Original Article

Association of serum magnesium with type 2 diabetes mellitus and diabetic retinopathy

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Abstract

Introduction and Objective: The rising burden of type 2 diabetes mellitus (T2DM) globally has led to huge morbidity and socioeconomic impact in developing countries. In India, too, it has become a silent epidemic and it is estimated that there are over 60 million diabetics. Although in recent years, a lot of research papers have come up on the management of diabetes, latest treatment modalities may not be affordable to all. So, it becomes imperative to prioritize research on prevention and primary care. Magnesium is an intracellular cation and coenzyme for various reactions of the glycolytic pathway. Hypomagnesemia has been shown to precipitate hyperglycemia and has, therefore, been implicated in insulin resistance and its microvascular complications. Poor glycemic control has been associated with retinopathy. Hence, we evaluated association of serum magnesium with T2DM and diabetic retinopathy. **Materials and Methods:** In a cross-sectional study in North India, 250 consenting adult patients from outpatient department of family medicine of our hospital were recruited. Critically ill patients and those on magnesium supplements were excluded. Clinicolaboratory profile was evaluated. Patients were divided based on serum magnesium level ≤ 1.7 mg/dL (group 1) and > 1.7 mg/dL (group 2). Glycemic control and proportion of diabetic retinopathy were compared between these two groups by using univariate regression analysis. **Results:** Out of 250 patients, 110 patients (44%) were found to have hypomagnesemia. Glycemia by fasting blood sugar (P = 0.02), post-Prandial blood sugar (P = 0.04), and HbA_{1C} (P = 0.01) was poorly controlled in hypomagnesemia group. In group 1, 62.7% had non proliferative diabetic retinopathy and 21.8% had proliferative diabetic retinopathy, whereas in group 2, 14.3% had nonproliferative diabetic retinopathy and 8.6% had proliferative diabetic retinopathy (P < 0.001). **Conclusions:** Magnesium deficiency is associated with increased risk of diabetic retinopathy and poor glycemic control. Dietary supplementation may be advised to prevent such complications and improve glycemic control.

Keywords: Diabetes, magnesium, retinopathy, T2dm

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Type 2 diabetes mellitus (T2DM) constitutes 90% of all DM cases and is characterized by progressive insulin secretory defect on the background of insulin resistance.[1] It is a growing public health burden across the world, particularly in the developing countries.

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India is almost in the grip of diabetes epidemic and warrants immediate corrective measures.

The Sixth Diabetes Atlas, published by the International Diabetes Federation (IDF), revealed that there was an estimated 65.1 million cases of diabetes in India in 2013, which was more than double of the 2000 statistics.[2] It was predicted that by 2030 DM may afflict up to 79.4 million individuals in India, whereas China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease.[3,4] However, these statistics for India represent mostly the urban

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profile and may not be representative or provide an exact prevalence in view of a rural-dominated population.

Indians have a high ethnic and genetic susceptibility for the disease and also have lower threshold limits for the environmental risk factors.[5] It is a matter of major concern that Indians develop T2DM at a younger age compared with western populations. They also develop diabetes with minor weight gain.[5]

Diabetes is considered a lifestyle disease and diet is widely believed to play an important role in the development of DM and its associated complications. These complications can be either microvascular (retinopathy, neuropathy, nephropathy) or macrovascular (coronary heart disease, peripheral arterial disease, cerebrovascular disease) or both.

Magnesium (Mg) is the fourth most abundant cation in the human body and plays a key role in many fundamental biological processes, including energy metabolism and DNA synthesis. It also plays an important role in the phosphorylation reactions of glucose and its metabolism. Its deficiency has been implicated in insulin resistance, carbohydrate intolerance, dyslipidemia, and complications of diabetes.[6]

Mg has received considerable attention for its potential role in improving insulin sensitivity and preventing diabetes and its complications. However, results are inconsistent among the studies.[7,8] Observations in Caucasian diabetics have linked hypomagnesemia as being an additional risk factor for the development of diabetic retinopathy, but this correlation was not observed in black African diabetics.[7] Most of these studies could not be compared because of different methodology and inclusion and exclusion criteria.

In this study, we evaluated serum magnesium with T2DM and diabetic retinopathy in north Indian population.

Materials and Methods

Study location: The study was done at the outpatient department of family medicine of the center with state-of-the-art facilities and all diagnostic modalities including research facility.

Study population: Patients with T2DM above the age of 18 years were selected from Out Patient Departments fulfilling the mentioned criteria, and their written informed consent was taken for participation in the study.

Study duration: The study was conducted over a period of 18 months from March 2014 to September 2015.

Study design: This was a cross-sectional observational study. Detailed history was taken from all patients regarding presenting complaints, symptoms of T2DM, its duration and complications, and current medications. Personal history was taken regarding alcohol, smoking, exercise, or any other addiction. Patients were thoroughly examined to look for signs of thyroid and adrenal dysfunction.

Sample size: Sample size was calculated using the formula for descriptive study $(Z^2 \times P \times q)/d^2$. When the expected prevalence of hypomagnesemia with T2DM (p) = 20%, precision error of estimation (d) = 0.05, and alpha = 0.05, a sample size of 250 cases were taken.

In this study, where a total of 320 subjects were recruited, 30 opted out of the study and 40 were excluded based on the defined criteria. In total, 250 eligible subjects were enrolled for the study. Double blinding was done to avoid any bias regarding conscious or unconscious bias in diagnosing retinopathy among hypomagnesemia group. They were then divided into two groups, viz., case and control based upon the serum magnesium level. These groups were as follows:

Group 1 (Case): T2DM with hypomagnesemia (S. Mg <1.7 mg/dL).

Group 2 (Control): T2DM with normal magnesium level (S. Mg 1.7–2.7 mg/dL).

The number of subjects in group 1 was 110, whereas in group 2, it was 140, in accordance with the sample size calculation.

Subjects

Inclusion criteria: Noncritically ill (APACHE score <10), T2DM patients of either sex with age >18 years were included.

Exclusion criteria: Patients with T2DM <18 years of age, on drugs known to affect magnesium levels [Table 1], with acute or chronic diarrheal/malabsorption states, on supplements containing magnesium, history of recent metabolic acidosis, pregnancy, lactation, and sepsis were excluded.

Methods

Consent and ethical approval: Written informed consent was taken from the participants at the time of enrollment. Ethical approval was procured before starting this study.

Enrollment: Patients were enrolled based on inclusion and exclusion criteria from outpatient department of family medicine.

For defining a case of T2DM, American Diabetes Association diagnostic criteria were used [Table 2].

Oral glucose tolerance test was performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

A detailed clinical history and examination [Annexure 1] was done for all consenting patients enrolled in the study. Diabetic retinopathy was classified as nonproliferative diabetic retinopathy

and proliferative diabetic retinopathy based on fundoscopy after dilation of eye. Fundus photo were also taken.

Investigations: About 5 mL of venous blood sample was taken after 12 h of fasting and again after 2 h of normal meal. About 10 mL of urine sample was collected from the patients. The samples were run in fully automated clinical chemical analyzer Beckman Coulter DXC-800. All patients were investigated for complete blood count, fasting blood sugar (FBS - Hexokinase); post-Prandial blood sugar (PPBS - Hexokinase), Glycated hemoglobin (HbA_{1C} - HPLC), and serum creatinine (IDMS - Jaffe Kinetic), and serum magnesium was measured by the xylidyl blue method. Biological reference interval in serum is taken as 1.7–2.7 mg/dL.

After collection of all data, relation of hypomagnesemia to glycemic control and diabetic retinopathy were done statistically.

Statistical analysis

SPSS version 17.0 was used to analyze the data. Results were reported as mean, standard deviation, frequency, and percentage. The comparison of normally distributed continuous variables between the groups performed using Student's *t*-test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using Mann–Whitney *U*-test. For all statistical tests, a *P* value <0.05 was taken to indicate a significant difference.

Results

In all, 320 subjects were interviewed out of which 30 opted out of the study and 40 were excluded based on the defined criteria. In total, 250 eligible subjects were enrolled for the study. They were then divided into two groups based upon the serum magnesium level in T2DM.

In our study, prevalence of hypomagnesemia was observed among 110 patients out of 250 (44%) of T2DM patients. Over all male to female ratio was 0.7:1. In groups 1 and 2, 57.3% and 57.9% were female, respectively. There was no significant difference in two groups ($P = 0.926$).

The mean age of patients was 55.8 ± 10.05 and 56.81 ± 11.45 years in groups 1 and 2, respectively. All the patients were >30 years of age. In groups 1 and 2, 34.5% and 27.1% were 30- to 40-year old, respectively. Similarly, in group 1, 34.5%, 32.7%, 24.5%, and 8.2% and in group 2, 27.1%, 24.3%, 30.7% and 14.3% were in the age groups of 41–50, 51–60, 61–70, and >70 years, respectively. Differences were not significant ($P = 0.0784$).

The mean body mass index (BMI) was 26.74 ± 3.76 kg/m^2 in group 1 and 24.48 ± 4.23 kg/m^2 in group 2 ($P = 0.017$). The mean value of FBS was 173.64 ± 38.56 mg/dL in group 1 and 148.87 ± 47.87 mg/dL in group 2 ($P = 0.02$). The mean PPBS were 241 ± 59.17 mg/dL in group 1 and 215 ± 77.37 mg/dL in group 2 ($P = 0.04$) [Table 3].

Table 1: Drugs known to affect magnesium status

Aminoglycosides
Amphotericin B
Cetuximab
Cyclosporine
Digoxin
Diuretics (loop, thiazide, osmotic)

Table 2: Criteria for the diagnosis of diabetes mellitus

Symptoms of diabetes plus random blood glucose concentration 11.1 mmol/L (200 mg/dL) or
Fasting plasma glucose 7.0 mmol/L (126 mg/dL) or
HbA_{1C} >6.5% or
Two-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test

Table 3: Hypomagnesemia association

	Hypomagnesemia	Normal magnesium	*P*
Number of patients	110	140	
Mean age±SD	55.8±10.05	56.81±11.45	0.458
BMI±SD	26.74±3.76	24.48±4.23	0.017
Mean FBS	173.64±38.56	148.87±47.87	0.02
Mean PPBS	241±59.17	215±77.37	0.04
Mean HbA1c	8.33±1.92	7.78±1.48	0.01
Mean urine ACR mg/g of creatinine	573.2±1748.05	135.2±823.1	0.01

The mean HbA_{1C} values were 8.33 ± 1.92% in group 1 and 7.78 ± 1.48% in group 2 ($P = 0.01$) [Table 3]. Blood pressure in both the groups was comparable.

Mean urine albumin/creatinine ratio (ACR) was 573.2 ± 1748.05 mg/g of creatinine in group 1 and 135.2 ± 823.1 mg/g of creatinine in group 2 ($P < 0.001$). In group 1, 53.6% had urine ACR >30, whereas in group 2, 25.7% had urine ACR >30.

In group 1, 62.7% had nonproliferative diabetic retinopathy (NPDR) (odds ratio [OR] – 21.73) and 21.8% had proliferative diabetic retinopathy (PDR) (OR – 12.65), whereas in group 2, 14.3% had nonproliferative diabetic retinopathy and 8.6% had proliferative diabetic retinopathy. There was significant difference among these two groups ($P < 0.001$) [Table 4, Figure 1].

Discussion

DM has put an enormous socioeconomic burden on developing countries like India. Early age of onset, associated comorbidity, costly drugs, and investigations and rising out-of-pocket expenditure have made it more challenging for primary care health professionals. Recent research on newer drugs have given promising results but are out of reach for an average earning majority of Indian population because of high prices.[9] So,

Table 4: Association of hypomagnesemia with retinopathy

Retinopathy	Total	Hypomagnesemia		Normal magnesium		Odds ratio	95% confidence interval	*P*
		n	Percentage	*n*	Percentage			
Absent	125	17	15.5	108	77.1			<0.001
NPDR	89	69	62.7	20	14.3	21.73	10.75-45.45	
PDR	36	24	21.8	12	8.6	12.65	5.37-30.30	
Total	250	110	100.0	140	100.0			

NPDR: Nonproliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy

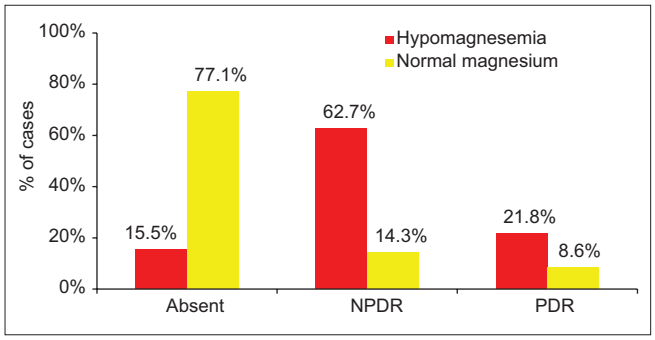

Figure 1: Correlation between Retinopathy and Hypomagnesemia

research priorities should be preventing or delaying complication with cost effective interventions. In this study, we focused on magnesium level in relation to glycemic control and retinopathy.

Prevalence of hypomagnesemia among noncritically ill patients with T2DM was 44%. Among various other studies, hypomagnesemia have been reported to occur in 13.5%–47.7% of non-hospitalized patients with type 2 diabetes.[10-14] The wide range in the reported prevalence of hypomagnesemia most likely reflects the difference in the definition of hypomagnesemia, techniques in Mg measurements, and the heterogeneity of the selected patient cohort.

In group with hypomagnesemia, the mean age of patients were 55.8 ± 10.05 years and in group of T2DM patients with normal serum magnesium level were 56.81 ± 11.45 years. There was no significant difference observed between these two groups. It was similar to the study conducted by Al-Osali *et al.* in Muscat, Oman, which concludes that diabetics have significantly lower total Mg levels with a difference of 0.12 mmol/L ($P < 0.001$) irrespective of age.[15]

There was significant difference of BMI between two groups in our study ($P = 0.017$). Gupta *et al.* also found inverse correlation of serum magnesium with BMI.[16] However, Ghattaura *et al.* reported weak association of BMI and hypomagnesemia (OR – 1.05, $P = 0.04$) and strongest association with T2DM, which was an independent risk factor for hypomagnesemia (OR – 3.77, $P = 0.001$).[17] T2DM is the main factor accounting for low serum magnesium levels in overweight diabetics. Hypomagnesemia may aggravate insulin resistance state in overweight subjects. This can predispose them to metabolic complications of DM.

Significant difference of FBS, PPBS, and HbA_{1C} was observed between two groups. Studies by Lecube *et al.*[18] and Dasgupta *et al.*[19] on diabetes and hypomagnesemia found significant negative correlations between magnesium and fasting plasma glucose. In another study by Rao *et al.*,[20] the mean value of FBS, PPBS, and HbA_{1C} was higher among the group with serum Mg <1.7 mg/dL. Intracellular magnesium plays a key role in regulating insulin action, insulin-mediated glucose uptake, and vascular tone. Reduced intracellular Mg concentrations result in a defective tyrosine-kinase activity, postreceptor impairment in insulin action, and worsening of insulin resistance in diabetic patients.[21,22]

HbA_{1C} is formed through the nonenzymatic binding of circulating glucose to hemoglobin. Higher levels of glucose in the blood contribute to more binding and consequent higher levels of HbA_{1C}. Since the life span of an RBC is 120 days, HbA_{1C} reflects average plasma glucose over the past few months.[23]

Diabetic retinopathy is one of the leading causes of blindness in the world. Decrease in visual acuity in diabetic retinopathy is either associated with maculopathy or its proliferative complications. Hypomagnesemia has been reported to occur at an increased frequency among patients with type 2 diabetes compared with their counterparts without diabetes.[24]

In our study, while evaluating serum magnesium with retinopathy, we found significant difference ($P < 0.001$). Similar findings have been reported by Kundu *et al.*[25] and Kauser *et al.*,[26] who observed serum magnesium levels significantly lower in patients with diabetic retinopathy compared with diabetics without complications.

Baihui *et al.*[27] in their study on Chinese diabetic patientsreported that low serum magnesium level is associated with microalbuminuria. HbA_{1C} and albuminuria are contributing factors in the degree of retinopathy and this correlation can be explained by the common mechanism involved in tissue damage by DM. HbA_{1C} has special affinity for oxygen, thereby causing tissue anoxia and plays a role in causation of micro- and macroangiopathy.[28] In our study, too, we found an inverse correlation between urine ACR and serum magnesium level.

Increased endothelial cell damage leads to microaneurysm, leakage of which causes maculopathy.[29] Low Mg levels may promote endothelial cell dysfunction and thrombogenesis via increased platelet aggregation and vascular calcifications.[28] Low Mg levels may also lead to induction of proinflammatory and profibrogenic response[30] and reduction of protective enzymes

against oxidative stress. Moreover, because Mg is crucial in DNA synthesis and repair,[31] it is possible that Mg deficiency may interfere with normal cell growth and regulation of apoptosis. This would explain our finding that hypomagnesemia was more pronounced in diabetic retinopathy group. Hypomagnesemia seemed to be a possible risk factor in the development and progression of diabetic retinopathy.

The inferences that can be drawn from our data are subject to some limitations. No blinding was done in the study and being a cross-sectional study, no follow-up of the patients was done. Since exact onset of T2DM may not be known, exact duration of T2DM could not be determined.

Summary and recommendations

Hypomagnesemia was seen in 44% of diabetes patients and it significantly correlated with poor glycemic control and diabetic retinopathy. We suggest institution of dietary recommendation for increased consumption of major food sources of magnesium (such as whole grains, nuts, and green leafy vegetables) at the time of diagnosis to prevent and minimize complications of T2DM.

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Nil.

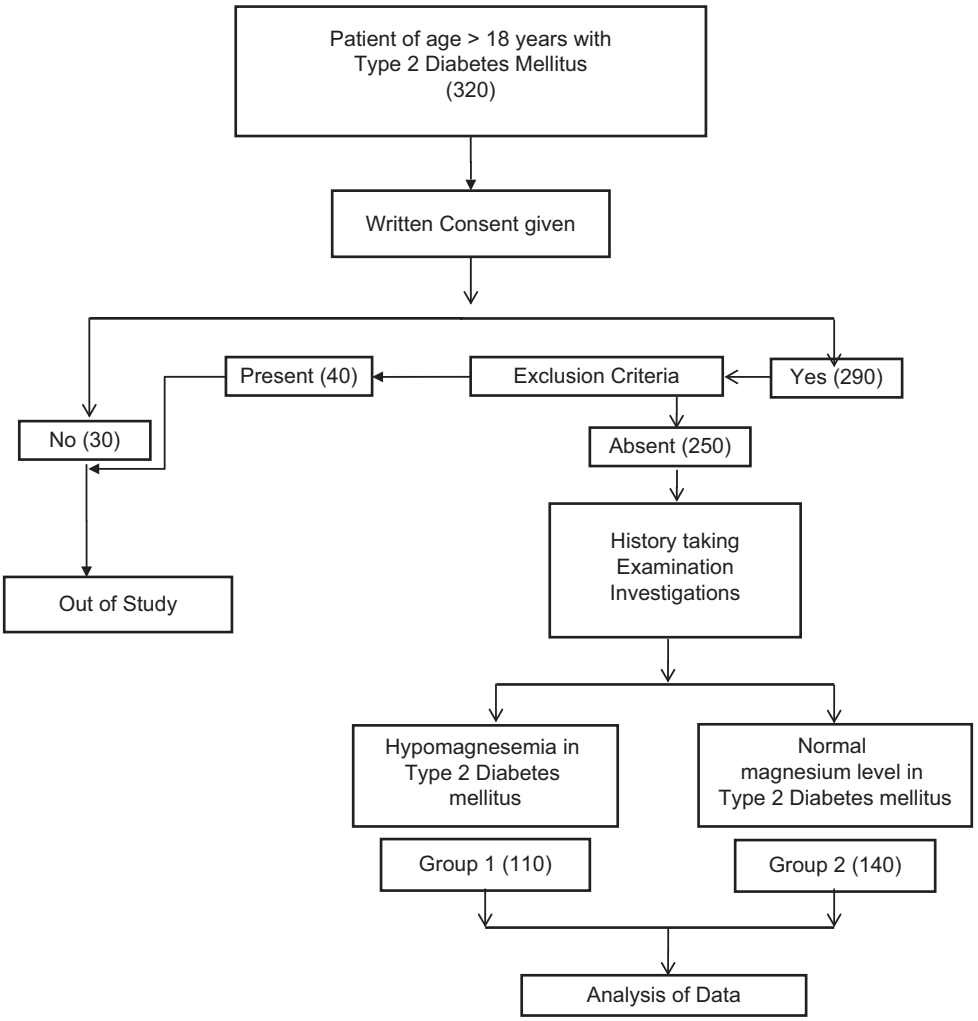
Conflicts of interest

There are no conflicts of interest.

References

1. Classification and Diagnosis of Diabetes. Diabetes Care 2014;38(Suppl 1):S8-16.
2. International Diabetes Federation. IDF Diabetes Atlas, 6th ed. Brussels, Belgium: International Diabetes Federation; 2013. Available from: http://www.idf.org/diabetesatlas.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes-estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
4. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diab Res ClinPract 2011;94:311-21.
5. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. Lancet 2010;375:408-18.
6. Resnick LM, Gupta RK, Bhargava KK, Hgruenspan H, Alderman MH, Laragh J. Magnesium deficiency in diabetes. Hypertension 1991;17:951-7.
7. Erasmus RT, Olukoga AO, Alanamu RA, Adewoye HO, Bojuwoye B. Plasma magnesium and retinopathy in black African diabetics. Trop Geogr Med 1989;41:234-7.
8. Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: The atherosclerosis risk in communities study. Arch Intern Med 1999;159:2151-9.
9. Yesudian C, Grepstad M, Visintin E, Ferrario A. The economic burden of diabetes in India: A review of the literature. Global Health 2014;10:80.
10. McNair P, Christensen MS, Christiansen C, Madsbad S, Transbøl I. Renal hypomagnesaemia in human diabetes mellitus: Its relation to glucose homeostasis. Eur J Clin Invest 1982;12:81-5.
11. Pham PC, Pham PM, Pham PA, Pham SV, Pham HV, Miller JM, *et al.* Lower serum magnesium levels are associated with more rapid decline of renal function in patients with diabetes mellitus type 2. Clin Nephrol 2005;63:429-36. [published erratum appears in Clin Nephrol 64: 248, 2005].
12. Mather H, Nisbet JA, Burton GH, Poston GJ, Bland JM, Bailey PA, *et al.* Hypomagnesemia in diabetes. Clin Chim Acta 1979;95:235-42.
13. Walti MK, Zimmermann MB, Spinas GA, Hurrell RF. Low plasma magnesium in type 2 diabetes. Swiss Med Wkly 2003;133:289-92.
14. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, *et al.* Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: The ARIC study. Atherosclerosis Risk in Communities Study. J Clin Epidemiol 1995;48:927-40.
15. Al-Osali ME, Al-Qassabi SS, ElSayed MK. Hypomagnesemia in type 2 diabetic Omani patients. Saudi Med J 2009;30:897-901.
16. Gupta N, Sharma S, Kaushik G, Gupta B. Association between indexes of insulin sensitivity/resistance and serum magnesium levels in overweight diabetic subjects. Indian J Clin Pract 2014;24:932-7.
17. Ghattaura N, Murphy C, Valen P. High prevalence of hypomagnesemia and its relation to BMI, type 2 diabetes, and clinical disease measures in a VA outpatient rheumatology clinic population [abstract]. Arthritis Rheumatol 2015;67(Suppl 10).
18. Lecube A, Baena-Fustegueras J, Fort J, Pelegrí D, Hernández C, Simó R. Diabetes is the main factor accounting for hypomagnesemia in obese subjects. PLoS One 2012;7:e30599.
19. Dasgupta A, Sarma D, Saikia UK. Hypomagnesemia in type 2 diabetes mellitus. Indian J Endocrinol Metab 2012;16:1000-3.
20. Rao PP, Shariff MG. Serum magnesium levels in type 2 diabetic patients with microalbuminuria and normoalbuminuria. Int J Sci Stud 2015;3:11-5.
21. Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. Arch Biochem Biophys 2007;458:40-7.
22. Takaya J, Higashino H, Kobayashi Y. Intracellular magnesium and insulin resistance. Magnes Res 2004;17:126-36
23. Cohen R, Franco R, Khera P, Smith E, Lindsell C, Ciraolo P, *et al.* Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. Blood 2008;112:4284-91.
24. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. Clin J Am Soc Nephrol 2007;2:366-73.
25. Kundu D, Osta M, Mandal T, Bandyopadhyay U, Ray D, Gautam D. Serum magnesium levels in patients with diabetic retinopathy. J Nat Sci Biol Med 2013;4:113-6.
26. Kauser MM, Afreen A, Kasi J. Study of serum magnesium levels in diabetic retinopathy. J Res Med Den Sci 2014;2:19-22.
27. Xu B, Sun J, Deng X, Huang X, Sun W, Xu Y, *et al.* Low serum magnesium level is associated with microalbuminuria in Chinese diabetic patients. Int J Endocrinol 2013;2013:1-6.

28. van den Oever I, Raterman H, Nurmohamed M, Simsek S. Endothelial dysfunction, inflammation, and apoptosis in diabetes mellitus. Mediators Inflamm 2010;2010:1-15.
29. Rayssignier Y. Role of magnesium and potassium in the pathogenesis of arteriosclerosis. Magnesium 1984;3:226-38.
30. Shivakumar K. Pro-fibrogenic effects of magnesium deficiency in the cardiovascular system. Magnes Res 2002;15:307-15.
31. Hartwig A. Role of magnesium in genomic stability. Mutat Res 2001;475:113-21.



Annexure 1: The flow diagram of study