Original Article

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Synergistic Roles of Selenium and Vitamin D in Modulating Insulin Resistance and Metabolic Health

Selenyum ve D Vitamininin İnsülin Direncini ve Metabolik Sağlığı Düzenlemedeki Sinerjik Rolleri

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ABSTRACT

Objective: Selenium (Se) and vitamin D are critical micronutrients linked to metabolic health and insulin sensitivity. In our study, we aimed to investigate the relationship between Se deficiency and insulin resistance (IR) in patients who were admitted for a periodic health examination, and we also aimed to explore the synergistic role of vitamin D and Se in relation to IR.

Methods: This cross-sectional study examined the association of serum Se levels, vitamin D, and IR in 161 adult patients attending periodic health examinations at the Family Medicine Outpatient Clinics of Bezmialem Vakıf University Hospital. Serum Se levels were measured by inductively coupled plasma mass spectrometry, and vitamin D levels were measured by liquid chromatography-mass spectrometry. Statistical analyses were conducted using SPSS® software (version 22). Statistical significance was set at p≤0.05.

Results: The mean age of the patients was 39.31±13.20 years. Of the study population, 72% (n=116) were female. The mean body mass index was 25.83±4.81. The mean Se level of the patients was 71.66±11.56 µg/L. Thirty-five percent of the participants had IR [homeostatic model assessment of IR (HOMA-IR ≥2.5)], with significantly higher prevalence among those with Se deficiency (<63 µg/L, p=0.016). Patients with Se deficiency had lower vitamin D levels (p=0.001) and higher HOMA-IR values (p=0.006).

Conclusion: The findings suggest a synergistic association between Se and vitamin D deficiencies and impaired insulin

ÖZ

Amaç: Selenyum (Se) ve D vitamini, metabolik sağlık ve insülin duyarlılığı ile ilişkili önemli mikro besin öğeleridir. Bu çalışmada, periyodik sağlık muayenesi için başvuran hastalarda Se eksikliği ile insülin direnci (IR) arasındaki ilişkinin araştırılması ve ayrıca D vitamini ile Se'nin IR üzerindeki olası sinerjik rolünün incelenmesi amaçlanmıştır.

Yöntemler: Bu kesitsel çalışma, Bezmialem Vakıf Üniversitesi Hastanesi Aile Hekimliği polikliniklerinde periyodik sağlık muayenesine başvuran 161 yetişkin hastada serum Se düzeyleri, D vitamini ve IR arasındaki ilişkiyi incelemiştir. Serum Se düzeyleri indüktif eşleşmiş plazma kütle spektrometrisi yöntemiyle, D vitamini düzeyleri ise sıvı kromatografi-kütle spektrometrisi yöntemiyle ölçülmüştür. İstatistiksel analizler SPSS® yazılımı (versiyon 22) kullanılarak yapılmıştır. İstatistiksel anlamlılık düzeyi p≤0,05 olarak kabul edilmiştir.

Bulgular: Hastaların ortalama yaşı 39,31±13,20 yıl idi. Çalışma popülasyonunun %72'si (n=116) kadındı. Ortalama vücut kitle indeksi 25,83±4,81 olarak bulundu. Hastaların ortalama Se düzeyi 71,66±11,56 µg/L idi. Katılımcıların %35'inde IR [IR'nin homeostatik model değerlendirmesi (HOMA-IR ≥2,5)] saptandı ve Se eksikliği olanlarda IR prevalansı anlamlı olarak daha yüksekti (<63 µg/L, p=0,016). Se eksikliği olan hastalarda D vitamini düzeyleri daha düşük (p=0,001) ve HOMA-IR değerleri daha yüksek bulundu (p=0,006).

Sonuç: Bulgular, Se ve D vitamini eksiklikleri ile bozulmuş insülin duyarlılığı ve değişmiş metabolik belirteçler arasında sinerjik bir ilişki olduğunu göstermektedir. Bu çalışma, insülin

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ABSTRACT

sensitivity and altered metabolic markers. This study highlights the potential importance of Se and vitamin D in relation to IR and metabolic health. Our results indicate that addressing deficiencies in these micronutrients may be relevant for insulin sensitivity and metabolic health.

Keywords: Insulin resistance, selenium, type 2 diabetes, vitamin D

ÖZ

direnci ve metabolik sağlıkla ilişkili olarak Se ve D vitamininin potansiyel önemini vurgulamaktadır. Sonuçlarımız, bu mikro besin maddelerindeki eksikliklerin giderilmesinin insülin duyarlılığı ve metabolik sağlık açısından önemli olabileceğini göstermektedir.

Anahtar Kelimeler: İnsülin direnci, selenyum, tip 2 diyabet, vitamin D

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia, affecting approximately 10% of the global population. Type 2 DM accounts for nearly 90% of all cases and is closely associated with insulin resistance (IR), a key pathophysiological mechanism in its development. IR is commonly defined by a homeostatic model assessment of IR (HOMA-IR) index above 2.5, reflecting impaired insulin sensitivity. This metabolic disturbance is linked to early alterations in glucose homeostasis, as prediabetes—defined by glycated hemoglobin (HbA1c) levels between 5.7% and 6.4%—represents an intermediate stage in which IR plays a central role and increases the risk of progression to type 2 DM. Therefore, addressing IR may be important for the prevention of prediabetes, diabetes, and related complications. Recent evidence suggests that several micronutrients are involved in glucose metabolism and may contribute to its regulation, highlighting their potential relevance in IR and prediabetic states (1-7).

Selenium (Se) and vitamin D are micronutrients implicated in metabolic health and IR. Se contributes to antioxidant defense through selenoproteins such as glutathione peroxidase (GPx) and selenoprotein S (SEPS), which support β-cell function and insulin secretion under metabolic stress. However, excessive Se exposure may adversely affect glucose metabolism, indicating a complex and dose-dependent role (8-11). Vitamin D, through its receptor expressed in β-cells and insulin-sensitive tissues, may enhance insulin secretion and sensitivity while reducing inflammation. Conversely, vitamin D deficiency has been associated with IR and impaired β-cell function (12-14).

Emerging evidence suggests potential synergistic effects of Se and vitamin D on glucose metabolism through complementary antioxidant and anti-inflammatory pathways (15,16). However, findings remain inconsistent, and studies evaluating both micronutrients in relation to IR are limited. In particular, data from Türkiye are scarce.

The present study aims to investigate the association between Se, vitamin D levels and IR in individuals undergoing routine health examinations and to evaluate the potential combined effects of vitamin D and Se. By addressing this gap, this study may contribute to a better understanding of the role of these micronutrients in metabolic health and support more comprehensive approaches to IR management.

Methods

Study Design

This research was designed as a retrospective cross-sectional study conducted in the Family Medicine Department of Bezmialem Vakıf University. The study included patients who presented for periodic health examinations between January 2023 and May 2024. Sample size calculation was performed using the website Statulator. Power was set at 0.80 and Type I error (alpha) at 0.05. Based on a mean Se level of 48 µg/L in the first group, 92 µg/L in the second group, with a standard deviation (SD) of 42 µg/L and a sampling ratio of 1, a minimum of 15 participants per group was considered sufficient (15).

Participants were classified according to Se, HOMA-IR, HbA1c and vitamin D status. For Se, patients with serum levels <63 µg/L were classified as the Se-deficient group, while those with levels ≥63 µg/L were considered Se-normal according to laboratory reference values. In addition, based on the median Se concentration observed in our study (70.63 µg/L), participants were further categorized as Se Group 1 (Se <70.63 µg/L) and Se Group 2 (Se ≥70.63 µg/L), consistent with previous reports linking lower Se levels to adverse metabolic outcomes (1,9,15). IR status was determined using the HOMA-IR index, with a cut-off of ≥2.5 defining the IR group and <2.5 the non-IR group, in line with established criteria (5). Participants without a diagnosis of diabetes were further categorized as prediabetic if their HbA1c levels were between ≥5.7% and <6.5%, and as non-prediabetic if HbA1c was <5.7%. This classification was based on the diagnostic thresholds recommended by the American Diabetes Association (ADA) (7). Vitamin D deficiency was defined as serum 25 (OH) D <20 µg/L, whereas levels ≥20 µg/L were considered sufficient, based on widely accepted guidelines (14,16).

Patient Selection (Inclusion and Exclusion Criteria)

A total of 161 patients aged 18-65 years, of both genders, who presented for periodic health examinations were included. Exclusion criteria were: history of diabetes, hypertension, hyperlipidemia, thyroid or parathyroid

disorders, chronic liver disease, chronic kidney failure, febrile illnesses, pregnancy, and the use of medications or supplements that could affect Se levels (including Se or multivitamin supplementation). Participants with abnormal laboratory results were also excluded. Type 2 DM was diagnosed if the fasting plasma glucose was higher than 126 mg/dL, 2-h post-challenged plasma glucose was above 200 mg/dL, or HbA1c ≥6.5%. This was based on the recommendation of ADA (7).

Data Collection

Data were collected using a routine structured form, which included demographic information [age, sex, body mass index (BMI), smoking status], medical history (chronic diseases, medication use), and lifestyle characteristics. Anthropometric measurements (weight, height) were recorded. These data were obtained from outpatient follow-up records. BMI (kg/m²) was calculated as weight in kilograms divided by the square of height in meters, according to the World Health Organization definition (17). IR was calculated using HOMA-IR formula: fasting insulin (μU/mL)×fasting glucose (mg/dL)/405, as originally described by Matthews et al. (5).

Laboratory Measurements

Subjects were requested to visit the family medicine outpatient clinic for blood withdrawal after fasting overnight for ≥8 hours. At the screening visit, blood samples were collected for blood tests [among the laboratory data were Se, vitamin D, HOMA-IR, HbA1c, fasting blood glucose (FBG), urea, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), uric acid, albumin, protein total, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), calcium (Ca), sodium (Na), potassium (K), chloride (Cl), iron (Fe), ferritin, thyroid-stimulating hormone (TSH), C-reactive protein (CRP), sedimentation, white blood cell (WBC), red blood cell (RBC), platelet (PLT), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR)]. Venous blood samples taken after fasting were collected in a dipotassium ethylenediaminetetraacetic acid tube for complete blood counts (CBC) testing and in a vacuum tube for biochemical tests. Samples were transported at room temperature and analyzed within 1 h to minimize changes due to standing. After the vacuum tube was centrifuged at 2500×g for 10 minutes, the parameters included in the study were analyzed in the Medical Biochemistry Laboratory of Bezmialem University Hospital. Se was measured by inductively coupled plasma mass spectrometry (Acıbadem LabMED). Serum 25 (OH) D was measured by liquid chromatography-mass spectrometry method (Zivak 25 (OH) D2-D3 kit, Tandem Gold 325-MS model, USA). Levels of HbA1c (%) were measured quantitatively using immunoturbidimetry from whole blood (Archem Diagnostics HbA1c kit, Siemens Atellica® CH 930 analyzer). The glucose oxidase method was used to analyse plasma glucose levels (Siemens Atellica® CH 930 analyzer, Germany). Lipid profile and other biochemical parameters were measured using a chemical auto-analyzer (Siemens Atellica® CH 930 analyzer, Germany). Parameters of CBC were measured using an automated haematology analyser (Sysmex XN1000, Germany).

Ethical Considerations

The study received approval from the Bezmialem Vakıf University Clinical Research Ethics Committee (approval no: 2024/194, dated 31.05.2024). The study was registered under ClinicalTrials registration number: E-54022451-050.04-152508.

Statistical Analysis

Data were analyzed using SPSS® software for Window® version 22 (SPSS Inc., Chicago, IL, USA). Descriptive statistics for qualitative variables were presented as frequency (n) and percentage (%), while quantitative variables were summarized using mean, median, SD, minimum, and maximum values. The normality of quantitative variables was assessed using the Shapiro-Wilk test, and the Levene's test was employed to evaluate the homogeneity of variance. The differences between groups were compared using Student's t-test, chi-square tests, Spearman's correlation test, binary logistic regression and two steps cluster analysis. Data were expressed as mean and SD. The statistical significance was set at the p-value of ≤0.05.

Results

The mean age of the patients was 39.31±13.20 years. Of the patients 72% (n=116) were women. The mean of BMI was 25.83±4.81. The HOMA-IR value of the patients was above 2.5 in 57 patients. Forty-five patients had low Se levels (serum Se <63 μg/L). Among the laboratory data, urea, BUN, creatinine, eGFR, albumin, LDL-C, Ca, HCT, HGB were statistically significant between the groups. However, vitamin D and HOMA-IR values were statistically and clinically significantly different between the groups (p≤0.05) (Table 1).

Levels of Se was low in 40% of patients with IR. Levels of Se was low in 21% of patients with non-IR. The differences were significant (p=0.016) (Table 2).

Based on available HbA1c data after excluding missing values, the study population consisted of 141 participants. In Se group 1, mean age was found to be significantly lower than the mean age of group 2 (p=0.043). In Se group 1, mean vitamin D level was found to be significantly lower than mean vitamin D level of group 2 (p<0.001). In Se group 1 (Se median <70.63), mean urea level was found to be significantly lower than the mean urea level of group 2 (Se median ≥70.63) (p<0.001). In Se group 1, mean BUN level was found to be significantly lower than the mean BUN

Table 1. The comparison of results between patients Se-deficient and normal

	Se-deficient (Se <63 µg/L) n=45	Se-normal (Se ≥63 µg/L) n=116	p-value
Vitamin D (µg/L)	14.31±8.34	20.33±11.36	**0.001**
HOMA-IR	3.09±1.91	2.33±1.33	**0.006**
Urea (mg/dL)	23.46±5.88	27.64±5.73	**0.001**
BUN (mg/dL)	10.32±2.61	12.64±2.95	**0.001**
Creatinine (mg/dL)	0.72±0.15	0.78±0.16	**0.028**
eGFR (mL/min/1.73 m²)	108.21±13.73	100.72±18.55	**0.014**
Albumin (g/dL)	4.68±0.37	4.71±0.24	**0.001**
LDL-C (mg/dL)	110.32±35.54	123.65±35.23	**0.047**
Ca (mg/dL)	9.54±0.31	9.76±0.48	**0.042**
HCT (%)	39.93±3.32	41.38±3.92	**0.043**
HGB (g/dL)	13.24±1.41	13.62±1.68	**0.038**

Note 1: Vitamin D (20-70 µg/L) HOMA-IR (<2.5) urea (12.8-42.8 mg/dL) BUN (6-20 mg/dL) creatinine (0.6-1.3 mg/dL) eGFR (>90 mL/min/1.73 m²) albumin (3.5-5 g/dL) LDL-C (<100 mg/dL) Ca (8.3-10.6 mg/dL) HCT (male 40-52%, female 35.5-48%) HGB (male 14.1-17.5 g/dL, female 12.2-16.2 g/dL)
Note 2: Data are presented as mean ± standard deviation (SD)
HOMA-IR: Homeostasis model assessment of insulin resistance, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, LDL-C: Low-density lipoprotein cholesterol, Ca: Calcium, HCT: Hematocrit, HGB: Hemoglobin, Se: Selenium

Table 2. The comparison of Se levels between IR and non-IR groups

	IR group (HOMA-IR ≥2.5) n=57	Non-IR group (HOMA-IR <2.5) n=104	p-value
Se-deficient (Se <63 µg/L) n=45	23/57 (40%)	22/104 (21%)	**0.016**
Se-normal (Se ≥63 µg/L) n=116	34/57 (60%)	82/104 (79%)	

Note: Data are presented as percentages (%)
HOMA-IR: Homeostasis model assessment of insulin resistance, Se: Selenium

level of group 2 (p<0.001). In Se group 1, mean creatinine level was found to be significantly lower than the mean creatinine level of group 2 (p=0.006). In Se group 1, mean eGFR was found to be significantly higher than the mean eGFR of group 2 (p=0.002). In Se group 1, mean albumin level was found to be significantly lower than the mean albumin level of group 2 (p<0.001). In Se group 1, mean total protein level was found to be significantly lower than the mean total protein level of group (p=0.009). In Se group 1, mean LDL-C level was found to be significantly lower than the mean LDL-C level of group 2 (p=0.03). In Se group 1, mean Ca level was found to be significantly lower than the mean Ca level of group 2 (p=0.013). In Se group 1, mean ferritin level was found to be significantly lower than mean ferritin level of group 2 (p=0.013). Other significant differences are presented in Table 3.

When we evaluated Se levels according to median level which was 70.63 µg/L; prediabetic patients group had significantly lower Se level (p=0.026) (Table 4).

In the results of binary logistic regression analysis (chi-square value was 6.361, p-value was 0.607, the Nagelkerke R-square value: 0.570). Albumin level was found to have a strong relationship with Se level. Those with high albumin levels were more likely to have high Se levels (p=0.022, odds ratio: 64.728). Total protein level, which was very close to the significance limit, stood out as another variable that might affect Se levels (p=0.073). Other variables were not found to be statistically significant (p>0.05).

Additionally, cluster analysis was performed. The most influential variables in grouping patients with similar clinical characteristics into clusters were determined to be HCT, HGB, creatinine, RBC, age, ferritin, eGFR, BUN urea, and HbA1c (Figure 1).

A significant difference in Se levels was observed between the clusters obtained from the clustering analysis (p=0.023). As a conclusion of cluster analysis, individuals with low Se levels also tended to have significantly lower mean values in age, BUN, urea, creatinine, LDL-C, RBC, HGB, HCT, and ferritin levels (p<0.001). This pattern suggests a possible association between low Se status and reduced levels in these physiological and biochemical markers, which may reflect a shared underlying factor or biological mechanism influencing both Se and these variables.

Discussion

In this single-center outpatient sample of adult patients, we observed significant differences in serum Se, vitamin D, HOMA-IR, and HbA1c levels between the groups. Vitamin D levels were significantly lower, while HOMA-IR values were significantly higher, in the low serum Se group. The current study extends previous findings on the association between serum Se level, vitamin D level and IR.

International evidence suggests that serum Se concentrations in healthy populations are generally around or below the 80 µg/L threshold, and many populations do not consistently reach this level (18-20). In contrast, Karataş et al. reported a higher mean Se level of 85.81±10.84 µg/L in a control group of Turkish adults, although the overall mean in their study was lower (76.49±11.36 µg/L) (21). In our cohort, the mean serum Se level was 71.66±11.56 µg/L, representing one of the lowest values among the referenced studies. These differences may reflect regional variability in Se status, potentially related to soil composition, dietary patterns, and environmental availability.

The role of Se in the management of IR remains a subject of ongoing debate. Our findings are consistent with

Table 3. The comparison of results between selenium (Se) groups 1 and 2

	Se group 1 (Se median<70.63 µg/L) n=71	**Se group 2 (Se median ≥70.63 µg/L) n=70**	**p-value**
Age	36.60±13.04 34 (26-46)	40.29±12.58 41 (30-50)	**0.043**
BMI (kg/m²)	26.58±5.76 24.97 (22.7-30.66)	25.09±4.02 25.21 (22.85-27.24)	0.349
Vitamin D (µg/L)	15.87±8.47 14.34 (8.81-20.97)	21.67±12.61 18.60 (14.78-25.20)	**0.001**
HOMA-IR	2.58±1.72 1.87 (1.37-3.27)	2.24±1.12 2.08 (1.46-2.69)	0.734
HbA1c (%)	5.25±0.37 5.19 (5.03-5.49)	5.16±0.36 5.10 (4.88-5.42)	0.120
FBG (mg/dL)	92.49±10.82	91.31±8.81	0.463
Urea (mg/dL)	23.46±5.88 24 (19-28)	27.64±5.73 28 (24-30.50)	**0.001**
BUN (mg/dL)	10.96±2.74	12.88±2.66	**0.001**
Creatinine (mg/dL)	0.73±0.13 0.70 (0.64-0.79)	0.80±0.15 0.78 (0.68-0.89)	**0.006**
eGFR (mL/min/1.73 m²)	107.36±16.43 109 (96-120)	98.76±18.03 101 (92-109)	**0.002**
Uric acid (mg/dL)	4.58±1.29 4.4 (3.80-5.3)	4.88±1.35 4.85 (4-5.50)	0.163
Albumin (g/dL)	4.61±0.24 4.7 (4.50-4.80)	4.78±0.19 4.8 (4.70-4.90)	**0.001**
Protein total (g/dL)	7.33±0.37 7.30 (7.10-7.60)	7.48±0.32 7.45 (7.30-7.62)	**0.009**
TG (mg/dL)	108.75±62.23 90 (67-133)	112.96±57.99 98 (69.5-138)	0.347
HDL-C (mg/dL)	56.12±14.59 53.15 (47.05-66.52)	58.5±15.50 56.05 (49.07-67.77)	0.263
LDL-C (mg/dL)	109.93±35.86	127.10±33.81	**0.003**
ALT (U/L)	20.25±15.16 16 (13-23)	27.49±25.12 19.5 (13-30.25)	0.058
Ca (mg/dL)	9.60±0.31 9.60 (9.30-9.80)	9.74±0.38 9.80 (9.50-10)	**0.013**
Na (mmol/L)	139.14±1.93 139 (138-141)	139.44±1.88 139 (138-141)	0.522
K (mmol/L)	5.73±1.81 4.33 (4.15-5.75)	4.31±0.28 4.34 (4.15-4.50)	0.462
Cl (mmol/L)	104.73±2.47 104 (103.75-106.25)	104.12±2.20 104 (102-106)	0.114
Fe (µg/dL)	84.24±42.23 82 (53-112)	95.22±40.79 85 (69-124.75)	0.120
Ferritin (µg/L)	33.60±54.09 15.51 (6.48-42.01)	40.77±42.47 29.20 (12.21-50.47)	**0.013**
TSH (mIU/L)	2.43±1.91 2 (1.16-3)	2.38±1.43 2.02 (1.51-2.96)	0.703

Table 3. Continued

	Se group 1 (Se median<70.63 µg/L) n=71	Se group 2 (Se median ≥70.63 µg/L) n=70	p-value
CRP (mg/L)	2.07±2.80 0.96 (0.26-2.67)	2.15±3.77 0.54 (0.20-2.14)	0.187
Sedimentation (mm/h)	9.63±6.50 7 (4-14)	7.40±4.38 6 (4-10)	0.069

Note 1: BMI (18.5-24.9 kg/m²) vitamin D (20-70 µg/L) HOMA-IR (<2.5) HbA1c (<6.5%) FBG (70-105 mg/dL) urea (12.8-42.8 mg/dL) BUN (6-20 mg/dL) creatinine (0.6-1.3 mg/dL) eGFR (>90 mL/min/1.73 m²) uric acid (3.1-7.8 mg/dL) albumin (3.5-5 g/dL) protein total (5.7-8.2 g/dL) TG (<150 mg/dL) HDL-C (>40 mg/dL) LDL-C (<100 mg/dL) ALT (10-49 U/L) Ca (8.3-10.6 mg/dL) Na (135-145 mmol/L) K (3.5-5.1 mmol/L) Cl (98-107 mmol/L) Fe (50-170 µg/dL) Ferritin (22-322 µg/L) TSH (0.55-4.78 mIU/L) CRP (0-5 mg/L) sedimentation (0-20 mm/h)
Note 2: In the tables, normally distributed quantitative variables are presented as mean ± standard deviation, whereas non-normally distributed variables are presented as median (minimum-maximum) values
BMI: Body mass index, HOMA-IR: Homeostasis model assessment of insulin resistance, HbA1c: Glycated hemoglobin, FBG: Fasting blood glucose, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, ALT: Aminotransferase, Ca: Calcium, Na: Sodium, K: Potassium, Cl: Chloride, Fe: Iron, TSH: Thyroid-stimulating hormone, CRP: C-reactive protein

Table 4. The comparison of HbA1c levels between selenium (Se) groups 1 and 2

	Selenium group 1 (Se median <70.63 µg/L) n=71	Selenium group 2 (Se median ≥70.63 µg/L) n=70	p-value
Prediabetic (HbA1c ≥5.7-<6.5) n=14	11/71 (15%)	3/70 (4%)	**0.026**
Non-prediabetic (HbA1c <5.7) n=127	60/71 (85%)	67/70 (96%)	

Note: Data are presented as percentages (%), HbA1c: Glycated hemoglobin

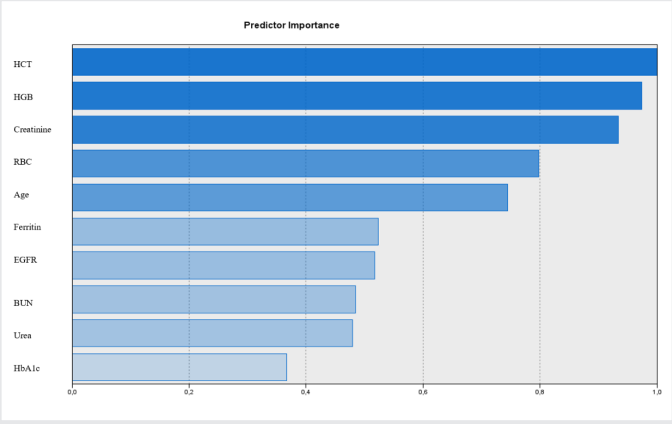

Figure 1. This figure shows the parameters selected for cluster analysis, including HCT, HGB, creatinine, RBC, age, ferritin, eGFR, BUN, urea, and HbA1c levels. These variables were chosen to explore potential associations among physiological and biochemical markers within the identified clusters

HCT: Hematocrit, HGB: Hemoglobin, RBC: Red blood cell, eGFR: Estimated glomerular filtration rate, BUN: Blood urea nitrogen, HbA1c: Glycated hemoglobin

previous studies, showing higher HOMA-IR and HbA1c levels in participants with lower serum Se concentrations (22-24). This observation supports the hypothesis that Se deficiency may be associated with poorer glycemic control. However, while observational evidence suggests an inverse association between Se levels and diabetes prevalence, causality remains uncertain. Further randomized controlled trials are needed to clarify whether Se supplementation may have a role in the prevention or management of diabetes. In addition, variability in baseline Se levels across populations underscores the need to further investigate potential regional and genetic factors influencing Se metabolism and its effects on glucose regulation.

A plausible biological mechanism underlying the inverse association between serum Se levels and IR may involve its effect on GPx activity. GPx contributes to cellular redox balance by reducing hydrogen peroxide (H_2O_2), and lower intracellular H_2O_2 levels may be associated with reduced activity of protein tyrosine phosphatase 1B (PTP1B). This, in turn, may support insulin receptor signaling and improve insulin sensitivity (25-27). However, findings in the literature are inconsistent. Some studies have reported positive associations between higher serum Se levels and increased risk of elevated fasting glucose or prediabetes (28-32). One possible explanation is the link between Se and obesity-related processes, including adipose tissue expansion, chronic inflammation, and oxidative stress (33). Through selenoproteins such as GPx, selenoprotein P (SEPP), and others, Se may influence insulin signaling in hepatic and muscle tissues (34). In particular, elevated Se and SEPP levels have been associated with prediabetes markers, potentially through effects on insulin signaling pathways, including altered phosphorylation of protein kinase B and partial inhibition of AMP-activated protein kinase (35,36). Nevertheless, other studies have found no significant association between serum Se levels and glucose metabolism or IR (37,38).

The relationship between Se and prediabetes in both animal and human studies remains ambiguous, primarily due to conflicting findings reported in the literature. Some studies have indicated positive associations, while others have observed negative associations or no

significant relationships. This inconsistency may stem from several factors, including a potential U-shaped relationship between Se levels and prediabetes, variations in epidemiological research methodologies, differences in sample sizes, the use of diverse biomarkers for Se, and the presence of single nucleotide polymorphisms in genes encoding selenoproteins.

Studies have shown that vitamin D deficiency is associated with an increased risk of IR and prediabetes. Most studies examining minerals and trace elements in relation to IR and diabetes have focused on these components independently (14,16). However, the present study evaluates vitamin D and Se deficiencies concurrently, which may provide insight into their combined roles and potential interactions in metabolic health and IR.

The synergistic roles of Se and vitamin D in relation to IR and metabolic health may be related to their complementary mechanisms. Se's antioxidant properties may help protect pancreatic β-cells and support redox balance, which may be associated with reduced oxidative stress-related IR (9). Vitamin D, through its receptor in β-cells and glucose-metabolizing tissues, may contribute to insulin secretion and sensitivity by modulating Ca signaling and inflammatory pathways (14). Combined, optimal levels of these micronutrients may support metabolic pathways, reducing IR risk and associated conditions. Further research into their combined supplementation is warranted.

Study Limitations

This study has several limitations. First, its single-center, retrospective, cross-sectional design did not allow for the determination of causal relationships between Se concentrations and IR. Furthermore, crucial data on dietary habits, living environment, ethnicity, and medication use (including vitamins, trace element supplements, and diuretics) were not collected, which may have affected the findings. In particular, the absence of data on dietary intake and sunlight exposure—both of which can significantly influence vitamin D levels—may have confounded the observed associations. Additionally, selenoproteins, which are critical indicators of Se function in the human body, were not measured. Using only HOMA-IR to assess IR was also limiting. A limitation of this study was the incomplete availability of HbA1c data. Although HOMA-IR was measured in all participants, HbA1c testing was performed only when clinically indicated during routine follow-up for glycemic control, resulting in available data for 141 individuals. This selective measurement might introduce selection bias and limit the generalizability of HbA1c-related findings. Including insulin-independent IR markers would strengthen the study, and this point could be suggested for future research. Future studies should aim to measure the concentrations or activities of multiple selenoproteins to validate the observed association between Se and prediabetes.

Conclusion

In conclusion, recent findings suggest a synergistic relationship between Se and vitamin D in relation to IR. Both micronutrients are essential for metabolic health, and deficiencies in either have been associated with an increased risk of IR and type 2 DM. In our study, we observed that lower vitamin D and Se levels were associated with elevated IR, further suggesting the potential relevance of adequate levels of both vitamin D and Se in metabolic regulation. These results may indicate that addressing deficiencies in these micronutrients could be associated with improved insulin sensitivity and metabolic health.

Ethics

Ethics Committee Approval: The study received approval from the Bezmialem Vakıf University Clinical Research Ethics Committee (approval no: 2024/194, dated 31.05.2024).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Concept: Z.İ.Y.S., Design: Z.İ.Y.S., Data Collection or Processing: Z.İ.Y.S., Analysis or Interpretation: Z.İ.Y.S., A.Ö., Literature Search: Z.İ.Y.S., Writing: Z.İ.Y.S.

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