

*Original article*

## Association of Serum Zinc and Selenium Concentration with Insulin Resistance in Apparently Healthy Adults

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### SUMMARY

**Introduction/Aim.** Zinc is a trace element involved in insulin metabolism, including its production, storage, and release. Selenium is regarded as a vital micronutrient for humans. It participates in insulin signaling and control. Zinc and selenium may be possibly linked to insulin resistance; however, these relationships have not been well investigated. Therefore, we sought to examine the relationship between blood zinc and selenium levels and insulin resistance in apparently healthy individuals.

**Methods.** This study used a cross-sectional design including 203 apparently healthy people. Measurements were taken to determine zinc and selenium serum levels, fasting insulin, fasting blood glucose, and glycosylated hemoglobin. Insulin resistance was measured by utilizing the Homeostatic Model Assessment (HOMA-IR).

**Results.** The prevalence of insulin resistance, as determined by HOMA-IR, was 26.11%. Patients with insulin resistance had higher age ( $59.96 \pm 12.28$  years), body mass index ( $26.66 \pm 3.16$  kg/m<sup>2</sup>), and waist-to-hip ratio ( $0.93 \pm 0.05$ ) compared to those with insulin sensitivity ( $54.19 \pm 9.88$  years,  $25.92 \pm 2.4$  kg/m<sup>2</sup>,  $0.91 \pm 0.05$ ), with statistically significant differences (p-values—0.013, 0.013, 0.029, respectively). Serum zinc levels were elevated in insulin-sensitive individuals ( $87.12 \pm 6.87$  mcg/mL) compared to those who were insulin-resistant ( $84.05 \pm 8.29$  mcg/mL), with a p-value of 0.036. HbA1c concentration and fasting Insulin levels were elevated in the insulin-resistant group ( $4.95 \pm 0.49$ ,  $15.78 \pm 1.59$ ) compared to the insulin-sensitive group ( $4.79 \pm 0.38$ ,  $10.1 \pm 2.34$ ), with p-values of 0.033 and 0.003, respectively.

**Conclusion.** In apparently healthy adults, there is an association between low serum zinc levels and insulin resistance. There is no association between selenium serum levels and insulin resistance.

**Keywords:** insulin resistance, zinc, selenium

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## INTRODUCTION

The association between zinc content and insulin secretion and function was identified in 1930 as the zinc ion was found to stimulate insulin crystallization (1). Further research demonstrated that zinc is necessary for the processing and storing insulin in the pancreatic  $\beta$ -cell. Zinc (Zn) helps the pancreas produce and store insulin, which augments the body's absorption of glucose. Low plasma levels of zinc impair islet cell production and secretion of insulin (2). Pancreatic  $\beta$ -cells store and crystallize insulin in granules along with free cytosolic zinc. Under normal conditions,  $\beta$ -cells form a hexamer by combining six insulin monomers with two zinc ions in the core. The insulin-Zn crystal is stored and transferred across the cell membrane. According to a study in 2015 by Slepchenko et al., only the insulin monomer remains an active form of the hormone after the Zn-insulin complexes dissociate after being secreted (3). The increase in insulin secretion is correlated with the elevated extracellular concentration of free zinc (3).

Selenium (Se) is a vital mineral for human organs proper functions. Selenium can be found in both organic and inorganic forms in nature. Selenate, selenite, selenide, and elemental selenium are examples of the inorganic forms of selenium. In contrast, the organic form is found in combination with amino acids and is referred to as selenomethionine (SeMet) and (selenocysteine) SeCys (4). Since selenium counteracts the effects of insulin through glutathione peroxidase (GPx-1) and selenoprotein p (SelP), elevated plasma selenium concentrations are linked to diabetes biomarkers (5). Pancreatic  $\beta$ -cells are protected from oxidative stress by the action of enzymes like GPx, catalase, and superoxide dismutase, peroxiredoxins, thioredoxins, and thioredoxin reductases. Since the bioavailability of selenium is essential for the activity of thioredoxin reductases and GPx, selenium deficiency causes  $\beta$ -cell oxidative damage and decreased insulin secretion. However, too much selenium also causes dysregulation of insulin secretion, which raises insulin levels and results in the T2DM phenotype. These antioxidant enzymes, including selenoenzymes, generally interfere with vital redox signaling for cell differentiation and insulin secretion to influence these processes (6).

HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) is a practical quantification

method for assessing insulin resistance from an epidemiological or clinical perspective. Nevertheless, significant diversity exists in its threshold values. Furthermore, these threshold values vary based on ethnicity, clinical evaluation methodologies, and the metabolic state of the tested populations (7). The HOMA-IR thresholds for diagnosing insulin resistance may differ among racial groups (8). A recent study involving 1,327 non-diabetic, normotensive people in Tehran established this threshold at 1.8. Certain investigators have attempted to identify HOMA-IR cut-offs in individuals predisposed to insulin resistance or metabolic syndrome, although their results were inconsistent (9).

In our investigation, the HOMA-IR threshold was determined to be 3.1, aligning with prior studies on healthy Iraqi adults. Higher than this, individuals were classified as having insulin resistance (10, 11). The relationship between zinc, selenium, and insulin resistance in healthy individuals is intricate. Although research links zinc insufficiency to insulin resistance, selenium's effects are multifaceted, revealing positive and negative associations. The role of zinc and selenium in insulin resistance is still a matter of discussion. In this study, we try to explain the association of serum zinc and selenium with insulin resistance in apparently healthy adults.

## SUBJECTS AND METHODS

The research included 203 apparently healthy Iraqi individuals of both genders who were identified as Arabs and were  $\geq 40$  years old. This cross-sectional study was conducted from May 2023 to February 2024. The study was conducted at Al Nahrain University/College of Medicine, Al-Farahidi University, and Mustansiriyah University, Baghdad, Iraq. It was approved by the Institutional Review Board (IRB) of the College of Medicine, Al-Nahrain University, under the reference number 20221027 on 01/02/2023. Prior to participating in the study, all participants provided their written informed consent.

### Inclusion criteria

Subjects enrolled in the study were apparently healthy adults  $\geq 40$  years old, euglycemic, non-diabetic with HbA1C less  $\leq 6.5\%$

### The exclusion criteria were as follows:

The presence of diabetes or other severe chronic disease such as heart and renal diseases, as well as the use of medications may influence IR or lipid metabolism (such as corticosteroids and lipid-lowering drugs), pregnancy, breastfeeding and women receiving oral contraceptive or hormone replacement therapy.

**Sample collection:** Participants were asked to fast for eight hours prior to samples' collection. The next morning, 5 ml of blood was taken from each participant. Blood samples were placed in a gel tube to collect serum. After that, the serum was recovered by centrifuging the sample for 15 minutes at 4000 rpm×g. The serum was collected and poured into many Eppendorf tubes for biochemical testing. Two milliliters of blood were obtained in two ethylene diamine tetra-acetic acid (EDTA) tubes for hematological tests.

**Demographic factors:** Demographic variables such as age, gender, smoking habits, place of residence, and family history of diabetes were obtained by direct interview. The participant's body weight (in kilograms) and height (in centimeters) were measured under the condition that they were wearing light clothes and without wearing shoes. The body mass index was determined using the following equation: weight (kg)/square height (m<sup>2</sup>). Measurements were taken for waist circumference, hip circumference, and waist-to-hip ratio.

**Biochemical tests:** Using a commercially available kit, the hexokinase technique was used to assess glycosylated hemoglobin and fasting plasma glucose. Fasting insulin was determined by immunoradiometric assay. The calculation of insulin resistance was performed using the HOMA-IR method, as follows:  $HOMA-IR = (FBS \text{ (mg/dl)} \times \text{fasting insulin (mU/L)}) / 405$ . In our investigation, the HOMA-IR cut-off value was established at 3.1, consistent with other research on apparently healthy Iraqi adults. Higher than this, individuals were classified as having insulin resistance (10, 11).

**Serum level of zinc:** A colorimetric method with 5-bromo-PAPS was used to measure the serum zinc concentration. The assay principle involves the formation of a chelate complex between zinc and 2-(5-bromo 2-pyridylazo)-5(N-propyl-N-sulfopropyl-amino)-phenol. The rise in absorbance may be

quantified and is directly proportional to the quantity of total zinc in the sample.

The normal range for males is 72.6-127 mg/dL, while in females it is 70.6-114 mg/dL.

**Serum level of selenium:** The serum level of selenium was measured by an atomic absorption spectrophotometer, which examined the wavelength of photons absorbed during the excitation of element atoms. The technique used to estimate the atomic absorption of elements is the graphite furnace method, in which the approximation reaches the limit of concentrations in parts per billion. The sample was placed in a graphite tube inside the electric furnace, evaporating until dry, burned, and converted to the atomic state. Here, the percentage of atoms that evaporated, decomposed, and became ready to absorb energy is more significant than in the case of direct flame. The results appeared directly on a screen linked to an atomic absorption spectrophotometer.

**Statistical analyses:** Statistical analyses were conducted using the SPSS software version 25.0 (SPSS, Chicago). The continuous data underwent a normality test using the Shapiro-Wilk test. Data that exhibited a normal distribution were reported as the mean and standard deviation and were analyzed using a Student's t-test. Data that did not follow a normal distribution were reported using the median and range, and were evaluated using the Mann-Whitney U test (for comparing two groups). Categorical variables were quantified using numerical values and percentages and then assessed using the Chi-square test. Participants were categorized into two groups based on whether they had insulin resistance or not according to HOMA-IR, in line with the previous population-based studies, the cutoff value of HOMA-IR was determined to be 3.1, beyond which subjects were considered to have IR (10, 11).

## RESULTS

### Demographic features of the study population

Table 1 displays the age, sex, weight, height, BMI, waist and hip circumferences, and the waist/hip ratio of the population under investigation.

**Table 1.** Demographic data of the study population

Parameter	Value
<b>Age, years</b>	
Mean $\pm$ SD	55.55 $\pm$ 10.75
Range	40-82
<b>Sex</b>	
Males	108 (53.2%)
Females	95 (46.8%)
<b>Weight (Kg)</b>	
Mean $\pm$ SD	72.01 $\pm$ 8.15
Range	47-89
<b>Height, cm</b>	
Mean $\pm$ SD	168.63 $\pm$ 9.71
Range	151-182
<b>Waist circumference, cm</b>	
Mean $\pm$ SD	89.42 $\pm$ 7.13
Range	70-103
<b>Hip circumference, cm</b>	
Mean $\pm$ SD	96.34 $\pm$ 7.91
Range	80-106
<b>Body Mass Index, kg/cm<sup>2</sup></b>	
Mean $\pm$ SD	26.09 $\pm$ 2.61
Range	20.34-34.6
<b>Waist/Hip ratio</b>	
Mean $\pm$ SD	0.92 $\pm$ 0.05
Range	0.77-1.02

Glycemic profile, insulin level, and HOMA-IR

**Table 2.** Glycemic profile, insulin level, and HOMA-IR of the study population

Parameter	Value
<b>Fasting blood glucose, mg/dL</b>	
Mean $\pm$ SD	88.49 $\pm$ 6.80
Range	71.4-109
<b>Glycosylated hemoglobin, %</b>	
Mean $\pm$ SD	4.83 $\pm$ 0.42
Range	4-5.9
<b>Fasting insulin, <math>\mu</math>U/mL</b>	
Mean $\pm$ SD	11.44 $\pm$ 3.26
Range	5.4-19.5
<b>HOMA-IR</b>	
Mean $\pm$ SD	2.5 $\pm$ 0.71
Range	1.17-4.02

Trace elements

The fasting blood glucose, HbA1c, and insulin levels and the HOMA-R of the study population are indicated in Table 2.

Table 3 shows serum zinc and selenium plasma levels for the studied population.

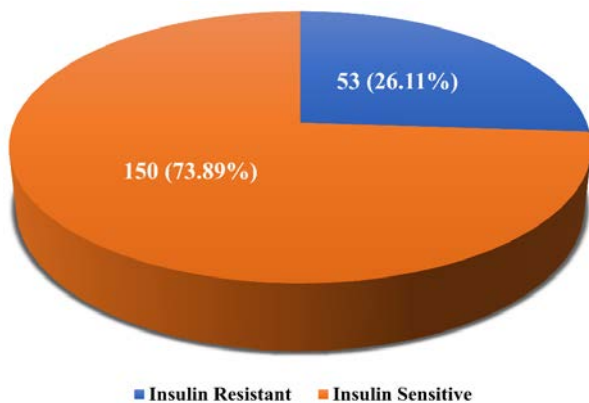
**Table 3.** Trace elements of the study populations

Parameter	Value
<b>Zinc, mcg/mL</b>	
Mean ± SD	86.11 ± 6.88
Range	71.5-101.5
<b>Selenium, µg/L</b>	
Mean ± SD	0.29 ± 0.15
Median	0.26
Range	0.06-0.74

Insulin status

### Insulin status

The study population was divided into insulin-resistant or not based on HOMA IR. One hundred and fifty (73.89%) subjects were insulin sensitive, and the rest, 53 (26.11%) subjects, were insulin resistant (Figure 1).



**Figure 1:** Distribution of the study population into insulin-sensitive and insulin-resistant subjects

### Demographic data according to insulin status

Subjects of the insulin-resistant group were older and had higher BMIs than those of the insulin-sensitive group ( $p = 0.013$ ,  $p = 0.013$ , respectively). Similarly, the WHR was higher in the insulin-resistant group than the insulin-sensitive group ( $p = 0.029$ ). Conversely, no significant difference was demonstrated in weight, height, waist, and hip circumferences. Likewise, no sex difference was noticed between the two subgroups, as shown in Table 4.

### Glycemic profile, insulin level, and according to insulin status

When subjects were divided into two groups, the HbA1c levels were  $4.95 \pm 0.49\%$  versus  $4.79 \pm 0.38\%$ :  $P = 0.033$ . The fasting insulin levels were  $15.78 \pm 1.59 \mu\text{U/mL}$  versus  $10.1 \pm 2.34 \mu\text{U/mL}$  ( $P = 0.003$ ). FBG levels were  $89.04 \pm 6.88 \text{ mg/dL}$  versus  $88.32 \pm 6.78 \text{ mg/dL}$  ( $P = \text{NS}$ ). Thus, subjects with IR appeared to have higher levels of HbA1c insulin levels compared with those with insulin sensitivity but retained FBG levels, as shown in Table 5. For the p-value, the t-test was used.

### Serum trace elements according to insulin status

Table 6 presents the level of trace elements in IR compared to insulin-sensitive subjects. Zinc serum level was  $84.05 \pm 8.29 \text{ mcg/mL}$  versus  $87.12 \pm 6.87 \text{ mcg/mL}$  ( $P = 0.036$ ) respectively, whereas selenium level was  $0.26 \pm 0.11 \text{ ppm}$  versus  $0.30 \pm 0.16 \text{ ppm}$  ( $P = \text{NS}$ ).

**Table 4.** Demographic data of the study population according to insulin status

Parameter	Insulin status		p-value
	Resistant (n = 53)	Sensitive (n = 150)	
<b>Age, years</b>			
Mean ± SD	59.96 ± 12.28	54.19 ± 9.88	0.013
Range	70-82	40-82	
<b>Sex</b>			
Males	31(58.5%)	77 (51.33%)	0.506 <sup>NS</sup>
Females	22 (41.5%)	73 (48.67%)	
<b>Weight (kg)</b>			
Mean±SD	72.88 ± 7.56	71.75 ± 8.33	0.775 <sup>NS</sup>
Range	55-85	47-89	
<b>Height, cm</b>			
Mean ± SD	170.1 ± 5.82	168.17 ± 6.92	0.250 <sup>NS</sup>
Range	159-182	151-182	
<b>Waist circumference, cm</b>			
Mean ± SD	92.1 ± 6.28	88.59 ± 7.18	0.244 <sup>NS</sup>
Range	77-103	70-102	
<b>Hip circumference, cm</b>			
Mean ± SD	97.81 ± 4.17	95.88 ± 5.04	0.133 <sup>NS</sup>
Range	84-106	80-105	
<b>Body mass index, kg/m<sup>2</sup></b>			
Mean ± SD	26.66 ± 3.16	25.92 ± 2.4	0.013
Range	20.4-34.2	20.34-34.6	
<b>Waist/Hip ratio</b>			
Mean ± SD	0.93 ± 0.05	0.91 ± 0.05	0.029
Range	0.79-1.02	0.77-0.98	

NS = not significant. P-value for all parameters, we used t-test except for the p-value for sexes; we used the chi-square test

**Table 5.** Insulin resistance-related parameters of those with and without insulin resistance

Parameter	Insulin status		p-value
	Resistant (n = 53)	Sensitive (n = 150)	
<b>FBG, mg/dL</b>			
Mean ± SD	89.04 ± 6.88	88.32 ± 6.78	0.305 <sup>NS</sup>
Range	77-109	71.4-106	
<b>HbA1c level, %</b>			
Mean ± SD	4.95 ± 0.49	4.79 ± 0.38	0.033
Range	4-5.9	4-5.7	
<b>Fasting insulin, μU/mL</b>			
Mean ± SD	15.78 ± 1.59	10.1 ± 2.34	0.003
Range	12.5-19.5	5.4-16.5	

FBG = fasting blood glucose; HbA1C = glycosylated hemoglobin; NS = not significant  
For the p-value, the t-test was used

**Table 6.** Serum trace elements according to insulin status

Parameter	Insulin status		p-value
	Resistant (n=53)	Sensitive (n=150)	
<b>Zinc, mcg/mL</b>			
Mean±SD	84.05±8.29	87.12±6.87	0.036
Range	71.5-101.5	74.1-101.4	
<b>Selenium, ppm</b>			
Mean±SD	0.26±0.11	0.30±0.16	0.222 <sup>NS</sup>
Range	0.06-0.74	0.06-0.74	

NS = not significant

For the p-value, the t-test was used

## DISCUSSION

The present study showed that the serum zinc was lower in insulin-resistant subjects than in insulin-sensitive subjects. Many studies worldwide have confirmed this finding. Research conducted in Bangladesh found a correlation between the zinc content in the blood and insulin resistance in 142 individuals with normal blood sugar levels (12). Research conducted by Ahn et al. in Korea showed that there is a negative correlation between the concentration of zinc in the blood and insulin resistance in a large group of adults without diabetes (13).

A review study involving 56 articles found that zinc deficiency is associated with glucose intolerance and IR; however, the effectiveness of the intervention with the zinc supplementation is still inconclusive (14). In a separate study undertaken by Bjørklund et al., it was shown that zinc, selenium, and copper have a role in the development of diabetes (15). However, these trace elements are in excessive quantities and have harmful effects. Zinc seems to stimulate essential molecules involved in cellular signaling, which regulate glucose homeostasis. Zinc also modulates insulin receptors, extends the duration of insulin activity, and enhances favorable lipid profiles (15).

A recent experimental investigation explored the impact of zinc on insulin levels in male rats. The study shows that levels of zinc in the food influence the levels of insulin in the bloodstream and change the distribution of pancreatic  $\beta$ -cells responsible for producing insulin. Their findings indicate that variations in blood insulin levels, triggered by varying plasma concentrations of zinc, may lead to metabolic changes in insulin target organs, such as the liver and adipose tissue (16).

Multiple further investigations have shown that zinc plays a crucial role in the pathophysiology of glucose metabolism and affects insulin homeostasis (17). Previous research showed that persons with impaired glycemic control had considerably lower serum levels of zinc than healthy individuals (18). Furthermore, there is an evidence indicating that decreased levels of zinc are linked to a higher likelihood of acquiring type 2 diabetes (T2D) in the future (19).

Multiple publications indicate the processes by which zinc is implicated in insulin action. Zinc acts as a catalyst in promoting the process of phosphorylation of the beta component of the insulin receptor. The activity of phosphoinositide 3-kinases (PI3K) protein kinase B (PKP) mediates the insulin-like action on glucose transport (20). Zinc exerts its insulin-like effects by directly inhibiting endogenous glycogen synthase kinase-3beta (GSK-3 $\beta$ ), a protein linked to insulin resistance (IR) and type 2 diabetes (21).

Another mechanism involves the interaction with oxidative stress, which has a role in developing and advancing insulin resistance (IR) and diabetes (22, 23). It is well established that pancreatic  $\beta$  cells are susceptible to damage from free radicals. Zinc, a cofactor of superoxide dismutase, reduces oxidative stress. Therefore, a zinc deficiency might worsen oxidative stress and contribute to the development of insulin resistance (24). Furthermore, zinc transporter 8 (ZnT8), situated on the surface of pancreatic  $\beta$ -cells, plays a crucial role in zinc's appropriate storage and functioning in insulin-secretory granules (25). The impairment of ZnT8 function or genetic mutations in the ZnT8 gene hinders the normal process of insulin crystallization. This results in increased degradation of insulin in the liver, decreasing the quan-

tity of insulin that reaches the target tissues. Consequently, this leads to the development of impaired glucose tolerance (26). The correlation between selenium and insulin resistance (IR) in animals and people is still unclear due to conflicting findings from prior research. Some studies indicate that an excessive buildup of selenium in the body is linked to type 2 diabetes (27), whereas other investigations do not uncover any significant connections (28). Research indicates that optimal levels of selenium are crucial for the production and effectiveness of insulin. However, an excessive amount of selenium in the body is linked to the development of insulin resistance (IR) and diabetes mellitus (DM) (29).

An extensive cross-sectional investigation on a representative sample of the U.S. population found a direct correlation between the levels of selenium in the blood and diabetes (30). The distinction in this research is that selenium was evaluated in plasma, which serves as a short-term indicator and is more responsive to immediate dietary fluctuations. More-

over, the study relied on a physician's self-reported diagnosis of diabetes, which might introduce bias and lead to an overestimation of the prevalence of diabetes. In contrast, a cross-sectional analysis of the health professionals' research revealed a negative correlation between toenail selenium levels and the incidence of diabetes among male health professionals (31). Zinc and selenium are both crucial for the metabolism of glucose and insulin. However, further studies are required to corroborate these results and clarify the underlying mechanisms.

## **CONCLUSION**

The study indicates an association between apparently healthy adults' serum zinc levels and insulin resistance. There is no association between selenium concentration and insulin resistance. Additional longitudinal or experimental studies may be required to ascertain a causal relationship.



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# Povezanost koncentracija cinka i selena u serumu sa insulinskom rezistencijom kod naizgled zdravih odraslih osoba

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## SAŽETAK

**Uvod/Cilj.** Cink je element koje je u tragovima uključen u metabolizam insulina, uključujući proizvodnju, skladištenje i oslobađanje insulina. Selen se smatra vitalnim mikronutrijentom kod ljudi i učestvuje u signalizaciji i kontroli insulina. Cink i selen mogu biti povezani sa insulinskom rezistencijom. Međutim, ovi odnosi još uvek nisu dobro istraženi. Iz tog razloga, nastojali smo da ispitamo odnos između nivoa cinka i selena u krvi i insulinske rezistencije kod naizgled zdravih osoba.

**Metode.** U ovoj studiji primenjen je poprečni presek, a u istraživanje su uključene 203 naizgled zdrave osobe. Merenja su izvršena da bi se odredili nivoi cinka i selena u serumu, insulin natašte, glukoza u krvi natašte i glikolizirani hemoglobin. Insulinska rezistencija merena je korišćenjem procene homeostatskog modela (engl. *homeostasis model assessment for insulin resistance* – HOMA-IR).

**Rezultati.** Prevalencija insulinske rezistencije, kako je utvrđeno HOMA-IR-om, iznosila je 26,11%. Bolesnici sa insulinskom rezistencijom bili su stariji (59,96 godina  $\pm$  12,28 godina), imali viši indeks telesne mase (26,66 kg/m<sup>2</sup>  $\pm$  3,16 kg/m<sup>2</sup>) kao i povećanu vrednost odnosa struka i kuka (0,93  $\pm$  0,05) u poređenju sa ispitanicima osetljivim na insulin (54,19 godina  $\pm$  9,88 godina, 25,92 kg/m<sup>2</sup>  $\pm$  2,4 kg/m<sup>2</sup>, 0,91  $\pm$  0,05), sa statistički značajnim razlikama (p vrednosti – 0,013, 0,013, 0,029, ponaosob). Nivoi cinka u serumu bili su povišeni kod osoba osetljivih na insulin (87,12 mcg/mL  $\pm$  6,87 mcg/mL) u poređenju sa osobama koje su bile otporne na insulin (84,05 mcg/mL  $\pm$  8,29 mcg/mL), sa p vrednošću od 0,036. Koncentracija HbA1c kao i nivoi insulina natašte bili su povišeni u grupi ispitanika rezistentnih na insulin (4,95  $\pm$  0,49, 15,78  $\pm$  1,59) u poređenju sa grupom ispitanika osetljivih na insulin (4,79  $\pm$  0,38, 10,1  $\pm$  2,34), sa p vrednostima od 0,033 i 0,003, ponaosob.

**Zaključak.** Kod naizgled zdravih odraslih osoba utvrđena je povezanost između niskog nivoa cinka u serumu i insulinske rezistencije. Ne postoji povezanost između nivoa seruma selena i insulinske rezistencije.

**Cljučne reči:** insulinska rezistencija, cink, selen