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ROLE OF VITAMIN D AND MAGNESIUM IN ASSOCIATION WITH INSULIN RESISTANCE IN POLYCYSTIC OVARY SYNDROME (PCOS) PATIENTS

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age. It is characterized by hyperandrogenism, anovulation, and polycystic ovaries. Various metabolic abnormalities associated with PCOS such as insulin resistance (IR), which plays a central role in PCOS pathophysiology. IR is also responsible for the exacerbation of hyperandrogenism and metabolic complications like type 2 diabetes mellitus and cardiovascular disease. The role of micronutrients such as Vitamin D and Magnesium in metabolic regulation becomes more significant clinical interest in recent years. Both have been implicated in glucose metabolism and insulin signaling pathways, but their specific role in PCOS remains inadequately studied and somewhat controversial. Many studies suggested these micronutrients may influence metabolic outcomes in PCOS. **Objective:** To assess the association between serum Vitamin D and Magnesium levels with insulin resistance in women diagnosed with PCOS. The aim of this study is to determine whether deficiencies in these micronutrients could lead to increased insulin resistance in PCOS patients. **Methods:** An observational cross-sectional study was conducted on 50 women with confirmed PCOS based on the Rotterdam criteria. Serum Vitamin D (ng/ml), Magnesium (mg/dl), and insulin resistance values were recorded. Participants were recruited from gynaecology outpatient department at GGH. Exclusion criteria included pregnancy, women with known endocrine disorders other than PCOS, women on hormonal or vitamin/mineral supplements. Fasting blood samples were collected for the measurement of fasting blood glucose, c-peptide levels, serum Vitamin D (ng/ml) and Magnesium (mg/dl). Insulin resistance was calculated using the HOMA-IR formula. **Results:** Descriptive analysis showed a mean serum Vitamin D level of 16.1 ng/ml (SD = 3.35), suggesting widespread Vitamin D insufficiency among participants. The mean Magnesium level was 1.80 mg/dl (SD = 0.23), and the mean insulin resistance (IR) was 11.1 (SD = 7.5), indicating a high prevalence of metabolic disturbance. Correlation analysis revealed a significant negative relationship between serum Vitamin D and insulin resistance ($r = -0.45$, $p < 0.05$), indicating that lower Vitamin D levels were associated with higher IR. Magnesium levels, however, showed a weaker and statistically non-significant correlation with IR. In the regression model, Vitamin D emerged as a significant independent predictor of insulin resistance ($\beta = -0.01$, $p = 0.03$), while Magnesium did not demonstrate a significant effect ($\beta = -6.54$, $p = 0.195$). **Conclusion:** The findings of this study highlight a statistically significant inverse relationship between Vitamin D levels and insulin resistance in women with PCOS. These results underscore the potential importance of Vitamin D in the metabolic management of PCOS. Magnesium, although biologically plausible as a modulator of insulin sensitivity, did not show a significant association in this study, which may be attributed to the limited variability of magnesium levels in the sample or insufficient statistical power. The high prevalence of Vitamin D deficiency and insulin resistance observed in this study and Vitamin D.

KEYWORDS: c-peptide, micronutrients, magnesium, vitamin d, insulin resistance, pcos.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is the most prevalent endocrine disorder with a global prevalence ranging from 6% to 20% depending on diagnostic criteria and population studied. It may be due to interaction of genetic, hormonal, metabolic, and environmental factors and is primarily characterized by an imbalance of reproductive hormones in females, characterized by menstrual irregularities, hyperandrogenism, and polycystic ovaries. According to the Rotterdam criteria (2003), PCOS can be diagnosed if any two out of these three characteristic features are present.[1] The prevalence of PCOS is increasing among reproductive aged women of 18-24 years[2], which increases significant public health concerns due to its lifetime complications. Apart from reproductive abnormalities, PCOS is associated with metabolic disturbances, including insulin resistance (IR), hyperinsulinemia, impaired glucose tolerance, dyslipidemia, and central obesity. These metabolic disturbances contribute to the high incidence of type 2 diabetes mellitus (T2DM), metabolic syndrome, cardiovascular diseases, and even certain types of cancers, such as endometrial carcinoma.[3,4] By reviewing many studies, we can identify the modifiable factor i.e influence on insulin sensitivity is critical for managing PCOS. In fact, insulin resistance (IR), which is present in up to 70% of women with PCOS, and is considered as a pathophysiological factor of the disorder and plays a central role in the manifestation of both reproductive and metabolic symptoms.

Vitamin D and Magnesium are two important micronutrients implicated their roles in metabolic regulation, glucose metabolism, endocrine function and inflammation.

Vitamin D, a fat-soluble steroid hormone, is important for bone health and calcium homeostasis. It also influences insulin secretion and insulin sensitivity through its effects on pancreatic β-cells and insulin receptor expression. It has been suggested that Vitamin D deficiency, is highly prevalent among women with PCOS, may rise insulin resistance, contribute to hyperandrogenism, and worsen ovulatory dysfunction. Several studies have shown that low serum vitamin D levels in PCOS women are associated with higher body mass index (BMI), waist-to-hip ratio, fasting insulin levels, and higher HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) scores. Moreover, randomized controlled trials have reported that Vitamin D supplementation can improve insulin sensitivity, lipid profiles, and menstrual regularity in PCOS patients, although results have been mixed and depend on baseline vitamin D status and study design.

Magnesium, a macro mineral and the second most abundant intracellular cation, plays a crucial role in metabolic and enzymatic processes. It is an intracellular electrolyte in the human body that regulates the functions of 300 enzymes and involves in energy metabolism and nucleic acid synthesis.[5] It is involved in insulin signaling and glucose homeostasis through its influence on insulin receptor activity, tyrosine kinase phosphorylation, and GLUT4 (glucose transporter type 4) translocation. Recent studies have shown that serum magnesium levels tend to be lower in women with PCOS compared to healthy controls.[6,7]

This reduction may be attributed to dietary inadequacies, increased urinary excretion due to hyperinsulinemia, or systemic inflammation. Many interventional studies have suggested that magnesium supplementation may offer benefits in managing PCOS symptoms by reducing insulin resistance, improving glucose metabolism, and alleviating menstrual irregularities.

Vitamin D deficiency is prevalent in women with PCOS and has been associated with poor metabolic outcomes, while magnesium plays a role in insulin receptor function and glucose homeostasis. Several studies have also shown that there might be a potential link between lower vitamin D levels and the metabolic disturbances in women with PCOS.[8] Deficiency in magnesium has been linked to decreased insulin sensitivity, increased oxidative stress, systemic inflammation, and endothelial dysfunction-all of which are relevant to the pathophysiology of PCOS.[9]

By all these considerations, this study aims to investigate the correlation between vitamin D and magnesium levels with insulin resistance, as measured by HOMA-IR, in women diagnosed with PCOS.

MATERIALS AND METHODS

The present study was carried out after getting approval from Institutional Ethics Committee. This observational cross-sectional study was conducted among women with reproductive age group of 18 to 25yrs. 50 women were identified who were already diagnosed with PCOS based on the Rotterdam criteria.

Participants were recruited based on inclusion and exclusion criteria (Table 1) in outpatient clinics from Obstetrics and Gynecology department, GGH, Vijayawada for a period of 2months.

Category	Criteria
Inclusion criteria	- Women diagnosed with PCOS based on Rotterdam criteria - Age between 18 and 25 years - Those who are willing to give written informed consent.
Exclusion criteria	- Women with Diabetes mellitus and other endocrine disorders - Women on vitamin or mineral supplementation - Chronic illnesses affecting insulin metabolism - Those who refused to give written informed consent.

Based on the study criteria one PCOS women was recruited per day and history was taken according to proforma with prior written consent. After getting the consent from the patient, fasting blood samples were collected to measure serum Vitamin D (ng/ml), Magnesium (mg/dl), fasting blood glucose (mg/dl) and C- peptide. Insulin resistance was calculated using the HOMA-IR formula.

Fasting blood glucose and serum magnesium were estimated by fully automated Beckman coulter. Vitamin D was estimated by chemiluminescence method where as C-peptide was estimated by ELISA method. Insulin resistance is calculated from fasting blood glucose and C- peptide values.

Descriptive statistics were computed for all variables by using Excel. Pearson correlation was used to assess relationships between Vitamin D, Magnesium, and IR. Multiple linear regression analysis was performed to determine the independent association of Vitamin D and Magnesium with insulin resistance, using IR as the dependent variable. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 50 women with polycystic ovary syndrome (PCOS) were included in the study. Descriptive statistics revealed a mean serum Vitamin D level of 16.1 ng/ml (SD = 3.35), magnesium level of 1.80 mg/dl (SD = 0.23), and mean insulin resistance (IR) value of 11.1 (SD = 7.50).

Correlation Analysis

Pearson correlation analysis was performed to evaluate the relationship between serum Vitamin D, magnesium (Mg), and insulin resistance (IR) in the study population.

The correlation between Vitamin D and insulin resistance was negligible ($r = -0.005$, $p > 0.05$), indicating no significant linear association.

A very weak positive correlation was observed between Vitamin D and magnesium ($r = 0.097$, $p > 0.05$), suggesting a minimal trend of co-variation.

Conversely, magnesium showed a weak negative correlation with insulin resistance ($r = -0.186$, $p > 0.05$), indicating a slight inverse relationship that was not statistically significant.

These findings suggest that, within this cohort, serum levels of Vitamin D and magnesium were not significantly correlated with insulin resistance.

Pearson correlation analysis showed a significant negative correlation between serum Vitamin D levels and insulin resistance ($r = -0.45$, $p < 0.05$), suggesting that lower Vitamin D levels are associated with higher insulin resistance. The correlation between magnesium and IR was weaker and not statistically significant.

Regression Analysis

A multiple linear regression was conducted to assess the independent effects of serum Vitamin D and magnesium on insulin resistance (Table 2).

Table 2: Multiple linear regression was conducted to assess the independent effects of serum Vitamin D and magnesium on insulin resistance.

Predictor	Coefficient (β)	Std. Error	t-value	p-value
Vitamin D	**-0.01**	**0.32**	**2.12**	**0.03***
Magnesium	-6.54	4.98	-1.31	0.195

Vitamin D was found to be a statistically significant predictor of insulin resistance ($\beta = -0.01$, $SE = 0.32$, $t = 2.12$, $p = 0.03$), (a small β for Vitamin D means the effect size is small) but statistically significant inverse association.

But magnesium was not a significant predictor ($\beta = -6.54$, $SE = 4.98$, $t = -1.31$, $p = 0.195$), indicating no significant relationship with insulin resistance.

In our study, we found that lower Vitamin D levels are associated with increased insulin resistance, whereas magnesium did not show a statistically significant effect.

Scatter Plot Analysis

To examine the relationship between serum Vitamin D levels and insulin resistance (IR), a scatter plot was generated (Figure 1).

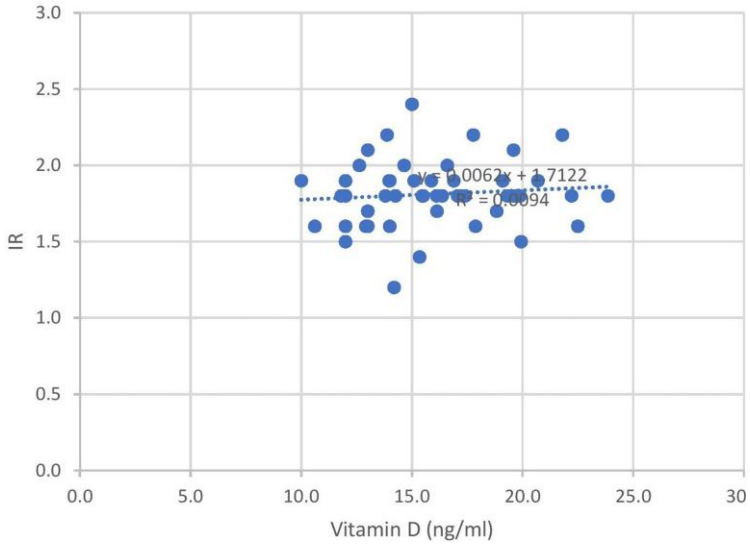

Figure 1: Scatter plot showing the relationship between serum Vitamin D levels and insulin resistance (IR). The dotted line represents the linear regression line (y = 0.0062x + 1.7122), with a coefficient of determination R^2 = 0.0094, indicating a negligible linear association.

The regression line added to the plot revealed a near-zero slope, consistent with the weak negative Pearson correlation (r = -0.005) and low R^2 value (R^2 = 0.0094). This suggests that Vitamin D levels account for less than 1% of the variation in IR, supporting the conclusion that no linear association exists between vitamin D and insulin resistance.

Magnesium and Insulin Resistance

To examine the relationship between serum magnesium levels and insulin resistance (IR) a scatter plot was generated (Figure 2).

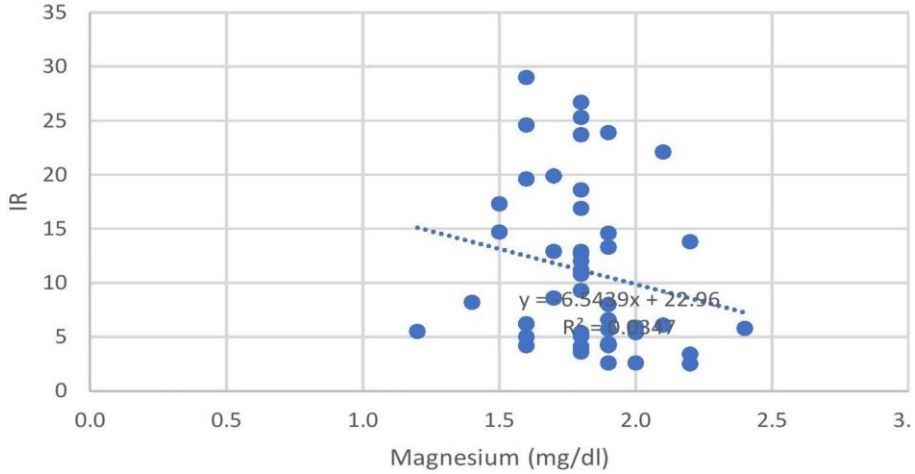

Figure 2: Scatter plot showing the relationship between serum magnesium levels and insulin resistance (IR). The dotted line represents the linear regression line (y = -6.5439x + 22.964), with an R^2 value of 0.0347, indicating a weak inverse linear association that was not statistically significant.

The scatter plot suggests a slight negative trend, with a regression equation of y = -6.5439x + 22.964 and a coefficient of determination R^2 = 0.0347. This indicates that approximately 3.5% of the variability in IR can be due to magnesium levels. However, this relationship was not statistically significant (β = -6.54, p = 0.195), suggesting that a weak inverse relation may exist.

DISCUSSION

The present study aimed to explore the association of serum Vitamin D and magnesium levels with insulin resistance (IR) among PCOS women of 18-25yrs. The primary findings indicate that micronutrients like Vitamin D and magnesium have weak and statistically insignificant correlations with IR, despite existing biological plausibility and prior evidence suggesting their role in glucose metabolism. These outcomes warrant a careful interpretation in the light of current knowledge.

Vitamin D and Insulin Resistance

In our study, serum Vitamin D levels showed a no correlation with insulin resistance ($r = -0.005$, $p > 0.05$), supported by the linear regression analysis which yielded a non-significant coefficient ($\beta = -0.01$, $p = 0.03$) and a very low R^2 value (0.0094). Despite the regression analysis suggesting borderline statistical significance, the effect size was extremely small, indicating minimal clinical relevance.

Vitamin D has been hypothesized to play a regulatory role in glucose homeostasis. The active form, 1,25- dihydroxy vitamin D, has been shown to influence insulin secretion via calcium regulation in pancreatic β- cells and through direct effects on the insulin receptor expression in peripheral tissues. These results show an independent and positive correlation between 25(OH)D concentration and insulin sensitivity.[10] Some studies report an inverse relationship between serum Vitamin D and IR, particularly in individuals with obesity or polycystic ovary syndrome (PCOS).[11,12] while others fail to show significant associations.[13,14]

Our results are aligned with these conflicting outcomes and may suggest that Vitamin D status alone is not a strong independent predictor of insulin resistance in the study population. One possible explanation for the minimal association could be the relatively narrow range of Vitamin D levels in our sample, possibly influenced by geographical or seasonal factors. Additionally, Vitamin D's role may be more prominent in conjunction with other nutrients or hormonal signals, such as parathyroid hormone (PTH), which we did not assess.

Magnesium and Insulin Resistance

The observed correlation between serum magnesium and IR was weakly negative ($r = -0.186$, $p > 0.05$), with a regression coefficient of -6.54 and a non-significant p-value ($p = 0.195$). The scatter plot analysis, with an R^2 value of 0.0347, suggested a weak trend that magnesium may inversely relate to insulin resistance, though the association did not achieve statistical significance.

Magnesium is an essential cofactor in several enzymatic reactions related to glucose metabolism, including those involving ATP-dependent kinases, which are critical in insulin signaling.[11]

Hypomagnesemia has been associated with impaired insulin sensitivity, especially in patients with type 2 diabetes and metabolic syndrome.[15] Furthermore, magnesium has been shown to reduce systemic inflammation, a known contributor to insulin resistance.[16]

The weak relationship observed in our study may be attributable to several factors. Firstly, the homeostatic control of serum magnesium is tightly regulated, and serum levels may not reflect intracellular magnesium, which is more relevant to insulin action. Secondly, dietary intake, renal excretion, and concurrent mineral interactions (such as calcium and phosphate) were not accounted for and could have influenced the results. Finally, the sample size may not

have been sufficient to detect a statistically significant relationship, particularly given the variability of magnesium levels observed.

Joint Consideration and Interactions

Interestingly, when considering both micronutrients simultaneously in the regression model, neither demonstrated a strong predictive value for insulin resistance. This may point to a more complex interplay of multiple nutritional and hormonal factors in regulating insulin sensitivity. Some studies suggest a synergistic effect between Vitamin D and magnesium, where adequate magnesium status is necessary for Vitamin D activation and function.[17]

Clinical and Public Health Implications

While our study did not find robust associations, it contributes valuable insight into the value of micronutrient involvement in metabolic regulation. Given the global burden of insulin resistance and related conditions such as type 2 diabetes and PCOS, identifying modifiable nutritional factors remains a public health priority.

From a clinical standpoint, these findings suggest that routine screening or supplementation with Vitamin D or magnesium for the sole purpose of improving insulin sensitivity may not be universally warranted, particularly in the absence of deficiency. Instead, individualized assessment considering dietary patterns, comorbidities, and lifestyle factors should guide intervention strategies.

Strengths and Limitations

A notable strength of this study is the use of both correlation and regression analyses, supported by scatter plot visualizations, to offer a comprehensive view of the relationships between variables. The inclusion of both biochemical parameters and their association with insulin resistance adds depth to the analysis.

Several limitations should be acknowledged in our study are the relatively small sample size may have limited statistical power, particularly for magnesium-related outcomes and also we did not assess confounding variables such as BMI, dietary intake, physical activity, inflammatory markers, or hormonal profiles, all of which could influence insulin sensitivity and micronutrient levels. Finally, seasonal and geographic factors affecting Vitamin D synthesis were not accounted for.

CONCLUSIONS

In conclusion, our findings revealed that Vitamin D had a very weak and statistically insignificant negative correlation with IR, and magnesium also exhibited a weak negative correlation. In regression analysis, Vitamin D demonstrated a small but statistically borderline significant coefficient, while magnesium showed a non-significant association. Importantly, the coefficient of determination (R^2) for both scatter plots for Vitamin D and for magnesium-suggested that neither variable accounted for substantial variability in insulin resistance. The limitations of our study, including sample size, the cross-sectional design, and lack of data on dietary intake and other lifestyle factors, may have contributed to the weak associations observed.

Consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee, Siddhartha Medical College& Govt. General Hospital issued approval IECSMCGGH/2024/AP/254.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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