Hypomagnesemia, Poor Glycemic Control and Microalbuminuria as Risk Factors of Diabetic Retinopathy

SWETHA NK, VIRUPAKSHA HS, PRASHANT VISHWANATH, SUMA MN, BHIMAPPA MALWADI

ABSTRACT

Background: Diabetic retinopathy (DR) is a sight threatening complication of diabetes mellitus and is one of the leading causes of acquired blindness in adults. Various precipitating factors such as duration of disease, glycemic control, dyslipidemia, hypomagnesemia and microalbuminuria have been implicated in the development and progression of diabetic retinopathy. This study is an attempt to evaluate the diagnostic value of HbA1c, serum magnesium, microalbuminuria in the onset & progression of Diabetic Retinopathy.

Aim: The aim of the study was to find the association between serum magnesium, HbA1c, lipid profile and microalbuminuria in diabetic retinopathy

Settings and Design: In this cross-sectional study, 30 diabetic patients with retinopathy, 30 diabetic patients without retinopathy, and 30 age & sex matched controls were selected.

Methods and Materials: The serum from these patients was used for the estimation of fasting blood sugar, magnesium, total cholesterol and triglyceride. Two ml of blood, collected in vacutainers containing EDTA was used for the estimation of HbA1c. The random, midstream urine sample (10ml) was collected in sterile containers and assayed for microalbumin and urinary creatinine.

Statistical Analysis: The Independent-Samples t-test procedure was used to compare the mean for two groups of cases. The One-Way ANOVA was used for one-way analysis of variance for a quantitative dependent variable by a single factor (independent) variable. The correlation between the parameters was worked out using Pearson's correlation. p-value < 0.05 was considered to be statistically significant.

Results: There was a positive correlation between HbA1c & microalbuminuria (r=0.597) in diabetic patients with retinopathy & negative correlation between serum magnesium & HbA1c (r=-0.611), microalbuminuria (r= -0.437) in diabetic patients with retinopathy.

Conclusion: Regular monitoring of all diabetic patients with various biochemical parameters like HbA1c, magnesium & microabuminuria might reduce the onset & progression of microvascular complications.

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disease caused by a variable interaction between hereditary and environmental factors. It is associated with a considerable mortality from a variety of complications, which tend to worsen over time and carries a significant premature mortality risk. Its main features are abnormal insulin secretion, high levels of blood glucose and variety of complications such as retinopathy, nephropathy, neuropathy and arteriosclerosis [1,2].

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The diabetes mellitus in urban population in developing countries is projected to double between 2000 and 2030. According to the latest World Health Organization (WHO) report, India has 31.7 million diabetic subjects, and the number is expected to increase to a staggering 79.4 million by 2030 [3].

Diabetic Retinopathy occurs in both type 1 and type 2 diabetes mellitus. It has been shown that nearly all type 1 and 75% of type 2 diabetes mellitus patients will develop diabetic retinopathy after 15 yrs of duration of diabetes mellitus as shown in earlier epidemiological studies. In India with the epidemic increase in type 2 diabetes mellitus, as reported by WHO, diabetes mellitus is fast becoming an important cause of visual disability [4].

The chance of loosing the sight is about 25 times higher compared to normal individuals. There are a series of risk

factors related to the development and progression of diabetic retinopathy such as duration of diabetes mellitus, poor glycemic control, dyslipidemia, hypertension and hypomagnesemia [1,5].

Chronic hyperglycemia is an important risk factor for the development of microvascular complications in DM. HbA1c has a special affinity for O_2 thereby causes tissue anoxia and plays a role in the causation of micro and macroangiopathy. There is a direct relation between the degree of glycemic control and the incidence and progression of retinopathy [6,7]. Hypomagnesemia has long been known to be associated with diabetes mellitus. Magnesium depletion is said to have a negative impact on glucose homeostasis and insulin sensitivity. This association between diabetes mellitus and magnesium is said to have a wide range of impact on diabetic control and complications [6,8].

The prevelance of microalbuminuria among diabetic patients is 15-20%. Persistence of microalbuminuria in DM patients is a risk marker not only for kidney & cardiac disorders, but also for severe ocular morbidity [9]. The association between serum lipids and diabetic retinopathy has been investigated in many studies with conflicting results. Some studies have shown a positive correlation between serum cholesterol, low density lipoproteins and retinal hard exudation [10].

The magnitude of damage caused by the microvascular complications of diabetes stresses the need for sensitive markers of screening for retinopathy. This study is an attempt to find the association between serum magnesium, HbA1c, lipid profile and microalbuminuria in diabetic retinopathy & to evaluate the diagnostic value of HbA1c, serum magnesium, microalbuminuria in the onset & progression of Diabetic Retinopathy.

MATERIALS AND METHODS

The study was carried out in a Tertiary care Hospital in Mysore. Subjects who attended the Ophthalmology OPD for a period of 6 months, with history of DM were considered for the study. Clinical diagnosis was based on history and fundoscopic findings. Subjects were divided into 2 groups: Group 1- Diabetic patients with retinopathy and Group 2- Diabetic patients without retinopathy. In the present study, the comparisons between the 2 groups were performed according to the presence or absence of DR, regardless of its grading or severity. There were about 40 patients belonging to group 1 & 54 patients belonging to group 2. Out of these 30 were included in each group & rest were excluded from the study considering the exclusion criterion. The results were compared with 30 age and sex matched controls. The exclusion criterion were chronic diarrhoea, alcoholism, pregnancy, drugs causing hypomagnesemia like diuretics, cisplatin, pentamidine, and urinary tract infection, inflammatory conditions like rheumatoid arthritis, myocardial infarction, H/o recent surgery and major

trauma. The study protocol was approved by the institutional ethical committee and informed consent was obtained from the subjects under study.

Under all aseptic precautions, about 5ml of venous blood was collected. 3ml of blood, collected in gel tubes was allowed to clot and it was centrifuged at 5000rpm for 5 minutes. The serum separated was then used for the estimation of fasting blood sugar, magnesium, total cholesterol and triglycerides. 2ml of blood, collected in vacutainers containing EDTA was used for the estimation of HbA1c.The random, midstream urine samples (10ml) were collected in sterile containers without preservative and assayed for microalbumin and urinary creatinine. The samples were stored at 2°C-8°C in a refrigerator till the tests were carried out.

Blood glucose was estimated by GOD-PAP method [11], Serum magnesium was estimated by Xylidyl blue method [12], HbA1c was estimated by Latex agglutination inhibition assay [13], Serum triglyceride was estimated by GPO-PAP method [14], Serum total cholesterol was estimated by enzymatic endpoint method [15], Microalbumin in urine was estimated by immmunoturbidimetric method [16], Urinary creatinine was estimated by Jaffe's method [17]. All the parameters were estimated using Rx Daytona autoanalyzer.

STATISTICAL ANALYSIS

SPSS for windows Version-16 (2007) was employed for statistical analysis. The Independent-Samples t-test procedure was used to compare the mean for two groups of cases. The One-Way ANOVA was used for one-way analysis of variance for a quantitative dependent variable by a single factor (independent) variable. The correlation between the parameters was worked out using Pearson's correlation. p-value < 0.05 was considered to be statistically significant.

RESULTS

The mean age in diabetic patients with retinopathy was 49.53 ± 5.82 yrs, in diabetic patients without retinopathy it was 46.77 ± 6.99 yrs and in controls, it was 45.50 ±6.14 yrs. The mean duration of diabetes mellitus in diabetic patients with retinopathy was 9.70 ± 4.66 yrs and in diabetic patients without retinopathy it was 3.56 ± 2.31 yrs. The duration of diabetes mellitus was significantly higher in diabetic patients with retinopathy when compared to diabetic patients without retinopathy. The Mean and S.D of the various parameters and their significant difference in the study groups is shown in [Table/Fig-1].

Correlation between the various parameters

There was a positive correlation between HbA1c & microalbuminuria(r=0.597) in diabetic patients with retinopathy & negative correlation between serum magnesium & HbA1c (r=-0.611) & microalbuminuria (r= -0.437) in diabetic patients with retinopathy [Table/Fig-2].

DISCUSSION

Diabetic Retinopathy is a sight threatening complication of diabetes mellitus and is one of the leading cause of acquired blindness. Various precipitating factors such as duration of

found to be a potent predictor of progression of proliferative diabetic retinopathy. The risk of diabetic retinopathy increases stepwise with increasing degrees of hyperglycemia [7,19].

There was a positive correlation between HbA1c &

		FBS (mg/dl)	HbA1c (% of total Hb)	Total cholesterol (mg/dl)	Triglyceride (mg/dl)	Magnesium (mg/dl)	Microalbuminuria (μg/mg of creatinine)
a.	DM with DR	194.10± 67.79	8.62± 1.44	200.80± 52.33	183.03± 68.58	1.85 ± 0.24	78.53 ± 48.46
b.	DM without DR	144.86± 29.35	7.05± 1.07	180.77± 25.93	158.88± 70.47	1.95 ± 0.15	50.33 ± 24.77
c.	Controls	99.4± 14.10	4.63± 0.49	191.96± 31.32	145.73± 64.80	2.25 ± 0.15	22.84 ± 5.53
a v/s b		<0.001	<0.001	NS	NS	<0.05	<0.05
a v/s c		<0.001	<0.001	NS	<0.05	<0.001	<0.001
b v/s c		<0.001	<0.001	NS	NS	<0.001	<0.05

[Table/Fig-1]: Mean and SD of the various parameters and their significant difference in the study groups
p-value < 0.05 → Statistically significant; NS → Not significant; DM → Diabetes Mellitus: DR → Diabetic Retinopathy

	FBS	HbA1c	Total Cholesterol	Triglycerides	Magnesium	Microalbuminuria
FBS	1.000	0.736*	0.113NS	0.338*	-0.532*	0.468*
HbA1c		1.000	0.106NS	0.227*	-0.611#	0.597#
T Cholesterol			1.000	0.382*	-0.176NS	0.220*
Triglycerides				1.000	-0.291*	0.348*
Magnesium					1.000	-0.437#
Microalbuminuria						1.000

[Table/Fig-2]: Correlation between the various parameters
* represents p-value <0.05; # represents p-value <0.001, NS- Not significant

disease, glycemic control, dyslipidemia, hypomagnesemia and microalbuminuria have been implicated in the development and progression of diabetic retinopathy [1].

In the present study, the duration of diabetes mellitus was significantly higher in diabetic patients with retinopathy when compared to diabetic patients without retinopathy. Our findings are comparable with the previous studies, which have shown that duration of diabetes mellitus is one of the important risk factors in the development of diabetic retinopathy [18].

There was a significant increase in the FBS levels and HbA1c levels in diabetic patients with retinopathy and in diabetic patients without retinopathy when compared to the control group. Our findings are comparable with the previous studies, who have found that there was a significant association between glycemic control with the severity of diabetic retinopathy. Hyperglycemia, as indicated by the increase in the FBS and HbA1c levels, is a potent predictor of progression of diabetic retinopathy. The possible mechanism is hyperglycemia leads to glycation of virtually all proteins, resulting in the formation of advanced glycation end products. The interaction of advanced glycation end products and their receptors and increased activity of the polyol pathway have been implicated as mediators of increased microvascular permeability, ischemia and angiogenesis. Elevated HbA1c levels have been

microalbuminuria (r=0.597) in diabetic patients with retinopathy. The presence of microalbuminuria in DM reveals damage to the glomerular basement membrane & should be considered as a marker of early diabetic nephropathy. Patients with microalbuminuria were 2.6 times more likely to suffer from severe retinopathy. Microalbuminuria and diabetic retinopathy share common determinants. Both are said to be due to generalized vascular dysfunction [9]. Elevated hydrostatic and oncotic pressures initially cause renal hyper filtration, mesangial hypertrophy and proliferation, as well as changes in the polyanionic charge and porosity of the glomerular basement membrane in the kidney and in other vascular sites (eg. retina, arteries, nerve) by deposition of advanced glycation end products. These advanced glycation end products result in the various micro vascular complications [20]. Enzymes involved in the metabolism of anionic components of the extracellular matrix (e.g.heparan sulphate proteoglycan) vulnerable to hyperglycaemia, seem to constitute the primary cause of albuminuria and its associated complications [21].

There was a negative correlation between serum magnesium & HbA1c (r=-0.611, p<0.010) & microalbuminuria (r= -0.437,p<0.010) in diabetic patients with retinopathy. Hypomagnesemia has been implicated in the cause as

well as consequence of DM. It has been suggested that hypomagnesemia may induce altered cellular glucose transport, reduced pancreatic insulin secretion, defective post receptor signaling or altered insulin-insulin receptor interactions [22]. Hypomagnesemia as a consequence of DM is due to decreased intake, increased urinary excretion. (Osmotic diuresis, Glomerular hyperfiltratrion, Defective reabsorption & Microalbuminuria). The diabetic state interferes in the maintenance of normal concentrations on body Mg, being able to trigger hypomagnesemia easily, mainly in poor metabolic control, which more spontaneously leads to diabetic chronic complications [23].

DR is characterized by gradually progressive alterations in the retinal microvasculature, leading to retinal nonperfusion, increased vascular permeability, and pathologically increased intraocular proliferation of retinal vessels. Both diabetic retinopathy and nephropathy are microvascular complications of diabetes. Diabetic retinopathy and nephropathy seem to progress in a parallel manner. This may be because diabetic retinopathy shares similar pathophysiologic features with diabetic nephropathy. Kidney microangiopathy is thought to come before retinal microangiopathy. All patients with proliferative DR should undergo an evaluation of renal function that comprises of urinary albumin measurements [9,24].

The limitations of this study include

1. The small sample size and

2. The stages of diabetic retinopathy not taken into consideration. Larger population-based studies, with oral magnesium supplementation are required to ascertain the association of Hypomagnesemia, & microalbuminuria in patients with Diabetic retinopathy.

CONCLUSION

We have observed a significant correlation between DR and Poor Glycemic control, Hypomagnesemia, Microalbuminuria. All diabetic patients with microalbuminuria should undergo retinal evaluation & all patients with DR should undergo an evaluation of renal function that comprises of urinary albumin measurements. Progression of DR can be halted in the initial stages by improving diabetes management, nutritional supplementation with magnesium & Regular ophthalmologic follow-up. Regular monitoring of all diabetic patients with biochemical parameters like HbA1c, magnesium & microalbuminuria might be helpful to prevent the onset & progression of Diabetic retinopathy.

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AUTHOR(S):
1. Dr. Swetha NK
2. Dr. Virupaksha HS
3. Dr. Prashant Vishwanath
4. Dr. Suma MN
5. Dr. Bhimappa Malwadi

PARTICULARS OF CONTRIBUTORS:
1. Lecturer, Department of Biochemistry, JSS Medical College, JSS University, Mysore, India.
2. Professor & Head, Department of Biochemistry, KMCT Medical College, Calicut, India.
3. Associate Professor, Department of Biochemistry, JSS Medical College, JSS University, Mysore, India.
4. Professor & Head, Department of Biochemistry, JSS Medical College, JSS University, Mysore, India.
5. Assistant Professor, Department of Biochemistry, Belgaum Institute of Medical Sciences, Belgaum, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Swetha NK,
Lecturer, Department of Biochemistry, JSS Medical College, JSS University, S.S Nagar Mysore, India.
Email: drswethasuresh@gmail.com
Ph: 9886403651

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