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Malondialdehyde and trace element levels in patients with type 2 diabetes mellitus

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2011, 28(1):83–88

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Μαλονδιαλδεΰδη και επίπεδα ιχνοστοιχείων σε ασθενείς με σακχαρώδη διαβήτη τύπου 2

Περίληψη στο τέλος του άρθρου

OBJECTIVE **To clarify the role of malondialdehyde (MDA), zinc, copper, chromium, magnesium and selenium in patients with type 2 diabetes mellitus (DM).** METHOD **Fifty patients with type 2 DM were enrolled in this study, together with 15 healthy subjects, matched for age and sex, who served as the control group. The patients with type 2 DM were classified into 2 groups: Group 1: Uncomplicated type 2 DM (20 patients). Group 2: Complicated type 2 DM (30 patients). Overnight fasting serum levels of glucose (FBS), cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), glycated hemoglobin A1c (HbA1c), MDA, zinc, copper, chromium, magnesium and selenium were estimated in all subjects.** RESULTS **Statistically significant differences between group 1, group 2 and the control group were found in zinc, magnesium, selenium and MDA. FBS showed high significant negative correlations with zinc and selenium and significant positive correlation with copper. The HbA1c showed significant negative correlation with zinc, magnesium and selenium, and positive correlation with copper. MDA showed significant increase, while zinc, magnesium and selenium showed significant decrease in both the uncomplicated and complicated DM groups than the control group. Magnesium showed significant decrease in uncomplicated DM than the complicated DM group. MDA showed high significant positive correlation with copper and negative correlation with zinc, magnesium and selenium.** CONCLUSIONS **Trace elements and MDA could have a role as cofactors in the pathogenesis and complications of type 2 DM. Trace element supplementation and antioxidants might have utility in the treatment of this complex disorder.**

Key words

Chromium
Copper
Magnesium
Malondialdehyde
Selenium
Type 2 diabetes mellitus
Zinc

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Type 2 diabetes mellitus (DM) is a major global health problem that affects over 200 million individuals worldwide.[1] It is characterized by insulin resistance (IR) in peripheral tissue and an insulin secretory defect of the beta cells of the pancreas.[2] IR is a major contributor to the pathogenesis of type 2 DM and plays a key role in associated metabolic abnormalities, such as dyslipidemia and hypertension.[3] At the high levels found in DM, glucose reacts with and forms adducts (advanced glycation end products) on macromolecules including proteins and DNA, eliciting cellular dysfunction and leading to vascular disease.[4]

The increased oxidative stress in DM contributes to the development of diabetic complications. Oxygen derived free radicals and reactive oxygen species interact with the lipid bilayer of the cell membrane resulting in lipid peroxidation. Malondialdehyde (MDA) is a stable end product of lipid peroxidation. Elevated MDA levels alter the structural integrity of the cell membranes. Inactivation of membrane bound enzymes and surface receptor molecules leads to cell-regulating errors. The involvement of oxidized low density lipoproteins (LDL) in the foam cell formation leads to atherosclerosis.[5]

DM may alter the copper, zinc, chromium, magnesium and lipid peroxidation status. Alterations in mineral metabolism are more pronounced in populations with DM with specific complications. It is not known whether differences in trace element status are a consequence of DM or whether they contribute to the expression of the disease.[6] Zinc has an important role in modulating the immune system and its dysfunction in DM may be related in part to the status of zinc. Copper ions serve as important catalytic cofactors in redox chemistry for biological functions of the patient that are required for growth and development.[7] Copper requiring proteins are involved in a variety of biological processes

and deficiency of specific enzymes or alterations of their activities often cause disease states or pathophysiological conditions.[8] Changes in the enzymatic activities of several metabolic pathways are seen in DM as a result of relative magnesium deficiency. Chromium can significantly influence glucose utilization by peripheral tissues. Patients with type 2 DM who demonstrate IR are at highest risk for chromium deficiency.[9] Chromium works by helping to lower insulin levels, which in turn aids in lowering cholesterol and triglyceride levels. An adequate level of chromium in the bloodstream is also believed to help prevent injury to the artery walls.[10]

Selenium has been shown to mediate a number of insulin like actions both *in vivo* and *in vitro*, including stimulating glucose uptake and regulating metabolic processes such as glycolysis, gluconeogenesis, fatty acid synthesis and the pentose phosphate pathway.[11] Selenium and copper concentrations in erythrocytes can improve the antioxidative status by decreasing the MDA level in type 2 DM.[12]

The aim of this study was to clarify the role of the oxidative stress parameter MDA, zinc, copper, chromium, magnesium and selenium in uncomplicated and complicated cases of type 2 DM, and the effect of hyperglycemia and hyperlipidemia on MDA.

MATERIAL AND METHOD

The study was conducted on 50 patients (27 males and 23 females) with type 2 DM who were attending the endocrine clinic at the Kasr-el-Aini Hospital in the period January to June 2008. Their ages ranged from 35 to 55 years. A control group consisted of 15 healthy non diabetic subjects (8 males and 7 females) within the same age range as the patients and who were not receiving any medication. The study was approved by the Ethics Committee of Kasr-el-Aini Hospital and informed written consent was taken from every subject.

The study patients were divided into two groups: Group 1 (controlled DM): This group included 20 patients with uncomplicated type 2 DM, 13 males and 7 females. Group 2 (uncontrolled DM): This group included 30 patients, 16 males and 14 females with type 2 DM, complicated by diabetic nephropathy, neuropathy and or retinopathy. All the patients and control subjects studied were subjected to complete history taking and thorough clinical examination. Laboratory investigations included fasting blood glucose (FBS), serum cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-c) and low density lipoprotein cholesterol (LDL-c). Glycated hemoglobin A1c (HbA1c) was quantified by direct photometric reading.[13] Serum MDA was determined using the thiobarbituric acid (TBA) reaction.[14] Determination of zinc, copper, chromium, magnesium and selenium was done using atomic absorption spectrophotometry.[15]

Statistical analysis

All tabulated data were interpreted and analysed using SPSS v.13, using ANOVA, and Student t-test used to compare quantitative variables. The p value was considered significant if $p<0.05$.

RESULTS

Results of the differences between the three groups according to ANOVA testing are shown in table 1. Statistically significant differences between the three study groups were demonstrated in the levels of FBS, cholesterol, triglycerides, LDL-c, HbA1c, MDA, zinc, magnesium and selenium.

Correlation between the various parameters is shown in table 2. MDA shows statistically significant positive correlation with HbA1c, cholesterol, triglyceride, LDL-c, copper and selenium, and negative correlation with HDL-c, zinc, chromium and magnesium.

DISCUSSION

Type 2 DM in middle aged and elderly individuals accounts for approximately 85% of all cases of DM in developed countries. DM is more prevalent in urban than in rural areas.[16] Improved glycemic control has been shown to be associated with significant reduction in the complication rates in patients with type 2 DM. The characteristic polyuria of DM that results from the glucose-mediated hyperosmotic glomerular filtrate may be largely responsible for enhanced urinary mineral loss. Such losses have been shown to affect optimal insulin secretion and action.[17]

MDA is a highly toxic by-product formed in part by oxidation derived from free lipid radicals, and studies have shown considerably raised concentrations in DM. MDA reacts both irreversibly and reversibly with proteins and phospholipids with profound effects.[18] In this study highly statistically significant differences in the levels of MDA were demonstrated between group 1, group 2 and the control group (tab. 1). MDA showed significant increase ($p<0.05$) in both uncomplicated and complicated DM compared with the control group, in agreement with the findings of Mahreen et al,[5] and Ozdem et al.[19] MDA showed statistically significant positive correlation with HbA1c ($r=0.30$, $p<0.05$), in agreement with Turk et al.[20] MDA also showed statistically significant positive correlation with cholesterol, triglycerides, and LDL-c ($r=0.39$, $r=0.32$, $r=0.35$, respectively; $p<0.05$) and negative correlation with HDL-c ($r=-0.31$, $p<0.05$). Nacitarhan et al[21] revealed significantly higher serum MDA level in patients with hyperlipidemic type 2 DM than in those with normolipidemic DM. Guerci et al[22] reported

Table 1. Comparison of biochemical parameters in study patients with type 2 diabetes mellitus (DM) (group 1, group 2) and control group (ANOVA, values are presented as mean±SD).

Parameter	Control group (n=15)	Group 1 Uncomplicated DM (n=20)	Group 2 Complicated DM (n=30)	p value
FBS (mg/dL)	83.13±16.46	101.45±14.99	264.07±92.36	<0.05*
Cholesterol (mg/dL)	170.40±21.72	211.30±20.15	234.43±42.71	<0.05*
Triglyceride (mg/dL)	69.20±14.88	117.20±76.34	194.67±53.76	<0.05*
HDL-c (mg/dL)	46.33±7.44	41.40±5.67	42.13±9.37	0.160
LDL-c (mg/dL)	113.73±23.31	147.08±21.29	153.83±43.21	<0.05*
HbA1c (%)	4.59±0.43	5.15±0.53	6.83±0.95	<0.05*
MDA (µmol/L)	5.81±2.39	11.13±3.13	10.03±4.5	<0.05*
Zinc (µg/dL)	83.73±24.71	48.97±15.92	49.62±16.39	<0.05*
Copper (µg/dL)	81.57±20.23	77.31±13.74	97.84±54.05	0.156
Chromium (µg/L)	0.21±0.12	0.16±13	0.19±0.14	0.574
Magnesium (mg/dL)	1.37±0.43	0.76±0.11	0.89±0.17	<0.05*
Selenium (µg/L)	78.1±5.9	63.64±6.24	61.11±6.99	<0.05*

*Statistical significance: p<0.05

FBS: Fasting blood glucose, HDL-c: High density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol, HbA1c: Glycated hemoglobin, MDA: Malondialdehyde

Table 2. Pearson correlation of biochemical parameters in study patients with type 2 diabetes mellitus control subjects.

Parameter	FBS	Cholesterol	Triglyceride	HDL-c	LDL-c	HbA1c	MDA	Zn	Cu	Cr	Mg	Se
FBS r	1											
p	–											
Cholesterol r	0.70*	1										
p	<0.05	–										
Triglyceride r	0.68*	0.63*	1									
p	<0.05	<0.05	–									
HDL-c r	-0.34*	-0.46*	-0.48*	1								
p	<0.05	<0.05	<0.05	–								
LDL-c r	0.56*	0.93*	0.37*	-0.53*	1							
p	<0.05	<0.05	<0.05	<0.05	–							
HbA1c r	0.90*	0.71*	0.63*	-0.39*	0.59*	1						
p	<0.05	<0.05	<0.05	<0.05	<0.05	–						
MDA r	0.22	0.39*	0.32*	-0.31*	0.35*	0.30*	1					
p	0.08	<0.05	<0.05	<0.05	<0.05	<0.05	–					
Zn r	-0.35*	-0.30*	-0.35*	0.12	-0.16	-0.36*	-0.31*	1				
p	<0.05	<0.05	<0.05	0.35	0.22	<0.05	<0.05	–				
Cu r	0.27*	0.34*	0.12	-0.15	0.37*	0.29*	0.31*	0.05	1			
p	<0.05	<0.05	0.36	0.22	<0.05	<0.05	<0.05	0.69	–			
Cr r	-0.11	-0.01	-0.11	0.08	0.02	-0.03	-0.20	0.03	-0.16	1		
p	0.39	0.93	0.38	0.51	0.86	0.82	0.10	0.84	0.21	–		
Mg r	-0.21	-0.40*	-0.23	0.06	-0.31*	-0.28*	-0.40*	-0.40*	-0.03	0.12	1	
p	0.09	<0.05	0.07	0.63	<0.05	<0.05	<0.05	<0.05	0.82	0.36	–	
Se r	-0.47*	-0.48*	-0.43*	0.19	-0.36*	-0.51*	-0.36*	0.60*	-0.07	0.06	0.50*	1
p	<0.05	<0.05	<0.05	0.125	<0.05	<0.05	<0.05	<0.05	0.57	0.63	<0.05	–

*Statistical significance: p<0.05

FBS: Fasting blood glucose, HDL-c: High density lipoprotein cholesterol, LDL-c: Low density lipoprotein cholesterol, HbA1c: Glycated hemoglobin, MDA: Malondialdehyde

that the MDA/LDL-c ratio was higher in women with type 2 DM, and concluded that this could explain why women with DM are at greater risk of cardiovascular disease. In the present study MDA showed significant positive correlation with copper (r=0.31, p<0.05) and negative correlation with zinc, magnesium and selenium (r=-0.31, r=-0.40, r=-0.36, respectively; p<0.05).

Statistically significant differences were found between group 1, group 2 and the control group in zinc, magnesium and selenium levels, but not in chromium and copper levels. Zinc, magnesium and selenium levels were significantly decreased (p<0.05) in both uncomplicated and complicated DM compared to the control group, in agreement with Lichten and Cousins,[23] who stated that patients with type 2 DM were more likely to have suboptimal zinc status. Kljai and Runje[24] also reported decreased levels of selenium in the serum of patients with type 2 DM. Magnesium deficiency has been associated with IR and increased risk of type 2 DM in adults.[25] No differences in copper and chromium were found between the study groups, and Zargar et al[26] reported that plasma copper and magnesium levels are not significantly altered in DM although in another study,[27] an increase in the copper level was found in type 2 DM but not in zinc and magnesium levels.

In the present study, HbA1c levels were found to be correlated positively with copper (r=0.31, p<0.05) and inversely with zinc (r=-0.31, p<0.05) and magnesium (r=-0.40, p<0.05), in agreement with the study of Viktorínová et al,[13] who reported that patients with DM had altered metabolism of copper, zinc and magnesium, possibly related to increases in HbA1c. They concluded that impaired metabolism of these elements may contribute to the progression of DM and diabetic complications.

This study showed that zinc had significant negative correlation with triglycerides and with cholesterol (r=-0.35, r=-0.30, respectively; p<0.05), and magnesium with cholesterol and LDL-c (r=-0.40, r=-0.31, respectively; p<0.05). Copper showed significant positive correlation with cholesterol and LDL-c (r=0.34, r=0.37, respectively; p<0.05). Chromium showed no significant correlation with cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol (p>0.05). This was in agreement with Balk et al,[28] who showed that there was no significant effect of chromium on lipid or glucose metabolism. Selenium showed significant negative correlation with cholesterol, triglycerides and LDL-c (r=-0.48, r=-0.43, r=-0.36, respectively; p<0.05). Kornhauser et al[29] stated that selenium is one of the most effective antioxidants and its protective role against oxidative damage play an important role in diabetic complications.

In conclusion, trace elements and MDA play a role as cofactors in the pathogenesis and complications of type 2 DM. Trace elements and antioxidant supplementations may be useful in the treatment of this complex disorder and help in preventing complications. Careful monitoring of these parameters in patients with type 2 DM is recommended.

ΠΕΡΙΛΗΨΗ

Μαλονδιαλδεΰδη και επίπεδα ιχνοστοιχείων σε ασθενείς με σακχαρώδη διαβήτη τύπου 2

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ΣΚΟΠΟΣ Η διευκρίνιση του ρόλου της μαλονδιαλδεΰδης (MDA), του ψευδαργύρου, του χαλκού, του χρωμίου, του μαγνησίου και του σεληνίου σε ασθενείς με σακχαρώδη διαβήτη (ΣΔ) τύπου 2. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Μελετήθηκαν 50 ασθενείς με ΣΔ τύπου 2, καθώς και 15 υγιή άτομα συμβατά ως προς την ηλικία και το φύλο, που χρησίμευσαν ως ομάδα ελέγχου. Οι ασθενείς με ΣΔ τύπου 2 ταξινομήθηκαν σε δύο ομάδες: Ομάδα 1: 20 άτομα με ΣΔ τύπου 2 χωρίς επιπλοκές και ομάδα 2: 30 διαβητικοί τύπου 2 που είχαν επιπλοκές. Σε όλα τα άτομα μετρήθηκε το πρωινό σάκχαρο νηστείας, η χοληστερόλη, τα τριγλυκερίδια, η HDL-c, η LDL-c, η HbAlc, η MDA, ο ψευδάργυρος, ο χαλκός, το χρώμιο, το μαγνήσιο και το σελήνιο του ορού. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Ανευρέθηκαν στατιστικά σημαντικές διαφορές μεταξύ της ομάδας 1, της ομάδας 2 και της ομάδας ελέγχου στις τιμές ψευδαργύρου, μαγνησίου, σεληνίου και MDA. Το σάκχαρο νηστείας παρουσίαζε υψηλή αρνητική συσχέτιση ως προς τις τιμές ψευδαργύρου και σεληνίου και σημαντικά στατιστική συσχέτιση με τα επίπεδα του χαλκού. Η HbA1c εμφάνιζε σημαντικά αρνητική συσχέτιση με τα επίπεδα ψευδαργύρου, μαγνησίου και σεληνίου και σημαντικά θετική συσχέτιση με τα επίπεδα του χαλκού. Η MDA παρουσίαζε σημαντική

αύξηση, ενώ ο ψευδάργυρος, το μαγνήσιο και το σελήνιο σημαντική μείωση και στις δύο ομάδες των διαβητικών με ή χωρίς επιπλοκές σε σχέση με την ομάδα ελέγχου των υγιών ατόμων. Το μαγνήσιο βρέθηκε σημαντικά μειωμένο στους διαβητικούς χωρίς επιπλοκές σε σχέση με αυτούς που εμφάνιζαν επιπλοκές. Η MDA παρουσίαζε σημαντικά θετική συσχέτιση με το χαλκό και σημαντική υψηλά αρνητική συσχέτιση με τις τιμές ψευδαργύρου, μαγνησίου και σεληνίου. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Διάφορα ιχνοστοιχεία, καθώς και η MDA, πρέπει να διαδραματίζουν ρόλο ως συμπαράγοντες στην παθογένεια και τις επιπλοκές του σακχαρώδους διαβήτη τύπου 2. Η χορήγηση ιχνοστοιχείων και αντιοξειδωτικών ουσιών πιθανόν να είναι χρήσιμα στην αντιμετώπιση αυτής της πολύπλοκης διαταραχής.

Λέξεις ευρετηρίου: Μαγνήσιο, Μαλονδιαλδεΰδη, Σακχαρώδης διαβήτης τύπου 2, Σελήνιο, Χαλκός, Χρώμιο, Ψευδάργυρος

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