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Comparison of serum copper and zinc in diabetics and non-diabetics subjects

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ABSTRACT

Introduction: Diabetes mellitus, the most common chronic metabolic disorder affecting about 300 million people all over the world. It occurs due to impaired insulin secretion, impaired insulin action or both whereas Prediabetes is the initial stage before diabetes mellitus and characterized by impaired fasting glucose or impaired glucose tolerance. Type 2 diabetes mellitus is associated with increased metabolic processes and oxidative stress. The trace elements are important co-factor in these events. Thus, this study was conducted to compare serum copper, zinc in prediabetes, diabetics with normal controls.

Materials and Methods: Institutional ethics committee permission was obtained prior to the study. Study included 71 prediabetes, 71 diabetics subjects and 71 controls between 40-60 years. Serum fasting blood sugar, glycated hemoglobin, copper, zinc was estimated. Statistical analysis was done using student t-test and Pearson's correlation. p value <0.05 was said to be significant.

Results: Serum copper was significantly increased in diabetic (77.87 ± 40.78) and serum zinc (128.05 ± 20.87) was significantly decreased in diabetics compared to apparently healthy controls. (Copper $=60.72\pm19.70$, zinc $=140.74\pm33.99$), where as in prediabetics both copper and zinc level were increased compared to healthy subjects.

Conclusion: Serum copper and zinc have a role in diabetes thus supplementation of micronutrients may be essential to maintain the diabetic status.

1. Introduction

Diabetes mellitus, is an endocrinological disease characterized by hyperglycemia. It occurs due to impaired insulin secretion, impaired insulin action or both.[1] Prolonged condition of hyperglycemia increases risk of renal failure, visual loss, and associated with complications like diabetic nephropathy, microangiopathy etc.[2,3] Several mineral metabolisms are responsible for alter in diabetes mellitus and this might have specific role in the pathogenesis and progress of the disease.[4,5] Among these trace elements zinc and copper plays an important role in the pathogenesis of diabetes mellitus and its complications.

These trace elements are essential for the growth and have many important biological functions. Trace elements are responsible for the production of reactive oxygen species (ROS), in turn which causes oxidative stress.[6] Oxidative stress is responsible for pathogenesis many diseases like cancers, cataract, including diabetes mellitus.[1] Copper is said to have oxidative property. Thus, it causes oxidative stress and acts as a pro oxidant and may participate in metal catalyzes formation of free radicals.[1] The increase in production of free radicals are likely to be associated with development of type 2 diabetes mellitus. Copper helps in the activation of cytochrome oxidase in electron transport chain of mitochondria. So, deficiency in copper causes reduced cytochrome oxidase activity which in turn leads to distortion of mitochondria of metabolically active tissues such as pancreatic acinar cells and hepatocytes etc. finally leading to

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insulin deficiency and lack of insulin secretion thus diabetes mellitus.[7,8]

Zinc is also an important trace element which is essential for healthy function of insulin, insulin release, to maintain insulin sensitivity and helps in the transport of insulin to the cells.[9] After synthesis of insulin zinc helps it to store in hexamer form.[10] Lack of zinc leads to lack of insulin release thus zinc deficiency persons are more prone for diabetes mellitus.

Prediabetes is the initial stage before diabetes mellitus and characterized by impaired fasting glucose or impaired glucose tolerance.[11–13] The prediabetics mainly occurs between the age of 40-70 years people.[11,14] Patients with glycated hemoglobin levels from 5.7% to 6.4% is known as prediabetics. They are more prone to diabetes mellitus but prediabetes subjects don't have all the symptoms that are required to measure diabetes mellitus. Patients with prediabetics have 5-15-fold more prone to type 2 diabetes mellitus compared to normal glucose subjects.[13,14] To the best of our knowledge this is the first of kind to measure copper and zinc in prediabetic in this study region. Thus, the study was to done to compare serum copper and zinc in type 2 diabetics, prediabetics and apparently healthy individual and to correlate these trace elements with FBS and glycated hemoglobin

2. Materials and Methods

The study was conducted in Department of Biochemistry, Kasturba Medical College Manipal, Manipal Academy of Higher Education, Karnataka. Institutional ethics committee was obtained prior to the study. The study included 71 diabetics subjects, 71 prediabetic subjects and 71 apparently healthy controls between the age group of 40-60 years. Serum zinc levels were estimated by kit method using spectrophotometer (Coral, Clinical Systems) and copper was estimated by Bathocuproine disulphonate method, glycated hemoglobin was estimated by immunoturbidimetric method (Cobas, Roche Diagnostic) and fasting blood glucose was estimated by hexokinase method (Cobas, Roche Diagnostic). Data were compiled and statistical analysis was done using ANOVA and Pearson's correlation value <0.05 was said to be significant.

3. Results

Table 1: Demographic profile of the study subjects

Parameters	Controls (n=71) Mean±SD	Prediabetics Mean±SD	Diabetics Mean±SD
Glycated hemoglobin	5.35±0.31	6.11±0.24	8.51±1.44
Fasting blood sugar	100.60±13.03	113.25±13.51	165.21±51.66

Table 2: Comparison of lipid profile among the study subjects

Lipid profile	Controls Mean±SEM	Prediabetics Mean±SEM	Diabetics Mean±SEM
TC	130.13±9.24	160.65±14.09	180.08±15.11
TG	189.72±5.93	183.82±5.55	182.29±7.43
HDL	47.10±1.84	45.64±1.73	42.95±1.85
LDL	118.04±5.31	107.75±4.63	106.50±7.02
Ratio	4.24±0.18	4.19±0.11	4.55±0.23

Table 3: Comparison of biochemical parameters among the study subjects

Biochemical parameters	Controls Mean±SD	Prediabetics Mean±SD	Diabetics Mean±SD
Copper	60.72±19.70	71.22±20.06	77.87±40.78
Zinc	140.74±33.99	143.27±20.30	128.05±20.87
Cu/zn	0.45±0.20	0.48±0.24	0.61±0.31

4. Discussion

Totally 213 subjects were enrolled for the study and based on glycated hemoglobin they were grouped into diabetics, prediabetics and controls. Most of the diabetic and prediabetic subjects were in 5^{th} decade of life. As the groups were based on glycated hemoglobin, i.e. why glycated hemoglobin and fasting blood sugar showed significant differences between the groups (Table 1).

This study also studied the lipid profile parameters in addition to trace elements. Total cholesterol was statistically increased from prediabetic to diabetic cases and HDL-cholesterol was statistically decreased from diabetic to prediabetics (Table 2)

The trace element serum copper was significantly increased in diabetics (p=0.001) and pre diabetics (p=0.07) compare to controls (Table 3) also copper showed significant positive correlation with glycated hemoglobin and fasting blood sugar which means as the glycated hemoglobin and fasting blood sugar value increases the serum copper value also increases (Table 4). In previous studies like Mohanty S et al.,[1] Tanaka A et al.,[6] Olaniyan O.O. et al.[10] have also shown increased levels of copper in diabetics compare to controls in different areas. Copper plays a vital role in oxidative stress.[15–17] The free form of copper shows toxic effect in the body. The increase in copper levels may be the reason of hyperglycemia, which in turn stimulates glycation and causes release of copper ion from copper binding sites of proteins. This released copper ions in blood is responsible for oxidative stress which can leads to tissue damage. The free radicals form due to oxidative stress are associated with causes of diabetes mellitus.[3,5,18,19] So, increased in serum copper level is associated with impaired glucose metabolism causing diabetes mellitus.

The 2^{nd} trace element serum zinc was significantly decreased in diabetics (p=0.008) as compared to con-

Table 4: Correlation of Glycated Hemoglobin and Fasting Blood Sugar with Other Biochemical Parameters

Parameters	Biochemical parameters	Controls		Prediabetics		Diabetics	
		r value	p value	r value	p value	r value	p value
Glycated Hemoglobin	Copper	0.247	0.037	0.063	0.601	0.194	0.105
	Zinc	0.090	0.456	-0.025	0.838	-0.030	0.803
	Copper/Zinc	0.184	0.125	0.007	0.953	0.173	0.150
Fasting Blood Sugar	Copper	0.199	0.097	0.179	0.135	0.148	0.219
	Zinc	-0.019	0.876	-0.015	0.670	-0.077	0.526
	Copper/Zinc	0.147	0.223	0.161	0.180	0.157	0.191
Copper	Zinc	-0.172	0.151	-0.253	0.034 *	-0.120	0.318

trols (Table 3) and between diabetic and prediabetics (p=0.002). Zinc showed significant negative correlation with glycated hemoglobin and fasting blood sugar. As the glycated hemoglobin and fasting blood sugar increases the serum zinc levels decreases (Table 4). In diabetes, there is disturbance in zinc homeostasis that the urinary elimination of zinc is increased causing hyperzincuria and intestinal absorption is decreased in diabetics leads to hypozincemia.[20,21] As zinc is an important trace element required for proper insulin synthesis, insulin secretion and insulin sensitivity. So, impaired zinc homeostasis leads to imbalance insulin synthesis, insulin secretion and insulin sensitivity.[15,22,23] In mechanism of action of insulin, the deficiency of zinc can also affect the steps of hosphorylation/dephosphorylation in insulin cell signaling.[24] Zinc also acts as an antioxidant. So, as an antioxidant it protects insulin and cells from the attack of free radical.[5,25,26] In some studies, it is shown that Zn transporter (ZnT8) is an important key protein for the secretion of insulin from the beta cells of pancreas. So, mutation in ZnT8 transporter causes impaired insulin secretion leads to type 2 diabetes.[8,27] Insulin is stored inside the secretory vesicles, where two zinc ions coordinate six insulin monomers to form in hexameric structure.[8,23]

In this study copper showed a positive correlation with glycated hemoglobin and fasting blood sugar in diabetics and in prediabetics but statistically not significant whereas zinc showed a negative correlation with glycated hemoglobin and fasting blood sugar in case of diabetics and prediabetics but statistically not significant. The copper showed negative correlation with zinc in both diabetics and prediabetics but statistically significant in prediabetics but not in diabetics (Table 4) which means with increase in serum copper there is a decrease in serum zinc levels. As we discussed above that zinc is required for function of insulin and copper zinc antioxidant mechanism is involve in the prevention of oxidative stress that occurs in diabetes mellitus. Thus, it is important to maintain copper zinc balance. Any impairment in copper zinc may be one of the reasons for diabetes mellitus.[3,28]

The study by Jenu et al.[3] showed increase copper levels in diabetics compare to controls whereas the serum zinc levels has shown reversed results that the serum zinc level is increased in diabetics compare to controls in the same region.

The study also showed significant increase in copper to zinc ratio in diabetics compared to normal controls and prediabetics (Table 3) and showed a significant positive correlation with glycated hemoglobin (Table 4) and fasting blood sugar (Table 4).

5. Conclusion

The present study conclude that increase in serum copper and decrease in serum zinc levels may be one of the cause of diabetics. Alteration in metabolism of trace elements leads to diabetes mellitus. Among the trace elements copper plays the role in prediabetics than levels of zinc. Further studies are needed to be carried out to determine the molecular role of copper and zinc in the development of prediabetics and diabetes and also to evaluate the beneficial effect of zinc supplementation in diabetes mellitus.

6. Limitatio

Treatment plan of diabetics (oral hypoglycemic drugs or insulin) not known. Diabetic complications history was not known.

7. Source of Funding

None.

8. Conflict of Interest

None.

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