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A study of serum levels of magnesium and C-Reactive Protein in Type 2 Diabetes Mellitus

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Abstract

Type 2 Diabetes Mellitus (DM) has emerged as a major public health issue associated with various complications. Patients with metabolic syndrome (MS) have increased risk of developing cardiovascular disease and type 2 diabetes mellitus. C-reactive protein (CRP) correlates with individual components of metabolic syndrome and confer cardiovascular and metabolic risk. Magnesium is an essential ion involved in glucose homeostasis at multiple levels. Hypomagnesaemia has been reported in both IDDM and NIDDM patients. The present study is aimed to find the level of serum magnesium and CRP in type 2 diabetes mellitus and their association with development of metabolic syndrome and further development of type 2 diabetes mellitus. We have undertaken study on 120 subjects, categorized into three groups were involved in the study. FBS, lipid profile, serum magnesium and serum CRP levels were estimated in addition to recording of BP and anthropometric measurements.

Results: Serum magnesium levels were towards lower limit of normal range in both T2DM and MS groups with respect to controls. Further, serum CRP levels were elevated to nearly two times in T2DM and MS groups.

Conclusion: Our study findings suggest that serum magnesium and CRP levels are inversely related inflammatory markers are independent of Type 2 DM. This study could help in further studying degree of Hypomagnesemia and correlated elevation in CRP levels. Moreover, dietary supplementations of magnesium and/or other nutrient should be tried in case of Metabolic Syndrome along with assessment of Magnesium, CRP or other markers, in view to control these end stage pre diabetes condition from the development of Type 2 DM and to reduce the mortality resulting from cardiovascular diseases.

Key Messages: Serum magnesium levels were significantly decreased in T2DM & Metabolic Syndrome. Serum CRP levels were significantly increased in T2DM & Metabolic Syndrome.

Keywords: CRP, Lipid profile, Magnesium, Metabolic Syndrome, Type 2 Diabetes Mellitus

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Introduction

Today with increase in aging population, Type 2 Diabetes Mellitus (DM) has emerged as a major public health problem worldwide. Diabetes mellitus is one of the major non-communicable diseases. Type 2 DM is associated with permanent and irreversible functional and structural changes in the cell of the body, mainly vascular system leading to well defined clinical entities affecting eyes, kidney and nervous system. The commonest cause is atherosclerotic or cholesterol plaques that is accelerated in type 2 diabetes mellitus.(1)

Metabolic syndrome (MS) refers to the clustering of cardiovascular risk factors including obesity, dyslipidemia and hypertension. It has significant impact on glucose and fat metabolism, cellular growth and differentiation. It is estimated that people with MS have a two-fold risk of developing cardiovascular disease compared to those without MS and a five-fold increased risk of developing type 2 diabetes mellitus. Metabolic syndrome is also called the end stage of pre-diabetes.(2,3)

Recently it has been proposed that markers of systemic inflammation can be included in the definition of the metabolic syndrome. In this regards, elevated peripheral levels of pro-inflammatory mediators, such as C-reactive protein (CRP) and interleukin IL-6 correlate with individual components of metabolic syndrome and confer cardiovascular and metabolic risk. Further mounting evidence suggest that inflammation plays a crucial role in the development of both obesity and insulin resistance which will further leads to the development of diabetes.(3)

Previous studies have shown that type 2 diabetes is considered a chronic inflammatory condition resulting from obesity induced deregulation of adipocytes, which produce excessive inflammatory cytokines such as tumour necrosis factor (TNF-α), interleukin -6 (IL-6) and CRP. This persistent inflammatory state further contributes to insulin resistance and abnormal endothelial vascular reactivity.(4,5)

Diabetes as such has been reported to alter copper, zinc and magnesium status, although differences in trace element levels occurring as a result of diabetes have not been confirmed.(6) Previous studies also show Magnesium is an essential ion involved in glucose homeostasis at multiple levels. A complex interplay

exists between magnesium and glucose metabolism. It plays an important role in the activities of various enzymes involved in glucose oxidation and may play a role in the release of insulin. Hypomagnesaemia has been reported in both Insulin Dependent Diabetes Mellitus (IDDM) and Non-Insulin Dependent Diabetes Mellitus (NIDDM) patients. So the present study aimed to estimate the level of serum magnesium and CRP in type 2 diabetes mellitus and their association with development of metabolic syndrome and further development of type 2 diabetes mellitus.

Materials and Method

This is a case-control study, carried out at Department of Biochemistry and Department of Medicine, SVS Medical College and Hospital, Mahabubnagar, Telangana. A total of 120 subjects between the age group 25-45 years were enrolled into the study. They were categorized into three groups as follows: Group 1 (T2DM): 40 cases (20 males and 20 females) of type 2 diabetes mellitus. Group 2 (MS): 40 cases (20 males and 20 females) of metabolic syndrome. Group 3 (HC): 40 healthy controls (20 males and 20 females). Patients with hepatic or renal or cardiac impairment were excluded from the study. The metabolic syndrome cases were based on the criteria set by modified NCEP ATP-III which required the presence of at least three risk factors.

Venous blood samples were collected after taking aseptic precautions from the study subjects. 5 ml of blood was collected in plain vacuum tubes. Samples were left for 20 minutes at room temperature, and centrifuged at 3000 rpm for 4 to 5 minutes. Serum was used for the estimation of fasting blood sugar (FBS) by GOD-POD method, Triglycerides (TGL) by GPO-PAP method, High-Density Lipoprotein Cholesterol (HDLC) by Phosphotungstate method, by using semi autoanalyzer. Serum magnesium by magnesium calmagnite method & CRP (Immunoturbidimetric method) was done by using Randox fully auto analyzer. All investigations were done on the same day. Anthropometric measurements like BMI, WC, Waist to hip circumference ratio were recorded on subjects. The study was approved by institutional ethical clearance committee.

Statistical analysis: The mean and standard deviation of all variables were calculated. Statistical significance was assessed using chi-square test (χ 2 test). p-values < 0.05 are considered significant and <0.001 considered highly significant. Yates correction of chi-square test is applied where ever necessary. The correlation was seen by applying correlation coefficient.

Results

All male subjects with metabolic syndrome had HDL ≤ 40 mg/dl. Out of 20, 18 subjects in the metabolic syndrome category had waist circumference more than normal limit (90 cm) and triglyceride level higher than 150 mg/dl. None of the subjects had deranged blood pressure. The fasting blood glucose level was above 100 mg/dl in 8 male metabolic syndrome subjects. Out of the 20 cases of metabolic syndrome, only four subjects reached maximum score of 4 while rest of them scored 3 on the point scale followed.

All females with metabolic syndrome had waist circumference > 80 cm. Deranged HDL was seen in 18 out of 20 females with metabolic syndrome. 2 females had more systolic blood pressure value, while 4 had increased diastolic value. Only 2 females had score of 4 while rest of them had score of 3.

In Table 1, comparison is done among controls and subjects with metabolic syndrome. The HDL values for males and females were calculated differently because as per the scoring system the HDL ≤ 50 mg/dl in female and ≤ 40 mg/dl in males were given the score of 1. Maximum HDL level in male metabolic syndrome subject is 40 as compared to 55 mg/dl in female metabolic syndrome subjects. Similarly a minimum value is 23 in males and 29 mg/dl in female metabolic syndrome subjects.

Table 1: Comparison of diagnostic parameters of Metabolic syndrome with those of Controls

Parameters		Controls (n= 40) Mean ± SD	Metabolic Syndrome (n= 40) Mean ± SD
Waist Circumference (cm)	Male (n=20)	84.2 ± 3.46	116.5 ± 15.17
	Female (n=20)	75.4 ± 2.95	96.2 ± 16.25
Blood Pressure (mm Hg)	Systolic	118.6 ± 4.59	121.8 ± 4.44
	Diastolic	78.8 ± 1.39	80.8 ± 3.138
Fasting blood sugar (mg/dl)		81.64 ± 8.44	90.96 ± 12.99
Triglycerides (mg/dl)		108.95 ± 15.36	156.7 ± 32.4
HDL Cholesterol	Male (n=20)	50.7 ± 4.88	30.65 ± 5.12
	Female (n=20)	54.8 ± 3.15	38.7 ± 7.61

As per the results tabulated in Table 2, serum CRP ranges from 0.45 to 2.9 mg/dl in case of controls. The same range increased in metabolic syndrome to 1.7 to 6.8 mg/dl and further increased in higher end was seen in case of type 2 DM to 7.58 mg/dl. Highest value of mean CRP was noted in case Metabolic syndrome which is 3.59 mg/dl

with standard deviation of ± 1.284, followed in Type 2 DM which is 3.52 mg/dl with standard deviation of ± 1.436. The mean CRP levels in case of controls are nearly half, i.e. 1.215 mg/dl with standard deviation of ± 0.688.

Serum Magnesium levels range from 1.98 to 2.4 mg/dl in case of controls. The same range very slightly decreased to 1.7 to 2.38 mg/dl both in case of metabolic syndrome and Type 2 DM. The mean value of Magnesium 2.15 mg/dl with standard deviation of ± 0.131 is seen in controls. The mean value of magnesium dropped to 2.01 mg/dl in case metabolic syndrome and 2.0 mg/dl in Type 2 DM. with standard deviation of ± 0.151 and ± 0.156 respectively.

Table 2: Comparison of Serum CRP and Magnesium levels in Controls, Metabolic syndrome and Type 2 DM patients

Parameters	Controls (n=40) Mean ± SD	Metabolic syndrome (n=40) Mean ± SD	Type 2 DM (n=40) Mean ± SD
CRP (mg/dl)	1.215 ± 0.688	3.59 ± 1.284 **	3.52 ± 1.436 **
Magnesium (mg/dl)	2.15 ± 0.131	2.01± 0.151 *	2.0± 0.156 *

* Statistically significant ** Statistically highly significant

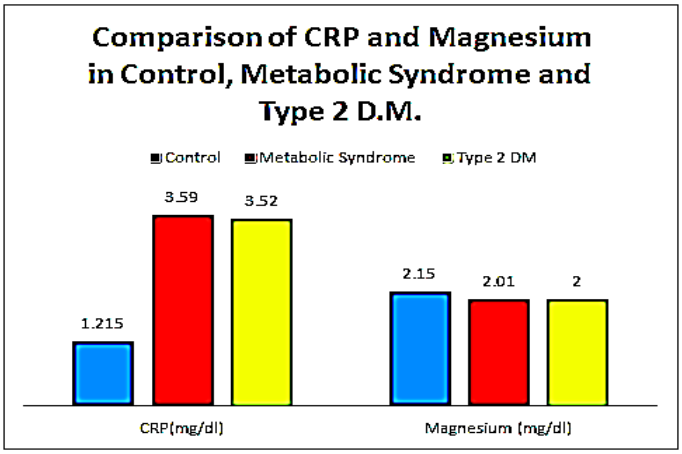


Table 3: Gender wise distribution of serum CRP and Magnesium levels in Controls, Metabolic syndrome and Type 2 DM patients

Parameter	Control (n=40)		Metabolic syndrome (n=40)		Type 2 DM (n=40)	
Gender	Male (n=20)	Female (n=20)	Male (n=20)	Female (n=20)	Male (n=20)	Female (n=20)
CRP (mg/dl)	1.15 ± 0.62	1.28 ± 0.779	3.66 ± 1.295**	3.478 ± 1.63**	3.55 ± 1.395**	3.63 ± 1.237**
Magnesium (mg/dl)	2.143 ± 0.096	2.157 ± 0.163	2.043 ± 0.137*	1.973 ± 0.173*	2.071 ± 0.157*	1.945 ± 0.121*

** P value <0.001, Highly significant, * P value <0.005, statistically significant

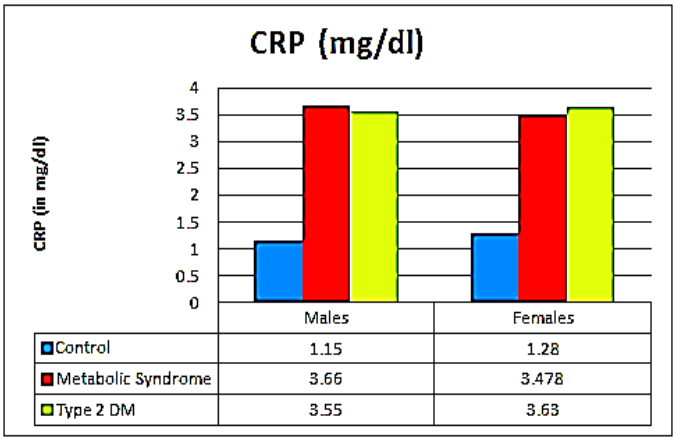
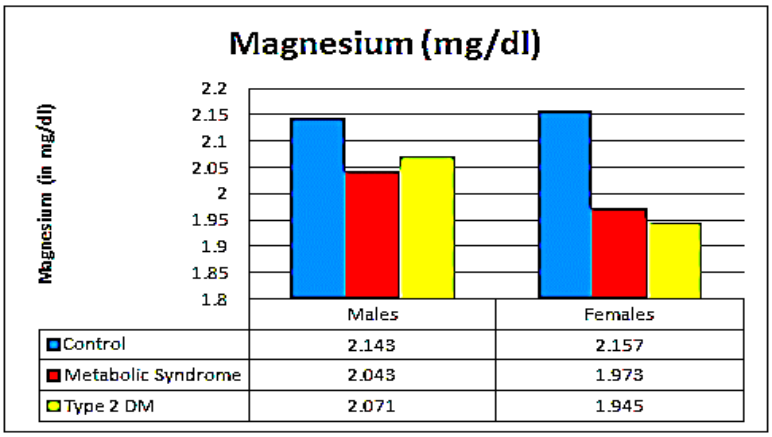


Table 3 depicts the gender wise comparison of CRP and Magnesium levels in controls, metabolic syndrome and type 2 D.M. These mean Magnesium level decreased in both males and females in case of metabolic syndrome and Type 2 D.M.



	Males	Females
Control	2.143	2.157
Metabolic Syndrome	2.043	1.973
Type 2 DM	2.071	1.945

Discussion

Today in this fast and growing world the life expectancy has increased. The average life expectancy of males in India is 63.20 yrs and females is 67.50 yrs.[6] Everyone wants there life to be disease free, but chronic diseases like Type 2 diabetes mellitus (DM) is far large emerging and is a major public health issue worldwide and it is increasing in aging populations.[1,7,6]

Being chronic systemic disease, type 2 DM leads to macrovascular and microvascular complications in older adults and premature mortality & morbidity related to cardiovascular disease.[1,8,9]

Metabolic Syndrome is considered as precursor of various systemic diseases including diabetes mellitus. Metabolic syndrome cases are prone for developing diabetes mellitus and cardiovascular disease.[10,11,12] This slow growing epidemic is a dangerous condition. The understanding of the mechanism involved in the metabolic syndrome will help us to intervene early so that its progression can be halted.[10] There is a need to develop various parameters for monitoring the progression of the same. Different studies suggest that magnesium levels may play an important role in the pathophysiology of insulin-resistance leading to metabolic syndrome and then diabetes mellitus.[10,13] Investigations have shown that metabolic syndrome and diabetes mellitus are chronic inflammatory processes, altering CRP and interleukin 6 in due process. Magnesium and CRP levels are also interlinked with one another.[14]

For adults, the reference interval for serum magnesium is approximately 1.7 to 2.4 mg/dl.[15] The range of magnesium in this study was within normal limits in all the three groups i.e. controls, metabolic syndrome and type 2 DM. The mean Magnesium value of the control group is 2.15 mg/dl. This mean value dipped significantly in metabolic syndrome subjects to 2.01 mg/dl and almost similar in Type 2 DM to 2.00 mg/dl. The drop in the mean value in case of metabolic syndrome compared with the controls was significant so is the case between controls and type 2 DM. when mean value of metabolic syndrome and type 2 DM was similar. Thus we can say that mean magnesium decreases in both metabolic syndrome and type 2 DM to similar lower levels when compared with controls or normal subjects.

The present study shows that metabolic syndrome and patients with type 2 diabetes mellitus are associated with low serum Mg. To our knowledge, it is observed that only few studies are done that investigate Mg status in relation to such a wide spectrum of metabolic syndrome parameters. Magnesium as a nutrient plays an important role in enzymatic activities in metabolism of glucose. In type 2 DM and Metabolic Syndrome the sensitivity to insulin is decreased. Few authors[16] has documented that the magnesium levels are inversely related to the sensitivity of insulin. Thus in our study mean magnesium decreases in both metabolic syndrome and type 2 DM to similar lower levels when compared with controls or normal subjects due to increase in the sensitivity.

This finding of our study goes with concept put forward by de Valk et al.[16] The finding of our study was similar to studies conducted by Villegas R et al.,[17] Lecube A et al.,[18] Munekage E et al.[19]

In our study hypomagnesiumia was not seen but only levels were in lower range. Some studies like Huang JH et al.[20] found hypomagnesiumia in 37% of cases studied. Huang JH et al.[20] concluded that serum magnesium may not be a good marker, but hypomagnesemiumia could indicate a higher possibility of critical situations associated to diabetes, metabolic syndromes or cardiovascular diseases. Thus, low magnesium levels can lead to further deficiency with metabolic abnormalities and depression.[20]

In the present study the mean level of magnesium in subjects with metabolic syndrome and type 2 DM showed almost same lower level. Patients with metabolic syndrome have multi system involvement, like central obesity, hypertension, dyslipidemia, and

impaired glucose tolerance. This group of conditions has also become synonymously being called as insulin resistance syndrome, which may be a more appropriate term. It is said that insulin resistance is likely a primary link between the components of the metabolic syndrome. The study by Guerrero-Romero F et al.[21] showed that in non-diabetic patients the metabolic syndrome is independently associated with low serum total (t-Mg) levels. The components of metabolic syndrome, like dyslipidemia and hypertension are strongly related to hypomagnesemia. Increased CRP is a marker of inflammation.[22] The mean value significantly doubled in case of metabolic syndrome cases to 3.59 mg/dl. Similar value (3.52 mg/dl) was seen in cases of type 2 DM patients.

The present study showed that mean value of CRP significantly increased in metabolic syndrome and type 2 DM. This finding of our study was similar to study conducted by Nakano S et al.[23] found that hs CRP level was more in metabolic syndrome group than diabetes group. This finding is similar to our study in which the mean CRP levels were slightly higher in case of metabolic syndrome group than the diabetic group. Han TE et al.[24] study showed that CRP was not a significant predictor of the development of metabolic syndrome in men. This may be due to ethnicity, which may also play a role in explaining inconsistent results.[8]

CRP is said to be one of the markers of inflammation. Most of the prospective epidemiological studies revealed that elevated C-reactive protein (CRP) levels within the normal range predict the development of incident type 2 diabetes mellitus.[22] The increase in the level of CRP both in case of metabolic syndrome and type 2 DM suggests the potential crucial role for inflammation in the pathogenesis of the disease process.[14] CRP might be a marker for risk that is present many years before the onset of metabolic syndrome or type 2 diabetes mellitus. It was also possible that CRP was a marker for an antidiabetic effect that was incrementally exhausted before diagnosis of diabetes or metabolic syndrome.[22] Monitoring the level of CRP in potential person of developing diabetes mellitus can be used as a surveillance tool. Thus, like CRP, which is one of the marker of inflammation in Metabolic syndrome and type 2 diabetes mellitus, further studies can be carried out to outline other inflammatory markers and their relation with metabolic syndrome and type 2 diabetes mellitus.

Our study shows in brief, that Magnesium level decreases to almost lower normal range in metabolic syndrome and type 2 diabetes mellitus while the CRP levels almost increases twice in case of metabolic syndrome cases and type 2 diabetes mellitus. The levels of magnesium and CRP (an inflammatory marker) are related to one another inversely. This combined finding of our study is supported by King DE et al.[14]

Conclusion

In the present study we found that Serum Magnesium level decreased to almost lower normal range and CRP levels increased almost twice in cases of Type 2 DM as compared with control and almost the similar result seen in cases of Metabolic syndrome. The decreased magnesium and elevated CRP levels found during the development of Metabolic Syndrome suggest that these two inversely related inflammatory markers are independent of Type 2 DM. This study could be pioneer in further studying degree of hypomagnesemia and correlated elevation in CRP levels, considering larger number of cases with comparative different cluster of metabolic syndrome and that too for a longer duration. Moreover, dietary supplementations of magnesium and/or other nutrient should be tried in case of Metabolic Syndrome along with assessment of Magnesium, CRP or other markers, in view to control these end stage pre diabetes condition from the development of Type 2 DM and to reduce the mortality resulting from cardiovascular diseases.

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