Vitamin D Deficiency

Subjects: Endocrinology & Metabolism

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Vitamin D was found to counteract insulin resistance via participation in the maintenance of normal resting reactive oxygen species level and regulation of Ca^{2+} level in many cell types. Both genomic and non-genomic action of vitamin D is directed to insulin signaling. Thereby, vitamin D reduces the extent of pathologies associated with insulin resistance such as oxidative stress and inflammation. Therefore, the beneficial actions of vitamin D include an improvement of glucose and lipid metabolism in insulin-sensitive tissues, and in consequence the diminish of insulin resistance.

Keywords: vitamin D, insulin resistance, ; inflammation ; oxidative stress

1. Introduction

There is mounting evidence that vitamin D deficiency is now a worldwide health problem. In addition, an alarming number of diseases connected with vitamin D deficiency such as obesity and type 2 diabetes mellitus (T2DM) are observed. Both basic and clinical studies demonstrated that the majority of common characteristics of these diseases result from defects in insulin signaling, systemic inflammation, and pancreatic β-cells dysfunction [1][2][3][4]. It should be stressed that according to recent investigations one of the major causative factors in insulin resistance development is vitamin D deficiency. The results of some clinical studies have demonstrated that vitamin D supplementation improves major metabolic parameters associated with insulin resistance, including low-density lipoprotein (LDL), total cholesterol (TC), glycated hemoglobin (HbA1c), triglyceride (TAG), and homeostatic model assessment-insulin resistance (HOMA-IR). We have shown that three-month supplementation with vitamin D of the elderly with metabolic disorders markedly elevates HDL level, reduces HOMA-IR, and TG/HDL ratio. Moreover, we observed that HbA1c percentage decreased about 0.5% in T2DM patients after vitamin D supplementation [5]. In turn, Upreti et al. have revealed that six-month supplementation with vitamin D of T2DM patients leads to distinct reduction of HbA1c [6]. The results of study carried out by Mirrhosseini et al. have showed that vitamin D decreases HbA1c, fasting plasma glucose (FPG), and HOMA-IR contributing to better glycemic control [7]. Interestingly, Tabesh et al. have observed that co-supplementation of vitamin D with calcium decreases serum insulin level, HbA1c, HOMA-IR, LDL, and TC/HDL. Additionally, they also detected the significant elevation of quantitative insulin sensitivity check index (QUICKI) and HDL [8]. El Hajj et al. have found that vitamin D triggers to significantly diminish of HOMA-IR, FPG, TC, and LDL, but without any significant changes in HbA1c [9]. The results of studies conducted by Barzegardi et al. have presented pronounced decrease in serum levels of TG, LDL, and TC in diabetic nephropathy patients after supplementation with vitamin D [10]. Taken together, these observations support that vitamin D improves metabolic control of diabetes.

Vitamin D is involved in many cellular processes, e.g., the presence of its receptor and its metabolizing enzymes have been found in the cells of various tissues, including pancreatic β-cells, adipocytes, hepatocytes, and myocytes [11][12][13][14]. It also controls blood glucose concentration by regulating insulin secretion and insulin sensitivity [15]. Furthermore, it has been found to act in adipose tissue which is a major storage site of the vitamin [11]. It should be underlined that adipose tissue secretes numerous adipocytokines involved in inflammation, a typical feature of insulin resistance, obesity, and T2DM [11]. Numerous studies have revealed that vitamin D reduces the extent of inflammation and chronic hyperglycemia-generated oxidative stress [5][15]. Appealingly, vitamin D was demonstrated to modulate hepatic lipid and glucose metabolism [16]. Finally, it has also been shown that vitamin D counteracts diet-induced insulin resistance in skeletal muscle [17].

However, it should be also emphasized that the results of clinical studies have revealed no effect of vitamin D on insulin resistance and related disorders, including oxidative stress and inflammation. Lerchbaum et al. have shown that vitamin D supplementation did not change significantly metabolic parameters regarding insulin resistance and lipids in heathy men [18]. Forouhi et al. have found no effect of vitamin D on HbA1c, lipid and apolipoprotein levels, CRP, as well as anthropometric measures in subjects with increased risk of T2DM [19]. Similarly, Heshmat et al. have revealed no changes in HbA1c, anthropometric measures, and HOMA-IR in diabetic patients treated with vitamin D [20]. No differences in the FPG oral glucose tolerance test (OGTT) between prediabetes subjects supplemented with vitamin D in comparison to the

placebo group have also been observed [21]. In addition, no significant changes between T2DM group and T2DM group supplemented with vitamin D have also been observed in the hs-CRP level, oxidative stress markers, LDL, HDL, and HbA1c [22]. In turn, Asemi et al. did not observe any significant changes in total plasma glutathione (GSH) and serum high sensitivity C-reactive protein (hs-CRP) level in pregnant women with gestational diabetes after supplementation with vitamin D [23].

2. How does Vitamin D Overcome Insulin Resistance and Related Disorders?

2.1. Vitamin D via the Regulation of Ca^{2+} Homeostasis Participates in Insulin Secretion by Pancreatic β-Cells

The secretion of insulin by the pancreatic β-cells is a consequence of elevated blood glucose concentration. Glucose molecules flow into the pancreatic β-cells via the glucose transporter 2 (GLUT-2). Then, glucose breaks down in numerous metabolic pathways, which is ultimately accompanied by ATP production. Increased ATP suppresses the ATP-sensitive K^+ channel resulting in the depolarization of β-cell membrane followed by the activation of the L-type voltage-operated channels to produce the localized Ca^{2+} pulses crucial for the secretion of insulin [24].

Numerous studies showed that vitamin D deficiency is associated with impaired secretion of insulin by pancreatic β-cells [25][26][27][28][29]. Importantly, it was demonstrated that the supplementation with vitamin D restored proper secretion of the hormone [25][27][30]. However, it should be underlined that the findings concerning this issue are not unambiguous especially with regard to clinical trials [3][31][32][33][34][35].

One of the molecular mechanisms by which vitamin D participates in insulin secretion by pancreatic β-cells is the regulation of intracellular Ca^{2+} concentration. It was reported that $1,25(OH)_2D_3$ reduced the expression of the L-type Ca^{2+} channels causing a decrease in intracellular Ca^{2+} concentration and thereby altering calcium signaling. In turn, rapid, non-genomic $1,25(OH)_2D_3$ action was found to be responsible for the increase of cytoplasmic Ca^{2+} level that activates exocytosis of insulin in the pancreatic β-cells. Two vitamin D-mediated signaling pathways are involved in this process. The first includes PKA activation that phosphorylates various proteins engaged in the function of L-type voltage-dependent Ca^{2+} channels associated with insulin secretion. The second engages PLC synthesis and the activation of inositol triphosphate ($InsP_3$) triggering the secretion of Ca^{2+} from ER leading to DAG synthesis. Subsequently, DAG activates PKC that is responsible for the phosphorylation of the K_{ATP} channels and L-type voltage-dependent Ca^{2+} channels. The latter trigger the depolarization of cytoplasmic membrane and opening of T-type Ca^{2+} and L-type channels that in consequence leads to the elevation of intracellular Ca^{2+} followed by insulin secretion [36]. PKC is also able to mobilize insulin secretory vesicles that together with increased Ca^{2+} concentration induce insulin secretion [37]. Furthermore, increased intracellular Ca^{2+} concentration stimulates insulin secretion via activation of CaMPKII. CaMPKII is a serine-threonine protein kinase occurring in secretory vesicles of insulin. Its primary function is the promotion of phosphorylation of numerous proteins involved in exocytosis, as well as mobilization of insulin vesicles [38]. Another study demonstrated that increased intracellular Ca^{2+} concentration is associated with the expression of insulin gene via cAMP-responsive element-binding protein (CREB). The activation of CREB occurs in response to numerous stimuli, including glucose growth factors (i.e., the insulin-like growth factor-1 (IGF-1)), incretin hormones (i.e., the glucagon-like peptide-1 (GLP-1), the gastric inhibitory polypeptide (GIP), the pituitary adenylate cyclase-activating polypeptide (PACAP)). All these stimuli lead to the phosphorylation of CREB at serine 133 residue. CREB is a crucial transcriptional element responsible for the efficient transcription of insulin gene, glucose sensing, exocytosis of insulin, and survival of pancreatic β-cells [39].

It is worth highlighting that the regulation of intracellular Ca^{2+} level by vitamin D is mediated by calbidin, a cytosolic Ca^{2+} -binding protein involved in the stimulation of insulin secretion. Calbidin-D28k expression was found to be regulated by vitamin D [33][40]. It was also reported that $1,25(OH)_2D_3$ increased the expression of calbindin D-9k, parvalbumin, the plasma membrane Ca^{2+}-ATPase 1b, the sodium/calcium exchanger (NCX), and the Ca^{2+} pumps. All of these proteins are involved in the maintenance of low resting Ca^{2+} concentration in pancreatic β-cells [41][42][43][44].

Taken together, vitamin D is a potential modulator of depolarization-induced secretion of insulin via intracellular Ca^{2+} level regulation in pancreatic β-cells [40]. The effect of vitamin D on pancreatic β-cells is presented in Figure 1.

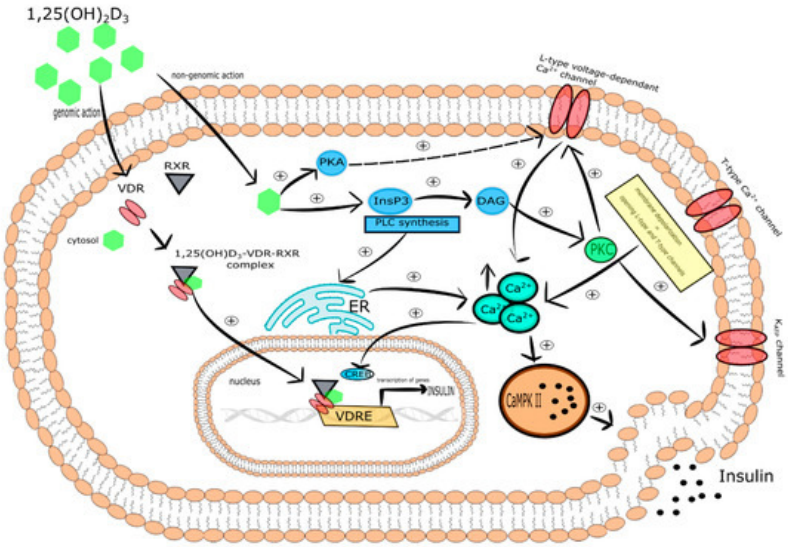

Figure 1. The effect of vitamin D on pancreatic β-cells. Stimulatory interactions are indicated by solid arrows and attenuation by dotted arrows. Enhancement is expressed by +. ↑ denotes increase.

2.2. Vitamin D Controls Ca^{2+} Level in Myocytes and Adipocytes

It is well known that Ca^{2+} are second messengers engaged in intracellular events induced by insulin in muscle and adipose tissue. That is why intracellular Ca^{2+} level changes have a substantial impact on multidirectional insulin actions. Numerous studies have demonstrated that the low level of Ca^{2+} in the cells of insulin targeted tissues is associated with reduced activity of glucose transporter followed by the development of peripheral insulin resistance [30].

Intracellular Ca^{2+} concentration in insulin-responsive tissues, including adipose tissue and skeletal muscle, is regulated by several mechanisms. The first mechanism involves the action of PTH that increases intracellular Ca^{2+} concentration in insulin-responsive tissues, including adipose tissue and skeletal muscle [45][46][47], as well as reducing insulin-induced transport of glucose [48][49]. Therefore, both growing intracellular Ca^{2+} concentration and the decreasing number of GLUT-1 and GLUT-4 on the cell membranes evoked by PTH promotes insulin resistance observed as reduced glucose uptake [49][50]. There is evidence that vitamin D deficiency is associated with increased PTH levels coexisting with insulin resistance [51][52]. Wright et al. have shown that vitamin D reduced insulin resistance in skeletal muscle as a result of elevation of intracellular Ca^{2+} concentration and strengthening of GLUT-4 translocation to the membrane of muscle cells and glucose uptake [53].

It has also been observed that vitamin D might decrease insulin resistance indirectly via the renin-angiotensin-aldosterone system (RAAS). It is well known that the RAAS system inhibits insulin action in peripheral tissues and regulates cellular Ca^{2+} concentration in skeletal muscle cells [53][54][55]. Interestingly, the increased expression of renin and secretion of angiotensin II, as well as $1,25(OH)_2D_3$-mediated inhibition of renin biosynthesis have been observed in VDR-null mice [56][57][58]. Therefore, it was shown that vitamin D improved insulin sensitivity via inhibition of RAAS [59].

To conclude, vitamin D alleviates the insulin resistance state via regulation of Ca^{2+} level and RAAS action in insulin targeted tissue, including skeletal muscle and adipose tissue.

2.3. Vitamin D-Mediated Improvement of Insulin Sensitivity Is Connected with Insulin Signaling

Accumulating evidence uncovers multiple potential mechanisms by which vitamin D deficiency can contribute to insulin resistance. It is generally accepted that abnormalities in the insulin signaling pathway are responsible for the development of insulin resistance that is characterized by reduced reaction of target cells to circulating insulin.

It has been found that vitamin D mediated increase in insulin sensitivity occurs via binding of calcitriol to VDR [60], induction of IRs expression [61], and the activation of peroxisome proliferator-activated receptor delta (PPAR-δ) [62]. The latter is a transcription factor engaged in the mobilization and metabolism of fatty acids in skeletal muscle and adipose tissue. What is more, activated PPAR-δ decreased FFAs-mediated insulin resistance in skeletal muscle. It was shown that $1,25(OH)_2D_3$ activated PPAR-δ and improved insulin sensitivity. [62]. Manna et al. documented that vitamin D improved glucose metabolism as a result of upregulation of the SIRT1/IRS1/GLUT-4 signaling cascade and enhanced glucose uptake in high glucose-treated C2C12 myotubes [63].

The genomic pathway induced by $1,25(OH)_2D_3$ in pancreatic β-cells, which express both VDR and CYP27B1, stimulates insulin synthesis and secretion since VDRE is present in the promoter region of the insulin gene [33][36][64]. Relevantly, studies performed on mice with the lack of functional VDR revealed that after glucose load, insulin synthesis and secretion were impaired [65]. Vitamin D-mediated improvement of insulin sensitivity is connected with insulin signaling. As a result of $1,25(OH)_2D_3$ -mediated transcriptional activation of IR gene, the number of IRs on the surface of insulin responsive cells increases. Thus, upregulation of the IR gene ensures proper insulin signaling [61][66][67] and in this way calcitriol maintains insulin sensitivity [61][66][68]. It is suggested that vitamin D deficiency is involved in the onset of insulin resistance as a consequence of reduced expression of IR [2]. However, the results of vitamin D-mediated activation of IR expression in the liver are unambiguous. George et al. reported that vitamin D supplementation upregulated liver expression of IRs in streptozotocin-induced diabetic rats [69]. On the contrary, several studies failed to identify alterations in IR expression in the liver of mice fed with high-fat diet or low-fat diet [70], as well as in streptozotocin-induced diabetic rats after vitamin D supplementation [71].

To sum up, vitamin D alleviates insulin resistance via improvement of insulin signaling.

2.4. Vitamin D Possesses Indirect Antioxidant Properties

The pathogenic mechanism of insulin resistance is complex and has yet to be fully elucidated. Undoubtedly, the trigger factor in insulin resistance is adiposity, especially visceral, which is accompanied by chronic hyperglycemia, oxidative stress, and low grade chronic inflammation [72][73]. Additionally, a balance in the physiologic redox state is crucial for normal β-cells function, glucose homeostasis, and insulin sensitivity [74][75][76]. Oxidative stress is an imbalance between the production of reactive oxygen species (ROS) and the efficacy of antioxidant defense system. Endoplastic reticulum (ER) stress, hyperglycemia, dyslipidemia, lipid peroxides, and nitric oxide synthase, as well as advanced glycation end-products are involved in ROS overproduction in the insulin resistance diabetic state. It is well recognized that oxidative stress may activate several factors contributing to the development of insulin resistance [77][78]. Inoguchi et al. found that hyperglycemia and FFAs might activate ROS production via PKC-dependent stimulation of NADPH oxidase [79]. It was also observed that increased production of ROS is a key activator of insulin resistance [80][81]. Moreover, the association between the degree of insulin resistance and oxidative stress is suggested to induce cellular damage [78][82][83]. ROS have the ability to directly oxidize and damage cellular macromolecules, i.e., DNA, proteins, and lipids. Additionally, ROS may act as a signaling molecule that activates numerous cellular stress-sensitive pathways, i.e., NF-κB, JNK/SAPK, p38MAPK, and hexosamine involved in cellular damage and related pancreatic β-cells dysfunction, insulin resistance, and diabetes complication [84].

It is generally known that the hyperglycemic state is a causative factor responsible for the overproduction of ROS and reduced ATP formation that in turn exerts an effect on Ca^{2+} homeostasis leading to β-cell exhaustion and reduced resting insulin secretion. Furthermore, it is well recognized that the elevated formation of ROS increases the release of Ca^{2+} from ER via sensitization of the ryanodine receptors (RYRs) and inositol 1,4,5-trophosphate receptors ($InsP_3Rs$). Reduced ATP level diminishes the capability of the Ca^{2+} pumps in ER and plasma membrane to press out Ca^{2+} from the cytoplasm outside of the cell. The effect may stimulate an increase of Ca^{2+} level in the pancreatic β-cells that triggers excessive insulin secretion leading to exhaustion of pancreatic β-cells [2]. Therefore, the elevated level of ROS strengthens Ca^{2+} signaling and may contribute to the onset of diabetes.

It was also proposed that oxidative stress coexisting with diabetes/chronic hyperglycemia is a result of increased FFAs levels that exert an effect on the mitochondria leading to increased ROS production (i.e., superoxide, hydrogen peroxide, hydroxyl radical ions) [85][86][87][88]. It was also suggested that vitamin D may regulate cellular bioenergetics in the mitochondria via VDR in the nucleus. This effect is related to the upregulation of numerous components involved in mitochondrial function, including mitochondrial respiration [89][90]. Additionally, VDR is capable of entering mitochondrion via permeability transition pores [91] and controls its functions, however this mechanism is still not fully understood [92]. It has also been found that vitamin D deficiency is connected with a decline in the mitochondrial respiration process. This effect is a consequence of the reduction of proteins and nuclear mRNA molecules engaged in this process [89][90]. Decreased respiration leads to a drop of mitochondrial bioenergetics related to alterations in oxidative phosphorylation, reduced ATP formation, and increased production of ROS [2]. Reduced expression of complex 1 of the electron transport chain contributes to the decrease of ATP production and ROS overproduction. In turn, increased ROS level reduces the activity of the insulin signaling pathways via lowering of GLUT-4 gene transcription, phosphorylation of IRS, disturbances in insulin signaling, and changes of mitochondrial activity [93][94][95]. These observations are supported by the results of a study showing that $1,25(OH)_2D_3$/VDR signaling inhibits the process of differentiation of brown adipose cells and mitochondrial respiration [96]. Recently, Ricca et al. have demonstrated that VDR-mediated action of vitamin D may protect cells from overproduction of ROS and excessive respiration that leads to cell damage [97]. Vitamin D controls the balance of mitochondrial respiration via maintenance of mitochondrial respiratory chain activity [98] and the regulation of expression

of uncoupling protein 1 (UCP1). UCP1 is localized on the inner membrane of mitochondria and is engaged in the regulation of thermogenesis [11]. The role of vitamin D in the maintenance of normal activity of mitochondria may explain at least partially the privileged relationship between diabetes and vitamin D deficiency.

Vitamin D has been shown to decrease ROS production in adipocytes [99] via the regulation of cellular antioxidants expression such as glucose-6-phosphate dehydrogenase (G6PD), glutathione peroxidase (Gpx), TR [100]. Interestingly, vitamin D together with Klotho and Nrf2 may control the expression of numerous antioxidants including catalase, Prx-2, Prx-3, SOD ½, GSH, TR, G6PD, TRX, Trxrd-1, Gpx. It has been documented that vitamin D decreases the expression of NADPH oxidase which is responsible for the production of ROS [101], while increasing the expression of SOD [100][102]. Furthermore, vitamin D elevated the production of glutathione (GSH), a major redox buffer through the upregulation of glutamate cysteine ligase, glutathione reductase, and G6PD [103][104][105]. To conclude, it seems that antioxidant properties of vitamin D are indirect and related to its genomic and non-genomic action.

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