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Review Article

Role of Vitamin D in Insulin Resistance

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Vitamin D is characterized as a regulator of homeostasis of bone and mineral metabolism, but it can also provide nonskeletal actions because vitamin D receptors have been found in various tissues including the brain, prostate, breast, colon, pancreas, and immune cells. Bone metabolism, modulation of the immune response, and regulation of cell proliferation and differentiation are all biological functions of vitamin D. Vitamin D may play an important role in modifying the risk of cardiometabolic outcomes, including diabetes mellitus (DM), hypertension, and cardiovascular disease. The incidence of type 2 DM is increasing worldwide and results from a lack of insulin or inadequate insulin secretion following increases in insulin resistance. Therefore, it has been proposed that vitamin D deficiency plays an important role in insulin resistance resulting in diabetes. The potential role of vitamin D deficiency in insulin resistance has been proposed to be associated with inherited gene polymorphisms including vitamin D-binding protein, vitamin D receptor, and vitamin D 1alpha-hydroxylase gene. Other roles have been proposed to involve immunoregulatory function by activating innate and adaptive immunity and cytokine release, activating inflammation by upregulation of nuclear factor κB and inducing tumor necrosis factor α, and other molecular actions to maintain glucose homeostasis and mediate insulin sensitivity by a low calcium status, obesity, or by elevating serum levels of parathyroid hormone. These effects of vitamin D deficiency, either acting in concert or alone, all serve to increase insulin resistance. Although there is evidence to support a relationship between vitamin D status and insulin resistance, the underlying mechanism requires further exploration. The purpose of this paper was to review the current information available concerning the role of vitamin D in insulin resistance.

1. Introduction

The incidence of type 2 diabetes mellitus (type 2 DM) is increasing at an alarming rate both nationally and worldwide. Defects in pancreatic β-cell function, insulin sensitivity, and systemic inflammation all contribute to the development of type 2 DM. Since insulin resistance is a risk factor for diabetes, understanding the role of various nutritional and other modifiable risk factors that may contribute to the pathogenesis of diabetes is important. Obesity and other lifestyle factors such as exercise, alcohol consumption, smoking, and certain dietary habits can also play an important role. Recently, a novel association between insulin resistance and vitamin D deficiency has been proposed. Vitamin D has in vitro and in vivo effects on pancreatic β-cells and insulin sensitivity. In this study, we place specific emphasis on the epidemiological evidence and possible mechanisms of these effects. In addition, we also review the therapeutic strategies involving vitamin D in the treatment of insulin resistance.

2. Synthesis and Metabolism of Vitamin D

2.1. Synthesis of 1,25-Hydroxyvitamin D. Vitamin D is obtained from exposure to sunlight, diet (fortified foods), and dietary supplements. When the skin is exposed to solar ultraviolet B radiation (wavelength, 290 to 315 nm), 7-dehydrocholesterol is converted to previtamin D_3, which is rapidly converted to vitamin D_3 (cholecalciferol) (Figure 1). Vitamin D from the skin and diet is transported in the blood by circulating vitamin D-binding protein

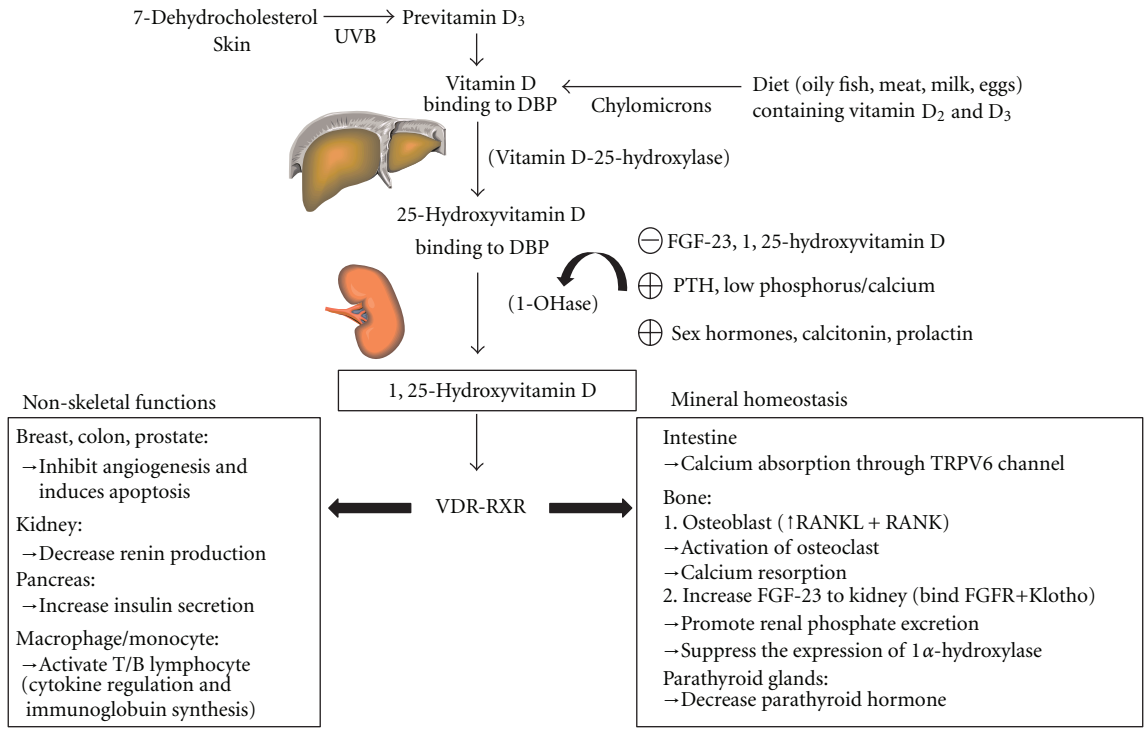

Figure 1: The synthesis and metabolism of vitamin D in the regulation of mineral homeostasis and nonskeletal functions. When under exposed to solar UVB (ultraviolet B), 7-dehydrocholesterol in the skin is converted to previtamin D_3, which is immediately converted to vitamin D_3. Vitamin D can also be obtained from dietary vitamin D_2 and D_3 incorporated into chylomicrons. Vitamin D in the circulation is bound to DBP (vitamin D-binding protein), which transports it to the liver where it is converted to 25-hydroxyvitamin D by vitamin D-25-hydroxylase. The biologically inactive 25-hydroxyvitamin D must be converted in the kidneys to active 1,25-hydroxyvitamin D by 1-OHase (25-hydroxyvitamin D_3 1α-hydroxylase). Serum PTH (parathyroid hormone), low phosphorus/calcium, sex hormones, calcitonin, and prolactin can increase ($\oplus$) the renal production of 1,25-hydroxyvitamin D. However, FGF-23 (fibroblast growth factor 23) and 1,25-hydroxyvitamin D have feedback functions to inhibit ($\ominus$) 1-OHase. Finally, the active 1,25-hydroxyvitamin D can bind to VDR-RXR (vitamin D receptor-retinoic acid x-receptor complex) in the intestine, bone, and parathyroid glands and then exert the classical function of mineral homeostasis. In addition, it also has nonskeletal functions when bound to VDR-RXR in other organs (breast, colon, prostate, kidney, pancreas) or immune cells (macrophages/monocytes). FGFR: FGF-23 receptor; TRPV6: transient receptor potential cation channel, subfamily V, member 6; RANKL: receptor activator of nuclear factor-κB ligand; RANK: the receptor for RANKL on preosteoclasts.

(DBP, a specific binding protein for vitamin D and its metabolites in serum) to the liver. In the liver, vitamin D is metabolized by P 450 vitamin D-25-hydroxylase to 25-hydroxyvitamin D, which is the major circulating metabolite and used to determine a patient's vitamin D status [1–5]. Almost all 25-hydroxyvitamin D is bound to circulating DBP and is filtered by the kidneys and reabsorbed by the proximal convoluted tubules. In the kidney, megalin and cubilin, members of the LDL receptor superfamily, play essential roles in endocytic internalization of 25-hydroxyvitamin D [6, 7]. In the proximal renal tubules, 25-hydroxyvitamin D is hydroxylased at the position of carbon 1 of the A-ring by the enzyme 25-hydroxyvitamin D_3 1α-hydroxylase (CYP27B1) to its active form, 1,25-hydroxyvitamin D. This enzyme is also found in extrarenal sites including the placenta, monocytes and macrophages [8–11].

2.2. Regulation of 1,25-Hydroxyvitamin D. The production of 1,25-hydroxyvitamin D is regulated by serum calcium and phosphorus levels, plasma parathyroid hormone (PTH) levels, and fibroblast growth factor 23 (FGF-23). Low serum calcium and phosphate levels result in enhanced activity of 1α-hydroxylase. PTH stimulates the transcription of 1α-hydroxylase and nuclear receptor 4A2 (NR4A2) is a key factor involved in the induction of 1α-hydroxylase transcription by PTH. 1,25-hydroxyvitamin D in turn suppresses PTH production at the level of transcription [12]. FGF-23 is a phosphaturic factor that promotes renal phosphate excretion by inactivating the sodium-phosphate cotransporter in the proximal tubule. 1,25-hydroxyvitamin D stimulates the production of FGF 23 in the bone, and an increased level of FGF-23 suppresses the expression of 1α-hydroxylase in the kidneys. FGF-23 requires a klotho (a multifunctional protein involved in phosphate and calcium homeostasis) as a cofactor for FGF signaling, and 1,25-hydroxyvitamin D upregulates klotho gene expression in the kidneys [12, 13].

2.3. Vitamin D Binding Protein (DBP) and Vitamin D Receptor (VDR). Vitamin D signaling may occur by binding of circulating 1,25-hydroxyvitamin D to VDR in β-cells

or by local production from the main circulating form, 25-hydroxyvitamin D. DBP (calbindin-D_{28K}), encoded by the *Gc* (group-specific component) gene, functions as a specific transporter of circulating vitamin D metabolites [14] and is essential for vitamin D endocytosis and metabolism [15]. DBP is a highly polymorphic single-chain serum glycoprotein synthesized and secreted by the liver that forms a complex with vitamin D ensuring that circulating vitamin D is delivered to target tissues [16]. Vitamin D exerts its actions in a variety of cell types through binding to the cytosolic/nuclear vitamin D receptor (VDR), which is a member of the steroid/thyroid hormone receptor family that functions as a transcriptional activator of many genes [17–19]. VDR is widely distributed in more than 38 types of tissue, where it clearly controls vital genes related to bone metabolism, oxidative damage, chronic diseases, and inflammation [20]. The VDR gene, located on chromosome 12q13.1, consists of 14 exons and has an extensive promoter region capable of generating multiple tissue-specific transcripts [21, 22]. Upon ligand binding, this nuclear hormone receptor in conjunction with its heterodimeric partner, the retinoid receptor (RXR), regulates gene transcription through vitamin D responsive elements (VDRE) in the promoter regions of vitamin D target genes, thereby modifying their expression [23]. In addition to cytosolic/nuclear VDR mediating transcriptional regulation, the possible existence of a vitamin D receptor localized to the plasma membrane VDR (mVDR) has been postulated recently [24]. Pancreatic β-cells express both the specific cytosolic/nuclear VDR and putative mVDR.

2.4. Extrarenal 1,25-Hydroxyvitamin D Production (Nonskeletal Functions). Vitamin D is characterized as a regulator of homeostasis of bone and mineral metabolisms. In addition to its classical actions on mineral homeostasis, 1,25-dihydroxyvitamin D also has nonskeletal actions (Figure 1). It has been reported that the brain, prostate, breast, colon, and pancreas, as well as immune cells, have vitamin D receptors (VDR-RXR) and respond to this active form of vitamin D [4, 25–27]. More than 200 genes are controlled by 1,25-hydroxyvitamin D directly or indirectly to regulate cellular proliferation, differentiation, apoptosis, and angiogenesis [28]. For example, breast, colon, prostate, and other tissues express 25-hydroxyvitamin D_3 1α-hydroxylase and produce 1,25-dihydroxyvitamin D which binds to VDR-RXR and then regulates a variety of genes that control proliferation, including p21 and p27, as well as genes that inhibit angiogenesis and induce differentiation and apoptosis. 1,25-dihydroxyvitamin D, an immunomodulator favoring the induction of regulatory T cells, can render dendritic cells tolerogenic with increased selective expression of immunoglobulin-like transcript 3 (ILT3) [29]. Meanwhile, 1,25-dihydroxyvitamin D inhibits rennin synthesis, and increases insulin production, myocardial contractility, the reproductive system, and hair growth [30–34]. Therefore, vitamin D may play an important role in modifying the risk of cardiometabolic outcomes, including type 2 DM, hypertension, and cardiovascular diseases.

3. Vitamin D Deficiency and Insulin Resistance

3.1. Vitamin D Deficiency. Vitamin D deficiency has been linked to a wide field of health problems including several types of cancer and autoimmune and metabolic diseases such as type 1 DM and type 2 DM. More than 30–50% of all children and adults are at risk of vitamin D deficiency, defined as a serum 25-hydroxyvitamin D level below 50 nmol/L [35]. However, this cutoff value is significantly higher than the 25 nmol/L (10 ng/mL) [36]. The association of vitamin D status and cardiometabolic disorders (cardiovascular disease, diabetes, and metabolic syndrome) was reviewed recently in a meta-analysis of 28 independently published studies [37]. The findings showed a significant 55% reduction in the risk of diabetes (9 studies), a 33% reduction in the risk of cardiovascular diseases (16 studies), and a 51% reduction in metabolic syndrome (8 studies) associated with a high serum 25-dihydroxyvitamin D concentration [37].

3.2. Evidence Linking Vitamin D to Insulin Resistance and Diabetes. Several studies have indicated a relationship between vitamin D status and the risk of diabetes or glucose intolerance. Vitamin D has been proposed to play an important role and to be a risk factor in the development of insulin resistance and the pathogenesis of type 2 DM by affecting either insulin sensitivity or β-cell function, or both [31, 38, 39]. Type 1 DM has been also reported to be associated with vitamin D deficiency based on animal and human observational studies [19, 23, 40]. The prevalence of hypovitaminosis D was found to be higher in diabetic patients (24%; $P < 0.001$) than in controls (16%) in one study [41]. Increasing evidence shows that vitamin D levels are also lower in patients with type 1 DM, especially at the onset [42].

3.3. Association between Vitamin D and Insulin Resistance. 1,25-dihydroxyvitamin D plays an important role in glucose homeostasis via different mechanisms. It not only improves insulin sensitivity of the target cells (liver, skeletal muscle, and adipose tissue) but also enhances and improves β-cell function. In addition, 1,25-dihydroxyvitamin D protects β-cells from detrimental immune attacks, directly by its action on β-cells, but also indirectly by acting on different immune cells, including inflammatory macrophages, dendritic cells, and a variety of T cells. Macrophages, dendritic cells, T lymphocytes, and B lymphocytes can synthesize 1,25-dihydroxyvitamin D, all contributing to the regulation of local immune responses [43]. The potential role of vitamin D deficiency in insulin resistance is shown in Table 1.

4. Role of Vitamin D Deficiency in Insulin Resistance

4.1. Vitamin D Associated Gene Polymorphisms and Insulin Resistance. Gene polymorphisms of the DBP, VDR, or vitamin D 1alpha-hydroxylase (CYP1alpha) genes may affect insulin release and result in insulin resistant. In addition, these gene polymorphisms may disturb vitamin D production, transport, and action.

Table 1: Role of vitamin D deficiency in insulin resistance.

Role	References
Inherited gene polymorphisms	
(1) Including DBP, VDR, and CYP1alpha gene polymorphisms	[44–68]
(2) Disturbance of vitamin D transport, action, and production	
Immunoregulatory function	
(1) Activating innate and adaptive immunity	
(2) Enhancing dendritic cell maturation and macrophage differentiation, and cytokine release	[69–83]
(3) Enhancing T-cell proliferation	
(4) Releases of IL-12, IL-2, INF-γ, and TNFα (destruction of the β-cell)	
Inflammation	
(1) Upregulation of NF-κB and inducing TNFα proinflammatory actions	[84–90]
(2) Downregulates IκB-α by decreasing mRNA stability and increasing IκB-α phosphorylation.	
(3) Enhancing the expression of TLR2 and TLR4 protein and mRNA in human monocytes, reducing the release of cytokines	
Other molecular actions of vitamin D to alter glucose homeostasis	
(1) Low calcium status: hypocalcemia can lower glucose-stimulated insulin secretion in β-cell	[90–95]
(2) PTH level: elevating PTH reduces glucose uptake by liver, muscle and adipose cell	
(3) Obesity: vitamin D deficiency can increase adiposity, and increasing sequestration of vitamin D in adipose tissue	

DBP: vitamin D binding protein; VDR: vitamin D receptor; CYP1alpha: vitamin D 1alpha-hydroxylase; IL-12: interleukin-12; INF-γ: interferon-γ; TNF α: tumor necrosis factor α; NF-κB: nuclear factor κB; IκB-α: the inhibitor of NF-κB; TLR: Toll-like receptors; PTH: parathyroid hormone.

4.1.1. Gene Polymorphisms of the DBP Gene. Electrophoretic variants of DBP have been associated not only with diabetes, but also with prediabetic traits. Two frequent missense polymorphisms at codons 416 GAT → GAG (Asp → Glu) and 420 ACG → AAG (Thr → Lys) in exon 11 of the DBP gene are the genetic basis for the three common electrophoretic variants of DBP (Gc1F, Gc1S, and Gc2) and the resulting circulating phenotypes (Gc1F/Gc1F, Gc1F/Gc1S, Gc1S/Gc1S, Gc1F/Gc2, Gc1S/Gc2, and Gc2/Gc2) [44]. These variants of DBP are the serum carriers of vitamin D metabolites and have been associated with a higher risk of type 2 DM or prediabetic phenotypes in several studies [45–49]. However, some studies have shown that the genetic variants of the DBP gene are not associated with diabetes [50, 51].

4.1.2. Gene Polymorphisms of the VDR Gene. VDR functions as a transcription factor when bound to 1,25-dihydroxyvitamin D. VDRs are present in pancreatic β-cells and vitamin D is essential for normal insulin secretion [52]. Several VDR polymorphisms have been found since the early 1990s, including Apa1 [53], EcoRV, Bsm1 [54], Taq1 [55], Tru91 [56], Fok1 [57], and Cdx2 [58]. To date, three adjacent restriction fragment length polymorphisms for Bsm1, Apa1, and Taq1at the 3′ end of the VDR gene have been the most frequently studied [59]. VDR polymorphisms have been reported to be related to type 1 DM [60–62]. The Bsm1 polymorphism has been shown to be associated with type 1 DM in Indians living in the south of the country [60], and combinations of Bsm1/Apa1/Taq1 have been shown to influence susceptibility to type 1 DM in Germans [61]. In a Taiwanese population, the AA genotype of the Apa1 polymorphism was found to be associated with type 1 DM [62]. In type 1 DM, four well-known polymorphisms (Fok1, Apa1, Bsm1, and Taq1) in the VDR gene have been implicated in the susceptibility to type 1 DM, however the results to date have been inconclusive. A meta-analysis (57 case-control studies in 26 published studies) indicated that the Bsm1 polymorphism is associated with an increased risk of type 1 DM (BB + Bb versus bb: OR = 1.30, 95% CI = 1.03−1.63), while the Fok1, Apa1, and Taq1 polymorphisms were not, especially in Asians [63]. The VDR genotype may affect insulin resistance, both with regards to insulin secretion (the Apa1 VDR polymorphism) and insulin resistance (the Bsm1 VDR polymorphism) [64].

In type 2 DM, the VDR gene polymorphism aa genotype was found to be associated with defective insulin secretion in Bangladeshi Asians, a population at increased risk of type 2 DM [65]. The associations of the Fok1, Apal, Bsm1 and Taq1 polymorphisms of the VDR gene with type 2 DM were also explored in a case-control study (308 type 2 DM patients and 240 control cases). In this study, no associations were found between the four polymorphisms examined and type 2 DM [66]. In another study, the distributions of alleles and genotypes of the four single-nucleotide polymorphisms in intron 8 (Bsm1, Tru91, Apal) and exon 9 (Taq1) of the VDR gene were similar in patients with type 2 DM ($n = 309$) and controls ($n = 143$) [67]. Therefore, the evidence supporting an association of VDR genotypes with the risk of diabetes is conflicting.

4.1.3. Gene Polymorphisms of the CYP1alpha Gene. Polymorphisms of the CYP1alpha gene involved in the metabolism of vitamin D may influence the susceptibility to type 2 DM. A study on the association of two markers, one in intron 6 and the other located upstream from the 5′ end of the CYP1alpha

gene, with type 2 DM in a Polish population found no differences in the distributions of genotypes, haplotypes, and haplotype combinations between the groups. However, the T-C/T-T heterozygous haplotype combination was more prevalent in the subgroup of obese type 2 DM patients (BMI $\geq$ 30) than in the controls (41.5% versus 28.6%, $P = 0.01$), suggesting an association with the risk factors for diabetes and obesity [68].

4.2. Effects of Vitamin D on the Immune System and Insulin Resistance

4.2.1. Immunoregulatory Function of Vitamin D. Basic science and epidemiological studies indicate that vitamin D has importance not only for cardiovascular health, but also for the immune response. Vitamin D has been shown to have a role in the development and function of the immune system. In fact, inadequate vitamin D and other nutrients during the development of the immune system may play a critical role in the development of autoimmune diseases. Evidence from animal models and prospective studies of rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, and type 1 DM suggests that vitamin D has an important role as a modifiable environmental factor in autoimmune diseases [69–71].

4.2.2. Immunoregulatory Function of Vitamin D on Insulin Resistance. The immune system plays a central role in the destruction of β-cells [72]. The detection of VDR in almost all cells of the immune system, especially antigen-presenting cells (macrophages and dendritic cells) and activated T cells [73–75], led to the investigation of a potential role for vitamin D as an immunomodulator. In addition, activation of nuclear VDR is also known to modify transcription via several intracellular pathways and influence proliferation and differentiation of immune cells [76, 77]. The importance of vitamin D in immune regulation is highlighted by the facts that VDR is expressed in activated inflammatory cells, that T-cell proliferation is inhibited by 1,25-dihydroxyvitamin D, and that activated macrophages produce 1,25-dihydroxyvitamin D [74, 78]. Vitamin D signaling pathways regulate both innate and adaptive immunity, maintaining the associated inflammatory response within physiological limits.

The innate immune response involves the activation of Toll-like receptors (TLRs) on polymorphonuclear cells, monocytes, macrophages, and a number of epithelial cells [79]. 1,25-dihydroxyvitamin D primarily influences dendritic cell maturation and macrophage differentiation, and also reduces the release of cytokines [80]. The adaptive immune response is initiated by cells specializing in antigen presentation, including dendritic cells and macrophages, which are responsible for presenting antigens for specific recognition by T lymphocytes and B lymphocytes [81]. 1,25-dihydroxyvitamin D exerts an inhibitory effect on the adaptive immune system by modifying the capacity of antigen-presenting cells (APCs) to induce T lymphocyte activation, proliferation and cytokine secretion [82]. 1,25-dihydroxyvitamin D decreases the maturation of dendritic cells and also inhibits the release of interleukin-12 (IL-12) (stimulating T-helper 1 cell development), IL-2, interferon-γ (INF-γ), and tumor necrosis factor α (TNFα) (stimulators of inflammation), which involves the destruction of β-cells resulting in insulin resistance. Overall, 1,25-dihydroxyvitamin D directly modulates T-cell proliferation and cytokine production, decreases the development of T helper 1 (T_H1) cells, inhibits T_H17 cell development, and increases the production of Thelper 2 (T_H2) cells and T regulatory cells [83]. These immunomodulatory effects of 1,25-dihydroxyvitamin D can lead to the protection of target tissues, such as β-cells.

4.3. Inflammation, Vitamin D, and Insulin Resistance. Chronic inflammation is involved in the development of insulin resistance, which increases the risk of type 2 DM. VDR is known to be expressed by macrophages and dendritic cells, suggesting that vitamin D plays an important role in the modulation of inflammatory responses [84]. Both cell types express the enzymes vitamin D-25-hydroxylase and 1α-hydroxylase and can produce 1,25-dihydroxyvitamin D [85]. Several studies have supported the role of vitamin D and 1,25-dihydroxyvitamin D as an anti-inflammatory agent. Macrophages are cells with a large capacity for cytokine production, in particular TNFα, which is one of the most important products released from these cells [78]. The transcriptional activation of the TNFα gene in macrophages is largely dependent on nuclear factor κB (NF-κB) dependent transcriptional activation [86]. In lipopolysaccharide-(LPS-) stimulated murine macrophages, 1,25-dihydroxyvitamin D upregulates IκB-α (the inhibitor of NF-κB) by increasing mRNA stability and decreasing IκB-α phosphorylation. Furthermore, increased IκB-α levels can reduce the nuclear translocation of NF-κB [87]. In addition, 1,25-dihydroxyvitamin D suppresses the expressions of TLR2 and TLR4 proteins and mRNA in human monocytes in a time- and dose-dependent fashion [88]. Recently, it has also been suggested that inflammation and activation of the innate immune system could be downregulated by hydroxyvitamin D by increased levels of inflammatory markers (TNFα, IL-6, IL-1, IL-8, cyclooxygenase-2, intercellular adhesion molecule-1, and B7-1) in monocytes from type 2 DM compared with monocytes from healthy controls [89]. In summary, 1,25-dihydroxyvitamin D inhibits the release of the pro-inflammatory cytokine TNFα and regulates the activity of NF-κB, [90] and suppresses the expressions of TLR2 and TLR4 proteins and mRNA in human monocytes, reducing the release of cytokines. Therefore, vitamin D may also function to reduce insulin resistance and the risk of diabetes by decreasing inflammatory responses.

4.4. Other Molecular Actions of Vitamin D to Alter Glucose Homeostasis. Several mechanisms have been proposed to explain the impact of vitamin D on insulin resistance including gene polymorphisms and the immunoregulatory function of vitamin D and inflammation as mentioned previously. The regulation of serum calcium via PTH and 1,25-dihydroxyvitamin D following changes in dietary

Table 2: Effects of vitamin D supplementation in insulin resistance.

Study	Intervention	Subjects	Effect
Pittas et al. [26]	vitamin D (700 IU/d for 3 years) and calcium intake	314	Decreased insulin resistance
Inomata et al. [99]	1α(OH) vitamin D (400 IU/d for 3 wks)	14 noninsulin-dependent diabetes	(1) Increased insulin secretion (2) A reduction in serum free fatty acid levels
Gedik and Akalin [100]	1,25 $(OH)_2$ vitamin D (2000 IU/d for 6 months)	4 patients with vitamin D deficiency	Increased insulin secretion
Borissova et al. [101]	1,25 $(OH)_2$ vitamin D (1332 IU/d for 1 month)	10 females with type 2 diabetes	A decrease of 21.4% in insulin resistance
Orwoll et al. [102]	1,25 $(OH)_2$ vitamin D (200 IU/d for 4 d)	20 patient with type 2 diabetes	No effect on insulin, glucose, c-peptide
Taylor and Wise [103]	1,25 $(OH)_2$ vitamin D (300000 IU intramuscular)	3 Asians with type 2 diabetes	Increased insulin resistance
Ljunghall et al. [104]	1α(OH) vitamin D (30 IU/d for 3 months)	65 Caucasian men with impaired glucose tolerance	No difference in insulin resistance
Kumar et al. [105]	1,25 $(OH)_2$ vitamin D (2000 IU/d for 1 month)	1 vitamin D deficient hypocalcemic woman	Increased glucose tolerance and β-cell function

calcium and obesity has been proposed to mediate the effects of vitamin D on insulin resistance.

4.4.1. Stimulation of Insulin Secretion by Vitamin D and Calcium. There is evidence that vitamin D may stimulate pancreatic insulin secretion directly. Vitamin D exerts its effects through nuclear vitamin D receptors [91]. The stimulatory effects of vitamin D on insulin secretion may only manifest when calcium levels are adequate. Insulin secretion is a calcium-dependent process, and therefore alterations in calcium flux can have adverse effects on β-cell secretary function. Glucose-stimulated insulin secretion has also been found to be lower in vitamin D-deficient rats when concurrent hypocalcemia has not been corrected [92].

4.4.2. Parathyroid Hormone (PTH). PTH regulates the activity of renal 1α-hydroxylase to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. However, extra-renal 1α-hydroxylase, which may lead to the local production of 1,25-dihydroxyvitamin D under conditions of high vitamin D status [93], has also been identified in a variety of tissues including muscles and adipocytes [94]. PTH may mediate insulin resistance by reducing glucose uptake by liver, muscle and adipose cells. PTH treatment (16 h) was found to decrease insulin-stimulated glucose transport [90, 95] in an osteoblast-like cell type. Another study indicated that PTH decreased insulin-stimulated glucose uptake in rat adipocytes [96]. These studies suggest that PTH may elicit insulin resistance by reducing the number of glucose transporters (both GLUT1 and GLUT4) available in cell membranes to promote glucose uptake [90]. PTH has also been shown to suppress insulin release [97] and to promote insulin resistance in adipocytes [90]. Therefore, PTH may negatively affect insulin sensitivity through altering body composition and inhibiting insulin signaling.

4.4.3. Muscle and Obesity. Vitamin D and PTH have also been associated with a variety of other actions beyond their classical functions, including cell growth, differentiation and apoptosis. Both hormones have been shown to increase levels of intracellular calcium and other rapid signaling pathways in a variety of tissues including adipocytes and muscle cells. Vitamin D may reduce adiposity, thereby improving insulin sensitivity indirectly through improving muscle mass and the reduction in vitamin D status with increased adiposity [90]. In addition, obesity, increasing sequestration of vitamin D in adipose tissue, is also known to be associated with reduced vitamin D status [98].

5. Therapeutic Interventions on Insulin Resistance with Vitamin D

5.1. Effect of Vitamin D on Insulin Resistance. Vitamin D may have a beneficial effect on improving pancreatic β-cell function, decreasing insulin resistance, and improving systemic inflammation [26].

5.1.1. Pancreatic β-cell Function. Several studies support a role of vitamin D in pancreatic β-cell function through direct and indirect effects. The direct effect is where vitamin D binds directly to the β-cell vitamin D receptor. The indirect effect may be via its important and well-recognized role in regulating extracellular calcium and calcium flux through β-cells [26].

5.1.2. Insulin Resistance. Vitamin D may have a beneficial effect on insulin action either directly, by stimulating the expression of insulin receptors and thereby enhancing insulin responsiveness for glucose transport [106], or indirectly via its role in regulating extracellular calcium and ensuring normal calcium influx through cell membranes and an adequate intracellular cytosolic calcium pool because calcium is essential for insulin-mediated intracellular processes

in insulin-responsive tissues such as skeletal muscles and adipose tissues [107].

5.1.3. Inflammation. Systemic inflammation has been linked primarily to insulin resistance, but elevated cytokines may also play a role in β-cell dysfunction by triggering β-cell apoptosis. Vitamin D may improve insulin sensitivity and promote β-cell survival by directly modulating the generation and effects of cytokines. Vitamin D interacts with vitamin D response elements in the promoter region of cytokine genes to interfere with nuclear transcription factors implicated in cytokine generation, and its action and can downregulate activation of NFκB [108–110].

5.2. Evidence of Intervention with Vitamin D Supplementation. The mainstay management for vitamin D deficiency is vitamin D supplementation to prevent or ameliorate the disease. Several studies support that vitamin D supplementation may affect glucose homeostasis or improve insulin resistance [99–101, 105] (Table 2). Restoration of vitamin D levels was shown to ameliorate glucose tolerance in a study on one hypocalcemic woman with vitamin D deficiency [105]. A significant increase in serum calcium levels and a reduction in serum free fatty acid levels have been found after taking vitamin D supplementations [99]. Recently, a New Zealand study found that south Asian women with insulin resistance improved markedly after taking vitamin D supplements [111]. The optimal vitamin D concentrations for reducing insulin resistance have been shown to be 80 to 119 nmol/L, providing further evidence for an increase in the recommended adequate levels [43].

Nevertheless, some studies have shown conflicting results of vitamin D supplementation for insulin resistance or improvement of type 2 DM [102–104] (Table 2). One report found that Asian patients with type 2 DM with vitamin D deficiency even had a worsening of glycemic control and an increase in insulin resistance [104]. These contrasting results suggest that the dose and method of supplementation, and the genetic background and baseline vitamin D status of individuals seem to be more important for the efficacy of vitamin D supplementations in insulin resistance.

6. Conclusion

Vitamin D is not only a regulator of bone and mineral metabolism, but also a potent immunomodulator linked to many major human diseases including glucose homeostasis and insulin resistance. Vitamin D deficiency has been shown to affect insulin secretion in both humans and animal models. Accumulating evidence suggests the role of vitamin D in the pathogenesis of insulin resistance including several vitamin-D-related gene polymorphisms and vitamin-D-related metabolic and immune pathways. Supplementations of vitamin D may provide for suitable management and act to ameliorate insulin resistance. Additionally, there is a need for randomized trials to evaluate the significant effects of vitamin D supplementations in insulin resistance.

Authors' Contribution

C.-C. Sung and M.-T. Liao contributed equally to this work.

Conflict of Interests

There is no conflict of interests.

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