GLOBAL JOURNAL OF BIO-SCIENCE AND BIOTECHNOLOGY

www.scienceandnature.org

CORRELATION BETWEEN SERUM TRACE ELEMENTS AND LIPIDS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS IN JEDDAH, SAUDI ARABIA

Syed M Farid
Department of Nuclear Engineering, King Abdulaziz University,
P.O. Box 80204, Jeddah 21589, Saudi Arabia

ABSTRACT
Diabetes is rising globally, particularly in the Kingdom of Saudi Arabia. Saudi Arabia is the number one country in the Gulf in terms of diabetes rate. Majority of diabetic patients also do suffer from dyslipidemia. Trace elements are tiny molecules that play important role in our bodies and alteration of some trace elements has been reported in Diabetes Mellitus. The present study investigates the relationship among diabetes mellitus, trace elements status and lipid profiles in serum of 118 male diabetic mellitus patients and healthy subjects. Serum lipid profile was measured by using the auto analyzer. The concentration of serum trace elements of each sample was determined using atomic absorption spectrometry. The results revealed that the serum levels of Fe and Cu were significantly increased, whereas, Zn, Mg and Mn levels were significantly decreased in diabetic patients as compared to the healthy subjects. The levels of total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-c) and very low density lipoprotein (VLDL) were found significantly higher in DM patients in comparison to the healthy subjects. The mean value of high density lipoprotein cholesterol (HDL-c) was significantly lower in diabetic patients. The correlation study revealed a significant positive correlations between serum copper and each of TC (r =0.312), TG (r =0.343), LDL-c (r =0.338), between serum iron and TC (r =0.43), and also a positive correlation was found between magnesium and HDL-c (r =0.452), while a negative correlation was found between Fe and HDL-c (r = -0.59) and between Mg and TG (r = -0.426) and VLDL (r = -0.502). The control group exhibited no such correlation.

KEYWORDS: Type 2 diabetes mellitus, serum lipids, trace elements.

INTRODUCTION

Diabetes, also known as the “life style disease”, is rapidly turning into a modern-day epidemic. It is constantly rising in the Kingdom of Saudi Arabia as a result of rapid urbanization associated with decreased physical activity and a luxurious, sedentary life style and unhealthy food habits. The prevalence of diabetes mellitus (DM) in the kingdom is at an alarming level. Over 25% of the adult population is suffering from DM and that figure is expected to be more than double by 2030[1]. Half of the people over 30 years of age are prone to diabetes. Saudi Arabia ranks seventh worldwide and the first in the Gulf in terms of diabetes rates[2]. The cost of diabetes is challenging health system even in the wealthiest countries. In low-income countries, it threatens to reverse health and economic progress made towards the Millennium Development Goals[3,4]. Dyslipidemia was seen in diabetic patients and was primarily responsible for risk of several complications in Type 2 Diabetes Mellitus (T2 DM) patients. Diabetes is associated with high risk of cardiovascular diseases (CVD) when compared to non-diabetic counterparts. Dyslipidemia is one of the most important CVD risk factor that co-occurs with type 2 diabetes mellitus (T2 DM) in more than 70% of the patients. Saudi Arabia is experiencing an alarming rising in incidence and death rates from CVD[5]. Diabetic dyslipidemia is characterized by high serum triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles[6]. Trace elements are accepted as essential for optimum health, because of their diverse metabolic characteristic and functions. Alteration of some trace elements has been reported in T2 DM. These trace elements might have specific role in the pathogenesis and progress of the disease. Among these trace elements– magnesium (Mg), zinc (Zn), copper (Cu) and iron (Fe) are important for the growth and biological functions. The determination of trace elements in the blood is of increasing interest in many clinical and research laboratories due to their role in maintenance of health and development of optimal physiological functions. It is frequently reported that deficiencies of some trace elements cause marked alterations in lipid and lipoprotein metabolism. The mechanisms of their effects are not completely understood and also there are contradictory findings regarding the relationship between serum trace elements with lipid and lipoproteins[7,8]. The aim of this study is to evaluate the correlations of serum concentrations of trace elements including Cu, Zn, Fe, Mn and Mg with lipid profile parameters of adult diabetic patients in Jeddah City, Saudi Arabia.

MATERIALS & METHODS

The study population is known Type 2 diabetic patients (DM group) attending King Abdulaziz University health clinic, Jeddah (Saudi Arabia) and non-diabetic individuals. Fifty male non-diabetic individuals were selected (control group) following medical examination and laboratory test that determined fasting blood glucose level. There were no clinical or laboratory disorder in the control group. A total

of 68 male non-obese, non-hypertensive patients of Type 2 DM with no other cardiovascular, renal or thyroid ailments attending King Abdulaziz University health clinic were enrolled in this study. Informed consent was sought and obtained from individuals before enrollment into the study. The study protocol was approved by institutional ethical committee. The age of both patients and controls was recorded. Body weight and height were measured and used to calculate the body mass index (BMI), which was used as a measure of relative body weight. Following enrollment, both patients and controls were instructed for the following: not to change their lifestyle or their dietary habits and not to take any dietary supplements. The diet was not monitored. Venous blood samples were collected from each male in both groups after at least 10 hours fasting into centrifuge tubes. The blood sample was allowed to clot and then centrifuged at 3000 rpm for 15 minutes at room temperature. The sera were analyzed for glycated hemoglobin (HbA1c), fasting serum glucose (FSG), total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-c) using an auto-analyzer(Roche Modular P-800, Germany). Serum low-density lipoprotein cholesterol (LDL-c) was calculated by Friedewald's formula [TC – (HDL-c + TG/2.2)]. Non-HDL-c, Risk ratio (TC/HDL-c), LDL-c/HDL-c were calculated from the essential lipid profile values. The concentration of trace elements of each sample was measured by Graphite Furnace Atomic Absorption spectrometer (Varian, Model Spectra AA 30P) using calibration method. Value of HbA1c was given as percentage of total hemoglobin and values of all other parameters were given in mg/dl.

Statistical analysis was done by SPSS version 17.0. Pearson's correlation test was performed to examine correlations between various parameters. Independent samples t-test (2-tailed) was used to compare means of different parameters. All values are expressed as mean ± SD. The results were considered significant when $p < 0.05$.

RESULTS

Age, height, weight, and body mass index (BMI) are shown in Table 1. The mean age and standard deviation of the control group was (52.17 ± 7.03) years, while the mean age and standard deviation of the diabetic group was (55.20 ± 6.82) years. The diabetic patients were generally heavier than the control subjects. The results of the BMI indicated that the diabetic patients were overweight. There was significant difference in the BMI of the diabetic patient when compared with the control group. Biomedical lipid profile characteristics (TC, TG, LDL-C, HDL-C and VLDL) are shown in Table 2. There was a significant increase in serum TC, TG, LDL-C, VLDL and a significant decrease in HDL-C in the patient group compared to the control group.

TABLE 1: Descriptive physical characteristics of control subjects and diabetic patients

Characteristics	Control N = 50	Patients N = 68	p - value
Age (years)	52.17 ± 7.03	55.20 ± 6.82	0.04*
Height (cm)	172.10 ± 2.31	170.67 ± 2.01	0.41
Weight (Kg)	72.51 ± 2.65	86.70 ± 2.34	0.03*
BMI (Kg/m^2)	24.48 ± 1.40	29.79 ± 1.72	0.01*

Statistically significant

TABLE 2: Descriptive biochemical characteristics of control subjects and diabetic patients

Biochemical characteristics	Control N = 50 Mean ± SD	Patients N = 68 Mean ± SD	p - value
TC (mg / dl)	169.23 ± 18.79	204. 09 ± 20.46	< 0.05
HDL-c (mg / dl)	45.47 ± 6.29	34.55 ± 5.38	< 0.05
LDL-c (mg / dl)	105.61 ± 11.56	141.43 ± 21.05	< 0.001
VLDL (mg/ dl)	29.27 ± 4.10	39.37 ± 6.82	< 0.001
TG (mg / dl)	119.16 ± 14.78	191.95 ± 21.83	< 0.001
Zn (µg / dl)	93.83 ± 8.23	71.42 ± 7.38	< 0.05
Cu (µg / dl)	107.24 ± 13.21	162.44 ± 17.24	< 0.001
Fe (µg / dl)	101.32 ± 12.30	132.03 ± 11.96	< 0.02
Mn (µg / dl)	3.92 ± 0.43	2.99 ± 0.36	< 0.05
Mg (mg / dl)	1.98 ± 0.23	1.32 ± 0.27	< 0.04

The concentration of trace elements (Zn. Cu, Fe, Mn and Mg) is also shown in Table 2. There were significant lower levels ($p < 0.05$) of serum Zn, Mn, and Mg in diabetic patients compared to the control group and significant higher levels ($p < 0.05$) of Cu and Fe in diabetic patients compared with the control group. Table 3 shows the correlations of serum concentrations of trace elements included in the study with serum concentrations of lipid profile parameters of diabetic patients (Pearson correlation, p-value). The results indicate that there was a significant positive correlations between serum copper and each of TC (r = 0.312), TG (r = 0.343), LDL-c (r = 0.338), between serum iron and TC (r = 0.43), and also a positive correlation between magnesium and HDL-c (r = 0.452), while a negative correlation was found between Fe and HDL-c (r = - 0.59) and between Mg and TG (r= - 0.426) and VLDL (r = - 0.502) in the patient group. The results also indicate that there was a significant weak negative correlation between serum Zn and TC and LDL-c and between Mg and TC, while a significant weak positive

correlation existed between serum Zn and TG and VLDL. All correlations between trace elements and lipid profile in control group were not significant (Table 4).

TABLE 3 : The correlations of serum concentrations of trace elements with lipid profile parameters in diabetic patients

Lipid profile \ Trace element	Zn	Cu	Fe	Mn	Mg
TC	r = - 0.251	r = 0.312	r = 0.43	r = 0.031	r = - 0.227
	p < 0.05	p < 0.05	p = 0.03	p < 0.05	p < 0.05
TG	r = 0.266	r = 0.343	r = - 0.27	r = 0.037	r = - 0.426
	p = 0.001	p < 0.05	p = 0.31	p < 0.05	p < 0.05
LDL-c	r = - 0.218	r = 0.338	r = 0.40	r = 0.07	r = - 0.296
	p = 0.001	p < 0.05	p = 0.058	p = 0.684	p = 0.028
HDL-c	r = 0.179	r = 0.295	r = - 0.59	r = - 0.033	r = 0.452
	p = 0.55	p = 0.078	p = 0.001	p = 0.598	p < 0.05
VLDL	r = 0.25	r = - 0.23	r = - 0.21	r = 0.005	r = - 0.502
	p < 0.05	p = 0.18	p = 0.30	p = 0.92	p < 0.05

TABLE 4 : The correlations of serum concentrations of trace elements with lipid profile parameters in control subjects

Lipid profile \ Trace element	Zn	Cu	Fe	Mn	Mg
TC	r = 0.210	r = 0.246	r = 0.212	r = 0.149	r = - 0.016
	p = 0.253	p = 0.183	p = 0.36	p = 0.283	p = 0.269
TG	r = 0.186	r = - 0.073	r = - 0.22	r = - 0.182	r = - 0.324
	p = 0.381	p = 0.668	p = 0.35	p = 0.210	p = 0.402
LDL-c	r = 0.270	r = 0.264	r = 0.31	r = 0.179	r = - 0.051
	p = 0.185	p = 0.163	p = 0.21	p = 0.189	p = 0.186
HDL-c	r = 0.029	r = 0.084	r = 0.36	r = 0.129	r = 0.312
	p = 0.868	p = 0.684	p = 0.09	p = 0.358	p = 0.500
VLDL	r = 0.32	r = - 0.07	r = - 0.27	r = 0.152	r = - 0.339
	p = 0.28	p = 0.83	p = 0.38	p = 0.276	p = 0.496

DISCUSSION

Diabetes has become an international health care crisis that requires new approach to prevention and treatment. Diabetes is a complex and multifactorial disease. The metabolic dysregulations associated with diabetes causes secondary pathophysiologic changes in multiple organ systems that impose a heavy burden of morbidity and mortality from macro vascular and micro vascular complications[9]. The trace elements play a vital role in different metabolic processes in the body[10]. Diabetes has been shown to be associated with abnormalities in the metabolism of Zn, Cu, Fe, Mn, Mg and the impairment of these metals had been reported as aggravating factors in the progression of disease[11,12].

In the present study, the results indicate that there was a significant decrease in serum zinc level in patients with type 2 DM as compared to control group, and that there was a significant negative correlation between serum Zn and LDL-C and a significant positive correlation existed between serum Zn and TG and VLDL in the patients group while the control group showed no such correlation. Therefore, these findings indicate the possible effect of Zn level in serum lipid profile and this effect may be due to the role of Zn as an antioxidant. Thus, the decrease in Zn level in patients may lead to increased lipid peroxidation and leading to increased levels of TC, TG and LDL-C according to the results of previous studies. All these results support the hypothesis that cholesterol stored in the lipid droplets of the adipose tissue cells is released into plasma and is the chief source of the hypercholesterolemia observed during stress[13,14,15]. Again there is evidence suggesting that Zn can act as an endogenous factor against atherosclerosis by inhibiting the oxidation of LDL-C in the presence of transition metals and that adequate Zn nutrition may protect against inflammatory diseases such as atherosclerosis by inhibiting the activation of oxidative stress[16]. These findings are in agreement with the previous studies which showed treatment with Zn reduce TC, TG, and LDL-C plasma levels and increased HDL-C levels[17]. A comprehensive systematic review and meta-analysis on the effects of Zinc supplementation in patients with diabetes demonstrates that Zinc supplementation has beneficial effects on glycemic control and promotes healthy lipid parameters[18]. A recent meta-analysis (00) demonstrates that zinc supplementation has favorable effects on plasma lipid parameters. Zinc supplementation significantly reduces TC, LDL cholesterol, and TG. In addition to that, Zinc supplementation in DM patients demonstrates a significant elevation of HDL cholesterol. Therefore it may have the potential to reduce the incidence of atherosclerosis related morbidity and mortality especially in DM patients who are at risk of atherosclerosis[19]. Partida-Hernandez *et al.* [20] showed a significant decrease in TG concentration following a 12-week supplementation with 100 mg Zn sulfate among diabetics who were not on cholesterol-lowering treatment. Furthermore, they showed a significant reduction in TC and an increase in HDL-C, indicating that

supplementation, in addition to improving glycemic indices, has favorable effects on cardiovascular risk factors. In the present study, a significant increase in serum copper in patients with type 2 DM was observed as compared to controls. Our finding was similar to the results of different investigators [12,21,22]. It is well known that copper plays a vital role in oxidative stress[21,23]. A high level of copper enhances the toxic effect of metal dependent free radicals. Moreover the increase in copper levels in patients with type 2 DM might also be attributed to hyperglycemia, which stimulates glycation and causes release of copper ions from copper binding sites of proteins. The release of copper ions into blood further accelerates the oxidative stress[24]. According to other studies increased Cu level found in T2 DM patients is due to increased level of ROS, which increases consumption of available antioxidants in the body. So these findings are due to various alterations of Cu in T2 DM patients, due to antioxidant imbalance [25]. In this study, increased levels of lipoproteins were also found. Insulin resistance with T2 DM is associated with plasma lipid and lipoproteins abnormalities, which includes reduced HDL Cholesterol and elevated LDL particles, and triglycerides (26). The relationship between an increase in Cu concentration and the oxidation of LDL-C has been confirmed [27].

Excess iron has been implicated in the pathogenesis of diabetes and its complications[28]. Free iron serves as a catalyst for lipid and protein oxidation and the formation of reactive oxygen species. Epidemiological studies have reported an association between high iron stores and type 2 diabetes[28]. In the present study, serum Fe is significantly increased in type 2 diabetes as compared to control group and this finding is consistent with the results of different authors [27,29,30]. Iron is strong pro-oxidant that catalyzed the formation of hydroxyl radicals, and the increase in oxidative stress may be associated with risk of diabetes. A link has been established between increased dietary Fe intakes; increase intestinal absorption particularly eating red meat, increased body iron stores. The concept of iron contributing to diabetes is supported by a few important recent animal studies[31]. Some investigators have reported the hypothesis that glycated proteins binding to transition metals such as Cu and Fe may result in glycocholates formation, which plays an important role in the etiology of peripheral vascular dysfunction and peripheral neuropathies in DM[30]. However, the association of these elements with HbA1c should be evaluated by more studies to better clarify the related mechanisms [23].

Manganese is a cofactor of many enzymes including mitochondrial superoxide dismutase[32]. Mn acts as a catalyst in breakdown of fats and cholesterol. It is essentially required for the metabolism of vitamin B_1, C and E, and for activation of various enzymes which are important for proper digestion and utilization of foods [33,34]. In our study, serum levels of Mn were significantly lower in diabetic patients than those of healthy group. It has been reported that people with diabetes may often have a serious Mn deficiency [23,34]. Appropriate Mn levels are required for the development of the normal insulin synthesis and secretion[32,34]. It has been reported that serum Mn levels were negatively correlated with serum insulin levels in the obese diabetic women [34]. People with diabetes have been shown to have significantly lower levels of Mn in serum than that in healthy people [11,34,35]. The finding of a recent study [36] indicated that the serum level of Mn is lower in atherosclerotic patients than in healthy controls and it decreases with severity of coronary atherosclerosis. The present study showed no significant correlation between serum Mn and lipid profile parameters in the two groups, although another study has demonstrated that Mn enhanced cholesterol synthesis in the liver and hypocholesterolemia has been reported in a human case of Mn deficiency (00), however, the cause of this finding is probably due to no significant difference in Mn between the two groups.

According to the results of the present study, mean serum Mg in diabetic patients was significantly lower as compared to healthy controls. These findings are also similar to other workers[23,37,38]. In the presence of diabetes, it is observed that inadequate metabolic control can affect the concentration of magnesium, developing hypomagnesemia, which may be still directly related with some micro and macrovascular complications observed in diabetes, as cardiovascular disease, retinopathy and neuropathy. Sales *et al.* [39] suggested Mg supplementation in patients with diabetes mellitus who have proven hypomagnesemia. Magnesium is a cofactor for several enzymes involved in carbohydrate metabolism[38]. Magnesium deficiency decreases insulin sensitivity via alteration of the insulin receptor associated tyrosine kinase in type 2 DM patients [38]. Hypomagnesemia can increase the platelet reactivity, increase vascular and adrenal responses to angiotensin II enhanced thromboxane A2 release and lead to organ damage from free radicals [38,40]. The reason for significant decreased magnesium in diabetic patients compared to controls may be due to higher urinary losses or impaired absorption of magnesium. The decrease in serum magnesium may also be due to magnesium depletion caused by osmotic diuresis and by indirect hormonal effects [41]. It is believed that diabetic state impairs the renal tubular reabsorption of magnesium from the glomerular filtrate [42].

In the present study we found a significant increase in TC, TG, LDL, VLDL and significant decrease in HDL in cases compared to controls. This is similar to the findings obtained by some authors [12,38,43]. Insulin resistance plays an important role in the development of diabetic dyslipidemia which leads to increased efflux of free fatty acids from adipose tissue, impairs insulin dependent muscles uptake of free fatty acids and causes increased fatty acid release to the hepatic tissue[44]. HDL cholesterol levels is associated with low risk of dyslipidemia, more number of HDL particles contribute to normal lipid profile effect, in the form of, cellular cholesterol efflux and direct antioxidant and anti-inflammatory properties. Moreover, low level of HDL cholesterol is responsible for elevated triglyceride levels [45]. Lipoprotein abnormalities increase with duration of T 2 DM [46]. Reports on the effect of magnesium on lipid profile in diabetic patients are controversial. While some indicate that administrating Mg supplementation to the diabetic did not improve lipid levels, others showed beneficial effects on lipid profile [47]. The results of a recent study show that oral magnesium

supplementation with proper dosage has beneficial effects on blood glucose, lipid profile, and blood pressure in patients with type 2 diabetes [48].

In this study, significant inverse correlations of serum Mg with TC, TG, LDL-c and VLDL were found. Moreover, a significant positive correlation of serum Mg with HDL-c was observed in the DM patients. The present result is in agreement with previous studies [37,38,49,50]. Due to the high incidence of cardiovascular morbidity in DM patients [50,51], an association of serum Mg with atherogenic lipids bears important clinical implications[38,50]. Based on the findings of this study, it may be prudent in clinical practice to periodically monitor serum Mg concentrations in diabetic patients. In case of low serum Mg, its supplementation or an intervention may be beneficial because Mg can act like stain medications in improving dyslipidemia in diabetic patients [52]. This fact is supported by Mg supplementation studies carried out in DM patients that significantly improved atherogenic lipid fractions [17,18,52,53]. This study also suggests that diabetic patients should take magnesium rich foods like whole grains, legumes, fruits and vegetables (especially dark-green, leafy vegetables) every day which will help to provide recommended intakes of magnesium and maintain normal storage levels of this mineral. Dietary intake of magnesium can often restore mildly depleted magnesium levels but magnesium supplementation is required to restore very low magnesium levels to normal. However, the association between lipid abnormalities and hypomagnesaemia has not been fully understood in humans and need further studies.

The results indicate that there are different correlations between trace elements and lipid profile in in DM patients while there is no such correlation in healthy men. The cause of these findings suggest that the correlations between the serum concentrations of trace elements with lipid profile in physiological concentrations may not be the same as the changes observed during deficiencies of the trace elements as in DM patients.

Extensive research and clinical outcomes analysis have demonstrated the increased risk of coronary heart disease (CHD) in patients with dyslipidemia and hyperlipidemia [54]. The treatment of dyslipidemia and hyperlipidemia is a combined strategy of consisting of lifestyle modification and the addition of lipid lowering medications if necessary. Nutrition is an important treatment for dyslipidemia, CHD risk factors and for the prevention and treatment of CVD. Numerous epidemiological studies and prospective clinical trials have clearly established the relationship between diet, serum lipids, inflammation and CVDs including coronary heart disease and stroke. General dietary recommendations include lowering saturated fat and cholesterol intake. Most studies clearly indicate that trans fatty acids and refined carbohydrates have an adverse effect on serum lipids and cardiovascular outcomes [54,55,56]. The MUFA and omega 3 fatty acids are consistently beneficial for dyslipidemia and CVD. The vegetarian diet with increased complex carbohydrates and fiber with lower dietary cholesterol is also beneficial. Protein intake of lean, wild and organic types of protein and cold water fish improves lipids and CHD risk factors. Exercise has been shown to provide a small but significant benefit to serum lipid profiles. Studies have shown an improvement in HDL-c, a decrease of LDL-c, and a decrease in TG [57]. Exercise in combination with a low fat diet appears to have a synergistic effect with studies showing a decrease in LDL-c of 7-15% along with an improvement in HDL-c of 5-14%[58]. Physical exercise has antiatherogenic effects because of its potential benefits on blood pressure levels, glucose tolerance, body weight and composition, plasma lipids, and lipoprotein metabolism [59]. Exercise reduces HbA1c by an amount that should decrease the risk of diabetic complications. Yogic exercises to enhance the antioxidant defense mechanism in diabetics by reducing oxidative stress, which affects the lipid peroxidation [60,61].

REFERENCES

[1]. Diabetes among Saudis, a major issue. Arab news (13 November, 2012).

[2]. Diabetes: KSA is 7th. in the world, 1st. in Gulf. Arab News (24 June, 2015).

[3]. Hashemnia, H., Oryan, A., Hamidi, A.R., Mohammadalipour, A. (2012) Blood glucose levels and pathology of organs in alloxan-induced diabetic rats treated with hydro-ethanol extracts of *Allium sativum* and *Capparis spinosa*. Afr J Pharm Pharmacol., 6(21) : 1559-1564.

[4]. IDF– International Diabetes Federation: 2010 – 2012 Strategy. (www.idf.org/2010-2012-strategy).

[5]. Nagarajrao, R. (2014) Study of trace elements and malondialdehyde levels in cardiovascular disease patients. Int. J. Adv. Res. Biol. Sci., 1(9): 25-32.

[6]. Mooradian, A.D. (2009) Dyslipidemia in type 2 diabetes mellitus. Nat. Clin. Pract. Endocrinol. Metab., 5(3) : 150-159.

[7]. Saraymen, R., Kich, E., Yazar, S., Saraymen, B., (2003) Magnesium, Copper, Zinc, Iron and Chromium levels in Sweat of Boxers. JIUMF, 10(3): 121-125.

[8]. Sulibursk a, J., Bogdanski, P., Krejpcio, Z. (2011) Dietary intake and serum and hair concentrations of minerals and their relationships with serum lipids and glucose levels in hypertensive and obese patients with insulin resistance. Biol. Trace Elem. Res., 139(2): 137-150.

[9]. Pasupathi, P., Farook, J., Chinnaswamy P. (2010) Oxidant-antioxidant status, high sensitive C-reactive protein and homocysteine levels in type 2 diabetic patients with and without microalbuminuria. Int. J. Biol. Med. Res., 1(3): 04-08.

[10]. Pujar, S., Pujar, B.L.L., Ganiger, A., Hiremath, K., Mannangi, N. (2014) Correlation of serum zinc, magnesium and copper with HbA1c in type 2 diabetes mellitus patients among Bagalkot population- A case study. Medica Innovatica, 3(2): 4-9.

[11]. Gawrishankar, R., Sai, K., Saravanan, K., Magudapathy, P., Nair, P., Divi, S., Venkataramaniah, K. (2011) Deficiency of iron, manganese chromium and zinc in diabetic patients of Anantapur district of Andhra paradesd, India. Research & Reviews, 1(3): 1-11.

[12]. Tamrakar, S., Kachhawa, K., Agrawal, D., Varma, M., Swain, T.K., Kumar, S. (2016) Study of trace elements (Mg and Cu) and dyslipidemia in type 2

diabetes mellitus patients in a tertiary care hospital of south east Asia. Int. J. Current Res., 8(2): 26972-26975.

[13]. Lata, H., Ahuja, G.K., Narang, A.P., Walia, L. (2004) Effect of Immobilization stress on lipid peroxidation and lipid profile in rabits. IJCB, 19(2): 1-4.

[14]. Lata, H., Ahuja, G.K., Narang, A.P. (2002) Effect of starvation stresson lipid peroxidation and lipid profile in rabits. Indian J. Physiol. Pharmacol., 46 (3): 371-374.

[15]. Venkatesan, A., Hemalatha, A., Bobby, Z., Selvaraj, N., Sathiyapriya, V. (2006) Effect of smoking on lipid profile and lipid peroxidation in normal subjects. Indian J. Physiol. Pharmacol., 50(3): 273-278.

[16]. Hennig, B., Toborck, M., McClain, C.J., Lekamwasam, S. (2001) High-energy diets, fatty acids and endothelial cell function: implication for atherosclerosis. J. Am. Coll. Nutr., 20: 91-105.

[17]. Gunasekara, P., Hettiarachchi, M., Liyanage, C., Lekamwasam, S. (2011) Effects of zinc and multimineral vitamin supplementation on glycemic and lipid control in adult diabetes. Diabetes Metab. Syndr. Obes., 4 : 53-60.

[18]. Jayawardena, R., Ranasinghe, P., Galappatthy, P., Constantine, G.R., Katulanda, P. (2012) Effect of zinc supplementation on diabetes Mellitus: a systematic review and meta-analysis. Diabetology Metab. Syndr., 4 : 13-24.

[19]. Ranasinghe, P., Wathurapatha, W.S., Ishara, M.H., Jayawardana, R., Galappattht, P. Katulanda, P., Constantine, G.R. (2015) Effect of zinc supplementation on serum lipids. Nutr. Metab., 12(26) : 1-16.

[20]. Partida-Hernandez, G., Arreola, F., Fenton, B., Cabeza, M., Roman-Ramos R., Revilla-Monsalve, M.C. (2006) Effects of zinc replacement on lipids and lipoproteins in type 2 diabetic patients. Biomed. Pharmacother, 60(4): 161-168.

[21]. Sarkar, A., Das, S., Barik, B.K., Kedage, V., Shetty, J.K. (2010) Copper and Ceruloplasmin levels in relation to total thiols and GST in type 2 diabetes mellitus patients. Ind. J. Clin. Biochem.,25 :74-76.

[22]. Mohanty S.S., Pinnelli, V.S., Murgod, R., Raghavendra, D.S. (2013) Evaluation of serum copper, magnesium and glycated hemoglobin in type 2 diabetes mellitus. Asian J. Pharm. Clin. Res. 6(2): 188-190.

[23]. Viktoriniva, A., Toserova, E., Krizkov, M., Durackova, Z. (2009) Altered metabolism of Cu, Zn, and Mg is associated with increased levels of glycated hemoglobin in patients with diabetes mellitus. Metabolism, 58(10): 1477-1482.

[24]. Quilliot, D., Dousset, B., Guerci, B., Dubois, F., Drouin, P., Ziegler, O. (2001) Evidence that diabetes mellitus favors impaired metabolism of Zn, Cu and Se in chronic pancreatitis. Pancreas, 22: 299-306.

[25]. Baloch, S., Memon, S.H., Memon, Y.M., Rafique, Z., Mahmood, A. (2013) Serum copper concentration in type 1 diabetes mellitus by Atomic Absorption Spectroscopy. Nat. Sci., 11(9): 14-16.

[26]. ADA (2003) American Diabetes Association: Management of dyslipidemia in adult with diabetes (position statement). Diabetes Care, 26(1): 83.

[27]. Tasneem, G., Hasan, I.A., Naveed, K., Mohammad, B.A., Nussarart, J. (2008) Copper, chromium, manganese, iron, nickel and zinc in biological samples of diabetes mellitus patients. Biol. Trace Elem. Res., 122: 1-18.

[28]. Thomas, M.C., Maclsaac, R.J., Tsalamandris, C., Jenum, G., 2004. Elevated iron indices in patients with diabetes. Diabetes Med., 21:

[29]. Swaminathan, S. Fonseca, V.A., Alam, M.G., Shah, S.V. (2007) The role of iron in diabetes and its complications. Diabetes Care, 30 : 1926-1933.

[30]. Somayeh, A.H., Neda, V., Khadem-Ansari, M.H., Rasmi, Y., Kheradmand, F. (2016) Altered concentration of Copper, Zinc and Iron are associated with increased levels of glycated hemoglobin with type 2 diabetes mellitus and their first-degree relatives. Intr. J. Endocrinol. Metab., e33273 , DOI : 10.5812/ijem.33273.

[31]. Cooksey, R.C., Jones, D., Gabrielsen, S. (2010) Dietary iron restriction or iron chelation protects from diabetes and loss of beta cell function in the obese mouse. Am. J. Physiol. Endocrinol. Metab., 298 : E1236-1243.

[32]. El-Nabarawy, K., Mohamed, A., Ahmed, M., Ei-Arabi, H. (2010) α-Lipoic acid therapy modulates serum levels of some trace elements and antioxidants in type 2 diabetic patients. Am. J. Pharm. Toxicol., 5(3: 152-158.

[33]. Rashed, M.N. (2011) The role of trace elements on hepatitis virus infections: A review. J. Trace Elem. Med. Biol., 25: 181-187.

[34]. Yerlikaya, F.H., Toker, A., Aribas, A. (2013) Serum trace elements in obese women with or without diabetes. Indian J. Med. Res., 137(2): 339-345.

[35]. Ekmekcioglu, C., Prohasks, C., Pomazal, K., Steffan, I., Schernthaner, G., Marktl, W. (2001) Concentration of seven trace elements in different hematological matrices in patients with type 2 diabetes as compared to healthy controls. Biol. Trace Elem. Res., 79: 205-219.

[36]. Bagheri, B., Shokrzadeh, M., Akbari, N., Mokhberi, V., Azizi, S. (2015) The relationship between serum level of Manganese and severity of coronary atherosclerosis. Zahedan J. Res. Med. Sci., 17(1): 30-33.

[37]. Rasheed, H., Elahi, S., Ajaz, H. (2012) Serum magnesium and atherogenic lipid fractions in type 2 diabetic patients of Lahore, Pakistan. 2012. Biol. Trace Elem. Res., 148(2): 165-169.

[38]. Mishra, S., Padmanaban, P., Deepti, G.N., Sarkar, G., Sumathi, S., Toora, B.D. (2012) Serum magnesium and dyslipidemia in type 2 diabetes mellitus. Biomedical Research, 23(2): 295-306.

[39]. Sales, C.H., and Pedrosa, L.F. (2006) Magnesium and diabetes mellitus: Their relation. Clin. Nutr., 25(4): 554-562.

[40]. Nagarajrao, R., Alharbi, S.A. (2015) Evaluation of serum zinc, copper, magnesium, and iron levels in type 2 diabetes mellitus patients. Int. J. Adv. Res., 3(2): 960-965.

[41]. Rusu, M.L., Marutom, C., Rusu, L.D., Marutoui, O.F., Hotoleanu, C., Poanta, L. (2005) Testing of magnesium, zinc, and copper blood levels in diabetes mellitus patients. Acta Universitatis Cibiniensis Seria F. Chemia., 8: 61-63.

[42]. Farid, S.M., Abulfaraj, T.G. (2013) Trace mineral status related to levels of glycated hemoglobin of type 2 diabetic subjects in Jeddah, Saudi Arabia. Medical J. Islamic World Academy of Sciences, 21(2): 47-56.

[43]. Patil, M., Kumar, N., Nusrath, A., Jayaram, S., Rajeshwari, A. (2015) Association of HbA1c with serum lipid profile and lipoprotein (a) in type 2 diabetes mellitus. Int. J. Cur. Res. Rev., 6(6): 20-25.

[44]. Habib, S.S., Aslam, M. (2004) Lipids and lipoprotein (a) concentrations in Pakistani patients with type 2 diabetes mellitus. Diabetes Obes. Metab., 6(5): 338-343.

[45]. Bittner, V., Johnson, D., Zineh, I., Rogers, W.J., Vido, D. (2009) The TG/HDL cholesterol ratio predicts all cause mortality in women with suspected myocardial ischemia: A report from theWomen's Ischemia syndrome Evaluation. Am Heart J., 157(3): 548-555.

[46]. Shabana, R., Sasisekhar, T.V.D. (2013) Effect of gender, age and duration on dyslipidemia in type 2 diabetes mellitus. Int. J. Cur. Rev., 104-113.

[47]. Soltani, N., Keshavarz, M., Dehpour, A.R. (2007) Effect of oral magnesium sulfate administration on blood pressure and lipid profile in streptozocin diabetic rat. Europ. J. Pharma.,560: 201-205.

[48]. Solati, M., Ouspid, E., Hosseini, S., Soltani, N., Keshavarz, M., Dehghani, M. (2014) Oral magnesium supplementation in type 2 diabetic patients. Med. J. Islam. Repub. Iran, 28: 67-74.

[49]. Nasri, H. (2006) Lipids in association with serum magnesium in diabetes mellitus patients. Acta Angiol., 12(4): 149-154.

[50]. Supriya, S.M., Murgod, R., Pinnelli, V.B.K., Raghavendra, D.S. (2012) Hypomagnesemia, lipid profile and glycosylated haemoglobin in type 2 Diabetes mellitus patients. Intl. J. Chem. Pharm. Res., 1(5): 116 -123.

[51]. Mane, M., Chaudhari, G.R., Reddy, E.P. (2012) Hypomagnesemia in diabetic patients and biochemical action on the cardiovascular system. Int. J. Biol. Med. Res., 3(1): 1273-1276.

[52]. Rosanoff, A., Seelig, M.S. (2004) Comparison of mechanism and functional effects of magnesium and stain pharmaceuticals. J. Am. Coll. Nutr., 23: 501S-505S.

[53]. Lal, J., Vasudev, K., Kela, A.K., Jain, S.K., (2003) Effect of oral magnesium supplementation on the lipid profile and blood glucose of patients of type 2 diabetes mellitus. J. Assoc. Physicians India. 51: 37-42.

[54]. Ito, M.K. (2012) Dyslipidemia: Management using optimal lipid-lowering therapy. Ann. Pharmacother., 46(10): 1368-1381.

[55]. Houston, M. (2014) The role of nutrition and nutritional supplements in the treatment of dyslipidemia. Clin. Lipidology, 9(3): 333-354.

[56]. Franklin, B.A., Durstine, J.L., Roberts, C.K., Barnard, J.B. (2014) Impact of diet and exercise on lipid management in the modern era. Best Practice & Research clinical Endocrinology & Metabolism, 28(3): 405- 421.

[57]. Kodama, S., Tanaka, S., Saito, K. (2007) Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta- analysis. Arc. Intern. Med., 167(10): 999-1008.

[58]. Varady, K.A., Jones, P.J. (2005) Combination diet and exercise interventions for the treatment of dyslipidemia: an effective preliminary strategy to lower cholesterol levels? [review]. J. Nutr., 135(8): 1829-1835.

[59]. Ratner, R., Goldberg, R., Haffner, S., Macrovina, S., Orchard, T. (2005) Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. Diabetes Care, 28: 888-894.

[60]. Singh, S., Malhotra, V., Singh, K.P., Madhu, S.V., Tandon, O.P. (2004) Role of yoga in modifying certain cardiovascular functions in type 2 diabetic patients. J. Assoc. Physician India, 52: 203-206.

[61]. Mishra, N. (2014) The role of physical exercise and diet modification on lipid profile and lipid peroxidation in long term glycemic control type 2 diabetics. Gen. Med. (Los Angel), 2(3): 140-142.