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INTERPLAY OF SERUM ZINC AND MAGNESIUM LEVELS WITH INSULIN RESISTANCE AND ATHEROGENIC INDEX: EMERGING INSIGHTS IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Diabetes Mellitus (DM) is a very prevalent metabolic disorder marked by either inadequate production of insulin or Insulin Resistance (IR), affecting an increasing number of people worldwide. Type 2 Diabetes Mellitus (T2DM) is associated with persistent Hyperglycemia and is a frequent trigger for developing various microvascular and macrovascular complications; the most common one is cardiovascular disease. The Atherogenic Index of Plasma (AIP) has been regarded as a valuable index for evaluating the risk of developing cardiovascular complications in the case of T2DM. HOMA-IR or Homeostasis Model Assessment for Insulin Resistance, is often employed in the evaluation of IR. Micronutrients such as zinc and magnesium are essential in managing blood sugar levels and ensuring cardiovascular wellness. Zinc facilitates insulin production, storage and secretion, and assists in improving the lipid profile through HDL elevation and triglyceride reduction. Magnesium, the second most prevalent intracellular cation, is an important cofactor in enzymes responsible for glucose metabolism.

Conclusion: Recent studies have emphasised the potential utility of Atherogenic Indices, especially AIP, as significant predictors of cardiovascular risk in T2DM. Serum zinc and magnesium levels have been found to be associated with adverse lipid profiles and AIP levels. The current review attempts to bring together the current scientific literature regarding the inter-relationship between zinc, magnesium, IR, and Atherogenic Indices with the potential utility of these micronutrient evaluations in the early identification of cardiovascular risk in T2DM patients.

KEYWORDS: Type 2 Diabetes Mellitus, Zinc, Magnesium, Insulin Resistance, HOMA-IR, Atherogenic Index, Cardiovascular risk

INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects approximately 589 million adults worldwide, a figure projected to reach 853 million by 2050 [1]. Cardiovascular disease (CVD) accounts for most T2DM-related mortality, with a two- to four-fold higher cardiovascular risk in affected individuals [2]. The disease is driven by peripheral Insulin Resistance (IR) and progressive beta-cell dysfunction [3], and chronic hyperglycaemia amplifies both through excess Reactive Oxygen Species (ROS) and low-grade inflammation, promoting atherogenic dyslipidaemia [4,5].

Zinc and magnesium are cofactors for enzymes of glucose and lipid metabolism and support insulin signalling and antioxidant defence. Both are consistently depleted in T2DM yet rarely measured in routine practice [6].

HOMA-IR was calculated as fasting glucose (mg/dL) × fasting insulin (μIU/mL) / 405. Atherogenic risk was assessed using the Atherogenic Index of Plasma (AIP), calculated as log10 (TG/HDL-C), which reflects the atherogenicity of the plasma lipoprotein profile [8].

Although the effect of zinc and magnesium on glycaemic control are well studied, evidence examining both minerals together with HOMA-IR and AIP is limited, largely observational, and lacks large trials with cardiovascular endpoints. This review therefore examines their roles, the consequences of their deficiency, and their relationships with HOMA-IR and AIP, to assess their value in early cardiovascular risk assessment in T2DM.

DISCUSSION:

Pathophysiological Background: Insulin Resistance, Oxidative Stress and Dyslipidaemia in T2DM

At the molecular level, impaired phosphorylation of insulin receptor substrates (IRS-1/IRS-2), reduced phosphoinositide 3-kinase (PI3K)/Akt activation and diminished translocation of glucose transporter 4 (GLUT4) to the cell membrane collectively reduce glucose uptake in skeletal muscle [9].

Systemic inflammation, driven by tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β), further impairs IRS-1 signalling through serine phosphorylation [5]. The same inflammatory and insulin-resistant milieu promotes hepatic very-low-density lipoprotein (VLDL) overproduction and reduces lipoprotein lipase (LPL) activity. This

produces the atherogenic dyslipidaemia triad of high TG, low HDL-C and increased small dense LDL (sdLDL), which raises the AIP [5, 10].

In T2DM, insulin resistance, oxidative stress and inflammation reinforce among one another and converge on atherogenic dyslipidaemia, providing the biochemical basis for using HOMA-IR and AIP as complementary markers.

Biomarkers of Insulin Resistance and Atherogenic Risk

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), described by Matthews et al. in 1985, remains the most widely used surrogate measure of IR [7]. It has been validated against the hyperinsulinaemic glycaemic clamp across diverse populations [11]. Higher HOMA-IR has also been associated with progression of nephropathy, retinopathy and CVD.

The Atherogenic Index of Plasma (AIP) is calculated as log10 (TG/HDL-C) with both values in mmol/L. Values below 0.11 indicate low, 0.11–0.21 intermediate and above 0.21 high cardiovascular risk [12]. Its predictive value reflects the underlying atherogenic dyslipidaemia: IR impairs LPL activity and elevates VLDL-TG, while enhanced cholesteryl ester transfer protein (CETP) activity lowers HDL-C, and together these changes generate small dense LDL particles of high atherogenic potential [13]. The AIP correlates significantly with HOMA-IR and other components of the metabolic syndrome, and is superior to low-density lipoprotein cholesterol (LDL-C) alone for predicting subclinical atherosclerosis in T2DM [14]. Because it is derived from a routine fasting lipid profile, it is a clinically integrative and practically accessible cardiovascular risk index.

HOMA-IR reflects insulin resistance, whereas AIP captures its atherogenic lipid consequences; both can be derived from routine fasting samples and are therefore suitable endpoints for evaluating micronutrient status.

Role of Zinc in T2DM

Zinc is a structural cofactor for more than 300 metalloenzymes and regulates gene expression through zinc finger proteins [15]. In pancreatic beta cells, zinc ions coordinate the assembly and storage of the insulin hexamer through the zinc transporter ZnT8, encoded by SLC30A8, which was identified as a T2DM susceptibility locus in genome-wide association studies [16]; rare loss-of-function variants of this gene are protective [17].

In peripheral tissues, zinc activates the insulin receptor tyrosine kinase and PI3K/Akt pathway, promoting GLUT4 translocation and glucose uptake in an insulin-mimetic manner [18]. Zinc may exert anti-inflammatory effects by inhibiting NF-κB activation, thereby reducing the generation of inflammatory cytokines such as TNF-α and IL-6, which are implicated in insulin resistance [15,19].

Serum zinc is consistently 20%–35% lower in patients with T2DM than in age- and sex-matched controls [20]. Glucosuria-driven polyuria increases urinary zinc loss, chronic inflammation redistributes zinc to non-metabolic tissues, and dietary restriction further limits intake. Zinc deficiency reduces PI3K/Akt-mediated GLUT4 translocation and, by impairing Cu/Zn-SOD, amplifies ROS-mediated serine phosphorylation of IRS-1, a key inhibitory modification that uncouples the insulin receptor from downstream signalling. Consistent with this mechanism, a meta-analysis of randomized controlled trials (RCTs) reported that zinc supplementation significantly reduced fasting glucose, HbA1c, and HOMA-IR [21].

Zinc is essential for insulin storage and signalling and for antioxidant defence; its depletion in T2DM is multifactorial and aggravates insulin resistance, whereas supplementation improves glycaemic indices.

Role of Magnesium in T2DM

Magnesium is a cofactor for more than 300 enzymes and is critical for Mg-ATP-dependent glycolytic enzymes, including hexokinase, phosphofructokinase and pyruvate kinase; its deficiency therefore directly impairs glycolytic flux and cellular glucose utilisation [22]. Magnesium also acts as an allosteric activator of insulin receptor tyrosine kinase, facilitating post-receptor signalling through PKC and GLUT4 translocation [23].

Insulin promotes renal Mg^{2+} reabsorption through the transient receptor potential melastatin 6 (TRPM6) channel. In IR, this effect is blunted, causing urinary magnesium wasting that worsens hypomagnesaemia and establishes a self-perpetuating cycle [24]. In addition, magnesium supports endothelial nitric oxide synthase (eNOS)-mediated nitric oxide production, antiplatelet activity and vascular tone regulation, effects directly relevant to cardiovascular risk in T2DM [25].

Hypomagnesaemia affects 25–47% of patients with T2DM, compared with about 15% of the general population [24]. A dose–response meta-analysis estimated that each 100 mg/day increment in dietary magnesium intake was associated with an 8–13% lower risk of T2DM [26]. At the cellular level, hypomagnesaemia reduces Mg-ATP availability for insulin receptor autophosphorylation and activates the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, triggering IL-1β secretion that directly interferes with IRS-1/PI3K signalling [27]. Meta-analyses of RCTs indicate that magnesium supplementation improves glycaemic control and insulin sensitivity (HOMA-IR), particularly in patients with baseline hypomagnesaemia [28,29].

Magnesium supports glycolysis, insulin receptor signalling and vascular function. Its deficiency and the renal losses caused by IR form a vicious cycle, and correction of hypomagnesaemia improves insulin sensitivity.

Zinc, Magnesium and Atherogenic Dyslipidaemia

Beyond their effects on insulin signalling, both minerals influence lipid metabolism. Zinc raises HDL-C through ApoA-1 transcription, inhibits hepatic VLDL-TG secretion, upregulates LDL receptor expression and activates LPL, effects that are collectively expected to lower AIP [30]. Magnesium inhibits HMG-CoA reductase, attenuates LDL oxidation, and reduces ROS-driven dyslipidaemia; hypomagnesaemia is consistently associated with higher TG, lower HDL-C, and elevated total cholesterol [31].

Insulin resistance leads to atherogenic dyslipidaemia by increasing free fatty acid flux to the liver, thereby increasing hepatic VLDL-triglyceride production and impairing triglyceride-rich lipoprotein clearance; altered zinc and magnesium status could influence insulin signalling or lipid metabolism, contributing to the metabolic disturbances of Type 2 Diabetes Mellitus. Therefore, decreased levels of zinc and magnesium might be related to enhanced insulin resistance and an

unfavourable lipid profile that could be demonstrated by an increased Atherogenic Index of Plasma (AIP). Therefore, the interactions could be related to and aggravate the metabolic abnormalities accompanying insulin resistance.

Summary of Key Studies Evaluating Zinc, Magnesium, HOMA-IR, and AIP in T2DM

Author (Year)	Study Design	Sample	Key Finding: Zinc	Key Finding: Mg	HOMA-IR / AIP
Wang et al. (2019)	Meta-analysis	18 RCTs; n=1,687	Zn supplementation reduced FBG by 14.15 mg/dL; HbA1c by 0.54%	Mg supplementation reduced FBG by 4.85 mg/dL; improved IR	Combined reduction in HOMA-IR
Akhtar et al. (2020)	Cross-sectional	90 T2DM patients	Serum Zn negatively correlated with AIP ($r = -0.44$, $p<0.01$)	Hypomagnesaemia is linked to elevated TG and reduced HDL	AIP >0.11 in 72% of Zn-deficient diabetics
Fatima et al. (2021)	Case-control	150 T2DM; 75 controls	Zn deficiency in 68% of T2DM patients	Hypomagnesaemia in 55% T2DM; correlated with dyslipidaemia	Negative correlation between Mg and HOMA-IR ($r = -0.52$)
Rao et al. (2022)	Cross-sectional	120 T2DM vs 60 controls	Serum Zn significantly lower in T2DM ($p<0.001$)	Serum Mg is lower; inversely correlated with HbA1c	HOMA-IR elevated; AIP significantly higher in T2DM
de Baaij et al. (2022)	Review / Meta-analysis	32 studies; n>5,000	Not assessed	Persistent hypomagnesaemia associated with progressive insulin resistance	Mg is inversely associated with HOMA-IR and TG/HDL ratio (AIP proxy)
Yin et al. (2023)	Cross-sectional (cohort data)	Large adult population sample	Not assessed	Not assessed	AIP independently associated with microvascular and macrovascular T2DM complications
Meng et al. (2023)	Longitudinal	350 T2DM; 5-yr follow-up	Baseline Zn deficiency predicted macrovascular complications.	Persistent hypomagnesaemia associated with progressive insulin resistance	Both Zn and Mg independently predicted the AIP trajectory
Swetha et al. (2023)	Cross sectional	100 T2DM patients (India	Serum zinc inversely correlated with AIP; zinc deficiency was more frequent in the high-AIP group	Not assessed	AIP is significantly higher in zinc-deficient T2DM subjects vs zinc-sufficient subjects
Prasad et al. (2023)	Prospective cohort	200 newly diagnosed T2DM	Low Zn associated with increased oxidative stress markers	Mg deficiency predicted higher cardiovascular events at 1 year	AIP correlated positively with HOMA-IR ($r = 0.61$, $p<0.001$)

Li et al. (2024)	Cross sectional	1,057 hospitalised T2DM patients	Not assessed	Not assessed	AIP was identified as a sensitive predictor of early chronic kidney disease and liver injury in T2DM
Zhang et al. (2025)	Cross-sectional	Hospital-based T2DM cohort	Not assessed	Not assessed	AIP independently associated with microvascular and macrovascular T2DM complications
Eladawy et al. (2026)	Case–control; 100 T2DM, 95 controls	Serum Zn lower in T2DM (median 64.5 vs 99.0 µg/dL, $p<0.001$); deficiency in 50% of patients; higher Zn linked to lower odds of diabetes	Not assessed	No assessed	Higher TG and lower HDL-C independently associated with diabetes; higher LDL-C raised odds of Zn deficiency.

FBG: fasting blood glucose; HbA1c: glycated haemoglobin; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; RCT: randomised controlled trial.

The evidence on the association of zinc (Zn) and magnesium (Mg) with T2DM has several clinical practice implications. It also identifies gaps in knowledge that require further investigation.

The levels of serum Zn and Mg should be routinely determined at the time of T2DM diagnosis and during follow-up visits. This is essential for identifying the population of patients with deficient levels of these minerals who may remain untreated. Further studies are needed to establish the reference ranges of serum Zn and Mg in different ethnic groups.

Zn and Mg supplements can be considered as an adjuvant treatment for patients with deficient levels of these minerals at the time of diagnosis or during follow-up, in combination with standard care and not as an alternative to it. Further research is needed to identify the most appropriate formulation and the duration of treatment to determine the optimal changes in HOMA-IR and AIP.

AIP can be routinely calculated in patients with T2DM as an additional tool for the assessment of cardiovascular risk. It is a simple and inexpensive calculation derived from a standard lipid profile that can provide more information than the standard lipid panel about a patient's risk for developing cardiovascular diseases. Further studies are needed to verify if AIP could be used as a reliable predictor of major adverse cardiovascular events (MACE) in patients with T2DM. Such an approach would allow clinicians to identify those patients who would benefit from more intensive lipid-lowering therapy.

HOMA-IR can be used in combination with HbA1c to assess the effect of micronutrient repletion on glucose metabolism in patients with T2DM. While HbA1c is a standard test for assessing average blood glucose levels over the past 3 months, fasting insulin and glucose levels can indicate whether a patient's level of insulin resistance is decreasing. It is critical to investigate if normalization of Zn and Mg status could reduce HOMA-IR and the risk of developing T2DM complications.

Nutritional counselling in patients with T2DM should emphasise the importance of a diet rich in whole foods that support healthy levels of Zn and Mg, such as seafood, legumes, nuts, leafy vegetables, and whole grains. Further studies are needed to determine associations between dietary patterns and micronutrient status in patients with T2DM and apply precision nutrition approaches accordingly.

Genetic and gut microbiota variations may also contribute to abnormal Zn and Mg levels in patients with T2DM. These variations could serve as novel therapeutic targets and biomarkers of treatment response. It is crucial to identify the causal relationships between gene variants (e.g., SLC30A8 and TRPM6) and dysregulated Zn and Mg homeostasis and how altered Zn and Mg levels contribute to the development of T2DM. These findings will allow clinicians to develop individualised therapeutic interventions targeting the unique genetic and microbiota profiles of patients with T2DM, including microbiota-directed therapies.

CONCLUSION

Zinc and Magnesium deficiencies are common among people with Type 2 Diabetes Mellitus (T2DM) and contribute to IR and Atherogenic Dyslipidaemia. The HOMA-IR and AIP are easily assessable tools for studying the relationships between various metabolic factors. Micronutrient assessments and supplementation for the identified deficiencies, along with the inclusion of AIP in the cardiovascular risk appraisal, should be considered in the management of T2DM patients. Studies with larger samples are needed to confirm the obtained results and further elucidate the relationship between these variables, which will facilitate the development of novel treatment strategies.

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