



Narrative review on role of vitamin D in type II diabetes and hyperlipidemia

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ABSTRACT

It is widely known that type II diabetes and hypo-vitaminosis D are very prevalent health problems worldwide. Vitamin D deficiency has emerged as an important risk factor in the pathogenesis and prevention of type II diabetes and hyperlipidemia. The key goal of this narrative review, through performing literature survey, is to consolidate results of relevant studies and consequently help direct future research in this area. Furthermore, highlighting the influence of vitamin D supplementation on beta-cell function, glycemic control; insulin sensitivity and lipid profile are other key aims of this review. For that end, several observational and interventional studies, conducted during the period (2003–2017) on animals and humans, have been reviewed.

The key findings of this review are the significant inverse associations between serum 25(OH)D3 level and insulin resistance, glycemic index, type II diabetes and lipid parameter has been noticed in the majority of such observational studies in human. In addition, both *in vivo* and *in vitro* animal studies have proved the significant role of vitamin D in regulating beta-cell function, insulin sensitivity, and cholesterol biosynthesis, while interventional studies revealed contradicting results. The short-term interventional studies reported improvement in fasting blood sugar (FBS), insulin secretion and insulin resistance in vitamin D deficient-type II diabetic patients. On the other hand, the long-term interventional studies did not produce consistent results. Hence, the key value of this work is to provide guidance to researchers and health professionals on such specific subject. Finally, the review concludes with research limitations and puts forward future recommendations.

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1. Introduction

In early times, vitamin D was known as an important factor in maintaining calcium homeostasis and bone health (Challoumas, 2014). Recently, it has emerged that vitamin D deficiency is associated with several metabolic diseases including obesity, diabetes, hyperlipidemia, and hypertension (Minambres *et al.*, 2015). Diabetes mellitus is a chronic metabolic disorder that can affect nearly every organ in the body (Kumar *et al.*, 2015; Seshadri *et al.*, 2011; Shahzad *et al.*, 2017). It is characterized by the disturbance in carbohydrate, protein, and fat metabolism besides long-term vascular complications (Chiamolera *et al.*, 2016; Masoud, 2014) that can decrease the quality of patient's life (Shahzad *et al.*, 2017).

Diabetes prevalence has rapidly increased as the number of people with this disease has risen from 173 million in 2002 to 371 million in 2013 worldwide (Chiamolera *et al.*, 2016; Shaafie *et al.*, 2013). It has been estimated that 552 million individuals would be affected with diabetes worldwide by the year 2030 (Shaafie *et al.*, 2013). Type II diabetes mellitus alone accounts for 90% of the diabetic cases globally (Swamy *et al.*, 2016). Type II Diabetes Mellitus is caused by beta cell failure (insulin depletion) or inability of insulin to properly exert its effects (insulin resistance) or both simultaneously in the course of the disease (Anyanwu *et al.*, 2017; Asegaonkar 2016; Chiamolera *et al.*, 2016; Masoud, 2014).

Furthermore, diabetes can be complicated by the disturbance in lipid profile, which includes elevation of total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL), and reduced serum level of high-density lipoprotein cholesterol (HDL). This disturbance is considered as a risk factor for cardiovascular disease that is associated with a high mortality rate in diabetic patients (Eftekhar *et al.*, 2014).

The growing burden of diabetes type II has led to further research to identify various predisposing factors of the disease in order to treat it and reduce the prevalence and the complication of the disease (Shaafie *et al.*, 2013). Several predisposing etiological factors have been implicated in the pathogenesis of diabetes type II such as genetic, lifestyle, nutritional, stress, and environmental factors (Asegaonkar 2016; Seshadri *et al.*, 2011; Souza *et al.*, 2016). More recently, vitamin D deficiency has emerged as an important modifiable nutritional risk factor that has generated widespread interest in the pathogenesis and prevention of type II diabetes and hyperlipidemia (Al Kadi, 2014; Asegaonkar, 2016; Challoumas, 2014; Seshadri *et al.*, 2011; Shaafie *et al.*, 2013; Shahzad *et al.*, 2017; Ozder *et al.*, 2015).

2. Method

Review articles of selected studies on vitamin D and its impact on type II diabetes and lipid profile. This conducted review by searching for the keywords "vitamin D, type II diabetes, Insulin resistance, hyperlipidemia, obesity" using different scientific websites including scholar goggle, science direct, pubmed and midline, limiting the search to English language articles, full text.

3. Vitamin D

3.1. Vitamin D structure, forms, sources, activation and bio-availability

Vitamin D is known as a sunshine vitamin (Swamy *et al.*, 2016), and it is a lipophilic secosteroid hormone (Candido & Bressan, 2014; Grimnes, 2011). Vitamin D exists in two forms, ergocalciferol "vitamin D2" and cholecalciferol "vitamin D3" (Chiamolera *et al.*, 2016). Vitamin D2 can be acquired from vegetable sources such as mushrooms, sweet potatoes, and yeasts, while vitamin D3 is derived from animal sources such as fish liver oil, salmon, sardines,

tuna, liver, egg yolk and fortified dairy products (Grimnes, 2011; Masoud, 2014). Additionally, vitamin D3 is synthesized in the human skin from 7-dehydrocholesterol by direct exposure to sunlight (UV- β rays) that results in previtamin D3, which is thermodynamically unstable. Once formed, previtamin D3 transforms to vitamin D3 by thermal induction (Chiamolera et al., 2016; Masoud, 2014; Souza et al., 2016). Sunlight exposure, as a source of vitamin D3, can produce 80%–90% of vitamin D in the body (Candido & Bressan, 2014; Souza et al., 2016). Regardless of the source, vitamin D is transported by vitamin D-binding protein to the liver, where it is rapidly hydroxylated by vitamin D-25-hydroxylase at carbon 25 to form 25-hydroxyvitamin D3 "25(OH) D3" (Chiamolera et al., 2016; Grimnes, 2011; Masoud, 2014). The 25-hydroxyvitamin D3 is further hydroxylated in the kidney at carbon 1 by 1- α hydroxylase to form 1, 25-dihydroxyvitamin D3 "1,25(OH)2D3" (Grimnes, 2011; Masoud, 2014; Minambres et al., 2015; Swamy et al., 2016).

The 25-hydroxyvitamin D3 is the most circulating form of vitamin D, and is considered as an indicator of vitamin D status, with long half-life (two-three weeks), and it reflects the vitamin D from all sources. Whereas, 1,25-dihydroxyvitamin D3 is the final active form of the vitamin with a half-life of 4 to 6 hours (Candido & Bressan, 2014; Chiamolera et al., 2016; Grimnes, 2011; Masoud, 2014; Seshadri et al., 2011).

Thereafter, the active form of vitamin D3 is linked to vitamin D-binding protein (DBP), in the circulation, until it reaches its target tissue, where it crosses the cell membrane and exerts its effects mainly through vitamin D receptors (VDR) (Masoud, 2014; Seshadri et al., 2011).

Excess of 25-hydroxyvitamin D3 will be sequestered and stored in adipose tissue as a result of its lipid solubility (Grimnes, 2011; Mauss et al., 2015), and it will be released again on demand, for example, during winter (Candido & Bressan, 2014).

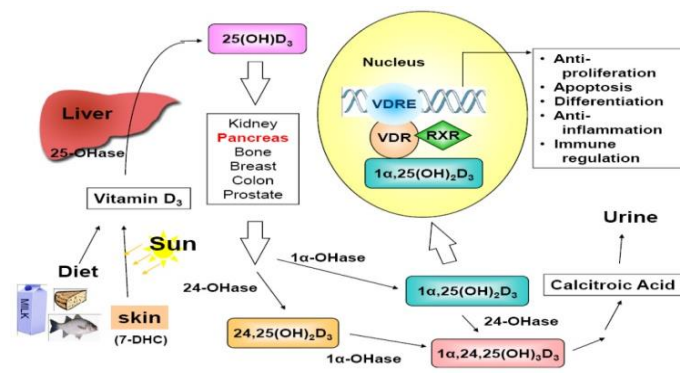


Fig. 1. Vitamin D metabolism (Chiang et al., 2011)

The hypovitaminosis D is common and occurs mainly because of inadequate sunlight exposure, use of sunscreen, clothing, decreased outdoor activities, darker skin pigmentation, pollution, higher latitudes, winter season, old age, obesity and low dietary vitamin D intake (Ozder et al., 2015; Polur et al., 2013; Simsek et

al., 2015; Souza et al., 2016). Whereas, the hypervitaminosis D is rare and is caused by supplementation of high doses of vitamin D (5000 to 10,000 IU/day for several months) rather than sunlight (Chiamolera et al., 2016).

The definition of vitamin D deficiency based on the status of circulating 25(OH)D3 levels is still a debatable matter. Some authors (Al sofiani et al., 2015; Candido & Bressan, 2014; Chiamolera et al., 2016; Harinarayan, 2014; Mauss et al., 2015; Polur et al., 2013; Seshadri et al., 2011; Shahzad et al., 2017; Simsek et al., 2015; Swamy et al., 2016) considered the deficiency of 25-hydroxyvitamin is below 20 ng/mL, insufficiency is ranged between 20-30 ng/mL and sufficiency is above 30 ng/mL. However, others (Kumar et al., 2015) considered deficiency of 25-hydroxyvitamin happens below 15 ng/mL, insufficiency ranged between 15-30 ng/mL and sufficiency is above 30 ng/mL. On the other hand, some authors (Grimnes 2011; Shaafie et al., 2013) perceive deficiency to happen below 10 ng/mL, insufficiency ranged between 10–20 ng/mL and sufficiency is above 20 ng/mL.

3.2. Vitamin D supplementation dosage

The required dose of vitamin D to maintain an optimal level of 25(OH)D3 differs. There are several factors contribute to this variation including age, degree of skin pigmentation, exposure to sunlight and basal level of vitamin D3 in the serum. Furthermore, the needed dose of vitamin D is affected by the medical condition and presence of some diseases that might interfere with vitamin D absorption such as liver diseases, celiac disease, and inflammatory bowel disease. Besides, people who live away from equator need higher doses of vitamin D (Raman R., (2017) Healthline [online]).

Elderly people need more vitamin D doses compared to the younger ones due to less exposure to sunlight, in addition to the reduced ability to synthesize vitamin D3 when exposed to the sun as a result of skin thinning. The recommended daily dose of vitamin D for elderly people is 1.000-2.000 IU (Raman R., (2017) Healthline [online]).

Similarly, the dark-skin people produce a lower level of vitamin D3 because the surplus of melanin protects skin from sunlight, therefore, vitamin D dose should be 1.000-2.000 IU (Raman R., (2017) Healthline [online]). For obese people, the recommended daily dose is different as it is calculated based on body weight 20-80 IU/Kg (Summary of vitamin D, 2018).

The Safe upper limit of vitamin D should not exceed 10.000 IU/Day (Summary of vitamin D, 2018). 400-800 IU/day is considered to be sufficient to maintain vitamin D within the normal range for most people. However, this dose, as explained above, is not enough for those individuals with special conditions such as elderly, dark-skin people, etc (Raman R., 2017, Healthline [online]).

3.3. Treatment of vitamin D deficiency and insufficiency

Table 1 explains the recommended doses of Vitamin D in the case of deficiency and insufficiency (Pearce & Cheetham, 2010).

Table 1

The recommended doses of Vitamin D in the case of deficiency and insufficiency

Vitamin D status	Adult dose of vitamin D	Child dose of vitamin D
Deficiency	10,000 IU/ day or 60,000 IU/ week for 8-12 weeks, or 300,000 or 600,000 IU orally or by intramuscular injection once or twice	< 6 months: 3000 IU/ day for 8-12 weeks. > 6 months: 6000 IU/ day for 8-12 weeks. > 1 year: 300,000 IU, as a one-off high dose therapy (Stoss regimen).
Insufficiency or maintenance therapy following deficiency	1000-2000 IU/ day or 10,000 IU/ week	< 6 months: 200-400 IU/day. > 6 months: 400-800 IU/day.

Note: The above table shows that, one off high dose treatments is effective, but should be followed by a maintenance therapy dose of vitamin D.

4. Role of vitamin D in diabetes

4.1. Vitamin D in type 2 diabetes mellitus

The active form of vitamin D may play an important influential effect on the insulin action as it acts through several mechanisms on pancreatic and extra-pancreatic tissues (Al Kadi, 2014; Seshadri et al., 2011; Swamy et al., 2016). It acts directly by stimulating the synthesis of insulin and expression of insulin receptors, and/or indirectly via its role in regulating extracellular calcium to ensure normal calcium influx through the cell membrane and sufficient intracellular calcium (Al Kadi, 2014; Seshadri et al., 2011; Swamy et al., 2016).

Synthesis of insulin in β -pancreatic cells and expression of insulin receptor in peripheral tissue are directly stimulated by 1,25(OH) $_2$ D $_3$, which is connected to the vitamin D receptor (VDR) to form the heterodimer VDR/RXR (retinoid x receptor) (Harinarayan, 2014; Masoud, 2014; Mohapatro et al., 2016; Seshadri et al., 2011; Souza et al., 2016; Swamy et al., 2016). The resulted complex is trans-located to the cell core and connected to vitamin D Response Elements (VDRE) in the promoter region of human insulin gene (Grimnes, 2011; Masoud, 2014; Mohapatro et al., 2016; Souza et al., 2016; Swamy et al., 2016). It will activate the transcription of the human insulin gene, which in turn, stimulates the cell proliferation and differentiation (Grimnes, 2011; Masoud, 2014; Mohapatro et al., 2016; Souza et al., 2016; Swamy et al., 2016).

Vitamin D indirectly induces β -cells insulin secretion by increasing the intracellular calcium concentration via activation of non-selective voltage-dependent calcium channels (Mohapatro et al., 2016; Swamy et al., 2016). Intracellular calcium is an important ion required during the process of insulin secretion, which is calcium-dependent process, and it works as a modulator of depolarization-stimulated insulin release (Harinarayan, 2014; Souza et al., 2016). The indirect action of vitamin D also includes the activation of β -cells calcium dependent endopeptidases, which converts proinsulin to insulin, thereby increasing the insulin concentration (Al sofiani et al., 2015; Anyanwu et al., 2017; Mohapatro et al., 2016). Additionally, beta-cells have their own 1 α -hydroxylase enzyme, which hydroxylates 25(OH)D $_3$ to produce the active form of vitamin D 1,25(OH) $_2$ D $_3$ (Al sofiani et al., 2015; Grimnes, 2011; Souza et al., 2016).

Peripherally in insulin-target tissues, such as skeletal muscle and adipose tissue, vitamin D maintains the normal level of cytosolic ionized calcium, which is important in signal transduction and insulin mediated-intracellular processes, thereby improving insulin sensitivity (Asegaonkar, 2016; Harinarayan, 2014; Mohapatro et al., 2016; Seshadri et al., 2011; Swamy et al., 2016). Reduced level of cytosolic ionized calcium in insulin target tissues may impair signal transduction of insulin causing peripheral insulin resistance that results in decreased glucose transport activity (Harinarayan, 2014; Mohapatro et al., 2016; Swamy et al., 2016).

Vitamin D can also act indirectly by activation of osteoblast to synthesize osteocalcin hormone that stimulates insulin synthesis in the pancreas (Candido & Bressan, 2014; Masoud, 2014). Vitamin D may also promote the survival of pancreatic cells and reduces beta-cell destruction by modulating the effects of inflammatory cytokines (Anyanwu et al., 2017; Harinarayan, 2014; Masoud, 2014).

On the other side, deficiency of vitamin D has been implicated in pathogenesis of type II diabetes by decreasing the extracellular calcium, leading to reduced secretion of insulin, and/or by decreasing the expression of insulin receptors, leading to peripheral insulin resistance (Mauss et al., 2015; Sharma et al., 2016).

The first indication of vitamin D potential role in type II diabetes was discovered in 1975 by a seasonal variation in glycemic control reported in type II diabetic patient. The glycemic control becomes worse during winter, which is correlated later on, by some authors, with high prevalence of hypovitaminosis D, as a result of reduced sunlight exposure during winter (Harinarayan,

2014; Mitri et al., 2011; Seshadri et al., 2011; Shaafie et al., 2013; Shahzad et al., 2017; Swamy et al., 2016). Moreover, the direct action of vitamin D on pancreatic β -cell was first generated by the detection of 1 α -hydroxylase enzyme and vitamin D receptors (VDR) inside the beta cells in animal studies (Al Kadi, 2014; Grimnes, 2011; Mohapatro et al., 2016; Seshadri et al., 2011; Souza et al., 2016). Additionally, vitamin D receptors (VDR) are widely expressed in skeletal muscles and adipose tissues (Candido & Bressan, 2014; Masoud, 2014).

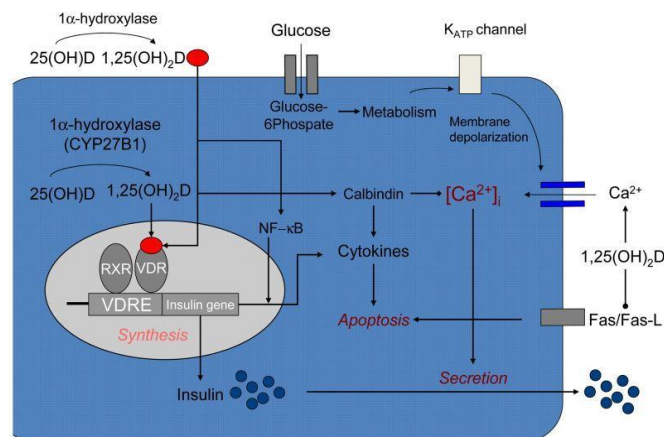


Fig. 2. Effect of Vitamin D on insulin secretion (Mitri J, Pittas AG., 2014).

The discovery of the broad distribution of vitamin D receptors in 36 different tissues, other than skeletal tissues, and the extra-renal production of 1,25(OH) $_2$ D $_3$ in several tissues, supported the perspective wide-ranging effects of vitamin D outside of skeletal health and increased the interest in the therapeutic role of vitamin D in chronic diseases, such as type II diabetes and obesity (Candido & Bressan 2014; Grimnes, 2011; Mitri et al., 2011; Souza et al., 2016).

4.2. Studies in animal

Both *in vivo*, and *in vitro*, studies in animal models and human have established an important role of vitamin D in the regulation of beta-cell function and insulin sensitivity (Anyanwu et al., 2017; Grimnes, 2011; Harinarayan, 2014). Studies employing animal models had indicated that vitamin D deficiency impaired insulin secretion, which produced glucose intolerance and subsequently type II diabetes (Kumar et al., 2015; Seshadri et al., 2011).

In vitro, isolated islets from vitamin D deficient animals displayed impairment of insulin release when cultured and tested with glucose. This impairment could be prevented when high concentrations of vitamin D is added to the cultured islets (Seshadri et al., 2011). Furthermore, *in vitro* study, Grimnes (2011) had reported that vitamin D increased the expression of the insulin receptor, thereby enhancing the insulin sensitivity.

Similarly, *in vivo* study using vitamin D deficient rats showed impaired glucose-mediated insulin release from beta-cells that could be restored by vitamin D supplementation (Harinarayan, 2014). Another *in vivo* study of vitamin D receptors in null mice showed impaired insulin secretion and sensitivity (Al Sofiani et al., 2015).

4.3. Studies in humans

4.3.1. Observational studies

The major evidence of the protective effect of vitamin D against the development of type II diabetes was noticed in an observational study of non-diabetic individuals over a 22 years period. Type II diabetes was less likely to develop in individuals with high level of vitamin D (Knekt et al., 2008). Another observational study was used to assess the risk of type II diabetes in 6119 participants and revealed the double risk of type II diabetes in the lowest serum 25(OH)D $_3$ participants as compared to the highest (Grimnes, 2011).

Considerable number of cross-sectional, case control and randomized controlled studies reported significant inverse associations between serum 25(OH)D3 level and glycemic indices "Fasting Blood Sugar (FBS), PostPrandial Blood Sugar (PPBS), Glycosylated hemoglobin (HbA1c)" (Grimnes, 2011; Harinarayan, 2014; Kumar et al., 2015; Masoud 2014; Mauss et al., 2015; Ozder et al., 2015; Polur et al., 2013; Shaafie et al., 2013; Swamy et al., 2016), insulin resistance (Asegaonkar, 2016; Grimnes, 2011; Harinarayan, 2014; Mohapatro, et al., 2016; Ozder et al., 2015; Polur et al., 2013; Seshadri et al., 2011), and type II diabetes (Candido & Bressan, 2014; Chiamolera et al., 2016; Grimnes, 2011; Harinarayan, 2014; Kumar et al., 2015; Mahmodina et al., 2017; Masoud, 2014; Mitri et al., 2011; Mohapatro et al., 2016; Ozder et al., 2015; Polur et al., 2013; Seshadri et al., 2011; Shaafie et al., 2013; Shahzad et al., 2017; Sharma et al., 2016; Swamy et al., 2016). Furthermore, a meta-analysis study on 4,996 cases explained 4% lower risk of type II diabetes when 25(OH)D levels increased by 10 nmol/L (Mauss et al., 2015).

Other observational studies confirmed a high prevalence of vitamin D deficiency in type II diabetes (Kumar et al., 2015; Mahmodina et al., 2017; Mauss et al., 2015). This deficiency

reached a high level of more than 90% (Shaafie, et al., 2013; Shahzad et al., 2017), and the incidence is more prevailing among the old population (Mahmodina et al., 2017; Shahzad et al., 2017).

In contrast, other studies did not detect any correlation between the glycemic index (HbA1c) and vitamin D levels in patients with type II diabetes (Harinarayan, 2014; Shahzad et al., 2017; Simsek et al., 2015). However, high frequency of vitamin D deficiency was observed in the diabetic patients compared to the healthy group (Simsek et al., 2015). This correlation supports the important role of vitamin D in the pathogenesis of type II diabetes (Kumar et al., 2015; Shaafie et al., 2013), and it could be used as a prophylactic measure (Grimnes, 2011).

These previous studies advise using vitamin D as a supplement by both of pre-diabetic and type II diabetic patients and assess its impact on glycemic control, insulin resistance, and type II diabetes. This supplementation is used to halt the progression from pre-diabetes to type II diabetes, improve the glycemic control of type II diabetes, and prevent the development of complication of type II diabetes (Asegaonkar, 2016; Candido & Bressan, 2014; Chiamolera et al., 2016; Kumar et al., 2015; Masoud, 2014; Shaafie et al., 2013; Swamy et al., 2016).

Table 2

Observational studies of vitamin D status and incidence of type II diabetes

Reference	Year	Country	Number of participants	Age (years)	Study design	Main outcome
Mahmodnia et al., 2017	2017	Iran	101 type II diabetic patients	50–75	Descriptive-analytic study	101 type II diabetic patients
Mohapatro et al., 2016	2016	India	140 type II diabetic and 150 healthy individuals.	50–60	Case-control study	Significant correlation was found between Vitamin D, triglyceride level, and severity of insulin resistance.
Swamy et al., 2016	2016	Bagalkot	100 cases of type II diabetic and 100 healthy controls.	30–70	Case-control study	Vitamin D levels were lower in patients with type II diabetic patients. Significant negative correlation between vitamin D and glycemic status (HbA1c, FBS, PPBS) in type II diabetes.
Shahzad et al., 2017	2016	Pakistan	126 type II diabetic patients	30–70		High prevalence of vitamin D deficiency in type II diabetes (92.1%) it is common among elderly
Simsek et al., 2015	2015	Turkey	203 Type II diabetes, 81 healthy	50–60	Cross section study	No correlation was identified between HbA1c and 25-OH-vitamin D levels in type II diabetic patients. However, diabetic patients had lower vitamin D levels than the healthy group.
Kumar et al., 2015	2015	India	50 type II diabetic patients	35–74	Cross section study	Vitamin D level inversely related to glycemic control. Vitamin D deficiency is prevalent in diabetes mellitus type II 76%.
Sharma et al., 2016	2015	India	50 f type II diabetic patients 50 healthy control	40–60	Cross section study	The patients of type II DM had significantly lower 25(OH) vitamin D levels compared to controls.
Mauss et al., 2015	2015	German	1821 participant	50–60	Cross-Sectional Study	Significant inverse association of glycemic control with 25(OH)D deficiency. Vitamin D deficiency is associated with prevalent DM in older adults.
Chiamolera et al., 2016	2015	Brazil	54 type II diabetic patients	50–70	Prospective cross-sectional cohort Study	High prevalence of vitamin D deficiency in type II diabetic patients.
Ozder et al., 2015	2014	Turkey	134 type II diabetic patient and 134 non-diabetic, healthy controls	45–70	Cross section study	Prevalent vitamin D deficiency in patients with type II diabetes and healthy subjects.
Masoud, 2014	2014	Gaza	58 type II diabetic patients and 58 healthy controls	45–65	Case-control study	Serum vitamin D was significantly lower in type II diabetic patients compared to controls. Significant negative correlations between vitamin D, glycemic control and BMI.
Al Kadi, 2014	2014	Saudi Arabia	60 women Type II diabetes and 60 women control	50–60		Although the diabetic women had vitamin D deficiency, lower levels of 25(OH)D was prevalent in both groups.
Shaafie et al., 2013	2013	UAE	192 randomly selected type II diabetic patients	35–65	Pilot study	Vitamin D deficiency & insufficiency was found among 96.8% of type II diabetic patients. HbA1C and LDLc showed a negative correlation with vitamin D levels.
Polur et al., 2013	2013	India	Randomly selecting 120 type II diabetic patients	35–70	Case-control study	Significant inverse association between vitamin D, glycemia and insulin resistance.
Grimnes, 2011	2011	Norway	6119 participant	20–87		The risk of type II diabetes was approximately doubled in the individual with lowest serum 25(OH)D as compared to the highest.
Grimnes, 2011	2011	Norway	Healthy adults 52 persons with high and 108 persons with low serum 25(OH)D levels		Randomized double-blinded	Negative correlation between vitamin D, glycemic control, and insulin sensitivity. Inverse association between serum 25(OH)D concentrations and the risk of developing type II diabetes
Knekt et al., 2008	2008	Finland	1398 individuals free of diabetes at baseline.	40–74	Case-control study	The subjects with a high level of vitamin D were less likely to develop type II diabetes after a follow-up period of 22 years. None of the individuals had diabetes at the start of the study.

4.3.2. Interventional studies

Several interventional studies were performed in pre-diabetics and type II diabetic patients by using vitamin D supplementation with/without calcium supplementation. Supplementation of oral vitamin D 50,000 IU per week for a period of 8 weeks has improved FBS, insulin secretion, and insulin resistance significantly in 100 patients with type II diabetes (Talaie, 2013).

A study on three groups of individuals with type II diabetes was conducted for a period of 12 weeks. Vitamin D and calcium were daily given to group 1 as a vitamin D-fortified yogurt (containing vitamin D3 1000 IU/day and calcium 300 mg/250 mL). Group 2 was given vitamin D + calcium-fortified yogurt (containing vitamin D3 1000 IU/day and calcium 500 mg/250 mL). Group 3, on the other hand, was given plain yogurt on a daily basis, that contains calcium 300 mg/250 mL without vitamin D. A significant improvement was observed in group 1 and group 2 in terms of glycosylated hemoglobin (HbA1c), insulin resistance, body mass index (BMI), and waist circumference, as compared to group 3 (Ni-kooyeh et al., 2011).

Similar studies were conducted with different doses of vitamin D for various periods with or without calcium. The results showed significant improvement in glycemic index (Kumar et al., 2015; Shaafie et al., 2013; Mitri et al., 2011), β -cell function (Al Sofiani et al., 2015; Harinarayan, 2014; von Hurst et al., 2010), and insulin sensitivity (Chiamolera et al., 2016; Mitri et al., 2011; Shaafie et al., 2013; von Hurst et al., 2010) in type II diabetic patients with vitamin D-deficiency.

On the other hand, additional studies reported improvement in β -cell activity, and insulin secretion only without improvement in HbA1c levels or insulin sensitivity. These studies were conducted using vitamin D 5000 IU/day for a period of 12 weeks, and vitamin D 1904 IU/day for a period of 6 months in vitamin D deficient type II diabetic patients (Al Sofiani et al., 2015; Strobel et al., 2014). Another contradictory study explained that vitamin D3 supplementation (3000 IU daily) for 6 months resulted in significant improvement in insulin sensitivity, but had no effect on β -cell function in vitamin D deficient type II diabetic patients (Hahn et al., 2006).

Other interventional studies on type II diabetic patients have reported that even with improvement of vitamin D status, there was no significant difference in glycemic status, β -cell activity and insulin resistance after 4 months supplementation with vitamin D 400 IU (group 1) and 1200 IU (group 2) daily (Patel et al., 2010). Additionally, the glycemic index, in another similar study, was not affected by supplementation of oral vitamin D 6000 IU /day for six months in vitamin D deficient type II diabetic patients (Grimnes, 2011).

In large prospective studies, the incidence of type II diabetes was reduced by 33% in those with the highest intake of vitamin D and calcium (>800 IU and >1200 mg daily, respectively) as compared with the lowest intake of vitamin D and calcium (<400 IU and <600 mg daily, respectively) (Pittas et al., 2007). Similarly, other studies showed that the supplementation of oral vitamin D 511 IU/day or more was associated with 27 % lower risk of developing type II diabetes as compared to the intake of 159 IU/day or less (Liu et al., 2005).

Conversely, in another study, the incidence of type II diabetes has not been reduced after supplementation of vitamin D with / without calcium in postmenopausal women during the follow-up period of seven years (de Boer et al., 2008), and in older persons during a follow-up period of 2-5 years as well (Avenell et al., 2009).

The discrepancies between the results of different interventional studies reviewed have been attributed by some authors (Mohapatro et al., 2016) to the effect of confounding factor(s) that might play a role as a mediator between vitamin D and type II diabetes, see Fig. 3.

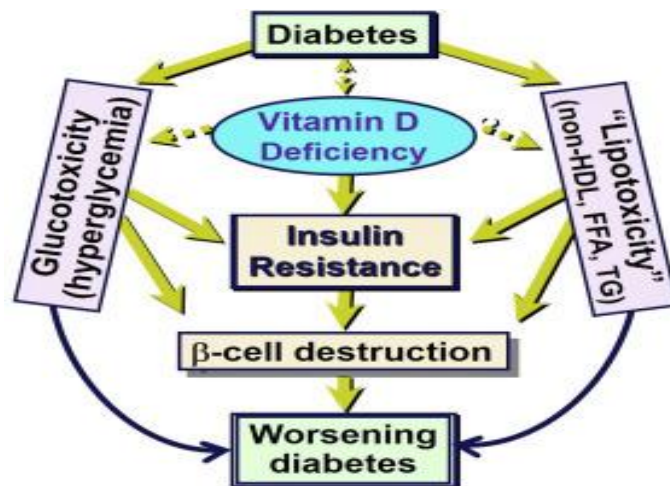


Fig. 3. Vitamin D deficiency leads to diabetes type II and hyperlipidemia (Wimalawansa, 2018)

To sum up, several limitations have been detected in these previous studies. The number of participants in the vast majority were less than 150 participants. Hence, this will be reflected negatively on the degree of confidence in the results. The duration of the studies is another limitation as the duration ranged between 4 weeks to 6 months. This, in turn, revealed contradicting results in most of the studies as the short-term duration resulted in positive conclusions, while the long-term revealed inconsistent results. In addition, these studies did not provide any details about the personal lifestyle of participants (exercise, weight, diet, stress, etc) as these elements have their own influences on insulin resistance and diabetes. Furthermore, these studies did not provide any background about diabetes treatment that had been involved details or ideas about anti-diabetic treatment. As the latter might have a positive effect on diabetes rather than vitamin D. Moreover, the long-term studies did not provide any details about whether patients have been regularly monitored to evaluate their compliance with the treatment regimen.

Finally, based on the limitations aforementioned, future well-designed interventional studies are needed to better understand the relationship between vitamin D supplementation, and diabetes type II. For instance, it is better to conduct randomized controlled studies over a long period of duration rather than a short duration (≤ 6 months). It is also recommended to increase the sample size to attain more accurate results and include pre-diabetic and early type II diabetic individuals. It is also advisable to conduct comparative studies that include males versus females, thin versus obese, white versus non-white, young versus old, etc.

5. Association between vitamin D and lipid parameters

5.1. Vitamin D and obesity

Vitamin D receptor (VDR) is highly distributed in adipose tissues, giving rise to its importance in altering lipid profile (Wimalansa, 2018). There is a close negative association between obesity and status of vitamin D. People with high body mass index (BMI), fat mass, and waist circumference have a lower level of serum vitamin D (Sadiya et al., 2014). The fat solubility of vitamin D is a factor of being sequestered and stored in adipose tissues, contributing to the reduction in bioavailability of vitamin D (Cheng et al., 2010). On the opposite side, people with vitamin D deficiency are susceptible to gain more fatty tissues. This is because of the elevated serum level of parathyroid hormone (PTH) as a consequence to vitamin D deficiency. PTH enhances adipogenesis via promoting more calcium influx into adipocytes. In addition, it has been suggested that vitamin D plays role in altering adipogenesis through VDR- dependent inhibition of peroxisome proliferator-activated receptor (PPAR- α) (Cheng et al., 2010).

Table 3

Effect of vitamin D supplementation on the glycemic index, insulin resistance and type II diabetes

Reference	Year	Country	Number of participants	Age (years)	Vitamin D form and dose	Intervention Study duration	Outcome
Anyanwu, et al., 2017	2017	Nigeria	42 type II diabetic patients	35–65	Vitamin D3 3000 IU daily	12 weeks	Significant improvement in insulin resistance, but has no effect on pancreatic beta-cell function in vitamin D deficient type II diabetic patients.
Al-Sofiani, et al., 2015	2015	Saudi Arabia	22 type II diabetic patients	21–75	Cholecalciferol (5000 IU/day)	12 weeks	Improvement in β -cell activity in vitamin D-deficient type II diabetes with no significant changes in HbA1c or insulin sensitivity.
Strobel, et al., 2014	2014	Germany	86 Type II diabetic patients	18–80	Vitamin D supplementation of 1904 IU/day	6 month	Improvement in β -cell activity and insulin secretion only without improvement in HbA1c levels or insulin sensitivity
Talaei, et al., 2013	2013	Iran	100 Type II diabetic patients	30–70	Oral vitamin D 50,000 per week	8 weeks	Significant improvement in FBS, insulin secretion and insulin resistance.
Nikooyeh, et al., 2011	2011	Iran	90 Type II diabetic patients	30–60	Three groups: daily consumption of 1. vitamin D-fortified yogurt (containing vitamin D3 1000 IU/day and calcium 300 mg/250 mL). 2. vitamin D + calcium-fortified yogurt (containing vitamin D3 1000 IU/day and calcium 500 mg/250 mL). 3. plain yogurt that contains calcium 300 mg/250 mL	12 weeks	Significant improvement in the glycemic index (HbA1c), insulin resistance, body mass index (BMI), and waist circumference.
Grimnes, 2011	2011	Norway	108 vitamin D deficient prediabetic and type II diabetic patients	50–80	6000 IU/day	6–months	No improvement in the glycemic index.
Patel et al., 2010	2010	USA	Type II diabetic Group-1 (13) Group-2 (11)	54–65	400 IU (group1) and 1200 IU (group2) oral cholecalciferol	4 months	No significant difference were noted in glycemic status, β -cell activity and insulin resistance.
von Hurst et al., 2010	2009	New Zealand	Vitamin D deficient Subjects =42 control=39	40–50	4000 IU Cholecalciferol/day	6–months	Significant improvement in insulin secretion, and insulin resistance.
Avenell et al., 2009	2009	UK	5292 with recent previous osteoporotic fracture	77	Daily oral intakes of 800 IU vitamin D3, alone or combined with 1000 mg calcium	2–5 years	Incidence of type II diabetes did not reduce after supplementation of vitamin D with and without calcium in older persons.
De Boer et al., 2008	2008	USA	33,951 Healthy postmenopausal women	50–79	D3 400 IU/day plus calcium carbonate 1000mg/day	7 years	Vitamin D supplementation did not reduce the risk of developing diabetes.
Pittas et al., 2007	2008	USA	Nurses' Health Study 83,779	46	A combined daily intake of >1,200 mg/day calcium and >800 IU vitamin D/day compared with an intake of <600 mg and 400 IU calcium and vitamin D	20 years	33% lower risk of incident type II diabetes.
Pittas et al., 2007	2007	USA	Normal fasting Glucose= 222 Impaired fasting Glucose= 92	≥ 65	D3 700 IU/day plus calcium citrate 500 mg/day	3 years	Improvement in fasting blood glucose and insulin resistance only in the group that had impaired fasting glucose at baseline.
Hahn et al., 2006	2006		120 untreated polycystic ovary syndrome	Median age 28	3000 IU per day	6–months	Improvement in insulin sensitivity.
Liu et al., 2005	2005	USA	Women's Health Study = 10,066 participating	>45	Daily intakes of vitamin D 511 IU/day or more compared to daily intakes of 159 IU/day or less.	Data analysis	27 % lower risk of developing type II diabetes in middle-aged and older women.

To sum up, several limitations have been detected in these previous studies. The number of participants in the vast majority were less than 150 participants. Hence, this will be reflected negatively on the degree of confidence in the results. The duration of the studies is another limitation as the duration ranged between 4 weeks to 6 months. This, in turn, revealed contradicting results in most of the studies as the short-term duration resulted in positive conclusions, while the long-term revealed inconsistent results. In addition, these studies did not provide any details about the personal lifestyle of participants (exercise, weight, diet, stress, etc) as these elements have their own influences on insulin resistance and diabetes. Furthermore, these studies did not provide any background about diabetes treatment that had been involved details or ideas about anti-diabetic treatment. As the latter might have a positive effect on diabetes rather than vitamin D. Moreover, the long-term studies did not provide any details about whether patients have been regularly monitored to evaluate their compliance with the treatment regiment.

Finally, based on the limitations aforementioned, future well-designed interventional studies are needed to better understand the relationship between vitamin D supplementation, and diabetes type II. For instance, it is better to conduct randomized controlled studies over a long period of duration rather than a short duration (≤ 6 months). It is also recommended to increase the sample size to attain more accurate results and include pre-diabetic and early type II diabetic individuals. It is also advisable to conduct comparative studies that include males versus females, thin versus obese, white versus non-white, young versus old, etc.

5. Association between vitamin D and lipid parameters

5.1. Vitamin D and obesity

Vitamin D receptor (VDR) is highly distributed in adipose tissues, giving rise to its importance in altering lipid profile (Wimalansa, 2018). There is a close negative association between obesity and status of vitamin D. People with high body mass index (BMI),

fat mass, and waist circumference have a lower level of serum vitamin D (Sadiya et al., 2014). The fat solubility of vitamin D is a factor of being sequestered and stored in adipose tissues, contributing to the reduction in bioavailability of vitamin D (Cheng et al., 2010). On the opposite side, people with vitamin D deficiency are susceptible to gain more fatty tissues. This is because of the elevated serum level of parathyroid hormone (PTH) as a consequence to vitamin D deficiency. PTH enhances adipogenesis via promoting more calcium influx into adipocytes. In addition, it has been suggested that vitamin D plays role in altering adipogenesis through VDR- dependent inhibition of peroxisome proliferator-activated receptor (PPAR- α) (Cheng et al., 2010).

5.2. Vitamin D status and lipid profile

Obesity is associated with hypovitaminosis D, which in turn, leads to B-cell dysfunction and insulin resistance. The later might

cause a disturbance in lipoprotein metabolism. This happens due to the reduction of lipoprotein lipase activity, which results in an increase in triglyceride and decrease in HDL-cholesterol levels (Wang et al., 2016). In addition, an elevation in PTH level, as a result of low serum level of vitamin D, leads to an increase in triglyceride level (Wang et al., 2016).

Vitamin D alter lipid profile indirectly through its effect on calcium. Vitamin D increases intestinal calcium absorption, which, in turn, reduces synthesis and release of triglycerides by the liver. High level of intestinal calcium disturbs fatty acid absorption by combining with the fat (Wang et al., 2016). Consequently, to reduced fat absorption and enhanced bile acid synthesis from cholesterol, under influence of calcium, a reduction in LDL-cholesterol is taken place (Wang et al., 2016).

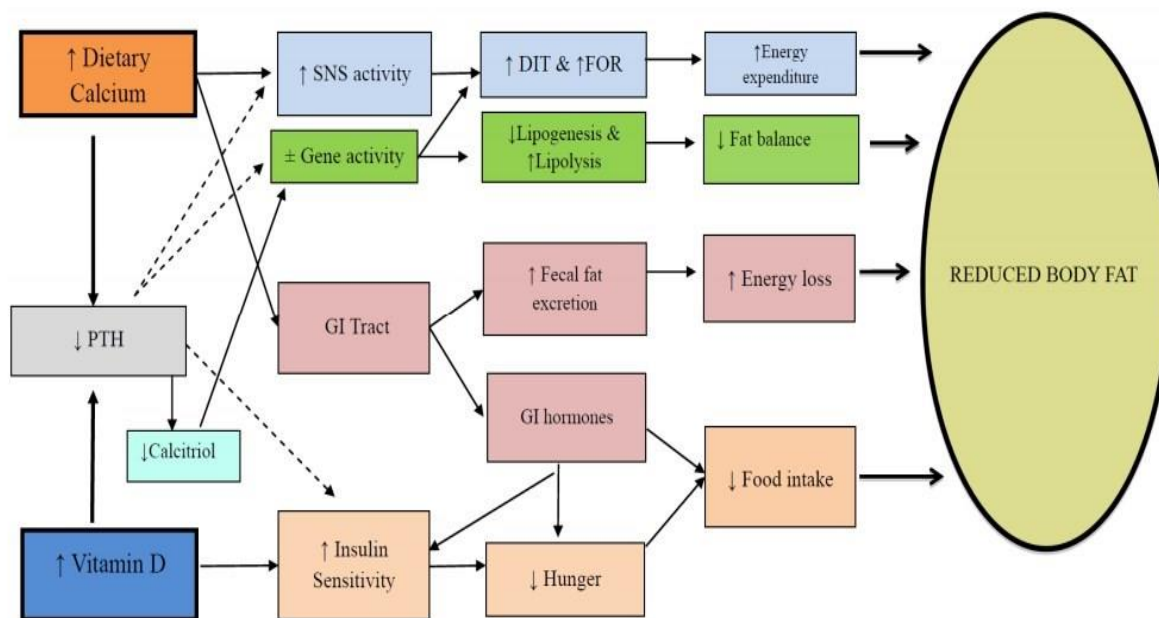


Fig. 4. Effect of Vitamin D on body fat (Soares et al., 2014)

In this respect, an *in vitro* study examined the effect of vitamin D on cholesterol biosynthesis in cultured cells. Vitamin D3 causes inhibition of cholesterol biosynthesis at two sites. This inhibition is a concentration-dependent process. At a concentration of $>2 \mu\text{g/ml}$, Vitamin D causes inhibition to lanosterol demethylation, and at a concentration $<2 \mu\text{g/ml}$, vitamin D inhibits HMG CoA reductase (Perez-Castrillon et al., 2010). In addition, several other studies involved type II diabetic patients suggested an association between vitamin D status and lipid profile, including serum level of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. However, the outcomes were inconclusive.

5.2.1. Observational studies

Recently it has been found that people with sufficient levels of vitamin D have a favored lipid profile compared to those with vitamin D deficiency or insufficiency (Challoumas, 2014). For instance, a cross-sectional study, involved 309 obese individuals with type II diabetes, shows an inverse significant association between vitamin D level and LDL-cholesterol, triglyceride, total cholesterol in patients who are on oral hypoglycemic drugs (Sadiya et al., 2014). This finding was in agreement with another study, which revealed a significant difference between vitamin D levels

for diabetic and healthy volunteers. The results were 80.7% of diabetic participants had vitamin D deficiency compared to healthy participants who represented only 43.2% (Mashahit et al., 2017). The percentage of dyslipidemia was more in individuals with a suboptimal level of vitamin D. It was inversely and significantly associated with triglyceride level, and positively associated with HDL in both diabetics and healthy participants (Mashahit et al., 2017). On the contrary, another study involved 192 type II diabetic patients, of which 96.8% were vitamin D deficient or insufficient showed a weak inverse association between vitamin D and both total cholesterol & LDL-cholesterol (Shaafe et al., 2013).

A similar study was conducted on 108 cases with type II diabetes. The study demonstrated an insignificant negative association between serum level of 25(OH)D and of triglycerides and total cholesterol, whereas 25(OH)D was positively correlated with HDL-cholesterol and LDL-cholesterol (Saedisomeolia et al., 2014). However, a descriptive cross-sectional study involved 120 participants with type II diabetes, divided into two groups, case group (Vitamin D $<30 \text{ ng/ml}$), and control group (vitamin D $>30 \text{ ng/ml}$) showed insignificant differences in lipid profile between two groups. Interestingly, a significant increase in the mean score of cholesterol level detected in the five-years diabetic cases (Mohammed & Ismail, 2014).

Table 4

Observational studies of vitamin D status and lipid profile

Reference	Year	Country	No. of participants	Age (years)	Study Design	Outcome
Mashahit, et al., 2017	2017	Egypt	176 88 diabetic 88 Healthy	30-60	Descriptive study	Significant positive association between vitamin D and HDL in diabetics. Statistically significant difference between vitamin D deficient and sufficient subjects in the healthy group regarding the inverse association between vitamin D and triglyceride, and positive association with HDL level.
Schmitt et al., 2017	2016	Brazil	463 Women (Post-menopausal)	45-75	Observational cross section cohort study	Vitamin D deficient women had a higher level of total cholesterol, triglyceride and lower level of HDL-C compared to vitamin D sufficient women.
Saedisomeolia et al., 2014	2014	Iran	108 Type II Diabetic individuals	20-80	Cross section study	Non-significant inverse association of vitamin D level with triglyceride, total cholesterol and positive correlation with HDL-C, LDL-C.
Mohammed and Ismail, 2014	2014	Sudan	120 Type II Diabetic cases Case Group (Vitamin D deficient) Control Group (Vitamin D sufficient)	25-80	Descriptive cross Section study	Insignificant difference in lipid profile between case and control groups. Significant higher level of cholesterol in patients who are diabetic for more than 5 years.
Sadiya et al., 2014	2014	UAE (Ajman)	309 Type II Diabetic Obese individuals	30-60	Cross section study	Inverse Association between Vitamin D and triglyceride, LDL-C. High prevalence of Vitamin D deficiency in diabetics.
Patel, et al., 2017	2014	India	120 premenopausal women	20-45	Cross section study	Significant negative association between Vitamin D level and total cholesterol, triglyceride, LDL-C. Positive association with HDL-C.
Al-Dabhani et al., 2017	2014	Qatar	1205, 702 women, 503 men	18-80	Cross section study	Inverse association with triglyceride. Positive association with HDL-C.
Park et al., 2012	2012	Korea	301 elderly people	≥ 70	Cross section study	Inverse association with triglyceride.
Yin et al., 2012	2012	China	601 (non-diabetic)	35-60	Cross section study	Significant negative association with LDL-C. This association was more prominent in men than women.
LU et al., 2009	2009	China	1443 men, 1819 women	50-70	Cross section study	Negative association between vitamin D level and triglyceride, negative association with HDL-C. This association was significant for men.
Auwerx et al., (1992)	1983	Belgian Germany	185 men 173 Women	Men mean age:37.1±11.1 Women mean age:36.8±10.2	Cross Section Study	Significant positive correlation of Vitamin D with HDL-C.

5.2.2. Interventional studies

In spite of a large number of observational studies that showed an inverse correlation between serum level of 25(OH)D and lipid profile, interventional studies on the other hand failed to produce the same. Several interventional studies were conducted on type II diabetic patients with 25(OH)D deficiency. These studies were performed to assess changes in lipid profile after correction of serum level of 25(OH)D.

One of these studies focused on giving 16,000 IU of vitamin D orally once a week to 28 vitamin D deficient-diabetic patients over a period of 8 weeks ([Ramiro-Lozano & Calvo-Ramero, 2015](#)). All participants reached an optimal level of vitamin D, and the results showed a significant reduction in total cholesterol level without reduction in the other lipid parameters. This finding was consistent with that of a randomized, double-blind placebo-controlled clinical trial targeted 54 pregnant women with gestational diabetes and vitamin D deficiency. The control group received two oral doses of 50,000 IU of vitamin D3, one at the start of the study, and the second after three-week interval. By the end of this study, the authors found an elevation in serum 25(OH)D correlated with a

significant reduction in serum level of total cholesterol and LDL-C compared to placebo group ([Asemi et al., 2013](#)). The above results were also consistent with the prospective interventional trial ([Al-Daghri et al., 2012](#)), which was carried out on 34 men and 58 women with type II diabetes, and lasted for 18 months. During the study, the participants were on a daily dose of 2000 IU vitamin D3. By the end of that study, all cases showed significant elevation in vitamin D level, which is associated with a significant reduction in LDL-cholesterol and total cholesterol. This finding was more obvious in women than in men. In another research, 70 patients with type II diabetes were selected for an interventional study, taking 0.25 µg-dihydrocholecalciferol daily for 12 weeks. The treated group showed a reduction of total cholesterol and LDL-cholesterol compared to the control group, but this beneficial effect was statistically insignificant ([Eftekhar et al., 2014](#)). However, these results were consistent with the finding of another study ([Witham et al., 2013](#)), which stated that vitamin D had an insignificant beneficial effect on serum level of total cholesterol when used once orally dose of vitamin D (100,000 IU). Similarly, an elevation of serum level of 25(OH)D, after supplementation with a higher dose of

vitamin D3, (2.000 IU vitamin D3 twice daily for 24 weeks combined with 100mg elemental calcium), did not affect the lipid profile (Ryu et al., 2014). The previous findings showed contradictory conclusions. The inability to achieve conclusive causal results can be attributed to numerous limitations. First of all, the small sample size in several studies. Secondly, in some studies, there were no detailed medical records of the participants. Selection bias is another obstacle that affected the results either for the patients, who participated in the trial or for the studies that had been selected for meta-analysis. Furthermore, disease duration may affect the interventional studies, as patients with DM>5 years have lower

vitamin D and a higher level of cholesterol (Mohammed & Ismail 2014). The most important influential factors were the used dose of vitamin D in the intervention, baseline level of vitamin D before giving the supplement, the formulation used, route of administration, the duration of intervention and the frequency of dosing. Infrequent and too high dosing regimen, that had been used in most of the previous studies, make it hard to achieve informative significant conclusion (Wimalawansa, 2018). In multivariable regression analysis, there were numerous variables that could not be adjusted such as diet, BMI, physical activity and the use of lipid lowering drugs (statin) (Wimalawansa, 2018).

Table 5

Effect of Vitamin D Supplementation on lipid profile

Reference	Year	Country	Number of participants	Age (years)	Vitamin D Form and Dose	Study Duration	Outcome
Namakin et al., (2015)	2014	Iran	40: 20case, 20 control	10-14	1.000 IU Vitamin D tablets daily for one month	One month	Significant increase in LDL-C, HDL-C, no significant difference in LDL/HDL Ratio, cholesterol, triglyceride.
Islam et al., 2014	2014	Bangladesh	200 females	16-36	400 IU/Day +600 mg Ca lactate	One Year	No significant changes in the serum level of total cholesterol, LDL-C, HDL-C, LDL-C/HDL-C Ratio Positive effect on VLDL-C, Triglyceride.
Ramiro-Lozano and Calvo-Romero, 2015	2013	Spain	28 male Type II DM (Vitamin D Deficient)	>70	16.000 IU Calcifediol orally once a week	8 Weeks	Significant reduction in total cholesterol.
Hirschler et al., 2014	2011-2013	Argentina	Total (96) Study group (60), 29 of them are male Control Group(36) 16 of them are male		Study group received 100.000 IU Vitamin D Control group received 50.000 IU vitamin D	2 Years	Study group had higher vitamin D level and improved lipid level compared to the control group. Higher serum level of vitamin D is significantly associated with healthier lipid profile.
Krul-Poel et al., 2015	2012-2013	Netherland	248 Type II Diabetes 126 Placebo 122 Case	Mean age 67±8	50.000 IU Vitamin D3 Once a month	6 Months	No significant improvement.
Ponda et al., 2012	2012	Rockefeller	151 (Vitamin D deficient)	18-85	50.000 IU vitamin D3 weekly for 8 weeks	8 weeks	No significant changes in lipid profile.
AL-Daghri et al., 2012	2012	Saudi Arabia	120 (Type II Diabetes)	30-70	2000 IU Vitamin D3 Daily	18 months	Significant reduction in LDL-C, total cholesterol, Favorable change in HDL/LDL ratio. More improvement in women than men.
Ryu et al., 2014	2011-2012	Korea	40 case Type II Diabetes Vitamin D deficient 41 control	30-69	1.000 IU Cholecalciferol + 100 mg Ca Twice daily	24 weeks	No improvement in lipid profile.
Eftekhari et al., 2014	2011	Iran	70 Type II Diabetes Case 35 Control 35	30-75	0.25µg Calcitriol 2 capsules daily	12 weeks	No significant difference between 2 groups. Significant reduction in total cholesterol, LDL-C, triglycerides in both case and control group.
Rajpathak et al., 2010	2010	US different ethnicity	1091 Postmenopausal women 592 case 599 placebo	50-79	400 IU Vitamin D3 + 1gm elemental Ca Daily	5 years	No significant difference in the changes in lipid profile.
Patel et al., (2010)	2009	Israel	24 Type II Diabetes	58±2.5	13 cases received 400 IU Cholecalciferol 11 cases received 1200 IU Cholecalciferol/day Daily	4 months	No improvement in both groups.
Andersen et al., 2009	2009	Denmark	89 women 84 men Pakistani Origin	Women:18-53 Men:18-64	2 doses of vitamin D: either 10µg/day or 20µg/day	1 year	No change in lipid profile.
Scragg et al.,1995	1991	Cambridge	95 case 94 control	63-76	Single oral dose 2.5 mg Cholecalciferol	5 weeks	No change in serum cholesterol.
Asemi et al., 2013	2013	Iran	54 Women Gestational diabetes 27 case 27 control	18-40	50.000 IU Vitamin D3 2 times, at the start and at day 21 of intervention	6 weeks	Significant reduction in total cholesterol, LDL-C.

6. Conclusion

The surveyed published literature strongly suggested an important role of vitamin D in the pathogenesis and prevention of type II diabetes. Vitamin D deficiency, in animal models and humans, affects beta-cell function, insulin sensitivity, leading to Type II diabetes and disturbance in lipid profile. It also showed lack of common specific definitions of vitamin D insufficiency and deficiency. These controversies were also extended to the dosing of vitamin D supplementation, which thought to be influenced by skin color, sun exposure, body weight, and geographic location.

A significant inverse association between the serum 25(OH)D3 level and type II diabetes with or without dyslipidemia has been observed in several observational studies. On the other hand, no conclusive findings can be drawn from interventional studies that used vitamin D with or without calcium. Whereas, the majority of short-term interventional studies showed improvement in the glycemic outcomes, insulin secretion and insulin resistance in type II diabetics with vitamin D-deficiency. Nevertheless, the long-term interventional (prospective) studies failed to illustrate consistent results regarding the relationship between vitamin D and incidence of type II diabetes. These inconclusive finding came as a result of adopting variable research design, different sample size, and type etc.

The results presented above are not enough to support the hypothesis that improving the status of type II diabetes and lipid profile can be achieved by raising 25(OH)D3 level. Further future studies are required to test the hypothesis that could have considerable implications for the prevention of type II diabetes and its complications. Meanwhile, it might also be advisable for people at risk of type II diabetes to be screened for 25(OH)D3 deficiency.

This narrative review is the first Libyan comprehensive attempt to tackle this issue. It is recommended to carry out a series of comparative interventional studies to retest aforementioned issues using a large sample for long period.

References

- Al-Dabhani, K., Tsilidis, K. K., Murphy N., Ward H. A., Elliott P., Riboli E., Gunter M., and Tzoulaki, I. (2017) 'Prevalence of vitamin D deficiency and association with metabolic syndrome in a Qatari population', *Nutrition & Diabetes*, pp. 1–6
- AL-Daghri, NM., Alkharfy, KM., AL-Othman, A., EL-Kholie, E., Moharram, O., Alokail, M. S., AL-Saleh, Y., Sabico, S., Kumar, S., Chrousos, G. P. (2012) 'Vitamin D supplementation as an adjunct therapy for patients with T2DM: An 18-months prospective interventional study', *Cardiovascular Diabetology*, 11, pp. 85.
- Al Kadi, H. (2014) 'Vitamin D status in Saudi women with type 2 diabetes mellitus: A Case control study', *International Journal of recent advances in multidisciplinary research*, 1(3), pp. 33-36.
- Al-Sofiani, M. E., Jammah, A., Racz, M., Khawaja, R. A., Hasanato, R., El-Fawal, H. A., Mousa, S. A., Mason, D. L. (2015) 'Effect of vitamin D supplementation on glucose control and inflammatory response in type II diabetes: A Double blind, randomized clinical trial', *International journal of endocrinology & metabolism*, 13(1), e22604
- Andersen R., Brot C., Mejborn H., Mølgaard C., Skovgaard L. T., Trolle E., Ovesen L., (2009) 'Vitamin D supplementation does not affect serum lipids and lipoproteins in Pakistani immigrants', *European Journal of Clinical Nutrition*, 63, pp. 1150–1153
- Anyanwu, A. C., Fasanmade, O. A., Coker HAB H. A., Ohwovoriole, A. E. (2017) 'Vitamin D supplementation improves insulin resistance in type 2 diabetes subjects in Lagos, Nigeria', *African Journal of Diabetes Medicine*, 5, pp. 14-17.
- Asegaonkar, S. B. (2016) 'Vitamin D and type 2 diabetes mellitus: Indian perspectives', *Journal of diabetic complications and medicine*, 1(3), pp. 110.
- Asemi, Z., Hashemi, T., Karamali, M., Samimi, M., Esmailzadeh, A. (2013) 'Effect of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation, and oxidative stress in gestational diabetes: A Double-blind randomised controlled clinical trial', *American journal of clinical nutrition*, 98, pp. 1425-1432.
- Auwerx, J., Bouillon, R., and Kesteloot, H. (1992) 'Relation between 25-Hydroxyvitamin D3, Apolipoprotein A-I, and high density lipoprotein cholesterol', *Arteriosclerosis and Thrombosis*, 12, pp. 671-676
- Avenell, A., Cook, J. A., MacLennan, G.S., Macpherson, G.C. (2009) 'Vitamin D supplementation and type 2 diabetes: a substudy of a randomized placebo-controlled trial in older people, (RECORD trial, ISRCTN 51647438)', *Age Ageing*, 38, pp. 606-609.
- Candido, F. G., Bressan, J. (2014) 'Vitamin D: Link between Osteoporosis, Obesity, and Diabetes?', *International journal of molecular sciences*, 15, pp. 6569-6591.
- Challoumas, D. (2014) 'Vitamin D supplementation and lipid profile: What does the best available evidence show?', *Atherosclerosis*, 235, pp.130-139.
- Cheng, S., Massaro, J. M., Fox, C. S., Larson, M. G., Keyes, M. J., McCabe, E. L., Robins, S. J., O'Donnell, C. J., Hoffmann, U., Jacques, P. F., Booth, S. L., Vasan, R. S., Wolf, M., Wang, T. J. (2010) 'Adiposity, cardiometabolic risk, and vitamin D status: The framingham heart study', *Diabetes*, 59, pp. 242-248.
- Chiamolera, P. S., Amaral, C. A., Russo, M. C., Netto, G. O., Fernandes, R. A., de Andrade, R. T., Buscariolli, JLG., Rocha, D. R., Arbex, A. K. (2016) 'Prevalence of low levels of vitamin D in type 2 diabetes at the city of Mangueirinha, Paraná, Southern Brazil', *Open journal of endocrine and metabolic diseases*, 6, pp. 8-12.
- Chiang, K.-C., Yeh, C.-N., Chen, T. C. (2011) 'Vitamin D and pancreatic cancer—An update', *Cancers*, 3, pp. 213-226.
- de Boer, I. H., Tinker, L. F., Connelly, S., Curb, J. D., Howard, B. V., Kestenbaum, B., Larson, J. C., Manson, J. E., Margolis, K. L., Siscovick, D. S., Weiss, N. S. (2008) 'Women's health initiative investigators. Calcium plus vitamin D supplementation and the risk of incident diabetes in the women's Health Initiative', *Diabetes Care*, 31, pp.701-707
- Eftekhari, M. H., Akbarzadeh, M., Dabbaghmanesh, M. H., Hasanzadeh, J. (2014) 'The effect of calcitriol on lipid profile and oxidative stress in hyperlipidemic patients with type 2 diabetes mellitus', *ARYA Atherosclerosis*, 10(2), pp. 82-8.
- Grimnes, G. (2011) Clinical and laboratory aspects of vitamin D in relation to type 2 diabetes and osteoporosis: Results from the Troms study and two randomized clinical trials, *doctorate thesis*, University of Tromsø, faculty of health sciences, department of clinical medicine. Tromsø: Norway, 1, pp.80.
- Hahn, S., Haselhorst, U., Tan, S., Quadbeck, B., Schmidt, M., Roesler, S., Kimmig, R., Mann, K., Janssen, O. E. (2006) 'Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome', *Experimental and clinical endocrinology & diabetes*, 114, 577-583.
- Harinarayan, C. V. (2014) 'Vitamin D and diabetes mellitus', *Hormones*, 13(2), pp. 163-181.
- Hirschler, V., Maccallini, G., Tamborenea, M. I., Gonzalez, C., Sanchez, M., Molinari, C., San Antonio de Los Cobres study group, castano, L., Colque, G., Hidalgo, M., Urzagasti, M. (2014) 'Improvement in lipid profile after vitamin D supplementation

- in indigenous argentine school children', *Cardiovasc hematomol agents Med Chem*, 12(1), pp. 42-49.
- Islam M. Z., Shamim A. A., Akhtaruzzaman M., Kärkkäinen M., Lamberg-Allardt, C. (2014) 'Effect of vitamin D, calcium and multiple micronutrients supplementation on lipid profile in premenopausal Bangladesh garment factory workers with Hypovitaminosis D', *J. Health popul nutr*, 32(4), pp. 687-695
- Knekt, P., Laeksonan, M., Mattila, C., Harkanen, T., Marniemi, J., Heliovaara, M., Rissanen, H., Montonen, J., Reunanen, A. (2008) 'Serum vitamin D and subsequent occurrence of type 2 diabetes', *Epidemiology*, 19(5), pp. 667-671.
- Krui-Poel YHM., Westra S., Boekel E. T., ter Wee M. M., van Schoor, N. M., van Wijland, H., Stam F., Lips, PTAM., Suat Simsek S. (2015) 'Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes (SUNNY Trial): A Randomized placebo-controlled trial', *Diabetes Care*, 38, pp.1420-1426.
- Kumar, H., Singh, V. B., Meena, B. L., Chandra, S., single, R., Jakhar, RS. (2015) 'Correlation of vitamin D level with glycemic control in type 2 diabetes mellitus', *Scholars Journal of Applied Medical Sciences*, 3(6B), pp. 2277-2283.
- Liu, S., Song, Y., Ford, E. S., Manson, J. E., Buring, J. E., Ridker, P. M. (2005) 'Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older U.S. women', *Diabetes Care*, 28, pp. 2926-2932.
- Lu, L., Yu, Z., Pan, A., Hu, F. B., Franco, O. H., Li, H., Li, X., Yang, X., Chen, Y., Lin, X. (2009) 'Plasma 25-Hydroxyvitamin D Concentration and metabolic syndrome among middle-aged and elderly Chinese individuals', *Diabetes Care*, 32(7), pp. 1278-1283.
- Mahmodnia, L., Tamadon, M. R., Sadoughi, M., Beigrezaei, S. (2017) 'Vitamin D status and its relationship with age in type 2 diabetic patients', *Journal of parathyroid disease*, 5(2), pp. 45-48.
- Mashahit, M., Elsayed, A., Eltoukhy, H. (2017) 'Influence of vitamin D level on diabetic dyslipidemia', *AJMAH*, 7(2), pp. 1-11.
- Masoud, A. D. (2014) Serum vitamin D level in type 2 diabetic patients from Gaza governorate, Gaza Strip. *Master thesis*. The Islamic University of Gaza, faculty of medicine. Gaza: Palestine. 1- pp. 104.
- Mauss, D., Jarczok, M. N., Hoffmann, K., Thomas, G. N., Joachim, E., Fischer, J. E. (2015) 'Association of vitamin D levels with type 2 diabetes in older working adults', *International journal of medical sciences*, 12(5), pp. 362-368.
- Minambres, I., Sanchez-Quesada, J. L., Perez, A. (2015) 'The association between hypovitaminosis D and metabolic syndrome: current understanding', *Journal of clinical lipidology*, 10(6), pp. 513-524.
- Mitri, J., Muraru, M. D., Pittas, A. G. (2011) 'Vitamin D and type 2 diabetes: a systematic review', *European journal of clinical nutrition*, 65, pp. 1005-1015.
- Mitri J., Pittas A. G. (2014) 'Vitamin D and diabetes', *Endocrinol Metab Clin North Am.*, 43(1), pp. 205-232
- Mohammed, M. S., Ismail, A. M. (2014) 'Evaluation of lipid profile in vitamin D deficiency diabetes mellitus type 2', *European academic research*, 2(9), pp. 12074-12084.
- Mohapatro, M., Mahapatra, S., Swain, S., Devi, N., Padhy, R. K., Ratan, R. (2016) 'Correlation of vitamin D with inflammation and hypertriglyceridemia in type 2 diabetes mellitus in Southeast India', *IOSR Journal of Dental and Medical Sciences*, 15(2), pp. 52-59.
- Namakin K., Tavakoli F., Zardast M. (2015) 'Effect of Vitamin D supplementation on lipid profile in children aged 10-14 years old', *Int J Pediatr*, 3(5).
- Nikooyeh, B., Neyestani, T. R., Farvid, M., Alavi-Majd, H., Houshiar-rad, A., Kalayi, A., Shariatzadeh, N., Gharavi, A., Heravifard, S., Salekzamani, N. T., Zahedirad, M. (2011) 'Daily consumption of vitamin D- or vitamin D+ calcium fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial', *American Journal of Clinical Nutrition*, 93, pp. 764-771.
- Ozder, A., Eker, H. H., Bilginc, M. (2015) 'Status of vitamin D among Turkish adults with Type 2 diabetes mellitus in primary health care', *Acta Medica Mediterranea*, 31, pp.229-236
- Park H. Y., Lim Y-H., Kim J. H., Bae S., Oh, S-Y., Hong, Y-C (2012) 'Association of serum 25-hydroxyvitamin D levels with markers for metabolic syndrome in the elderly: a repeated measure analysis', *J. Korean Med Sci*, 27, pp. 653-660.
- Patel, P. A., Patel, P. P., Mughal, Z., Padidela, R., Patel, A. D., Patwardhan V., et al. (2017) 'Interrelationship between serum 25-hydroxyvitamin D3 concentration and lipid profiles in premenopausal Indian women', *Indian J Endocr Metab*, 21, pp. 96-101
- Patel, P., Poretsky, L., and Liao, E. (2010) 'Lack of effect of subtherapeutic vitamin D treatment on glycemic and lipid parameters in type 2 diabetes: a pilot prospective randomized trial', *J Diabetes*, 2(1), pp. 36-40
- Pearce, S. H., Cheetham, T. D. (2010) 'Diagnosis and management of vitamin D deficiency', *The British Medical Journal*, 340, pp.142-147.
- Pérez-Castrillón J., Abad Manteca L., Vega, G., Del Pino Montes J., de Luis D, Duenas, Laita A. (2010) 'Vitamin d levels and lipid response to atorvastatin', *Int J Endocrinol*, 320721. doi: 10.1155/2010/320721.
- Pittas, A. G., Harris, S. S., Stark, P.C., Dawson-Hughes, B. (2007) 'The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults', *Diabetes Care*, 30, pp. 980-986.
- Pittas, A. G., Lau, J., Hu, F. B., Dawson-Hughes, B. (2007) 'The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis', *J Clin Endocrinol Metab.*, 92, pp. 2017-2029.
- Polur, H., Kedam, D., kumar, R., Vinodh, P. (2013) 'Study of vitamin D: A risk factor of type2 diabetes mellitus', *Journal of Pharmaceutical Sciences & Research*, 5(1), pp. 5-7.
- Ponda, M. P., Dowd, K., Finkelstein D., Holt, P. R., Breslow, J. L. (2012) 'The short-term effects of vitamin D repletion on cholesterol a randomized, placebo-controlled trial', *Arterioscler Thromb Vasc Biol*, 32, pp. 2510-2515.
- Rajpathak, S. N., Xue, X., Wassertheil-Smoller, S., Van Horn, L., Robinson, J. G., Liu, S., Allison, M., Martin, L. W., Ho G. Y., Rohan, T. E. (2010) 'Effect of 5 y of calcium plus vitamin D supplementation on change in circulating lipids: results from the women's health initiative', *The American Journal of Clinical Nutrition*, 91(4), pp. 894-899.
- Raman, R., (2017) 'What Vitamin D Dosage Is Best?', *Health line newsletter*, Available at (<https://www.healthline.com/nutrition/vitamin-d-dosage>) accessed at 21/01/2018
- Ramiro-Lozano, J. M., Calvo-Ramero, J. M. (2015) 'Effects on Lipid Profile of Supplementation with Vitamin D in type diabetic patients with vitamin D deficiency', *Therapeutic Advances in Endocrinology and Metabolism*, 6(6), pp. 245-248.
- Ryu, O. H., Chung, W., Lee, S., Hong, K. S., Choi, M. G., Yoo, H. J. (2014) 'The effect of high-dose vitamin D supplementation on insulin resistance and arterial stiffness in patients with type 2 diabetes', *Korean Journal of Internal Medicine*, 29, pp. 620-629.
- Sadiya, A., Ahmed, S. M., Skaria, S., Abusnana, S. (2014) 'Vitamin D status and its relationship with metabolic markers in person with obesity and type 2 diabetes in the UAE: A cross sectional study', *Journal of Diabetes Research*, 869307, doi: 10.1155/2014/869307.

- Saedisomeolia, A., Taheri, E., Djalali, M., Moghadam, A. M., Qorbani, M. (2014) 'Association between serum level of vitamin D and lipid profiles in type 2 diabetic patients in Iran', *Journal of Diabetes and Metabolic Disorders*, 13, 7. doi: 10.1186/2251-6581-13-7
- Schmitt, E. B., Nahas-Neto J., Bueloni-Dias, F., Poloni, P.F., Orsatti, C. L., Nahas, EAP., (2007) 'Vitamin D deficiency is associated with metabolic syndrome in postmenopausal women', *Maturitas*, 107, pp. 97–102
- Scragg, R., Khaw, K. T., Murphy S. (1995) 'Effect of winter oral vitamin D3 supplementation on cardiovascular risk factors in elderly adults', *Eur J Clin Nutr.*, 49(9), pp.640-646
- Seshadri, K. G., Tamilselvana, B., Rajendrana, A. (2011) 'Role of Vitamin D in Diabetes', *Journal of Clinical Endocrinology & Metabolism*, 1(2), pp. 47-56.
- Shaafie, I. A., Hesham, R. A., Basha, A. A. (2013) 'Vitamin D status in type 2 diabetic patients and its association with glycemic control, lipids & microalbuminuria: A pilot study', *Gulf Medical Journal*, 2(1), pp. 6-13.
- Shahzad, A., Sahto, A. A., Memon, A. A. (2017) 'Type 2 diabetics, frequency of vitamin Deficiency', *Professional Medical Journal*, 24(1), pp. 31-35.
- Sharma, A. K., Agrawal, R. P., Sharma, J. K., Agrawal, R., Kumar, S., Thacker, K., Saini, K. C. (2016) 'Vitamin D: A Critical Micronutrient for Vascular Health in Type 2 Diabetes Mellitus', *Journal of The Association of Physician of India*, 64, pp. 28-33.
- Simsek, Y., Kucukler, F. K., Arduc, A., Guler, S. (2015) 'Is there an association between vitamin D level and microvascular complications of type 2 diabetes mellitus?', *West Indian medical journal open*, 2(3), pp.138-141.
- Soares, M. J., Pathak, K., & Calton, E. K. (2014) 'Calcium and Vitamin D in the regulation of energy balance: Where do we stand?', *International Journal of Molecular Sciences*, 15(3), pp.4938–4945. <http://doi.org/10.3390/ijms15034938>
- Souza, C. L., de Sá, L. B., Rocha, D. R., Arbex, A. K. (2016) 'Vitamin D and diabetes mellitus: A review'. *Open Journal of Endocrine and Metabolic Diseases*, 6: pp. 1-7.
- Strobel, F., Rensch, J., Penna-martinez, M., Ramos- Lopez, E., Klahold, E., Klepzig, C., Wehrle, J., Kahles, H., Badenhoop, K. (2014) 'Effect of a randomised controlled vitamin D trial on insulin resistance and glucose metabolism in patients with type 2 diabetes mellitus', *Hormone and Metabolic Research*, 46(1), pp. 54-58.
- Summary of Vitamin D (2018), available at: <https://examine.com/supplements/vitamin-d/>, accessed at 16/1/2018.
- Swamy, M., Ganiger, A., Prasad, DS., Sanjeev Ratna S. (2016) 'Serum 25- hydroxy vitamin D levels in type 2 diabetes mellitus-A comparative study". *International Journal of Clinical Biochemistry and Research*, 3(2), pp. 255-258.
- Talaei, A., Mohammad, M., Adgi, Z. (2013) 'The effect of Vitamin D on insulin resistance in type 2 diabetes', *Diabetology and Metabolic Syndrome*, 5(1), pp.8.
- von Hurst, P. R., Stonehouse, W., Coad, J. (2010) 'Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomised, placebo-controlled trial', *Br J Nutr.* 103, pp. 549-555.
- Wang, Y., Si, S., Liu, J., Wang, Z., Jia, H., Feng, K., Sun, L., Song, S. J. (2016) 'The associations of serum lipids with vitamin D status'. *PLoS ONE*, 11(10),. doi: 10.1371/journal.pone.0165157.
- Wimalawansa, S. J. (2018) 'Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome'. *Journal of Steroid Biochemistry & Molecular Biology*, 175, pp. 177–189.
- Witham, M. D., Adams, F., Kabir, G., Kennedy, G., Belch, JFF., Khan, F. (2013) 'Effect of short-term vitamin D supplementation on markers of vascular health in South Asian women living in the UK – A randomised controlled trial', *Atherosclerosis*. 230, pp. 293-299.
- Yin, X., Sun, Q., Zhang, X., Lu, Y., Sun, C., Cui, Y., Wang, S.(2012) 'Serum 25(OH)D is inversely associated with metabolic syndrome risk profile among urban middle-aged Chinese population', *Nutrition Journal*, 11, 68. doi: 10.1186/1475-2891-11-68.