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Correlation of micronutrient status with atherogenic index and oxidative stress markers in metabolic syndrome

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ABSTRACT: The prognostication of cardiovascular events in people with metabolic syndrome (MetS) is paramount due to their heightened risk profile. MetS is typified by a cluster of medical conditions such as raised blood pressure, hyperglycemia, central adiposity, and anomalous levels of cholesterol or triglycerides, which collectively increase the likelihood of developing cardiovascular disease. Anticipating cardiovascular events in these individuals enables enhanced prevention approaches, more efficient management, and better patient results. The present investigation involved an examination of the correlation between a range of biomarkers, namely Lp-PLA2, Apo A1, Apo B, hs-CRP, OxLDL, MDA, and Vitamin C, and the atherogenic index in a population afflicted with MetS. The results indicated no statistically significant association between the markers mentioned above and the atherogenic index within the sample population. This suggests that these markers may not possess sufficient predictive value for cardiovascular events in this demographic. Nevertheless, it was noted that although there was no discernible correlation with the atherogenic index, the MetS cohort exhibited increased serum concentrations of Lp-PLA2, OxLDL, and MDA. The markers mentioned above are widely recognized as reliable indicators of inflammation and oxidative stress, two crucial processes in the development of atherosclerosis and subsequent cardiovascular events. As a result, the increased prevalence of MetS may indicate heightened susceptibility to cardiovascular

disease, underscoring the importance of implementing a comprehensive approach to managing cardiovascular risk in affected individuals. In summary, although the markers analyzed in this investigation may not directly associate with the atherogenic index, their increased concentrations warrant prudence and emphasize the significance of vigilant management of cardiovascular risk in individuals diagnosed with MetS. Accurately forecasting cardiovascular events remains a multifaceted obstacle that necessitates the examination of numerous variables and persistent scholarly endeavors.

KEYWORDS: Metabolic syndrome. Vascular inflammation, Oxidative stress, Lp-PLA2, Coronary heart disease, Cardiovascular disease, Micronutrients, Magnesium, Zinc

1. INTRODUCTION

Metabolic syndrome represents a collection of health issues that, when occurring together, heighten the likelihood of cardiovascular disease and type 2 diabetes. These conditions encompass central obesity, insulin resistance, abnormal cholesterol or triglyceride levels, and high blood pressure [1]. The escalation of MetS in India has risen in recent decades, primarily attributed to swift urbanization, alterations in dietary habits, and sedentary habits. The phenomenon's estimated prevalence exhibits regional and population-based variations, ranging from 20-30% in urban areas and 10-20% in rural areas [2]. Nevertheless, specific investigations have documented elevated incidence levels in particular demographics or geographical regions. The heterogeneity in the prevalence rates of MetS can be ascribed to the utilization of distinct diagnostic criteria alongside variations in lifestyle factors, genetic predisposition, and environmental factors across diverse Indian populations [3].

The phenomenon of swift urbanization has resulted in a notable alteration in eating habits, characterized by heightened intake of processed and high-energy foods and decreased physical activity levels. This trend has been identified as a contributing factor to the development of obesity, insulin resistance, and other risk factors associated with MetS [4]. Adopting diets high in refined carbohydrates, unhealthy fats, and sugars has replaced traditional Indian diets, potentially resulting in obesity and other components of MetS.

Additionally, it has been suggested that individuals of Indian descent may exhibit increased genetic susceptibility to insulin resistance, central adiposity, and dyslipidemia, all of which are fundamental features of MetS. The escalating incidence of MetS in India is an important matter of public health apprehension, given its correlation with an augmented susceptibility to type 2 diabetes, cardiovascular ailments, and other associated complications [5]. It is imperative to mitigate the risk factors associated with MetS by implementing lifestyle modifications such as adhering to a nutritious diet, engaging in consistent physical activity, and sustaining a healthy body mass index. This approach is pivotal in preventing the onset of MetS and alleviating its strain on the healthcare system.

The relationship between micronutrient status, atherogenic index (AI), and oxidative stress markers in MetS patients has been the research subject in recent years. Micronutrients are essential vitamins and minerals crucial in numerous metabolic processes and have

antioxidant properties [6]. Several micronutrients, such as vitamins A, C, E, and D, and minerals like zinc, selenium, and copper, have been studied for their potential role in MetS. The atherogenic index is a marker used to estimate the risk of atherosclerosis, a condition characterized by plaque buildup in the arteries, leading to cardiovascular diseases [7]. AI is calculated as the ratio of non-HDL cholesterol to HDL cholesterol. Higher AI indicates a greater risk of atherosclerosis. Markers of oxidative stress are compounds that emerge in response to an imbalance where the production of reactive oxygen species (ROS) surpasses the body's detoxifying capacity or its ability to counteract the resultant biochemical disruption. This disproportion not only leads to oxidative harm to essential biological molecules such as lipids, proteins, and DNA but is also implicated in a spectrum of health disorders, one of which is MetS. The perturbation caused by this oxidative stress underscores its role as a crucial component in the pathogenesis and progression of MetS.

Numerous research initiatives have identified significant relationships between micronutrient levels, the atherogenic index, and oxidative stress markers in individuals suffering from Mets. These studies highlight a concerning trend: patients with MetS often exhibit diminished concentrations of crucial antioxidants, including vitamins A, C, and E, compared to their healthier counterparts. This deficiency in essential vitamins can precipitate heightened oxidative stress, thereby fostering the development of atherosclerosis and additional MetS-related complications. Furthermore, inadequacies in specific minerals, such as zinc and selenium, are associated with an escalated susceptibility to MetS [8]. These trace elements are integral to the human body's antioxidant mechanisms and help modulate inflammatory responses, which are fundamental in thwarting atherosclerosis and sustaining metabolic equilibrium. In the same context, several scholarly inquiries suggest a correlation between a deficit in vitamin D and an increased propensity for MetS and associated cardiovascular conditions [9]. Vitamin D is hypothesized to influence various metabolic pathways, including insulin sensitivity, blood pressure regulation, and inflammation control. These functions are pivotal in preserving cardiovascular integrity, underscoring the importance of adequate vitamin D levels in metabolic and heart health. Thus, maintaining balanced levels of these micronutrients is beneficial and essential in a strategic approach to mitigating the risks and complications interconnected with MetS and cardiovascular anomalies.

The status of micronutrients significantly correlates with the atherogenic index and oxidative stress markers among individuals grappling with MetS. Ensuring an optimal micronutrient intake, achievable through a well-rounded diet and judicious use of supplements, could pave the way for enhanced metabolic health. This strategic approach is particularly pertinent in mitigating risks tied to MetS, including atherosclerosis and other cardiovascular conditions. However, despite these correlations, the medical and scientific communities must pursue more extensive research to unravel the precise biochemical and physiological mechanisms that define these relationships. Understanding these underlying processes is paramount in crafting targeted and effective intervention strategies.

Furthermore, managing micronutrient deficiencies in MetS patients is not a one-size-fits-all remedy. It necessitates a more granular approach, considering individual patient profiles, to determine the most beneficial therapeutic protocols. Future investigations should focus on establishing these nuanced strategies, underpinned by robust empirical evidence, to enhance

the management of MetS and reduce the incidence of its potentially life-threatening complications. By fortifying the body's internal defense mechanisms through micronutrient optimization, there is a promising potential to improve overall patient outcomes in metabolic health.

2. MATERIALS AND METHODS

This cross-sectional study, featuring a comparative design, was conducted among patients undergoing treatment for MetS at the diabetic clinic of MES Medical College and Hospital, located in Malappuram, Kerala. The participants, all between the ages of 25 and 75, were selected based on their willingness to engage in the study and the absence of critical medical conditions that could confound the study's outcomes. These conditions included liver disease, kidney disease, various endocrine disorders, and cancer. To ensure a balanced and equitable analysis, participants were matched with controls based on age and gender. Upon preliminary investigations, these control individuals, aged 25 to 75, exhibited no clinical signs of significant health issues. The research parameters included demographic details, foundational lipid profile numbers, and various biochemical markers, all meticulously collected and documented for further analysis.

Ethical considerations were paramount; relevant institutional ethics and scientific committees vetted and approved the study design and methodology to ensure adherence to established ethical research standards. In alignment with these standards, every participant contributed informed written consent before their inclusion. The study sample comprised 100 participants, each clinically diagnosed with MetS based on the criteria set forth by the Adult Treatment Panel III (ATP III) guidelines. Complementing this group was a control cohort, also numbering 100 individuals, who were equivalently matched for age and gender with the MetS patients. These control participants were deemed healthy based on initial health screenings conducted during their attendance at a medical camp. This rigorous selection and pairing process ensured a robust comparative foundation, allowing for more reliable and nuanced insights into the MetS condition. The examined blood parameters included glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), lipoprotein-associated phospholipase A2 (LpPLA2), high-sensitivity C-reactive protein (hs-CRP), apolipoprotein A1 (Apo-A1) and apolipoprotein B (Apo-B). Glucose, TC, TG, HDL, and LDL were estimated using enzymatic endpoint methods and automated analyzers with the cholesterol oxidase-peroxidase reaction. Apo-A1 and Apo-B were assessed via liquid-phase immunoprecipitation assays with nephelometric endpoints. LpPLA2 determination used diagnostic reagents with a photometric system. Malondialdehyde (MDA) was estimated using an ELISA based on the MDA-thiobarbituric acid reaction. Autoantibodies against oxidized LDL were quantified using an enzyme immunoassay.

3. STATISTICAL ANALYSIS

The investigator employed a range of suitable statistical methodologies to examine the parameters. The demographic data, including age, gender, height, body weight, and blood pressure, were analyzed using descriptive statistics. The study utilized the Pearson correlation test to investigate the association between micronutrients and AI and oxidative markers. The statistical analysis was conducted using version 28.0 of the SPSS software.

4. RESULT AND DISCUSSION

Age of the participants ranged from 19 to 76 years. The mean age was similar in the test and control groups, [45.7 (SD=4.9) v/s 46.1 (SD=13.1) years, p=0.781]. Weight, Waist circumference, and BMI were significantly higher among patients with metabolic syndrome.

Figure 1: Age distribution of test and control groups

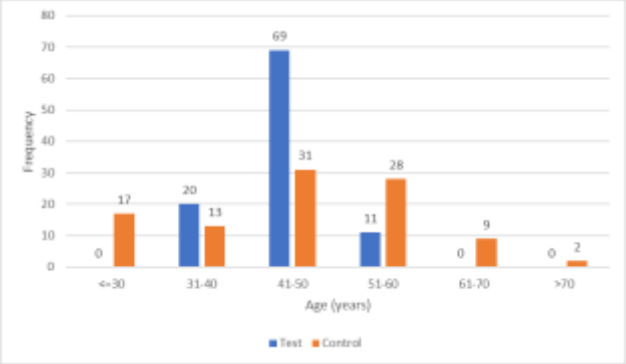

Table 1 demonstrates the differences between the Test and Control groups in the MDA and vitamin C levels. The p-values for both MDA and vitamin C indicate statistically significant differences between the two groups. The Test group has higher MDA and lower vitamin C levels than the Control group. A comparison of Oxidative Stress Markers among test and control groups is given in Figure 2.

Table 1: Oxidative Stress Markers in Metabolic Syndrome Patients and Normal Controls

	Group	Minimum	Maximum	Mean	Std. Deviation	Mean difference	P-value (t-test)
MDA	Test	0.80	2.40	1.554	0.418	0.856	0.000
	Control	0.38	1.10	0.698	0.198		
Vitamin C (mg/dl)	Test	0.2	1.3	0.822	0.274	-0.290	0.000
	Control	0.3	1.9	1.112	0.404		

Figure 2: Comparison of Oxidative Stress Markers among test and control groups

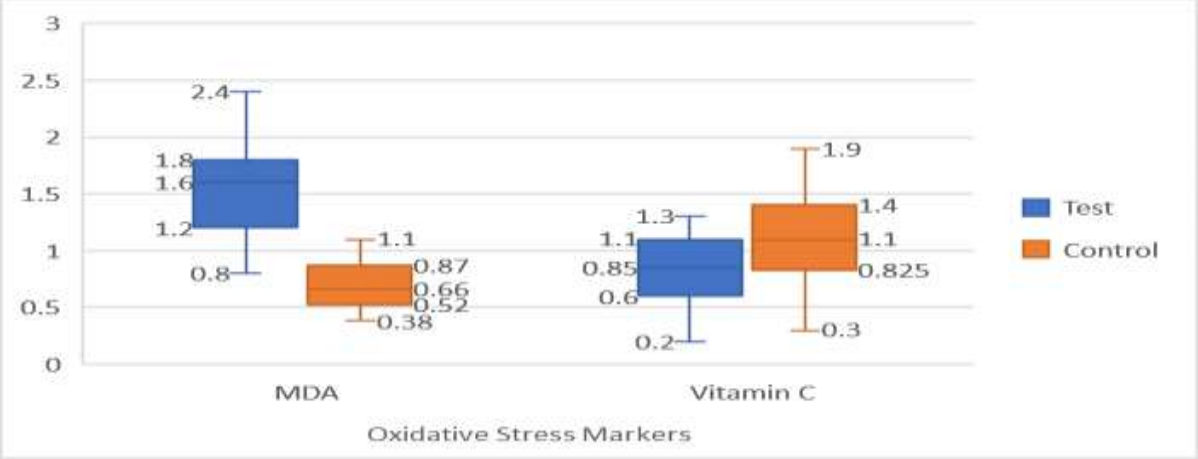

Table 2 compares various blood parameters between the test and control groups. The test group has a significantly lower mean for APO A1 (1.252) than the control group (1.461), with a mean difference of -0.209 and a p-value of 0.000. The test group has a higher mean APO B level (1,578) than the control group (1,231), with a mean difference of 0.347 and a p-value of 0.000. In addition, the test group's Hs-CRP level (2,0168) is greater than the control group's (0,6521), with a mean difference of 1,3647 and a p-value of 0.000. Ox LDL is higher in the test group (85.15), with a mean difference of 26.4 and a p-value of 0.000. The test group has a higher LpPLA2 level than the control group, with a mean difference of 208.5 and a p-value of 0.000. The p-value of 0.000 indicates statistically significant differences between the test and control groups.

Table 2: Emerging markers of metabolic syndrome

	Group	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**	**Mean difference**	**P-value (t-test)**
APO A1	Test	0.50	2.50	1.252	0.3498	-0.209	0.000
	Control	0.43	1.99	1.461	0.1705		
APO B	Test	0.97	2.58	1.578	0.2217	0.347	0.000
	Control	0.88	1.62	1.231	0.1337		
Hs-CRP	Test	0.227	4.430	2.0168	0.9361	1.3647	0.000
	Control	0.121	2.150	0.6521	0.4105		
Ox LDL	Test	51	102	85.15	10.892	26.4	0.000
	Control	36	86	58.77	12.479		
LpPLA2	Test	499	689	589.50	60.97	208.5	0.000
	Control	154	532	381.00	132.0		

The Pearson correlation coefficients and p-values for the relationship between the atherogenic index of plasma and various biomarkers (LpPLA2, Apo A1, Apo B, hs-CRP, and Ox LDL) in a test group with metabolic syndrome are presented in Table 3. All p-values are more significant than 0.05, the commonly used threshold for statistical significance, indicating that none of the correlations are statistically significant. The Pearson correlation coefficients range between -0.100 (hs-CRP) and 0.088 (Ox LDL), respectively, indicating weak negative and positive correlations. Given the high p-values, however, these correlations lack statistical significance. Consequently, the data suggest no significant linear correlation between the atherogenic index of plasma and these biomarkers in the metabolic syndrome test group.

Table 3: Correlation of LpPLA2, Apo B, Apo A1, hs-CRP, and OxLDL with atherogenic index in Metabolic syndrome

Group			Atherogenic index of plasma
Test	LpPLA2	Pearson Correlation	-0.027
		Sig. (2-tailed)	0.789

	APO A1	Pearson Correlation	0.001
		Sig. (2-tailed)	0.994
	APO B	Pearson Correlation	0.033
		Sig. (2-tailed)	0.741
	Hs-CRP	Pearson Correlation	-0.100
		Sig. (2-tailed)	0.324
	Ox LDL	Pearson Correlation	0.088
		Sig. (2-tailed)	0.385

Correlation between conventional & and emerging cardiac markers and oxidative markers was carried out; for MDA, there is a significant negative correlation with HDL in the test group ($r = -0.206$, $p = 0.039$). The control group shows a significant positive correlation between MDA, TC ($r = 0.220$, $p = 0.028$), and LDL ($r = 0.226$, $p = 0.024$). For MDA, there are no significant correlations with any of the variables in the test group, as all the p-values exceed the typical threshold of 0.05. However, the control group has a strong and significant negative correlation with Ox LDL ($r = -0.310$, $p = 0.002$). For Vitamin C, there are no significant correlations with any variables in the test group. The control group strongly and significantly negatively correlated with LpPLA2 ($r = -0.304$, $p = 0.002$). Also performed was a correlation between oxidative markers and the atherogenic index of plasm. The test group has a weak positive correlation between MDA and the atherogenic index ($r = 0.172$). Still, it is not statistically significant because the p-value (0.088) exceeds the typical threshold of 0.05. The correlation between Vitamin C and the atherogenic index is extremely weak and negative ($r = -0.028$) and statistically insignificant ($p = 0.786$). The MDA ($r = 0.024$, $p = 0.811$) and vitamin C ($r = 0.008$, $p = 0.937$) correlations with the atherogenic index are extremely weak and insignificant in the control group.

The study investigates the relationships between specific cardiac and oxidative markers, revealing critical insights into cardiovascular health's biochemical aspects, particularly regarding atherosclerosis. One significant finding is the negative correlation between MDA, a marker of oxidative stress, and HDL in the test group. HDL is known for its protective role against atherosclerosis, often termed 'good' cholesterol [11]. This negative correlation suggests that higher MDA levels, indicating heightened oxidative stress, are associated with lower protective HDL levels. This relationship underscores oxidative stress's detrimental effects on the lipid profile and highlights the potential role of antioxidant mechanisms in maintaining cardiovascular health [12].

In contrast, in the control group, MDA positively correlated with total cholesterol and LDL, known as 'bad' cholesterol, due to its atherogenic properties. These correlations suggest that increased oxidative stress, as indicated by higher MDA, coincides with elevated levels of TC and LDL. This is crucial given LDL's susceptibility to oxidative modification, forming OxLDL, a primary factor in atherogenesis, which is central to the development of atherosclerosis [13]. The results also indicate complex relationships involving OxLDL and Lp-PLA2, an enzyme implicated in the inflammatory processes of atherosclerosis [14]. Notably, the control group exhibited a significant negative correlation between Vitamin C

levels and Lp-PLA2. Considering Vitamin C's antioxidant properties, this finding suggests that higher Vitamin C levels might be associated with reduced oxidative and inflammatory states, offering potential protective benefits in cardiovascular health [15]. Lastly, concerning the atherogenic index, which evaluates cardiovascular risk based on lipid profiles, the study presents a more complex scenario. The weak and non-significant correlations of MDA and Vitamin C with the atherogenic index in both test and control groups imply that while these oxidative markers are crucial, they are part of a more comprehensive network of factors influencing cardiovascular health. This multifaceted nature of cardiovascular risk factors underscores the need for comprehensive assessment and intervention strategies [16].

To sum up, these intricate correlations underscore the complex biochemical interplay governing cardiovascular health. The study highlights the importance of holistic strategies in managing cardiovascular risk, taking into account oxidative stress, cholesterol levels, and systemic inflammation. Furthermore, it points toward the need for more extensive research to explore these correlations' underlying causal relationships and mechanisms, which could significantly inform future therapeutic interventions.

5. CONCLUSION

This research elucidates the complex interplay between conventional and emerging cardiac markers with oxidative stress indicators, highlighting pivotal insights into the multifaceted mechanisms underlying cardiovascular health. A significant discovery of the study is the inverse relationship between MDA, a primary oxidative stress marker, and HDL cholesterol, underscoring the detrimental impact of oxidative stress on lipid metabolism, particularly in the test group. Conversely, the positive association of MDA with potentially atherogenic elements like total cholesterol and LDL in the control group emphasizes the contributory role of oxidative stress in exacerbating cardiovascular risk factors.

Furthermore, the study's findings accentuate the nuanced role of antioxidants, represented by Vitamin C, in potentially mitigating inflammatory responses associated with cardiovascular diseases, as evidenced by the negative correlation with Lp-PLA2 in the control group. This aspect underscores the antioxidative defense mechanism's significance in cardiovascular health and suggests a broader spectrum of protective factors beyond traditional cholesterol management. However, the associations of MDA and Vitamin C with the atherogenic index present an intricate scenario, with both test and control groups showing non-significant correlations. This outcome points towards the complexity and diversity of factors influencing atherogenesis, suggesting that, while critical, oxidative stress operates within an extensive network of other systemic influences.

This study reinforces that a complex biochemical milieu underpins cardiovascular health and atherosclerosis, extending beyond cholesterol to oxidative stress and inflammation. The nuanced relationships identified between these markers signal the need for a more holistic approach to cardiovascular risk assessment and management. They advocate for strategies encompassing lipid regulation, oxidative stress reduction, and immune response modulation. Future research endeavors should further unravel these complex relationships, mainly through longitudinal studies, to pave the way for innovative, comprehensive, and more effective therapeutic interventions in cardiovascular care.

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7. 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.

8. CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest concerning this article's research, authorship, and publication.

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