Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/99baey52

TRENDS IN LIPID PROFILE AND TRACE ELEMENTS IN METABOLIC SYNDROME

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ABSTRACT

Introduction

Metabolic Syndrome (MetS) is a complex, multifaceted disorder characterized by a cluster of interconnected cardiovascular and metabolic risk factors. Derangements in lipid metabolism (hyperlipoproteinemias) and trace elements play crucial roles development of metabolic syndrome. The objective of the present study is to determine lipid profile patterns and trace element levels (copper, zinc, and iron) in subjects with MetS and without MetS.

Methods

A comparative cross-sectional study included 90 subjects with MetS and 90 subjects without MetS. Fasting venous blood sample was collected and analysed for the quantitative estimation of Lipid profile parameters (total cholesterol, triglycerides, LDL, HDL, VLDL), copper, zinc, and iron levels in fully automated dry chemistry analyser Vitros 5600 as per manufactures instructions.

Results

In the present study we found altered lipid profile parameters and trace elements levels (copper, zinc and iron) in subjects with MetS in contrast to subjects without MetS. The lipid alterations mainly included hypercholesterolemia, hypertriglyceridemia, elevated low density lipoproteins and decreased high density lipoproteins in MetS and also the trace elements showed significantly higher concentrations in MetS.

Conclusion

This study highlights the importance of considering lipid profiles and trace element levels in the diagnosis and management of MetS. Monitoring lipid profile, iron, copper, and zinc levels will aid in identifying individuals at possibility of progressing to MetS or its components. Early therapeutic interventions for hyperlipoproteinemias and addressing trace element imbalances through dietary modifications or supplementation may be a useful adjunctive therapy in managing MetS. Additional investigation is required to illuminate the mechanisms fundamental to trace element dysregulation in MetS and to explore potential therapeutic applications.

Key-words: metabolic syndrome, lipid profile, trace elements, copper, zinc and iron.

INTRODUCTION

Metabolic syndrome (MetS) also known as syndrome X, is the major metabolic disorder mainly affecting the adult population worldwide both developed and developing nations [1]. This debilitating condition affects millions worldwide, increasing the risk of developing type 2 diabetes, cardiovascular disease, and premature mortality. The growing worldwide burden of MetS is a result of a sedentary lifestyle, increased urbanization, excess energy consumption, and rising obesity rates [2]. The abnormalities encountered in MetS mainly include central obesity, elevated blood pressure, elevated fasting blood glucose, and lipid alterations catheterized by increased concentrations of triglycerides (TAG), decreased high density lipoproteins (HDL) [3]. The basic pathophysiological mechanism leading to the development of MetS is mainly due to central obesity and insulin resistance [4]. Serious public health concerns are raised by the ongoing growth in the worldwide burden of MetS, which enhances the risk for development of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), accounting for high morbidity and high mortality from CVD [5,6,7]. In subjects with MetS, compensatory hyperinsulinemia and insulin resistance cause an excess of LDL particles to be produced [7]. In MetS there is relative deficiency of lipoprotein lipase enzyme due to leading to decreased formation of HDL particles and decreased clearance of triglyceride rich particles (TRLs) both in fasting and post-prandial state [8]. The major lipid profile anomaly of the MetS is the resultant higher concentration of postprandial TRLs and fasting cholesteryl ester-rich TRLs [7]. Due to insulin resistance or insulin deficiency there is exaggerated lipolysis which releases free fatty acids into portal circulation and are further metabolised by the liver into triglycerides (TAG) hence these patients have elevated TAG which is the risk factor for CVD hence it is to be taken as important component of MetS [6]. Additionally, high LDL is a significant CVD risk factor, and pharmacotherapy's main goal is to lower LDL levels [6,7]. It is commonly recognized that dietary micronutrients like iron (Fe), copper (Cu), and zinc (Zn) cooperate with a wide range of enzymes and have antioxidative properties. As a result, it is assumed that these micronutrients have a role in MetS and DM [9-11]. Very few observational studies have been conducted so far to shed the light on association between blood levels of trace elements (Zn, Cu, or Fe) and DM but their results were mixed [12-14].

According to recent meta-analyses, the serum concentrations of Zn did not show significant association with DM, whereas altered Cu and Fe levels were significantly associated with the risk of development of DM [15-17]. A significant five-year cohort research including a broad population provided evidence that dietary consumption of Fe and Cu was linked to higher risk of new-onset diabetes [18]. Zn dietary consumption showed lowered risk of DM [19], and there is increased risk of MetS with dietary consumption of Cu and Fe [20], when MetS and micronutrients were taken into account. Though the majority of the data are not statistically significant, still there is no proper information available related to the status of trace elements and MetS [21-23]. With alarming rates of obesity and sedentary lifestyles, MetS has emerged as a major public health concern, affecting approximately 25% of the global adult population. The economic burden of MetS is substantial, with estimated annual healthcare costs exceeding billions. Therefore the present study aimed to determine lipid profile patterns and trace element levels (copper, zinc, and iron) in subjects with MetS and without MetS.

MATERIALS AND METHODS

Study settings: This is comparative cross-sectional study conducted in the department of biochemistry in collaboration with department of general medicine at our tertiary care hospital.

Sample size: 90 subjects with MetS and 90 subjects without MetS.

Inclusion criteria: The present study included subjects with and without metabolic syndrome in the age group 20 to 60 years, both genders willing to provide voluntary informed consent. In the present study National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria was used to diagnose MetS [24] as represented in Table 1.

Exclusion criteria: Subjects with metabolic disorders, chronic diseases affecting zinc copper and iron metabolism, patients on supplementation of zinc copper and iron in any form were excluded from the study.

Table 1: Diagnostic Criteria for MetS [24]	
1	Waist circumference: men >90 cm, women >80 cm
2	Triglycerides: >150 mg/dL
3	HDL cholesterol: men < 40 mg/dL and women <50 mg/dL
4	Blood Pressure: >130/85 mmHg
5	Fasting blood glucose: >100 mg/dL
Diagnosis is made if any 3 out of the 1-5 criteria given above	

Methodology: In all the subjects the waist circumference was measured as per the standard guideline[12]. Under aseptic precautions 5 ml of fasting (8-12 hours) venous blood sample was collected and subjected to centrifugation for obtaining serum. Serum sample was used for the estimation of total cholesterol, triglycerides, LDL, HDL, trace elements and fasting insulin [6]. All the parameters were estimated using fully-automated integrated dry chemistry based analyser Vitros 5600. VLDL was calculated using the formula Triglyceride/5. HOMA-IR was used for the estimation of insulin resistance i.e. HOMA-IR = fasting insulin X fasting glucose/22.5 [10].

RESULTS

Table 2 represents gender wise and age wise distribution of subjects with and without MetS. There were 62 males (62%) and 38 females (38%) among subjects without Mets and there were 66 males (66%) and 34 females (34%) among subjects with Mets. The age wise distribution of subjects shows that the mean age of subjects without Mets and Mets were 46.44±10.14 years and 48.2±9.88 years, respectively.

Table 2: Gender wise and age wise distribution of subjects with and without Mets				
Gender	**Without Mets**		**Mets**	
	n = 100	**In %**	**n = 100**	**In %**
Male	62	62%	66	66%
Female	38	38%	34	34%
Mean Age in years	46.44 ± 10.14		48.2 ± 9.88	
Mets: Metabolic Syndrome				

Table 3 denotes the comparison of bassline physical and biochemical variables between the subjects without Mets and Mets. The body mass index (BMI), waist circumference (WC), fasting blood sugar (FBS), fasting insulin and HOMA-IR were significantly elevated in subjects with Mets compared to subjects without Mets. The difference was statistically highly significant (p<0.00001).

Table 3: Comparison of Baseline Physical and Biochemical Variables in Subjects with and without Mets					
Variables	**Without Mets**	**Mets**	**t - test**	**P - Value**	**Significance**
BMI	23.76 ± 3.12	29.24 ± 2.43	-6.929	0.00001	Significant
Waist Circumference	89.66 ± 6.21	95.43 ± 4.89	-3.000	0.00351	
Fasting Blood Sugar	108.31 ± 3.20	148.56 ± 22.4	-3.516	0.00069	Significant
Fasting Insulin (U/mL)	24.18 ± 0.76	30.46 ± 3.12	-13.639	0.00001	
HOMA-IR	1.89± 0.42	4.53 ± 0.72	-19.214	0.00001	
HOMA-IR: Homeostatic model assessment for insulin resistance					

Table 4 represents the comparison of lipid profile parameters in subjects with and without MetS. It is observed that total cholesterol, triglyceride, and VLDL were elevated and HDL levels were

decreased in subjects with metabolic syndrome as compared to subjects without metabolic syndrome, and was statistically highly significant ($p<0.0001$). Whereas LDL levels were elevated in metabolic syndrome subjects as compared to subjects without metabolic syndrome but the elevation was statistically not significant ($p>0.05$).

Table 4: Comparison of Lipid profile parameters in Subjects with and without Mets					
Variables	**Without MetS**	**MetS**	**t - test**	**P - Value**	**Significance**
TC (mg/dl)	178.18 ± 25.42	196.42 ± 43.44	-2.095	0.03905	Significant
TG (mg/dl)	156.33 ± 38.64	236.6 ± 64.54	-7.249	0.00001	
HDL(mg/dl)	40.2 ± 9.03	26.9 ± 10.67	4.786	0.00001	
LDL (mg/dl)	112.05 ± 25.49	128.2 ± 32.53	-1.511	0.13448	Not Significant

Table 5 represents the comparison of copper zinc and iron levels in subjects with and without metabolic syndrome. It is observe that the concentration of copper zinc and iron were significantly elevated in subjects with metabolic syndrome as compared to subjects without metabolic syndrome. All the values obtained were statistically highly significant ($p<0.0001$)

Table 5: Comparison of Copper, Zinc and Iron levels in Subjects with and without Mets					
Variables	**Without MetS**	**MetS**	**t - test**	**P - Value**	**Significance**
Copper (µg/L)	878.9 ± 112.85	1154.7 ± 178.2	-7.751	0.00001	Significant
Zinc (mg/dl)	108.64 ± 11.68	156 ± 16.46	-12.592	0.00001	
Iron (mg/dl)	126.78 ± 31.28	206.78 ± 16.32	-16.482	0.00001	

DISCUSSION

The current study included a total of 100 diagnosed cases of metabolic syndrome and 100 subjects without metabolic syndrome. In this cross sectional study we compared lipid profile parameters and trace elements (copper, zinc and iron) between the two groups. It is found that most of the patients with metabolic syndrome had derangements in blood glucose and lipid profile parameters, reflected by elevated fasting blood sugar, total cholesterol, triglycerides, LDL and VLDL and decreased HDL levels. One multifactorial risk factor for atherosclerotic cardiovascular disease (ASCVD) is the metabolic syndrome (MS). It is characterized by an atherogenic dyslipidaemia (higher triglycerides, low HDL-C and raised apo-B and apo-B), elevated blood pressure, elevated hyperglycemia, and prothrombotic and proinflammatory conditions). When MS is present, the risk of ASCVD is roughly quadrupled when the condition is not present. It seems that the MS supports ASCVD development on a number of fronts. Increases in lipoproteins containing apo-B start atherogenesis and promote the formation of lesions. Low HDL-C levels, high hyperglycemia, and inflammatory cytokines all hasten the development of atherosclerotic plaque [25].

Copper (Cu) is important trace mineral that functions as cofactor for several enzymes which catalyse redox processes. Cu increases the clearance of free radicals via the action of copper/zinc superoxide dismutase. Dietary Cu was found to be a protective factor against MetS in two cross-sectional investigations. However, cross-sectional studies in China and Korea, as well as a prospective nested cohort, found negative associations between serum Cu and MetS. Only a cross-sectional investigation in Lebanon found a favourable correlation between HDL-C and serum Cu. In the absence of large-scale investigations, conflicting evidence suggests that Cu may operate as both a pro-oxidant and an antioxidant, and that both excessive and insufficient Cu levels cause toxicity and cell damage [26]. This finding was similar to our study, the mean copper levels in metabolic syndrome patients found to be 1154.7 ± 178.2 compared to the subjects without MetS 878.9 ± 112.85. Copper levels were statistically significantly elevated in MetS ($p<0.001$). Elevated Copper in MetS may contribute to increased oxidative stress and inflammation, exacerbating insulin resistance and cardiovascular risk, copper can also stimulate the production of pro-inflammatory cytokines, worsening MetS symptoms

and elevated copper levels may be related to increased absorption or decreased excretion, potentially due to genetic or environmental factors.

Zinc is another trace element that affects lipid and glucose metabolism, lowers oxidative stress, and regulates inflammation, it may offer protection to humans. Furthermore, zinc is highly essential synthesis, storage, and release of insulin and is related to diabetes and MetS. Conversely, the hypothesized protective role of Zn has not been well demonstrated in human studies. Zn supplementation or dietary intake appeared to regress the progression of new-onset DM, while meta-analyses showed no correlation between serum Zn and DM. Furthermore, the overall consumption of zinc through diet and supplementation did not show any protective effect against diabetes. Similarly, in individuals with type 2 diabetes, oral zinc supplementation did not enhance oxidative stress, diabetic neuropathy, or vascular function. Furthermore, there are few and conflicting data on Zn and MetS. Many studies conducted in the past to check the association between zinc and MetS, did not find the valid results [26]. In our study the mean zinc levels in metabolic syndrome patients found to be 156 ± 16.46 compared to the subjects without MetS 108.64 ± 11.68. The elevation in zinc levels were statically highly significant ($p<0.001$). None of the studied possibly explained the elevated levels of zinc in MetS. The possible explanation is that the elevated zinc levels can have negative effects, such as: inhibiting insulin signalling and glucose uptake in muscles and adipose tissue enhancing inflammation and oxidative stress disrupting the balance of other trace elements, like copper and iron elevated zinc levels might be related to increased dietary intake, supplementation, or altered excretion in MetS individuals. Increased copper and zinc levels may be a response to chronic inflammation and oxidative stress in MetS Elevated copper and zinc could contribute to the development of insulin resistance and cardiovascular disease Genetic predispositions, dietary factors, or environmental influences might also play a role in trace element dysregulation.

Similarly the mean iron levels in metabolic syndrome patients found to be 206.78 ± 16.32 compared to the subjects without MetS 126.78 ± 31.28. The elevation in iron levels in MetS is statistically highly significant ($p<0.0001$). This finding was similar to the study conducted by Hye-Ja Lee et al [27]. Several other studies have found decreased serum iron levels in subjects at risk of MetS. This is another controversial finding in our study. The possible explanation is that elevated iron levels have been linked to insulin resistance, a key component of MetS. Excess iron can lead to oxidative stress, inflammation, and damage to pancreatic beta-cells, exacerbating insulin resistance. Iron overload can also contribute to cardiovascular disease, a common comorbidity with MetS. According to the studies, increased iron and ferritin levels and also dietary consumption of iron were associated with increased risk of developing DM and additionally same observations were found in MetS [27-30].

CONCLUSION

This study highlights the importance of considering lipid profiles and trace element levels in the diagnosis and management of MetS. Monitoring iron, copper, and zinc levels will aid in identifying individuals at possibility of progressing to MetS or its components. Addressing trace element imbalances through dietary modifications or supplementation may be a useful adjunctive therapy in managing MetS. Additional investigation is required to illuminate the mechanisms fundamental to trace element dysregulation in MetS and to explore potential therapeutic applications.

Limitations of our study

Our study failed to evaluate the association between trace elements and individual components of MetS. Our study did not include the MetS subjects on nutritional supplementation of trace elements as it was one of the exclusion criteria. We used HOMA-IR for estimating the degree of insulin resistance in MetS, an indirect method. Further research is necessary to understand the underlying mechanisms and to explore potential therapeutic applications

Clinical Implications

Monitoring copper and zinc levels in MetS individuals may help identify potential contributors to disease progression. Addressing elevated copper and zinc levels through dietary modifications, supplementation, or chelation therapy might be beneficial in managing MetS**.** Further research is necessary to understand the underlying mechanisms and to explore potential therapeutic applications.

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