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RESEARCH ARTICLE

ROLE OF HYPOMAGNESAEMIA IN PROMOTION OF METABOLIC SYNDROME IN PREMENOPAUSAL WOMEN

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Abstract

Metabolic syndrome (MetS) is a group of disorders indulge into high risk of developing for hyperglycemia, hypertension, obesity and cardiovascular disease (CVD). Studies suggested that low circulatory magnesium levels are related to MetS, type 2 diabetes mellitus (T2DM), and CVD. Present study was planned and designed to find out the association between circulatory magnesium levels and risk for development of MetS. A total of 200 premenopausal women aged 21-45 years were included. MetS was defined by NCEP-ATP III criteria. The biochemical parameters were analyzed on fully autoanalyzer. Data analyzed by using SPSS software, version 22.0 and $p<0.05$ was considered as statistically significant. Present study highlights that incidence of MetS and hypomagnesemia were 26% and 39% respectively. Circulatory magnesium levels were significantly decreased in study group (with MetS) (1.7±0.3) as compared with control group (2.0±0.5, $p<0.001$). A significant inverse correlation wasobserved between serum magnesium levels and fasting blood sugar, triglyceride levels, systolic and diastolic blood pressure ($p<0.05$), whereas a positive correlation with high-density lipoprotein levels were found in study group with MetS. Present study concluded that hypomagnesemia plays a significant role in the pathogenesis of MetS and its associated complications. In view of these findings, supplementation of magnesium improves the status of components of MetS by reducing high blood pressure, hyperglycemia, and dyslipidemia as well.

Introduction:-

A debate has immersed whether the concept of metabolic syndrome (MetS) has validity and clinical utility in the field of medical and health sciences? Some believe it's useful, others disagree. TheMetS is risk factor for metabolic abnormalities which includes abdominal obesity, glucose intolerance, hypertension, elevated triglycerides and low

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high density lipoprotein cholesterol (HDL-C)[1]. MetS refers to collection of interconnected biochemical, physiological, clinical and metabolic factors which in an individual indulge into a higher risk for the development of T2DM, CVD and all-cause mortality.

Magnesium (Mg^{++}) is the fourth most abundant cation in the body with about 50% present in bones associated with calcium and phosphate. Majority of magnesium is intracellular and only small amount is found in extracellular fluid. Magnesium functions as an activator for various physiochemical processes, including phosphorylation of insulin receptor, protein synthesis and DNA metabolism. Magnesium also involved as neuromuscular conduction and excitability of skeletal and cardiac muscle[2]. Depletion of intracellular Mg^{++} cause functional defect of tyrosine kinase at insulin receptor, leading to decreased insulin capability to stimulate glucose uptake in insulin sensitive tissues [3]. Kidneys effectively control Mg^{++}homeostasis through tubular reabsorption which conserves $Mg^{++}$when intake is elevated.An alteration in magnesium homeostasis whether due to treatment or any disease condition leads to hypomagnesaemia. Impaired magnesium homeostasis is associated with chronic diarrhea, hypokalemia, hypocalcemia and cardiac arrhythmias[4,5] therefore, ionic Mg^{++} concentration is necessary to be monitored routinely.

Hypomagnesemia has a depressing effect on the central nervous system (CNS), causing general anesthesia and respiratory failure. Hypomagnesemia alters the conduction mechanism of the heart causing convulsions and cardiac arrhythmias. The risk of hypomagnesemia depends on multiple characteristics in various healthcare settings, the latest report published by the Mayo Clinic that about 2% in the general population, 10% to 20% in hospitalized patients, 25% in outpatients with DM and more than 30% in ICU patients respectively [4]. Nowadays magnesium deficiency is the most underestimated electrolyte imbalance. Studies have reported that low levels of magnesium can occur secondary to chronic disease, alcohol abuse, renal and gastrointestinal losses[3] . Recently studies suggested that magnesium deficiency frequently been seen in obese, T2DM and CVD; all of these are risk factors of MetS[5-7].

TheMg^{++} deficiency is more frequent in women than men because estrogen hormone stimulates magnesium utilization by tissues and therefore hormonal rhythms in women may affect and modulates magnesium status[8].There is paucity of literature on role of magnesium deficiency for the progression of MetS in premenopausal women. Therefore, the present study was conducted to find out the association between serum magnesium levels and risk for development of MetS in premenopausal reproductive agedwomen.

Objective:-

The present study planned and designed to find out-

1. The incidence of hypomagnesaemia and MetS in premenopausal women.
2. To find out the association between hypomagnesaemia and risk for development of MetS.

Methods:-

The present study was held in 200 premenopausal women of age group 21-45 years who were referred for routine health checkup at Medanta-The Medicity hospital, Gurgaon (Haryana).

Exclusion Criteria:

Pregnant mothers and women who are in habits of smoking, drinking alcohol and tobacco chewing were excluded. Apart from these, women who are suffering and on treatment for T2DM, hypertension or any other chronic diseases and those who are not willing to participateand don't follow the instructions were excluded from the study.

Inclusion Criteria:

Women who are willing to participate and leading healthy life style were included in the study. The participated women were divided into two groups as MetS (53, 26%) considered as cases and without MetS (147, 74%) considered as control group.

Anthropometric measurements were assessed by standard methods and tools. Body mass index (BMI) was calculated as weight (Kg)/ height (m^2). Biochemical parameters (fasting blood sugar (FBS), lipid profile and serum calcium were analyzed on fully automated analyzer. Serum Magnesium level was estimated by formazan dye method on dry chemistry analyzer VITROS 5600 with in build quality control.

Diagnostic Criteria for MetS and Hypomagnesemia:

TheMetS was defined by National Cholesterol Education Program -Adult Treatment Panel III (NCEP-ATP III)criteria for Asian Indian population[9]. As per the criteria, co-occurrence of at least three of the following risk factors in an individual:

1. Abdominal obesity (Waist circumference WC >88 cm in women),
2. High blood pressure (BP ≥130/85 mmHg),
3. Hyperglycemia (FBS ≥100 mg/dL),
4. Hypertriglyceridemia (Triglycerides TG ≥ 150 mg/dL),
5. Low HDL-Cholesterol (HDL-C < 50 mg/dL)

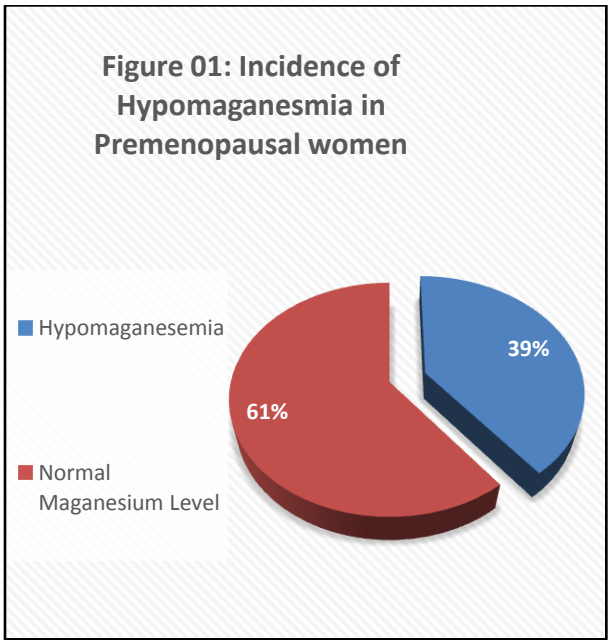
The status of magnesium deficiency was diagnosed depending upon the presence of circulatory magnesium levels. However, normal level of magnesium >1.8-2.3 mg/dL and hypomagnesemia were defined when serum magnesium levels ≤1.8 mg/dL respectively.

Statistical Analysis:

Data were analyzed by using SPSS software, version 22. Study results were expressedas mean ± Standard deviation and percentage(%). The student's t-test was used to compare with case and control groups. Pearson's correlation was used to find out the correlation.Odds ratio (OR) was used to measure the association between hypomagnesemia and MetS. p-value <0.05 considered statistically significant.

Results:-

The present study highlights the incidence of hypomagnesaemia and MetS in study group39.5% and 26% respectively (Figure 01, 02). The Characteristics of Premenopausal women with MetS (Case) and without MetS (Controlgroup) were shown in Table 01. BMI, WC, BP, FBS, TC,TG, LDL-C were increased significantly (p<0.001) whereas HDL-C, serum calcium levels were significantly decreased (p<0.001) in MetS as compared to Control group. Serum magnesium levels were significantly decreased in women with MetS (1.7±0.28) as compared with control group (2.0±0.21), p<0.001 (Table 01). A statistically significant inverse correlation was found between serum magnesium levels and WC, FBS, systolic blood pressure (p<0.05) whereas a highly significant positive correlation was found with HDL-C and calcium levels (p<0.001) in premenopausal women (Table 02). Further more significant association was observed between MetS and hypomagnesemia in premenopausal women with odd ratio 2.11 (1.11-3.98, p<0.05) (Table 03).



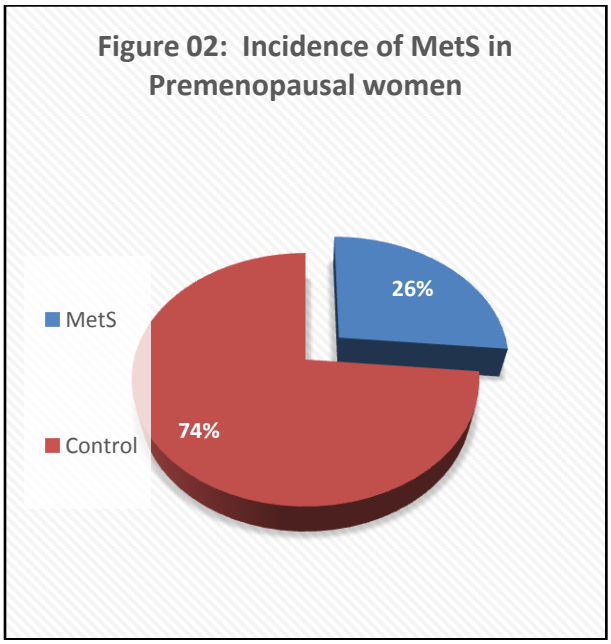


Table 01:- Characteristics of Premenopausal reproductive aged women with MetS (Case) and without MetS (Controls).

Parameters	Total (N=200)	Case (N=53)	Control (N=147)	p-Value
Age (years)	34.70 ±6.97	35.91±7.04	33.5±6.91	p<0.05*
Body Mass Index (BMI)	26.8±5.42	30.4±5.73	25.59±4.47	p<0.001**
Waist Circumference (WC) (cm)	94.8±12.02	102.57±9.76	91.99±11.34	p<0.001**
Systolic Blood Pressure (SBP) (mm/Hg)	110.16±15.61	120.32 ±19.68	106.53±12.03	p<0.001**
Diastolic Blood Pressure (DBP) (mm/Hg)	71.41±9.15	77.7±10.31	69.17±7.59	p<0.001**
Fasting Blood Sugar (FBS) (mg/dL)	91.48±16.64	104.89 ±24.86	86.64±8.29	p<0.001**
Total Cholesterol (TC) (mg/dL)	185.25±28.15	191.3±32.1	179.2±24.2	p<0.05*
Serum Triglyceride (TG) (mg/dL)	109.77±55.48	159.09±67.71	91.99±36.88	p<0.001**
HDL-Cholesterol (HDL-C) (mg/dL)	48.01±12.16	40.64±8.23	50.67±12.27	p<0.001**
LDL-Cholesterol (LDL-C) (mg/dL)	104.57±28.40	115.69±35.17	100.56±24.45	p<0.001**
VLDL-Cholesterol (VLDL-C) (mg/dL)	21.95±11.09	31.82±13.54	18.39±7.37	p<0.001**
Serum Calcium (mg/dL)	9.35±0.93	8.9±0.91	9.33±0.94	p<0.001**
Serum Magnesium (mg/dL)	1.84±0.33	1.70±0.28	2.04±0.21	p<0.001**

Values are Mean ± Standard deviation.
p<0.001** Highly Significant, p<0.05* Significant, $p>0.05^{NS}$ Non-Significant

Table 02:- Pearson correlation coefficient between serum magnesium levels and characteristics of Premenopausal reproductive aged women.

Parameters	r- value	P-Value
Age (years)	-0.123	$p>0.05^{NS}$
Body Mass Index (BMI)	-0.108	$p>0.05^{NS}$
Waist Circumference (WC) (cm)	-0.167	p<0.05*
Systolic Blood Pressure (SBP) (mm/Hg)	-0.129	p<0.05*
Diastolic Blood Pressure (DBP) (mm/Hg)	-0.065	$p>0.05^{NS}$
Fasting Blood Sugar (FBS) (mg/dL)	-0.175	p<0.05*
Total Cholesterol (TC) (mg/dL)	0.005	$p>0.05^{NS}$
Serum Triglyceride (TG) (mg/dL)	-0.071	$p>0.05^{NS}$
HDL-Cholesterol (HDL) (mg/dL)	0.196	p<0.001**
LDL-Cholesterol (LDL) (mg/dL)	-0.052	$p>0.05^{NS}$
Serum Calcium (mg/dL)	0.365	p<0.001**

p<0.001** Highly Significant, p<0.05* Significant, $p>0.05^{NS}$ Non-Significant

Table 03:-Association between Hypomagnesemia and MetS in premenopausal reproductive aged women

		With MetS (Case)	WithoutMetS (Control)
		Yes (N=53)	**No (N=147)**
Hypomagnesemia	**Yes**	**28 (52.8%)**	**51 (34.6%)**
	No	**25 (47.2%)**	**96 (65.3%)**
Odds ratio (OR)	2.11		
95 % CI	1.11to 3.98		
p-Value	p<0.05*		

p<0.05* Significant.

Discussion:-

The MetS is a burning problem of discussions among clinicians because patients having MetS are at higher risk for developing clusters of diseases. Studies reported that obesity, hypertension, hyperglycemia, hyperlipidemia, and hypomagnesemia with MetS are susceptible for major risk of CVD [10,11].Astudy reported that hypomagnesemia and MetS are independently linked whereas the interaction of inflammation and oxidative stress are associated with increased risk for MetS[6]. Survey of literature documented thatlow serum Mg^{++} levels were strongly related to

T2DM, dyslipidemia, hypertension and MetS[11,12].The present study highlights that there were significant inverse association between serum Mg^{++} levels and the components of MetS in reproductive aged women. The possible mechanism of low serum Mg^{++}levels and risk for development of MetSinduce an increase of vascular tone by intracellular magnesium depletion, resulting in an elevation of blood pressure [13] . Furthermore, it might cause impaired insulin secretion, insulin-resistance (IR), hyperlipidemia, hypertension and finally development of MetS[14] . Therefore, the importance of dietarymagnesium intake for maintenance ofbetter health must be highly graded.

The Mg^{++} homeostasis is strongly regulated and depend upon balance between intestinal absorption and renal excretion[15]. It's evident from studies that Mg^{++} depletion is frequently observed in T2DM, and believed that an impairment of Mg^{++} homeostasis favors the onset and progression of diabetic complications[5,16]. The Atherosclerosis Risk in the Community (ARIC) study documented significant association between hypomagnesemia and the incidence of T2DM [17]. The present study findings are consistent with earlier documented results that hypomagnesemia plays a contributing factor for the development of T2DM [18] as low serum Mg^{++} levels were significantly correlated with FBS.The possible mechanism is that hypomagnesemia may alter cellular glucose transport, reduce pancreatic insulin secretion, defective post-receptor insulin signaling, and altered insulin–insulin receptor interactions, which in turn include poor dietary intake, autonomic dysfunctions, altered insulin metabolism, osmotic diuresis, recurrent metabolic acidosis, hypophosphatemia, and hypokalemia[19]. Hypomagnesemia has also been linked to poor glycemic control, coronary heart disease (CHD), hypertension, diabetic retinopathy, nephropathy, neuropathy, and foot ulcerations [20].

Magnesium deficiency is a common and under-recognized problem throughout the world. Importantly, subclinical magnesium deficiency does not manifest as clinically apparent symptoms hence ignored by the clinician. Despite the fact, subclinical magnesium deficiency likely to lead hypertension, cardiac arrhythmias, arterial calcifications, atherosclerosis, heart failure and an increased risk for thrombosis[21]. It's evident from reported studies that low circulating Mg^{++} levels has been related to elevated BP, atherogenic dyslipidemia, impaired clotting, increased inflammatory burden, oxidative stress, carotid wall thickness and CHD [6,17] . Magnesium deficiency produces hypertriglyceridemia and low levels of HDL-C by modulating the actions of enzymes involved in cholesterol metabolism. Low Mg^{++} levels diminish the activity of lecithin cholesterol acetyl transferase (LCAT) andlipoprotein lipase(LPL) and increase the activity of HMG-CoA reductase. Impaired LCAT activity can reduce the formation of HDL and impair transport and disposal of TG [22]. Hypomagnesemia also affects the electrical activity of the myocardium and vascular tone, that's why patients with hypomagnesemia are at risk for cardiac arrhythmias[4]. Available data suggest that low Mg^{++} levels promote endothelial cell dysfunction and thrombogenesis via increased platelet aggregation and vascular calcifications[13]. TheLow Mg^{++} levels may lead to induction of proinflammatory and profibrogenic response , reduction of protective enzymes against oxidative stress, induction or augmentation of vasoconstriction, hypertension, and stimulation of aldosterone [23] . Vasoconstriction and subsequent high BP was observed in patients with low Mg^{++} intake, whereas the pharmacological administration of magnesium reduces the BP [24] . Moreover, because $Mg^{++}$is crucial in DNA synthesis and repair, it is documented that Mg^{++}deficiency interfere with normal cell growth and regulation of apoptosis [25].

The Mg^{++} could function as a mild, natural calcium antagonist;hence, the level of intracellular calcium is increased in patient having hypomagnesemia. This increased intracellular calcium may compromise the insulin responsiveness of adipocytes and skeletal muscles leading to the development of IR[26,27]. Hypomagnesemia also cause hypocalcemia and hypokalemia because impaired magnesium-dependent adenyl cyclase generation of cyclic adenosine monophosphate (cAMP), which decrease the release of parathyroid hormone (PTH). Hypomagnesemia is associated with hypocalcemia due to both lower PTH secretion and end-organ resistance to its effect and also linked with hypokalemia due to urinary potassium wasting[28].The present study highlights that there is significant positive correlation between hypomagnesemia and calcium.

Low serum Mg^{++} level documented in obese patients due to reduced intestinal Mg^{++} absorption secondary to higher fat and lower fiber intake [29, 30] . It's hypothesized that Mg^{++} have anti-obesity effect because of its capability of forming soaps with fatty acids in the intestine and reducing absorption of fat from the diet[5,29]. Hypomagnesaemia may develop due of reduced dietary intake of Mg^{++} and moved towards westernization of lifestyle. Nowadays women in modern society are privileged toward packed, fastfood instead of healthy Mg^{++} rich food intake like whole grain, barley, seaweed, green leafy vegetable, legumes and nuts[31]In view of these, drastic changes of food habits and lifestyle, MetS has become a major problem of Indians health in recent years. The elevated incidence of MetSis

probably due to multi-factorialfactors, such as daily intake of processed and packedjunk food, lack of physical exercise, and day to day stress etc[32].

The present study strongly recommends the association between low serum Mg^{++} levels lead to progression of MetS. However, there are certain limitations which need attention. Firstly, the study population was hospital-based with low sample size and lack of dietary Mg^{++} measurement. Secondly, total serum Mg^{++}estimation rather than free magnesium. It's established that only free or ionized magnesium is biologically active so the possibility of finding pseudo-hypomagnesemia could not be excluded. In view of these, total serum magnesium concentration is well correlated with intracellular free magnesium level. Limitation could be overcome by conducting study on community-based large sample size as well as, by analysing free or ionized magnesium levels.

Conclusion:-

Recently, in clinical practice hypomagnesemia is more commonly encountered leads to T2DM, hypertension, CVD and risk for promotion of MetS. Magnesium deficiency is a principal, yet under-recognized, promoter of CVD. There have been no recent studies identifying which age groups are at higher risk of hypomagnesemia?Present study highlights that hypomagnesemia plays a significant role in the pathogenesis of MetS and its associated complications like CVD in premenopausal women. Thus, it is necessary for clinician to find out the primary cause and rapid resolution of hypomagnesemia to overcome the risk due to magnesium deficiency. Awareness of public health effort will be needed to inform both the patient and clinician about the prevalence, diagnosis and associated complications of magnesium deficiency. In view of these, supplementation of magnesium to hypomagnesemia patients might reduce the incidence of MetS by controlling obesity, hypertension, hyperglycemia and dyslipidemia.

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Conflict of Interest:-

None

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