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Serum Chromium is Inversely Correlated with the Carotid Intima–Media Thickness in Type 2 Diabetic Subjects

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Abstract

Objective: The aim of this study was to determine and correlate the serum chromium in Carotid intima - media thickness (CIMT) in type 2 Diabetes Mellitus (T2DM) subjects.
Materials and Methods: The present case – control study included 40 healthy controls and 45 T2DM subjects that were selected through non-probability (purposive) sampling by prior inclusion and exclusion criteria. Serum chromium (Cr) was detected and measured on inductively coupled "Plasma Optical Emission Spectrophotometer" (ICP- OES)- Carotid artery was examined with a 7.5-MHz linear-array transducer (Siemens Acuson x300) sonography. Data was analyzed by Student's t test and Chi square test in the SPSS 22.0 (USA). Linear regression model was used for predicting carotid intima media thickness. Level of confidence interval of statistical significance was 95% ($P \leq 0.05$).
Results: Serum Cr in controls and cases was noted 0.873 (± 0.162) and 0.281 (± 0.240) µg/ml ($P = 0.001$). Serum Cr proved negative correlation with random blood sugar (r= -0.145, $P = 0.185$), HbA1c (r= -0.145, $P = 0.0001$) and CIMT (r= -0.730, $P = 0.0001$). Multiple regression analysis model showed significant association of serum Cr (r= -0.730, $P < 0.0001$) and HbA1c (r= 0.754, $P < 0.0001$) with the CIMT.
Conclusion: The present study reported serum Cr was inversely correlated with the carotid intima - media thickness that is a marker of atherosclerosis. Cr supplements may be advised to diabetics in clinical management.
Keywords: Serum chromium, Carotid intima - media thickness, Atherosclerosis, Diabetes mellitus

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Introduction

Chromium (Cr) is one the essential trace elements. Cr participates in glucose and lipid metabolism. Cr improves glucose intolerance and decreases blood lipid levels. Cr deficiency is characterized by abnormalities of glucose tolerance and blood lipid levels. Serum Cr is essential for normal homeostasis of both blood glucose and lipids (1). Cr deficiency is reported in type 2 diabetics mellitus (T2DM). Cr deficiency interferes with insulin receptor binding and decreased insulin receptors resulting in altered glucose homeostasis (2).

Chromomodulin is a peptide composed of amino acids glutamate, glycine, aspartate and cysteine (3). Chromomodulin is also termed the Low molecular weight chromium peptide (LMW- Cr). Chromomodulin is assumed to be an integral part of insulin signaling amplification cascades (4).

It is suggested that the Cr in its LMW-Cr form stabilizes the conformation of insulin receptor “tyrosine kinase” activity, this way it facilitates the insulin effects on glucose homeostasis (5). The supposed mechanism by which LMW-Cr increases insulin sensitivity through inhibition of “phosphotyrosine phosphatase” which inactivates insulin receptor “tyrosine kinase” activity (6)

Cr has also a role in normal nerve functions. Its deficiency manifests as impaired immune response, mental impairment, and neuropathy (7). It is suggested that the Cr content decreases in sweat, hair and blood with senility (7). Total body Cr is measured by serum levels. Low serum Cr levels in T2DM subjects have been reported in previous studies (8,9). Serum Cr deficiencies is associated with other trace element deficiency such as zinc and manganese (10). Cr deficiency has been reported in Gestational DM as well (11,12). Many of previous studies (13,14) had reported deficiency of Serum Cr in individuals with T2DM associated with glycemic poor control.

T2DM is a risk factor for the atherosclerotic coronary artery disease (CAD) and carotid artery disease. The carotid intima-media thickness (CIMT) is actually a surrogate marker of atherosclerosis (15,16).

In this context, the present research was designed to determine serum Cr and glycemic control correlate with the CIMT in T2DM subjects.

Material and methods

The study subjects of present case control study were selected from the Department of Medicine, Liaquat University Hospital Hyderabad/Jamshoro from November 2017-August 2019. A sample of 45 T2DM diagnosed cases and 40 healthy controls were included in study protocol. Cases and controls were age, gender and body weight grouped matched. Study subjects were selected through non-probability purposive sampling according to inclusion and exclusion criteria. Diabetic cases of age 40-70 years were randomly selected irrespective of sex, duration, glycemic control with or without hypertension and with or without diabetic macrovascular complication. Normal liver function test was also an inclusion criterion. Patients with alcoholism, acute illness, congestive cardiac failure, chronic lung disease, chronic renal disease, liver disease, and patients taking drugs –lipid lowering, vitamins, minerals, steroids, or hepatotoxic drugs were excluded. Volunteers were facilitated to comply with the study protocol. 8-12 hour fasting was ensured for blood samples. Blood lipids, serum creatinine, blood glucose and glycated HbA1 (HbA1c) were analyzed (Cobas e 411 analyzer- Roche Diagnosis GmbH, Mannheim, Germany). Blood glucose was estimated by glucose oxidase method, HbA1c by immuno Turbidometric immunoassay method and serum creatinine by Jaffe`s method.

Triglycerides and cholesterol were determined by enzymatic colorimetric (CHOD-PAP & GPO-PAP) methods. Precipitant method was used for HDL-Cholesterol. Friedewald’s formula (LDL-C =

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TC - HDL-C – (TG/5)) was used for LDL-Cholesterol (17). A 5ml of blood was collected in a trace element free vacutainer irrespective of when the last meal was taken. The sample was centrifuged at 2000g within one hour of collection. Serum Cr was detected and measured on inductively coupled "Plasma Optical Emission Spectrophotometer" (ICP-OES). ICP-OES is a sequential plasma emission device. Serum Cr concentration was estimated from the observed spectrophotometric values. Serum chromium values were expressed in µg/ml. Patients were positioned in supine with an extended neck. Pillow was put under the shoulder blades. The carotid artery was examined with a 7.5-MHz linear-array transducer (Siemens Acuson x300) sonography. The anterior and posterior walls of the carotid artery were displayed as 2 bright white lines separated by a hypoechogenic space on a longitudinal image. The CIMT was measured as the distance between first (lumen-intima interface) and second (media-adventitia interface) leading edge of bright lines. Three sites were examined first the carotid artery bulb (1 cm proximal to the carotid bulb), second within the carotid bulb (maximum diameter) and third reading 1 cm distal to the carotid bulb in the direction of the internal carotid artery (18). Continuous and categorical data was analyzed by student's T-test and Chi square test respectively on the SPSS 22.0 (USA) and Graph Pad Prism. Pearson`s correlation measured linear correlation of variables. Linear regression model was used for predicting carotid intima-media thickness. Data was analyzed at 99% Confidence interval and $P \leq 0.05$ was considered significant.

Ethical considerations

The study was approved by the ethical review committee (ERC) vide letter no.1786/2019/IU/0005. Research was conducted in accordance to the Helsinki`s declaration for conducting the human research.

Results

Table 1 shows the demographic and laboratory findings of study subjects.

Table 1. Demography and biochemical findings of study subjects

Variable	Study groups	Mean	SD	*P*
Age (years)	Controls	56.97	3.91	0.051
	T2DM	57.55	4.15	
Body weight (kg)	Controls	82.25	11.81	0.56
	T2DM	83.00	11.98	
Systolic BP (mmHg)	Controls	127.64	14.24	0.01
	T2DM	153.0	44.80	
Diastolic BP(mmHg)	Controls	94.00	13.01	0.001
	T2DM	77.4	14.56	
RBG (mg/dl)	Controls	150.90	17.48	0.037
	T2DM	206.40	61.29	
HbA1 (%)	Controls	5.37	0.72	0.0001
	T2DM	11.00	2.42	
Serum Creatinine (mg/dl)	Controls	0.873	0.14	0.021
	T2DM	1.054	0.27	
Serum Cholesterol (mg/dl)	Controls	170.52	28.17	0.0001
	T2DM	213.155	40.49	
Triglycerides (mg/dl)	Controls	197.85	22.07	0.0001
	T2DM	335.62	129.73	
LDL-c (mg/dl)	Controls	97.92	16.61	0.77
	T2DM	95.80	39.32	
HDL- c (mg/dl)	Controls	47.023	2.84	0.76
	T2DM	40.808	9.23	
CIMT (mm)	Controls	0.521	0.07	0.0001
	T2DM	0.754	0.06	
Serum Chromium (µg/ml)	Controls	0.873	0.16	0.0001
	T2DM	0.281	0.24	

BP- blood pressure, RBG- random blood glucose, HbA1c- glycated HbA1, LDL- low density lipoprotein, HDL- high density lipoprotein, CIMT- carotid intima media thickness.

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Male and female in control and cases were 30 and 31, 10 and 14 respectively (*P*= 0.632). CIMT in controls and cases (T2DM) was noted as 0.521 (± 0.078) and 0.754 (±0.067) mm (*P*= 0.0001) respectively. Significant serum Cr difference was noted between controls and cases; 0.873 (±0.162) and 0.281 (±0.240) µg/ml respectively (*P*= 0.001). Serum Cr showed negative correlation with random blood glucose (r= -0.145, *P*= 0.0001), HbA1c (r= -0.145, *P*= 0.0001) and CIMT (r= -0.730, *P*= 0.0001) (Table 2).

Discussion

The present case control study is being reported that determined the serum Cr and its correlation with CIMT. The CIMT is a surrogate marker of atherosclerosis (15,16). The present study observed low serum Cr in T2DM subjects that is risk factor for the CIMT and atherosclerosis. Serum Cr in controls and cases was noted 0.873 (± 0.162) and 0.281 (±0.240) µg/ml respectively. The present study finds low serum Cr in T2DM subjects and negative correlation with Carotid intima–media thickness (Table 1 & 2). Table 2 shows the serum Cr negative correlated with random blood glucose, HbA1c and CIMT. Multiple regression analysis models showed significant inverse correlation of serum Cr, HbA1c and the CIMT. The finding of low serum Cr is in agreement with previous studies (17,19,20). The present study reports severely low serum Cr in T2DM subjects that is in contrast to previous studies form Western countries (18,21), but are in keeping with previous studies from Asia (18,20,22). Diwan et al (23) reported low serum Cr among the diabetics and concluded its role in the pathogenesis of diabetic vascular complications hence demands an elaborated research on its role.

In the present study; the serum Cr was detected and measured by ICP- OES that is highly sensitive method, hence the serum Cr levels are validated. A previous study (18) studied serum Cr in normal healthy Indian subjects and reported high serum copper that is paradoxical. But the study reported this might be due to geographical, environmental, and dietary habits. In the present study, serum chromium was inversely associated with age which is in agreement with Ding et al (22). Chromium deficiency is reported worldwide (2).

Volpe et al reported controversial results on the chromium supplementation have no effect on the insulin and C-peptide concentrations in both normal controls and diabetic population (21). Another study reported the serum chromium declines severely in diabetics with complications (24). The findings of low serum chromium of present study are in agreement with above study as we have analyzed serum chromium from chronic diabetics developed the complication long before.

Finding of low serum Cr is supported by previous studies (25,26) Low serum Cr is reported in GDM (27) and postmenopausal women with T2DM (8). Previous studies (28,29) reported low serum Cr in diabetic retinopathy with increased oxidative stress. A previous experimental study (30) reported chromium supplementation improves diabetic retinopathy with up regulation of serum insulin, GLUT-1 and GLUT-3 and findings were reversed when chromium supplementations were stopped.

In summary the low serum Cr levels in T2DM subjects raises the need of Cr supplementation in diabetics to halt the atherosclerosis and associated vascular complications. Based on the observations it is suggested for large sample size studies to be conducted on the serum chromium and carotid

Table 2. Correlation of serum chromium & random blood glucose, HbA1c

Variable		RBG (mg/dl)	Glycated HbA1(%)	CIMT (mm)
S. Chromium (µg/mL)	r	-0.145	-0.665**	-0.730**
	P	0.185	0.0001	0.0001
	Numbers		85	

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).
RBG- random blood glucose, CIMT- carotid intima media thickness

intima - media thickness. Strength of study lies in its case control design where normal healthy age and gender matched subjects were included for comparison, however; limitations are; a small sample size and a particular ethnic population therefore the findings cannot be generalized to other geographical and ethnicity. Hence the inverse correlation of serum chromium and carotid intima - media thickness may be interpreted cautiously for other ethnicity and geography population.

Conclusions

The present study reports low serum chromium levels in T2DM and was negatively correlated with the carotid intima - media thickness that is a marker of atherosclerosis. Maintaining optimal serum Cr levels may help prevent atherosclerosis in T2DM subjects.

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Conflict of Interest

All authors declare no competing interests.

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