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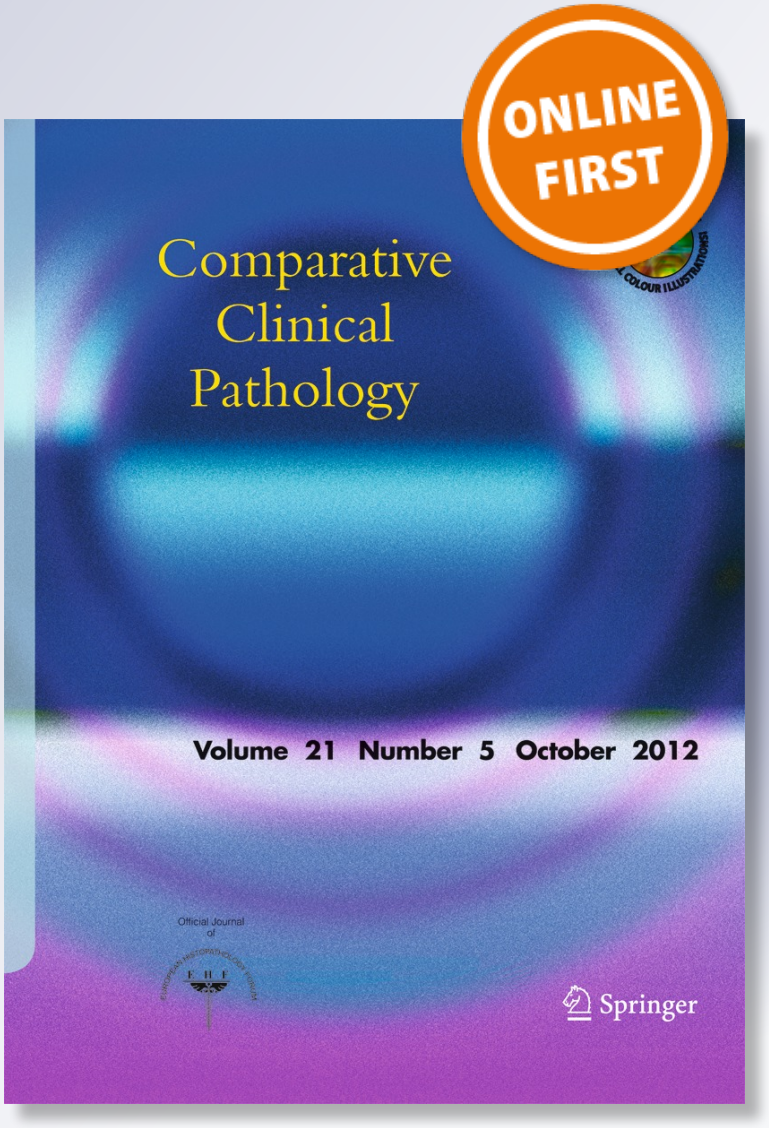

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ORIGINAL ARTICLE

Selenium and lipid subfractions in Egyptian type 2 diabetes patients

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Abstract The purpose of this study was to examine the relationship between serum selenium (Se) levels and lipid subfraction among Egyptian type 2 diabetes patients and their association with the severity of the disease. The study was conducted on 60 type 2 diabetic adults with BMI <30 divided according to disease duration into two groups: group 1 with disease duration less than 5 years and group 2 with a disease duration more than 5 years. Thirty age- and sex-matched apparently healthy volunteers were considered as the control group. Serum selenium was measured by atomic absorption spectrometry lipid subfractions including small dense low density lipoprotein (sd LDL) which was measured by enzyme-linked immunosorbent assay and glycated hemoglobin (HbA1c) by high-performance liquid chromatography. All participants do not receive Se supplementation. The mean serum Se level in participants with diabetes was as follows: group 2=62.70±5.73, group 1=70.58±4.158, and control subjects=79.80±5.37 μg/l (p=0.00). Se was found to be an independent protective factor with an OR of 0.29 and 95 % CI of 0.06–1.3. Mean serum sd LDL in participants with diabetes was as follows: group 2=43.81±13.70, group 1=25.77±5.28, and control group=15.99±5.32 (p=0.00). Correlation study, between studied parameters, revealed positive correlation between sd LDL and apolipoprotein B (Apo B) (r=0.730, p=0.001). On the other hand, negative correlation was encountered between apolipoprotein A (Apo A) and Apo B (r=−0.514, p=0.001) as well as Apo A and sd LDL (r=−0.697, p=0.001). Selenium correlated negatively with both Apo B (r=−0.669, p=0.001) and sd LDL (r=−0.671, p=0.001) and positively with Apo A (r=0.513, p=0.001). In a sample of the Egyptian population, low serum Se levels were positively associated with the prevalence of diabetes. Until findings from prospective studies and randomized controlled trials are available, Se intake, including Se supplementation, should be recommended for primary or secondary diabetes prevention in populations with inadequate selenium status.

Keywords Selenium · sd LDL · Diabetes

Introduction

Type 2 diabetes mellitus (DM) is rapidly rising as a global health care problem that is threatening to reach pandemic levels by 2030. In 2003, an estimated 194 million adults had diabetes worldwide (5.1 %) (ADA 2010). This prevalence increased to 6.0 % in 2007 and is predicted to increase to 7.3 % by 2025; 380 million individuals are expected to have diabetes in 2025 (Shaw et al. 2010). Prevalence of DM is 9.3 % of the Egyptian population (≥20 years) which is classified encompassing 2.4 % of rural residents, 8.4 % of lower socioeconomic status urban residents, and 10.0 % of higher socioeconomic status urban residents. The estimated number of persons with diagnosed and undiagnosed diabetes in 2025 is 8.80 million; Egypt will have the largest

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number of people with diabetes in the Mediterranean countries by 2025 (Helmy and Khalil 2006).

Dyslipidemia is a major risk factor for macrovascular disease. The prevalence of dyslipidemia is increased by at least twofold in the presence of type 2 DM and involves all classes of lipoprotein. Lipid abnormalities in type 2 diabetes are characterized by high triglyceride concentrations (TG), low high density lipoprotein-cholesterol concentrations (HDL-c), and normal total and low density lipoprotein-cholesterol (LDL-c) concentrations. However, low density lipoprotein (LDL) particles are small and dense, designated as small dense (sd LDL) or oxidized LDL. These LDL particles are more atherogenic than those which are large and fluffy. An increase in the proportion of sd LDL may increase risk for any given level of LDL-c. This increased risk may be due in part to increased deposition in the subendothelial space where plaque forms or to increased uptake by macrophages and increased susceptibility to oxidation, both early steps in atherogenesis. It may be due in part to decreased clearance because of reduced affinity for the LDL receptor. Observational and epidemiological studies suggest that those having a predominance of small dense particles may have an increase in risk up to 300 % greater than those having a predominance of large and fluffy LDL particles. This observed increase in risk forms the basis of the rationale in using particle size as an adjunct to the standard proven means of risk assessment (Lamarche et al. 1997).

Epidemiological evidence for these lipid abnormalities and for the associations between lipid abnormalities and the increased risk of cardiovascular disease in type 2 diabetes is presented. Most of the lipid abnormalities in type 2 diabetes can be explained by reduced action of insulin at the tissue level (Valalhji and Lkeles 2003).

Olin et al. (2003) reported that diabetes can alter copper, zinc, chromium, selenium (Se), and lipid peroxidation status. Disturbance in mineral metabolism is more pronounced in diabetic populations with specific complications. The essential trace element Se has long been considered to exhibit antidiabetic and insulin mimetic properties; it is believed to exert beneficial influence on human health based on the antioxidant capacity of selenoproteins such as glutathione peroxidases (GPx) and thioredoxin reductases containing the twenty-first proteinogenic amino acid, selenocysteine, in their active center (Steinbrenner and Sies 2009).

Recent studies, however, indicated supranutritional Se intake and high plasma Se levels as possible risk factors for the development of type 2 diabetes, pointing to adverse effects of Se on carbohydrate metabolism in humans. Furthermore, several studies have reported that high plasma Se levels were associated with increased prevalence of type 2 diabetes as well as hyperglycemia and enhanced plasma levels of total and LDL cholesterol and TG in the Se-repleted US American population (Steinbrenner et al. 2011; Stranges et al. 2010).

Aim of the work

The purpose of this study was to examine the relationship between serum Se levels and lipid subfraction among Egyptian type 2 diabetes patients and their association with the severity of the disease.

Subjects and methods

This study included 60 Egyptian diabetic patients and 30 age- and sex-matched healthy subjects as the control group. Patients were recruited from the outpatient clinic of the Diabetic and Endocrine Clinic at Kasr Al Aini hospital, Faculty of Medicine, Cairo University. Patients were divided into two groups: group 1 included 30 diabetic patients with duration of illness less than 5 years and group 2 included 30 type 2 diabetic patients, duration of illness ranging from 5 to 10 years. Patients who were obese (BMI $\geq$30 kg/m^2) and suffering from any condition that might influence the kidney or hepatic function were excluded from the study.

Selected groups were subjected to full history taking, general examination, and anthropometric measurement and BMI calculation. All subjects did not receive Se supplementation. Laboratory investigations include fasting blood sugar (FBS), glycated hemoglobin (HbA1c), full lipid profile including total cholesterol (TC), TG, HDL-c, measured low density lipoprotein (LDL-c), sd LDL, apolipoprotein (Apo) B, Apo A1, Apo B/Apo A1 ratio, and Se. All subjects were informed about the purpose, nature, and potential risks of the study. The experimental protocol was approved by the Ethical Committee of the Clinical and Chemical Pathology Department Cairo University guidelines.

Sampling

Five milliliters of 12-h fasting venous blood was withdrawn from each subject under complete aseptic conditions on a dry vacutainer. The separated sera were used for the analysis of lipid profile, namely TC which is measured by the cholesterol esterase method (Rautela and Liedtke 1978), HDL-c by the accelerator selective detergent methodology (Harris et al. 1997), and serum triglycerides according to the method of Fossati and Prencipe (1982) using lipoprotein lipase enzyme. Also, LDL-c was directly measured by the homogenous method (Nauck et al. 2000) using the dimension clinical chemistry system supplied by Siemens (Tarrytown, NY, 10591-5097, USA). Apo A1, Apo B, and sd LDL assays were carried out by enzyme-linked immunosorbent assay using the AssayMax Human kits (Cell Biolabs, Inc., 7758 Arjons Drive, San

Table 1 Laboratory data of studied groups

	Group 2	Group 1	Control	*p*
FBS mg/dl	248.70±96.36 a	113.56±24.25 b	87.30±7.36 b	0.000
HbA1c%	10.03±2.11 a	6.68±1.61 b	5.35±0.50 c	0.000
TC mg/dl	262.46±43.68 a	202.40±28.89 b	168.26±24.98 c	0.000
TG mg/dl	176.86±61.98 a	107.10±15.81 b	79.96±14.93 c	0.000
HDL-c mg/dl	44.83±8.81 a	44.70±9.22 a	48.96±10.19 a	0.144
LDL-c mg/dl	160.70±29.80 a	134.43±23.84 b	102.19±24.78 c	0.000
Apo A1 (μg/ml)	8.23±2.06 a	8.13±2.10 a	13.05±1.59 b	0.000
Apo B (μg/ml)	15.81±2.45 a	12.74±2.25 b	9.11±2.05 c	0.000
sd LDL (μg/ml)	43.81±13.70 a	25.77±5.28 b	15.99±5.32 c	0.000
Selenium (μg/l)	62.70±5.73 a	70.58±4.15 b	79.80±5.37 c	0.000

Data presented as mean±SD. Groups bearing the same letters are not statistically different at $p<0.05$

Diego, CA, 92126, USA). Serum Se was measured by atomic absorption spectrophotometry graphite furnace with Zeeman background correction to provide optimal separation from spectral interference using Varian Spectra AA 220/880, Zeeman AAS (Varian Analytical Instruments, 5301 Stevens Creek Blvd, Santa Clara, CA, 95051, USA) according to Jacobson and Lockitch (1988).

Another sample was withdrawn from each subject after 6–8 h of fasting on fluoride for plasma fasting glucose using the hexokinase method. Three milliliters of blood in EDTA vacutainer was withdrawn for the measurement of HbA1c using high-performance liquid chromatography according to method of Little et al. (1983). Glycated hemoglobin analysis was performed using Bio-Rad D-10 HbA1c Testing (Bio-Rad Laboratories Headquarters, 1000 Alfred Nobel Drive, Hercules, CA, 94547, USA).

Statistical analysis

The results were analyzed using the SPSS computer software package, version 15.0 (Chicago, IL, USA). Qualitative data were expressed as frequencies and percentages. Associations between qualitative data were investigated using Fisher's exact test. Normally distributed quantitative data were represented as mean and standard deviation and compared between two groups using Student's *t* test and between more than two groups using ANOVA test. Correlations were determined using Pearson ranked correlation test. Differences were considered significant at $p<0.05$.

Results and discussion

Groups 1 and 2 had a mean age of 42.26±7.8 and 48.03±5.6 years versus the control group with a mean age of 41.43±7.5 years. On comparing the laboratory results of the studied groups, the mean values of studied parameters showed statistical significant difference between the three groups regarding all studied parameters, namely FBS, HbA1c, TC, TG, LDL-c, Apo A1, Apo B, sd LDL, and Se ($p=0.000$). The only exception was encountered with the HDL-c which showed no statistical significant difference between groups with a *p* value of 0.144. Further analysis of results showed that group 2 differed statistically from group 1 regarding the all studied parameters. The results showed higher mean value of FBS, TC, TG, LDL-c, Apo B, and sd LDL and lower mean values of Apo A1 and Se in group 2. Both groups differed statistically from the control group with the exception of the FBS which showed no statistical significant difference between group 1 and the control group (Table 1).

Se correlated positively with Apo A1 ($r=0.513$, $p=0.000$). On the other hand, negative correlation was encountered between Se and Apo B, sd LDL, TC, TG, LDL-c, and HbA1c ($r=-0.669$, $p=0.000$; $r=-0.671$, $p=0.000$; $r=-0.662$, $p=0.000$; $r=-0.607$, $p=0.000$; $r=-0.592$, $p=0.000$; and $r=-0.637$, $p=0.000$, respectively).

Other parameters correlated as follows: positive correlation between sd LDL and Apo B ($r=0.730$, $p=0.001$) and negative correlation between Apo A1 and Apo B ($r=-0.514$, $p=0.001$) as well as Apo A and sd LDL ($r=-0.697$, $p=0.001$) (Table 2). On performing logistic regression for studied analytes, Se was found to be an independent protective factor with an odds ratio (OR) of 0.29 and 95 % confidence interval (CI) of 0.06–1.3.

In the current study, serum Se correlated positively with Apo A1 and negatively with Apo B, sd LDL, TC, TG, and

Table 2 Correlation study between studied parameters

	Apo A1	Apo B	sd LDL	HbA1C	TC	TG	HDL-c	LDL-c	Glucose
Apo B	$r=0.514$**								
	$p=0.000$								
sd LDL	$r=0.697$**	$r=0.730$**							
	$p=0.000$	$p=0.000$							
Selenium	$r=0.513$**	$r=-0.669$**	$r=-0.671$**	$r=-0.637$**	$r=-0.662$**	$r=-0.607$**	$r=0.29$	$r=-0.592$**	$r=-0.724$**
	$p=0.000$	$p=0.000$	$p=0.000$	$p=0.000$	$p=0.000$	$p=0.000$	$p=0.783$	$p=0.000$	$p=0.000$

** Correlation is significant at the 0.01 level

Table 3 Association between sd LDL level in cases and controls

	Low sd LDL <26.5	High sd LDL >26.5	
Controls (n=30)	27/30 (90 %)	3/30 (10 %)	OR (95 % CI) 27 (5.8–125.1)
Cases (n=60)	20/60 (33 %)	40/60 (67 %)	p=0.00

Data presented as n (percent)

Table 5 Association between Se level in cases and controls

	Normal Se (>67 μg/l)	Low Se (<67 μg/l)	
Controls (n=30)	30/30 (100 %)	0/30 (0 %)	OR (95 % CI) 1.5 (1.3–1.9)
Cases (n=60)	38/60 (63 %)	22/60 (27 %)	p=0.00

Data presented as n (percent)

LDL-c which enlightens the protective role of Se as an important component of the antioxidant enzyme GPx that protects the cells from the adverse effects of free radicals. Negative correlation was also encountered with both glucose and HbA1c, which emphasizes the inverse relation between the Se concentration and disease severity.

At a cutoff value of 26.5 μg/ml for the sd LDL results revealed a statistically significant association between high values of sd LDL and the presence of diabetes (OR p=0.00; 95 % CI 27 (5.8–125.1) (further analysis revealed an increase in the sd LDL levels with the severity of diabetes (p=0.00; Tables 3 and 4). On the other hand, at a cutoff value of 67 μg/l for Se, a statistically significant association between low values of Se and the presence of diabetes (OR p=0.00; 95 % CI 1.5 (1.3–1.9)) was encountered, Se values were statistically significantly lower with advanced disease in group 2 (p=0.00; Tables 5 and 6). High levels of sd LDL and subnormal Se were both associated with diabetes and its severity.

Few studies have evaluated the association of serum selenium with the different components of the lipid profile, and the relations appear to differ across studies. For instance, one study reported a positive correlation between Se and LDL-c cholesterol (Gamez et al. 1997), whereas two studies reported no correlation (Coudray et al. 1997; Salonen et al. 1988); two studies reported a positive correlation with HDL-c (Coudray et al. 1997; Salonen et al. 1988), whereas two other studies did not (Suadicani et al. 1992; Jossa et al. 1991). Small sample sizes and selective reporting of findings may explain some of those inconsistencies (Bleys et al. 2007).

Yang et al. (2010) reported that serum Se concentrations were positively associated with serum concentrations of TC, LDL-c, TG, and glucose; this is in contrary to this study except glucose. In both groups, serum selenium level was negatively associated with the glucose level (Table 2).

Relationships between serum Se and TC concentrations are discussed in several studies of various serum Se concentrations (Navarro-Alarcon et al. 1999; Rayman 2000; Bates et al. 2002; Karita et al. 2008; Obeid et al. 2008; Yang et al. 2010). Many studies failed to show a significant association between serum Se and TG concentrations (Karita et al. 2008; Jossa et al. 1991; Hercberg et al. 2005) and few have shown a positive association (Yang et al. 2010).

From the results of the current study, it is safe to suggest that Se is an important component of the antioxidant enzyme GPx that protects cells from the adverse effects of free radicals and lipid peroxides. A deficiency of Se lowers the tissue activity of GPx which in turn may have unfavorable effects on lipoprotein metabolism. These metabolic changes associated with compromised Se status may lead to damage of the vascular endothelium and increased platelet adhesion which increase the risk of atherosclerotic heart disease (Mahboob et al. 2005).

In the current study, low Se levels were encountered in diabetics compared to the normal controls (p=0.000). Furthermore, lower serum Se levels were encountered in the diabetic group 2 patients compared to the diabetic group 1 (p=0.000) showing an association with the severity of the disease as indicated by the higher mean value of HbA1c in group 2 compared to group 1 (10.03±2.11 and 6.68±1.61, respectively). Results regarding the level of Se in diabetics have been controversial; studies conducted by Bleys et al. in 2007 revealed high levels of Se in the diabetic US population studied. There results might be attributed to the fact that most participants received Se supplementations as a daily routine and warranted cessation of supplementation.

However, studies carried out by Raipathak et al. (2005) on toenail Se level revealed an overall lower level of toenail selenium in diabetic men with cardiovascular disease and in men with prevalent diabetes than in healthy controls. Their

Table 4 Association between sd LDL level in cases

	Low sd LDL <26.5	High sd LDL >26.5	
Group 2 (n=30)	1/30 (3 %)	29/30 (97 %)	p=0.00
Group 1 (n=30)	19/30 (63 %)	11/30 (37 %)	

Data presented as n (percent)

Table 6 Association between Se levels in cases

	Normal Se (>67 μg/l)	Low Se (<67 μg/l)	
Group 2 (n=30)	9/30 (30 %)	21/30 (70 %)	p=0.00
Group 1 (n=30)	29/30 (97 %)	1/30 (3 %)	

participants did not receive Se supplementations and the levels were indicative of the actual levels as in the case of the current study that is carried out on a sample of Egyptian population receiving no Se supplementation.

More recent studies carried out in 2008 by Kornhauser et al. assessed GPx and Se in type 2 diabetes mellitus patients with microalbuminuria (group 1), without microalbuminuria (group 2), and in control subjects (group 3). Although their study design was somewhat different than the current study as they focused on microalbuminuria as a marker of disease severity, yet their results revealed that the control group showed higher serum Se concentrations as compared to the diabetic groups which comes in accordance with this work. However, their two groups of diabetic patients showed similar serum Se levels unlike the lower levels that are encountered in group 2 of this study.

In accordance to this work, a study carried out by Kasar in 2011 on an Iraqi population of diabetic patients showed significantly low Se levels in diabetic patient groups compared to the control group. Furthermore, the decrease in Se level is directly proportional to the severity of the disease. These findings indicate that the decrease in serum Se was associated with elevated serum concentrations of FBS, TC, LDL-c, VLDL-c, TG, duration, and severity of diabetes. The similarity of the results of both studies is quite striking, and questions might be raised that some ethnic background, dietary habits, lack of supplementations, or socioeconomic factors are a common denominator in both Middle East countries when compared to results encountered in Western countries where there is a general better orientation of patients towards receiving mineral supplementation or lipid-lowering drugs hence the controversial results.

Conclusion and recommendations

Lower Se levels were encountered in diabetics and decreased with the severity of disease as indicated by the level of HbA1c. Lipid subfraction abnormalities, including sd LDL, correlate with the disease and its severity. Se supplementation is indicated for diabetics within limits of the recommended daily allowance.

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