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A Comparative Study of Serum Magnesium, Copper and Serum Total Cholesterol in Type 2 Diabetes Mellitus with and Without Retinopathy and Healthy Controls

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Abstract

Background: Type II Diabetes Mellitus (DM) is a metabolic disorder primarily characterized by hyperglycemia caused by insulin resistance and/or relative insulin deficiency. Complications of the diabetes are the major cause of morbidity and mortality in persons with type II DM. Magnesium and copper are divalent cations. Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation. It serves as a cofactor for all enzymatic reactions that require ATP and is a key component in various reactions that require kinases (300 enzymes). In the current study we plan to bring the relationship between Copper, Magnesium and Total Cholesterol and their role in the development of diabetic retinopathy. **Subjects and Methods:** The study was carried out on a total of 90 subjects included over a period of one year. 30 were confirmed cases of Type II DM with retinopathy patients and 30 were age matched Controlled Diabetes without retinopathy, and 30 were normal healthy controls. Informed consent was obtained from each subject. The subject's medical history was recorded according to the questionnaire (proforma-see annexure) all the subjects before any investigations were carried out on them. Based on the analysis of medical history, clinical examination and investigation results the patients were grouped. **Results:** On comparison with healthy controls and Diabetes mellitus without retinopathy we found there is significant($p<0.05$) increase in fasting blood glucose, serum copper, triglycerides and total cholesterol. No significant change is found in serum magnesium. On comparison with healthy controls in Diabetes mellitus with retinopathy we found there is significant ($p<0.05$) increase in fasting blood glucose, serum copper, triglycerides, total cholesterol and LDL cholesterol. Significant ($p<0.05$) decrease in serum magnesium and HDL cholesterol is found in serum magnesium. **Conclusion:** The serum magnesium levels were decreased (hypomagnesaemia) in diabetic retinopathy and were significantly correlated ($p=0.022$) as compared to controls. The copper levels were higher in diabetic retinopathy and correlated highly significant as compared to control ($p<0.001$). The serum concentration of TC and LDL showed increase in diabetic retinopathy and highly significantly correlated ($p<0.001$) as compared to controls where as there was mild increase in serum TG but found to be highly significantly correlated (<0.001).

Keywords: Diabetic retinopathy, Hyperglycemia, Hypomagnesaemia, Retinopathy.

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Introduction

Type II Diabetes Mellitus (DM) is a metabolic disorder primarily characterized by hyperglycemia caused by insulin resistance and/or relative insulin deficiency. Complications of the diabetes are the major cause of morbidity and mortality in persons with type II DM.[1] Chronic hyperglycemia is a major initiator of microvascular complications, including nephropathy, retinopathy and neuropathy. These complications are predominantly seen in patients in the age group of 40 to 60 years.[2]

Magnesium and copper are divalent cations. Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation. It serves as a cofactor for all enzymatic reactions that require ATP and is a key component in various reactions that require kinases (300 enzymes). It is also an essential enzyme activator for neuromuscular excitability, cell permeability and is a critical element in cellular proliferation and apoptosis.[3]

Kinases are involved in carbohydrate metabolism. Hypomagnesemia has been linked to poor glycemic control.[4]

Copper has been shown to be elevated in experimentally diabetic rats5. The biochemical role for copper is primarily catalytic, with many copper metalloenzymes acting as oxidases to achieve the reduction of molecular oxygen. Many copper metalloenzymes have been identified in humans.[5] Ferroxidase I, also called ceruloplasmin, is the predominant copper carrying protein in plasma and may also have antioxidant functions. Defects in ceruloplasmin function produce cellular iron accumulation, a result that supports its ferroxidase role. {Ferroxidase II is found in human plasma, but it may have a role in iron metabolism in specific cellular sites}. A transmembrane copper-containing

protein (hephaestin) with ferroxidase activity has been described.[5] Copper is required in oxidation-reduction reactions in energy metabolism and also is a cofactor for enzymes including lipid and glucose metabolism. It is also known that ROS production is facilitated in the presence of copper ion through the Fenton reaction.[6]

Copper when excess becomes toxic and act as pro-oxidant. There is a significant increase in the levels of copper in type 2 DM subject. Diabetic patients with vascular complications have higher plasma copper levels than diabetic patients without complications or normal controls.[7]

Diabetic retinopathy is a major cause of blindness in population of working age. It is age of the leading causes of blindness in the world where the chances of losing the sight are about 25 times higher than normal population. Decrease in visual acuity in diabetic retinopathy is either associated with Maculopathy or proliferative complications of it.[8]

In the current study we plan to bring the relationship between Copper, Magnesium and Total Cholesterol and their role in the development of diabetic retinopathy

Subjects and Methods

The study was carried out on a total of 90 subjects included over a period of one year. 30 were confirmed cases of Type II DM with retinopathy patients and 30 were age matched Controlled Diabetes without retinopathy, and 30 were normal healthy controls. Informed consent was obtained from each subject. The subject's medical history was recorded according to the questionnaire (proforma-see annexure) all the subjects before any investigations were carried out on them. Based on the analysis of medical history, clinical examination and investigation results the patients were grouped as follows.

Control Group I (Diabetes Without Retinopathy)

Inclusion Criteria

1. Age matched clinical proven and confirmed cases of Diabetes mellitus but without retinopathy or any other complications.
2. Control group will be screened for the all parameters, cases with controlled diabetes without retinopathy (on fundoscopy diagnosed by Ophthalmologist) will be included.
3. If any abnormality is found in these parameters, they will be excluded from the control group.

GROUP II (Diabetes with Retinopathy)

Inclusion Criteria

1. Clinically proven cases of diabetes with Diabetic retinopathy attending at ophthalmology OPD, Shadan Institute of Medical Sciences, Hyderabad.

Exclusion Criteria

1. Non diabetic cases.
2. Diabetics with other complications such as neuropathy, nephropathy, hypertension and other vascular complications.
3. Diabetic patients with any other concurrent chronic disease such as cardiac diseases, thrombotic stroke etc.
4. Gestational diabetes mellitus.
5. Liver and renal disorders.

GROUP III (Normal Healthy controls)

Inclusion Criteria

1. Normal Healthy individuals without any history of Diabetes mellitus were included in the control group.

Exclusion Criteria

1. Individuals suffering with any chronic or acute illness
2. Individuals on any medications since last six months.

Methods

1. After obtaining informed consent, 5ml of blood from the study and the control group was drawn under full aseptic precautions.
2. Fasting samples was collected for analysis.
3. Samples collected in the fluoride tube were used for estimation of blood glucose.
4. Serums from the remaining sample collected in plain tubes were used for the estimation of magnesium, copper and ((Total cholesterol or lipid profile)).
5. The parameters are estimated using the following techniques.

- Serum magnesium by xylidyl blue method.
- Serum copper by spectrophotometric method
- Blood glucose by Glucose oxidase enzymatic method.
- Triglyceridesby enzymatic method using Glycerol-3-phosphate as substrate.
- Total cholesterol by Cholesterol oxidase-peroxidase method.
- HDL cholesterol by CHOD-PAP method.
- LDL cholesterol using fried wald formula LDL = TC – (HDL + TG/5).

Results

On comparison with healthy controls and Diabetes mellitus without retinopathy we found there is significant($p<0.05$) increase in fasting blood glucose, serum copper, triglycerides and total cholesterol. No significant change is found in serum magnesium.

On comparison with healthy controls in Diabetes mellitus with retinopathy we found there is significant($p<0.05$) increase in fasting blood glucose, serum copper, triglycerides, total cholesterol and LDL cholesterol. Significant ($p<0.05$) decrease in serum magnesium and HDL cholesterol is found in serum magnesium.

Although the levels of fasting blood sugar were higher in diabetic retinopathy, the correlation was not significant ($p=0.064$) as compared to controls (diabetes without retinopathy).

The average concentration of copper (µg/dl) in DM without retinopathy and diabetic retinopathy was 122.3±29.5 and 179±34.8. The serum copper levels were increased in diabetic retinopathy and were significant ($p=0.001$) when compared to controls (diabetes without retinopathy). [Table 3]

The average concentration of serum lipids (mg/dl) TC, TG, HDL and LDL in diabetic retinopathy were 202.93+51.00, 240+101.79, 34.46+5.98 and 119.50+43.66 respectively. While in the diabetic without retinopathy the average

concentration of serum lipids were 171.66+16.70, 229+33.67, 44.13+8.16 and 99.53+18.58 respectively. The serum concentration of TC and LDL showed marked increase in diabetic retinopathy and highly significantly correlated. [Table 4]

The average concentration of magnesium (mg/dl) in DM without retinopathy and diabetes with retinopathy was 2.16+2.06 and 1.43+0.17. The serum magnesium levels were decreased (hypomagnesaemia) in diabetic retinopathy and were significant (p=0.022) when compared to controls. [Table 5]

Table 1: Mean Age (Yrs) In Three Group

Groups	N	Min. Age	Max. Age	Mean ± SD
Normal healthy control	30	25	52	37.3±7.8
Diabetic without retinopathy	30	46	78	60.7±8.05
Diabetic Retinopathy	30	47	79	61.3±7.04

Table 2: Comparison of fasting blood sugar (mg/dl) in three groups

Groups	N	Min. Value	Max. Value	Mean + SD	Independent T-test
Normal healthy control	30	83	106	94.6±6.9	p value ≤0.05(S)
Diabetic without retiopathy	30	83	120	104.43±11.68	
Diabetic Retinopathy	30	100	179	143.13±19.27	

Table 3: Comparison of serum copper(µg/dl) levels between three groups

Groups	N	Min. Value	Max. Value	Mean + SD	Independent T-test
Normal healthy control	30	75	112	90.9±11.6	p value = 0.001(S)
Diabetic without retiopathy	30	75	180	122.3±29.5	
Diabetic Retinopathy (group 2)	30	130	260	179±34.8	

Table 4: Comparison of serum lipids (mg/dl) between healthy control, diabetes without retinopathy and diabetic retinopathy

Groups	Serum lipids	N	Min. Value	Max. Value	Mean+SD
Normal healthy controls	TC	30	110	175	144.3±14.5
	TG	30	74	175	127±19
	HDL	30	38	62	46±7
	LDL	30	50	104	86±12
Diabetic without retinopathy	TC	30	141	199	171.66±16.70
	TG	30	54	243	229±33.67
	HDL	30	31	59	44.13±8.16
	LDL	30	55	133	99.53±18.58
Diabetic without retinopathy	TC	30	140	308	202.93±51.00
	TG	30	75	410	240±101.79
	HDL	30	30	57	34.46±5.98
	LDL	30	64	237	119.50±43.66

Table 5: Comparison of serum magnesium (mg/dl) levels between diabetes without retinopathy and diabetic retinopathy

Groups	N	Min. Value	Max. Value	Mean + SD	Independent T-test
Normal healthy control	30	2.4	0.8	2.1±0.3	
Diabetic without retiopathy	30	1.2	2.71	2.16+0.26	p value = 0.02(S)
Diabetic Retinopathy (group 2)	30	2.13	2.80	1.43+0.17	

Discussion

In our study we found there was a significant decrease in serum magnesium levels in diabetic retinopathy cases.

Magnesium (Mg) is an electrolyte of chief physiological importance in the body, being the most abundant divalent intracellular cation in the cells, the second most abundant cellular ion next to potassium and the fourth cation in general in the human body.[9]

Magnesium is cofactor in more than 300 enzymes involved in carbohydrate metabolism, and it activates many enzymes involved in protein and lipids metabolism. It has been suggested that hypomagnesemia may induce altered cellular glucose transport, reduced pancreatic insulin secretion, defective postreceptor insulin signaling, and/or altered insulin–insulin receptor interactions.[10]

Many studies have reported an inverse relationship between glycemic control and serum Mg levels110-115. Paolisso G and Nadler J, demonstrated from their study that the induction of Mg deficiency has been shown to reduce insulin sensitivity in individuals without diabetes, whereas Mg supplementation during a 4-wk period has been shown to improve glucose handling in elderly individuals without diabetes.[11-16] Some other studies have shown that higher Mg intake may confer a lower risk for type2 diabetes.[17]

Rodriguez in their study on patients with type 2 diabetes, found that oral Mg supplementation during a 16-wk period associated with improve insulin sensitivity and metabolic control.[18]

The link between hypomagnesemia and diabetic retinopathy was reported in two cross-sectional studies that involved both “insulin-dependent” patients and patients with type 2

diabetes. Not only did patients with diabetes have lower serum Mg levels compared with their counterparts without diabetes, but also the serum Mg levels among the cohort with diabetes had an inverse correlation with the degree of retinopathy.[19]

Similar to the above studies in our study we found, significant hypomagnesemia which can be attributed as an important contributing factor in the pathogenesis of diabetic retinopathy.

A similar link, however, was not observed when Mg was measured within mononuclear cells. In a study that involved 128 patients with type 2 diabetes and poor glycemic control (glycosylated hemoglobin>8.0%), intramononuclear Mg concentrations were not observed to be lower among those with diabetic retinopathy but rather among those with neuropathy and coronary disease.[20]

Magnesium deficiency may induce the increase of insulin-resistance in non-diabetic persons.[21] Thus, Deficiency of this cation may be considered as a factor involved in pathogenesis and complications of type 2 diabetes mellitus.

Hypomagnesaemia is also involved in type 2 Diabetes Mellitus pathogenesis and its complications. Both experimental and clinical studies suggest that Hyperglycaemia may be the major factor involved in diabetic Hypomagnesaemia. A specific renal tubular magnesium defect in diabetes, together with the increased osmotic diuresis is responsible for large magnesium losses.[22]

Conclusion

The average concentration of magnesium (mg/dl) in DM without retinopathy, and diabetic retinopathy was 2.16+0.26 and 1.43+0.17 respectively. The serum magnesium levels were decreased (hypomagnesaemia) in diabetic retinopathy and were significantly correlated (p=0.022) as compared to controls. The copper levels were higher in diabetic retinopathy and correlated highly significant as compared to control (p<0.001). The serum concentration of TC and LDL showed increase in diabetic retinopathy and highly significantly correlated (p<0.001) as compared to controls whereas there was mild increase in serum TG but found to be highly significantly correlated (<0.001). There was decrease in HDL levels in diabetic retinopathy and correlated significantly (0.02) as compared to controls. Uncontrolled hyperglycemia and hypomagnesaemia area associated with microvascular complications like retinopathy.

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