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Research Article

The Correlation Between Serum Magnesium & Zinc with Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) In Patients with Metabolic Syndrome

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Abstract: Metabolic syndrome (MS) increases cardiovascular disease and death risk. Many studies have found a link between vascular inflammation and metabolic disorders. Discovering unique and specific blood-based indicators for vascular inflammation, particularly in metabolic syndrome related to obesity, such as (lipoprotein-associated phospholipase A2) and Lp-PLA2, could provide valuable assistance in identifying individuals at an elevated risk for cardiovascular incidents. Lp-PLA2 has been implicated in metabolic dysregulation, playing a crucial role in the onset of microvascular dysfunction and the exacerbation of oxidative stress. Lp-PLA2 is essential in the pathogenesis of atherosclerosis and may be used as a biomarker to predict future cardiovascular events. The study comprised 200 participants categorized into two groups: individuals diagnosed with MS (Metabolic Syndrome) (Test, n = 100) and those without MS (controls, n = 100). The serum activity levels of hs-CRP and Lp-PLA2 were measured and subsequently analysed for correlation with micronutrients (magnesium (Mg) and zinc (Zn)) and lipoprotein markers (Ox LDL, Apo-A1, and Apo-B). The study showed a significant correlation between Lp-PLA2 and the Mg level of patients with MS, whereas Hs-CRP did not exhibit a significant correlation. The test population did not exhibit a noteworthy elevation in oxidized LDL level, despite the presence of inflammatory changes as indicated by the level of Lp-PLA2. A significant correlation was observed between the Zn level in patients with MS and Lp-PLA2, whereas Ox LDL did not exhibit a significant correlation. The current study revealed a significant link between Mg and Zn and CVD risk in the Kerala population. The study found elevated levels of LpPLA2, an emerging biomarker for cardiovascular risk, in people with MS.

Keywords: Metabolic syndrome. Vascular inflammation, Oxidative stress, Lp-PLA2, Cardiovascular disease, Micronutrients.

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1. INTRODUCTION

Metabolic syndrome is linked to increased cardiovascular disease and risk of death[1]. A wealth of research has unveiled a biological interplay between microvascular dysfunction, oxidative stress, inflammation, and metabolic disorders, highlighting their interconnected roles in the pathophysiology of these conditions[2]. The detection of individuals at heightened risk for cardiovascular incidents could be enhanced by discovering novel and dependable blood-based indicators of vascular inflammation associated with obesity-induced metabolic syndromes, such as Lp-PLA2, which is a biomarker correlated with metabolic dysregulation and plays a vital role in microvascular dysfunction and oxidative stress[3]. This article will delve into the significance of Lp-PLA2 as a predictive biomarker for cardiovascular incidents among individuals linked with metabolic syndrome. Additionally, we explore the correlation between magnesium and zinc levels in patients suffering from metabolic syndrome. MS, a notable risk factor for both diabetes and heart disease, is associated with various complications, including obesity, elevated blood triglyceride, and LDL cholesterol levels, increased Apo lipoprotein B (Apo B), insulin resistance, hyperglycemia, and a rise in high-sensitivity C-reactive protein (hs-CRP). Traditionally, pinpointing individuals at high risk for cardiovascular disease (CVD) has been a formidable challenge. Yet, discovering novel and accurate blood-based markers of plaque inflammation, such as Lp-PLA2, linked to obesity-induced metabolic syndrome and diabetes, could potentially revolutionize this landscape[3]. New research suggests that Lp-PLA2 may be utilized as a biomarker for predicting cardiovascular events in the future, and it plays a crucial role in the genesis of atherosclerosis[5]. The Lp-PLA2 evaluation is integral to managing patients with type 2 diabetes who receive pharmacological medication and the more well-known cardiovascular risk factors. Lp-PLA2 is an inflammatory biomarker exclusive to the vascular system, making its measurement a potential asset for research into atherosclerosis within the context of metabolic syndrome and early identification of individuals at heightened risk for cardiovascular disease. The link between Lp-PLA2 and atherogenic risk holds notable importance, given that Lp-PLA2 is discharged by macrophages in atherosclerotic plaques and may indicate plaque instability[6]. Amidst episodes of arterial wall inflammation, the Lp-PLA2 protein is found in high concentrations within atherosclerotic plaques. There is a recognized association between elevated Lp-PLA2 levels and the rupture of atherosclerotic plaques, leading to the formation of blood clots. Such events may trigger cardiovascular incidents, further underscoring the clinical importance of Lp-PLA2 as a biomarker[7]. Current guidelines endorse the treatment of low-density lipoprotein cholesterol (LDL-C) as a fundamental approach to managing dyslipidemia and preventing CVD. These guidelines also encourage the assessment of vascular inflammation markers for accurate risk stratification. Women and younger people, as well as those at a higher risk for complications from diabetes, familial hypercholesterolemia, and dyslipidemia, are urged to take this advice to heart. Magnesium is acknowledged for its contribution to the cardiomyocytes' intrinsic redox homeostasis and electrical stability[8]. Given the links between hypomagnesemia and arrhythmias of the heart's atrium and ventricle, low serum magnesium levels may also be a risk factor for sudden cardiac death (SCD)[9]. Vital to cardiovascular health, magnesium also has many other beneficial effects. It plays a crucial part in the body's antioxidative pathways, is needed for the regular maintenance of cellular membrane potential, and is essential for the efficient operation of the mitochondria. Zinc (Zn), a fundamental component of cell-to-cell signaling, is one of the most prevalent trace elements in the human body. It is crucial in promoting normal development, thereby underscoring its importance in maintaining overall health and wellbeing[10]. Zinc, a vital micronutrient, helps regulate chronic inflammation by hindering the production of inflammatory cytokines. Besides its significant role in curbing oxidative stress through the production of antioxidant enzymes, zinc also acts as a catalyst for various enzymes, playing an integral part in lipid, carbohydrate, and protein metabolism. Its multifaceted functions thereby contribute significantly to cellular and physiological homeostasis[11]. Zinc generates, stores, and releases insulin, suggesting its critical influence on the pathophysiology of type 2 diabetes, atherosclerosis, and multiple sclerosis. Various studies have highlighted its significant impact on the development of metabolic syndrome through its regulatory effects on cytokine production, reduction of inflammation, and activation of antioxidant enzymes, which scavenge reactive oxygen species to mitigate oxidative stress. Furthermore, zinc modulates insulin expression and significantly influences its role in the metabolism of lipids and glucose, further solidifying its indispensable position in metabolic health[12]. Numerous studies have demonstrated the potential benefits of zinc supplementation, including lowering blood pressure, reducing hyperglycemia, and decreasing LDL cholesterol levels. These findings highlight the therapeutic potential of zinc in managing and mitigating the risks associated with metabolic and cardiovascular diseases[13]. Enhancing our understanding of zinc's physiological properties could significantly improve the management of metabolic syndrome, potentially preventing severe health events such as strokes and angina pectoris and, ultimately, reducing mortality risk. Hence, further exploration into zinc's multifaceted role in metabolic health remains essential to advancing our preventive and therapeutic strategies[14]. This study's primary objective was to investigate and identify potential associations between Mg and Zn levels, Lp-PLA2 levels (an emerging biomarker for cardiovascular risk), and the risk of cardiovascular disease in the Kerala population. Specifically, we aimed to examine the association between these factors and MS and the potential CVD risk implications.

2. MATERIALS AND METHODS

2.1. *Subjects*

A case-control study was done at M.E.S Medical College in Kerala, an academic medical center for people needing the highest level of care. The research was already approved by the institution's ethics and scientific committees. All of the individuals who participated in this study gave their written permission. The test group (n=100) comprised individuals with MS, as defined by the Adult Treatment Panel III (ATP III) guidelines. The control population (n=100) included healthy people of the same age and gender who attended the medical camp.

2.2. *Ethical Committee Approval*

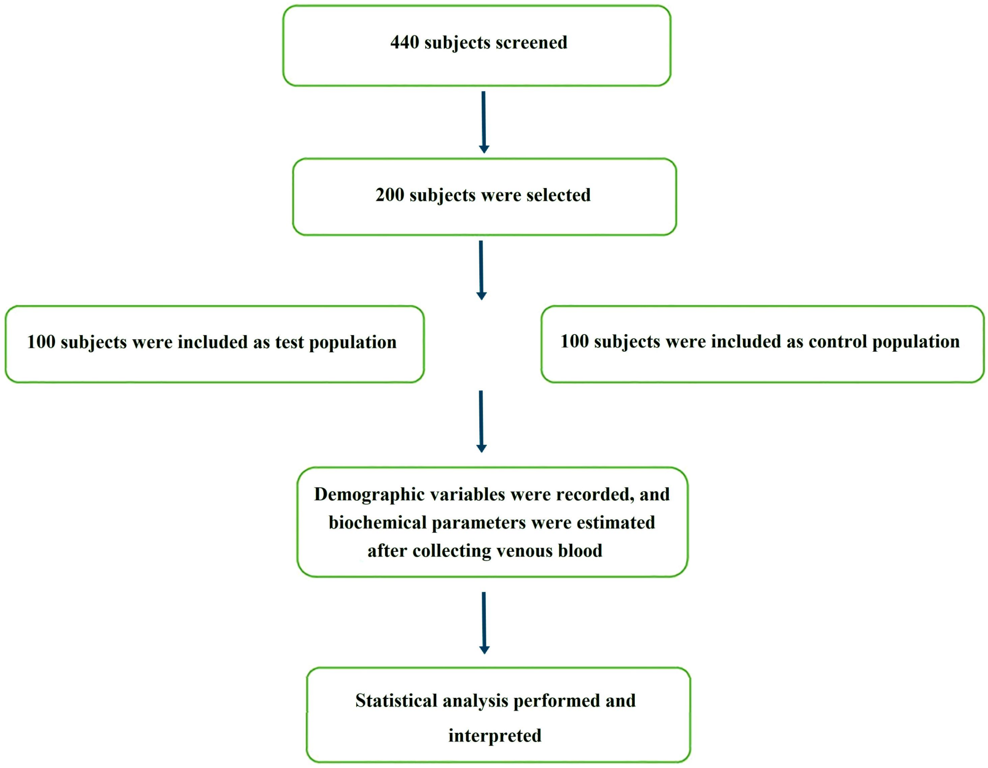
The protocol was approved by the Ethical Review Committee of MES Medical College on 10th October 2019, with IEC No. IEC/MES/09/2019).

2.3. *Inclusion criteria*

The population of interest comprises individuals above 18 who demonstrate central obesity, ascertained by a waist circumference of 90 cm or greater for males and 80 cm or more significant for females, with a specific focus on the Indian demographic. Furthermore, these patients must exhibit a minimum of two among the following four factors: Individuals exhibiting elevated levels of triglycerides (TG) at or above 150 mg/dl, or those undergoing targeted treatment for this particular lipid abnormality, as well as those with diminished levels of high-density lipoprotein (HDL) cholesterol below 40 mg/dl, or those receiving specific treatment for this lipid abnormality, are considered to be at risk. Additionally, individuals with elevated blood pressure, indicated by a systolic reading of 130 or higher and diastolic reading of 85 or higher, or those receiving treatment for previously diagnosed hypertension, as well as those with elevated fasting plasma glucose (FPG) levels of 100 mg/dl or higher, or those previously diagnosed with type 2 diabetes, are also considered to be at risk.

2.4. *Exclusion criteria*

The study excluded patients who presented with hypothyroidism, malignant neoplasms, severe renal insufficiency, acute and chronic hepatic disorders, or chronic alcoholism. Furthermore, the study excluded patients prescribed specific medications, including antiepileptics, oral contraceptive agents, trimethoprim, sulphamethoxazole, erythromycin, or cimetidine. It is presumed that these conditions and medications were identified as potential factors that could compromise the study's validity or jeopardize the well-being of the participants.



Flow chart of the study

2.5. *Biochemical measurements*

Following venepuncture, 5 mL of blood was collected; serum was separated according to standard protocol. The biochemical parameters LpPLA2, hs-CRP, Apo-A1, Apo-B, Mg, and Zn were analyzed spectrophotometrically using a fully automated analyzer. The concentration of ApoA1 in serum was determined utilizing a liquid phase immunoprecipitation assay employing a nephelometric endpoint method[15]. The concentration of Apo B in serum was determined using a liquid phase immuno-precipitation assay with a nephelometric endpoint method[15]. High-sensitivity C-reactive protein was detected through a solid phase, sandwich immuno-metric assay[16]. The present study describes the utilization of a diagnostic reagent for the quantitative determination of LpPLA2 in serum and plasma samples. The assay was performed on photometric systems using 1-myristoyl-2-(4-nitrophenyl succinyl)-sn-glycero-3-phosphocholine as the substrate[17]. Mg and Zn were analyzed spectrophotometrically using a fully automated analyzer[18,19].

2.6. *Statistical analysis*

The authors used various appropriate statistical tools to analyze the parameters. Descriptive statistics were used to analyze demographic data such as age, gender, height, body weight, and blood pressure. The Pearson correlation test examined the relationship between micronutrients and cardiovascular risk markers. The study used Pearson correlation coefficients to assess the correlation between micronutrients and other continuous parameters. The variables LpPLA2 and hs-CRP were subjected to a logarithmic transformation to conduct statistical analyses. Multiple linear regression analyses were performed to identify potential predictors for CVD, incorporating major risk factors. A t-test was utilized to compare the parameters among groups of subjects with and without metabolic syndrome. The statistical analyses were conducted using SPSS 13.0. In statistical analysis, P values are typically two-tailed and are deemed statistically significant if they are less than .05.

3. RESULTS

Table 1 presents a comparative evaluation of specific health metrics, namely Age, Weight, Height, Waist size, and BMI, between a test group and a control group. While there was no notable disparity in Age and Height among the two cohorts, significant variations existed in Weight, Waist circumference, and BMI. The experimental cohort exhibited a statistically significant increase in mean Weight, Waist circumference, and BMI relative to the control group, as evidenced by a p-value below 0.001 for these parameters.

Table 1: Characteristics of the subjects

	Group	Minimum	Maximum	Mean	Std. Deviation	Mean difference	P-value (t-test)
Age	Test	35	60	45.69	4.925	-0.39	0.781
	Control	19	76	46.08	13.135		
W(Kg)	Test	40	93	67.68	12.002	8.24	0.000
	Control	42	85	59.44	8.129		
H(M)	Test	1.50	1.83	1.60	.05631	0.017	0.142
	Control	1.40	1.90	1.59	.10371		
Waist	Test	16.33	41.33	34.5	3.2289	3.50	0.000
	Control	28.0	35.0	31.0	1.7609		
BMI	Test	27.0	43.0	26.28	4.75375	2.432	0.000
	Control	15.00	42.15	23.85	4.53009		

Measurements are expressed as mean ± S.D.

- ***AGE: The age of the subjects***
- ***W(Kg): Weight of the subjects in kilograms***
- ***H (m): Height of the subjects in meters***
- ***WAIST: Waist circumference of the subjects***
- ***BMI: Body Mass Index of the subjects***

The table presents the characteristics of the subjects in two groups: the "Test" group and the "Control" group. The minimum and maximum values, mean, standard deviation, mean difference, and p-value (from the t-test) are provided for each characteristic. Table 2 demonstrates that the test group exhibited notably elevated levels of LpPLA2, APO B, and Hs-CRP; LpPLA2 is measured in nanograms per milliliter (ng/mL), APO A1 and APO B are measured in grams per liter (g/L), Hs-CRP is measured in milligrams per liter (mg/L), Mg is measured in milligrams per deciliter (mg/dL). Zn is measured in micrograms per deciliter (µg/dL). While concurrently displaying significantly reduced levels of APO A1 and Zinc compared to the control group. The corresponding p-values support this. The study findings indicate no statistically significant variation in the Magnesium levels among the groups.

Table 2: Biochemical Characteristics

	Group	Minimum	Maximum	Mean	Std. Deviation	Mean difference	P-value (t-test)
LpPLA2 (ng/mL)	Test	499	689	597.25	43.168	238.67	0.000
	Control	154	532	358.58	91.890		
APO A1 (g/L)	Test	0.50	2.50	1.252	0.3498	-0.209	0.000
	Control	0.43	1.99	1.461	0.1705		
APO B (g/L)	Test	0.97	2.58	1.578	0.2217	0.347	0.000
	Control	0.88	1.62	1.231	0.1337		
Hs-CRP (mg/L)	Test	0.227	4.430	2.0168	0.9361	1.3647	0.000
	Control	0.121	2.150	0.6521	0.4105		
Mg (mg/dl)	Test	1.5	2.2	1.820	.1595	-.0130	0.549
	Control	1.5	2.2	1.833	.1464		
Zn (µ g/dl)	Test	54	99	74.39	12.462	-5.600	0.001
	Control	54	99	79.99	10.854		

Measurements are expressed as mean ± S.D.

Table 3 and Figure 1 account for the correlation between Magnesium Status and emerging markers in patients with Metabolic Syndrome and individuals without the condition. The Mg level of MS patients was found to correlate significantly with Lp-PLA2, whereas Hs-CRP does not show a significant correlation. No significant increase in oxidized LDL level was found in the test population, even though inflammatory changes were noted as per the level of Lp-PLA2.

Table 3: Correlation of Magnesium Status with emerging markers in Metabolic syndrome patients and normal controls

Group			TEST	CONTROL
Magnesium	$Lp\text{-}PLA_2$	Pearson Correlation	0.212*	-0.141*
		Sig. (2-tailed)	0.049	0.162
	APO AI	Pearson Correlation	-0.187	0.089
		Sig. (2-tailed)	0.063	0.383
	APO B	Pearson Correlation	0.106	0.072
		Sig. (2-tailed)	0.293	0.475
	Hs-CRP	Pearson Correlation	0.046	0.038
		Sig. (2-tailed)	0.647	0.707
	Ox LDL	Pearson Correlation	-0.071	0.030
		Sig. (2-tailed)	0.483	00.766

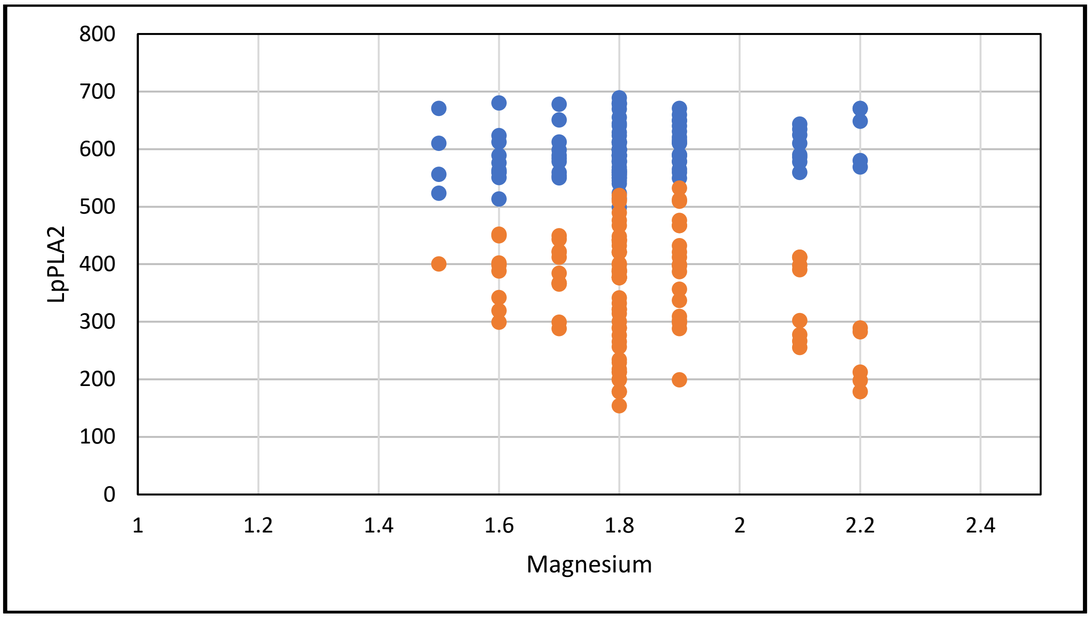


Fig 1: Correlation between Magnesium and LpPLA2 in test and control

Table 4 and Figure 2 indicate the correlation between Zinc status and emerging markers in patients with Metabolic syndrome and individuals without the condition. The Zn level in MS patients was significantly correlated with Lp-PLA2, whereas Ox LDL did not show a significant correlation. Even though Lp-PLA2 levels indicated inflammatory changes, no significant increase in APO A1 and APO B levels was found in the test population.

Table 4: Correlation of Zinc status with emerging markers in Metabolic syndrome Patients and normal controls

Group			TEST	CONTROL
Zinc	LpPLA2	Pearman Correlation (PC)	0.194	-0.364**
		Sig. (2-tailed)	0.053	0.000
	APO AI	PC	-0.098	-0.110
		Sig. (2-tailed)	0.333	0.276
	APO B	PC	0.021	0.070
		Sig. (2-tailed)	0.838	0.489
	hs-CRP	PC	-0.040	0.150
		Sig. (2-tailed)	0.693	0.136
	Ox LDL	PC	0.122	0.078
		Sig. (2-tailed)	0.227	0.441

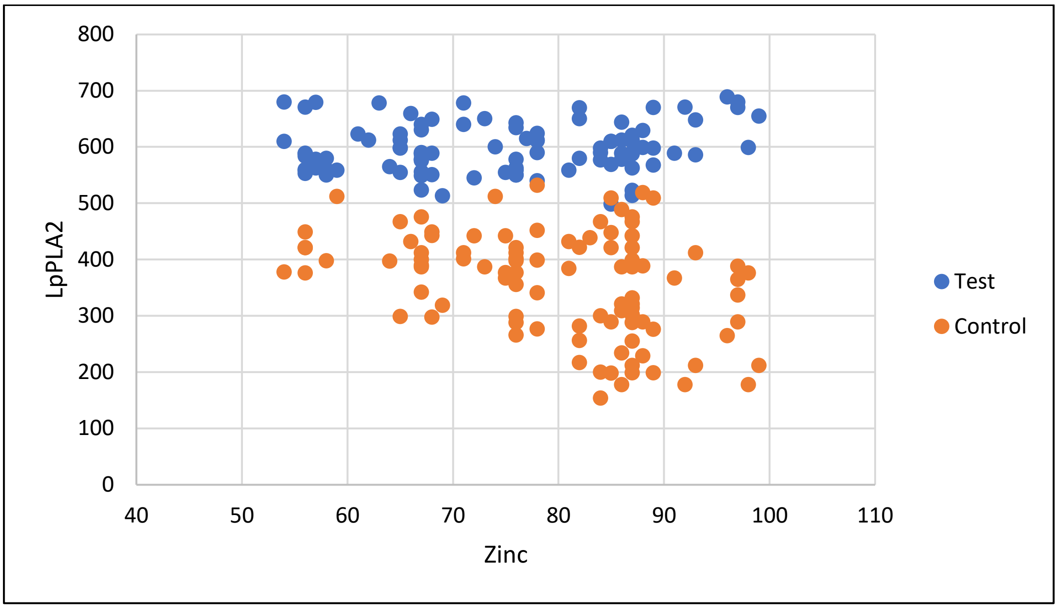


Fig 2: Correlation between Zinc and LpPLA2 in test and control

The Pearson correlation test was used to assess the relationship between micronutrients and markers of cardiovascular risk. Mg demonstrated a strong correlation with Lp-PLA2. These findings suggest that individuals with magnesium deficiency may have an increased risk of cardiovascular disease. In addition, a significant correlation was observed between Zn levels and Lp-PLA2. There was no correlation between micronutrient status and cardiac markers such as apo A1, apo B, hs-CRP, and ox LDL. As a result, micronutrient deficiency may result in vascular calcification, increasing the risk of cardiometabolic diseases.

3. DISCUSSION

Magnesium is a mineral that is very important to the body. It is found naturally in many foods and sold as a supplement. It helps with more than 300 enzyme reactions, including those that control blood pressure, glucose levels, and lipid peroxidation[20]. So, it is also vital for the heart and blood vessels. Mg is known to be essential for various physiological processes and has been proposed to confer a safeguarding influence against MS[21]. The involvement of this particular factor in glucose metabolism and insulin homeostasis implies its potential to mitigate insulin resistance, which is a pivotal feature of metabolic syndrome[22]. Additionally, it influences blood pressure control and has been linked to a decrease in systemic inflammation[23]. Furthermore, certain research studies propose that there exists an inverse association between magnesium consumption and the likelihood of acquiring metabolic syndrome, thereby implying the potential involvement of magnesium in enhancing lipid profiles[24]. Nevertheless, additional investigation is required to comprehend and validate these associations comprehensively. Zinc has been identified as a potential protective agent against MS via multiple mechanisms. It plays a crucial role in insulin synthesis, storage, and action, potentially augmenting insulin sensitivity and counteracting insulin resistance[25]. Additionally, it exhibits antioxidant characteristics that aid in mitigating oxidative stress, a pivotal factor in advancing metabolic syndrome. The anti-inflammatory properties of zinc can mitigate the chronic inflammation frequently associated with metabolic syndrome[26]. The potential impact of this intervention on lipid metabolism could lead to favorable alterations in lipid profiles, which are crucial for the effective management of MS[27]. Notwithstanding their potential, the protective functions of zinc necessitate additional investigation through extensive studies. Zinc protects against MS by reducing proinflammatory cytokine expression, thus curbing the generation of reactive oxygen species (ROS) and guarding against oxidative stress damage[28]. Its involvement in ROS neutralization, as well as glucose and lipid metabolism, underscores its significance. Given the crucial role of zinc in the pathophysiology of metabolic syndrome, supplementation with zinc may contribute to the regression of this condition[29]. However, further investigation into its relationship with inflammatory markers is warranted better to comprehend zinc's role in health and disease. With a deeper understanding, modifying zinc status could be a therapeutic target for preventing and treating metabolic diseases[30]. Even though magnesium is essential for adequately functioning the heart, people in Kerala often do not get enough magnesium from their food[31]. It is the same pattern seen in other states in India. The current study's outcome revealed a significant relationship between Mg and Zn and risk for CVD in the Kerala population. The notion that hs - CRP, a highly responsive indicator of mild inflammation, is a prognosticator for the prospective onset of atherosclerotic cardiovascular disease has gained broad acceptance [32]. The metabolic syndrome or its components are supported by CRP function in epidemiological and experimental studies. Nevertheless, the lack of specificity of its up-regulation is attributed to its dependence on the preceding proinflammatory events occurring upstream [33]. The study demonstrates that individuals with MS exhibit notably elevated levels of Lp-PLA2 compared to those without the syndrome. Several studies have indicated that individuals with metabolic syndrome exhibit elevated Lp-PLA2 activity compared to those who do not have the condition[34]. Furthermore, the degree of metabolic risk burden can be inferred from the level of Lp-PLA2. A growing body of evidence suggests a correlation between elevated levels of Lp-PLA2 and an augmented susceptibility to cardiovascular events[35]. The analysis demonstrated that elevated levels of LpPLA2, an emerging biomarker for cardiovascular risk, were seen in MS. The study's results indicate that Lp-PLA2, a marker specific to the vascular system, may be responsible for the combined effects of the various components of the metabolic syndrome. Additionally, the study found that Lp-PLA2's impact was not influenced by traditional risk factors such as hs - CRP. These findings suggest that Lp-PLA2 may initiate inflammation pathways that ultimately lead to insulin resistance and the development of MS. However, these biomarkers seem to possess supplementary significance in forecasting cardiovascular risk, underscoring the necessity for enhanced comprehension of inflammatory pathophysiology. A prospective follow-study needs to be conducted to establish the incidence of this relationship. The primary drawback of our research was its cross-sectional design, which prevented us from determining the causal nature of the link. Further investigation into whether micronutrients such as Mg and Zn may play a role in preventing CVD needs to be established with a randomized controlled trial.

4. CONCLUSION

The findings of this study highlights the significance of the outcomes regarding the relationship between magnesium (Mg) and zinc (Zn) levels and the risk for cardiovascular disease (CVD) in the Kerala population. Despite the essential role of magnesium in heart function, the study revealed that individuals in Kerala, as well as in other states in India, often do not obtain sufficient magnesium from their diets. The analysis further demonstrated a significant association between elevated levels of LpPLA2, an emerging biomarker for cardiovascular risk, and metabolic syndrome (MS). However, it is important to note that this research had certain limitations, primarily its cross-sectional design, which prevented establishing a causal relationship between micronutrients and CVD risk. Therefore, a prospective follow-up study should be conducted to determine the incidence and causality of this relationship. A randomized controlled trial is warranted to investigate further the potential role of micronutrients such as magnesium and zinc in preventing CVD. It would provide more robust evidence regarding the preventive effects of these micronutrients and potentially guide interventions aimed at reducing cardiovascular risk in the population.

5. AUTHORS CONTRIBUTION STATEMENT

Khaleel Ahmed Manik conceived the whole project, including sample collection and analysis at the Department of Physiology, MES Medical College, and authored the paper. Sheela Joice wrote part of the manuscript. All authors have read and approved the final manuscript version.

6. CONFLICT OF INTEREST

Conflict of interest declared none.

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