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The Association between Vitamin D Deficiency, Obesity, and Insulin Resistance among the Jordanian Population

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Abstract

Vitamin D deficiency is a worldwide health concern that is linked to a wide range of chronic diseases such as cardiovascular diseases, hypertension, autoimmune diseases, and type 1 and 2 diabetes mellitus. Low levels of vitamin D may result in an increase in body fat (obesity), which has been widely identified as a risk factor for developing type 2 diabetes. The purpose of this study was to investigate the relationship between vitamin D deficiency, body mass index, and insulin resistance among the Jordanian population. A cross-sectional study design was conducted with a sample size of 205 participants (63 males and 142 females) from the Hashemite University, Jordan. Blood serum was obtained and the 25-hydroxy vitamin D, fasting glucose, and insulin levels were measured for all participants. Height, weight, waist, and hip measurements were also taken. Results showed that vitamin D deficiency is significantly ($P < 0.05$) associated with an increase in BMI. 115 individuals (57%) had a BMI below 25 kg/m^2, and 85 individuals (43%) had a BMI above 25 kg/m^2.While 134 individuals (65.4%) had normal vitamin D levels, vitamin D deficiency was found to be present in 71 individuals (34.6%). Furthermore, Vitamin D deficiency was significantly ($P < 0.05$) associated with an increase in HOMA-IR. HOMA-IR index results were elevated in 107 individuals (52.2%), and normal in 98 individuals (47.8%) in which 23 individuals (11%) were vitamin D deficient with normal HOMA-IR, while 48 individuals (23%) with vitamin D deficiency had elevated HOMA-IR. Moreover, in the studied population, vitamin D deficiency prevalence (25-hydroxy vitamin D < 25 nmol/l) was 34.6%, with the prevalence being higher in females (48.6%) than males (1.6%). In conclusion, these results showed that vitamin D deficiency is associated with an increase in body mass index and insulin resistance.

Keywords: Vitamin D, Obesity, Insulin resistance.

1. Introduction

Vitamin D is a fat soluble vitamin (Vanlint, 2013). It can be obtained from diet, but its major source of synthesis is the skin from the precursor 7-dehydrocholesterol after exposure to ultraviolet light (Melmed, 2016). Vitamin D deficiency is now considered a worldwide public health issue (Wacker and Holick, 2013). Currently, around 1 billion people worldwide are considered to have vitamin D deficiency and insufficiency (Pfotenhauer and Shubrook, 2017). The Jordanian population is no exception, as shown by a study conducted on women and their children in northern Jordan, the results of which showed that 97.8% of the women and 39% of the children had 25(OH)D levels less than 50 nmol/L (Gharaibeh and Stoecker, 2009). Another study on women of child-bearing age resulted in a prevalence of 95.7% (Nichols *et al*., 2012), a finding that is compatible with the previous study. A study of preschool children found that the prevalence of vitamin D deficiency among this age group is 56.5% (Nichols *et al*., 2015). Batieha *et al*. (2011) reported in his study that the prevalence of vitamin D deficiency among adults is 37.3% in females, compared to 5.1% in males.

Many factors might cause low levels of vitamin D, including limited sun exposure, concealing clothing, sunscreen use, degree of skin pigmentation, aging, certain medications, and chronic illnesses. Added to that is the limited dietary sources of the vitamin (Tsiaras and Weinstock, 2011). Many studies suggest that vitamin D might have a protective role in preventing several chronic diseases, such as cardiovascular diseases, hypertension, certain types of cancer, autoimmune diseases, type 1 and type 2 diabetes, and obesity (Earthman *et al*., 2012; Pfotenhauer and Shubrook, 2017). Vitamin D deficiency is associated with increased risk of developing these diseases (DeLuca, 2004).

It is well-known that obesity is considered a risk factor for type 2 diabetes (Shoelson *et al*., 2007). Additionally, insulin resistance is a major condition that leads to type 2 diabetes mellitus (Teegarden and Donkin, 2009). Since vitamin D deficiency seems to be associated with obesity and insulin resistance, it is likely that vitamin D deficiency indirectly contributes to an increased risk of type 2 diabetes (Holick, 2012).

Many studies have discussed an inverse relationship between body fat content and vitamin D concentrations. This negative correlation is found in all age groups and ethnicities (Drincic *et al*., 2012; Hyppönen and Boucher,

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2018). Several mechanisms have been proposed to explain this relationship, such as limited sun exposure of the skin in overweight and obese people due to social stigma, elevated levels of 1.25(OH)2D and parathyroid hormone leading to reduced synthesis of 25(OH)D in the liver through negative feedback, and reduced skin ability to synthesize vitamin D from 7-dehydrocholesterol (Drincic *et al*., 2012; Looker, 2005). Another proposed explanation for the reduced levels of 25(OH) D is the sequestration of vitamin D in the adipose tissue which reduces its availability for the body (Earthman *et al*., 2012; Lagunova *et al*., 2009). A study by Tzotzas *et al*. (2010) supports this mechanism, showing that 10% weight loss in obese women raised their 25-hydroxyvitamin D levels by 34%. Another study on obese children also reported an increase in 25-hydroxyvitamin D levels after weight loss (Reineh *et al*., 2007).

However, low levels of vitamin D might be causing an increase in body fat. This is supported by the studies that have shown that 1.25-dihydroxyvitamin D inhibits adipocyte differentiation and adipogenesis in vitro (Bouillon *et al*., 2008; Kong and Li, 2006).

Given the roles that vitamin D plays in the secretion of insulin and the function of pancreatic β cells, several studies tried to investigate the effect of low vitamin D on insulin sensitivity and the development of type 2 diabetes mellitus. Chiu *et al*. (2004) carried out a study on healthy adults and concluded that vitamin D deficiency is associated with increased risk of insulin resistance and type 2 diabetes. The same study also evaluated the function of β cells in the pancreas, and results showed that the function of β cells was affected in the case of low vitamin D levels. There is growing evidence suggesting that low levels of 25-hydroxyvitamin D are a risk factor for type 2 diabetes (Mathieu *et al*., 2005; Wimalawansa, 2018). Several cross-sectional studies reported that diabetes mellitus patients have lower concentrations of 25-hydroxyvitamin D (Liu *et al*., 2008). The interactive relationship between vitamin D and diabetes might rise from different possible contributors. It might be that obesity, usually associated with vitamin D deficiency, is the cause of diabetes, because it is well- known that obesity is a strong contributor to type 2 diabetes (Shoelson *et al*., 2007), or diabetes might develop as a result of insulin resistance caused by vitamin D deficiency, as it is known that insulin resistance is a major factor in the pathogenesis of type 2 diabetes (Knekt *et al*., 2008).

Thus, due to a dearth of studies conducted in Jordan, our objective in this research was to study the association between vitamin D deficiency, body mass index and insulin resistance among the Jordanian population with a hypothesis that vitamin D deficiency would contribute to obesity and insulin resistance.

2. Materials and methods

This is a cross-sectional study that was designed to determine the relationship between vitamin D deficiency, body mass index (BMI), and insulin resistance among the Jordanian population. The protocol for this study was approved by the Institutional Review Board committee (IRB) at the Hashemite University, Zarqa, Jordan.

205 apparently healthy participants were recruited in the study from the Hashemite University, Zarqa, Jordan, during the period of mid-March till mid-April2019. Participants who agreed to be part of the study signed a consent form and their data were collected using a questionnaire. Selection of participants was based on the inclusion and exclusion criteria listed in Table 1 below.

Table 1. Participant inclusion and exclusion criteria

Exclusion Criteria	Inclusion Criteria
Aged less than 18 years	Aged 18 and above
Vitamin D supplements intake	Adults with no health issues (apparently healthy)
Calcium supplements intake	No history of previous vitamin D supplements intake
Multivitamin supplements intake	
Diabetes Mellitus type 1 and 2	
Thyroid disease	
Gallbladder disease	
Kidney disease	
Liver disease	

Participants were requested to fast 10-12 hours prior to blood collection. Five to seven milliliters of venous blood samples were obtained from each participant in a plain tube with gel (Greiner bio-one, Austria). Samples were allowed to coagulate at room temperature, after which they were centrifuged at 3500 rpm for 5 minutes using a laboratory clinical centrifuge (HettichZentrifugen, Germany). Serum samples were separated into 1.5 ml microcentrifuge tubes using disposable plastic Pasteur pipettes (two tubes for each sample) that were properly labeled and kept at -20 °C until being analyzed. Height, weight, hip circumference, and waist circumference were measured for each participant in duplicate and the mean for each reading was calculated. Body mass index (BMI) was calculated according to the following formula:

BMI= Weight in kilograms / Height in meters^2 (Ness-Abramof and Apovian, 2008). BMI values are classified according to the World Health Organization (WHO) as follows:

Normal: BMI < 25 kg/m^2

Overweight: BMI 25 - 29.9 kg/m^2

Obese: BMI ≥ 30 kg/m^2

Waist to hip ratio (WHR) was calculated according to the following formula:

W/H= Waist circumference / Hip circumference.

Serum level of vitamin D was measured using enzyme-linked immunosorbent assay technique (ELISA), using 25-OH Vitamin D Total ELISA kit (Diasource, Belgium).25-OH vitamin D levels ≥ 50 nmol/L are considered sufficient, 25- 49 nmol/L are insufficient, and levels < 25 nmol/L are deficient (Wolpowitz and Gilchrest, 2006). Serum samples were analyzed for glucose using glucose oxidase method on automated biochemistry analyzer (Mindray, China). Normal glucose levels are less than 110 mg/dl. The insulin test was done using TOSOH analyzer (Japan). The ST AIA-PACK IRI is a two-site immunoenzymometric assay which is performed entirely in the ST AIA-PACK IRI test cups. Normal level for

fasting insulin is 2.6 - 10.0 μU/mL. Homeostasis model assessment of insulin resistance (HOMA-IR) index is considered a simple and reproducible method for determining insulin resistance (Singh and Saxena, 2010). Fasting blood glucose and insulin levels were used to calculate HOMA-IR according to the following formula:

HOMA-IR = serum insulin level (μU/mL) * blood glucose (mmol/L))/22.5 (Singh *et al*., 2013).

Cut-off point of HOMA-IR ≥ 1.9 indicates insulin resistance (Ghasemi *et al*., 2015).

2.1. Statistical analysis

Collected data were summarized using Excel sheets and statistical analysis was performed using Statistical Package for Social Sciences software (SPSS). Data was analyzed using a two-independent t- test. Vitamin D was considered deficient if it was below 25 nmol/L, while a BMI of over 25 was considered obese, and a reading of over 1.9 indicated HOMA insulin resistance.

3. Results and discussion

3.1. 3.1. Vitamin D and BMI

205 students were enrolled in this study. BMI data were obtained for 200 students (5 were absent). 115 (57.5 %) had a BMI below 25 kg/m^2, and 85 (42.5 %) had a BMI above 25 kg/m^2. 33 students (16.5%) were vitamin D deficient with normal body weight, while 36 students (18%) with vitamin D deficiency were overweight or obese.

Vitamin D deficiency was present in 71 of the students (34.6%), and 134 (65.4%) had normal vitamin D levels, from the total of 205 students.

The data described in Tables 2 and 3 provide sufficient evidence (P value= 0.044) to conclude that body mass index for vitamin D deficient students is significantly greater than normal students. With 95% confidence, vitamin D deficiency increases mean BMI by a value between 0.03 and 2.6kg/m^2.

According to our results, vitamin D deficiency significantly increased (P = 0.044) with body mass index (Tables 2 and 3). This finding is consistent with the results of Arunabh *et al*. (2003), who reported that 25(OH)D levels are inversely related to body mass index and body fat content in healthy women, and Gannagé-Yared *et al*. (2009) who showed that 25(OH)D concentrations are inversely associated with BMI in a group of healthy non-obese young adults. The results of Chiu *et al*. (2004) also showed an inverse relationship between BMI and 25(OH)D concentrations in healthy young adults, but no relation between 25(OH)D and waist to hip ratio (WHR). Muscogiuri et al. (2010) also concluded that there is a significant correlation between 25(OH)Dand BMI, as did Liu *et al*. (2008).

Lower 25-hydroxyvitamin D levels are associated with higher BMI, as reported by Vilarrasa *et al*. (2007), who showed that 25(OH)D concentrations decreased with the increase of body mass index. Lagunova *et al*. (2009) reported a similar pattern of a significant decrease in 25(OH)D levels with the increase in BMI.A study by Garanty-Bogacka *et al*. (2011) showed that vitamin D deficiency is associated with higher body mass and increased fat content in adolescents, while Poomthavorn *et al*. (2012) reported no association between 25(OH)D and BMI in obese Thai adolescents and children.

In a population-based study, Jorde *et al*. (2010) also confirmed the strong negative association between serum levels of 25(OH)D and BMI. They also investigated the relationship between BMI and the improvement of 25(OH)D serum levels after vitamin D supplementation and concluded that the increase in 25(OH)D levels are also inversely correlated with BMI. In clinical application, this finding means people with higher BMI would need higher doses of vitamin D supplementation to correct its deficiency (Lee *et al*., 2009).

It is thought that the increase in body mass index that is accompanied with an increase in fat tissue causes sequestration of vitamin D in the adipose tissue and limits its bioavailability (Earthman *et al*., 2012). This possibility was investigated in a study by Wortsman *et al*. (2000). They exposed obese and non-obese subjects to UV light to induce vitamin D synthesis and found that the increase in vitamin D levels were 57% less in obese subjects compared to non-obese, although the percentage of producing vitamin D from previtamin D was similar in both groups. This indicates that obesity did not affect the production of vitamin D from the skin, but subcutaneous fat tissue in obese subjects might have sequestered the synthesized vitamin D. Furthermore, oral doses of vitamin D given to both groups resulted in less bioavailability with the increase in BMI, further supporting the sequestering of vitamin D in the body fat. This explanation could be supported by the results of some studies that reported an increase in 25-hydroxyvitamin D concentrations following weight loss (Tzotzas *et al*., 2010; Reinehr *et al*., 2007).

Another proposed explanation of the relationship between vitamin D deficiency, body mass index, and obesity, is the limited sun exposure or time spent outdoors. The only way to activate the chemical reaction that results in vitamin D production is for sunlight to reach your skin directly.

Additional proposed causes of low 25-hydroxyvitamin D levels seen in obesity is the increased catabolism of vitamin D, that is mediated by the enzyme 24-hydroxylase, which is expressed by adipose tissue. Another possible cause is reduced synthesis of 25-hydroxyvitamin D from liver in obese individuals as a result of non-alcoholic fatty liver disease that is associated with obesity (Earthman *et al*., 2012).

Although vitamin D deficiency is more prevalent in obesity, the causal direction of the relationship is still undetermined (Rosen *et al*., 2012). However, the results of a major analysis of multiple cohorts that tried to find the direction of causality suggested that higher body mass index leads to lower 25-hydroxyvitamin D concentrations (Vimaleswaran *et al*., 2013).

The current study found no significant association between vitamin D deficiency and increased waist to hip ratio (WHR). This might be due to the lack of high WHR in the studied group, since none of the students fell into the WHR range that is considered high.

Table 2. Distribution of Vitamin D Normal and Vitamin D Deficient Students according to BMI

	BMI		
Vitamin D	Normal[1]	Obese[2]	Total
Normal[3]	82 (41%)	49 (24.5%)	131
Deficient[4]	33 (16.5%)	36 (18%)	69
Total	115 (57.5%)	85 (42.5%)	200

[1] BMI < 25Kg/m^2

[2] BMI > 25Kg/m^2

[3] Vitamin D > 25 nmol/L

[4] Vitamin D < 25 nmol/L

Table 3. Results of BMI according to Vitamin D Status

Vitamin D	Insulin		
	Normal[1]	Resistant	Total
Normal[2]	75 (37%)	59 (29%)	134
Deficient[3]	23 (11%)	48 (23%)	71
Total	98(48 %)	107(52 %)	205

[1] Vitamin D > 25 nmol/L

[2] Vitamin D < 25 nmol/L

3.2. Vitamin D and Insulin Resistance

205 students were enrolled in this study. HOMA-IR index results were elevated in 107 students (52%), and normal in 98(48%).

Vitamin D deficiency was present in 71 of the students (34.6%), and 134 (65.4%) had normal vitamin D levels. 23 students (11%) were vitamin D deficient with normal HOMA-IR, while 48 students (23%) were vitamin D deficient with elevated HOMA-IR.

The data described in Tables 4 and 5 provides sufficient evidence (P value= 0.046) to conclude that insulin resistance for vitamin D deficient patients is significantly greater than for normal patients. With 95% confidence, vitamin D deficiency increases mean insulin resistance (HOMA-IR) by a value between 0.01 and 0.8.

Our results showed that there was a significant association between 25-hydroxyvitamin D levels and HOMA-IR (P = 0.046) (as shown in Tables 4 and 5), where vitamin D deficiency caused an increase in insulin resistance. These findings are consistent with those of Chiu *et al*. (2004) who reported an increase in insulin resistance risk in subjects with low 25-hydroxyvitamin D levels. Subjects who participated in this study were healthy with normal glucose tolerance. Also, a study by Liu *et al*. (2008) of non-diabetic adults revealed that 25(OH)D concentrations were inversely associated with fasting glucose, fasting insulin, and HOMA-IR, which means that low 25(OH)D levels is associated with increased insulin resistance. Abdelkarem, El-Sherif, and Gomaa (2016) also reported similar results in their research on female university students from Saudi Arabia. Gannagé-Yared *et al*. (2009) explored the association on a group of healthy non-obese university students in Lebanon and found that 25(OH)D concentrations were inversely correlated with HOMA-IR values.

Alemzadeha,Kichlerb, Babara, and Calhoun's (2008) research on obese children and adolescents with mean age 13 years old, reported that vitamin D deficiency was associated with increased insulin resistance independent of body obesity. However, their results are not consistent with those of Poomthavorn *et al*. (2012) who found no relationship between 25(OH)D levels and insulin sensitivity, or even between 25(OH)D and body mass index in obese children and adolescents.

Muscogiuri *et al*. (2010) reported a significant correlation between 25(OH)D with body mass index and insulin sensitivity. They found that low 25(OH)D levels are associated with decreased insulin sensitivity, and the lowest concentrations of 25(OH)D were associated with higher degrees of insulin resistance. Also, higher BMI was associated with lower concentrations of 25(OH)D. In this study, they attributed the increase in insulin resistance seen in lower levels of 25(OH)D to be the result of increased BMI, rather than being caused by low 25(OH)D.

Several mechanisms were proposed to explain the relationship between vitamin D and insulin resistance, and how vitamin D deficiency affects it. It is known that vitamin D is essential for normal secretion of insulin from β pancreatic cells (Chiu *et al*., 2004; Rosen *et al*., 2012), and its deficiency inhibits insulin secretion and induces glucose intolerance (Bouillon *et al*., 2008). Vitamin D enhances the synthesis of various proteins within the cells and accelerates the transformation of proinsulin into insulin (Chiu *et al*., 2004). It also stimulates the expression of insulin receptors in target tissues leading to enhanced glucose uptake by peripheral tissues and increased insulin responsiveness (Pittas *et al*., 2007).

Insulin secretion is a calcium-dependent process. Vitamin D facilitates insulin secretion indirectly by regulating extracellular calcium and calcium influx to β cells. Any disturbance in the intracellular calcium levels or its influx toward the cell will impair β cells' function (Muscogiuri *et al*., 2014; Pittas *et al*., 2007). Calcium is equally important in cells and tissue that responds to insulin to regulate their glucose uptake and intracellular processes. Any alteration in intracellular levels of ionized calcium in insulin target tissues may lead to insulin resistance in these tissues, due to impaired insulin signal transduction, which in turn affects glucose transporter-4 function (Pittas *et al*., 2007).

Low levels of vitamin D cause an increase in parathyroid hormone (PTH) levels. High PTH will affect intracellular free calcium concentrations in cells, including pancreatic cells, which in turn will decrease insulin sensitivity and impair glucose tolerance (Mezza *et al*., 2012).

Another proposed mechanism involves the immunomodulatory effect of vitamin D. Vitamin D regulates the production and function of cytokines. Inadequate vitamin D status may result in inflammatory response, which may lead to insulin resistance, but this hypothesis is still debatable (Liu *et al*., 2008; Muscogiuri *et al*., 2014; Pittas *et al*., 2007).

Increasing 25(OH) levels by supplementation to satisfactory level would lead to good outcomes. Some studies have reported an increase in insulin secretion by 60% after correcting 25(OH) levels (Holick, 2008). Von Hurst *et al*. (2010) reported that the treatment of vitamin D deficiency would improve insulin sensitivity and reduce its resistance, but other studies showed no improvement in

insulin resistance or any of the obesity parameters (Tai *et al*., 2008; Wamberg *et al*., 2013).

Whether vitamin D supplementation results in improved insulin sensitivity or not, vitamin D deficiency should be treated, and improving vitamin D levels to satisfactory levels will not lead to negative outcomes.

Table 4. Distribution of Vitamin D Normal and Vitamin D Deficient Students according to Insulin Resistance

BMI (kg/m^2)	Vitamin D	
	Deficient[1]	Normal[2]
Minimum	20.22	17.46
Maximum	40.22	46.43
Mean	25.85	24.51
Standard Deviation	4.17	4.94
Missing data	2	3

[1]2.6 - 10.0 μU/mL

[2] Vitamin D > 25 nmol/L

[3] Vitamin D < 25nmol/L

Table 5: Results of HOMA-IR Index according to Vitamin D Status

HOMA-IR Index	Vitamin D	
	Deficient[1]	Normal[2]
Minimum	1.08	0.39
Maximum	10.47	12.52
Mean	2.51	2.10
Standard Deviation	1.33	1.53

[1] Vitamin D < 25 nmol/L

[2] Vitamin D > 25 nmol/L

4. Conclusion

Our study showed that vitamin D deficiency caused an increase in BMI and an increase in insulin resistance measured by homeostatic model assessment of insulin resistance (HOMA-IR). However, this study showed no association between vitamin D deficiency and waist to hip ratio.

The obtained results uncovered that the Jordanian population has a high rate of vitamin D deficiency which might highly correlate with increasing rates of insulin resistance among them. As a preventative procedure for insulin resistance and increased BMI, we recommend that individuals take a regular vitamin D test and take the needed vitamin D supplement as soon as deficiency or insufficiency is detected with consultation with physicians.

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