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Association of Serum Selenium, Zinc and Magnesium Levels with Glycaemic Indices and Insulin Resistance in Pre-diabetes: a Cross-Sectional Study from South India

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Abstract A growing understanding of antioxidant mechanisms and *insulin-like* actions of trace elements selenium and zinc has rekindled researchers' interest towards their role in diabetes mellitus, nutritional management of which concentrates predominantly on macronutrient intake. However, selenium studies limiting largely to diabetes have yielded inconsistent results with sparse knowledge in the pre-diabetes population. This hospital-based cross-sectional study screened 300 people who came to the institutional hospital laboratory with fasting plasma glucose and glycosylated haemoglobin requisition over a period of 6 months. Thirty-five pre-diabetes subjects aged 25–45 years and 35 age-matched healthy controls were selected as per inclusion criteria and clinical history. Serum selenium was estimated by inductively coupled plasma-mass spectrometry, zinc and magnesium by colorimetric end-point methods and insulin by enzyme-linked immunosorbent assay, and insulin resistance was calculated using a homeostasis model assessment (HOMA) 2 calculator. Data analysis was done using SPSS ver. 16 employing an independent sample *t* test for intergroup comparison of means and Pearson's correlation for correlation analysis. Serum mineral levels in the pre-diabetes group (selenium 63.01 ± 17.6 μg/L, zinc 55.78 ± 13.49 μg/dL, magnesium 1.37 ± 0.38 mg/dL) were significantly reduced ($p < 0.05$) in comparison to the healthy controls (selenium 90.98 ± 15.81 μg/L, zinc 94.53 ± 15.41 μg/dL, magnesium 2.12 ± 0.22 mg/dL). A significant negative correlation was seen with glycaemic indices and insulin resistance. This study conducted in pre-diabetes subjects highlights a considerable deficiency of serum selenium, zinc and magnesium observed at a much earlier pre-clinical phase. This coupled with the evidence of a strong inverse association with glycaemic indices and insulin resistance postulates the role of mineral alterations in the pathophysiology of hyperglycaemia and insulin resistance.

Keywords Antioxidant · Insulin resistance · Magnesium · Pre-diabetes · Selenium · Zinc

Background

A growing understanding of the biochemical mechanisms and cellular targets of trace minerals has rekindled the interests of researchers towards their role in diabetes mellitus, nutritional management of which concentrates largely on macronutrient intake [1, 2]. Potent trace minerals like selenium (Se) and zinc (Zn) apart from their antioxidant role have also been implicated in glucose regulation and insulin signalling pathways. The pancreatic β cells are susceptible to free radical injury, thus implicating the role of oxidative stress in the pathophysiology of diabetes. Primarily an antioxidant, Se also has an insulin-mimetic action through activation of protein kinases; therefore, its deficiency could be responsible for impaired insulin sensitivity [3, 4]. However, literature survey with reference to Se and glucose metabolism has yielded inconsistent results with several case-control studies [5, 6] and the prospective French Epidemiology of Vascular Ageing (EVA) study [7] (a 9-year follow-up) linking high selenium status with a reduced risk of progression to diabetes, while the US National Health and Nutrition Examination Surveys [8] associated high serum selenium concentration with an increased occurrence of diabetes. A similar direct association was observed between plasma Se and fasting plasma glucose levels both initially and

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after a dose of 100 μg/day of Se along with other antioxidants for a period of 7.5 years in the French Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) trial [9]. Gao et al. [4], on the other hand, did not support a substantial association of selenium status with insulin sensitivity, insulin secretion or risk of type 2 diabetes. Thus, the exact role of Se in the progression of diabetes remains ambiguous.

Similarly, a deficiency in serum Zn and magnesium (Mg) is associated not only with hyperglycaemia but also with hyperinsulinaemia and insulin resistance (IR) [10]. A meta-analysis of 22 studies [11] on type 2 diabetes reported a beneficial role of zinc supplementation on glycaemic control. The insufficiency of zinc, being a cofactor of superoxide dismutase and an inhibitor of protein tyrosine phosphatase 1B, leads to exacerbation of oxidative stress and inactivation of insulin receptors, respectively, thus contributing further to the development of insulin resistance [3]. It also has a role in the stabilisation of insulin hexamers and its storage in the pancreas [11, 12]. Apart from being a cofactor in the glucose transport system of hepatocyte plasma membranes and catalysing the key enzymes in the phosphorylation of glucose; Mg is also known to increase the affinity and number of insulin receptors [2, 13]. Hruby et al. [10] observed a 6 % lower HOMA-IR in subjects with higher Mg intake after 7 years than those with lower Mg intake, thus indicating the importance of Mg for maintenance of long-term healthy insulin metabolism. A large cohort study of Coronary Artery Risk Development in Young Adults (CARDIA) [14] and a meta-analysis of 13 prospective cohort studies [15] have also reported an inverse link between Mg intake and the possibility of progression to diabetes. Guerrero et al. [1] have shown an independent association of hypomagnesaemia with the development of impaired glucose tolerance (IGT) and type 2 diabetes, but not impaired fasting glucose (IFG).

Investigators have highlighted the significance of minerals in diabetes mellitus, but very little has been studied in the pre-diabetes population. As is known that the pathological changes contributing to hyperglycaemia and IR begin in the pre-clinical phase, it may well be expected that the pathophysiologies seen in overt diabetes including an imbalance between free radical production and their scavenging by antioxidants might have been initiated in the pre-diabetes stage itself [12, 16]. However, pre-diabetes has not been adequately addressed by the consortium in terms of prevention or management. This high-risk group thus forms the target group in this study which aims at estimating the serum levels of selenium, zinc and magnesium in pre-diabetes and analysing their correlation with glycaemic indices and insulin resistance.

Methods

A hospital-based cross-sectional study was conducted at institutional constituent hospitals screening 300 people who came with the requisition for fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c) over a period of 6 months. Based on their values and clinical history, 35 pre-diabetes subjects of either sex aged 25–45 years and 35 age-matched healthy controls were taken as per the diagnostic criteria by the American Diabetes Association according to which FPG and HbA1c are independent diagnostic indicators [17]. The sample size (n) of each group was calculated to be 35 using the following formula:

$$n = \left[2\left(Z_\alpha + Z_\beta\right)^2 \cdot \sigma^2\right] \Big/ \delta^2$$

where Z_α = 1.96 at 95 % confidence interval, Z_β = 1.28 at 90 % power, σ = 25 (S.D.) and δ = 20 (mean difference). Two such groups were included to form a total sample size of 70 subjects [18]. Ethical clearance was obtained from the Institutional Ethics Committee (IEC KMC MLR 09-13/165). Informed written consent was obtained from the subjects. Patients with diabetes mellitus, hypertension, dyslipidaemia on treatment and liver, renal, cardiovascular and endocrine diseases or had acute complications such as major surgeries or trauma in the past 1 year; pregnant and lactating women; and subjects on nutritional supplements, magnesium-containing laxatives, diuretics and herbal treatment were excluded from the study along with smokers and alcoholics.

Fasting venous blood samples were collected in plain vacutainers, serum separated by centrifugation at 2500 rpm for 10 min and stored at −20 °C until analysis. FPG was estimated on a daily basis by a glucose oxidase peroxidase method in a Roche Cobas P800 automated analyser and HbA1c by a high-performance liquid chromatography method in a Bio-Rad D-10 automated analyser. Serum selenium estimation was done by inductively coupled plasma-mass spectrometry (ICP-MS), a Thermo Scientific ELEMENT XR instrument at the Sophisticated Analytical Instruments Facility, IIT Bombay. Serum zinc and magnesium estimation was done using the semi-automated analyser Star 21 Plus by a Nitro-PAPS end-point method and a xylidyl blue end-point method, respectively. Serum insulin estimation was done using solid-phase enzyme-linked immunosorbent assay (ELISA) kits by DRG International, Inc., USA, based on the sandwich principle in an ELx800 ELISA reader by BioTek® Instruments, Inc. Insulin resistance was then computed using the homeostasis model assessment (HOMA) 2 calculator. Anthropometric measurements including height, weight and waist and hip circumference were measured using the standard protocol. BMI was calculated as weight (kg) / height $(m)^2$ using Quetlet's index, and waist-to-hip ratio (WHR) was also calculated. Statistical analysis was done using SPSS ver. 16 employing independent sample t test for intergroup comparison of means and Pearson's correlation for correlation analysis. $p < 0.05$ was considered statistically significant.

Results

Following the inclusion criteria, 35 pre-diabetes and 35 age-matched healthy controls were enrolled in the study. Out of the 70 subjects, 43 were males and 27 females. The mean age of the study population was 35.8 ± 4.9 years. Baseline characteristics of pre-diabetes and control group are shown in (Table 1). Data was of normal distribution (non-skewed); therefore, the parametric tests were applied. Mean weight, BMI and waist-to-hip ratio were significantly higher in the pre-diabetes group ($p < 0.05$). The pre-diabetes group had significant hyperinsulinaemia and moderate degree of insulin resistance (Table 2). The mean serum levels of selenium (63.01 ± 17.6 μg/L), zinc (55.78 ± 13.49 μg/dL) and magnesium (1.37 ± 0.38 mg/dL) in the pre-diabetes group were decreased as compared to levels in the healthy controls (Se 90.98 ± 15.81 μg/L, Zn 94.53 ± 15.41 μg/dL and Mg 2.12 ± 0.22 mg/dL) (Table 3). This difference was found to be statistically significant ($p < 0.05$). Correlation analysis illustrated a significant negative correlation of Se, Zn and Mg with FPG (Figs. 1a, 2a and 3a), insulin and insulin resistance (Figs. 1b, 2b and 3b) and Zn and Mg with HbA1c (Table 4).

Discussion

This study aimed at estimating the concentrations of selenium, zinc and magnesium in pre-diabetes subjects, and a significant decrease in the levels of these minerals was observed in pre-diabetes subjects as compared to the healthy controls. This is in corroboration with the majority of the previous studies conducted in diabetes mellitus [12], but the scenario in the pre-diabetes population remains largely unexplored.

Pancreatic beta cells are among the most deprived cells in terms of intrinsic antioxidant activity with expression of antioxidants like glutathione peroxidase (GPx1) and catalase in beta cells being only 1 % of that in hepatocytes, thus making them vulnerable to oxidative damage [5]. The deficiency of Se, being an integral part of antioxidant enzymes like glutathione peroxidase, at the pre-diabetes level could be responsible for the development of insulin resistance which is known to be initiated by oxidative stress and improved by antioxidant treatment [5, 6].

The mean serum Se levels in pre-diabetes (63.01 ± 17.6 μg/L) obtained in this study indicate a significant insufficiency as compared to the healthy controls (90.98 ± 15.81 μg/L), and these levels were inversely linked to FPG and IR in the pre-diabetes group, thus indicating a possible role of this potent trace element in the key processes of glucose and insulin metabolism. Similar findings were observed in the French EVA cohort study [7] wherein the investigators illustrated that participants with higher Se levels (median plasma levels 104 μg/L) were better protected from oxidative stress and progression of IR as compared to those with lower Se levels (median plasma levels 71 μg/L). Our observations are also in corroboration with studies by Kornhauser et al. [19] reporting a deficiency in diabetes together with increased oxidative stress and Ozkaya et al. [20] showing a deficiency in first-degree relatives of diabetic patients. However, a longitudinal cohort study by Gao et al. [4] indicated no substantial association of selenium status with incidence of diabetes.

High selenium also has an effect on insulin signalling cascade. Upon binding to its receptor at the plasma membrane of adipocytes, insulin elicits a transient burst of reactive oxygen species via the activation of NADPH oxidase which generates superoxide and, subsequently, hydrogen peroxide (H_2O_2), which acts as a second messenger, attenuating the activity of phosphatases with redox-sensitive cysteine residues and thereby enhancing the phosphorylation of components downstream in the insulin signalling cascade. Thus, high supra-nutritional doses of antioxidants (mainly GPx1) may have the capability to impair insulin sensitivity via removal of H_2O_2 [5]. The pivotal element here is the complex U-shaped relationship of selenium status, with studies pointing towards both beneficial and harmful roles of Se supplements in individuals with deficiency and normal to increased levels, respectively [6].

Selenoprotein P (SeP), a physiological selenium transporter constituting the major fraction (about 50–60 %) of plasma

Table 1 Baseline characteristics of the pre-diabetes group and healthy controls

Parameter	Healthy controls (mean ± SD) ($n = 35$)	Pre-diabetes group (mean ± SD) ($n = 35$)	p value
Age (years)	34.8 ± 5.1	36.8 ± 4.7	0.089
Weight (kg)	57.24 ± 6.63	65.75 ± 10.42	<0.001*
BMI (kg/m^2)	22.52 ± 1.51	25.35 ± 3.2	<0.001*
WC (cm)	89.6 ± 7.07	91.6 ± 10.23	0.336
HC (cm)	104.1 ± 4.21	99.82 ± 8.67	0.012*
WHR	0.86 ± 0.05	0.92 ± 0.06	<0.001*

n number of subjects, *SD* standard deviation, *BMI* body mass index, *WC* waist circumference, *HC* head circumference, *WHR* waist-to-hip ratio

*$p < 0.05$, statistically significant using Student's independent sample *t* test

Table 2 Comparison of glycaemic indices, insulin and HOMA 2 IR between the pre-diabetes group and controls

Parameter	Healthy controls (mean ± SD) (n = 35)	Pre-diabetes group (mean ± SD) (n = 35)	p value
FPG (mg/dL)	92.46 ± 4.19	113.29 ± 8.81*	<0.001*
HbA1c (%)	5.3 ± 0.20	6.0 ± 0.35*	<0.001*
Insulin (μIU/mL)	7.55 ± 2.63	26.97 ± 4.06*	<0.001*
HOMA 2 IR	0.99 ± 0.34	3.56 ± 0.56*	<0.001*

n number of subjects, *SD* standard deviation, *FPG* fasting plasma glucose, *HbA1c* glycosylated haemoglobin, *IR* insulin resistance

*$p < 0.05$, considered statistically significant using Student's independent sample *t* test

selenium, is known to be a promoter of IR and, being regulated like a gluconeogenic enzyme, provides a rationale for the hypothesised link between selenium and carbohydrate metabolism. The peroxisomal proliferator-activated receptor gamma coactivator 1α (PGC-1α) is a key regulator for biosynthesis of this SeP as well as for transcriptional regulation of the gluconeogenic enzymes glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. Thus, elevated hepatic PGC-1α may trigger not only hyperglycaemia but also a disturbance in selenium homeostasis [5]. At supra-physiological doses, Se supplements could lead to a reversal of antioxidant effect leading to aggravation of these metabolic disorders [12]. This raises an important concern regarding the narrow safety range for oral dosage and serum/plasma status of Se in humans necessitating supplementation only in confirmed deficient individuals.

A significant decrease in zinc levels among the pre-diabetes group along with a strong inverse correlation with glycaemic indices and insulin resistance as recorded in the present study indicates a significant role of this metal in the progression of diabetes. The findings of this study are in coherence with similar studies conducted earlier in pre-diabetes [3, 21]. The observational Nurses' Health Study [22] positively associated higher zinc intake with a decreased risk of diabetes. In an interventional study by Marriero et al. [23] conducted in euglycaemic obese individuals, an improvement in insulin sensitivity was seen with 30 mg/day of zinc given for a period of 4 weeks. Vashum et al. [11] observed a significant association of zinc levels with insulin sensitivity in pre-diabetes even though no significant difference in serum levels was found in their study between pre-diabetes, diabetes and controls. Xu et al. [24] also observed a deficiency similar to the present study in pre-diabetes. This spectrum of observations from different studies conducted in different countries could be attributed to the population profiles differing substantially in dietary composition and geographical distribution [24].

The association between zinc and insulin resistance is attributed to the inhibition of protein tyrosine phosphatase 1B (a crucial regulator of the active phosphorylation form of the insulin receptor) by zinc ions. The deficiency of zinc, being a cofactor of antioxidant enzyme superoxide dismutase, also elicits an oxidative stress that further stimulates stress pathways causing IR [3, 11]. Zn also has direct insulin-like effects via inhibition of glycogen-regulating enzyme GSK3, activation of post-receptor proteins Akt and PI3 kinase and reduction of cytokines IL-1b and NF_B [12]. Thus, it is postulated that Zn deficiency could be linked to a defect in insulin secretion, sensitivity and its action on target tissues playing a significant role in the pre-diabetic phase [25, 26].

Despite the mechanisms described above, Wiernsperger and Rapin [12] concluded in their review that the low levels of zinc seen in diabetic patients are due to an increased excretion in urine secondary to diabetic nephropathy rather than an absolute deficiency. In view of this, the use of pre-diabetes subjects who have not yet developed diabetes-related renal complications is a refinement in the present study which proposes that the decreased Zn levels seen in pre-diabetes subjects is not simply due to a loss in urine as seen in diabetic nephropathy cases. However, this study did not measure urine zinc levels; hence, change in excretion levels could not be assessed.

In corroboration with the studies demonstrating hypomagnesaemia in type 2 diabetes [2, 27, 28] and in pre-diabetes [29], the present study reports a significant deficiency in Mg levels in the pre-diabetes phase, the mechanism for which is not completely known. Other researchers like Hans et al. [27] attributed the deficiency in diabetes to persistent glycosuria and osmotic diuresis leading to a loss of Mg.

Table 3 Comparison of serum mineral levels between the pre-diabetes group and healthy controls

Parameter	Healthy controls (mean ± SD) (n = 35)	Pre-diabetes group (mean ± SD) (n = 35)	p value
Selenium (μg/L)	90.98 ± 15.81	63.01 ± 17.6	<0.001*
Zinc (μg/dL)	94.53 ± 15.41	55.78 ± 13.49	<0.001*
Magnesium (mg/dL)	2.12 ± 0.22	1.37 ± 0.38	<0.001*

*$p < 0.05$, statistically significant using Student's independent sample *t* test

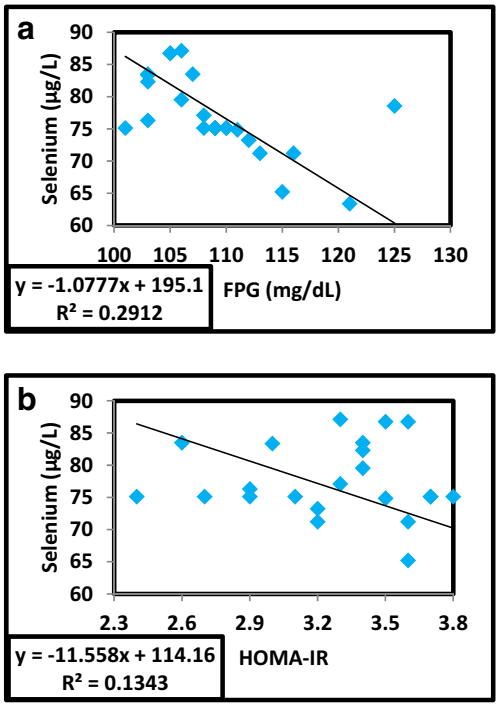

Fig. 1 **a** Scatter plot of serum selenium with FPG in pre-diabetes. **b** Scatter plot of serum selenium with insulin resistance in pre-diabetes

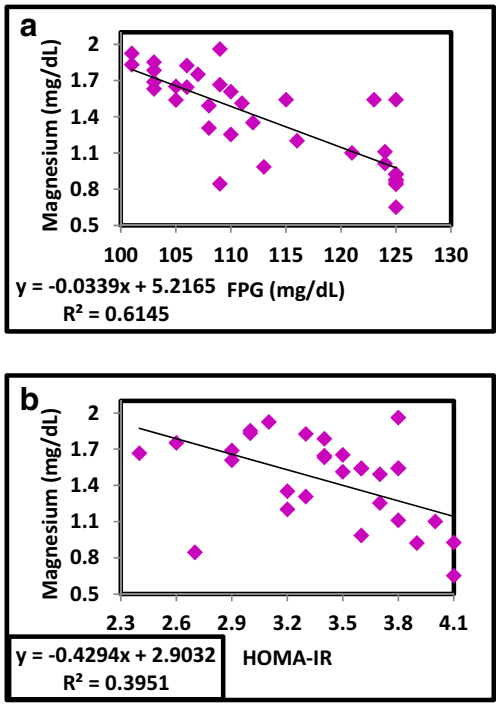

Fig. 3 **a** Scatter plot of serum magnesium with FPG in pre-diabetes. **b** Scatter plot of serum magnesium with insulin resistance in pre-diabetes

Hruby et al. [10], in a large follow-up study, concluded that individuals with higher magnesium intake are 32–47 % less likely to develop incident diabetes, thus emphasising the role of magnesium in lowering the risk of progression to overt diabetes. Fang et al. [29] postulated that hypomagnesaemia may partially result in a high hepatic glucose production, which may be related to hepatic IR by demonstrating an association between the low level of serum Mg at baseline and the increased fasting glucose at 3-year follow-up. A deficiency in serum Mg is associated not only with impaired glycaemic response but also with hyperinsulinaemia and IR as evident from the strong inverse correlation of Mg levels with glycaemic indices, insulin and HOMA 2 values in the present study. This finding is in coherence with the findings of Hruby et al. [10] and Fang et al. [29], thus indicating the importance of Mg for maintenance of long-term healthy insulin metabolism.

The relationship of Mg and insulin resistance is rather interesting wherein studies have proposed low serum Mg levels as a cause for IR in peripheral tissue via decreased autophosphorylation of tyrosine kinase which is a component of beta subunit of insulin receptor having Mg as a cofactor [10,

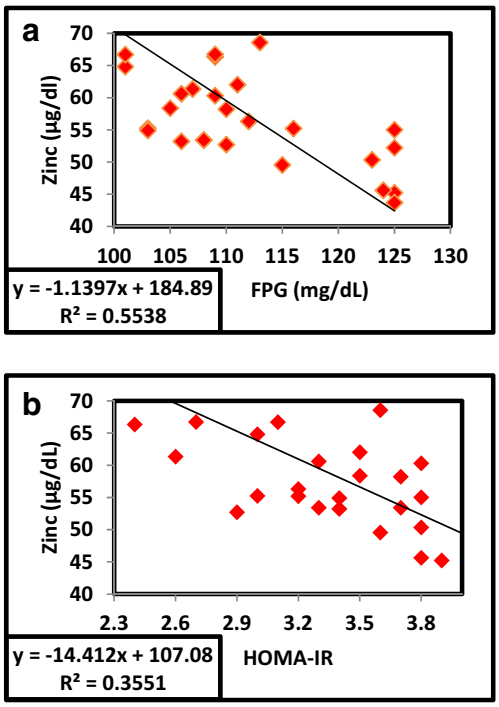

Fig. 2 **a** Scatter plot of serum zinc with FPG in pre-diabetes. **b** Scatter plot of serum zinc with insulin resistance in pre-diabetes

Table 4 Correlation of biochemical parameters with glycaemic indices in pre-diabetes

Parameter	Selenium, *r*	Zinc, *r*	Magnesium, *r*
FPG	−0.540*	−0.744*	−0.784*
HbA1c	−0.104	−0.426*	−0.434*
Insulin	−0.337*	−0.546*	−0.583*
HOMA 2 IR	−0.336*	−0.596*	−0.629*

FPG fasting plasma glucose, *HbA1c* glycosylated haemoglobin, *IR* insulin resistance, *r* Pearson's correlation coefficient

*$p < 0.05$, considered statistically significant

30]. Also, Mg acts as a mild, natural calcium antagonist. Thus, Mg-deficient subjects have increased levels of intracellular calcium which is responsible for the compromised insulin responsiveness of adipocytes and skeletal muscles leading to the development of insulin resistance [29, 31, 32]. Alternatively, Chinyere et al. [2] attributed the decreased serum Mg levels to insulin resistance as compensatory hyperinsulinaemia (as seen in IR) increases intracellular Mg concentration by activation of ATPase pumps present in the plasma membrane and also by affecting tubular reabsorption leading to increased excretion in urine. Hence, a vicious cycle of mutual influence is initiated between hypomagnesaemia and IR, resulting in further aggravation of IR [10, 31]. Interestingly, Song et al. have identified a genetic variant in TRPM6 that might confer susceptibility to type 2 diabetes in women with low Mg intake [33].

Thus, adequate intake and status of these minerals may lower the chances of the development of diabetes especially among the high-risk groups like pre-diabetes. Hence, periodic monitoring of serum levels is advisable along with the glycaemic indices in such patients and in case of a deficiency; an intervention to increase the dietary intakes may be advisable to prevent associated complications.

Conclusions

The present study conducted in pre-diabetes subjects highlights the fact that considerable deficiency of selenium, zinc and magnesium is seen at a much earlier pre-clinical phase in the pathophysiology of diabetes, thus strengthening the hypothesis that these minerals might have a specific role in glucose and insulin metabolism and an alteration in their levels contributes to a defect in these metabolic pathways. Although a deficiency of these minerals and an inverse association with glycaemic indices and insulin resistance have been implicated in pre-diabetes, a beneficial role of supplementation in the prevention of progression to overt diabetes remains contradictory as it is unclear whether mineral deficiencies contribute to the disease pathogenesis or is the deficiency a result of the disease manifestations.

Future Scope of the Study

Further longitudinal studies and randomised controlled trials are warranted to ascertain these results and to establish a cause-effect relationship, if any. Further studies with inclusion of IGT and IFG + IGT as the study groups should be taken up to look for any additive effects if both fasting glucose and post-prandial glucose are impaired.

Strengths and Limitations

The estimation of selenium, being a very sensitive trace element, was done using ICP-MS rather than atomic absorption spectroscopy as ICP-MS provides much lower detection limits, high precision and accuracy compared to other methods for estimation of trace elements. The use of both FPG and HbA1c as glycaemic indicators for intergroup comparison and correlation analysis strengthens the reliability of this study.

A possible limitation could be the sample size, although it was calculated statistically with 95 % confidence interval and 90 % power. The cross-sectional study design in this study limits the cause-effect relationship. Other important trace elements such as copper and chromium which may influence serum zinc concentration could not be estimated.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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