Iraqi Journal of Pharmacy 21(4) (2024) 162-170

Online ISSN: 2664-2522

Print ISSN: 1680-2594

Iraqi Journal of Pharmacy

Journal homepage: https://iphr.mosuljournals.com

Research Article:

Vitamin D Levels Aptly Sustained Insulin Resistance Markers

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Article Information

Article history:
Received on: 15 July 2024
Revised on: 19 August 2024
Accepted on: 22 August 2024
Published on: 01 December 2024

Keywords:
Insulin,
Vitamin D,
Lipid profile,
Diabetes,
Metabolic syndrome,
Obesity.

Abstract

Background: Insulin resistance is the underlying etiology for a variety of metabolic diseases including metabolic syndrome, type 2 diabetes, and obesity, alongside with their complication. The insulin resistance mechanism is complex and yet obscure. Vitamin D is a fundamental parameter involved in various ailments. We aimed to identify the link between vitamin D levels and glycemic/lipid parameters using patients with different metabolic diseases as a model. **Methods:** Serum samples were collected from patients with diabetes (n=20), metabolic syndrome (n=20), and obesity (n=15) versus the control group (n=18) with matched age, sex, and health status. Vitamin D and insulin were quantified by colorimetric technique and the total cholesterol (TC), triglyceride (TG), high density-lipoprotein (HDL) were measured in the studied groups using standard kits. Low density-lipoprotein (LDL), very low-density lipoprotein, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were calculated using standard formula. **Results:** The study found that insulin and vitamin D levels were significantly lower in diabetic [18.7±2.2, 16.5±4.4], metabolic syndrome [23.6±1.6, 18.6±3.4], and obese patients [15±1.9, 14.1±4.8] compared to the control group [9.8±4, 25±5.1]. Serum TC levels were higher in metabolic syndrome and obese subjects compared to control and diabetic subjects, TG levels were significantly higher in metabolic syndrome compared to the other groups, HDL levels were reduced in diabetic, metabolic syndrome, and obese groups compared to the control group, LDL levels were elevated in metabolic syndrome and obese groups compared to diabetic and control groups, VLDL levels were significantly higher in metabolic syndrome than in other groups. **Conclusion:** Vitamin D reduced in metabolic diseases reciprocally aligned with insulin level and associated with variation in lipid parameters.

1. Introduction

The rate of type 2 diabetes mellitus (T2DM) is hastily escalating, both nationwide and worldwide (1,2), with the exact cause obscure (3,4). Researchers referred to multiple factors, including damage in pancreatic β-cell function, insulin hyposensitivity, and systemic immune response (5-9). The deficit in insulin sensitivity is a fundamental factor, being crucial to comprehend how lifestyle modalities, like diet, exercise, and even alcohol consumption and smoking, can impact the development of T2DM (10,11). Recent studies have shed light on a potential conjoin between insulin hyposensitivity and vitamin D deficiency (12-15). Vitamin D may play a key role in the pathogenesis of diabetes. Preclinical and clinical studies have shown that vitamin D can affect pancreatic β-cells and insulin hyposensitivity, steering to an emergent attention to its potential as a therapeutic approach for curing insulin hyposensitivity (13-15). Metabolic syndrome is a clustering of at least three of the following five medical conditions: abdominal obesity, high blood pressure, high blood sugar,

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How to cite:
Ismail, F., K., Alnori, M., KJ., Ajeel, M., A.,Razak, A., A., (2024). Vitamin D Levels Aptly Sustained Insulin Resistance Markers. Iraqi J. Pharm. 21(4), 162-170.

DOI: https://doi.org/10.33899/iraqij.p.2024.151925.1108

high serum triglycerides, and low serum high density-lipoprotein (4).

The latest findings have conjoined vitamin D deficiency to a broad range of health issues, including cancer, autoimmune disorders and metabolic ailments, such as, type 1 and T2DM (16-18). More than 50% of the general population is at risk for vitamin D deficiency (19). vitamin D deficiency is marked when subjects have a serum 25-hydroxyvitamin D level lower than 50 nmol/L (20-23). A meta-analysis of 28 studies revealed a strong connection between vitamin D levels and cardiometabolic disorders, including a 55% decrease in the risk of diabetes, a 33% decrease in the risk of cardiovascular diseases, and a 51% decrease in the risk of metabolic syndrome associated with high levels of 25-dihydroxyvitamin D (24). The etiology of low vitamin D and associated metabolic diseases have been associated with insulin resistance leading to lipid andglycemic abnormalities (16-24). The present study sought to identify the association of metabolic markers with declined vitamin D levels in diabetic, metabolic syndrome, and obese subjects.

2. Materials and Methods

2.1. Study design and settings

The study is a prospective cross-sectional study, commenced on September 2023 to March 2024, the study recruited the patients from outpatient private clinics and teaching hospitals (Mosul City, Iraq). Referred patients were either allocated to control group (n=18), or diabetic (n=20), or metabolic syndrome (n=20), or obesity (n=15) groups, after being diagnosed by a specialist endocrinologist. Those patients with thyroid diseases, cancer, pregnancy, and lactation were excluded.

2.2. Blood collection

A 10 ml venous blood sample was collected and the serum was separated, aliquoted (50 µl each), and frozen to measure the biochemical parameters

2.3. Biochemical parameters

The serum lipid profile, vitamin D, insulin, and glucose were measured using kit supplied by Mindray (USA). As per the manufacturers instruction, the serum samples were used to measure these biochemical parameters based on the colorimetric principle and extrapolated against the standard for quantification (1-4). The measured lipid parameters include serum total cholesterol (TC), triglyceride (TG), and high- density lipoprotein (HDL) (16-18). Low-density lipoprotein (LDL) was calculated using the equation below:

LDL= TC – HDL – (TG/2.2)

While very low-density lipoprotein (VLDL) is calculated using the equation below:

VLDL = TG/5

Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) is calculated based on the following equation:

HOMA-IR = glucose (mg/dL) × insulin (mU/L)/405

2.4. Statistical analysis

Analysis was conducted using GraphPad Prism (Prism 8) data expressed as mean ± SD. One-way ANOVA was conducted to check for differences between groups and followed by a series of t-test to identify the differences between each group and the other. The differences were considered significant at p value less than 0.05. Pearson correlation (r) were conducted between vitamin D and other biochemical parameters to check correlations.

3. Results

Patients demographic factors closely matched with control regarding age and sex with no significant differences between the groups. Regarding body mass index (BMI), obesity group is significantly higher than other groups, while metabolic syndrome group is significantly higher than diabetic patients with control being the lowest (**Table 1**).

Table 1. Demographic parameters of the studied group.

Groups	Control (n=18)	DM (n=20)	MS (n=20)	Obesity (n=15)	p value	Chi-square
Age	49.8±4	49±4	47.9±6	48.5±3	0.8	
Sex (M/F)	9/9	12/8	12/8	5/10	0.37	3.14
BMI (kg/m^2)	24.5±0.7	26.7±1	31.4±2	36.6±1.6	0.001	
Duration of diseases (Years)	….	10	11	7		….

Analysis of results revealed that the concentration of vitamin D in diabetic group [16.5±4.4], metabolic syndrome [18.6±3.4], and obesity [14.1±4.8] were significantly (p<0.05) lower than that of the control group [25±5.1], with non-significant differences existed between the patients groups. The serum concentration of insulin was significantly lower in the control group [9.8±4] compared to diabetic [18.7±2.2], metabolic syndrome [23.6±1.6], and obesity [15±1.9]. Insulin level is the highest in the metabolic syndrome group compared to diabetic or obese subjects with non-significant differences existing between diabetic or obese groups (**Figure 1**).

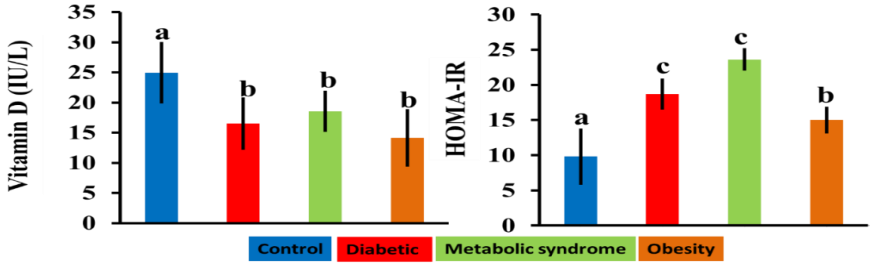

Figure 1. Vitamin D and Insulin level in studied groups. Data expressed as mean ± SD. Different letters express significant differences at p<0.05, while the same letters express non-significant difference at p>0.05 using a two sample t-test.

The results have confirmed that serum TC levels were significantly higher in metabolic syndrome [209±10.3] and obese [215.5±12] subjects compared to control [181±12.6] and diabetics [178.9±13]. The level of TG in metabolic syndrome [197.15±24.8] was significantly higher compared to control [97.2±41], diabetic [124.9±36.4], and obese [134.2±34.9] subjects. The HDL level was significantly reduced in diabetic [48.3±4.9], metabolic syndrome [44.4±5], and obese [49.36±6] groups compared to the control [59.7±3.8] group with the lowest in the metabolic syndrome group. The LDL level was significantly elevated in the metabolic syndrome [125.8±6], and obese [139.3±7.2] groups compared to the diabetic [105.8±6.7] and control [101.9±6.3] group. The level of VLDL in metabolic syndrome [38.85±7.3] was significantly higher compared to control [19.4±4.2], diabetic [25±5.3], and obese [20.84±4] subjects (**Figure 2**).

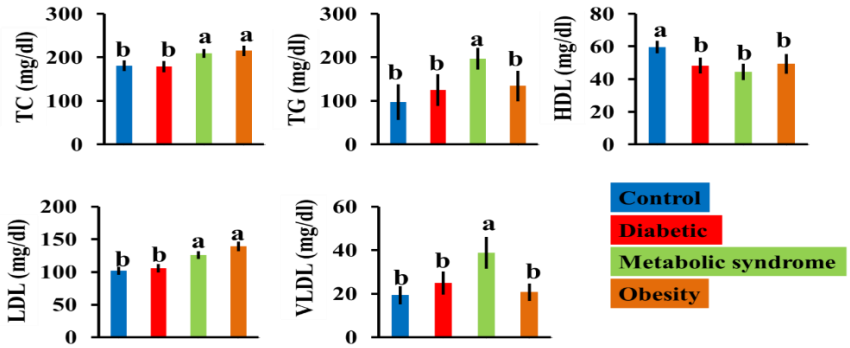

Figure 2. Lipid profile in studied groups. Data expressed as mean ± SD. Different letters express significant differences at p<0.05, while the same letters express non-significant differences at p>0.05 using a two-sample t-test. TC=total cholesterol, TG=Triglyceride, HDL=High density-lipoprotein, LDL=Low density-lipoprotein, VLDL=Very low density-lipoprotein.

To analyze the correlation between measured parameters, Pearson Correlation test was applied. The results revealed that vitamin D weakly correlated with TC, TG, LDL, and VLDL. Positive correlation existed between vitamin D and insulin or HDL. Insulin weakly correlated with the lipid profile parameters. The lipid parameters have shown discrepant correlations with each other, TC positively correlated with TG, and hence LDL and VLDL as well. However, HDL negatively correlated with TC,TG, LDL, and VLDL (**Table 2**).

Table 2. Pearson correlation of the measured parameters between studied groups.

Pearson Correlation	Vitamin D	Insulin	TC	TG	HDL	LDL	VLDL
Vitamin D		**0.210**	0.0800	0.051	**0.119**	0.059	0.044
Insulin			0.023	0.083	-0.095	0.025	0.089
TC				**0.255**	-0.051	**0.948**	**0.247**
TG					-0.567	0.092	**0.994**
HDL						-0.078	-0.577
LDL							0.084
VLDL							

Less than 0.1=weak positive correlation;More than 0.1= positive correlation
Negative values=negative correlation

4. Discussion

The present study revealed that metabolic derangement has been associated with reduced plasma vitamin D alongside reciprocal insulin hyposensitivity when compared to the control group. the studied group of metabolic derangements includes diabetes, metabolic syndrome, and obesity. These findings were further subsidized by derangement of lipid parameters which are harmonized with vitamin D levels and insulin desensitization .

The present study confirmed that diabetes, metabolic syndrome, and obesity were associated with low vitamin D levels. This finding agrees with Song et al. (2013) study conducted on 21 prospective studies (70,000 participants), have found that individuals with a higher serum vitamin D level reciprocally associated with a 38% lower risk of emerging diabetes mellitus, with a 4% reduction of T2D risk for each 10nmol/L increased vitamin D levels. These findings were still present regardless of compiling diseases of hypertension association with diabetes or body mass indices and irrespective of stratified study design based on sex, sample size, diagnostic criteria, follow-up periods, and assay methods of vitamin D (25). A separate meta-analysis study conducted by Afzal et al. (2013) confirmed that low serum vitamin D levels were associated 50% higher risk of T2D (19). In contrast, vitamin D and insulin sensitivity are positively integrated in hyperparathyroidism (26) and mixed ethnicity groups (27), however, the correlation becomes negatively associated when coexisted with diabetes (20), obesity (28), and metabolic syndrome (22). Alternatively, no correlation existed between the onset of diabetes and vitamin D levels when BMI was taken into consideration (29).

The association between reduced vitamin D level and increased risk of developing metabolic syndrome has been reported by Ju et al.(2014) based on a dose-response meta-analysis confirming that for each 10ng/mL increase in serum vitamin D, there was a 0.87 decrease in the risk of metabolic syndrome (30). In a Korean cross-sectional study Song et al. (2013) also proved an increased risk of developing metabolic syndrome with reduced vitamin D level (31). In a 5 years prospective study conducted on 4164 subjects by Gagnon et al to find a relationship between serum vitamin D level and metabolic syndrome, the outcome confirmed that low vitamin D levels (23 ng/mL or less) were at higher risk of developing metabolic syndrome that high vitamin D levels group (34 ng/mL or above) (32). In 489 subjects Canadian a three-year follow-up cohort study in non-diabetic multi-ethnic adults with pre-existing risk factors, the result analysis indicated that elevated baseline serum vitamin D levels were associated with declined risk of metabolic syndrome despite differences in demography or season or insulin resistance (33). In 287 subjects Turkish follow-up study in non-diabetic obese adults, the outcome revealed that low vitamin D levels were more common in metabolic syndrome adults. Moreover, no significant conjoined was demonstrated between vitamin D levels and HDL-C, hypertension, or insulin resistance (34).

The association of obesity with low vitamin D levels has been confirmed through different mechanisms (35,36), such as, higher BMI leading to reduce vitamin D levels; reverse effects in negligible (37). Interventions with vitamin D supplementation have significantly decreased body fat in healthy and obese subjects (38). These conflicting outcomes need further elucidation to clarify the link between obesity and vitamin D levels (37). Experimental animal studies revealed that adipogenesis is linked to vitamin D levels due to the expression of vitamin D receptors in adipose tissues (39,40). These assumptions are further emphasized by atrophy of adipocytes in VDR gene knockout mice (41), however, the link between

adipose tissue formation and vitamin D is obscure and confirmed by findings of stable vitamin D levels in patients with gastrectomy irrespective of vitamin D supplementation (42). In contrast, some researchers suggested that obesity is linked to a low exercise lifestyle and hence less outdoor presence and less sun exposure resulting in low vitamin D levels (43,44).

The reduced vitamin D levels associated with deranged insulin sensitization have been previously reported in diabetic patients and have been explained in the context of the presence of vitamin D receptors in the cells of skeletal muscles and binding of which is responsible for increased insulin sensitivity and thereby reduced vitamin D levels will reciprocally downregulate insulin sensitivity (45), moreover, vitamin D expresses insulin receptors in the bone cell thereby increasing insulin sensitivity and encouraging glucose consumption (46). Surprisingly, insulin basal secretion is not modulated by vitamin D in healthy (47,48) or in patients with diabetes with exhausted insulin secretagogues (49), despite reports confirming that vitamin D supplementation might improve insulin secretion (21,22,50,51). Vitamin D receptor is expressed by pancreatic b-cells (13) and their overexpression increased insulin sensitization in diabetic mice (13,15). The absence of vitamin D receptors in mice models has been conjoined with compromised insulin secretion (48).

The present study confirmed that TC and LDL were elevated in metabolic syndrome and obesity, while TG and VLDL were elevated in metabolic syndrome only, these findings harmonized with low levels of vitamin D and correlated reciprocally with each other and with insulin levels that indicated insulin hyposensitivity. Vitamin D deficiency results in low levels of HDL-C (52). There is robust evidence that a deficiency of vitamin D results in increased LDL-C concentrations (53). The deficiency of vitamin D3 is linked to a high risk of dyslipidemia. This seems to be the reason why vitamin D deficient individuals exhibit an elevated risk of CVD (54). Evidence also states that a deficiency of vitamin D results in raised total cholesterol (TC) levels. Hence, vitamin D administration could be used to decrease LDL-C and TC values and increase HDL-C levels, the latter known for its cardioprotective actions (27).

Supplementation with vitamin D has been shown to display benefits in terms of cardiovascular health, primarily by reducing TC, LDL-C, and TG concentrations (55). Other researchers have highlighted that high doses of vitamin D supplements can also increase HDL-C levels (56). In an interventional study higher dietary intakes of vitamin D were linked with lower changes in TC and LDL-C concentrations. No correlation was detected between vitamin D intake and changes in TG or HDL-C concentrations (57). However, these results contradict with another investigation in which higher intakes of vitamin D in Caucasian and Asian females were associated with lower TG values (58). Thus, we may hypothesize that gender and race might modulate the interplay between dietary consumption of vitamin D and serum lipids concentrations .

The functions of vitamin D are also linked to serum lipids levels. Vitamin D is involved in regulating the metabolism of calcium. It increases the absorption of intestinal calcium, helping to reduce fatty acids' absorption in the intestine (59). This reduction in the absorption of intestinal fat could lower serum TC levels. Moreover, an increase in calcium levels would activate cholesterol conversion into bile in the liver and promote the reduction of serum TC concentrations (60). Our findings were similar to some other studies (61,62). Vogt et al. analyzed the relationship between serum vitamin D levels and serum lipids concentrations, discovering that obesity indices can modulate the interplay between the two aforementioned variables. Lower HDL-C and elevated TG concentrations were linked to reduced vitamin D values in subjects diagnosed with obesity. However, in subjects with normal weight or who were overweight, there was a positive association between vitamin D concentrations and TC and LDL-C, respectively, contradicting our findings (61). Thus, we may hypothesize that dietary patterns based on foods rich in vitamin D might be associated with a decreased prevalence of abnormalities of lipid metabolism. Jeenduang and Sangkaew depicted negative correlations between TC, LDL-C, TG and vitamin D levels in women. Females who did not suffer from vitamin D insufficiency or deficiency had lower odds of having higher TG concentrations and lower HDL-C concentrations (62).

Interventional studies indicated that vitamin D improved insulin sensitivity in diabetic and non-diabetic patients and also vitamin D improved glycemic control in impaired fasting tolerance (23,51). The coexistence of diabetes with obesity further complicated the study and confirmed that insulin sensitivity less well responded to vitamin D supplementation with sequentially improved sensitivity in

dose response wise especially when reaching the dose above 80 nmol/L (63,64). Vitamin D is involved in the activation of peroxisome proliferator-activated receptor delta (PPAR-δ), a transcription factor that is involved in the controlling of fatty acid catabolism within adipose tissue and skeletal muscle, providing a potential role in directing lipid profiles and encouraging energy expenditure within these tissues (65,66).

The study limitations include a small sample size which may precipitate bias. Patients' diets and physical exercise cannot be controlled which are acknowledged as limitation points. The study didn't carry out an intervention study to confirm the exact mechanism of vitamin D in the regulation of glycemic parameters and associated measured parameters pertained to insulin sensitivity.

5. Conclusion

Vitamin D received increasing attention in metabolic diseases due to its inverse relationship with insulin levels and its impact on lipid parameters. Low levels of vitamin D were observed in individuals with metabolic disorders such as obesity, T2DM, and metabolic syndrome. Moreover, variations in lipid profiles have been closely associated with differing concentrations of vitamin D. Adequate levels of this nutrient contribute to favorable lipid parameters such as lower TG and higher HDL cholesterol levels. Conversely, deficiency is linked to dyslipidemia characterized by heightened LDL and TG, exacerbating cardiovascular risk factors associated with metabolic diseases. Thus, maintaining optimal vitamin D levels may serve as a therapeutic target for mitigating insulin resistance and managing lipid abnormalities within the broader context of metabolic health management.

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تزامن مستوى فيتامين (د) مع علامات مقاومة الأنسولين المستدامة بشكل مناسب

المقدمة: مقاومة الأنسولين هي المسببات الكامنة وراء أمراض التمثيل الغذائي بما في ذلك متلازمة التمثيل الغذائي ومرض السكري من النوع 2 والسمنة ، إلى جانب مضاعفاتها. ومع ذلك ، فإن آلية مقاومة الأنسولين معقدة ولكنها غامضة. وقد ثبت أن فيتامين (د) هي المعلمات الأساسية المشاركة في الأمراض المختلفة. كنا نهدف إلى تحديد العلاقة بين مستوى فيتامين (د) ومعلمات نسبة السكر في الدم / الدهون باستخدام المرضى الذين يعانون من أمراض التمثيل الغذائي المختلفة كنموذج. **الطريقة:** للقيام بذلك ، تم جمع عينات المصل من مرضى السكري ومتلازمة التمثيل الغذائي والسمنة مقابل المجموعة الضابطة ذات العمر والجنس والحالة الصحية المتطابقة. تم قياس كمية فيتامين (د) والأنسولين بتقنية قياس الألوان وتم قياس معلمات الدهون في المجموعة المدروسة. **النتائج:** وجدت الدراسة أن مستويات الأنسولين وفيتامين (د) كانت أقل بكثير في مرضى السكري [18.7±2.2 ، 16.5±4.4] ، متلازمة التمثيل الغذائي [23.6±1.6 ، 18.6±3.4] ، والمرضى الذين يعانون من السمنة المفرطة [15±1.9 ، 14.1±4.8] مقارنة بالمجموعة الضابطة [9.8±4 ، 25±5.1]. كانت مستويات الكولسترول في المصل أعلى في متلازمة التمثيل الغذائي والأشخاص الذين يعانون من السمنة المفرطة مقارنة بالأشخاص الضابطين ومرضى السكري. كانت مستويات الشحوم الثلاثية أعلى بكثير في متلازمة التمثيل الغذائي مقارنة بالمجموعات الأخرى. تم تخفيض مستويات جسيمات الدهن عالية الكثافة في مجموعات السكري ومتلازمة التمثيل الغذائي والسمنة مقارنة بالمجموعة الضابطة. كانت مستويات جسيمات الدهن منخفضة الكثافة مرتفعة في متلازمة التمثيل الغذائي ومجموعات السمنة مقارنة بمجموعات السكري والسيطرة. كانت مستويات جسيمات الدهن منخفضة الكثافة جدا أعلى بكثير في متلازمة التمثيل الغذائي مقارنة بالمجموعات الأخرى. **الاستنتاج:** فيتامين (د) انخفاض في الأمراض الأيضية تتماشى بشكل متبادل مع مستوى الأنسولين ويرتبط مع الاختلاف في المعلمات الدهون.

الكلمات المفتاحية: الأنسولين ، فيتامين د ، ملف الدهون ، مرض السكري ، متلازمة التمثيل الغذائي ، السمن