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Vitamin D, sub-inflammation and insulin resistance. A window on a potential role for the interaction between bone and glucose metabolism

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Abstract Vitamin D is a key hormone involved in the regulation of calcium/phosphorous balance and recently it has been implicated in the pathogenesis of sub-inflammation, insulin resistance and obesity. The two main forms of vitamin D are cholecalciferol (Vitamin D3) and ergocalciferol (Vitamin D2): the active form (1,25-dihydroxyvitamin D) is the result of two hydroxylations that take place in liver, kidney, pancreas and immune cells. Vitamin D increases the production of some anti-inflammatory cytokines and reduces the release of some pro-inflammatory cytokines. Low levels of Vitamin D are also associated with an up-regulation of TLRs expression and a pro-inflammatory state. Regardless of the effect on inflammation, Vitamin D seems to directly increase insulin sensitivity and secretion, through different mechanisms. Considering the importance of low grade chronic inflammation in metabolic syndrome, obesity and diabetes, many authors hypothesized the involvement of this nutrient/hormone in the pathogenesis of these diseases. Vitamin D status could alter the balance between pro and anti-inflammatory cytokines and thus affect insulin action, lipid metabolism and adipose tissue function and structure. Numerous studies have shown that Vitamin D concentrations are inversely associated with pro-inflammatory markers, insulin resistance, glucose intolerance and obesity. Interestingly, some longitudinal trials suggested also an inverse association between vitamin D status and incident type 2 diabetes mellitus. However, vitamin D supplementation in humans showed controversial effects: with some studies demonstrating improvements in insulin sensitivity, glucose and lipid metabolism while others showing no beneficial effect on glycemic control and on inflammation. In conclusion, although the evidences of a significant role of Vitamin D on inflammation, insulin resistance and insulin secretion in the pathogenesis of obesity, metabolic syndrome and type 2 diabetes, its potential function in treatment and prevention of type 2 diabetes mellitus is unclear. Encouraging results have emerged from Vitamin D supplementation trials on patients at risk of developing diabetes and further studies are needed to fully explore and understand its clinical applications.

Keywords Vitamin D · Sub-inflammation · Insulin resistance · Metabolic syndrome · Type 2 diabetes mellitus · TNF-α · Il-6 · MCP-1 · Sclerostin · Osteopontin · Osteoprotegerin · Fractalkine · Osteocalcin

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1 Introduction

Vitamin D plays a key role in the regulation of mineral homeostasis, being mainly involved in bone and calcium/phosphorus balance [1]. However, over the last several years, a potential extra skeletal role of vitamin D has begun to emerge [1, 2].

In particular, many studies have revealed profound immunomodulatory effects of vitamin D and its derivatives [3] and that vitamin D deficiency may be associated with sub-inflammatory state, insulin resistance and obesity/ metabolic syndrome.

Obesity, metabolic syndrome, essential hypertension and type 2 diabetes are all insulin-resistant states, in which different hormones and cytokines are implicated. However, all these pathologic states are characterized by a condition of chronic sub-inflammation. Considering the importance of sub-inflammation in the development of insulin resistance and obesity/metabolic syndrome, it has been speculated that Vitamin D deficiency could play a contributory role in it [4].

The focus of this review is to explore the pathophysiology of the mechanistic relationship between vitamin D, bone metabolism, inflammation and insulin resistance, in humans.

2 Vitamin D: Metabolism, actions

Cholecalciferol (Vitamin D3) and ergocalciferol (Vitamin D2) are the two main forms of vitamin D. The first one is mainly endogenous and produced in the skin, as a result of sun exposure; only a minor portion, instead, is exogenous and extracted from food such as fatty fish, egg yolk, mushrooms and yeast. Dairy products with nutritional supplements and nutritional supplements by themselves usually contain vitamin D2, that is the vegetal form of vitamin D [5].

Vitamin D3 is a lipophilic precursor of the major circulating form: 25(OH) Vitamin D. During sun exposure 7-dehydrocholesterol is converted to pre-vitamin D3 and then to vitamin D3 in a non-enzymatic reaction that takes place in the skin. The excess of sunlight causes degradation of pre-vitamin D3 and vitamin D3 into inactive form. Through the binding to the vitamin D-binding protein, Vitamin D3 is then transported in the bloodstream from the skin to the liver, where it is converted by vitamin 25-hydroxylase to the circulating form, 25(OH)Vitamin D [6].

To exert its biological function, interacting with the vitamin D nuclear receptor, the vitamin D's circulating form must be subjected to a second hydroxylation reaction [7]. This reaction takes place mainly in the kidney, being carried out by a single enzyme (1 α-hydroxylase), leading to the most active vitamin D, known as 1,25 (OH)2 Vitamin D. The activating process could also take place in other cells that contains this enzyme, such as immune cells [8] or pancreatic cells [9].

Vitamin D 24-hydroxylase is in charge for the inactivation process. This event is regulated by the concentration of the active form of Vitamin D, that could induce the expression of 24-hydroxylase and convert 25(OH) vitamin D and 1,25(OH)2 vitamin D into less-active metabolites (e.g. 24,25(OH)2 vitamin D and 1,24,25(OH)3 Vitamin D) which are in turn further catabolized into inactive calcitroic acid [10].

The 1,25(OH)2 Vitamin D is the main active form and has about 1000-fold higher affinity than 25(OH) Vitamin D for the vitamin D receptor (VDR). All Vitamin D metabolites circulate in the bloodstream bound to the vitamin Dbinding protein [11]. 1,25 (OH)2 Vitamin D and 25(OH)Vitamin D are predominantly stocked in adipose and muscle tissue [12]. In particular, adipose tissue is generally considered the reservoir for Vitamin D in human subjects and rats [13–17] Interestingly, visceral fat was found to contain 20% more of this nutrient than subcutaneous fat [18].

The 25(OH) Vitamin D has a half-life between 15 to 50 days and circulates in plasma in nanomolar concentrations [12]. Vitamin D status is usually determined by serum concentrations of 25(OH) Vitamin D: a 25(OH) Vitamin D concentrations between 20 and 30 ng/mL defines insufficiency and a 25-OH Vitamin D concentration less than 20 ng/mL defines deficiency [19]. Vitamin D deficiency is considered a pandemic problem because most part of the population, even among people living in tropical areas, has this nutritional deficiency that could lead to both skeletal and extra-skeletal problems [20].

In the 2011, the Institute of Medicine set the Vitamin D Recommended Dietary Allowance (RDA, the level of intake of a nutrient judged adequate to meet the known nutrient needs of nearly all healthy people), at 600 IU/d for persons aged 1–70 years and 800 IU/d for persons aged 71 years and older [5].

3 Sub-inflammation and insulin resistance

Insulin resistance is defined as a reduced ability of insulin to exert its metabolic and biological actions at the whole-body level, where insulin in concert with glucagon, somatostatin and a number of extra-pancreatic hormones plays a key-role in the regulation of glucose homeostasis [21–23]. This condition is characterized by a decreased signaling of insulin receptors on insulin sensitive cells. In the natural history of insulin resistance/type 2 diabetes mellitus (T2DM), initially, an insulin resistant subject compensates with a greater production of insulin (compensating hyperinsulinism with normoglycemia) but, with time, beta-cell insulin secretion is reduced, leading to glucose intolerance and clinically overt type 2 diabetes mellitus [24].

This sequence of molecular and biological events occurs in humans [25] non-humans primates [26–30] and rodent models of T2DM and insulin resistance [31–33].

Insulin resistance is one of the hallmarks of type 2 diabetic patients, but it is also recognizable in more than 50% of patients without diabetes who suffered a cardiovascular event. The presence of insulin resistance increases the risk of vascular disease, also because of its association with hypertension, hyperglycemia, hyperinsulinemia, dyslipidemia, endothelial dysfunction, hypercoagulability, sub-inflammation and increased platelet reactivity [34–38].

The mechanistic link between insulin resistance, diabetes and cardiovascular diseases is not fully understood, but it is known that visceral obesity is associated with further increased cardiovascular morbidity and mortality [35–39].

Sub-inflammation is an important factor involved in the pathogenesis of insulin resistance. Pro-inflammatory cytokines and acute phase proteins can affect negatively several

signaling and metabolic pathways which are activated by the insulin receptor signaling machinery, the functions of lipoproteins lipase and adipose tissue function and structure [40].

Also, the metabolic syndrome, is classically characterized as a chronic state of low-grade inflammation (sub-inflammation), identifiable by slightly elevated levels of adipocyte-released Tumor necrosis factor α (TNF- α) and interleukin 6 (IL-6) [41]. Inflammation occurs primarily in adipose tissue, but also in other tissues with important metabolic activity, such as liver, pancreatic islets and hypothalamus [42].

Adipose tissue is also an endocrine organ since it secretes a variety of cytokines (TNF-α, IL-6, interleukin 1 β (IL1β)), predominantly produced by local macrophages, as well as leptin and adiponectin [43]. Interestingly leptin has also been implicated in the development of cardiac hypertrophy in obese patients [44].

A cause for cytokines overproduction in obesity and type 2 diabetes is the alteration of the tissue inhibitor of metalloproteases 3 - TNF-α converting enzyme (TIMP3-TACE) dyad in human skeletal muscle, where an elevated TACE activity and a diminished TIMP3 protein levels are present, leading to an augmented release of TNF-α. The TIMP3–TACE dyad is involved in the regulation of TNF-α shedding from pro-TNF-α as well as IL-6 release [39, 45, 46].

This abnormal release of adipokines may help explaining some features of the metabolic syndrome. Inflammation is linked to metabolic abnormalities such as increased triglycerides, insulin, glucose, reduced high density lipoproteins (HDL) levels, sympathetic over activity, endothelial dysfunction and oxidative stress. All these alterations are associated with the development of T2DM, arterial hypertension, platelet increased aggregability and accelerated atherosclerosis. [38, 47–50].

The effect of TNF-α and other pro-inflammatory cytokines on peripheral insulin sensivity occurs through the inhibition of insulin-mediated tyrosine phosphorylation of insulin receptor and insulin receptor substrate (IRS)-1, leading to defective activation of downstream insulin signaling (for example to phosphatidylinositol-3 (PI3)-kinase and translocation of GLUT4 to the cell surface) [51, 52].

Molecular and cell triggers have been recognized in metabolic sub-inflammation: 1) endoplasmic reticulum stress (ERS), 2) activation of toll-like receptor (TLR) 4 and 3) stimulation of protein kinase R (PKR).

The endoplasmic reticulum, in the presence of lipid overload becomes unable to correctly synthetize and fold proteins; long-chain saturated fatty acids can activate TLR4, leading to insulin resistance and inflammatory gene transcription; finally, nutrient overload can stimulate PKR, inducing inflammatory signaling (through c-Jun N terminal kinase (JNK) and IkB kinase (IKK)). These three signaling pathways are connected and can target the insulin signaling pathway negatively. Furthermore, dietary fats can promote changes to gut microbiota which through the activation of TLR4 and the alteration of ERS, contribute to metabolic inflammation [37, 42, 53].

Angiotensin II, cytokines, such as TNF- α, IL-6 and Monocyte chemotactic protein 1 (MCP1), and other inflammatory factors produced in the context of metabolic inflammation can activate intracellular stress kinases (protein-kinases), such as JNK, IKK, S6 kinase (S6 K) and protein kinase C (PKC), promoting the inhibitory serine phosphorylation of the insulin receptor substrates, IRS1 and IRS2, thus providing the molecular basis for insulin resistance [31, 37, 51, 52, 54–57].

4 Vitamin D and inflammation

An interesting as well as unexpected role of Vitamin D in the modulation of immune function and inflammatory processes has emerged from cellular studies [58]. Vitamin D inhibits adipose tissue inflammation both *in vitro* and *in vivo*, acting upon preadipocytes, adipocytes as well as on leucocyte infiltration [59, 60].

Vitamin D seemingly exerts broad regulatory effects on adaptive and innate immune cell system [61]. The conversion of 25(OH)Vitamin D to its active form 1,25(OH)2 Vitamin D can occur inside immune system cells that possess the 1 α-hydroxylase enzyme: dendritic cells, macrophages, T and B cells [62].

Vitamin D's effect on dendritic cells includes increased interleukin 10 (IL-10) production (which is an anti-inflammatory cytokine) and reduced release of TNF-α, interferon γ (IFN-γ) and interleukin 12 (IL-12) (which are pro-inflammatory cytokines). With the stimulation of Vitamin D, dendritic cells acquire a peculiar immunoregulatory role as well as tolerogenic properties [3].

The effect on monocytes consist in down-regulation of the expression and production of several pro-inflammatory cytokines including TNF- α, IL-1β, IL-6 and interleukin 8 (IL-8) [63, 64].

On the other hand, on lymphocytes, the overall effect is a switch from the more inflammatory T-helper 1 (Th1)/Th17 response to the less inflammatory Th2/Treg profile [65].

The immunoregulatory effects of vitamin D have been studied in type 1 diabetes and in particular in islet transplantation. Islet transplantation is a novel and effective treatment, able to significantly change the natural history of the disease, but it is burdened by the need of an appropriate immunosuppression to avoid the risk of rejection. Traditional immunosuppressive regimens are in fact responsible for numerous side effects (risk of infections, neoplastic diseases, nephrotoxicity, now onset diabetes etc.) and this lead to development of new immunoregulatory protocols. Animal studies demonstrated that 1,25 (OH)2 Vitamin D administration with mycophenolate mofetil is able to induce tolerance after islet transplantation: it affects antigen presenting cells (APCs) and in particular dendritic cells (DCs), promoting down regulation of the expression of CD40, CD80, and CD86 costimulatory

molecule, inhibits alloreactive T cells and responsiveness to alloantigens. These results suggest a potential role in transplant immunosuppression and could allow reduction of traditional immunosuppressive regimen doses [66–69].

The effect of the active form of vitamin D can occur in two ways: through the interaction with the membrane Vitamin D receptor (mVDR) or through binding with the nuclear Vitamin D receptor (nVDR), that has high affinity and avidity for the active metabolite and regulate gene expression [70]. There are more than a thousand genes that are directly or indirectly regulated by (OH)2 Vitamin D and involved in various physiological processes such as cell proliferation, differentiation, apoptosis and angiogenesis [71]. The nVDR is found in multiple cells of the immune system such as human T-reg cells, neutrophils, dendritic cells, B cells and macrophages [70]. Moreover, numerous studies demonstrated the expression of VDRs in pancreatic β-cells and in all insulin-responsive tissues [2, 72–74].

Vitamin D can affect inflammation also through the mediation of TLRs, that are trans-membrane receptors located on monocytes and macrophages, implicated in the innate immune response to pathogens [75, 76]. In fact, it has been reported that elevated vitamin D levels during the summer coincided with decreased monocyte expression of TLR-2 and TLR-4; decreased vitamin D levels, on the opposite, were associated with an increased expression of TLRs [77]. In obese subjects a reduced degree of plasmatic Vitamin D seasonal variations has been observed: this may contribute to an up-regulation of TLRs expression and consequent increased level of inflammation [78].

5 Vitamin D, insulin sensitivity and insulin secretion

Vitamin D, besides its effect on inflammation and immune system, also seems to directly influence insulin sensitivity/resistance.

In fact, several studies have shown an increase in insulin sensitivity which could be mediated through the interaction with VDRs in skeletal muscles [79], the stimulation of expression of insulin receptors on target tissues [80] and, finally, through the activation of peroxisome proliferator activator receptorδ (PPAR δ) [81], that is a transcription factor involved in metabolism and mobilization of fatty acids in adipose tissue and skeletal muscle [82].

Other proposed mechanisms for increasing insulin sensitivity are the inhibition of the renin-angiotensin-aldosterone system (RAAS), which is a well-known inhibitor of insulin action in peripheral tissues, and the regulation of cellular calcium concentration in skeletal muscle cells, that might enhance glucose transport through the membrane via the recruitment of Glucose transporter type 4 (GLUT4). [83–85].

In addition, vitamin D could stimulate insulin release through the regulation of beta cell intracytoplasmic calcium concentration and stimulation of exocytosis mechanism. The interaction between 1,25 (OH)2 Vitamin D and nVDR lead to the transcription of insulin, cellular structure and growth genes. Two pathways have been recognized: the first includes the activation of protein kinases A (PKA) that phosphorylates voltage-dependent calcium channels and proteins involved in exocytosis; the second, instead, includes the activation of phospholipase C (PLC), synthesis of inositol 1,4,5-trisphosphate (IP3), that causes the release of calcium from the endoplasmic reticulum, and diacylglycerol (DAG), that activates protein kinase C (PKC), in turn responsible for the activation of voltage-dependent calcium Channels and the K_{ATP} channels, but also the mobilization of insulin secretory vesicles. All these steps lead to the depolarization of the cytoplasmic membrane, opening of calcium channels, increasing of intracellular calcium content and subsequent insulin secretion. [86].

However, in neoplastic β-cell lines, Vitamin D has a pro-apoptotic and anti-insulinogenic effect. In fact, some cellular studies demonstrated that calcitriol inhibits growing, induce apoptosis, decrease cell viability, gene expression, insulin content and secretion in murine insulinoma β-cells [87, 88].

6 Interaction between vitamin D, inflammation and insulin resistance

A number of basic experimental, epidemiological and clinical studies support the role of low-grade inflammation in the development of metabolic diseases, insulin resistance and type 2 diabetes [12].

As discussed above, several studies have demonstrated that vitamin D acts as a negative modulator of TNF-α and IL-6 release [54, 55, 89], decreasing TNF-α, IL-6, and C-reactive protein (CRP) both *in vivo* as well as *in vitro* [90, 91] and thus acting on adipose tissue and immune system [56, 57].

The importance of inflammation in the pathogenesis of metabolic syndrome, the evidence of the anti-inflammatory activity and the direct effects on insulin sensitivity of Vitamin D, suggest a possible role for this hormone in insulin resistant clinical conditions.

In recent years, several cross-sectional, cohort, longitudinal as well as interventional clinical studies, have investigated the relationship between Vitamin D, inflammation and insulin resistance.

Many cross-sectional and cohort studies showed an association of 25(OH) Vitamin D concentrations with inflammatory status, glucose intolerance, insulin resistance, metabolic syndrome and the risk of type 2 diabetes mellitus [92–106].

These association seem to be more relevant in patient with Vitamin D deficiency than in patients with normal level: in a large Canadian cohort study on non-diabetic adults it was demonstrated that vitamin D status was inversely associated with insulin responsiveness. Furthermore, insulin response correlated with 25(OH) Vitamin D level after adjusting for BMI, waist

circumference, weight, age and sex, in patients with a 25 (OH) Vitamin D baseline level from 40 to 90 nmol/L [107].

In addition, Vitamin D plasma levels were found to be inversely correlated to the classical parameters of obesity such as BMI, fat mass and waist circumference [108, 109]. Interestingly, it has been demonstrated that serum 25(OH) Vitamin D is significantly lower in obese individuals as compared to lean ones [110]. The prevalence of Vitamin D deficiency is respectively a 25% and 35% higher in overweight and obese than lean subjects [111]. Some authors, considering the fat-soluble nature of this nutrient and the adipose tissue as its main storage place, have suggested that vitamin D and its metabolites could be sequestered in the excess fat mass which is present in obese persons [112–114]. Another hypothesis is that individuals with a higher BMI might have a higher volume in which 25-OH Vitamin D is diluted and would require greater Vitamin D dietary intake as compared to lean individuals to achieve a normal Vitamin D level [115].

Furthermore, vitamin D seem to be a predictive factor for death by cardiovascular disease in diabetic patients [116, 117].

Type 2 diabetic patients showed a prevalent impairment of Ventricular diastolic filling but a similar ventricular systolic performance, if compared to type 1 diabetic patients.

In type 1 diabetic patients an alteration of high-energy phosphates (HEPs) metabolism may contribute to Left ventricular dysfunction. [118, 119].

In diabetic patients, the effect of vitamin D on cardiac diastolic or systolic function have not been studied while some animal models suggested some effect of vitamin D supplementation on cardiac metabolism. 1,25(OH)2 Vitamin D treated rats had lower body weight, smaller left ventricular end-diastolic diameter, shorter QT interval, higher cardiac PPAR-α and PPAR-δ protein expressions, but lower cardiac PPAR-γ protein levels and inflammatory cytokines (TNF-α and IL-6) than non-treated diabetic rats. [120].

Some beneficial effects of Vitamin D administration on arterial pressure and stiffness have also been reported. [121–125].

An inverse association between vitamin D status and incident type 2 diabetes mellitus was also demonstrated by longitudinal studies [6]. Furthermore, two meta-analyses [126, 127] of longitudinal observational studies, have confirmed these results.

Nevertheless, confounding factors that may influence type 2 diabetes incidence but also vitamin D status, such as age, diet and lifestyle, may have influenced the results of these studies and therefore causality cannot be established with certainty. This is a major limitation of these studies [6, 128, 129].

7 Vitamin D supplementation clinical trials

Whereas animal studies have found that vitamin D supplementation in deficient animals can improve insulin sensitivity and inflammation, these findings have not been unequivocally reproduced in humans.

In Tables 1 and 2 we have listed the main prospective and interventional clinical trials with Vitamin D.

No significant effects on inflammation status have been observed in clinical trials after supplementation with vitamin D [12, 96, 128, 130, 131].

Clinical trials in humans affected by type 2 diabetes mellitus produced controversial results. In some of them there were improvements in glycaemia, insulin sensitivity, lipid profile and endothelial function [121, 132]. Other studies however, demonstrated no significant effects on glycaemia, glucose metabolism, insulin sensitivity, as well as no reduction in diabetes incidence [122, 123, 133–137]. To add further fuel to this controversy some others showed no significant changes in insulin sensitivity and inflammatory markers, although there was a minimal improvement of insulin secretion [138].

Controversial effects were observed also in interventional trials on healthy subjects.

In particular, a neutral effect of vitamin D supplementation was seen in two large clinical trials: Avenell and colleagues demonstrated no changes in the incidence of diabetes and no beneficial effect on glucose metabolism in a group of 5292 participants aged ≥70 years, followed for 24–62 months. This was a blinded randomized trial lead in UK from 1999 to 2002; the patients were randomized to take oral 800 IU (20 μg) daily vitamin D_3 and 1000 mg calcium or placebo. [134] In USA, De Boer and colleagues in a double blinded clinical trial with a median follow-up time of 7 years, observed no reduction in the development of diabetes after administration of Calcium plus vitamin D3 supplementation (1000 mg elemental calcium plus 400 IU of vitamin D3 daily) in a group of 33,951 women without self-reported diabetes at baseline clinical trial. 2291 of these women had a new diagnosis of diabetes. [135].

A positive effect of Vitamin D supplementation, instead, was described by Tepper et al. in a double blind randomized controlled trial lead in Israel on 130 men aged 20–65 years without diabetes with serum 25-hydroxyvitamin D levels <50 nmol/l. It was observed that insulin levels and HOMA-IR values remained steady during the study period in the treatment group but increased in the control group. The patients were treated with 100,000 IU vitamin D bimonthly or placebo and revaluated at 6 and 12 months of follow up. [139].

Von Hurst and colleagues also find positive results following for 6 months a group of 81 subjects in a randomized controlled, double-blind intervention. 42 patients were given 100 microg (4000 IU) of vitamin D (3) and 39 were given placebo. This study demonstrated that after vitamin D supplementation there was a significant decrease in fasting insulin and a significant improvement in insulin sensitivity and resistance. [140].

Although the effect of Vitamin D supplementation on diabetic patients seem to be non-significant, more interesting could be to study the effect on people at risk of developing

Table 1 Association between vitamin D levels and metabolic parameters in observational studies

References	Evaluated parameters	Study Design	Country	Study subjects	Results	Outcome
[92] Chiu KC et al. Am J Clin Nutr 2004.	- 25 OH Vitamin D - Insulin sensitivity index (ISI) - first- and second-phase insulin responses (1stIR and 2ndIR)	Cohort study cross sectional	USA	126 healthy Glucose tolerant patients	- 25(OH)D concentration has a positive correlation with insulin sensitivity- Hypovitaminosis D has a negative effect of on beta cell function - Subjects with hypovitaminosis D are at higher risk of insulin resistance and the metabolic syndrome.	Positive
[93] Dutta D et al. Indian J Med Res 2013.	- 25 OH vitamin D - fasting glucose - fasting insulin - insulin sensitivity (QUICKI) - Insulin resistance (HOMA2-IR) - Estimated beta cell mass (HOMA-β)	Cohort study cross sectional	India	157 patients with pre-diabetes	- There was an inverse correlation between serum 25 OH vitamin D and insulin resistance (HOMA2-IR) - There was a positive correlation between serum 25 OH Vitamin D and insulin sensitivity (QUICKI), after adjusting for BMI and HbA1c.	Positive
[94] Manickam B et al. Endocr Pract 2013.	- 25 OH vitamin D - HbA1c - lipid profile	Cohort study cross sectional	USA	1074 man With and without diabetes (urban Veteran Administration Medical Center)	- 25(OH)D level has an inverse association with HbA1c - 25(OH)D level is an independent determinant of HbA1c in African American Men, but not in Caucasian American Men, including men with and without diabetes.	Positive
[95] Scragg R et al. Diabetes Care 2004.	- 25 OH vitamin D - Fasting glucose - 2-h plasma glucose - Serum insulin	Cohort study cross sectional	USA	6228 people (2766 non-Hispanic whites, 1736 non-Hispanic blacks, and 1726 Mexican Americans)	- Insulin resistance (log e) was inversely associated with serum 25 OH Vitamin D in Mexican Americans and non-Hispanic whites, adjusting for confounders.	Positive
[97] Laird E et al. J Clin Endocrinol Metab 2014.	- 25 OH vitamin D - IL-6, - TNF-α, - IL-10 - C-reactive protein	Observational cohort study cross sectional	Northern Ireland	957 Irish adults (>60 years of age	- Concentrations of IL-6, CRP, IL-6/IL-10 ratio CRP/ IL-10 ratio were significantly higher in individuals with deficient (<25 nmol/L) 25OH vitamin D compared with those with sufficient 25 OH Vit D (>75 nmol/L) after adjustment for age, sex and BMI. - Vitamin D status was a significant predictor of the IL-6 to IL-10 cytokine ratio.	Positive
[98] Ganji V et al. Am J Clin Nutr 2011.	- 25 OH Vitamin D - CRP - homeostatic model assessment–insulin resistance index - waist circumference - blood pressure - lipid profile	Observational cohort study cross sectional	USA	5867 adolescent (aged 12-19y)	- Likelihood of having Metabolic syndrome was significantly higher in the first tertile of serum 25(OH)D than in the third tertile of 25(OH)D - HDL cholesterol was directly related with serum 25(OH)D - No association was observed between 25(OH)D and C-reactive protein.	Positive
[99] Tepper S et al. Nutr Metab Cardiovasc Dis 2014.	−25 OH Vitamin D - CRP - Homa IR - fasting glucose - fasting insulin - lipid profile - blood pressure - BMI - waist circumference	Observational cohort study cross sectional	Israel	400 men agreed to participate, 358 (90%) completed the study	- BMI, waist circumference, FPI, HOMA-IR, TG, hs-CRP levels, DBP, and SBP were negatively associated with serum 25(OH)D. - A curved linear association was found with insulin and HOMA-IR with a significant spline knot at 11 ng/ml. - For hs-CRP a spline knot at 14 ng/ml was observed. - TG, SBP, and DBP exhibited linear associations with 25(OH)D.	Positive
[101] Pittas AG et al. Diabetes Care, 2006.	- Vitamin D intake - Calcium intake	Observational prospective cohort studies	USA	83,779 women (Nurses' Health Study) 4843 developed diabetes. 20 years of follow up.	- There was no association between total vitamin D intake and DMT2 - RR of type 2 diabetes was 0.87 (P for trend =0.04) highest VS lowest category of vitamin D intake from supplements. - RRs of type 2 diabetes were 0.79 (P for trend <0.001) highest VS lowest category of calcium intake from all sources and 0.82 (P for trend <0.001) from supplements.	Positive effect (calcium and Vit D)
[102] Liu S et al. Diabetes Care, 2005.	- Calcium intake - Vitamin D intake	Observational Prospective Cohort study	USA	10,066 women (Women's Health Study) aged > = 45 years; free of cardiovascular disease, cancer, or diabetes and who never used postmenopausal hormones.	- ORs of having the metabolic syndrome for increasing quintiles of total calcium intake were 1.00, 0.82 (95% CI 0.70–0.97), 0.84 (0.71–0.99), 0.70 (0.59–0.83), and 0.64 (0.54–0.77) (P for trend <0.0001).	Neutral effect (vit D)

Table 1 (continued)

References	Evaluated parameters	Study Design	Country	Study subjects	Results	Outcome
					- In contrast, neither total (P for trend =0.13) nor supplemental (P for trend =0.45) vitamin D was significantly associated with metabolic syndrome.	
[103] Kayaniyil S et al. Diabetes Care, 2010.	−25 OH Vitamin D -Matsuda insulin sensitivity index - HOMA-IR - IGI/IR - ISSI-2	Observational cohort studies Cross sectional	Canada	712 subject at risk for diabetes	- Independent associations of 25OH Vitamin D with IS (OGTT) and HOMA-IR (P = 0.0003 and P = 0.0072, respectively) - Independent association with IGI/IR and ISSI-2 (P = 0.0286 and P = 0.0011, respectively) after adjusting for socio-demographics, physical activity, supplement use, parathyroid hormone and BMI.	Positive
[104] Broder AR et al. Arthritis Research and Therapy, 2010.	25 OH vitamin D	Observational cohort studies cross sectional	USA	3914 subject: 23 SLE, 100 RA, and 3691 T2DM.	- T2DM patients have much higher odds of being vitamin D deficient. - T2DM, serum creatinine and vitamin D supplementation were associated with vitamin D deficiency in some, but not all, racial/ethnic groups.	Positive
[105] Hypponen E et al. Diabetes. 2008.	- 25 OH vitamin D -IGF 1 - Abdominal obesity; - HbA1C - Blood pressure - Lipid profile	Observational cohort studies Cross sectional	UK	6810 subjects aged 45 years	- 25 OH Vitamin D and IGF-1 were inversely associated with metabolic syndrome. - IGF-1 was not significantly associated with metabolic syndrome among those with the lowest levels of 25 OH Vitamin D (P > 0.09), whereas higher 25(OH)D was associated with metabolic syndrome at all IGF-1 concentrations (P </= 0.006). - Metabolic syndrome prevalence was lowest for participants with the highest concentrations of both 25(OH)D and IGF-1 (P < 0.0001; adjusted for sex, month, hour, inactivity, alcohol consumption, smoking, and social class). - 25 OH Vitamin D was associated with the prevalence of higher HbA1C, blood pressure, and triglycerides after adjustment for IGF-1, obesity and social and lifestyle variations (P </= 0.004 for all comparisons).	Positive
[106] Lu L et al. Diabetes Care. 2009.	- 25 OH vitamin D - HbA1c - HOMA IR - Fasting plasma glucose - Insulin - lipid profile - inflammatory markers	Cohort study cross sectional	Cina	1443 men and 1819 women aged 50–70 years	- The odds ratio for metabolic syndrome in the lowest quintile (<or = 28.7 nmol/l) compared to the highest (>or = 57.7 nmol/l), was 1.52 (P(trend) = 0.0002) after multiple adjustment. - There was an inverse association between 25 OH Vitamin D and individual metabolic syndrome components plus HbA1C. - There was a significant inverse association of 25 OH Vitamin D with fasting insulin and HOMA-IR in overweight and obese but not in normal-weight subjects.	Positive
[107] Heaney RP et al. Adv Nutr. 2013.	−25 OH vitamin d - Fasting glucose - Fasting insulin - Blood pressure - BMI - Waist circumference -Weight - Age - Sex	Observational cohort study Cross sectional	Canada	4116 Non diabetic adults	- Vitamin D status is inversely associated with insulin responsiveness and blood pressure. - The vitamin D association was localized to the serum 25(OH)D range extending from ~40 to ~90 nmol/L (16–36 mg/L)	Positive

Table 2 Effects of vitamin D administration on metabolic parameters and progression to type 2 diabetes

	Evaluated parameters	Study	Place	Study subjects	Results	Outcome
[96] Chandler PD et al. Cancer Prev Res (Phila) 2014.	- Serum 25(OH)D, - High-sensitivity C-reactive protein (CRP), - IL-6, - IL-10, - Soluble TNF-α receptor type 2 (sTNF-R2)	Randomized, double-blind, placebo-controlled trial (placebo or 1000, 2000, or 4000 IU/day of vitamin D3 orally for 3 months)	USA	328 African Americans total; 292 (89%) participants were measured inflammation markers.	- Baseline 25 OH Vitamin D has inverse association with baseline CRP level in unadjusted and adjusted models. - After the vitamin D supplementation period no statistically significant changes in CRP, IL-6, IL-10, and sTNF-R2 were observed.	Positive association; neutral effect
[100] Knekt P et al. Epidemiology, 2008.	25 OH vitamin D	Case control study	Finland	412 subject non diabetic at baseline that developed diabetes; 986 controls. 22 years of follow up	- In the highest vitamin D quartile there was a reduced risk of type 2 diabetes - The relative odds between the highest and lowest quartiles was 0.28 (95% confidence interval = 0.10–0.81) in men and 1.14 (0.60–2.17) in women (after adjustment for smoking, BMI, physical activity and education)	Positive effect
[110] Gallagher JC et al. J Steroid Biochem Mol Biol 2013.	- 25OHD, - PTH, - 1,25(OH)2D - Body composition	Study1 (ViDOS): one-year randomized, double-blind placebo controlled study (increasing doses of vitamin D3) Study2: (STOP IT) three-year intervention study (calcitriol 0.25mcg twice daily, plus estrogens 0.625 mg daily)	USA	Study1: 163 Caucasians, aged b 57–90 years Study2: 488 elderly women, age 65–77 years	- In all BMI categories the response to the low doses of vitamin D (400-800 IU/d) was significantly less than that of the medium (1600-2400 IU/d) and high doses groups (3200-4800 IU) ($p < 0.0001$). - The highest increase in serum 25OHD after vitamin D occurs in thinner women with BMI <25 kg/m^2	Neutral effect
[121] Sugden JA et al. Diabetic Medicine, 2008.	−25 OH vitamin D - Flow mediated vasodilatation (FMD) of the brachial artery	Double-blind, parallel group, placebo-controlled randomized trial (A single dose of 100,000 IU vitamin D2 or placebo) evaluation at 8 weeks	UK	34 type 2 diabetic patients with 25-hydroxyvitamin D level < 50 nmol/l	- Vitamin D supplementation significantly improved flow mediated vasodilatation (FMD) of the brachial artery by 2.3%, even after adjusting for changes in blood pressure - Vitamin D supplementation significantly decreased systolic blood pressure by 14 mmHg compared with placebo	Positive effect
[122] Forouhi N et al. Diabetes Obes Metab 2015.	- HbA1c - Blood pressure - Lipid levels - Apolipoprotein levels - C-reactive protein levels - Pulse wave velocity (PWV) - Anthropometric measures	double-blind placebo-controlled randomized trial (placebo VS 100000 IU vitamin D_2 VS 100000 IU vitamin D_3 orally administered monthly for 4 months)	UK	340 adults with elevated risk of type 2 diabetes (non-diabetic hyperglycemia or positive diabetes risk score)	- No effect on HbA1c, blood pressure and inflammation - Modest reduction in arterial stiffness in (measured with PWV) with both D_2 and D_3 compared with placebo	Neutral effect
[123] Witham MD et al. Diabetologia, 2010.	- Endothelial function, - Office blood pressure, -B-type natriuretic peptide, - Insulin resistance - Glycosylated hemoglobinn	Randomized, parallel group, placebo-controlled trial (placebo =22, 100,000 IU vitamin D(3) = 19, 200,000 IU vitamin D(3) =20)	UK	61 type 2 diabetes and baseline 25-hydroxyvitamin D levels <100 nmol/l	- No significant difference in endothelial function at 8 weeks or at 16 weeks. - Insulin resistance and glycosylated hemoglobin did not improve with either dose of vitamin D(3). - Systolic blood pressure was significantly lower in both treatment arms than in the placebo group at 8 weeks - B-type natriuretic peptide levels were significantly lower in the 200,000 IU group by 16 weeks	Neutral effect
[124] Asemi Z et al. J Nutr, 2013.	- Fasting blood glucose - hs-CRP - Lipid concentrations, - Insulin - Biomarkers of oxidative stress - 25 OH vitamin D - Plasmatic calcium - Blood pressure	Randomized, double-blind, placebo-controlled clinical trial (400 IU/d cholecalciferol supplements (n = 24) or placebo (n = 24) for 9 wk.)	Iran	48 healthy pregnant women, at 25 weeks of gestation.	Vitamin D supplementation resulted in: - Significant decrease in serum hs-CRP and insulin concentrations - Significant increase in the Quantitative Insulin Sensitivity Check Index score, plasma total antioxidant capacity and total glutathione concentrations - Significant decrease in fasting plasma glucose, systolic and diastolic blood pressure	Positive effect
[125] Lind L et al. Diabetes Res, 1989.	- Fasting glucose - Fasting insulin - Insulin sensitivity (hyperinsulinemic euglycemic clamp)	Interventional study (2 micrograms of alpha-calcidol daily for 18 months)	Sweden	14 middle aged men: non Vitamin D deficient, with IGT and low glucose-stimulated insulin values	After Vitamin D supplementation, there was: - A transient increase of both peak and late insulin response to IVGTT - No alteration of glucose tolerance after IVGTT or OGTT - No modification of insulin sensitivity - Reduction in blood pressure (both systolic and diastolic)	Neutral effect

Table 2 (continued)

	Evaluated parameters	Study	Place	Study subjects	Results	Outcome
	- Glycaemia after IVGTT and OGTT - Insulin after IVGTT and OGTT - 25-hydroxyvitamin D - 1,25-dihydroxyvitamin D				- A small reduction in body weight	
[128] Pittas AG et al. Diabetes Care, 2007.	- 25 OH vitamina D - HOMA-IR - Fasting plasma glucose - C reactive protein - Interleukin 6	Double-blind, randomized, controlled trial (500 mg calcium citrate and 700 IU vitamin D3 or placebos daily for 3 years)	USA	314 Caucasian adults aged > = 65 years.	- Patients with IFG taking calcium-vitamin D supplements had a lower rise in FPG at 3 years compared with those on placebo ($P = 0.042$) and a lower increase in HOMA-IR ($P = 0.031$). - In the NFG subgroup, there was no difference in the change in FPG or HOMA-IR between the two treatment arms. - In either subgroup, there were no differences in C-reactive protein or interleukin-6 between the two treatment arms.	Positive (in IFG)
[129] Mitri J et al. Am J Clin Nutr. 2011.	- Disposition index after an IGTT - Acute insulin response - Insulin sensitivity - Glycaemia - HbA1c - 25 OH Vitamin D - Plasmatic calcium	2-by-2 factorial-design, double-masked, placebo-controlled trial (cholecalciferol (2000 IU once daily) or calcium carbonate (400 mg twice daily) for 16 wk.	USA	92 Adults at risk of type 2 diabetes	- Disposition index increased in the vitamin D group and decreased in the no-vitamin D group ($P = 0.011$) - In the Vitamin D group, there was an improvement in insulin secretion ($P = 0.046$). - Hb A(1c) increased less, but non-significantly, in the vitamin D group ($P = 0.081$). -No significant differences in any outcomes with calcium compared with no calcium.	Positive effect
[131] Tzotzas T et al. J Clin Endocrinol Metab 2010.	- 25 OH vitamin D - PTH - Lipid profile - Body weight - FAT mass - Waist circumference	Interventional study (4 and 20 weeks after low-calorie diet-induced weight loss.)	Greece	69 subjects: 44 obese women, 25 controls	-The 4-wk. low-calorie diet ($n = 37$) reduced BW and improvements in HOMA index and lipid levels. -The 20-wk. low-calorie diet ($n = 26$) resulted in reduction of BW and BMI by 10%, HOMA index (4.7 +/− 3.8 vs. 3.10 +/− 1.7, $P < 0.01$), and lipids levels (except high density lipoprotein cholesterol) and increase in 25 OH Vitamin D (15.4 +/− 6.0 vs. 18.3 +/− 5.1 ng/ml, $P < 0.05$) - The increase of 25 OH Vitamin D levels was associated with the reduction of insulin levels and HOMA index (r − 0.43, $P < 0.05$).	Positive effect of weight loss on Vit D3 and on insulin sensitivity
[132] Shab-Bidar S et al. BMC Medicine, 2011.	- Glycemic status - Lipid profile - Endothelin-1 - E-selectin - Matrix metalloproteinase (MMP)-9 - Anthropometric measures - Body FAT Mass	Randomized controlled trial either plain yogurt drink (170 mg calcium and no vitamin D/250 mL, $n_1 = 50$) or vitamin D3-fortified yogurt drink (170 mg calcium and 500 IU/250 mL, $n_2 = 50$) twice a day for 12 weeks.	Iran	100 subjects with type 2 diabetes	In FYD compared to PYD: - significant improvement in fasting glucose, the Quantitative Insulin Check Index (QUICKI), glycated hemoglobin (HbA1c), triacylglycerols, high-density lipoprotein cholesterol (HDL-C), endothelin-1, E-selectin and MMP-9	Positive effect
[133] Jorde R et al. Eur J Nutr. 2009.	- Fasting glucose - Insulin - C-peptide - Fructosamine - HbA1c - 25 OH vitamin D	Randomized controlled trial (supplementation with cholecalciferol (40,000 IU per week) versus placebo for 6 months)	Norway	36 subjects with type 2 diabetes, treated with metformin and bed-time insulin (32 participated to all the study)	- Fasting glucose, insulin, C-peptide, fructosamine, and HbA1c levels were not significantly different from baseline values. - Changes in these parameters (values at 6 months minus values at baseline) did not differ between the vitamin D and the placebo group	Neutral effect
[134] Avenell A et al., Age Ageing 2009.	- Annual postal or telephone questionnaire (anamnesis of diabetes, or assumption of medication for diabetes).	Blinded randomized trial (from 1999 to 2002 (oral 800 IU (20 μg) daily vitamin D3, 1000 mg calcium (calcium carbonate), both, or placebo) and followed up for 24–62 months.	UK	5292 participants aged ≥70 years with a recent previous osteoporotic fracture	- No evidence that vitamin D_3 in a daily dose of 800 IU, or in combination with 1000 mg calcium, was able to prevent the development of diabetes or a reduction in the need for medication for diabetes.	Neutral effect
[135] de Boer IH et al. Diabetes Care, 008.		Double blind randomized clinical trial	USA	33,951 women without self-reported diabetes at	- Calcium plus vitamin D3 supplementation did not reduce the risk of developing diabetes	Neutral effect

Table 2 (continued)

	Evaluated parameters	Study	Place	Study subjects	Results	Outcome
	- Anamnesis of diabetes or assumption of medication for diabetes - Fasting insulin (measured in 6% of the sample at 1,3,6 years) - Fasting glycaemia (measured in 6% of the sample 1,3,6 years) - 25 OH vitamin D (measured in 6% of the sample 1,3,6 years)	(1000 mg elemental calcium plus 400 IU of vitamin D3 daily, or placebo); median follow-up time of 7 years		baseline (2291 were newly diagnosed with diabetes)		
[136] Parekh D et al. Endocr Pract 2010.	- Serum 25-hydroxyvitamin D - HbA1c - Fructosamine - Glycaemia after oral glucose tolerance test - Insulin after oral glucose tolerance test	Randomized, double-blind, placebo-controlled pilot study (Vitamin D- group (group D) or placebo (group P); 4 weeks of follow up	India	28 Asian Indian patients with T2DM	- No improvement in glucose tolerance, insulin secretion, or insulin sensitivity after Vitamin D supplementation.	Neutral effect
[137] Heshmat R et al. Journal of Faculty of Pharmacy, 2012.	-Blood glucose - 25 OH vitamin D3 -Insulin - Glycosylated hemoglobin A1c (HbA1c) - Homeostasis Model Assessment Index (HOMA) - Waist circumference - BMI - Blood pressure	Randomized double-blind clinical trial (intervention group with single intramuscular injection of 300,000 International Unit (IU) of vitamin D3 and the placebo group)	Iran	42 diabetic patients	Three months after vitamin D injection: - HbA1c, anthropometric factors and HOMA index in intervention group stayed constant - Serum 25- OHD3 was significantly increased	Neutral effect
[138] Kampmann U et al. Metabolism, 2014.	- 25 OH vitamin D - Plasmatic Calcium - Inflammation markers - Lipid profile - C peptide - Insulin pulsatility - Insulin after IVGTT - Insulin sensitivity (hyperinsulinemic euglycemic clamp) - ABPM	Randomized double blind placebo controlled (280 μg daily for 2 weeks, 140 μg daily for 10 weeks or placebo for 12 weeks)	Denmark	16 patients with T2DM and D hypovitaminosis	- No significant changes in insulin sensitivity, inflammation, blood pressure, lipid profile, or HbA1c after Vitamin D supplementation - Borderline ($0.05 < p < 0.10$) improvements of insulin secretion (increase in c-peptide levels), first phase incremental AUC insulin and insulin secretory burst mass.	Neutral effect
[139] Tepper S et al. Diabetes, Obesity and Metabolism, 2016.	- Fasting glucose - Insulin - High-sensitivity C-reactive protein - Lipid profile - 25 OH Vitamin D3 - Anthropometric measures	1-year double-blind randomized controlled trial (treatment (100,000 IU vitamin D bimonthly) or placebo); evaluation after 6 and 12 months	Israel	130 men aged 20–65 years without diabetes with serum 25-hydroxyvitamin D levels <50 nmol/l (mean 38.89 ± 8.64 nmol/l)	- Levels of insulin and HOMA-IR values remained steady during the study period in the treatment group - Levels of insulin and HOMA-IR values increased by 16% in the control group ($p = 0.038$ and $p = 0.048$, respectively.	Positive effect
[140] Von Hurst PR et al. British Journal of Nutrition, 2010.	- Homeostasis model assessment 1 (HOMA1) - 25 OH vitamin D - Reactive C protein - Lipid profile - C peptide	Randomized controlled, double-blind intervention administering 100 microg (4000 IU) vitamin D(3) (n 42) or placebo (n 39) daily for 6 months	New Zealand	81 subject: 42 vitamin D, 39 placebo. South Asian women, aged 23–68 years	- There was a significant improvement in insulin sensitivity and IR ($P = 0.003$ and 0.02, respectively), and fasting insulin decreased ($P = 0.02$) with Vitamin D supplementation compared with placebo. - There was no change in C-peptide with supplementation. - IR was most improved when endpoint serum 25 OH Vitamin D reached > or =80 nmol/l. - Secondary outcome variables (lipid profile and high sensitivity C-reactive protein) were not affected by Vitamin D supplementation.	Positive effect

Table 2 (continued)

	Evaluated parameters	Study	Place	Study subjects	Results	Outcome
[141] Nazarian S et al. Transl Res, 2011.	- Intravenous glucose tolerance (mFSIGT) test - Acute insulin response to glucose (AIRg) - Insulin sensitivity (SI) - Disposition index (DI)	Open label study (supplementation with Vitamin D3 as 10,000 IU daily for 4 weeks)	USA	8 subjects with Vitamin D deficiency and prediabetes	After an intervention with vitamin D: - AIRg decreased ($P = 0.011$) - SI increased ($P = 0.012$)	Positive effect
[142] Davidson MB et al. Diabetes Care, 2013.	- 25 OH vitamin D - HbA1C - Fasting glucose - 2 h glucose - Insulin secretion - Insulin sensitivity	Double-blind, randomized control study (weekly placebo ($n = 53$) or vitamin D ($n = 56$) at different doses	USA	109 subjects ≥40 years with prediabetes and vitamin D deficiency	- No effect on insulin secretion, insulin sensitivity, or the development of diabetes was observed after Vitamin D supplementation	Neutral Effect
[143] Ljunghall S et al. Acta Med Scand 1987.	- Fasting glucose - Fasting insulin - Lipid profile - Serum calcium - HbA1c - Glucose after IVGTT	Prospective randomized double-blind study (0.75 μg alpha-calcidol ($1\alpha(OH)D_3$) daily or placebo for three-months)	Sweden	65 middle-aged men with IGT and normal serum Vitamin D	- No improvements in glucose tolerance or insulin secretion was observed after supplementation with vitamin D - There was a significant reduction in body weight in the alpha-calcidol treated group	Neutral effect
[144] Tai K et al. Nutrition, 2008.	- Fasting glucose - Fasting insulin - 25-hydroxyvitamin D - PTH - Plasmatic calcium - Insulin sensitivity after OGTT (SiM, ISI, QUICKI, HOMA)	Interventional study (two oral doses of 100,000 IU of cholecalciferol, 2 weeks apart)	Australia	33 adults, 19–75 y, with vitamin D insufficiency and without diabetes (21 NGT; 12 IGT)	After vitamin D supplementation, there was no effect on blood glucose, insulin concentrations or insulin sensitivity	Neutral effect

diabetes such impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).

In fact, some recent trials demonstrated that vitamin D supplementation could be useful for patients with IFG or IGT which are at high (50%) risk of type 2 diabetes: patients with IFG taking vitamin D had a lower rise in FPG at 3 years compared to those on placebo in a trial on non-diabetic adults [128]; a low calorie diet that lead to a rise in serum 15 OH Vitamin D was associated with an increase in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and improved lipid profile in a group of obese women [131]; vitamin D supplementation in adults at risk for type 2 diabetes lead to improved β-cell function and to a minor, but non-significant, increase in HbA1c values than in the control group [129]; finally, insulin sensitivity improved after 4 weeks of vitamin D administration in persons with IFG [141].

On the contrary, other authors found no effect of vitamin D supplementation on insulin secretion, insulin sensitivity or incident diabetes in a population affected by IGT or IFG [125, 142–144].

Two meta-analysis of randomized clinical trials concluded that at the moment there are not enough evidences to recommend supplementation with vitamin D to improve glycemic metabolism and prevent diabetes, even in high risk IGT or IFG individuals [145, 146].

8 Conclusions and perspective

Numerous studies have demonstrated that vitamin D plays a critical role in the regulation of inflammation, insulin resistance and, probably, insulin secretion. These findings suggest a potential function of vitamin D deficiency in the pathogenesis of the metabolic syndrome and type 2 diabetes, in which low-grade inflammation and alteration in insulin signaling pathways are key elements.

Many authors investigated the connection between vitamin D, inflammation and insulin resistance: numerous cross sectional, cohort and longitudinal studies showed an association between 25-OH Vitamin D levels, metabolic syndrome and diabetes. Interventional studies failed to demonstrate an unequivocal beneficial effect of vitamin D supplementation in type 2 diabetic patients, but some encouraging results have emerged from trials on patients at risk of developing diabetes (insulin resistant, IFG and IGT).

In conclusion, despite the presence of evidences of a mechanistic connection between signaling pathways of vitamin D, inflammatory cytokines (IL-6 and TNF- α) and insulin, the current available data are insufficient to demonstrate a general causal role of vitamin D deficiency in the pathogenesis of diabetes and metabolic syndrome, nor a therapeutic role for its supplementation in type 2 diabetes. We believe that long term, well designed, interventional clinical trials will be started to achieve a better understanding of the therapeutic potential of supplementation in Vitamin D deficient pre-diabetic subjects with attention to doses, duration of therapy, side effects, short term and long term results. In fact, we believe that Vitamin D deficient patients at risk of developing diabetes are the most promising target for supplementation: administration doses should be decided according to RDA, considering vitamin D status (insufficient or deficient) and age; supplementation should be long term (years); there must be a complete assessment of metabolic and cardiovascular parameters.

Interestingly also, the bone is emerging as a new important organ in the regulation of glucose metabolism in humans and it is conceivable that Vitamin D action and status in the regulation of calcium-phosphorous balance and bone metabolism might also mirror the interplay between other bone remodeling hormones such as sclerosin, osteopontin, osteoprotegerin, fractalkine and insulin in insulin resistant states and type 2 diabetes mellitus [44, 147–149].

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests.

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