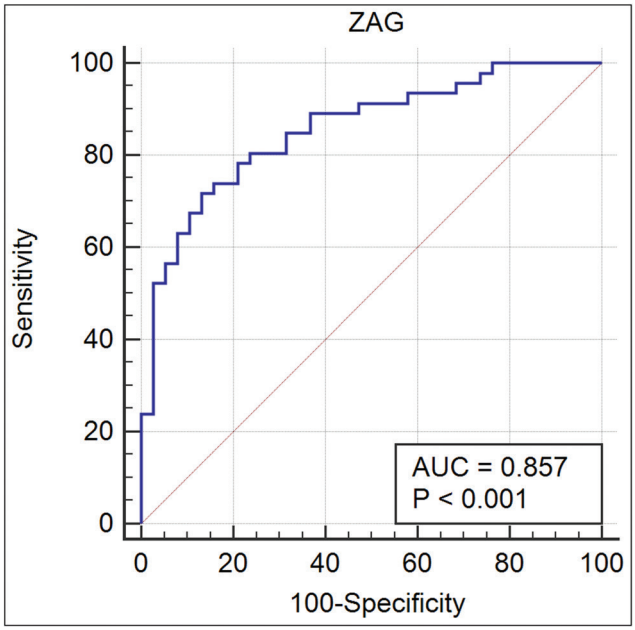

Figure 2: Receiver operating characteristic curve analysis to explain the discriminative ability of zinc alpha 2-glycoprotein in the differentiation of patients with type 1 diabetes mellitus. AUC = area under the curve

β cells by various immune mechanisms such as β-cell autoantigens, B cells, T cells, and macrophages.[30] It is widely considered a proinflammatory condition, characterized by elevated levels of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and adipokines in circulation.[31] ZAG, structurally resembling MHC class I antigen-presenting molecules, appears to possess immunoregulatory properties.[32] In animal models, topical treatment with ZAG has demonstrated immune-modulatory effects by directly suppressing inflammation in T cells, macrophages, and epidermal keratinocytes, resulting in decreased cytokine production and increased FOXP3 expression in skin cells.[33] Consistent with these findings, elevated levels of ZAG have been reported in other autoimmune diseases.[18,19] The increased levels of ZAG observed in newly diagnosed T1DM patients, along with its correlation with FPG, suggest that ZAG upregulation occurs early in the development of T1DM and may not solely serve as a compensatory response to chronic inflammation in these patients. Nevertheless, further studies are required to elucidate the role of ZAG in the onset and progression of T1DM.

Diabetes and hyperglycemia are linked to an increased risk of vascular complications and early-onset cardiovascular diseases, which contribute dramatically to morbidity and mortality in patients with T1DM.[34] Several research has indicated that patients with T1DM exhibit atherogenic abnormalities in lipoproteins, even with adequate glycemic control, substantially heightening the risk of cardiovascular diseases. While the causes of these alterations remain unclear, they persist despite optimal glycemic control, suggesting the involvement of other factors in T1DM-related dyslipidemia.[6] In our study, we observed significantly lower levels of HDL-C and a higher LDL/HDL ratio in patients compared to controls, suggesting that dyslipidemia manifests in the early phases of the disease, placing T1DM patients at an increased risk for cardiovascular diseases even before the onset of diabetic complications. Notably, no association between leptin and ZAG was found in this study, indicating that the elevated ZAG levels in T1DM patients are independent of adipose tissue.

ZAG is recognized as a lipid-mobilizing adipokine.[35] It exerts its effects by upregulating adipose TG lipase and hormone-sensitive lipase, leading to increased lipolysis and utilization of non-esterified fatty acids in rats.[26] Conversely, the knockdown of ZAG expression in hepatocytes has been shown to promote lipogenesis and elevate lipid levels.[36,37] In our study, we demonstrated a significant positive correlation between ZAG and the LDL/HDL ratio, as well as a negative correlation between ZAG and HDL-C concentrations. This aligns with previous reports indicating an inverse relationship between serum ZAG levels and HDL-C levels in individuals with metabolic syndrome (MetS).[38] Therefore, the dyslipidemia observed in T1DM patients may, at least in part, be attributed to altered levels of ZAG. However, further investigations utilizing animal models of T1DM are recommended to gain a better understanding of the role of ZAG in the pathogenesis of lipid abnormalities in T1DM.

Furthermore, a significantly positive correlation between ZAG and blood glucose levels was observed. Studies on the impact of ZAG on the metabolism of glucose are limited. ZAG has been reported to increase urinary excretion of glucose and reduce the peak plasma glucose and insulin levels during oral glucose tolerance tests in experimental animals. It also facilitates glucose transfer into skeletal muscle and adipocytes, promoting glucose consumption and excretion.[39] β-adrenergic receptors are thought to play a significant role in ZAG-mediated regulation of glucose metabolism. On the contrary, a relationship between ZAG and insulin resistance has been reported,[38] and it has been shown that ZAG can induce insulin resistance in adipocytes.[27] ZAG has also been investigated in type 2 diabetes (T2DM) and reported to be lower in these patients and associated with diabetic complications.[40] ZAG has been suggested as an early biomarker of early-stage diabetic nephropathy.[41,42] ZAG levels were evaluated in children with overweight or obesity. Although no significant difference was reported compared with the normal-weight control group, correlations were found between ZAG and FPG, the homeostatic model of insulin resistance, BMI z-score, and lipid profile.[43] ZAG levels were also assessed in patients with MetS, presenting significantly higher levels compared to healthy control

subjects and an inverse correlation between ZAG and serum HDL-C.[44] However, the results have been controversial regarding MetS and lower levels have also been reported.[45]

In this study, we encountered some limitations, including a small sample size and a lack of patient follow-up to assess alterations in ZAG over time. However, given our findings, investigating ZAG in a larger cohort of patients and throughout disease progression warrants further study. Due to the limited research and conflicting findings, it remains challenging to determine the precise role of ZAG in insulin function and glucose metabolism. Further investigations are warranted to elucidate the mode of action and mechanism by which ZAG influences glucose metabolism.

Conclusion

We identified ZAG as a protein that is elevated in patients with recent-onset T1DM, suggesting its potential as a diagnostic biomarker. Given that a significant loss of beta cells occurs during the initial diagnosis of T1DM, often resulting from poor glycemic control, the identification of a biomarker for early detection or screening of the condition is crucial. The observed association between ZAG and the atherogenic lipid profile further underscores its involvement in diabetes-related dyslipidemia, positioning ZAG as a promising target for the management of diabetes and its associated complications.

Acknowledgement

This study was financially supported by the Institute of Endocrinology and Metabolism, Tehran University of Medical Sciences (Grant number: 1401-4-221-63449).

Author contributions

Investigation, writing–original draft: PG. Investigation, resources: MN. Investigation, supervision: MRA. Conceptualization, methodology, analysis, funding acquisition, writing–review and editing: MN.

Ethical policy and Institutional Review board statement

This study adhered to the principles of the Declaration of Helsinki, and informed consent was obtained from all patients and their guardians. Ethical approval was granted by the Ethics Committee of the Institute of Endocrinology and Metabolism, Tehran University of Medical Sciences (IR.TUMS.EMRI.REC.1401.143).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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