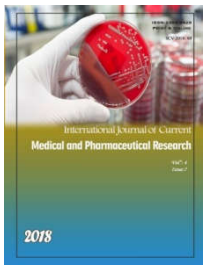
Research Article

INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 4; Issue 7(A); July 2018; Page No. 3474-3480
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr20180489



IGF-I AND ZINC AS A BIOMARKER IN EARLY DIAGNOSING CARDIOVASCULAR COMPLICATIONS IN TYPE 2 DIABETICS IN THE CENTRAL INDIA

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ARTICLE INFO

Article History:
Received 2nd April, 2018
Received in revised form 10th May, 2018
Accepted 25th June, 2018
Published online 28th July, 2018

Key words:
Diabetes mellitus, Hyperglycemia, Lipid Profile panel, Insulin Like Growth Factor-1 and Zinc.

ABSTRACT

Introduction: Diabetes mellitus (DM) is a group of metabolic diseases which if not controlled can cause life threatening complications. We hypothesize that serum IGF-1 and Zinc levels can be used as a Biomarker for early diagnosing cardiovascular complications in the Type 2 Diabetic patients in the Central India.
Methods and Materials: Fasting (FBS) and Post meal blood sugar (PMBG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), triglyceride (TG), Insulin Like Growth Factor-1 (IGF-1) and Zinc (Zn) levels were evaluated. Total sample size was 80, which was divided into 40 study group with type 2 DM who attended the Medicine OPD of AVBRH Hospital, Wardha and 40 age and sex matched healthy controls included in the study. Study period from June 2017 to June 2018.
Statistical Analysis: Software used in the analysis were SPSS 22.0 version and GraphPad Prism 6.0 version.
Results: Serum lipid profile showed higher mean of TC, TG and LDL in patients with diabetes. IGF-1 and Zinc level was significantly lower in subjects with diabetes as compared to the controls ($p<0.0001$). IGF-1 shows positive correlation with all the parameters.
Conclusions: Early detection of IGF-1, Zinc and lipid profile abnormalities can minimize the risk for development of cardiovascular complications in the type 2 diabetic patients. IGF-1 and Zinc levels may be a useful biomarker for identifying subjects at risk for cardiovascular complications in the Type 2 diabetics.

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INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[1] Type 2 DM is caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretary response. This form of DM accounts for approximately 90-95%. According to the International Diabetic Foundation, currently, the disease affects >62 million Indians, which is >7.1% of India's adult population. As per World Health Organization (WHO), 171 million people suffering from diabetes worldwide. Its incidence is increasing rapidly and estimated that by the year 2030, this number will be double. India leads the world with largest number of diabetic subjects, so WHO termed India as "the diabetes capital of the world." Diabetes is associated with a greater risk of morbidity and mortality from Cardiovascular Disease (CVD). Serum lipids are frequently abnormal and are likely to contribute to the risk of coronary artery disease.[2] Worsening of glycaemic control deteriorates lipid abnormalities in diabetes mellitus.[3] As the disease progresses, individuals are at risk for the development of specific complications including retinopathy leading to blindness, nephropathy causes renal failure and atherosclerotic heart disease. Atherosclerosis accounts for around 80% of all deaths among diabetic patients. Hyperglycaemia induces a large number of alterations at the cellular level of vascular tissue that potentially accelerate the atherosclerotic process. There are three major mechanisms that encompass most of the pathological alterations observed in the diabetic vasculature- 1) Nonenzymatic glycosylation of proteins and lipids, which can interfere with their normal function by disrupting molecular conformation, alter enzymatic activity, reduce degradative capacity and interfere with receptor recognition; 2) Oxidative stress; and 3) Protein Kinase C (PKC) activation with subsequent alteration in growth factor expression.

Insulin resistance syndrome also called metabolic syndrome is a clustering of abnormalities including -altered glucose

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tolerance, visceral adiposity, hypertension, low HDL cholesterol, and high triglyceride levels is linked with atherosclerotic cardiovascular diseases.[4-5] In the last few years increasing evidence has suggested that IGF-1 may have a role in glucose homeostasis and cardiovascular disease. Animals with liver-specific IGF-1 gene deletion are characterized by hyperinsulinemia and skeletal muscle insulin resistance.[6-7] Treatment of these animals with recombinant human IGF-I caused a reduction in insulin levels and an increase in insulin sensitivity.[6] **C**linical studies performed on normal subjects, patients with extreme insulin resistance, and patients with type 1 or type 2 diabetes have shown that recombinant IGF-I administration significantly lowered blood glucose and increased insulin sensitivity.[8-11]

In a recent study stated that low concentrations of IGF-1 in the circulation increased the risk for developing type 2 diabetes considerably during a 4.5-year follow-up.[12] Low circulating IGF-I levels have been associated with angiographically documented coronary artery disease in non-diabetic subjects, atherosclerotic plaques in the carotid arteries and with coronary artery disease.[13-14] Reduced IGF-1 levels have been observed in individuals with angina pectoris and angiographically normal epicardial coronary arteries, also called cardiac syndrome X.[15] Individuals without ischemic heart disease but with low IGF-1 levels have an increased risk of developing ischemic heart disease during a 15-year follow-up period.[16] Nondiabetic patients who died after an acute myocardial infarction during 2 years of follow-up had significantly lower IGF-1 levels than survivors at the time of admission.[17] Furthermore, nondiabetic patients with myocardial infarction had significantly lower IGF-1 levels at admission than age and sex-matched healthy control subjects.[18] For mitogenic actions, including stimulation of vascular smooth muscle cell (VSMC) proliferation and migration[19-21] IGF-1 known to be central events in the formation of atherosclerotic plaques and in development of CVD. In addition, the concentration of IGF-I in coronary VSMCs in patients with *de novo* and restenotic plaques has been shown to be significantly higher than in those without CVD[22]. Cellular senescence and impaired vascular endothelial proliferation, adhesion and incorporation are now believed to play a pivotal role in the development of macrovascular disease[23], and increasingly experimental and epidemiological studies suggest that IGF-I may in fact be a vascular protective factor.

There are multiple mechanisms by which IGF-I may have beneficial actions on the vasculature: (i) it can directly oppose endothelial dysfunction by stimulating nitric oxide (NO) production from endothelial cells and VSMCs[24]; (ii) it also stimulates vasodilatation through the activation of potassium channels, with a consequent reduction in intracellular calcium[25]; and (iii) it may protect against plaque instability and rupture by counteracting oxidized LDL-induced cytotoxicity and VSMC apoptosis.

Consistent with this, levels of IGF-I have been found to be reduced in advanced atherosclerotic plaque[26-27]. Moreover, IGF-I has also been shown to promote insulin sensitivity and prevent postprandial dyslipidaemia[28].

Micronutrients are essential nutrients that are required by the body in trace amounts on a day to-day basis in order to function our body properly. Direct associations of macro and trace elements with diabetes mellitus have been observed in many research studies.[29]

Insulin action on reducing blood glucose was reported to be potentiated by some trace elements like zinc.[30]

The zinc plays an important role in glucose metabolism, like it helps in the utilization of glucose by muscle and fat cells. It is required as a cofactor for the function of intracellular enzymes that may be involved in protein, lipid, and glucose metabolism. It may be involved in the regulation of insulin receptor-initiated signal transudation and insulin receptor synthesis.[31]

IGF-1 is also a sensitive nutritional marker which is negatively influenced by poor mineral levels in our body. In type 2 diabetes mellitus patients, there is decreased level of HDL-C with moderate hypertriglyceridaemia. Since glycaemic control is often insufficient, serum triglycerides are elevated. The glucose hypothesis suggests that treatment that normalizes glucose levels prevents or delays the long term complications of diabetes mellitus. Based on the UK Prospective Diabetes Study (UKPDS) it has been suggested that the benefits of strict glycaemic control in type 2 diabetes are less than those of tight blood pressure control. [32]

Therefore, we studied the relationships between serum IGF-1 concentrations, Zinc and lipid profile levels in type 2 diabetics hypothesizing that IGF-1 and Zinc levels can be used as a Biomarker for early diagnosing cardiovascular complications in the Type 2 Diabetic patients. The aim of the present study is IGF-1 and Zinc as a biomarker for early diagnosing cardiovascular complications in type 2 diabetics in the central India. The study was carried out in the Department of Biochemistry in association with Department of Medicine, Jawaharlal Nehru Medical College and Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha, Maharashtra, India.

MATERIALS AND METHODS

A comparative and cross-sectional study was conducted. Institutional Ethical Committee approved the study and informed consent was obtained from the patients. The study was done from June 2017 to June 2018 among total sample size 80 patients including males and females and divided into two groups. Informed written consent was taken for the study purpose. 40 study group with type 2 DM who attended the outpatient clinic of the Medicine Department of AVBRH Hospital, Sawangi (Meghe), Wardha, and 40 age, sex matched healthy controls. All patients with known history of type 2 DM within the age group of 30-80 years included in the study. Information about subject's age, sex, lifestyle, family history of diabetes and other chronic diseases/disorders were written in pre-designed format. Fasting blood glucose by GOD/POD method,[33] total cholesterol by enzymatic endpoint method,[34] triglycerides liquid stable GPO-POD method,[35] HDL direct enzyme method, LDL using Friedewald formula, VLDL by appropriate formula and Zinc by colorimetric method[36] - all measured by Randox auto-analyzer on the same day of collection. Plasma IGF-1 concentrations were determined by ELISA[37] method (Robonik, Readwell Touch, ELISA plate analyser).

Sample Collection

5mL blood sample was collected from each subject. Fasting and post meal blood sample in sterile fluoride bulb, plain bulb for lipid profile, zinc and IGF-1under all the aseptic conditions with consent of the patients. Sample was allowed to stand for

clotting for 25 to 30 minutes. Serum was separated by centrifuging blood at 3000 rpm for 10 minutes.

Inclusion Criteria

All patients with known history of type 2 DM, age group between 30-80 years and diabetic patients, those who gave the consent for the study were included in the study.

Exclusion Criteria

Patient with major illness like liver disease, renal failure, cardiovascular disease, which can directly or indirectly affect the result, previous or current treatment with drugs known to interfere with glucose and lipid metabolism were excluded from the study.

Statistical Analysis

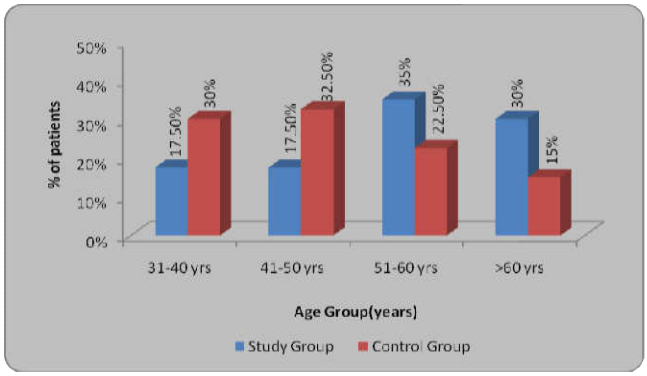
Statistical analysis was done by using descriptive and inferential statistics using chi-square test, student's unpaired t test, Pearson's correlation coefficient and multivariate regression analysis. Software used in the analysis was SPSS 22.0 version and GraphPad Prism 6.0 version. The p value ($p< 0.05$) is considered as significant.

RESULTS

The present study consists of 40 patients of type 2 DM and 40 age and sex matched healthy controls. In our study, we found Diabetes patients were of older age group as compared to control group (table-1). Also, we found higher number of males in diabetes as compared to female (table-2).

Table 1 Age wise distribution of patients

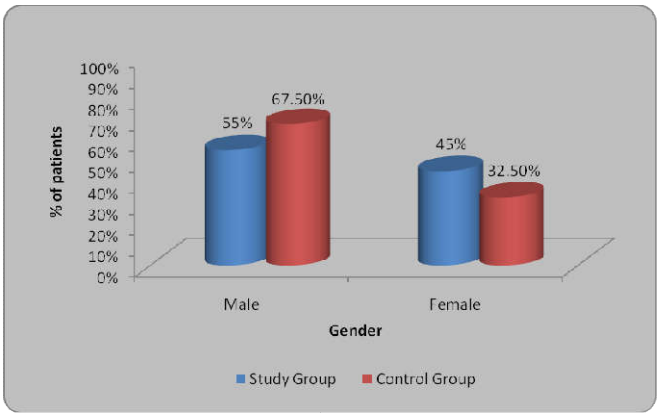
Age Group(yrs)	Study Group	Control Group	χ2-value
31-40 yrs	7(17.5%)	12(30%)	6.20 p=0.10,NS
41-50 yrs	7(17.5%)	13(32.5%)	
51-60 yrs	14(35%)	9(22.5%)	
>60 yrs	12(30%)	6(15%)	
Total	40(100%)	40(100%)	
Mean±SD	54.17±11.96	48.12±12.01	
Range	32-76	30-80	



Graph 1 Age wise distribution of patients

Table 2 Gender wise distribution of patients

Gender	Study Group	Control Group	χ2-value
Male	22(55%)	27(67.5%)	1.31 p=0.25,NS
Female	18(45%)	13(32.5%)	
Total	40(100%)	40(100%)	

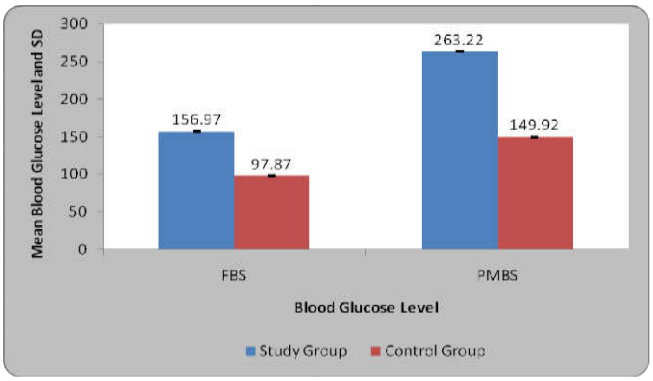


Graph 2 Gender wise distribution of patients

Table-3 shows mean value of fasting and post meal plasma glucose (mg/dl) in the cases of diabetes mellitus were found to be 156.97±33.04 and 263.22±77.01 respectively which was statistically highly significant ($p<0.0001$).

Table 3 Comparison of blood glucose level in two groups Student's unpaired t test

	Group	N	Mean	Std. Deviation	Std. Error Mean	t-value	p-value
FBS	Study	40	156.97	33.04	5.22	10.72	0.0001,S
	Control	40	97.87	11.06	1.75		
PMBS	Study	40	263.22	77.01	12.17	8.57	0.0001,S
	Control	40	149.92	32.42	5.12		

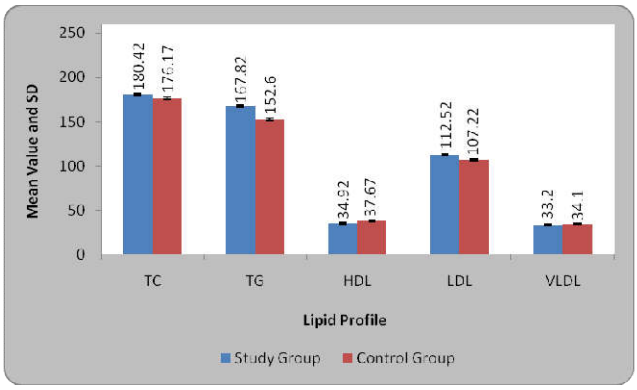


Graph 3 Comparison of blood glucose level in two groups

Table-4 shows Higher mean value for TC, TG and LDL-C in diabetes mellitus as compared to control group.

Table 4 Comparison of lipid profile level in two groups Student's unpaired t test

	Group	N	Mean	Std. Deviation	Std. Error Mean	t-value	p-value
TC	Study	40	180.42	51.46	8.13	0.42	0.66,NS
	Control	40	176.17	35.82	5.66		
TG	Study	40	167.82	80.47	12.72	0.81	0.41,NS
	Control	40	152.60	87.13	13.77		
HDL	Study	40	34.92	7.06	1.11	0.81	0.41,NS
	Control	40	37.67	20.22	3.19		
LDL	Study	40	112.52	39.49	6.24	0.65	0.51,NS
	Control	40	107.22	32.52	5.14		
VLDL	Study	40	33.20	16.46	2.60	0.18	0.85,NS
	Control	40	34.10	25.77	4.07		

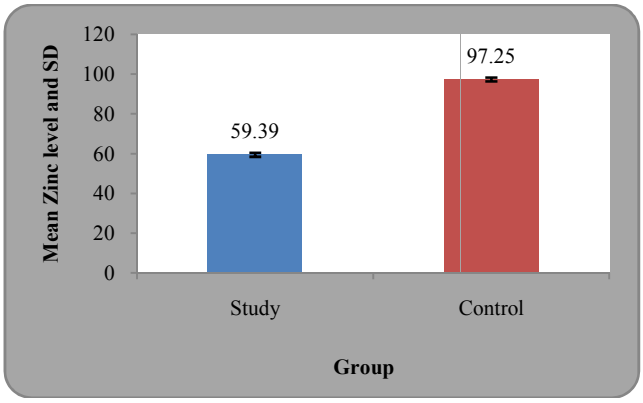


Graph 4 Comparison of lipid profile level in two groups

Table-5 and table-6 shows the mean value of Zinc and IGF-1 levels in diabetes mellitus found to be lower as compared to the control group (P<0.0001).

Table 5 Comparison of Zinc level in two groups
Student's unpaired t test

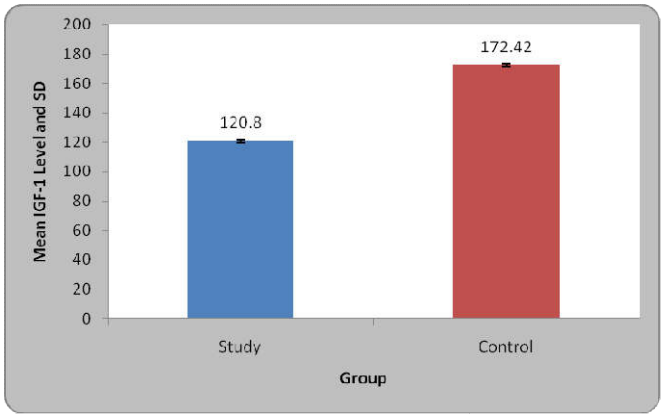
Group	N	Mean	Std. Deviation	Std. Error Mean	t-value	p-value
Study	40	59.39	1.87	0.29	100.46	0.0001,S
Control	40	97.25	1.47	0.23		



Graph 5 Comparison of zinc level in two groups

Table 6 Comparison of IGF-1 level in two groups
Student's unpaired t test

Group	N	Mean	Std. Deviation	Std. Error Mean	t-value	p-value
Study	40	120.80	2.54	0.40	75.33	0.0001,S
Control	40	172.42	3.48	0.55		



Graph 6 Comparison of IGF-1 level in two groups

In our study, we found positive correlation of FBS, PMBS, TC, TG, HDL, LDL, VLDL, Zinc level with IGF-1shown in table-7.

Table 7 Correlation between IGF-1 level and other parameters
Pearson's Correlation Coefficient

	Mean	Std. Deviation	N	Correlation 'r'	p-value
IGF-1	120.80	2.54	40	-	-
FBS	156.97	33.04	40	0.04	0.78,NS
PMBS	263.22	77.01	40	0.09	0.54,NS
TC	180.42	51.46	40	0.10	0.50,NS
TG	167.82	80.47	40	0.04	0.77,NS
HDL	34.92	7.06	40	0.18	0.24,NS
LDL	112.52	39.49	40	0.10	0.53,NS
VLDL	33.20	16.46	40	0.02	0.89,NS
Zinc	59.39	1.87	40	0.10	0.52,NS

DISCUSSION

The present study **"**IGF-1 and Zinc as a biomarker for early diagnosing cardiovascular complications in type 2 diabetics in the central India**"** conducted in the Dept. of Biochemistry and AVBRH, Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha, India. The findings are as follows-
Plasma IGF-I concentration was positively correlated with HDL cholesterol. Furthermore, a low plasma IGF-I concentration was significantly associated with the metabolic syndrome according to the WHO definition. These results extend previous observations showing that low IGF-I levels are associated with risk for the metabolic syndrome, as defined by the WHO.[38]

In this respect, a polymorphism in the promoter region of the *IGF-I* gene was associated with low total serum IGF-I levels and increased risk of type 2 diabetes.[39]

IGF-I has hypoglycemic effects and enhances insulin sensitivity in both experimental animals and human subjects. The biological action of IGF-I is thought to be mediated via its type 1 receptors and/or hybrid insulin/ IGF-1 receptors.[40] Clinical studies showing the effectiveness of recombinant human IGF-I treatment in improving insulin sensitivity and metabolic control in patients with type 1 or type 2 diabetes and in patients with extreme insulin resistance.[41]

There is evidence that IGF1 protects against production of free fatty acids, systemic inflammation, *b*-cell dysfunction, insulin resistance, and hypertension and, thus, low IGF1 promotes metabolic syndrome and development of diabetes.[42]

Several studies, suggest that the premature and progressive decline in serum IGF-I bioactivity during ageing in patients with type 2 diabetes may result in insufficient protective and regeneration effects of IGF-I on the cardiovascular system. In comparison with other growth factors, these 'survival' effects of IGF-I on the myocardium seem rather unique.[43]

An early intervention to normalize circulating lipid levels has been shown to reduce cardiovascular complications and mortality (Windler, 2005).[44] Serum lipids are frequently abnormal and are likely to contribute to the risk of coronary artery disease.[45]

Defective insulin secretion leads to various metabolic diseases in Type 2 diabetes, spanning from hyperglycemia due to defective insulin-stimulated glucose uptake and up regulated hepatic glucose production, along with dyslipidemia, which

includes impaired homeostasis of fatty acids, triglycerides, and lipoproteins.[46]

In our study, it was observed that mean serum zinc level was significantly low in diabetics as compared to control subjects, which correlates with other studies[47-48] in different parts of the world. The possible explanation for decreased level of zinc observed in diabetics can be due to increased excretion and/or decreased gastrointestinal absorption of zinc. Zinc also plays a major role in glycemic control of type 2 diabetic patients.

In the mammalian pancreas, Zinc is essential for the correct processing, storage, secretion, and action of insulin in beta (β)-cells. Insulin is stored inside secretory vesicles or granules, where two Zn++ ions coordinate six insulin monomers to form the hexameric-structure on which maturated insulin crystals are based.[49]

Hyperglycemia in diabetes is usually associated with hyperzincuria and increased urinary loss of Zn++, which is responsible for decreases in total body Zn++.[50-52] Zinc has antioxidant properties; thus it can stabilize macromolecules against radical induced oxidation.[53] Zinc is a component of the important antioxidant enzyme superoxide dismutase (Cu-ZnSOD).[54] Thus the protection of this antioxidant against free radicals generated in the disease[55] will be diminished.

Zinc supplementation resulted in a significant reduction of plasma total cholesterol, LDL-c and TG, while increasing HDL-c levels in patients with type-2 diabetes. These findings are in contrast to results from a previous meta-analysis of controlled trials involving healthy subjects, where no beneficial effects of Zinc supplementation were observed on plasma total cholesterol, LDL-c, HDL-c or TAG concentrations.[56] Thus, it appears that the beneficial effects of Zinc supplementation on metabolic parameters can be seen mainly in individuals with Zinc deficiency or diseases causing Zinc deficiency such as diabetes.

Interestingly, zinc seems also to be involved in nutritional regulation of IGF-1 bioactivity. In cultured bone cells, some studies suggest that zinc potentiates the action of IGF-1[57] and increases endogenous IGF-1 synthesis.[58] In animal models, severe zinc deficiency has been shown to decrease hepatic IGF-1 gene expression and to impair intracellular GH signaling pathway.[59-61] By these mechanisms, zinc may affect circulating concentrations of insulin, IGF-1 and GH. Roth and Kirchgessner[62] showed that force-feeding a zinc-depleted diet to rats for 14 days results in a 28% decrease in serum IGF-1 compared with rats fed a zinc-adequate diet, although there was no difference in caloric food intake. Similarly, Droup *et al*. demonstrated that low IGF-1 levels were related to decreased zinc concentration.[63]

In humans, poor zinc status has been associated with low circulating IGF-1 concentrations even in presence of adequate caloric intake.[64] Thus, zinc supplementation may be beneficial in selected categories of subjects with low baseline zinc serum levels. During ageing, nutritional deficits coupled with decreased absorptive efficiency contribute to zinc depletion. A zinc deficit could exacerbate the age-related decline in IGF-1 serum levels. The link between zinc and IGF-1 can be at least in part attributed to antioxidant activity of zinc.

CONCLUSION

The prevalence of Type 2 diabetes mellitus is increasing and associated with a very high mortality rate, reduced quality of life and high costs of treatment, despite intensive insulin treatment. New strategies are urgently needed which can prevent or slowdown the development of diabetes and its associated complications better than currently available treatment options. IGF-1 has the characteristics to be a marker for insulin resistance syndrome and it can also predict the diabetic complications (like cardiomyopathies) early in type 2 DM. Individuals with normal or elevated IGF-1 levels may be protected, at least in part, against disease. Zinc plays an important role in glucose metabolism, so understanding the impact of micronutrient deficiencies and the potential utility of supplementation is relevant to the prevention and management of type 2 diabetes mellitus. Low IGF-1 and Zinc levels and dyslipidemia are risk factors for developing diabetic complications. IGF-1and Zinc levels are useful biomarker to predict the Cardiovascular complications very early in type 2 diabetic patients.

Acknowledgment

I would like to thank the Department of General Medicine and Central Clinical Biochemistry Laboratory at Jawaharlal Nehru Medical College, AVBR Hospital and Research Centre for their valuable help.

Funding: This study was supported in part by PG Thesis grant from the Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Deemed University, Sawangi (Meghe), Wardha, Maharashtra, India.

Conflict of interest: None declared

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How to cite this article:

Sarmistha Sarkar and Ajay Meshram (2018) 'IGF-I and zinc as a biomarker in early diagnosing cardiovascular Complications in type 2 diabetics in the central India', *International Journal of Current Medical and Pharmaceutical Research,* 04(7), pp. 3474-3480.

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