Original Research Article

Impact of uncontrolled diabetes on trace elements in cardiomyopathy patients - A south Indian study

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Abstract

Background: Middle aged group with increased incidence of cardiomyopathies has become common worldwide. One of the causes of cardiomyopathies is due to high glycemic index. Diabetes is a chronic metabolic and endocrine disease, which on long term leads to varied complications such as nephropathy, neuropathy, micro and macro angiopathies etc. **Purpose:** The trace elements may play a role in the cardiomyopathies. In the present study, we aimed to assess concentrations of Magnesium (Mg) and Zinc (Zn) in patient's serum and urine with uncontrolled diabetes and compared with healthy controls. **Methods:** This study population included 100 patients (Patients with uncontrolled diabetes and cardiomyopathies) and 100 healthy subjects. Serum and urine levels of creatinine, magnesium and zinc were assessed using automatic bio-analyzer. **Results:** Diabetic subjects (n=1000) with macro and micro-angiopathies and non-diabetic subjects (n=100) with no complications were selected for the study and their serum and urine were analyzed for quantifying the levels of HbA1C, creatinine, Mg and Zn. Serum and urine concentrations of Mg and Zn in uncontrolled diabetes patients were significantly lower than in healthy controls ($p<0.05$, respectively). There was significant difference in the trace elements status between control and uncontrolled diabetic patients ($p>0.05$ for all parameters). Relationships of the serum and urine trace element concentrations studied with hemodynamic parameters were statistically significant.
Conclusion: Results from present study indicates that south Indian population have high chances of incidence of cardiomyopathies and diabetes induced ailments due to higher glycemic index and decreased levels of Mg and Zn.
Key Word: Cardiomyopathies, Zinc, magnesium, uncontrolled diabetes, and HbA1c.

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Received Date: 16/06/2019 Revised Date: 02/07/2019 Accepted Date: 11/08/2019
DOI: https://doi.org/10.26611/1031129

Access this article online	
Quick Response Code:	Website: www.medpulse.in
	Accessed Date: 19 August 2019

INTRODUCTION

Diabetes is metabolic disorder characterized by high glycemic index, lack of insulin production, and insulin resistance. Diabetic induced co-morbidities or complications such as coronary heart disease, peripheral arterial occlusive disease, and cerebrovascular insufficiency, blindness, nephropathy, neuropathy, renal dysfunction, diabetic foot syndrome and lower limb amputation[1].Diabetes is linked to augmented increased risk of cardiac dysfunctions and failure in spite of keeping hypertension and coronary artery disease under control. Hence, diabetic cardiomyopathy (DC) is being considered as major health condition by clinicians, and continuous efforts are put into understanding its pathophysiology for early diagnosis and treatment strategies for diabetes-associated cardiovascular dysfunction. The term diabetic cardiomyopathy (DC) is widely used by epidemiologists and clinicians, but it was Rubler *et al*[2] were the first to introduce to DC. DC illustrates the diabetes induced alterations in the structure and function of the myocardium which is not directly attributed to hypertension or coronary artery disease (CAD). The co-morbidities such ischemic stroke, left ventricular hypertrophy and heart failure in type 2 diabetes patients is

How to cite this rticle: G Sandeep. Impact of uncontrolled diabetes on trace elements in cardiomyopathy patients - A south Indian study. *MedPulse International Journal of Physiology.* August 2019; 11(2): 53-57. https://www.medpulse.in/Physiology/

amplified due to chronic uncontrolled diabetes[3]. The etiopathogenesis of DC is implicated with several mechanisms involved in calcium metabolism and signaling, myocardial structural changes were depicted as early defects observed mainly in animal models and which may precede as clinically manifest i.e. cardiac dysfunction. According to the report published by World Health Organization (WHO) in 2016, stated that 422 million people worldwide have succumbed to diabetes[4]. The International Diabetes Federation (IDF) predicted that the number of Type 2 Diabetes cases will be doubled in 2030 and among them 85-90% of all cases will be Type 2 Diabetes. The risk factors which are increasing the prevalence of type 2 diabetes is largely accredited to genetic susceptibility, sedentary lifestyle, high calorie diet etc[4].According to the International Diabetes Foundation (IDF), India stands second to the china in the number of diabetic cases [5,6]. Although the country has now been surpassed in the top spot by China[7].More than 62 million Indians are suffering with diabetes, which includes over 7.1% of the adult population[7]. The onset of diabetes has come done to 42.5 ears and nearly 1 million diabetic patients die in Indians[6]. It is suggested that the India will be home to 109 million people will be diagnosed with diabetes by 2035 as per the statistics given by Indian Heart Association (IHA)[8,9]. The trace elements govern most of the metabolic reactions in animal body and among them Zinc (Zn) is pivotal as it plays big role in regulating the enzymatic activity of over 300 enzymes and also involved in cellular processes such as cell division and apoptosis[10]. Hence, the human body tightly regulates the concentration of zinc because any discrepancies in zinc homeostasis can lead to various diseases including diabetes mellitus[11]. The pancreatic cells produce insulin, which is a peptide hormone that exists as a hexamer with two Zinc ions (Zn^{+2}) and during de-granulation of cells it is released into portal veins[12,13] and regulates the insulin action and carbohydrate metabolism. The oxidative stress is considered as one of factors inducing diabetes[14]due to impaired synthesis of superoxide dismutase (SOD), which is the major anti-oxidant enzyme, and for its functionality to be intact it requires Zinc, which acts as an anti-oxidant and its supplementation has reduced oxidative stress in *in-vitro* and *in-vivo* models[15]. Literature review suggests that hypozincemia is linked with rise in diabetes incidence in developing countries[16,17]. Magnesium (Mg) is another trace element which is required for glucose homeostasis and glucose metabolisms. Mg is also required for functioning of various enzymes similar to that of Zn, and it is required for release of insulin and glucose oxidation[18-20].Low secretion of insulin in pancreas is due to deficiency of Mg. The intracellular uptake of Mg is stimulated in the presence of insulin[21]. The deficiency of Mg can cause alteration in inositol transport and the activity of membrane bound Na+-K+- ATPases[22-25].According to Srivastava *et al*. (1993)[26]diminished levels of trace elements is due to alterations in glycemic levels and enhanced glycation of proteins in diabetics. The objective of the present study to quantify Zn and Mg serum and urine of cardiac patients with uncontrolled diabetes when compared to non-diabetics and also compare the levels of Zn and Mg in varied glycemic controls in South India population (Andhra Pradesh), India.

MATERIALS AND METHODS

1000 diabetic subjects (Males and Females, aged between 40-70years) who were admitted as in-patients tertiary care Hospitals in Kurnool were selected for the study and the patients briefed about the study protocol took their consent before enrolling them into the study. We obtained ethical approval from an independent ethical committee approval (**795/02-2019**). Once subjects were enrolled into the study we collected their medical and family history, body mass index, and height scores. The enrollment of cardiomyopathy patients with uncontrolled diabetes was done based on their fasting plasma glucose levels (<140mg/dL or 7.8 mmol/L on two consecutive days, or if the postprandial plasma glucose levels greater than 160mg/dL or 8.9 mmol/L on two consecutive days[25,26]. The subjects with no medical history and aged over 40 years were enrolled in the study as non-diabetics (100-males and female). The blood from diabetic and non-diabetic subjects was drawn for assessing the fasting plasma glucose (FGP), glycated hemoglobin (HbA1c), serum (creatinine, magnesium (Mg) andzinc (Zn)) and similarly the urine samples were collected into sterile containers for quantifying the levels of creatinine, zinc and magnesium. The glucose oxidase-peroxidase method was used for analyzing FGP, and automatic bioanalyzer (Beckman Coulter. Inc) was used for analyzing the levels of glycated hemoglobin, Magnesium in serum and urine. The quantification of creatinine in serum and urine[27] was done using modified Jaffes reaction method, levels of zinc was quantified using an Abcam's Zinc Quantification Kit (i.e. absorbance at 560nm).Statistical analysis of results was performed on SSPS software.

RESULTS AND DISCUSSION

The mean levels of fasting blood glucose (FBS), HbA1c, urine Creatinine, urine Zinc and urine Magnesium of diabetics (both sexes) were observed to be significantly higher than the non-diabetics (Table 1) andthe levels of Creatinine, Magnesium and Zinc of diabetics and non-diabetics were assessed in their serum and urine samples (Table 2).

Table1: Serum and urine from diabetic and non-diabetic subjects were assessed for the levels of fasting blood glucose (FBG), glycated hemoglobin (HbA1c), creatinine and trace elements in both sexes.

Subjects	FBS	HbA1c
Diabetic N=500 (Males)	**166.34± 32.16**	**8.2±2.33**
Non-diabetic N=100 (Males)	**72.3± 10.07**	**5.54±0.40**
p- value	p<0.05	p<0.05
Diabetic N=500 (Females)	**152.51± 41.26**	**8.07±3.13**
Non-diabetic N=100 (Females)	**75.3± 11.22**	**5.07±0.84**
p- value	p<0.05	p<0.05

Table 2: Serum and urine from diabetic and non-diabetic subjects were assessed for the levels of creatinine and trace elements in both sexes.

Subjects	Serum- Creat (mg/dL)	Urine- Creat (mg/dL)	Serum- Zn (µmol/L)	Urine- Zn (µmol/L)	Serum- Mg (mg/dL)	Urine- Mg (mg/dL)
Diabetic N=500 (Male)	3.03±0.33	3.57±0.27	3.23±0.57	11.87±0.57	5.24±0.17	12.27±0.17
Non-diabetic N=100 (Male)	0.73±0.10	0.43±0.22	9.13±0.21	3.35±0.36	11.05±0.49	2.08±0.31
p- value	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05
Diabetic N=500 (Female)	2.76±0.861	2.77±0.27	4.03±0.57	11.58±0.77	5.18±0.57	11.78±0.34
Non-diabetic N=100 (Female)	0.70±0.19	0.26±0.32	8.73±0.25	3.05±0.89	11.55±0.03	1.94±0.11
p-value	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05

There was noticeable difference observed in the levels of FBS, HbA1c, serum and urine Creatinine, serum and urine Zinc, serum and urine magnesium in between male and female subjects.

Table 3: Glycemic index and levels of Zinc and Magnesium levels in serum and urine of uncontrolled diabetic subjects of both sexes

Subjects	Serum- Mg (mg/dL)	Serum- Zn (µmol/L)	Urine- Mg (mg/dL)	Urine- Zn (µmol/L)
Poor HbA1c (>8.00 mmol/L) N=38 (Male)	5.65±0.67	3.35±0.52	13.25±0.76	8.65±0.57
Good HbA1c (6.25-8.00 mmol/L) N=116 (Male)	8.44±0.57	5.65±0.41	8.15±0.75	6.65±0.49
p- value	p<0.05	p<0.05	p<0.05	p<0.05
Poor HbA1c (>8.00 mmol/L) N=350 (Female)	6.25±0.74	3.88±0.70	12.98±0.27	7.89 ±0.47
Good HbA1c (6.25-8.00 mmol/L) N=150 (Female)	8.82±0.22	5.95±0.59	7.58±0.37	6.88±0.70
p-value	p<0.05	p<0.05	p<0.05	p<0.05

Zinc and Magnesium concentration in serum and urine was expressed in µmol/L, the blood and urine samples were collected once in a day, the sample from diabetics was collected in morning and non-diabetics were collected randomly and subjects blood samples were also collected in similar fashion. Analysis of urine Zinc and Magnesium levels was done in different states of glycemic control in diabetic patient's i.e. good and poor management of diabetes in both sexes (Table 3).

Table 4: Correlation of magnesium and zinc levels between Poor glycemic control and non-diabetic subjects of both sexes

Subjects	Urine- Mg (mg/dL)	Urine- Zn (µmol/L)
Poor HbA1c (>8.00 mmol/L) N=384 (Male)	13.25±0.76	8.65±0.57
Non- diabetic N=50 (Male)	2.28±0.29	3.98±0.94
p- value	p<0.05	p<0.05
Poor HbA1c (>8.00 mmol/L) N=350 (Female)	12.98±0.27	7.89 ±0.47
Non- diabetic N=50 (Female)	2.45±0.32	3.85±0.25
p-value	p<0.05	p<0.05

The comparison of urine Zinc and Magnesium concentrations were done in between poor glycemic control and non-diabetic controls of both sexes (Table 4) and it is observed that the female subjects were losing more zinc and magnesium in urine in comparison to male subjects. WHO (1996)[25]suggested that chronic aliments like diabetes mellitus, anemia, cardiovascular disease, cancer etc is to the deficiency of trace element and metabolic dysfunction. Literature suggests that Zinc, Magnesium, Molybdenum, Chromium, Selenium, Vanadium, and Manganese plays pivotal role in carbohydrate metabolism and insulin action, but their actual role in etiology of diabetes is still elusive[28]. Comparing the levels of FBS, HbA1c, serum and urine(Creatinine, Magnesium and Zinc) levels in diabetic and non-diabetic subjects showed significant loss of Zn and Mg in diabetics than non-diabetics and it was observed that the diabetic females were losing more Zn and Mg in comparison to males and also showing high glycemic index (Table 1 and 2). The levels of zinc and magnesium in serum and urine of diabetics with different states of glycemic control which was determined by considering glycated hemoglobin levels between male and female diabetics (Table 3 and 4). Chausmer (1998)[12] indicated that the diabetic populations are suffering from hypozincemia as the absorption of zinc in intestine less or due to hyperzincuria and it was also suggested that high glycemic index may also hinder the active transport of zinc back into the tubular cells. Zinc and Magnesium concentration in urine was observed to be significantlyhigher in diabetics than in non-diabetics population studied. Our findings are coherence with El-Yazigi *et al*. (1991)[29] work, who also reported that diabetics loose more zinc in urine and hyperzincuria is due to hyperglycemia. The results obtained in this study clearly showed that there is correlation between HbA1c and Creatinine, zinc and magnesium levels (serum and urine) in diabetics of both sexes, and it is found that the female's subjects were losing more zinc and magnesium in comparison to male diabetic subjects and similar observation made even in non-diabetic subjects; the reason for this phenomenon is not clear why females are losing more zinc and magnesium to that of males. The glycemic index is also seen to be more in females than to males.

CONCLUSION

From our observations, we therefore conclude that diabetes and poor glycemic control alters the availability of zinc and magnesium in the diabetes patients and increasing the incidence of allied complications such as Angiopathies, cardiomyopathies, neuropathies, nephropathies etc. This study has documented previous history and food intake details of all subjects, and gives a scope in management of Diabetes and allied complications in poor diabetics through counseling and proper diet suggestions.

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Source of Support: None Declared
Conflict of Interest: None Declared