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Circulatory leptin levels as a key link in the potential association between insulin resistance and vitamin D deficiency: A review Article

Mahmoud Abu-Samak[a], Beisan A Mohammad[b], Ibrahim Mosleh[c], Omar Abdel-Majeed[a], Abeer Braham[a], Shady H Awwad[d], Ahamed Abu-Zaiton[e], Abdel Rahman M. Tawaha[6]

[a] Department of Clinical Pharmacy and Therapeutics, Applied Science Private University, Amman, Jordan
[b] Pharm D Department, Fakeeh College for Medical Sciences, Jeddah, Kingdom of Saudi Arabia
[c] Department of Clinical Laboratories Sciences, University of Jordan, Amman, Jordan
[d] Department of Pharmaceutical Chemistry & Pharmacognosy, Applied Science Private University, Amman, Jordan
[e] Department of Biological Sciences, Al al-bayt University, Al-Mafraq, Jordan
[f] Department of Biological Sciences, Al Hussein bin Talal University, P.O. Box 20, Maan, Jordan
Correspondence: Mahmoud S Abu-Samak
Department of Clinical Pharmacy and Therapeutics, Applied Science Private University, Al Arab Street 21, Amman 11931, Jordan
Email m_abusamak@asu.edu.jo

ABSTRACT

Vitamin D deficiency (VDD) and diabetes mellitus (DM) are worldwide problems. Many recent studies have shown a high prevalence of T2DM and VDD in Mediterranean countries including Jordan. Remarkably, VDD is more prevalent in obese people with inverse association with 25-hydroxy vitamin D (25OHD). Nevertheless, randomized clinical trials (RCTs) point did not confirm that yet in particular the association with an obesity marker (leptin hormone). Leptin is involved in the insulin resistance (IR) pathogenesis and development of T2DM. Some RCTs showed that the treatment of VDD by 1,25OHD2D3 (VD3) may improve the control of diabetes and insulin sensitivity or decrease the risk of disease. Conversely, leptin levels were positively associated with 25OHD levels. Overall, taking into account the U-shaped curve, it seems that the association between VD3 supplementation is a dose dependent. In this context, it can be concluded that when VD intake is below, the serum leptin level will be low and vice versa VD supplementation may cause raising serum leptin as shown in this review. Therefore, we suggest further clinical trials wither to confirm or negation of existence of diabetogenic or anti-diabetogenic effects for VD3 supplementations.

KEYWORDS: VDD, diabetes, T2DM, vitamin D, leptin, obesity, insulin resistance.

Correspondence: Mahmoud S Abu-Samak
Address: Department of Clinical Pharmacy and Therapeutics, Applied Science Private University, Al Arab Street 21, Amman 11931, Jordan
Email: m_abusamak@asu.edu.jo

Introduction

Vitamin D deficiency (VDD), obesity and diabetes mellitus (DM) are worldwide problems. There has been growing interest in the association of type 2 DM (T2DM) with VDD in relation to obesity (Smith and Singleton, 2013). Many studies have shown a high prevalence of T2DM and VDD in many populations including Mediterranean countries (Qatatsheh *et al.*, 2015; Al-Shaer *al.,* 2016). Some reports have shown that VDD was more prevalent in obese people (Vimaleswaran *et al*., 2015; Hajimohammadi *et al.,* 2016; Chadt *et al*., 2018). An inverse association between 25-hydroxy vitamin D (25OHD) levels and BMI was also observed (Ruiz-Ojeda *et al.,* 2018). In this manner, leptin hormone, the obesity gene product, is one of the most important obesity and insulin resistance markers (Yadav *et al.,* 2013). However, the association between VDD and serum leptin levels is not settled yet (Kim *et al.,*2013; Hajimohammadi *et al.,*2016). Meta-analysis of data from 6 RCTs did not find a significant change in plasma leptin concentrations after vitamin D_3 (VD_3) intervention (Dinca *et al.,*2016). Contrary to Dinca *et al.* (2016), a significant positive association between 25OHD and leptin has been reviewed by Hajimohammadi *et al.* (2016). High prevalence of T2DM among people with VDD were spread dramatically during last decade. Therefore, the current review aims highlight the association between vitamin D deficiency and serum leptin as a potential key link and circulatory marker of insulin resistance.

Vitamin D Deficiency

Vitamin D (VD) is an essential fat-soluble vitamin, endogenously produced by the action of sunlight on 7-dehydrocholestrol in skin (also known as D_3 or cholecalciferol) or obtained from dietary food stuff as either VD_2 (known as ergocalciferol) or VD_3 11 (Hewison, 2012). VD occurs in food in small amounts, mainly in the raw material of an animal origin, whereas in plant products VD is not present. Chemically, the various forms of VD belong to secosteroids; a biochemical class of 'broken' ring steroids: VD_2, and VD_3 or cholecalciferol are the two major forms which are known collectively as VD or calciferol (Newberry *et al.,* 2014).

Circulatory levels of 25OHD as well as other calciotropic hormones and predictors such as parathyroid hormone (PTH), FGF23, calcitonin and sex hormones are involved in the interrelationships that maintain normal calcium levels (Kovacs, 2014; Mundy and Guise, 1999). The cutaneous synthesis of VD_3 depends on the age, skin color, latitude, season of the year and time of the day (Newberry *et al.,* 2014), sunscreen use, air pollution (Hossein-nezhad and Holick, 2013) and it is also proportional to the skin surface area exposed to the sun (Wimalawansa, 2016). This way of VD production is considered safe since prolonged exposure to UVB rays will not produce toxic levels of VD_3 duo to the conversion of pre VD_3 to inactive metabolites tachysterol and lumisterol (Zhang and Naughton, 2010). After formation VD_3 will be discharged from keratinocytes plasma membrane to the dermal capillary tube by DBP, then VD_3 will be assimilated into chylomicrons, released into lymphatic system and enter the blood (Hossein-nezhad and Holick, 2013). Cutaneous synthesis of VD may not be sufficient to produce adequate amounts of VD, because of that the VD supplementations are advisable to prevent VDD (Chen *et al.,* 2007). Exogenous dietary form of VD is absorbed in the jejunum and ileum with the simplifying of bile salts (Teske *et al.,* 2016). In healthy human, there is no difference between VD_2 and VD_3 in absorption rate, the efficiency of VD absorption varies between 55% and 99%. Patients with fat malabsorption, particularly steatorrhea are unable to absorb VD (Nair and Maseeh, 2012). The absorbed VD is incorporated into chylomicrons before entering the circulation. 85-90% of VD forms are transported by a liver protein DBP to the target tissues (Jovičić *et al.,* 2012). 10-15% of the total circulating VD is bound to albumin and less than 1% is in the free form (Powe *et al.,* 2013).

Vitamin D deficiency and health problems

VDD remains a public health concern, due to its association with many health outcomes, VDD is linked to increased risk of cancer, cardiovascular disease, diabetes, autoimmune disease (Lerchbaum and Obermayer, 2012), metabolic disorders, infectious diseases (Theodoratou *et al.,* 2014), and multiple sclerosis. The correlation between vitamin deficiencies including vitamins B12 and VD with obesity was previously mentioned (Abu-Samak *et al.,* 2008; Pearce and Cheetham, 2010). High prevalence of VDD may be related to several factors, such as less VD photosynthesis in response to insufficient ultra-violate radiation, low VD intake, age, obesity, hyperlipidemia dark-skinned, stress can also contribute to VDD (Mallah, *et al.,* 2011; Gonzalez, 2014; Abu-Samak *et al.,* 2019)

Type 2 diabetes mellitus (T2DM) and Insulin resistance

T2DM is a multifactorial metabolic disorder resulting from a complex inheritance-environment interaction along with other risk factors (Gudjinu and Sarfo, 2017). The risk factors in children are similar to those in adults: ethnicity, family history, hyperlipidemia, sedentary lifestyle, and obesity (Abu-Hasheesh *et al.*, 2010; Abu-Samak *et al.*, 2013; Abu-Samak *et al.*, 2018; Abu-Taha *et al.*, 2019). Severe obesity represented a major risk factor for the development of T2DM (Chadt *et al.*, 2018). Insulin resistance (IR) is the key factor in linking between obesity and T2DM. T2DM accounts the majority of diabetic cases (Gao *et al.*, 2017). In many countries, T2DM became a significant health problem due to an increase in obesity among the young, unhealthy dietary habits and a sedentary lifestyle (Jarab *et al.*, 2018). It is well known that obesity increases the risk for T2DM through induction of IR (Abu-Hasheesh *et al.*, 2010). Obesity is the excessive or abnormal accumulation of fat in the body sufficient to increase overall morbidity and mortality. The importance of obesity in the etiology of T2DM is highlighted by the fact that the development of diabetes is due to rising rates of obesity (most of T2DM are obese). Moreover, weight loss in obese patients of T2DM can ameliorate or even terminate the disorder. Before the onset of clinical diabetes, during the early stages of T2DM pathogenesis, also known as prediabetics, IR continues to be questioned so it is characterized by high insulin levels. This explains the hypothesis that IR could be the primary reason, resulting in a compensatory increase in insulin secretion that ultimately cannot be maintained by the exhausted pancreas which cannot keep up with insulin demands (Tong *et al.*, 2016).

Insulin Resistance: Role of leptin

Adipose tissue is the primary source for IR mediators (González , 2012). Lipotoxicity (excess free fatty acids) that decreases skeletal muscle insulin sensitivity by interfering with insulin receptor substrate -1 (IRS-1) signaling and central adiposity that increases IR appears to include dysregulated secretion of leptin which is produced the fat tissue. Leptin is 167-amino-acid metabolic peptide, discovered in 1991 (Ferguson, 2014) that controls and maintains body weight by regulating appetite and fat metabolism**.** Leptin hormone acts centrally to control satiety and enhance insulin sensitivity (Lanzerstorfer *et al.*, 2015). Obesity can be a result of leptin resistance. Therefore leptin resistance is likely to be involved in the development of T2DM (Finucane *et al.*, 2009). Leptin deficiency is also considered to be noteworthy in the pathogenesis of IR in uncontrolled T2DM. Accordingly, many studies have considered that leptin has anti-diabetogenic effects via improving IR or by mediating the release of insulin from pancreatic β cells (D'Souza *et al.*, 2014). Animal models also, showed that leptin administration reversed diabetes in lipoatrophic mice. Finally, diet and leptin treatment should be thoroughly explored as a method of diabetes control (Silva *et al*., 2017).

The association between VDD and Insulin Resistance: Leptin role

Adipose tissue is the primary source of mediators of IR (Frayn, 2001). The mechanisms by which fat tissue, particularly central (abdominal) adiposity, increases IR continues to be explained and appears to include: lipotoxicity which decrease skeletal muscle insulin sensitivity by interfering with IRS signaling; and dysregulated secretion of the anti-diabetogenic hormone, leptin in the fat tissue which acts centrally to control satiety and enhance insulin sensitivity (D'Souza *et al.*, 2014). IR in turn is strongly associated with increased leptin hypersecretion which may play the key role in the development of insulin insensitivity (Klöting and Blüher ,2014) . Parental history of diabetes has been linked also as a potential predictor (Abu-Hasheesh *et al.*, 2010. In concerning to VDD, nemours global studies have reported a negative correlation between BMI and serum 25OHD levels (Konradsen *et al.,* 2008; Lagunova *et al.,* 2009; Khawaja *et al.,* 2017). The lack of morning sun exposure was one of the predominate percentages in this study as previously agreed (Mead, 2008). Some of reports have reviewed that VDD increases DM risk (Boucher *et al.,*2004; Pittas *et al.,*2019) refereed that VDD enhances IR and develops T2DM. A correlation study by (Gandhe, 2013) observed a negative association between 25OHD levels and the risk of DM. Further, recent RCTs showed that treatment of VDD by VD_3 may improve the control of diabetes in Asian subjects (Upreti *et al.,* 2018**)**. Accordingly, it has concluded that the effect of VD supplementation might play a role in the prevention of T1DM (Monnier and Colette, 2010). Recently, in pre-diabetic patients with VDD, high dose of VD3 improved insulin sensitivity and decreases risk of progression toward diabetes (Niroomand *et al.,* 2019). However, the association of VDD with DM is still not clarified and needs more studies particularly clinical trials. Therefore, vitamin D receptors (VDR) in obese subjects has been drawing attention in related VD studies including it is a potential mediating role in the effect of VD on insulin hormone action (Knekt *et al.*, 2008). Despite that Kim *et al*. (2013) have mentioned no correlation between BMI and 25(OH)D, many studies had shown that the VDD is more prevalent in obese people with inverse association between 25OHD levels and BMI (Eganet *et al.,*2014). These observations confirmed an existence of relationship between serum leptin and 25OHD in men and women with VDD. Nevertheless, conflicting results have been reported by Kim *et al*. (2013). For example, circulatory 25OHD variation has not been associated with BMI values (Forsythe *et al.,* 2011). Conversely, an inverse correlation has been showed between serum 25OHD levels with fat volume (Vimaleswaran *et al*.,2015) and with leptin in different age groups (Hajimohammadi *et al.,*2016). In relation to VDD, it was noted that each increase in BMI unit corresponds to a 1.15% reduction in the 25OHD level (Harroud and Richards, 2018). Similarly, but in relation to fat weight, a 1% increase in fat weight was associated with a (1.15 ± 0.55) nmol/L reduction in serum 25OHD level (Lenders *et al.,*2009).

On the other hand, findings of randomized clinical trials (RCTs) that examined the effect of different doses of VD_3 supplementations on serum leptin levels in healthy subjects or patients, were also mixed. In healthy subjects, no significant change in circulatory leptin levels had been noted according to different protocols of VD3 doses (Dinca *et al.,*2016; Duggan *et al.,* 2015; Mousa *et al.*, 2019). Conversely, significant increase (Hajimohammadi *et al.,*2016.) or decrease (Vahdat *et al.,*2016) in the mean value of leptin levels were observed. It seems that high doses of VD3 have significant influence to decrease of leptin levels in some populations. It has shown that one shoot of a very high dose (600,000 IU D3) significantly reduced leptin levels in obese subjects (Mai *et al.,* 2017**)**. Also, high doses of VD_3 (50,000 IU/w for 6 weeks) also reduced significantly the mean of BMI and body weight in Iranian population (Entezari *et al.*,2018). BMI variation based on the mean age value might be positively correlated with body fat mass (Mott et al., 1999). Furthermore, an inverse correlation between serum 25OHD levels with fat volume was more significant than BMI (Vimaleswaran *et al*., 2015). This is because of leptin is more associated with obesity than BMI as mentioned by Abu-Samak *et al.* (2011) or due to the absorption of vitamin D by adipose tissue (Wortsman et al. 2000), which clarifies, in part, the inverse association between 25OHD and obesity. Although observational studies contributed contraindicating findings that to high heterogeneity sources of heterogeneity such as age and health condition, it seems that the effect of VD_3 on blood leptin levels is a dose dependent (Hajimohammadi *et al.,*2016).

Leptin hypersecretion by adipocyte hypertrophy may plays the key role in the development of insulin insensitivity in obese people (Targher *et al.,* 2007) as well as may impair 25OHD synthesis via VDR mediated mechanism (Drincic et al.,2012). Despite the consensus of many previous observational studies that linked VDD to obesity (Goldner *et al*., 2008), RCTs findings were contradictory about the effect of VD3 on obesity in people with VDD or VD insufficiency (Turer *et al.,*2012). However, in the overwhelming majority of those trials have shown a positive effect of VD_3 on 25OHD and leptin. Independent association between 25OHD and leptin levels from adiposity was observed after a 1-year lifestyle intervention (Gangloff *et al.,* 2019). These observations may underscore the role of lifestyle modifications to decrease leptin levels during clinical management of VDD. Nevertheless, there is no certainty that the modulatory effect of VD3 supplementation on leptin is involved in the improvement of insulin resistance in susceptible individuals to T2DM. Overall, Taking into account the U-shaped curve. (Kojima G et al ,2017) and based on the dose dependent hypothesis, it has supposed that when VD intake is below, the serum leptin level will be low and vice versa VD supplementation may cause raising serum leptin (Tarcin *et al*., 2010; Ghavamzadeh and Mahdavi, 2014) as sown in this review. In conclusion, we suggest further clinical trials wither to confirm or negation of existence of diabetogenic or anti-diabetogenic effects for VD_3 supplementations.

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Disclosure

The authors report no conflicts of interest in this work.

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