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MAGNESIUM AND PHOSPHORUS IN TYPE-2 DIABETES MELLITUS: A HOSPITAL-BASED CROSS-SECTIONAL STUDY

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ABSTRACT

INTRODUCTION: Type-2 diabetes mellitus (T2DM) is a complex metabolic disorder, with the roles of macrominerals such as magnesium & phosphorus in its pathogenesis remaining unclear.

AIM & OBJECTIVES: To evaluate and compare serum magnesium & phosphorus levels in T2DM cases & healthy controls, and investigate their associations with plasma glucose levels in T2DM by analyzing correlations.

MATERIALS AND METHODS: The study was hospital-based, observational, analytic cross-sectional type and included 122 T2DM patients and 122 age- and sex-matched controls. FPG, PPPG, serum magnesium & phosphorus levels were measured. Statistical analyses were performed using SPSS® version 28.0.0, with unpaired t-tests and Pearson's correlation. A p-value of < 0.05 was considered statistically significant, and $p< 0.001$ highly significant.

RESULTS: FPG (170±52.91 mg/dl vs. 75.88±15.8 mg/dl) and PPPG (216±39.19 mg/dl vs. 111±14 mg/dl) were significantly higher in T2DM ($p=0.0001$). Magnesium levels were significantly lower in T2DM (1.88±0.35 mg/dl vs. 1.99±0.32 mg/dl, $p=0.011$), with a negative correlation between PPPG and magnesium ($r= -0.201$, $p=0.026$). Serum phosphorus levels were lower in T2DM but not significant (2.83±0.96 mg/dl vs. 3.06±0.95 mg/dl, $p=0.062$) and showed a negative correlation with PPPG ($r= -0.2$, $p=0.027$), which was statistically significant. A

positive correlation between phosphorus and magnesium levels (r=0.215, p=0.017), was statistically significant.

CONCLUSION: Deficiencies in magnesium & phosphorus may contribute to T2DM development and progression. Phosphorus depletion potentially contribute to lower magnesium levels in T2DM. Adequate magnesium & phosphorus levels could support glucose homeostasis, and their laboratory analyses may play a critical role in T2DM prevention and management.

Keywords: Diabetes, glucose, macromineral, magnesium and phosphorus

INTRODUCTION:

Type-2 diabetes mellitus (T2DM) is a long-term metabolic condition marked by insulin resistance, where target tissues like muscle, liver, and adipose tissue exhibit reduced responsiveness to insulin. Additionally, it involves dysfunction of pancreatic beta-cells, resulting in insufficient insulin secretion to compensate for the resistance. These factors collectively lead to sustained hyperglycemia. [1,2] Over 60% of individuals with diabetes worldwide live in Asia, with approximately 8.7% of India's adult population affected, positioning the country at the heart of the global diabetes crisis.[3] Nutritional deficiencies in India, particularly mineral deficiencies, are becoming increasingly rampant in both urban and rural settings. Most of the mineral deficiencies are exacerbated by poverty, limited access to healthcare, and cultural dietary patterns that do not prioritize these essential nutrients. Recent findings suggest that deficiencies in macrominerals such as magnesium & phosphorus contribute to the development and progression of T2DM, indicating that these may be crucial for maintaining proper glucose homeostasis. [4]

Magnesium deficiency is prevalent in the general population and frequently goes undiagnosed. It has been recently associated with an increased risk of chronic diseases. [5,6] Emerging research has highlighted its potential impact on T2DM, where low magnesium levels may be a contributory factor for insulin resistance & impaired glucose homeostasis. In T2DM patients, magnesium deficiency is often observed & is associated with worse glycemic control as evident in various studies. [7,8,9] However, contrasting studies such as Masood N et al, [10] and Walter RM Jr et al. [11] reported that serum magnesium levels are normal in T2DM, while Saeed H et al. [12] revealed that serum magnesium and HbA1c levels showed no statistical correlation. Such contrasting results highlight the requirement for further research. The increased intake of highly processed foods, which leads to dietary phosphorus overload, has been overtly linked to the genesis and

progession of diseases, including obesity and diabetes in humans. [13] Research on low-phosphorus diets has shown positive effects on glucose metabolism alongwith insulin resistance & glucose tolerance, among other outcomes. [14] On the contrary, few studies have markedly shown that pancreatic insulin secretion could be slightly hampered by hypophosphatemia. [15,16] Therefore, it is overtly possible for hypophosphatemia to cause glucose intolerance and detrimental insulin resistance as demonstrated in other research studies. [17,18] These mixed and inconsistent results underscore the need for deeper investigations so as to clarify the relationship between phosphorus levels and T2DM.

In light of the increasing prevalence of T2DM and widespread nutritional deficiencies in India, it is essential to investigate the relationship of macrominerals- particularly magnesium and phosphorus with glucose levels, particularly in view of the inconsistent findings reported in various studies. Thus, the present study aims to evaluate and compare the serum levels of magnesium & phosphorus in T2DM subjects and healthy controls, and to investigate their associations with glucose levels (fasting plasma glucose ie. FPG and postprandial plasma glucose ie. PPPG) in T2DM by analyzing correlations. By addressing the existing gaps in research pertaining to these macromineral levels in T2DM, the study seeks to elucidate their potential roles in glucose homeostasis and the genesis of insulin resistance, thereby contributing to a deeper understanding of the complex interrelationship between these macrominerals and T2DM.

MATERIALS AND METHODS:

The study was a hospital-based, observational, analytic cross-sectional type conducted in the Department of Biochemistry at Index Medical College, Hospital and Research Centre, Indore. Ethical approval was obtained from the Institutional Ethics Committee of IMCH & RC, Indore. The study involved 244 participants (122 T2DM patients ie. cases and 122 healthy subjects ie. controls), age- and sex-matched, belonging to 30-65 years of age-group. All study participants provided their informed consent in writing. T2DM patients were included in the case group based on the diagnostic criteria of the American Diabetes Association. [19] Study participants were excluded if they had any acute or chronic illnesses, or conditions affecting the pancreas, liver, or kidneys, as well as any condition that could significantly impact blood glucose level, or if they had used multimineral or magnesium supplements within the past 6 months.

A 2-hour OGTT was carried out on 122 cases and 122 controls after a 12-hour overnight fast to determine FPG and PPPG levels. Fasting venous blood samples (3 ml) were collected under aseptic techniques, with 2 ml placed in a plain vial for magnesium and phosphorus measurements, and 1 ml in a fluoride vial for FPG testing. After drinking a 75 gm glucose solution, participants stayed seated and

avoided physical exertion for 2 hours. A 2 ml blood sample was subsequently collected in a fluoride vial to measure PPPG. Inverting all vials 5–10 times ensured proper mixing of the anticoagulants. The blood samples in plain vials were kept at room temperature for 30 minutes to allow clotting, whereas the samples in fluoride vials were processed without delay. Subsequently, all samples underwent centrifugation at 2000–3000 rpm for 10–15 minutes, enabling the separation of serum from the plain vials and plasma from the fluoride vials. [20,21,22] The plasma was used to measure FPG and PPPG levels with the ERBA clinical chemistry analyzer by Glucose Oxidase-Peroxidase method.[23] The serum was analyzed for magnesium using the Xylidyl blue method [24,25], and for phosphorus using the Ammonium molybdate method, [26,27] on the ERBA clinical chemistry analyzer.

For statistical analysis, Microsoft® Excel® was used to record the data, and IBM® SPSS® version 28.0.0 was used for analysis. Continuous variables were presented as the mean ± standard deviation. The relationship between continuous variables was examined using Pearson's correlation. Differences in continuous variables between two groups were analyzed using Student's unpaired t-test. Statistical significance was assigned to a p-value of < 0.05, whereas a p-value of < 0.001 was regarded as statistically highly significant.

RESULTS:

The present study was conducted with a total of 244 participants, comprising 122 cases of type-2 diabetes mellitus and 122 healthy controls.

Table-1: Demographic characteristics in cases and controls

Variables		**Cases (N =122)**	**Controls (N =122)**	**(x^2)**
Gender	**Male**	53	51	0.873
	Female	69	71	
Age	**30-40**	21	34	0.667
	41-50	33	35	
	51-65	68	53	
Area	**Rural**	71	73	0.765
	Urban	51	49	

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The demographic characteristics of cases and controls are illustrated in Table-1, with chi-square test results for all demographic variables (gender, age, and area) showing non-significance (x^2=0.873 for gender, x^2=0.667 for age, and x^2 =0.765 for area). This suggests that the cases and controls are demographically well-matched and comparable, minimizing the potential for confounding effects from these variables in subsequent analyses.

Table-2: Tabulated comparison of FPG, PPPG, serum phosphorus and serum magnesium between case and control groups.

Parameter	Type of subjects		
	Cases (n=122)	**Controls (n=122)**	**p value**
FPG (mg/dl)	170 ± 52.91	75.88 ±15.8	p= 0.0001**
PPPG (mg/dl)	216 ± 39.19	111 ± 14	p= 0.0001**
Serum phosphorus (mg/dl)	2.83 ± 0.96	3.06 ± 0.95	p= 0.062 (NS)
Serum magnesium (mg/dl)	1.68 ± 0.35	1.99 ± 0.32	p= 0.011*

* - Statistically significant ($p < 0.05$)

** - Statistically highly significant ($p < 0.001$)

NS- Statistically not significant ($p > 0.05$)

Table-3: Correlation analysis of FPG, PPPG, Phosphorus and Magnesium levels

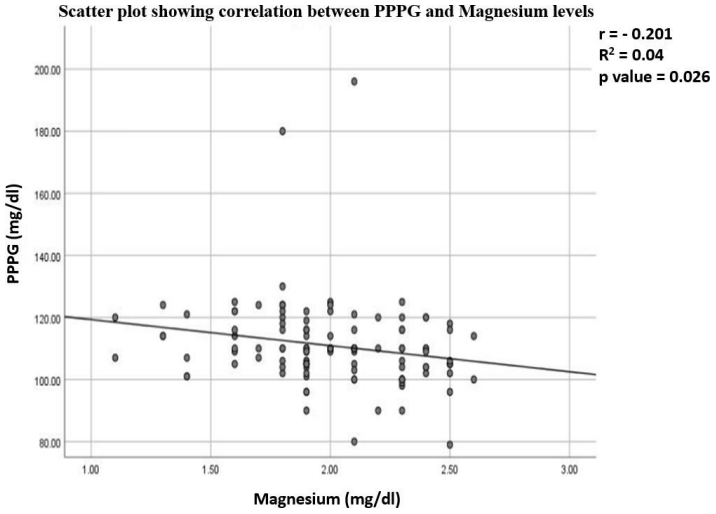
	FPG	PPPG	PHOSPHORUS	MAGNESIUM
FPG	1	0.054 (0.553)	0.08 (0.381)	0.073 (0.423)

PPPG	-	1	**- 0.2*** (0.027)	**-0.201*** (0.026)
PHOSPHORUS	-	-	1	**0.215*** (0.017)
MAGNESIUM	-	-	-	1

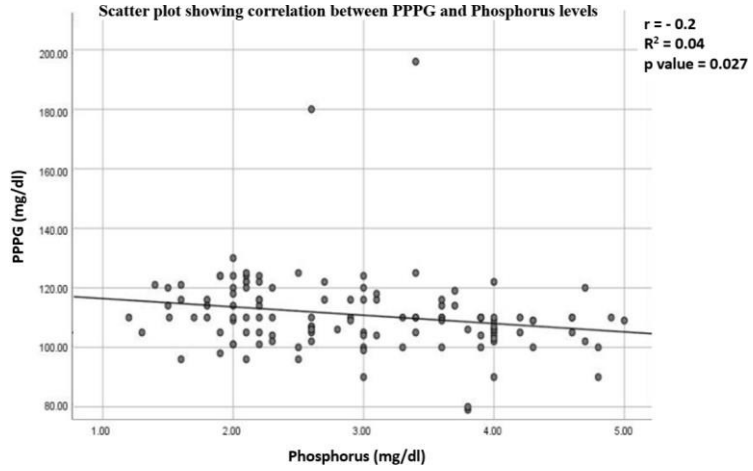
Note:-

- Sample size: 122 cases and 122 controls.
- Only the upper triangular part of the table matrix has been shown to remove duplicate values.
- Each cell shows the Pearson's correlation ie. r value followed by the p-value in brackets.
- Correlation cells with negligible r value ($r \approx 0$) are shaded in light grey to indicate no correlation between the variables
- * Statistically significant as $p < 0.05$ with r values marked in bold
- ** Statistically highly significant as $p < 0.001$ with r values marked in bold

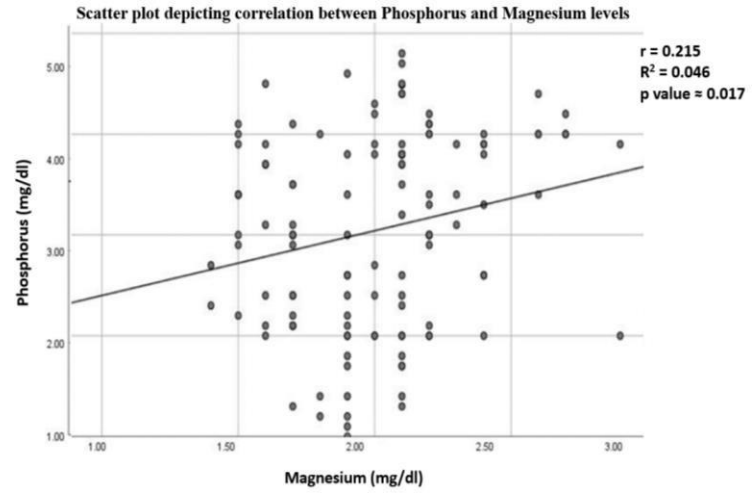
As presented in table-2, FPG (170 ± 52.91 mg/dl vs. 75.88 ± 15.8 mg/dl, p = 0.0001) and PPPG (216 ± 39.19 mg/dl vs. 111 ± 14 mg/dl, p = 0.0001) levels were significantly higher in cases than controls. Serum magnesium level (1.68 ± 0.35 mg/dl vs. 1.99 ± 0.32 mg/dl, p = 0.011) was significantly low in T2DM. Table-3 and graph-1 depicts a negative correlation between PPPG and magnesium (r = -0.201, p = 0.026), which is statistically significant. As illustrated in table-2, serum phosphorus level (2.83 ± 0.96 mg/dl vs. 3.06 ± 0.95 mg/dl, p = 0.062) was low in T2DM but not statistically significant. Additionally, table-3 and graph-2 indicates a negative correlation between PPPG and phosphorus (r = -0.2, p = 0.027), which is statistically significant. Furthermore, the table-3 & graph-3 reveal a positive correlation between phosphorus and magnesium levels (r = 0.215, p = 0.017), which is also statistically significant.



Graph-1: Scatter plot showing correlation between PPPG and serum magnesium levels



Graph-2: Scatter plot showing correlation between PPPG and serum phosphorus levels



Graph-3: Scatter plot showing correlation between serum phosphorus & magnesium levels

DISCUSSION:

In the present study, the authors have observed statistically significant low magnesium levels in T2DM patients, alongwith a statistically significant negative correlation between PPPG and magnesium levels. These findings are supported by various studies conducted by Kumar SR et al. [28] & Arpaci D et al. [29] Also, studies by Luo B et al. [30] and Lima Mde L et al. [31] among others, have observed that low magnesium level is correlated statistically with insulin resistance, indicating the role of low magnesium levels in developing insulin resistance and further T2DM. Nadler JL et al. [32] observed that low-magnesium diet led to development of insulin resistance. This suggests a potential metabolic link between magnesium

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metabolism and glucose homeostasis, indicating that reduced magnesium levels may adversely affect glycemic control. In magnesium deficiency, the ATP-dependent potassium (K-ATP) channels remain hyperpolarized and permanently open, preventing proper cell depolarization of beta-pancreatic cells. This inhibits calcium influx into the cell, thereby impairing insulin secretion & contributing to glucose dysregulation. [33] Chronic low magnesium levels can cause tyrosine kinase dysfunction in insulin receptors, thereby desensitizing the insulin receptors, and potentially leading to insulin resistance and T2DM. [34,35]

In the present study, the authors have demonstrated low phosphorus level in T2DM patients but was statistically non-significant (p value=0.062). This outcome suggests that further research with larger, more diverse subjects is needed to determine whether phosphorus has a more pronounced effect on glucose homeostasis. However, the observed trend of slightly lower phosphorus in diabetics, even if not statistically significant, might prompt a closer evaluation of serum phosphorus levels in T2DM over time. Therefore, routine laboratory measurements of phosphorus could be used alongside other metabolic parameters to monitor overall health in T2DM. Numerous studies, including those by Nigah SL et al. [36], Bora GK et al. [37] and Nagasaka S et al. [38], suggest an inverse relationship between glucose and phosphorus levels, which align with the negative correlation observed in the present study. This indicates that as phosphorus levels decline in T2DM individuals, FPG levels may rise, suggesting a potential metabolic link between phosphorus metabolism and glucose homeostasis. Hypophosphatemia-induced insulin resistance may be explained by the essential role of phosphate in carbohydrate metabolism, such as in glucose phosphorylation, which helps trap glucose within cells. So, reduced levels of phosphate may impair peripheral glucose utilization.[39] This may potentially contribute to the onset, progression or worsening of insulin resistance.[40] Additionally, phosphate is involved in multiple cellular processes, including phosphorylation, which is crucial for insulin signaling pathways. Lowered phosphate can impair these signaling pathways, reducing insulin sensitivity in target tissues like muscle & adipose tissue. [41]

Additionally, the present study has demonstrated a positive correlation between phosphorus and magnesium levels ($r = 0.215$, $p = 0.017$). This implies that as phosphorus levels decrease, there is a tendency for magnesium levels to decrease slightly. A possible mechanism is that phosphate depletion leads to increased urinary magnesium excretion and consequently hypomagnesemia, as proposed by Paunier L [42] and Nacul FE et al. [43] Moreover, studies by Dai LJ et al. [44] and Perez Gonzalez E et al. [45] have confirmed that phosphate depletion negatively affects magnesium transport by decreasing reabsorption across the luminal membrane of distal convoluted tubular cells, ultimately causing magnesium loss and reducing serum magnesium levels.

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Limitations: The observational cross-sectional design precludes the establishment of causal relationships, limiting our ability to determine the cause-effect link between macromineral levels and T2DM. Moreover, the present study lacked dietary data or detailed nutritional records, making it impossible to assess the participants' intake of phosphorus and magnesium.

CONCLUSION:

The present study observed significantly lower magnesium in T2DM implicating its potential role in glycemic control, possibly by playing critical roles in the genesis and progression of T2DM. Although phosphorus levels were lower in T2DM, the differences were not statistically significant, suggesting a subtle trend rather than a definitive relationship, thereby warranting further investigation with larger and more diverse populations. Correlation analyses revealed that both magnesium and phosphorus are one of the contributory factors in regulating glucose metabolism, with a significant positive correlation between the two, suggesting the crucial involvement of phosphorus in maintaining magnesium homeostasis, which may together influence glycemic control.

The authors of the present study further suggest that maintaining adequate serum levels of magnesium & phosphorus and regular monitoring are crucial in preventing and managing T2DM. Given the widespread deficiencies of these macrominerals-particularly magnesium in our country, physicians should regularly assess their levels as part of glucose control in T2DM patients. Further research, including supplementation trials and longitudinal studies with larger sample sizes, is needed to better understand their roles in glucose metabolism and T2DM management. Such studies could inform clinical practices and public health guidelines for monitoring and supplementing these macrominerals.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have equally contributed in this study, and they all have agreed on the final manuscript.

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