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Review article

The molecular mechanisms by which vitamin D improve glucose homeostasis: A mechanistic review

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ABSTRACT

Diabetes mellitus (DM) is a complex metabolic disorder involving multiple deleterious molecular pathways and cellular defects leading to disturbance in the biologic milieu. It is currently a global health concern with growing incidence, especially among younger adults. There is an unmet need to find new therapeutic targets for the management of diabetes. Vitamin D is a promising target in the pathophysiology of DM, especially since vitamin D deficiency is common in patients with diabetes compared to people without diabetes. Evidence suggests that it can play significant roles in improving peripheral insulin sensitivity and glucose metabolism, however, the exact pathophysiological mechanism is not clarified yet. In this current study, we have reviewed the evidence on the effect of vitamin D in improving insulin resistance via distinct molecular pathways.

1. Introduction

The prevalence of diabetes mellitus (DM), primarily type 2 diabetes (T2DM) is growing in an epidemic proportion [1]. This chronic disorder is now considered as the most prevalent metabolic disease worldwide [2]. It is predicted that the total diagnosed and undiagnosed cases of DM will rise from 14% in 2010 to about 33% by 2050 among the US adult population [3]. DM imposes a significant economic burden on individuals and health care systems [4]. DM gives rise to various long-term complications [5]. DM and its complications through various pathophysiological mechanisms result in significant morbidity and mortality [5]. There is a growing need for better pharmacological agents to prevent and manage DM and its complications [6,7].

Colecalciferol or vitamin D3 (vitD3), belongs to a class of steroid hormones known as vitamin D, is involved in many cellular and molecular mechanisms such as calcium and magnesium metabolism and thereby normal mineralization of bones [8,9]. There is growing evidence that vitamin D is associated with other metabolic disorders such as insulin resistance and DM [10–13]. In view of this, vitamin D is widely consumed as a dietary supplement worldwide [14]. There is evidence demonstrating that vitamin D deficiency is more common among patients with diabetes compared to people without diabetes, suggesting that it may be involved in normal glucose homeostasis [15–17]. However, the exact role of vitamin D in DM has not been completely elucidated yet [17]. In this current study, we review about the possible interactions between the pharmacologic role of vitamin D and normal glucose homeostasis, insulin resistance and DM so as the develop new preventive and therapeutic strategies for management of DM.

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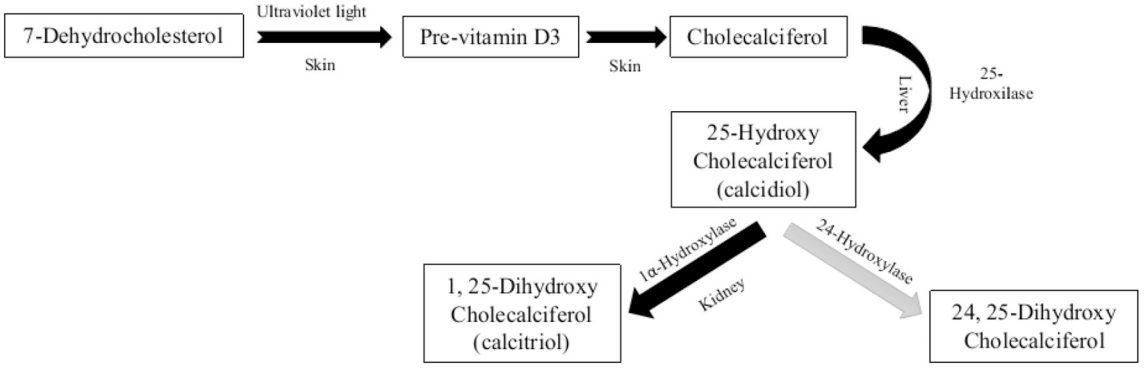


Fig. 1. Sequential steps in the formation of the active form of vitamin D3.

2. Vitamin D3 physiology

Vitamin D is a group of fat-soluble steroid hormones responsible for reabsorption of various ions such as calcium, magnesium, and phosphate [18]. Vitamin D3 or colecalciferol is the most potent member of this family which is synthesised via various biochemical processes and ingestion [18,19]. In mammals, it is produced under the influence of ultraviolet light on certain provitamins as 7-dehydrocholesterol in the skin [20]. This process involves the rapid formation of previtamin D3, which is then slowly converted to the active form of vitamin D3 (Fig. 1) [20]. Subsequent steps are occurred in the liver and kidneys [21]. In the liver, vitamin D3 is converted to 25-hydroxycolecalciferol (calcidiol) by 25- hydroxylase, which is then converted in the proximal renal tubules by 1α-hydroxylase enzyme to the more active metabolite as 1,25-dihydroxycolecalciferol or calcitriol [21]. The less active metabolite as 24, 25-dihydroxycolecalciferol is also produced by 24- hydroxylase in the kidneys (Fig. 1) [20,21]. Colecalciferol and its derivatives are transported in the plasma by binding to a specific globulin known as vitamin D-binding protein (DBP) [20,21].

Vitamin D3 is also ingested through the diet [21]. Moreover, it can be made in other tissues such as the placenta, keratinocytes (skin), and macrophages [21]. The normal plasma levels of calcidiol and calcitriol are about 30 ng/ml, and 0.03 ng/ml, respectively [21]. The synthesis of vitamin D3 is under delicate control of serum calcium, phosphorus, magnesium and PTH (parathyroid hormone) levels [21]. Calcitriol is metabolized by the cytochrome P450 (CYP) superfamily members [21]. Vitamin D exerts its effects via specific receptors known as vitamin D receptors (VDRs), which are nuclear receptors of transcription factors regulating a wide range of gene expression [22]. VDR has also involved in the microRNA-dependent post-transcriptional processes [23]. Thereby, calcitriol plays significant roles in transcriptional and post-transcriptional cellular events [23].

The classic role of calcitriol was initially detected as Ca^{2+} and PO_4^{3-} ions reabsorption in the intestine and renal tissues [19]. However, further studies demonstrated that it has other significant roles with immunosuppressive, anti-proliferative, pro-differentiating, anti-oxidative and anti-inflammatory properties [18]. Also, it has physiologic roles in other organs such as kidney, skin, immune cells, pancreas, and parathyroid glands [24]. It is also involved in gene expressions [25]. For instance, its specific receptor was detected in the human insulin gene promotors (between −761 and −732 base pairs), which enabled it to regulate insulin expression [25,26]. However, chronically taking higher dose of colecalciferol can result in undesirable side-effects such as nausea, vomiting, headache, hypercalcemia, kidney stones, arrhythmia and bone pathologies [27,28]. Beyond its effects on bone homeostasis, vitamin D is now considered as an active biologic multi-potential compound [18].

3. Vitamin D3 and diabetes mellitus

There is strong evidence suggesting that normal levels of vitD3 is associated with normal insulin sensitivity and glucose homeostasis [15,17,22,24,29]. For instance, a recent clinical trial in T2DM patients demonstrated that 6 months of vitD3 therapy significantly improved metabolic deterioration and glucose homeostasis [30]. Also, DM is more prevalent in vitD3 deficient subjects [16,31]. Moreover, the polymorphism of genes involved in calcitriol synthesis has been demonstrated to increase the risk of insulin resistance and DM [32,33]. This evidence suggests that vitD3 is involved in the pathophysiology of insulin resistance and DM [15,17,24,29]. In the following sections, we discuss the molecular interactions between vitamin D and pathways which maintains glucose homeostasis. A list of some experimental evidence is presented in Table 1. The clinical evidence in humans is presented in Table 2.

3.1. VitD3 and beta-cell function

A healthy and functional mass of pancreatic beta cells is necessary for maintaining the glucose homeostasis and normal metabolism [53]. Patients with diabetes have a varying degree of beta-cell dysfunction

Table 1
Experimental evidence confirming vitD3 induces insulin sensitivity.

Treatment	Tissue	Type of study	Effects	Ref.
Calcitriol/24 h	L6 myotube cells	In vitro	Up-regulates Glut-4	[34]
Calcitriol/24 h	3T3L1 Adipocytes	In vitro	Up-regulates Glut-4	[35]
Calcitriol/2 h	murine C2C12 myoblasts	In vitro	Induces Glut-4 expression	[36]
Colicalciferol/8 weeks	Adipose tissue of diabetic male C57BL/6 J mice	In vivo	Alleviates oxidative stress, promotes AMPK signaling pathway and Glut-4 localization	[37]
vitD3/12 weeks	Testicular tissues of diabetic rats	In vivo	Induces PI3K/Akt signaling	[38]
vitD3/2 months	Myocytes of high-fed diet induced T2DM mice	In vivo	Improves insulin signaling pathways	[39]
Calcitriol /48 h	C2C12 myotubes	In vitro	Improves IST by promoting Akt, IRS-1 and ERK signaling pathways	[40]
vitD3/6 weeks	Rats with T2DM	In vivo	Promotes IRS-1 phosphorylation	[41]
vitD3/500 IU/kg/10 weeks	STZ-induced diabetic rats	In vivo	Alleviate oxidative damage and improve glucose homeostasis	[42]

Table 2
Clinical trial evidence about insulin-sensitizing effects of calcitriol.

Treatment	Population of study	Effects	Ref.
5000 IU/day/6 months	96 prediabetic patients	Increased peripheral insulin sensitivity and β-cell function	[30]
5000 IU/day/12 weeks	22 patients with T2DM	Improves beta-cell function accompany with lowering inflammatory cytokines	[43]
–	712 healthy subjects	Plasma levels of vitD3 is correlated to insulin sensitivity and islet function	[44]
50,000 IU/week/8 weeks	100 patients with T2DM	Improves insulin sensitivity	[45]
10,000 IU/daily/4 weeks	8 prediabetic subjects	Improves FBS control and insulin sensitivity	[46]
131 IU/3 days	20 non-diabetic paraplegic patients	Improves insulin sensitivity and glucose profile	[47]
–	300 hypertensive non-diabetic patients	Postprandial glucose tolerance is related to plasma levels of vitD3	[48]
1200 IU/day/16 weeks	130 prediabetic subjects	Improves insulin sensitivity	[49]
100,000 IU/2 week/12 weeks	200 patients with T2DM	Improves insulin sensitivity	[50]
–	17 healthy subjects	increased GSK-3 and Akt and induce insulin sensitivity in adipocytes	[51]
50,000 IU/3 week/6 weeks	25 women with gestational diabetes	Improved metabolic profile and glucose homeostasis by lowering oxidative stress and MDA levels	[52]

and thereby, improving islets' function is one of the main targets in research studies [53–55]. There is evidence suggesting that calcitriol preserves beta-cell mass and improves islets function via several pathways [56,57]. As stated before, the active form of vitD3 participate in various molecular pathways and can play a significant modulatory role in different cellular events such as ion homeostasis [56,58–60]. As insulin secretion process is a calcium-dependent mechanism, it has suggested that active form of vitD3 in plasma is correlated to normal insulin release by the beta cells [61]. This suggestion is confirmed by the fact that serum PTH[1] level is inversely related to insulin sensitivity [62,63].

Since discovering its specific receptor (VDR) on pancreatic beta cells, the roles of active vitD3 on beta cells' function was confirmed [64]. Also, the active form of α-hydroxylase enzyme responsible for the activation of vitD3 was detected in beta cells [65]. Moreover, specific response element for vitD3 has been detected in insulin gene promoter suggesting the important role of calcitriol on insulin production by the beta cells [65]. Additionally, calcitriol is able to up-regulate the insulin gene in islets directly [25]. These findings strongly suggest that insulin secretion from pancreatic cells is dependent on plasma levels of calcitriol [25,65]. This theory is confirmed by studies on VDR deficient animals in which, these animals are unable to secrete enough insulin in response to postprandial glucose [29,66,67].

It has also been demonstrated that calcitriol has adverse and inhibitory effects on various pathophysiologic mechanisms contributing to beta-cell dysfunction such as inflammation, apoptosis, autoimmune responses and oxidative stress [56]. Al-Sofiani et al. [43] through a randomized controlled trial study reported that vitD3 supplement markedly improved beta-cells function in T2DM patients [43]. Lemieux et al. [30] conducted a clinical study suggesting that vitD3 supplement in prediabetic subjects improves beta-cell function and readjusts glucose homeostasis [30]. Kayaniyil et al. [44], demonstrated that plasma levels of vitD3 are correlated to the efficiency of beta-cells and insulin sensitivity in non-diabetic population [43]. These findings suggest that calcitriol has positive effects on islets' functions and improves the efficiency of beta-cells and thereby, glucose homeostasis [43,56] Table 3.

3.2. VitD3 and peripheral insulin sensitivity

Emerging evidence suggests that calcitriol effectively improves insulin sensitivity [67,75]. This could be through several pathways as described below.

3.2.1. VitD3 and insulin signal transduction

Insulin signal transduction (IST) is a complex process involving sequential cellular signaling events [76,77]. Briefly, IST is initiated by the binding of the insulin (as well as IGFs[2]), to the α chain of its specific receptor known as insulin receptor (IR), which promotes structural changes in β chain of IR and recruits different adaptor proteins such as insulin receptor substrates (IRSs), (and other adaptors such as Shc protein (SHC-transforming) and APS protein (adapter protein with a PH and SH2 domain)) [76]. These events provide a binding site for IRS-1 that in turn, links to the PI3K (phosphoinositide 3-kinase) and activates it [76]. In next step, activated PI3K catalyzes the conversion of PIP2 (phosphatidylinositol 4,5-bisphosphate) to PIP3 (phosphatidylinositol 3,4,5-trisphosphate) [76]. PIP3 is itself a potent activator for PKB (protein kinase B, also known as Akt), which facilitates glucose entering into the cells by localization of Glut-4 (glucose transporter type 4) on the cell membrane (Fig. 2) [77].

There are other types of insulin-dependent kinases as ERK1/2 (extracellular signal-regulated kinase 1/2), S6K1 (ribosomal protein S6 kinase beta-1), mTOR (mammalian target of rapamycin), SIK2 (serine/threonine-protein kinase 2), atypical PKC (protein kinase C), ROCK1 (Rho-associated protein kinase 1), AMPK (AMP-activated protein kinase) and GSK3 (Glycogen synthase kinase), which can also be activated by insulin, and then phosphorylate IRSs and promote IST [76].

Therefore, normal peripheral insulin sensitivity is dependent on the appropriate expression and function of all the involved elements of IST [77,78]. For example, a proper profile of Glut-4 expression on the cell membrane of insulin-dependent tissues is critical for normal insulin sensitivity [79–81]. It has been shown that calcitriol up-regulates insulin receptors at mRNA and protein levels [25,82,83]. Recent evidence demonstrated that calcitriol could up-regulate Glut-4 expression as well as its localization on cell membranes of adipocytes and myocytes [34,35]. Tamilselvan et al. [34] reported that vitD3 increased glucose uptake via up-regulating glucose transporters in myotubes [34]. Also, Manna and Jain [35] found that the active form of vitD3 directly up-regulates Glut-4 expression in 3T3L1 adipocyte cell lines [35]. This effect was accompanied by improved insulin sensitivity in adipocytes [35].

Other elements of IST are also under the influence of vitD3 [36,37]. Manna et al. [36] found that vitD3 increases Glut-4 dependent glucose uptake by promoting IRS-1 phosphorylation in murine C2C12 myotubes [36]. Also, Manna et al. [37] reported that vitD3 increased insulin sensitivity by promoting SIRT-1/AMPK signaling pathway and inducing Glut-4 localization in the diabetic mice [37]. Moreover, Tamilselvan et al. [34] showed that calcitriol upregulates IRS in L6 adipocytes [34]. He et al. [38] found that vitD3 is a potent inducer for PI3K/Akt pathway in the diabetic milieu [38]. This effect may explain some aspects of the insulin-sensitizing effects of vitD3 [38]. Zhou et al. [40] found that the active form of vitD3 improved IST by promoting Akt, IRS-1 and ERK signaling pathways [40]. Benetti et al. [39] demonstrated that vitD3 supplementation improves insulin signaling

[1] Parathyroid hormone.

[2] Insulin like growth factors.

Table 3
Molecular mechanisms by which vitD3 induces insulin sensitivity.

Molecular mechanism		Effects	Ref.
β-cell function		Attenuates pathophysiologic mechanisms involved in beta-cell dysfunction and improve islets' efficiency	([43], [56], [30])
Peripheral insulin sensitivity	Insulin Signal Transduction	Up-regulates IST elements and promotes their functions such as PI3K/Akt and IRS-1 pathways and Glut-4 expression/localization, induces PPAR-δ pathways	([39], [68], [41], [69], [36,37], [40])
	Systemic/local Inflammation	Ameliorates inflammatory responses and inhibits inflammation dependent insulin resistance	([43], [39], [70], [71], [72], [73])
	Redox state	Normalizes the redox state, prevent of oxidative stress-induced insulin resistance and thereby, promotes islet' function and insulin signaling pathways as SIRT-1/AMPK and Glut-4 localization	([52], [74], [37])

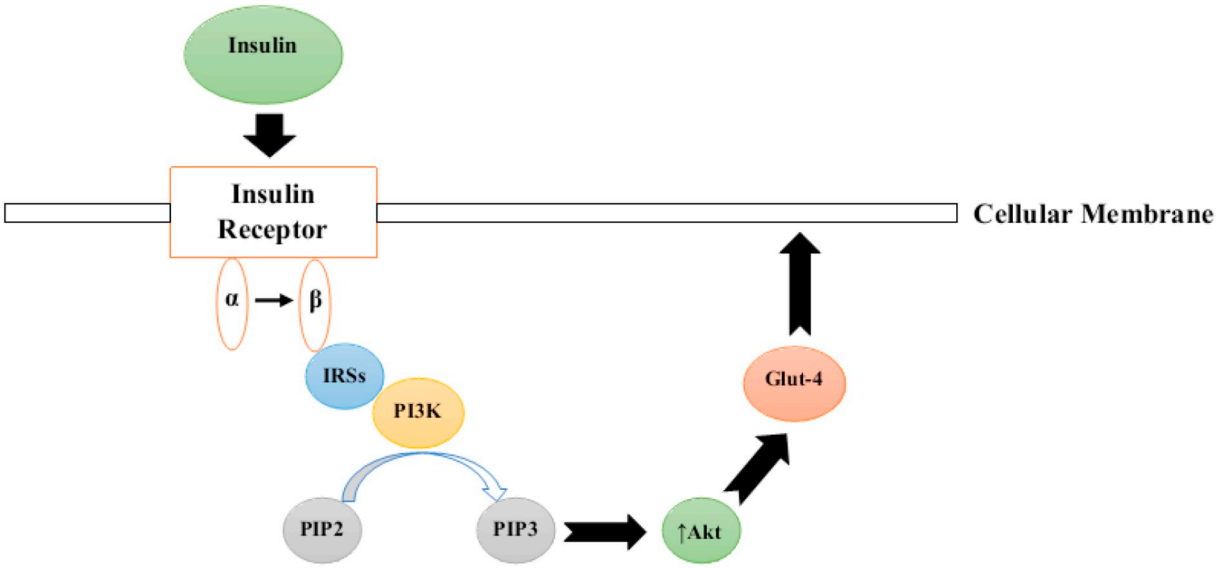


Fig. 2. Schematic representation of insulin signal transduction (IRSs = insulin receptor substrates, PI3K = Phosphoinositide 3-kinase, PIP2 = Phosphatidylinositol 4, 5-bisphosphate, PIP3 = Phosphatidylinositol 3, 4, 5-trisphosphate, Akt = protein kinase B, Glut-4 = glucose transporter type 4).

pathways in high-fat diet induced T2DM mice [39]. It also promotes IRS-1 phosphorylation [41]. Elseweidy et al. [41] reported that calcitriol intake in diabetic animals improved glucose homeostasis by inducing IRS-1 phosphorylation and promoting IST [41].

Calcitriol also has interactions with molecular pathways involved in the activation of IST such as PPAR[3] [84–86]. There is evidence suggesting that vitD3 may improve IST via PPAR-δ molecular pathway [68]. Dunlop et al. [68] found that human PPAR-δ is a primary target for $1\alpha,25(OH)_2D_3$ and activates it [68]. Hoseini et al. [69] demonstrated that the beneficial effects of vitD3 supplementation on glucose homeostasis and insulin sensitivity during physical activity are dependent on the activation of PPAR-γ molecular pathway [69]. Parker et al. [51] through a cohort study found that activity levels of Akt and GSK are dependent on the plasma levels of calcitriol in healthy subjects [51]. They suggest that these main elements of IST work under the influence of calcitriol availability which further confirmed the essential roles of vitD3 in glucose homeostasis [51]. In another study by Sciacqua et al. [48], postprandial glucose tolerance was closely dependent on the plasma levels of vitD3 [48].

3.2.2. vitD3 and systemic and local Inflammation

Inflammatory responses have pivotal roles in insulin resistance and DM [87,88]. Systemic inflammation negatively modulates insulin signaling pathways and reduces insulin sensitivity in peripheral tissues [87]. Also, local inflammatory responses in pancreatic tissues disturb beta-cell function and reduce islets' ability for postprandial insulin secretion [89–91]. Therefore, lowering the levels of inflammatory resulted in improved insulin sensitivity [90,92].

Evidence suggests that calcitriol has potent anti-inflammatory effects and reduces systemic inflammation [71,73]. For example, Meghil et al. [70] reported that vitD3 supplement markedly reduces systemic inflammation in periodontitis patients [70]. Also, Pfeffer et al. [72] demonstrated that vitD3 exerts anti-inflammatory potentials in human epithelial cells [72]. Moreover, some evidence suggested that insulin-sensitizing effects of vitD3 is related to its anti-inflammatory potentials [39,43]. Benetti et al. [39] reported that insulin sensitizing effects of vitD3 is dependent on its anti-inflammatory potentials via SCAP[4]/SREBP[5] lipogenic pathway in diabetic mice [39]. Al-Sofiani et al. [43] conducted a trial study on T2DM participants suggesting vitD3 improves islets' efficiency by alleviating inflammatory markers [43]. The above evidence suggests that vitD3 improves insulin sensitivity at least partly via attenuating the inflammatory events [70].

4. VitD3 and redox state

A balanced physiologic redox state is critical for normal insulin sensitivity, beta-cell function and glucose homeostasis [93–95]. It has been well confirmed that oxidative stress; which refers to an imbalance between free radical species and antioxidant system potency favor to free radicals; has pivotal roles in the pathophysiology of insulin resistance and DM [95,96]. Oxidative stress induces insulin resistance via

[3] Peroxisome Proliferator-activated Receptor.

[4] SREBP cleavage activating protein.

[5] Sterol regulatory element binding protein-1c.

a variety of molecular mechanisms such as β-cell dysfunction, mitochondrial dysfunction, inflammatory responses, down-regulating IST elements and thereby impairing the normal insulin signaling pathways [96–102]. Consequently, using antioxidative agents to prevent oxidative could be potentially beneficial in rising the insulin sensitivity in peripheral tissues [81,103,104].

There is recent evidence on the antioxidative properties of calcitriol [72,105,106]. It suggests that calcitriol has potent modulatory effects on the redox state and can normalize it [37,42,107,108]. Salum et al. [37] demonstrated that oral administration of vitD3 markedly improves glucose homeostasis in diabetic rats [42]. They found that glucose-lowering effects of vitD3 are associated with its antioxidative properties since it potentiated antioxidative capacity in the serum and reduced oxidative damages in these animals [42]. Manna et al. [37] demonstrated that calcitriol improved insulin sensitivity by alleviating oxidative stress in high fat diet induced diabetic mice [37]. They found that readjusting the redox state by calcitriol, promoted SIRT-1[6]/AMPK signaling and increased Glut-4 localization in the adipocytes [37]. In a randomized clinical trial in 2014, Asemi et al. demonstrate that vitD3 supplement improved the metabolic profile and glucose homeostasis by lowering oxidative stress and MDA[7] levels in women with gestational diabetes [52]. In another clinical study by Gradinaru et al. (2012), it has suggested that in elderly diabetic patients, vitD3 has inverse relationships with oxidative stress markers such as oxLDL[8] and AOPPs[9] [74]. This findings strongly suggest that some aspects of antidiabetic effects of vitD3 may be related to its antioxidative potentials which prevent oxidative stress-induced impairment in IST [37,74] [52].

4.1. Other possible pathways

Additionally, other pathways may be involved in vitD3-induced insulin sensitivity [41]. For instance, Elseweidy et al. [41] provided evidence suggesting that vitD3 may exerts regulatory roles on insulin degrading enzyme and suppress glucagon secretion [41]. They demonstrated that vitD3 alleviates insulin resistance by reducing the insulin degrading enzyme activity in high-fed diet diabetic rats [41]. More involved molecular mechanisms may be elucidated in the future.

5. Conclusion

Calcitriol or activated vitamin D, which was initially recognized as an important component of ion homeostasis and bone metabolism regulator. But further studies demonstrated that it has pleiotropic potentials in a variety of other molecular pathways and cellular signalings. Calcitriol is now considered as a potent nuclear factor regulating transcriptional and post-transcriptional processes of different genes. Emerging evidence suggests that the active form of vitamin D is also involved in glucose homeostasis and thereby contributes to the pathophysiology of insulin resistance and DM. but the exact mechanism is not elucidated yet. In this current review, we conclude that vitamin D improves glucose homeostasis and promote insulin sensitivity via at least two distinct molecular pathways. Calcitriol improves glucose homeostasis by promoting beta-cell function by ameliorating deleterious molecular mechanisms involved in the pathophysiology of beta-cell dysfunction. Also, it can increase peripheral insulin sensitivity by at least three separate pathways including lowering of the oxidative damages, suppressing inflammatory responses and by promoting IST expression and activity. Findings of preliminary clinical studies are in concordance with pre-clinical studies. However, more clinical studies are needed to confirm the beneficial role of vitamin D in diabetes mellitus.

[6] Sirtuin-1.
[7] Malondialdehyde.
[8] Oxidized LDL.
[9] Advanced oxidation protein products.

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Declaration of competing interest

All the authors declare that they have no conflict of interest in this study.

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