Journal of Trace Elements in Medicine and Biology 51 (2019) 86–90

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

The comparison of zinc, copper and iron levels in serum, aorta and left internal mammarian artery tissues in coronary by-pass graft surgery patients☆

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ARTICLE INFO

Keywords:
Zinc
Copper
Iron
Atherosclerosis
Coronary artery by-pass graft operation
Left internal mammary artery

ABSTRACT

Trace elements are crucial for vital enzymatic reactions in all metabolic processes. Zinc (Zn) acts as a co-factor for many enzymes. Copper (Cu) and iron (Fe) have pro-atherogenic effects resulting in atherosclerosis. Aorta exposing high pulsatile pressure is sensitive for atherosclerosis because of its fast metabolism and poor nutrition by diffusion from vasa vasorum. We aimed to determine the relationship between serum Zn, Cu and Fe levels with aortic and left internal mammary artery (LIMA) tissues in 33 atherosclerotic individuals who inevitably underwent coronary artery by-pass graft (CBAG) surgery that is an end-point treatment for atherosclerosis. Trace elements in serum and tissues were measured using inductively coupled plasma-optical emission spectrophotometer. Pre-operative (Pre-op) serum Fe levels were statistically 46% higher than post-operative (Post-op) values ($p = 0.009$). Aortic Fe level was 49.8% higher than LIMA Fe ($p = 0.0001$). Our study points out the tendency of aortic tissue to atherosclerosis via pro- atherogenic effect of Fe. LIMA, being a potential graft for CBAG, is resistant to atherosclerosis with its intimal specialty of graft patency. In conclusion, serum Zn, Cu and Fe levels in atherosclerotic CBAG patients might be monitored to reveal minor alterations pre-operatively and post-operatively for ameliorating the treatment and life quality.

1. Introduction

Cardiovascular diseases (CVD) are the leading global cause of death, accounting 1 of every 7 deaths in the United States and 45% of all deaths in Europe. The financial cost of CVD in Europe is estimated €210 billion a year, moreover the estimated global cost of CVD would reach $1044 billion by 2030 [1,2]. Turkey had a 6.7% prevalence of CVD in 1990 that gradually increased to 12.7% in recent years. The mortality rates of CVD in Turkey that was 42% in 1990 reached a value of 39.8% by the year 2010 [3,4]. CVD are related with several risk factors including hypertension, diabetes mellitus, dyslipidemia and atherosclerosis [5–8].

Atherosclerosis is a chronic inflammatory process that includes the thickening of arterial intima and proliferation of fibrous tissue [9]. Dyslipidemia is one of the most crucial leading pathologies among the other atherosclerotic risk factors. The increase in low density lipoprotein (LDL) triggers an inflammatory site in vessel wall simplifying cell adhesion and leukocyte infiltration towards intimal space [10]. Monocytes adhere to endothelial surface and differentiate to macrophages in sub-endothelial space promoting atherosclerotic plaque growth. Tissue macrophages have the ability to endocytose modified lipids resulting in foam cell formation [11]. The modification of LDL by intimal vascular cells are accepted to be dependent on low levels of trace elements like copper (Cu) and iron (Fe), whereas zinc (Zn) governs an important role in defense mechanisms [12].

Trace elements that constitute 0.02% of total body weight have vital functions at biological, chemical and molecular levels whether as active centers of enzymes or as being a cofactor for metabolic reactions [13,14]. Zn is an antioxidant essential trace element for physiologic membrane structure and enzymatic reactions. Zn plays a protective role in atherosclerosis via inhibiting the formation of modified LDL, displacing Cu and Fe from sensitive sites located on erythrocyte membranes and LDL, and protecting the cell against oxidative stress [15–17]. Zn deficiency is revealed to be associated with pro-

☆ The study was carried at Trace Element Analysis Laboratory at Biophysics Department of Cerrahpasa Medical Faculty.

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https://doi.org/10.1016/j.jtemb.2018.10.003
Received 15 January 2018; Received in revised form 12 September 2018; Accepted 2 October 2018
0946-672X/

atherogenic events and induction of inflammatory markers resulting in CVD [18]. Cu is a transition trace element that is essential for various enzymatic reactions carrying a dual effect of being both pro- and anti-atherogenic property due to its level in serum and tissues. Cu promotes LDL modification and foam cell formation in pro-atherogenic process. Zn antagonizes Cu driven pro-atherogenic effects via balancing the bioavailability and metabolism of Cu [10,17,19,20]. Fe is involved in several metabolic processes, including oxygen transport, DNA synthesis, and electron transport [21]. Besides, Fe induces modification of LDL and initiates the atherosclerotic plaque via pro-inflammatory cytokines [9,22]. Increased Fe level in serum and tissues promote lipid peroxidation in artery wall gradually resulting in atherosclerosis [5–8].

The structure of aorta differentiates due to its proximity to heart and its response to unidirectional flow with high pressure. Aorta is prone to atherosclerosis based on its mechanical and metabolic factors related with the multiple fenestrations among its lumen [23–25]. Left internal mammary artery (LIMA) has been used as an important potential graft since 1970s for coronary artery by-pass graft (CBAG) surgery. LIMA is a branch of subclavian artery located proximally to heart and supplies oxygen and nutrients directly from its lumen differently from other arterial grafts. LIMA has a potent biological function with its production of vasodilatatory and platelet inhibiting factors. The specialty of LIMA having fewer fenestrations, lower tendency of intimal hyperplasia and less permeability at intercellular junctions prevents lipoproteins from entering subendothelial space [26,27].

CBAG surgery is an end-point treatment for atherosclerotic patients, thus the patency of the graft used in CBAG surgery is of great importance [27]. The aim of our study is to analyse the effect of surgical trauma on the serum levels of Zn, Cu and Fe and the resistance of LIMA to atherosclerosis by means of tissue levels of Zn, Cu and Fe in 33 male individuals inevitably underwent CBAG surgery. The patient group was standardized by means of gender and biochemical parameters in order to reveal the absolute effect of Zn, Cu and Fe over serum, aortic tissue and LIMA tissue.

2. Materials and methods

2.1. Patient population

Thirty three male patients attended to the Outpatient Clinic of Department of Cardiovascular Surgery at Kartal Kosuyolu State Hospital in Istanbul were enrolled in the study. The patients were grouped as Pre-op (24 h before the surgery) and Post-op (7 days after the surgery in the clinic) prospectively after written informed consent had been obtained. The study group was operated electively for CBAG surgery due to coronary artery disease. The mean age of the study group was 61.69 ± 5.65 years. Patients with congenital valvular disease (bicuspid, unicuspid aortic valve), inherited connective tissue disease (Marfan, Ehlers Danlos syndrome, Loeys-Dietz syndrome, and so on.), redo cases, dissecting aortic aneurysm, ruptured ascending aorta aneurysms and patients with the diagnosis of malignancy and inflammatory diseases were not included to the study. Five patients were excluded from the study with diagnosis of systemic infection (3), acute renal failure (1) and acute myocardial infarction (1). The protocol was approved by the local ethics committee (Kartal Kosuyolu Training and Research Hospital, Ethics Committee; 2013.1/23) and conducted in accordance with the Declaration of Helsinki.

2.2. Blood sample collection

Blood was drawn from the antecubital vein of each subject 24 h before the surgery after twelve hours overnight fasting (Pre-op) and 7 days after the surgery (Post-op). Blood samples were collected in test tubes containing citrate, ethylenediamine-tetraacetic acid (EDTA) and test tubes without anticoagulant for biochemical analysis. Serum samples were obtained from Eppendorf tubes after centrifugation at 4000 rpm for 10 min for trace element analysis. All serum samples were kept in a −80 °C until the analysis.

2.3. Biochemical parameters assay

Biochemical parameters were analysed at the Biochemistry Department of Kartal Kosuyolu Education & Research Hospital. Hemogram was studied using electro impedance method with Coulter LH 780 device of Beckman Coulter Company. Serum glucose, total cholesterol, triglyceride (TG), high density lipoprotein (HDL) cholesterol and creatinine were determined on a Hitachi Modular P analyser using commercial kits (Roche Diagnostics, GmbH, Mannheim). LDL was calculated using the Friedewald's formula if the TGs were less than 4.5 mmol/L. Other biochemical parameters were studied using spectrophotometric method with Advia 2400 device of Siemens Company.

2.4. Premedication and anesthesia

Patients were premedicated with diazepam 10 mg orally before the night from surgery. The left radial artery was catheterized for arterial monitorization. Electrocardiogram, systolic arterial pressure, central venous pressure and pulse oximetry were monitozied throughout the operation for hemodynamic stability. Urine output was monitorized utilizing a Foley catheter in every patient intra-operatively and post-operatively. 0.2 mg/kg midazolam and 20 μg /kg of fentanyl were given for the induction of anesthesia. 0.1 mg/kg rocuronium was given to provide muscular relaxation before endotracheal intubation. Right internal jugular vein catheter was inserted for central venous catheterization. The use of activated clotting time was held between 400–600 s to optimize heparinization during the operation. Blood sugar level was measured in half-hour intervals to keep blood glucose level below 200 mg/dL.

2.5. Surgery technique

Cardiac arrest was supplied by antegrade cold blood cardioplegia following the sternotomy and cardiac exploration procedure. LIMA with its pedicule was resected up to subclavian artery in proximal segment and up to the bifurcation of epigastrica superior artery and musculophrenica artery in distal segment. The sub-branches of LIMA were cut by utilizing metallic clips. LIMA accompanied with its peripheral surroundings were protected in pleural space in a sterile gause embedded with papaverin until the anostomosis. The myocardium was protected continuously by retrograde blood cardioplegia with potassium during the operation. Systemic perfusion output and systemic perfusion pressure were maintained between 2.4 $L/min/m^2$ and 50 mmHg, respectively.

Aorta punch biopsy samples and LIMA samples were prepared from the ***identical individual*** undergone CBAG surgery and were stored at −80 °C until trace element analysis.

2.6. Tissue preparation

The tissue samples were weighed and transferred into metal-free glass tubes for digestion. All the glassware was kept in 10% (v/v) nitric acid solution before use. The samples were first digested with 2 mL of concentrated nitric acid at 100 °C in the furnace (Heraeus W.C. Heraeus GmbH, Hanau, Germany) and 2 mL of perchloric acid was added to the cooled materials. The materials were then completely digested at 120 °C until the materials diminished to half of the original total volume. Digested materials were diluted with deionized water to 10 mL. The last dilutions of the samples were mixed in a shaker for 15 min just before measurement. Results were calculated as μg/g wet weight ($\mu g/g_{tissue}$) [28]. 1 mL of serum was diluted in deionized water to 10 mL and then vortexed before the analysis [29]. Serum Zn, Cu and Fe levels of serum samples were indicated in microgram per milliliter (ppm = μg/mL).

2.7. Trace element measurements

The analysis of serum levels of Zn, Cu and Fe were measured using inductively coupled plasma-optical emission spectrophotometer (ICP-OES) (iCAP 6000 series, Thermo Fischer Scientific Inc., Istanbul, Turkey) at the Trace Element Analysis Laboratory at Biophysics Department of Cerrahpasa Medical Faculty. The ICP-OES system used was an emission spectrophotometer prepared with the plus auto sampler and was controlled by a computer. ICP-OES was operated under acceptable circumstances including choosing the favorable wavelength for Zn (206.200 nm), Cu (324.7 nm) and Fe (259.9 nm) with plasma gas flow rate 5 L/min, argon carrier flow rate of 0.5 L/min, sample flow rate of 1.51 L/min, flow rate of elusion, and peristaltic pump speed of 100 rpm. All reagents were of analytical reagent grade, and daily deionized water was used. Stock solutions of Zn, Cu and Fe were prepared by taking appropriate amounts of standards in daily deionized water. All work was done on a clean bench to decrease the risk of contamination from ambient air and dust. All the glassware used was cleaned by being soaked in with 10% (v/v) nitric acid solution for 1 day before use. These were rinsed thoroughly with deionized water and dried in an oven overnight at 100 °C.

2.8. Statistical analysis

Statistical analysis was performed with SPSS (Statistical Package for Social Sciences) for Windows 17.0. For comparison of parameters between the independent groups (Aorta-LIMA), Independent Sample *t*-test and Mann-Whitney *U* test were used for parametric and non-parametric groups, respectively. Paired Sample *t*-test and Wilcoxon test were used in parametric and non-parametric dependent groups (Serum Pre-op and Post-op), respectively. On the other hand, the Pearson correlation test (for parametric groups) and the Spearman correlation test (for non-parametric groups) was used for determination of correlation. The mean and median values were presented along with their 95% confidence interval. Data are presented as the mean ± standard deviation (SD). All the analyses were assumed statistically significant at $p < 0.05$.

3. Results

Demographic data and biochemical parameters of the study group in Pre-op are given in Table 1. Serum Zn levels were 3.6% lower in Post-op compared with Pre-op with no statistical significance. Serum Cu levels were 17% higher in Post-op compared with Pre-op ($p = 0.018$). Serum Fe levels were 31% lower in Post-op compared with Pre-op ($p = 0.009$). Serum Cu/Zn ratio values were 26.8% higher in Post-op compared with Pre-op ($p = 0.015$) (Table 2).

Zn and Cu levels in aorta tissue were respectively 8.7% and 20.3% higher than LIMA with no statistical significance. The Cu/Zn ratio values were 0.8% higher in aorta tissue than LIMA with no statistical significance. Aorta tissue had 49.8% statistically significantly increased levels of Fe compared with LIMA ($p = 0.0001$) (Table 3).

Fe level in aorta was positively correlated with the Zn Pre-op level in serum ($r = 0.439$, $p = 0.041$) and Zn level in LIMA ($r = 0.622$, $p = 0.004$). Zn level in aorta was positively correlated with the Fe level in aorta ($r = 0.718$, $p = 0.0001$) and the Cu level in aorta ($r = 0.627$, $p = 0.001$). The Zn Post-op level in serum was positively correlated with the Cu Post-op level in serum ($r = 0.717$, $p = 0.0001$), the Fe Pre-op level in serum ($r = 0.508$, $p = 0.022$) and the Fe Post-op level in serum ($r = 0.488$, $p = 0.018$) (r:correlation coefficients).

4. Discussion and conclusion

The main reasons associated with pre – operative and post – operative trace element alterations in CBAG surgery have not been fully elucidated [13,30]. Individuals are faced with a secondary trauma with CBAG surgery besides their clinical syptoms of atherosclerosis. Trace elements in serum and plasma are closely related with the tonicity of body as other proteins and soluble molecules. Fluid replacement therapy (FRT) for CBAG patients is standard for all individuals except special conditions related with the patient. Thus, any minor alteration of a trace element(s) in atherosclerotic patients might be of great clinical importance in this catabolic and anabolic time period [31–33]. The aim of our study is to investigate the surgical trauma effect on serum levels of Zn, Cu and Fe and LIMA's resistance to atherosclerosis via tissue levels of these trace elements in CBAG surgery.

Our study revealed that Zn, Cu and Fe tended to accumulate in aorta and LIMA tissues. Serum levels of Zn and Cu decreased without any significance. Aortic tissue is induced by inflammatory effect of increased serum pre-op Fe level, whereas LIMA is protected from inflammation and atherosclerosis being a potential graft for CBAG surgery.

Zn functions as a stabilizer of molecular structure and membranes,

Table 1
Demographic data and biochemical values (Mean ± SD).

	Pre -op (n = 33)
Age (year)	61.69 ± 5.65
BMI (kg/m^2)	27.06 ± 3.72
SBP (mmHg)	116.00 ± 18.25
DBP (mmHg)	70.10 ± 8.35
Hgb (g/dL)	14.41 ± 1.41
Hct (%)	39.72 ± 6.08
Creatinine (mg/dL)	1.00 ± 0.14
Urea (mg/dL)	44.2 ± 0.7
TC (mg/dL)	202.69 ± 15.55
TG (mg/dL)	198.8 ± 114.55
LDL (mg/dL)	116.85 ± 3.53
HDL (mg/dL)	41.36 ± 3.53
TC/HDL	5.42 ± 1.41
LDL/HDL	3.01 ± 0.38
Glucose (mg/dL)	91.06 ± 9.05
Fibrinogen (mg/dL)	124.51 ± 53.59
WBC (10^3/mL)	7.88 ± 0.50
CRP (mg/dL)	3.59 ± 0.62

Pre-op: 24 h before the surgery; **BMI:** Body mass index; **SBP:** Systolic blood pressure; **DBP:** Diastolic blood pressure; **Hgb:** Hemoglobin; **Hct:** Hematocrit; **TC:** Total cholesterol; **TG:** Triglyceride; **LDL:** Low density lipoprotein; **HDL**: High density lipoprotein; **WBC:** White blood cell; **CRP:** C-reactive protein.

Table 2
Serum Zn, Cu, Fe levels and Cu / Zn ratio of study groups.

Parameters	Pre-op (n = 33)	Post-op (n = 33)	p
Zn (μg/mL)	0.883 ± 0.259	0.851 ± 0.408	0.858
Cu (μg/mL)	1.178 ± 0.356	1.419 ± 0.378*	0.018
Fe (μg/mL)	0.940 ± 0.445	0.645 ± 0.340**	0.009
Cu / Zn	1.475 ± 0.537	2.017 ± 0.756*	0.015

Zn: Zinc; **Cu:** Copper; **Fe:** Iron; **Pre-op**: 24 h before the surgery; **Post-op:** 7 days after the surgery. Mean ± SD. Serum Pre-op vs Serum Post-op.
* $p < 0.05$.
** $p < 0.01$.

Table 3
Zn, Cu, Fe levels and Cu/Zn ratio in aorta and LIMA tissues.

Parameters	Aorta (n = 33)	LIMA (n = 33)	p
Zn (μg/g_{tissue})	18.89 ± 7.32	17.23 ± 7.06	0.509
Cu (μg/g_{tissue})	2.245 ± 0.956	1.790 ± 1.065	0.155
Fe (μg/g_{tissue})	20.78 ± 8.12	10.43 ± 5.04 ***	0.0001
Cu / Zn	0.125 ± 0.042	0.124 ± 0.086	0.719

Zn: Zinc; **Cu:** Copper; **Fe:** Iron; **LIMA:** Left internal mammary artery. Mean ± SD. Aort vs LIMA.
*** $p < 0.001$.

participates in synthesis and degradation of biomolecules [15,19,34]. Reiterer et al. [18] reported that plasma lipids increased in zinc-deficient mice. Stadler et al. [16] emphasized the protective effect of Zn against atherosclerosis in lesions of post-mortem aorta tissues. On the contrary, a study with carotid atherosclerosis revealed out that there was no significance by means of serum Zn between atherosclerotic and healthy subjects [17]. Stoppe et al. [31] stated in their study of CBAG surgery that Pre-op serum Zn level was higher than Post-op, consistenly with our results. Iyigun et al. [32] revealed in their sudy concerning CBAG surgery that Pre-op serum Zn level was statistically higher versus Post-op serum Zn levels analysed 1 h after admission to intensive care unit (ICU). Conversely, Cebi et al. [5] demonstrated that serum levels of Zn in CVD patients decreased with no significance. Our study results concluded that serum Zn level was higher in Pre-op compared with Post-op with no significance. The reason of this decrement between Pre-op and Post-op might be due to consumption of Zn in inflammatory process due to CBAG surgery and to hemodilution after CBAG surgery in ICU. Another reason of Zn decrease at Post-op might be redistribution of Zn from serum to tissues for wound healing and epithelization at the sites of surgery. Post-op serum Zn levels were positively correlated with Post-op serum Cu levels, Pre-op serum Fe levels and Post-op serum Fe levels. Pre-op serum Zn levels were positively correlated with Fe levels in aorta. All these correlations between Zn and, Cu and Fe might indicate the balance of Zn against the inflammatory and anti-atherogenic effects of Cu and Fe.

Cu is crucial in the structure and function of many enzymes covering dismutase, cytochrome C oxidase and lysyl oxidase [35]. Cu promotes lipid peroxidation and atherosclerosis with its pro-atherogenic property [17]. Serum Cu level was found to be strongly associated with CVD mortality among US adults in 1999 [20]. Cebi et al. [7] demonstrated that serum levels of Cu decreased in CVD patients indicating the anti-atherogenic feature of Cu. Moreover, Yan et al. [36] reported that low serum Cu levels at the onset of the surgery decreased to minimum levels at the end of CBAG surgery. However, Reunanen et al. [37] and Lukaski et al. [38] both reported increased serum levels of Cu in CVD patients in 1990s. Similarly, Iyigun et al. [32] recently determined that Pre-op serum Cu level was statistically significantly higher compared with Post-op serum Cu levels analysed 1 h after admission to ICU. Serum Cu levels could diminish due to per – operative and post – operative hemodilution in CBAG surgery [39]. The difference between our study and the study by Stoppe et al. [31] was that serum Cu levels decreased at post-op 1st hour after CBAG surgery compared with pre-op values. Consistently with our study, Antila et al. [33] Cu levels decreased intraoperatively to 44% of preoperative values, but increased to two-fold values on the seventh day after CBAG surgery. Our study results concluded that serum Cu level was higher in Post-op compared with Pre-op ($p < 0.05$) proposing that inflammatory burden effect of CBAG surgery on serum Cu. Aortic Cu levels were positively correlated with aortic Zn levels emphasizing the protective effect of Zn over Cu metabolism.

Moreover, aorta Zn and Cu levels in our study were higher than LIMA Zn and Cu levels with no significance. We may explain higher aorta Zn and Cu level compared with LIMA Zn and Cu with the fact that the inflammatory effect of Cu over aorta might be balanced with higher Zn level in LIMA. Besides, aorta is encountered with high pulsatile pressure throughout its endothelium having less elastic lamina and more muscle tissue. LIMA is contrarily nourished with intraluminal diffusion with a continuous elastic lamina. Post-op serum Cu/Zn ratios were statistically higher than Pre-op serum value ($p < 0.05$) probably indicating the increased inflammatory effect of surgery beyond the basic inflammation. Moreover, Cu/Zn ratio in LIMA in our study was lower than aortic tissue value with no statistical significance. Lower Cu / Zn ratio in LIMA might be defined with its specialty of being resistant to atherosclerosis.

It has been known that high serum Fe level induces the inflammatory process stimulating lipid peroxidation [9,21,33]. Antila et al. [33] reported in 1988 that Fe levels statistically decreased reaching a half value by the seventh day after CBAG surgery. The study related with CBAG determined pre-op serum Fe level was statistically significantly higher compared with post-op serum Fe levels analysed 1 h after admission to ICU, consistently with our study [32]. With regard to serum Fe level in our study, Pre-op Fe level was higher than Post-op ($p < 0.01$). Besides, aorta Fe level was higher than LIMA Fe level ($p < 0.001$). Fe facilitates oxygen delivery to all cells and tissues including aorta. Aorta exposing high pulsatile pressure is sensitive for atherosclerosis because of its fast metabolism and poor oxygenation. Arterial grafts acquire vasa vasorum for their oxygenation, nutrition and stability, whereas LIMA has long vasa vasorum just located from its adventitia to its media for luminal oxygenation and nutrition [26]. That's why LIMA is more successful than the other arterial or venous grafts. This data might be supported by our finding of a negative correlation between Zn levels of LIMA. There was a positive correlation between aortic Fe levels with Zn levels in aorta and LIMA tissue emphasizing the defensive effect of Zn over Fe.

Our study points out that aorta is prone to atherosclerosis compared to LIMA due to different metabolism of Zn, Cu and Fe. Inflammatory effects resulting in atherosclerosis can be explained with higher content of Fe both in serum and aortic tissue. The decrease in inflammatory effects of serum Fe ameliorated after CABG surgery even in seven days. Higher Zn content of serum and aortic tissue accompanied with higher Cu content of aortic tissue can be defined with the defensive property of Zn against atherosclerosis over Cu. We can hypothesize that LIMA has improved oxygenation and nourishment in cardiac tissue indicating its graft patency after CBAG surgery. Serum Zn, Cu and Fe levels in ***atherosclerotic individuals and CBAG patients*** should be monitored during diagnosis and periods covering pre-operative, intra-operative and post-operative follow-up to reveal minor alterations. Further detailed studies based on a long-term follow-up are warranted to clarify all the details about minor differences of Zn, Cu and Fe in CBAG patients.

The limitations of the current study are that our research was held in males in a short period of time not including the oxidative stress biomarkers (such as GSH and MDA) as a pilot study. We scheduled a study covering 33 males in order to get rid of gender differences. The study period referred to a time approximately one week to line out alterations of trace elements at a glance before and just after the surgery.

The interactions of other atherogenic and protective trace elements and mineral except from Zn, Cu and Fe were not evaluated in this study.

Our plans for future are wide-based studies conducted with both genders using oxidative stress biomarkers and other trace elements and minerals based on a longer time period.

Conflict of interest

None

Acknowledgements

This work was not supported by any funding.

This study was presented as an oral presentation at 16th International Symposium on Trace Elements in Man and Animals (TEMA - 16), 12th Conference of the International Society for Trace Element Research in Humans (ISTERH - 2017) and 13th Conference of the Nordic Trace Element Society (NTES - 2017) in St. Petersburg - Russia. (TEMA – 16/ISTERH/NTES Abstracts; Volume 41S1 (2017) 0-3-018; pp 23).

References

[1] Heart disease and stroke statistics—2017 update: a report from the American Heart Association, Circulation 135 (10) (2017) e146–e603, https://doi.org/10.1161/CIR.

0000000000000485.
[2] E. Wilkins, L. Wilson, K. Wickramasinghe, P. Bhatnagar, J. Leal, R. Luengo-Fernandez, R. Burns, M. Rayner, N. Townsend, European Cardiovascular Disease Statistics, European Heart Network, Brussels, 2017 (Access date: 06 May 2018), http://www.ehnheart.org/images/CVD-statistics-report-August-2017.pdf.
[3] A. Onat, G. Can, H. Yüksel, E. Ademoğlu, N. Erginel-Ünaltuna, A. Kaya, S. Altay, TEKHARF, A. Onat (Ed.), The Leadership of Medical World's Attitude Towards Chronic Diseases, Logos Yayıncılık Tic. A.Ş., İstanbul, 978-975-349-081-8, 2017(Access Date: 08 May 2018), http://file.tkd.org.tr/PDFs/TEKHARF-2017.pdf.
[4] Prevention and Control Program of Heart and Vascular Diseases in Turkey 2015-2020, Turkish Government, Ministry of Health,Turkey Public Health Foundation, Ministry of Health, 978-975-590-553-2, 2015 (Access Date: 08 May 2018) Publication Nummber: 988, Ankara, https://www.tkd.org.tr/TKDData/Uploads/files/Turkiye-kalp-ve-damar-hastaliklari-onleme-ve-kontrol-programi.pdf.
[5] M. Ercan, D. Konukoglu, T.Y. Erdem, Association of plasma viscosity with cardiovascular risk factors in obesity: an old marker, a new insight, Clin. Hemorheol. Microcirc. 35 (4) (2006) 441–446.
[6] J. Kakadiya, Causes, symptoms, pathophysiology and diagnosis of atherosclerosis - a review, Pharmacologyonline 3 (2009) 420–442.
[7] A. Cebi, Y. Kaya, H. Gungor, H. Demir, I.H. Yoruk, N. Soylemez, Y. Gunes, M. Tuncer, Trace elements, heavy metals and vitamin levels in patients with coronary artery disease, Int. J. Med. Sci. 8 (2011) 456–460.
[8] Y. Agmon, B.K. Khandheria, I. Meissner, G.L. Schwartz, T.M. Petterson, W.M. O'Fallon, J.P. Whisnant, D.O. Wiebers, J.B. Seward, Relation of coronary artery disease and cerebrovascular disease with atherosclerosis of the thoracic aorta in the general population, Am. J. Cardiol. 89 (3) (2002) 262–267.
[9] P. Kraml, The role of iron in the pathogenesis of atherosclerosis, Physiol. Res. 66 (Suppl. (1)) (2017) S55–S67.
[10] K. Tjaden, E. Pardali, J. Waltenberger, Hypercholesterolemia induces vascular cell dysfunction: molecular basis for atherosclerosis, Austin J. Vasc. Med. 2 (1) (2015) 1–9 id1011.
[11] P. Libby, P.M. Ridker, G.K. Hansson, Progress and challenges in translating the biology of atherosclerosis, Nature 473 (2011) 317–325.
[12] R. Stocker, J.F. Keaney Jr., Role of oxidative modifications in atherosclerosis, Physiol. Rev. 84 (2004) 1381–1478, https://doi.org/10.1152/physrev.00047.2003.
[13] L. Prashanth, K.K. Kattapagari, R.T. Chitturi, V.R.R. Baddam, L.K. Prasad, A review on role essential trace elements in health and disease, J. Dr. NTR Univ. Health Sci. 4 (2) (2015) 75–85, https://doi.org/10.4103/2277-8632.158577.
[14] Trace Elements in Human Nutrition and Health, World Health Organization, Macmillan/Ceuterick, Belgium, 1996.
[15] D. Konukoglu, A.M. Ercan, O. Serin, M.S. Turhan, Relationship between plasma leptin and zinc levels and the effect of insulin and oxidative stress on leptin levels in obese diabetic patients, J. Nutr. Biochem. 15 (12) (2004) 757–760.
[16] N. Stadler, N. Stanley, S. Heeneman, V. Vacata, M.J.A.P. Daemen, P.G. Bannon, J. Waltenberger, M.J. Davies, Accumulation of zinc in human atherosclerotic lesions correlates with calcium levels but does not protect against protein oxidation, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 1024–1030.
[17] N.M. Tasić, D. Tasić, P. Otašević, M. Veselinović, V. Jakovljević, D. Djurić, D. Radak, Copper and zinc concentrations in atherosclerotic plaque and serum in relation to lipid metabolism in patients with carotid atherosclerosis, Vojnosanit. Pregl. 72 (9) (2015) 801–806.
[18] G. Reiterer, R. MacDonald, J.D. Browning, J. Morrow, S.V. Matveev, A. Daugherty, E. Smart, M. Toborek, B. Hennig, Zinc deficiency increases plasma lipids and atherosclerotic markers in LDL-receptor–deficient mice, J. Nutr. 135 (2005) 2114–2118.
[19] A. Mezzetti, S.D. Pierdomenico, F. Costantini, F. Romano, D. De Cesare, F. Cuccurullo, T. Imbastaro, G. Riario-Sforza, F. Di Giacomo, G. Zuliani, R. Fellin, Copper/zinc ratio and systemic oxidant load: effect of aging and aging-related degenerative diseases, Free Radic. Biol. Med. 25 (6) (1998) 676–681.
[20] E.S. Ford, Serum copper concentration and coronary heart disease among US adults, Am. J. Epidemiol. 151 (12) (2000) 1182–1188.
[21] L.M. Bystrom, S. Rivella, Cancer cells with irons in the fire, Free Radic Biol. Med. 79 (2015) 337–342.
[22] D. Formanowicz, Do changes in iron metabolism contribute to the acceleration of the atherosclerosis process? Bio. Technol. 92 (2) (2011) 180–192.
[23] L. Weis (Ed.), Cell and Tissue Biology. A Textbook of Histology, 6th ed, Urban and Schwarzenberg, Baltimore, 1988, pp. 367–374.
[24] Z. Yang, B.S. Oemar, T. Carrel, B. Kipfer, F. Julmy, T.F. Luscher, Different proliferative properties of smooth muscle cells of human arterial and venous bypass vessels: role of PDGF receptors, mitogen-activated protein kinase, and cyclin-dependent kinase inhibitors, Circulation 97 (2) (1998) 181–187.
[25] S.Y. Lu, M.Z. Zhu, D.S. Wang, S.Y. Chen, W.D. Zhang, H. Dong, J. Yu, H.T. Guo, Inhibition of the proliferation of smooth muscle cells from human coronary bypass vessels by vasonatrin peptide, Physiol. Res. 32 (2004) 387–393.
[26] J. Tatoulis, B.F. Buxton, J.A. Fuller, Patencies of 2127 arterial to coronary conduits over 15 years, Ann. Thorac. Surg. 77 (January (1)) (2004) 93–101, https://doi.org/10.1016/S0003-4975(03)01331-6.
[27] F. Otsuka, K. Yahagi, K. Sakakura, R. Virmani, Why is the mammary artery so special and what protects it from atherosclerosis? Ann. Cardiothorac. Surg. 2 (4) (2013) 519–526, https://doi.org/10.3978/j.issn.2225-319X.2013.07.06.
[28] C. Koksal, M. Ercan, A.K. Bozkurt, T. Cortelekoglu, D. Konukoglu, Abdominal aortic aneurysm or aortic occlusive disease: role of trace element imbalance, Angiology 58 (2) (2007) 191–195, https://doi.org/10.1177/0003319707300354.
[29] E.O. Bursalıoglu, F.A. Alkan, U.B. Barutcu, M. Demir, Y. Karabul, B. Balkan, E. Oz, O. Icelli, Prediction of electron density and trace element concentrations in human blood serum following radioiodine therapy in differentiated thyroid cancer patients, Measurement 100 (2017) 19–25, https://doi.org/10.1016/j.measurement.2016.12.035.
[30] E.M. Alissa, S.M. Bahijri, D.J. Lamb, G.A. Ferns, The effects of coadministration of dietary copper and zinc supplements on atherosclerosis, antioxidant enzymes and indices of lipid peroxidation in the cholesterol-fed rabbit, Int. J. Exp. Pathol. 85 (2004) 265–275.
[31] C. Stoppe, G. Schalte, R. Rossaint, M. Coburn, B. Graf, J. Spillner, G. Marx, S. Rex, The intraoperative decrease of selenium is associated with the postoperative development of multiorgan dysfunction in cardiac surgical patients, Crit. Care Med. 39 (8) (2011) 1879–1885, https://doi.org/10.1097/CCM.0b013e3182190d48.
[32] T. Iyigun, H.F. Altin, M. Kaya, U. Kafa, B.O. Kurt, S. Ozdemir, S. Gode, M. Yeniterzi, I. Bakir, The effect of cardiopulmonary bypass on trace elements in patients undergoing coronary artery bypass grafting surgery, J. Cardiovasc. Surg. 4 (1) (2016) 8–12, https://doi.org/10.5455/jcvs.2016412.
[33] H. Antila, M. Salo, V. Nanto, K. Irjala, R. Brenner, M. Vapaavuorı, Serum iron, zinc, copper, selenium, and bromide concentrations after coronary bypass operation, J. Parenter. Enteral. Nutr. 14 (1) (1988) 85–89.
[34] M. Ercan, C. Koksal, K. Kazımoglu, C. Arslani, D. Konukoglu, K. Bozkurt, A.G. Sayın, The role of trace elements in the ethiology of varicose vein, Turkish J. Thorac. Cardiovasc. Surg. 9 (2001) 168–170.
[35] Y.Q. Yan, X.C. Liu, W.B. Jing, Z. Wang, X.Y. Bai, Q. Yang, G.W. He, Alteration of plasma trace elements in patients undergoing open heart surgery, Biol. Trace Elem. Res. 151 (2013) 344–349.
[36] Y.Q. Yan, L.J. Zou, Relation between zinc, copper, and magnesium concentrations following cardiopulmonary bypass and postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting, Biol. Trace Elem. Res. 148 (2012) 148–153.
[37] A. Reunanen, P. Knekt, P.J. Marniemi, J. Maki, J. Maatela, A. Aromaa, Serum calcium, magnesium, copper and zinc and risk of cardiovascular death, Eur. J. Appl. Physiol. 50 (1996) 431–437.
[38] H.C. Lukaski, L.M. Klevay, D.B. Milne, Effects of dieatary copper on human autonomic cardiovascular function, Eur. J. Appl. Physiol. 58 (1988) 74–80.
[39] R. Zamparelli, G. Carelli, M.A. Pennisi, E. Baruffi, R. Schiawello, M.A. Intonti, F. Intonti, Zinc and copper metabolism during open-heart surgery, Scand. Cardiovasc. J. 20 (Suppl. (3)) (1986) 241–245, https://doi.org/10.3109/14017438609105932.