RESEARCH ARTICLE/ARAŞTIRMA MAKALESİ

Relationship Between Insulin Resistance and Vitamin D Deficiency with Blood Parameters

İnsülin Direnci ve Vitamin D Eksikliğinin Kan Parametreleriyle İlişkisi

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Abstract

Aim	It was aimed to investigate HOMA-IR and vitamin D levels in patients complaining of weight gain and to determine the relationship between other parameters measured in the blood and insulin resistance and vitamin D.
Materials and Methods	A total of 99 individuals, 74 women and 25 men, were included in the study. Fasting glucose and insulin, cholesterol, complete blood count, aspartate/alanine transaminase, thyroid stimulating hormone and 25-OH D levels were studied. Two separate groups were created in the study.HOMA IR was calculated; those ≥ 2.5 and above were placed in the insulin resistance group, while those < 2.5 were included in the non-insulin resistance group. In the vitamin D classification, those with 25 OH D < 20 were categorized as deficient, and those with ≥ 20 OH D were classified as sufficient. The correlation of the groups with blood parameters regarding these classificationswas identified.
Results	Body Mass Index, Alanine Transaminase, Triglycerides, Ferritin, Fasting Glucose, Insulin, Hemoglobine and Hematocrit values were significantly higher in Insulin Resistance group, while High Density Cholesterol values were lower ($p < 0.05$). Positive correlation was noticed between HOMA-IR and Mean Platelet Volume ($p=0.289$; $p=0.04$). Body Mass Index was significantly higher ($p=0.05$) and a significant negative correlation was observed with Fasting Glucose ($r=-0.274$; $p=0.013$) and Thyroid Stimulating Hormone ($r=-0.263$; $p=0.018$) in VitD deficiency group.
Conclusion	Body mass index was higher in both groups with HOMA-IR ≥ 2.5 and 25 OH D <20. However, while HOMA IR was positively related to Mean Platelet Volume , 25 OH D was negatively associated with Fasting Glucose and Thyroid Stimulating Hormone.
Keywords	HOMA-IR, vitamin D, fasting glucose, MPV, TSH

Özet

Amaç	Kilo alma şikayetiyle başvuran hastalarda HOMA-IR ve D vitamini düzeylerinin araştırılması ve kanda ölçülen diğer parametreler ile insulin direnci ve D vitamini arasındaki ilişkinin belirlenmesi amaçlanmıştır.
Gereç ve Yöntemler	Çalışmaya 74 kadın ve 25 erkek olmak üzere toplam 99 kişi dahil edilmiştir. Tetkik olarak açlık glukoz ve insulin, kolesteroller, tam kan sayımı, aspartat/alanin transaminaz, tiroid stimülan hormon,25-OH D düzeyleri çalışıldı.Çalışmada 2 farklı grup oluşturuldu. HOMA IR hesaplanarak ; ≥ 2.5 ve üzeri insulin direnci grubuna alınırken, < 2,5 olanlar ise insulin direnci olmayan gruba alındı. D vitamini sınıflandırmasında ise 25 OH D < 20 olanlar eksiklik, 20 ≥ 25 OH D olanlar yeterli olarak sınıflandırıldı. Grupların bu sınıflandırmalara ilişkin kan parametreleri ile korelasyonu belirlenmiştir.
Bulgular	Vücut kitle indeksi, Alanin Transaminaz, Trigliserid, Ferritin, Açlık Glukozu, İnsülin, Hemoglobin ve Hematokrit değerleri insülin direnci grubunda anlamlı olarak daha yüksekken, yüksek yoğunluklu kolesterol değerleri daha düşüktü ($p < 0.05$).HOMA-IR ile ortalama trombosit hacmi arasında pozitif korelasyon görüldü ($p=0.289$; $p=0.04$). VitD eksikliği grubunda vücut kitle indeksi anlamlı derecede yüksekti ($p=0.05$) ve açlık glukozu ($r=-0,274$; $p=0,013$) ve tiroid uyarıcı hormon ($r=-0,263$; $p=0,018$) ile anlamlı negatif korelasyon gözlendi.
Sonuç	HOMA-IR ≥ 2,5 ve 25 OH D <20 olan her iki grupta vücut kitle indeksi daha yüksek bulundu. Bununla birlikte, HOMA IR ortalama trombosit hacmi ile pozitif ilişkili iken, 25 OH D açlık glukozu ve tiroid stimülan hormon ile negatif ilişkili bulunmuştur.
Anahtar Kelimeler	HOMA IR, vitamin D, açlık glukoz, MPV, TSH

INTRODUCTION

Insulin is an anabolic hormone that regulates carbohydrate, fat and protein metabolism, released from the beta cells of the pancreas. It increases glucose uptake in muscles and glycogen synthesis in the liver, while suppressing lipolysis in adipose tissue(1). Insulin resistance (IR) is a complex process in which target tissues such as liver, muscle and fat tissue do not respond adequately despite high insulin levels (2). Obesity and high-fat diet worsen IR (3). It predisposes to metabolic syndrome, atherosclerosis, type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver diseases (2). Chronic hyperinsulinemia, which occurs with high IR, initially maintains plasma glucose levels, but if this resistance continues, dysfunction in Beta cells occurs over time, leading to hyperglycemia and T2DM(4). The gold standard method used to evaluate IR is the Homeostasis Model Assessment (HOMA-IR)(5).

The relationship of IR with various biochemical parameters and vitamin D (VitD) level has been demonstrated in previous studies. It is known that increased HOMA-IR in overweight or obese individuals increases liver enzymes and is linked with the risk of hepatosteasis (6,7). A relationship was found between liver enzymes and HOMA-IR in individuals with T2DM (8).In particular, there is a relationship between increased alanine transaminase (alt) levels and high IR(9).

Vitamin D is a secosteroid that regulates and supports musculoskeletal system functions by regulating calcium and phosphorus metabolism. However, its deficiency not only negatively affects the musculoskeletal system, but also may be related toIR and obesity/metabolic syndrome (10). Cohort studies have depicted an association between 25(OH) D levels and glucose intolerance, IR, metabolic syndrome and T2DM (11,12,13). It is also known that VitD levels are inversely proportional to insulin sensitivity (14) and are at lower levels in obese individuals than in lean individuals (15).

The aim of the present study was to investigate 25(OH)D levels and IR in patients with no known disease who applied to the Internal Medicine outpatient clinic with complaints of weight gain and to determine their correlation with routine blood parameters.

MATERIALS AND METHODS

This present research was conducted prospectively between January and March 2021 on patients who applied to Kırşehir Training and Research Hospital with complaints of weight gain. A total of 99 patients participated to the research. Participants' age, gender and BMI (Height/kg(m2)) measurements were recorded. Body Mass Index (BMI) was obtained by dividing body weight in kg by the square of height in metres.Following 8-10 hours of fasting, blood samples were taken from the cubital vein.Fasting blood glucose (fpg) , fasting insulin, cholesterols, aspartate transaminase (ast), alanine trans aminase (alt), thyroid stimulating hormone (tsh), white blood cell (wbc), hemoglobin (hbg), hematocrit (hct), platelet (plt), mean platelet volume (mpv), ferritin and 25(OH) D levels were studied from these samples.

The tests obtained from biochemistry were taken into anti-coagulant-free gel tubes and centrifuged for 10 minutes after clotting. Complete blood count (CBC) was performed from the blood samples taken into K2 EDTA tubes. The results of all samples were obtained on the auto analyzer in the laboratory (AU5840; Beckman Coulter, Calif., USA).

HOMA-IR was calculated with the formula Fasting Glucose(mg/dl) * Fasting serum Insulin(μIU/mL)/405(16). Those with HOMA IR ≥ 2.5 were categorized into the IR group, while those with HOMA IR<2.5 were categorized into the non-IR group. Vit D classification was made as follows: Deficiency: 25(OH) D < 20 nmol/L, Normal: 25(OH) D ≥20 nmol/L. Correlations with the blood tests obtained in both groups were examined.

T2DM, hypertension (HT), metabolic syndrome, coronary artery disease (CAD), acute or chronic infection, presence of malignancy and toxic hypervitaminosis d (>150 nmol/L) were ruled out from the study.

Statistical Analysis

Mean ± standard deviation, median [minimum – maximum] were reported as descriptive statistics. Shapiro-Wilk Test was used to assess normality assumption. In group comparisons, t-test, and Mann-Whitney U Test were performed depending on normality assumption. The association between 25(OH) D and other biochemical parameters was evaluated via Pearson and Spearman Correlation coefficients. Two-sided p≤0.05 was taken statistically significant. SPSS v.21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used in all analyses.

RESULTS

The mean age in the total sample was 35.545±12.498 years, 33.581±1.81 years in women and 41.360±12.9 years in men (p=0.006). It consisted of 25.3% (n=25) men and 74.7% (n=74.7) women.

A significant difference was found between the two groups in terms of ALT (p=0.002), TG (p=0.024), HDL (p=0.043), Ferritin (p=0.008), Fbg (p=0.001), insulin (p<0.001), HBG (p=0.011) and HCT (p=0.025) values. While HDL values were observed to be higher in those without IR, higher values were recorded in those with IR for all remaining parameters (Table 1).

Table 1. Group comparison between demographic data and blood parameters of the groups according to HOMA IR

Parameter	Non-IR (n=48)	IR (n=51)	p-value
Age	**36.521 ± 9.446**	**34.627 ± 14.849**	**0.448**
Gender (M/F)	**10/38 (20.8 /79.2)**	**15/36 (29.4/70.6)**	**0.362**
BMI (kg/M²)	31.869 ± 5.048	33.695 ± 4.921	**0.038**
Fbg(mg/dL)	89.48 ± 7.833	96.37 ± 12.229	**0.001**
Insulin(IU/mL)	8.29 ± 2.123	19.25 ± 10.06	**<0.001**
25-OH D(ng/mL)	14.44 ± 6.919	12.51 ± 7.061	0.174
Tsh(IU/mL)	2.0856 ± 1.087	2.0276 ± 3.033	0.799
Total Cholesterol (mg/dl)	187.38 ± 38.084	188.84 ± 0.412	0.841
LDL(mg/dl)	111.02 ± 33.443	107.61 ± 34.761	0.591
HDL(mg/dl)	56.44 ± 39.917	47.75 ± 12.288	**0.043**
TG(mg/dl)	125.1 ± 66.69	178.59 ± 143.092	**0.024**
Wbc(10³/µL)	7.5938 ± 1.934	7.7776 ± 29.487	0.632
Hbg(gr/dL)	13.638 ± 1.696	14.484 ± 1.871	**0.011**
Hct(%)	41.813 ± 4.409	43.692 ± 1.696	**0.025**
Plt(10³/µL)	288.67 ± 62.423	297.67 ± 66.678	0.49
Mpv(fL)	10.529 ± 0.86	10.302 ± 0.742	0.162
Ast (U/L)	19.62 ± 6.743	20.04 ± 6.292	0.494
Alt(U/L)	17.96 ± 8.914	24.34 ± 13.566	**0.002**
Ferritin (ng/mL)	19 [3 – 234]	33 [4 – 258]	**0.008**

HOMA-IR: Insulin Resistance Hemostasis Model, M:Male, F:Female, kg:kilograms, mg:miligram, dL: decilitre , IU; International Unit , µL : microlitre ,fL:Fentalitre, ng:nanogram ,BMI: Body Mass Index, FBG: Fasting Blood Glucose, TSH: Thyroid Stimulating Hormone, T.KOL: Total Cholesterol, LDL: Low Density Cholesterol, HDL: High Density Cholesterol, TG: Triglyceride, WBC: White Blood Cell, HBG: Hemoglobin, HCT: Hematocrit, PLT: Platelet, MPV: Mean Platelet Volume, AST: Aspartate Transaminase, ALT: Alanine Transaminase.

In the IR group; a positive correlation was recorded between HOMA-IR level and insulin (r=0.980; p<0.001) and MPV (r=0.289; p=0.04) (Table 2). However, there was no significant correlation between other blood parameters and HOMA-IR (Table 2).

Table 2. Correlation findings between HOMA IR and blood tests in the group with HOMA IR≥2.5

Variables	HOMA-IR
Fbg(mg/dL)	0.266 (0.059)
Insulin(IU/mL)	**0.980 (<0.001)**
25-OH D(ng/mL)	-0.211 (0.137)
Tsh(IU/mL)	0.028 (0.847)
Total Cholesterol (mg/dl)	0.007 (0.961)
LDL(mg/dl)	0.066 (0.643)
HDL(mg/dl)	0.013 (0.930)
TG(mg/dl)	0.141 (0.324)
Wbc(10³/µL)	-0.139 (0.330)
Hbg(gr/dL)	-0.149 (0.298)
Hct(%)	-0.067 (0.642)
Plt(10³/µL)	0.153 (0.285)
Mpv(fL)	**0.289 (0.04)**
Ast (U/L)	0.102 (0.481)
Alt(U/L)	0.206 (0.152)
Ferritin (ng/mL)	-0.118 (0.415)

HOMA-IR: Insulin Resistance Hemostasis Model, M:Male, F:Female, kg:kilograms, mg:miligram, dL: decilitre, IU; International Unit, µL : microlitre, fL:Fentalitre, ng:nanogram, BMI: Body Mass Index, FBG: Fasting Blood Glucose, TSH: Thyroid Stimulating Hormone, T.KOL: Total Cholesterol, LDL: Low Density Cholesterol, HDL: High Density Cholesterol, TG: Triglyceride, WBC: White Blood Cell, HBG: Hemoglobin, HCT: Hematocrit, PLT: Platelet, MPV: Mean Platelet Volume, AST: Aspartate Transaminase, ALT: Alanine Transaminase.

BMI values were higher in the Vit D Deficiency group (p = 0.05). In addition, AST values were significantly higher in the Normal Vit D group (p=0.05) (Table 3).

In the vitamin D deficiency group; there was a negative correlation between 25 OH-D values and TSH (r=-0.263; p=0.018) and fbg (r=-0.274; p=0.013). As 25 OH-D decreased, FBG and TSH levels increased (Table 4). Any significant correlation was reported between other parameters and Vit D (Table 4).

Table 3. Comparison of demographic variables and blood values of the groups in terms of vitamin D deficiency classification

Parameter	Deficient 25 OH D < 20 (n=81)	Normal 25(OH) D ≥20 (n=18)	p-value
Age	35.519 ± 13.467	35.667 ± 6.851	0.964
Gender (M/F) (%)	21/60 (25.9/74.1)	4/14 (22.2/77.8)	0.744
BMI (kg/M²)	33.272 ± 5.274	30.728 ± 3.165	**0.050**
Fbg (mg/dL)	93.23 ± 11.649	92.11 ± 6.239	0.693
Insulin (IU/mL)	14.47 ± 9.739	11.56 ± 5.586	0.225
HOMA-IR	3.373 ± 2.456	2.617 ± 1.254	0.208
Tsh(IU/mL)	2.083 ± 1.166	1.932 ± 0.940	0.609
Ast (U/L)	18 [11 - 47]	20.5 [14 - 39]	**0.050**
Alt(U/L)	20.32 ± 10.585	26.25 ± 16.874	0.07
Total Cholesterol (mg/dl)	185.33 ± 35.941	200.72 ± 35.816	0.103
LDL(mg/dl)	107.41 ± 30.161	117.61 ± 35.989	0.213
HDL(mg/dl)	47 [26 - 86]	46 [31 - 81]	0.614
TG(mg/dl)	122 [51 – 945]	136,5 [25 – 442]	0.700
Wbc(10^3/µL)	7.813 ± 1.912	7.13 ± 1.752	0.168
Hbg(gr/dL)	14.116 ± 1.647	13.883 ±1.849	0.597
Hct(%)	42.860 ± 4.07	42.422 ± 4.811	0.690
Plt(10^3/µL)	295.63 ± 65.471	282.83 ± 60.448	0.449
Mpv(fL)	10.472 ± 0.784	10.144 ± 0.870	0.119
Ferritin (ng/mL)	51.4 ± 61.082	51.78 ± 69.775	0.982

HOMA-IR: Insulin Resistance Hemostasis Model, M:Male, F:Female, kg:kilograms, mg:miligram, dL: decilitre, IU; International Unit, µL : microlitre, fL:Fentalitre, ng:nanogram, BMI: Body Mass Index, FBG: Fasting Blood Glucose, TSH: Thyroid Stimulating Hormone, T.KOL: Total Cholesterol, LDL: Low Density Cholesterol, HDL: High Density Cholesterol, TG: Triglyceride, WBC: White Blood Cell, HBG: Hemoglobin, HCT: Hematocrit, PLT: Platelet, MPV: Mean Platelet Volume, AST: Aspartate Transaminase, ALT: Alanine Transaminase.

Table 4. Correlation analysis findings between VitD and blood parameters in the deficient VitD group.

Parameter	25 OH D
Fbg (mg/dL)	**-0.274 (0.013)**
Tsh (IU/mL)	**-0.263 (0.018)**
Insulin(IU/mL)	-0.182 (0.104)
HOMA-IR	-0.238 (0.032)
Ast (U/L)	-0.026 (0.821)
Alt(U/L)	0.005 (0.966)
T.Chol(mg/dl)	0.077 (0.494)
LDL(mg/dl)	0.141 (0.211)
HDL(mg/dl)	0.026 (0.817)
TG(mg/dl)	-0.183 (0.102)
Wbc(10^3/µL)	-0.123 (0.272)
Hbg(gr/dL)	0.097 (0.388)
Hct(%)	0.113 (0.317)
Plt(10^3/µL)	-0.118 (0.293)
Mpv(fL)	0.069 (0.543)
Ferritin (ng/mL)	-0.136 (0.228)

HOMA-IR: Insulin Resistance Hemostasis Model, M:Male, F:Female, kg:kilograms, mg:miligram, dL: decilitre, IU; International Unit, µL : microlitre, fL:Fentalitre, ng:nanogram, BMI: Body Mass Index, FBG: Fasting Blood Glucose, TSH: Thyroid Stimulating Hormone, T.KOL: Total Cholesterol, LDL: Low Density Cholesterol, HDL: High Density Cholesterol, TG: Triglyceride, WBC: White Blood Cell, HBG: Hemoglobin, HCT: Hematocrit, PLT: Platelet, MPV: Mean Platelet Volume, AST: Aspartate Transaminase, ALT: Alanine Transaminase.

DISCUSSION

FBG, TG, Alt, Hbg, Hct, Ferritin levels were higher in IR group, while HDL levels were lower in this study. Additionally, there was a positive correlation only between HOMA-IR and MPV. Previous researches have pointed out that IR is closely related to impaired fasting glucose and the development of T2DM (17,18). At the same time, abnormal body fat distribution and lipid anomalies worsen the development and progression of IR(19). Insulin prevents lipolysis by monitoring lipoprotein lipase activity, but when resistance to the effect of insulin develops, the inhibition on lipolysis is removed and TRG synthesis increases (20). However, the synthesis of fatty acids in the liver increases, the inhibition of ApoA-I expression, which is necessary for HDL synthesis, decreases and a decrease in HDL levels occurs(21). Boursier et al. emphasized that TRG and glycosylated Hb (HbA1C) parameters are widely used in the screening of IR in obese patients (22).

Insulin and Insulin-like growth factor-1 (IGF-1) are effective in hematopoiesis and serve as cofactors in the increase of erythrocytic series. Accordingly, it causes an increase in red blood cells and hematocrit, which also causes an increase in blood viscosity(23,24).In a cohort study by Ferreira et al., they showed that IR in young adults led to an increase in red blood cells and hematocrit(25). Serum ferritin level is a marker reflecting iron stores in the body and has also been shown in epidemiological studies to be related toIR (26).Nakamura et al. noted the presence of higher serum ferritin levels in groups with an increase in HOMA-IR in a normoglycemic Japanese male population(27).

Liver enzymes, especially alt, have important relationships with IR(28,9).Liu et al reported that ALT, AST, and GGT enzymes increased with increased IR and were an important risk factor for hepatostatosis/steatohepatitis in Chinese people without diabetes. Additionally the relationship between ALT and GGT and HOMA-IR was emphasized as stronger than AST in this study (29). Parrinello et al also found significant relationships between BMI and HOMA IR and liver enzymes in Latino/Hispanic population (30).

In our study, it is a remarkable result that the increase in HOMA-IR caused an increase in MPV ($r = 0.289$; $p = 0.04$).MPV refers to mean platelet volume, and higher levels reflect increased platelet production, activation, and aggregation (31). A possible mechanism is that insulin, through its growth hormone-like effects, causes an increase in megakaryocytes in the bone marrow, leading to an increase in MPV (32).MPV increases in the presence of metabolic syndrome, diabetes mellitus and IR and has a positive correlation with HOMA-IR, as previous research was pointed out (33).Varol et al. indicated that MPV levels were higher in non-diabetic, non-obese patients compared to the control group and had a positive relationship with HOMA-IR (34).

This current research's findings demonstrsted that as the Vit D level decreases, fasting glucose and TSH levels increase according to the 25-OH D classification ($p<0.05$), and BMI was also higher in the deficient group.This result suggests that Vit D deficiency may be linked to obesity, diabetes mellitus and hypotrophy.According to the literature, Vit D has the crucial role in the pathogenesis of T2DM and has a positive relationship with beta cell functions and insulin sensitivity (11). The association of Vit D deficiency with impaired fasting glucose and liver fibrosis was shown in a cross-sectional research by Zuluaga et al (35).VitD can affect glucose metabolism through anti-inflammatory and immunomodulation (36, 37).Vit D deficiency, low-grade chronic inflammation associated with IR and increased parathyroid hormone (PTH) levels that reduce insulin secretion have been shown (37).Several studies indicate that vit D deficiency increases the risk of developing obesity, T2DM, hypertension, dyslipidemia and IR (38).The reduced effects of Vit D deficiency on immune modulation also contribute to the pathogenesis of hypothyroidism (39).Shimmi et al.showed vit D deficiency and iron deficiency in women with hypothyroidism (39).However, some researchers have documented the relationship between hypovitamin D and hypothyroidism (40,41), and pointed out the presence of a significant negative correlation between Vit D and TSH (39,42,43). In our study, HOMA-IR level was higher in deficient VitD group compared to normal VitD, but it was not statistically significant. Small sample size could be listed as the reason for this circumstance.

CONCLUSION

HOMA-IR and VitD deficiency have significant effects on some blood parameters. BMI was higher in both groups in IR and VitD deficiency compared to the control groups. However, while HOMA-IR was positively related to MPV, 25 OH D was negatively associated with Fasting Glucose and TSH. Along with increased HOMA-IR, Hbg/Hct/Ferritin levels and dyslipidemia increase. Our study showed that insulin resistance and vitamin D deficiency have multifaceted and similar effects on metabolic changes.

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Conflicts of interest

There are no conflicts of interest.

Availability of data and materials

The corresponding author will provide any information about the data presented in the article when requested.

Ethical Confirmation

Ethical approval was received from Kırşehir Ahi Evran University Faculty of Medicine Ethics committee (Ethics number: 2020-17/125).

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