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Review

Vitamin D in Diabetes: Uncovering the Sunshine Hormone's Role in Glucose Metabolism and Beyond

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Abstract: Over the last decades, epidemiology and functional studies have started to reveal a pivotal role of vitamin D in both type 1 and type 2 diabetes pathogenesis. Acting through the vitamin D receptor (VDR), vitamin D regulates insulin secretion in pancreatic islets and insulin sensitivity in multiple peripheral metabolic organs. In vitro studies and both T1D and T2D animal models showed that vitamin D can improve glucose homeostasis by enhancing insulin secretion, reducing inflammation, reducing autoimmunity, preserving beta cell mass, and sensitizing insulin action. Conversely, vitamin D deficiency has been shown relevant in increasing T1D and T2D incidence. While clinical trials testing the hypothesis that vitamin D improves glycemia in T2D have shown conflicting results, subgroup and meta-analyses support the idea that raising serum vitamin D levels may reduce the progression from prediabetes to T2D. In this review, we summarize current knowledge on the molecular mechanisms of vitamin D in insulin secretion, insulin sensitivity, and immunity, as well as the observational and interventional human studies investigating the use of vitamin D as a treatment for diabetes.

Keywords: vitamin D; type 2 diabetes; beta cells; vitamin D receptor; insulin

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1. Introduction

Vitamin D is a group of fat-soluble secosteroids. This term generally refers to vitamin D_2 (ergocalciferol), a plant-derived product of sterol ergosterol, and vitamin D_3 (cholecalciferol), an animal-derived product of 7-dehydrocholesterol. A small quantity of vitamin D, including vitamin D_2 and vitamin D_3, can be acquired from dietary sources. The majority of circulating vitamin D, in the form of vitamin D_3, is formed in the skin from 7-dehydrocholesterol (7-DHC) in the presence of sunlight [1]. Through two successive steps of hydroxylation catalyzed by 25-hydroxylase and 1α-hydroxylase, respectively, vitamin D in humans is progressively converted into 25-hydroxyvitamin D (25(OH)D) in the liver and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) in the kidney (Figure 1) [2]. While 25-hydroxyvitamin D (25(OH)D) is the primary circulating form and an excellent biomarker for overall vitamin D levels [3], 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is the metabolically active form of vitamin D [4].

Vitamin D exerts its effects via both genomic and nongenomic actions. For the genomic pathway, $1,25(OH)_2D$, as a ligand, binds to vitamin D receptor (VDR), a ligand-dependent nuclear receptor that functions as a transcription factor by generating a heterodimer with the retinoid X receptor (RXR) upon ligand binding [5]. The VDR/RXR complex recognizes vitamin D-responsive elements (VDRE), a direct tandem repeat of two hormone response element in the regulatory regions of target genes [5], activating or repressing gene expression in a context-dependent manner (Figure 1). The downstream effects of VDR are tightly regulated by the specific composition of its coregulatory partners, such as chromatin remodelers, co-activators, and co-repressors [6]. Additionally, $1,25(OH)_2D$ may

bind to membrane-anchored receptors to regulate the activity of signaling molecules or the production of second messengers [7].

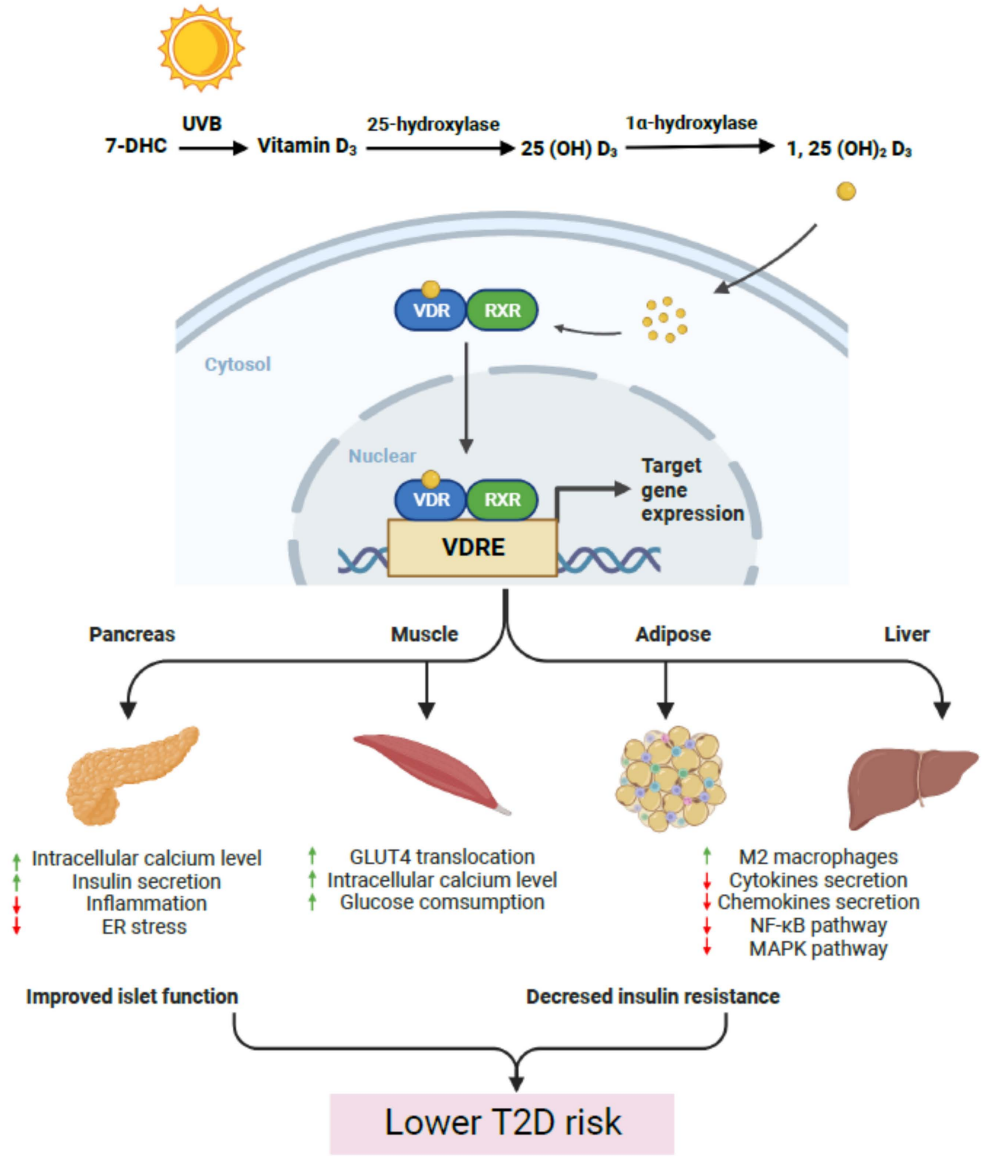

Figure 1. Vitamin D protects against type 2 diabetes. 1,25 $(OH)_2$ D_3, the active form of vitamin D3, is produced from cholesterol through successive hydroxylation of UVB generated 7-dehydrocholesterol (DHC). 1,25 $(OH)_2$ D_3 activates the vitamin D receptor (VDR) retinoid X receptor (RXR) heterodimer in the major metabolic tissues. The active VDR/RXR heterodimer binds to vitamin D response elements (VDREs) to induce changes in gene expression that in combination, improve islet function and decrease insulin resistance.

In addition to the canonical functions in regulating calcium absorption, bone growth and remodeling [8], vitamin D has other roles in metabolism and immunity. Notably, growing evidence supports that vitamin D plays a relevant role in islet dysfunction and insulin resistance in T2D [9–12]. From an epidemiology perspective, the worldwide trend of prevalent vitamin D insufficiency [13,14] may be linked to the growing incidence of T2D in humans. We summarize the molecular mechanisms of vitamin D in regulating insulin secretion and insulin action in both homeostasis and T2D, as well as the epidemiology and clinical evidence ascertaining a protective role of vitamin D in T2D pathogenesis. Lastly, we discuss the role of vitamin D in suppressing autoimmunity and preserving islet function in T1D.

2. Vitamin D and Islet Dysfunction in T2D Progression

Already a prevalent endocrine disease, the incidence of T2D is expected to escalate rapidly in the coming decades. T2D is characterized by diminished insulin secretion from pancreatic islets and insulin resistance in peripheral organs. Insulin secretion defects and insulin resistance, triggered by chronic and excess nutritional intake, cause glucose intolerance and hyperglycemia. Both β cell mass and glucose-stimulated insulin secretion (GSIS) are reduced even in the early prediabetic stage [15]. The deterioration of β cell function and reduced β cell mass is likely caused by multiple risk factors, including glucotoxicity, lipotoxicity, and elevated inflammation [15–17].

β cells express both the vitamin D receptor transcript (*Vdr*) and 1α-hydroxylase (*Cyp27b1*), which catalyzes the activation of 25(OH)D into 1,25$(OH)_2$D, consistent with the cell-intrinsic role for VDR [18]. Furthermore, the presence of a VDRE in the human insulin receptor gene promoter region suggests a potential role of vitamin D in influencing insulin action [19], although direct evidence of VDR occupancy at the *INS* locus is still lacking. Several in vivo and ex vivo studies in rats have indicated that vitamin D deficiency in vivo resulted in reduced serum insulin levels and impaired islet insulin secretion in isolated islets [20–22]. Conversely, in vitamin D-deficient mice, several studies showed that vitamin D supplementation could restore islet insulin secretion [20–24], suggesting a direct role of vitamin D in regulating islet insulin secretion function. In addition, serum insulin and *Ins2* expression are significantly decreased in VDR-mutant mice [23], suggesting that vitamin D-VDR controls the expression of genes related to insulin expression and secretion.

Evidence corroborating the function of vitamin D in human β cells has been shown in clinical studies in T2D patients [25], prediabetic [26], and non-diabetic populations [27]. However, while the correlation between vitamin D levels and islet function is robust, it should be noted that whether vitamin D treatment can directly improve insulin secretion in humans remains unclear, with intervention clinical trials showing mixed results of vitamin D supplementation in improving human islet function [18,28,29].

Vitamin D regulates insulin synthesis and secretion through multiple mechanisms. On the one hand, the active form of vitamin D, 1,25 $(OH)_2$D, binds to VDR and induces genes related to glucose transport, insulin secretion [19], and cellular growth in β cells [30]. On the other hand, vitamin D may indirectly regulate insulin secretion by impacting intracellular calcium concentrations. Calcium triggers insulin release [31] by promoting the mobilization of insulin vesicles and their exocytosis [32]. 1,25 $(OH)_2$D leads to depolarization of cytoplasmic membranes in β cells, opening of Ca^{2+} channels and elevation of intracellular Ca^{2+} levels [33,34]. One possible molecular mechanism of this action is that 1,25 $(OH)_2$D activates PKA and enhances channel function by phosphorylating L-type voltage-dependent Ca^{2+} channel-related proteins [33]. Moreover, 1,25 $(OH)_2$D activates VDR to regulate the expression of voltage-gated calcium channel to enhance insulin secretion [35]. Another mechanism is that 1,25 $(OH)_2$D promotes PLC synthesis and activates inositol triphosphate that releases Ca^{2+} from the ER [34,36]. In addition, vitamin D adjusts the expression of calbindin [37,38], a Ca^{2+}-binding protein involved in maintaining Ca^{2+} concentrations.

In T2D, islet dysfunction is caused by a combination of stress factors, including glucolipotoxicity, inflammation, ER stress, and Islet Amyloid Polypeptide (IAPP) toxicity. Vitamin D has long been identified as an anti-inflammatory hormone in the immune response. Vitamin D or over-expression of VDR has also been shown to repress cytokine-induced proinflammatory responses and apoptosis in β cell lines and islets [39–41]. The inflammation suppressive function of vitamin D is likely because of the direct suppression of NF-κB activation by liganded VDR. In addition to its anti-inflammatory role, vitamin D is also an active suppressor of ER stress and IAPP-induced β cell dysfunction [39]. Vitamin D is able to downregulate essential ER stress players, such as p-PERK, p-IREa, and CHOP in monocytes, liver, and islets [42]. It is unclear, though, whether the suppression is through direct repression of ER stress gene expression or a secondary effect of the anti-inflammatory function of vitamin D.

Although the pleiotropic protective role of vitamin D in islets is clear, vitamin D supplementation showed mixed results in glucose metabolism [1,43–46]. This may be partly due to the significant reduction in VDR expression in both T1D and T2D islets [41]. A recent elegant mouse study showed that overexpressing VDR in islets was able to rescue the islet dysfunction, suggesting that a supraphysiological activation of VDR may be required to achieve a functional improvement in islet dysfunction [41]. Pharmacologically, we have shown that a combination of vitamin D and BRD9 inhibitors can induce a synergistic activation of the anti-inflammatory response in β cells and protect against islet dysfunction in several T2D mouse models [39]. Mechanistically, we showed that the balance between two antagonizing chromatin remodeling complexes, BRD9-containing BAF, and BRD7-containing PBAF, defined the amplitude and duration of VDR activation [39]. Future dissection of the epigenetic mechanisms regulating VDR activity may provide additional targets to maximize vitamin D signaling potential in reverting islet dysfunction in T2D.

It is noteworthy that the contributions of vitamin D in regulating islet function may also come from non-β endocrine and non-endocrine cells in islets. Islet macrophages express VDR, which suggests that vitamin D may function in islet-resident immune cells [47]. Interestingly, the vitamin D binding protein (DBP, encoded by the GC gene), is highly expressed in dysfunctional α cells and contributes to α cell adaptation [48] and β cell dedifferentiation [49]. Future studies using tissue-specific knockout models will be essential to define the precise function of vitamin D in different islet cell types.

3. Vitamin D and Insulin Sensitivity and Resistance

Insulin resistance, defined as an impaired ability of insulin to induce glucose uptake in peripheral tissues resulting in hyperglycemia, is a hallmark of prediabetes and T2D. Vitamin D has been suggested to regulate insulin sensitivity in cell lines and peripheral metabolic organs [43]. Several in vitro studies showed that $1,25(OH)_2D$ activates VDR to increase insulin receptor expression [19,50,51], which could subsequently increase insulin sensitivity. Dunlop et al. showed that peroxisome proliferator-activated receptor (PPAR) δ was the primary $1,25(OH)_2D$ activated target in several cancer cell lines [52], while subsequent studies suggested an association between PPAR δ and insulin sensitivity through $1,25(OH)_2D$ [53,54]. More recent studies have started dissecting the tissue-specific role of vitamin D in insulin resistance. Skeletal muscle is a major organ contributing to insulin resistance. Zhou et al. concluded that $1,25(OH)_2D$ ameliorated insulin resistance in C2C12 myotube cells triggered by free fatty acid [55]. Manna et al. demonstrated that $1,25(OH)_2D$ enhanced glucose uptake via the SIRT1/IRS1/GLUT4 axis by activating SIRT1, phosphorylating IRS1, and ultimately translocating GLUT4 in myotubes [10]. Moreover, activation of VDR increases Ca^{2+} concentrations in muscle, enhances the translocation of GLUT4, and increases glucose uptake [56]. Together, these results indicate a protective role of vitamin D against insulin resistance in skeletal muscle. In liver and adipose tissue, whether vitamin D directly regulates insulin receptor expression remains unclear. The reduction in insulin receptor gene expression in the livers of diabetic Wistar rats could be rescued with the treatment of vitamin D3 [57]. A different conclusion from high-fat diet-fed mice, however, indicated that vitamin D did not influence the transcript level of the insulin receptor gene in the liver [58]. In contrast, the anti-inflammatory function of vitamin D in liver and adipose is more verified. A recent study showed that activation of VDR acts on resident liver macrophages to reduce liver inflammation and insulin resistance in diet-induced obese mice [59]. Some evidence from VDR macrophage knockout mice supports the beneficial role of vitamin D by showing that deletion of VDR promotes insulin resistance in liver [60]. In obese adipose tissue, vitamin D downregulates the expression of proinflammatory cytokines (IL-1β, IL-6, TNF-α) [61,62] and chemokines (CCL2, CCL5, CXCL10, CXCL11) [63] released by adipocytes and resident immune cells [64], to consequently repress inflammatory responses. A study in human monocytes suggested that the mechanism of downregulation might involve a reduction in transcript and protein levels of TLR2 and TLR4 via VDR [65]. The anti-inflammatory activity of vitamin D partly relies on

the suppression of NF-κB and MAPK signaling by VDR [66,67], which binds to and activates MAPK phosphatase-1 [68] and IKBa [39,69]. Moreover, the vitamin D/VDR axis also inhibits monocyte recruitment into adipose tissue and promotes a shift to anti-inflammatory M2 macrophages in adipose tissue [70].

A number of studies have shown that vitamin D is involved in lipid metabolism by regulating adipogenesis, lipolysis, and lipogenesis. The exact function of vitamin D in these processes is likely to be context-dependent. For in vitro studies using mesenchymal cells (MSCs) from adipose tissue or bone marrow, vitamin D promotes differentiation of the adipocyte progenitors, likely through upregulating lineage factors, such as PPARγ and AP2 [71–74]. In human MSCs, supplementing vitamin D can promote terminal differentiation by increasing the expression of adipogenesis regulators, such as PPARγ and AP2 and functional enzymes, such as LPL [73]. However, these results are contradictory to the fact that the MSCs from VDR whole-body knockout mice also showed an increase in PPARγ and AP2, and an enhancement of differentiation [75]. A similar trend is observed in adipocyte differentiation using glucocorticoids or thiazolidinedione (TZD) [76]. Moreover, in 3T3-L1 cells, a widely used adipocyte progenitor cell line, vitamin D suppresses lipid deposition and terminal differentiation [77,78]. Since most of these studies were performed on in vitro cultured primary cells or cell lines, the various culture conditions could be a major confounding factor.

Several animal models have been used to interrogate vitamin D's role in adipose tissue function and lipid homeostasis. Mice fed with vitamin D3-containing diet for 3 weeks showed an increase in subcutaneous and visceral fat [79], while mice administrated with calcitriol through a continuous pump showed reduced adipose weight [80]. Mice with whole body knockout of VDR showed a reduced white adipose tissue mass, reduced serum triglyceride, and cholesterol [81–83]. Interestingly, the UCP1 expression is significantly elevated in the WAT of these mice [81], suggesting that elevated energy production could be a cause for the reduced WAT mass. Mice with adipose-specific deletion of VDR, on the other hand, have increased visceral fat in females but not in males [84]. Interestingly, the adipose specific knockout of VDR does not change the glucose tolerance [84], suggesting a limited impact of adipose vitamin D signaling on glucose homeostasis.

In addition to the mechanisms discussed above, the pleiotropic role of vitamin D/VDR in insulin resistance may involve (1) vitamin D-induced increases in parathyroid hormone (PTH), which reduces insulin resistance by increasing the quantity of GLUT1 and GLUT4 in vitamin D-deficient adipose tissue, liver, and muscle [85,86]; (2) suppression of the renin-angiotensin-aldosterone system (RAS) activity which impairs β cell function, inhibits peripheral insulin sensitivity [87], hinders GLUT4 recruitment [88], and triggers insulin resistance [89]; (3) a high dose of 1,25$(OH)_2$D supplement that can activate the Ca^{2+}/CaMKKβ/AMPK pathway to ameliorate insulin resistance and ER stress [90]; and (4) vitamin D preventing ROS formation, an essential activator of insulin resistance [91].

Several clinical studies also support a protective role of vitamin D in insulin resistance. Chiu et al. performed univariate regression analyses on 126 glucose-tolerant subjects and concluded that patients with hypovitaminosis D have a higher risk of developing insulin resistance [92]. Low plasma 25(OH)D levels are also proposed to be a risk factor for T2D [93,94]. A decrease in insulin resistance and increased insulin secretion has been reported with vitamin D supplementation [18,28,95,96]. However, in a separate study in patients with normal levels of vitamin D, supplementation with 1(OH)D failed to improve glucose homeostasis [97], while ergocalciferol supplementation was reported to increase insulin resistance in three vitamin D-deficient T2D patients [98]. These apparently contradictory findings highlight the need for additional clinical studies.

4. Vitamin D Deficiency and Type 2 Diabetes—Results of Observational and Intervention Studies and Meta-Analyses

Vitamin D deficiency is defined as a 25(OH)D level of less than 20 ng/mL, according to established consensus [99]. Vitamin D deficiency has long been associated with islet dysfunction, insulin resistance, and increased T2D incidence [43]. While growing evidence in animal models has illustrated the underlying mechanisms of vitamin D in diabetes pathogenesis, as described above, whether vitamin D supplementation could act as a preventative or interventional therapy for T2D remains unclear, with several studies showing mixed results.

The overall link between vitamin D serum levels and metabolic health has been observed in multiple studies. A cross-sectional study including 10,229 subjects showed a negative association between serum 25(OH)D and BMI during winter months [100]. In a cohort study with 9841 participants and 29 years of follow-up, low plasma 25(OH)D was associated with a higher risk of T2D after adjustment for sex, age, BMI, and other health factors [101]. A similar conclusion has been reported in several studies [102–105]. In a meta-analysis summarizing 21 prospective studies that included 76,220 subjects and 4996 T2D cases, Song et al. highlighted the monotonical association between higher 25(OH)D levels and lower diabetes risk [106]. An increase of 10 nmol/L in 25(OH)D serum concentration is estimated to correlate with a 4% reduction in the T2D incidence [106]. A positive link between 25(OH)D levels and insulin sensitivity and β cell function has been shown in a Californian study measuring insulin sensitivity index and islet secretion capacity in 126 subjects [100]. However, several other studies showed no significant correlation between vitamin D and insulin levels [107] or T2D incidence [108,109].

Based on epidemiological results, it has been postulated that supplementing vitamin D may ameliorate insulin resistance and enhance glycemic control. A single-center, double-blind, randomized placebo-controlled trial performed on 96 non-diabetic participants suggested a significant beneficial effect of vitamin D3 supplement on peripheral insulin sensitivity compared with placebo after six months [26]. A similar conclusion was drawn in trials performed on overweight, and vitamin D-deficient subjects [110] and subjects with impaired fasting glucose [111]. Improvements were also observed in HOMA-IR [13,112], serum fasting plasma glucose and insulin [112], and body weight [113] in patients with T2D after being treated with vitamin D. Additional trials on females with T2D [28] or with gestational diabetes [114] who were given vitamin D supplements or placebo confirmed the positive role of T2D. In contrast, no differences in insulin resistance were observed when 65 Caucasian men with impaired glucose tolerance received vitamin D supplements [97]. Similarly, in a large, multicenter, randomized clinical trial (D2d), daily supplementation with 4000 IU vitamin D_3 did not appreciably decrease the risk of diabetes among people with a high risk of T2D [115]. Moreover, increases in fasting insulin levels and insulin resistance were reported in three British Asian patients with non-insulin-dependent diabetes and vitamin D deficiency after three months of vitamin D administration [98]. However, a recent meta-analysis, including this dataset, reaffirmed the beneficial role of vitamin D in non-obese subjects, suggesting that supplementation can promote the reversion from prediabetes to normoglycemia [116]. Hence, whether vitamin D can prevent or revert T2D in humans will still need further research.

5. Vitamin D in T1D Progression

Type 1 diabetes (T1D) is caused by the autoimmune destruction of pancreatic β cells, leading to insulin deficiency. The development of T1D is a gradual process of breaking tolerance to autoantigens. β cell-specific autoantigens (such as insulin, proinsulin, and IGRP) are presented by antigen-presenting cells (APCs), triggering cytotoxic T cell responses, which cause β cell damage [117,118]. Several studies in non-obese diabetic (NOD) mice have elucidated that pancreas-infiltrated dendritic cells and macrophages function in presenting islet autoantigens [119,120]. Thereafter, islet antigen-reactive $CD4^+$ and $CD8^+$ T cells induce β cell damage that consequently potentiates the immune response

by releasing more self-antigens [121–124]. In addition to T cells, autoantibody-producing B cells and innate immune cells also participate in destroying β cells [125–127].

Animal models and epidemiological studies strongly support the ability of vitamin D to prevent T1D pathogenesis. In CD-1 mice with diabetes induced by daily intraperitoneal injections of low doses of streptozotocin (STZ), intraperitoneal administration of 1α,25(OH) $_2D_3$ protected the diabetic mice from developing hyperglycemia [128]. Long-term treatment with a high dose of 1,25$(OH)_2D_3$ on NOD mice reduced the incidence of insulitis and hyperglycemia [129–131]. In humans, epidemiological studies have shed light on the association between vitamin D intake and T1D incidence. In a birth cohort study, a significant reduction in T1D risk was observed in 10,366 children who received 2000 IU of vitamin D daily [132]. Similarly, maternal intake of vitamin D is relevant to a reduced risk of islet autoimmunity in offspring [133], which is consistent with the conclusion from a more recent case–control study that showed that the lower maternal serum concentration of 25(OH)D during pregnancy is correlated with a higher risk of childhood-onset T1D [134]. Zipitis and colleagues concluded that vitamin D supplementation in early childhood prevented the development of T1D in a meta-analysis-based study [135]. A similar conclusion was generated in a EURODIAB (European Community Concerted Action Programme in Diabetes) subgroup multicenter study [136]. Although data from healthy subjects are promising, there are only limited studies supporting the role of vitamin D in delaying T1D development. Gabbay and colleagues [137] suggested that as an adjunctive therapy with insulin, 2000 IU daily supplementation of vitamin D3 slowed the decline of residual β cell function in patients with new-onset T1D. Two other studies, however, showed that there was no protective effect of 1,25$(OH)_2D_3$ treatment in subjects with new-onset T1D [138,139]. Therefore, more trials evaluating the function of vitamin D supplementation in treating T1D are still needed.

The beneficial effects of vitamin D in T1D could be rooted in its versatile functions in various immune populations. VDR is expressed in nearly all immune cells, including activated T and B cells, dendritic cells, macrophages, and neutrophils [140–143]. Differentiation of monocytes to macrophages or dendritic cells correlates with a decreased expression of VDR [144,145], whereas T cell activation is accompanied by increased expression of VDR [140,146]. The presence of VDR in both T cells and antigen-presenting cells suggests distinct, cell-type specific mechanisms of vitamin D in suppressing adaptive immunity [147,148]. In monocytes/macrophages, 1,25$(OH)_2D_3$ reduces MHC II and co-stimulatory molecules (CD40, CD80 and CD86) expression and prevents T cell activation [149,150]. In rat and human dendritic cells, 1,25$(OH)_2D_3$ inhibited dendritic cell maturation and stimulatory functions. 1,25$(OH)_2D_3$ treatment inhibits the expression of $CD1a^+$ (dendritic cell marker), MHC II, and co-stimulatory genes while maintaining the expression of monocytic markers [151–154]. 1,25$(OH)_2D_3$ has also been demonstrated to induce dendritic cell apoptosis [151,155], or induce tolerogenic dendritic cells featuring a reduced expression of CD40, CD80, and CD86 [156,157]. Tolerogenic dendritic cells inhibit autoimmune processes by enhancing Treg cell development in NOD mice [156]. Another potential role of 1,25$(OH)_2D_3$ in dendritic cells is to induce the expression of the mannose receptor, the endocytic capacity-related molecule involved in antigen-capturing [158]. Lymphocytes are also profoundly impacted by 1,25$(OH)_2D_3$. Th1 and Th17 cells are essential in T1D initiation [159,160]. 1,25$(OH)_2D_3$ inhibits the expression of multiple cytokines, such as IL-12 and IL-23, and consequently drives a T cell subpopulation shift from Th1/Th17 to Th2 [161–164]. On the other hand, the recruitment of T cells to the pancreas by cytokines and chemokines aggravates β cell damage. 1,25$(OH)_2D_3$ is able to suppress T cell infiltration by reducing gene expression and/or secretion of multiple cytokines (IL-6, IL-15) and chemokines (CCL2, CCL5, and CXCL10) that manipulate T cell migration [69,165,166]. Furthermore, 1,25$(OH)_2D_3$ suppresses autoreactive T cells and maintains tolerance [167] by promoting Treg cell development [168] and suppressing proinflammatory cytokines (IL-2, IFN-ɤ, IL-17, and IL-21) expression [169]. In addition to its effect on T cells, 1,25$(OH)_2D_3$ also inhibits B cell proliferation, differentiation in memory B cells, and production of im-

munoglobulins [170]. Whether the action of vitamin D on B cells is required for its T1D prevention capacity remains to be elucidated.

6. Conclusions

In addition to its canonical role in skeletal function, vitamin D modulates insulin secretion and action in diabetes. Vitamin D/VDR directly regulates functional genes, including critical genes in the secretion pathway and insulin action. As an anti-inflammatory hormone, vitamin D also acts on tissue resident immune cells to reduce local and systemic inflammation, thus preventing islet, liver, and muscle dysfunction. Though vitamin D is known to work on multiple organs and cell types, the relative contribution of individual cell types to the anti-diabetic effects remain to be determined. Mechanistically, how does vitamin D activate essential functional genes while repressing inflammatory targets? The cell type-specific regulatory circuitry of vitamin D-VDR remains to be elucidated. Vitamin D deficiency is prevalent in the general population and is linked to a higher type 2 diabetes incidence. Normalizing the vitamin D levels in deficient patients has slowed T2D progression. However, large-scale clinical trials have not demonstrated the clinical benefit of vitamin D supplements in ameliorating type 2 diabetes [171]. These results raise more questions for future studies: What is the optimal vitamin D level? Can vitamin D supplements achieve this level without causing side effects? Further larger-scale prospective trials may still be required to test whether vitamin D intake is able to prevent or reverse type 2 diabetes. In T1D, the evidence of vitamin D in preventing at-risk subjects from developing diabetes is lacking. It is also unclear whether the beneficial effects of vitamin D depend on its ability to reprogram autoimmunity, prevent B cell damage, or both.

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References

1. Mohammadi, S.; Hajhashemy, Z.; Saneei, P. Serum vitamin D levels in relation to type-2 diabetes and prediabetes in adults: A systematic review and dose-response meta-analysis of epidemiologic studies. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 8178–8198. [CrossRef] [PubMed]
2. Holick, M.F.; Schnoes, H.K.; DeLuca, H.F.; Suda, T.; Cousins, R.J. Isolation and identification of 1,25-dihydroxycholecalciferol. A metabolite of vitamin D active in intestine. *Biochemistry* **1971**, *10*, 2799–2804. [CrossRef] [PubMed]
3. Talwar, D.; O'Reilly, D.S.J.; McMillan, D.C. Serum 25-hydroxyvitamin D is a reliable indicator of vitamin D status Reply. *Am. J. Clin. Nutr.* **2011**, *94*, 620. [CrossRef]
4. Henry, H.L.; Norman, A.W. Vitamin D: Metabolism and biological actions. *Annu. Rev. Nutr.* **1984**, *4*, 493–520. [CrossRef] [PubMed]
5. Umesono, K.; Murakami, K.K.; Thompson, C.C.; Evans, R.M. Direct Repeats as Selective Response Elements for the Thyroid-Hormone, Retinoic Acid, and Vitamin-D_3 Receptors. *Cell* **1991**, *65*, 1255–1266. [CrossRef]
6. Hanel, A.; Malmberg, H.-R.; Carlberg, C. Genome-wide effects of chromatin on vitamin D signaling. *J. Mol. Endocrinol.* **2020**, *64*, R45–R56. [CrossRef]
7. Hii, C.S.; Ferrante, A. The Non-Genomic Actions of Vitamin D. *Nutrients* **2016**, *8*, 135. [CrossRef]
8. Cranney, A.; Horsley, T.; O'Donnell, S.; Weiler, H.; Puil, L.; Ooi, D.; Atkinson, S.; Ward, L.; Moher, D.; Hanley, D.; et al. Effectiveness and safety of vitamin D in relation to bone health. *Evid. Rep. Technol. Assess. (Full Rep.)* **2007**, *158*, 1–235.
9. Seshadri, K.; Tamilselvan, B.; Venkatraman, G. Role of vitamin D on the expression of glucose transporters in L6 myotubes. *Indian J. Endocrinol. Metab.* **2013**, *17* (Suppl. S1), S326–S328. [CrossRef]
10. Manna, P.; Achari, A.E.; Jain, S.K. Vitamin D supplementation inhibits oxidative stress and upregulate SIRT1/AMPK/GLUT4 cascade in high glucose-treated 3T3L1 adipocytes and in adipose tissue of high fat diet-fed diabetic mice. *Arch. Biochem. Biophys.* **2017**, *615*, 22–34. [CrossRef]

11. Benetti, E.; Mastrocola, R.; Chiazza, F.; Nigro, D.; D'antona, G.; Bordano, V.; Fantozzi, R.; Aragno, M.; Collino, M.; Minetto, M.A. Effects of vitamin D on insulin resistance and myosteatosis in diet-induced obese mice. *PLoS ONE* **2018**, *13*, e0189707. [CrossRef]
12. Elseweidy, M.M.; Amin, R.S.; Atteia, H.H.; Ali, M.A. Vitamin D3 intake as regulator of insulin degrading enzyme and insulin receptor phosphorylation in diabetic rats. *Biomed. Pharmacother.* **2017**, *85*, 155–159. [CrossRef]
13. Al-Shoumer, K.A.; Al-Essa, T.M. Is there a relationship between vitamin D with insulin resistance and diabetes mellitus? *World J. Diabetes* **2015**, *6*, 1057–1064. [CrossRef]
14. James, W.P. 22nd Marabou Symposium: The changing faces of vitamin D. *Nutr. Rev.* **2008**, *66*, 286–290. [CrossRef]
15. Ashcroft, F.M.; Rorsman, P. Diabetes mellitus and the beta cell: The last ten years. *Cell* **2012**, *148*, 1160–1171. [CrossRef]
16. Prentki, M.; Peyot, M.L.; Masiello, P.; Madiraju, S.R.M. Nutrient-Induced Metabolic Stress, Adaptation, Detoxification, and Toxicity in the Pancreatic beta-Cell. *Diabetes* **2020**, *69*, 279–290. [CrossRef]
17. Rohm, T.V.; Meier, D.T.; Olefsky, J.M.; Donath, M.Y. Inflammation in obesity, diabetes, and related disorders. *Immunity* **2022**, *55*, 31–55. [CrossRef]
18. Inomata, S.; Kadowaki, S.; Yamatani, T.; Fukase, M.; Fujita, T. Effect of 1 alpha (OH)-vitamin D3 on insulin secretion in diabetes mellitus. *Bone Miner.* **1986**, *1*, 187–192.
19. Maestro, B.; Dávila, N.; Carranza, M.; Calle, C. Identification of a Vitamin D response element in the human insulin receptor gene promoter. *J. Steroid Biochem. Mol. Biol.* **2003**, *84*, 223–230. [CrossRef]
20. Norman, A.W.; Frankel, B.J.; Heldt, A.M.; Grodsky, G.M. Vitamin D Deficiency Inhibits Pancreatic Secretion of Insulin. *Science* **1980**, *209*, 823–825. [CrossRef]
21. Cade, C.; Norman, A.W. Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat in vivo. *Endocrinology* **1986**, *119*, 84–90. [CrossRef] [PubMed]
22. Tanaka, Y.; Seino, Y.; Ishida, M.; Yamaoka, K.; Yabuuchi, H.; Ishida, H.; Seino, S.; Seino, Y.; Imura, H. Effect of vitamin D3 on the pancreatic secretion of insulin and somatostatin. *Acta. Endocrinol.* **1984**, *105*, 528–533. [CrossRef] [PubMed]
23. Zeitz, U.; Weber, K.; Soegiarto, D.W.; Wolf, E.; Balling, R.; Erben, R.G. Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. *FASEB J.* **2003**, *17*, 509–511. [CrossRef] [PubMed]
24. Bourlon, P.M.; Billaudel, B.; Faure-Dussert, A. Influence of vitamin D3 deficiency and 1,25 dihydroxyvitamin D3 on de novo insulin biosynthesis in the islets of the rat endocrine pancreas. *J. Endocrinol.* **1999**, *160*, 87–95. [CrossRef] [PubMed]
25. Al-Sofiani, M.E.; Jammah, A.; Racz, M.; Khawaja, R.A.; Hasanato, R.; El-Fawal, H.A.N.; Mousa, S.A.; Mason, D.L. Effect of Vitamin D Supplementation on Glucose Control and Inflammatory Response in Type II Diabetes: A Double Blind, Randomized Clinical Trial. *Int. J. Endocrinol. Metab.* **2015**, *13*, e22604. [CrossRef]
26. Lemieux, P.; Weisnagel, S.J.; Caron, A.Z.; Julien, A.-S.; Morisset, A.-S.; Carreau, A.-M.; Poirier, J.; Tchernof, A.; Robitaille, J.; Bergeron, J.; et al. Effects of 6-month vitamin D supplementation on insulin sensitivity and secretion: A randomised, placebo-controlled trial. *Eur. J. Endocrinol.* **2019**, *181*, 287–299. [CrossRef]
27. Kayaniyil, S.; Vieth, R.; Retnakaran, R.; Knight, J.A.; Qi, Y.; Gerstein, H.C.; Perkins, B.A.; Harris, S.B.; Zinman, B.; Hanley, A.J. Association of vitamin D with insulin resistance and beta-cell dysfunction in subjects at risk for type 2 diabetes. *Diabetes Care* **2010**, *33*, 1379–1381. [CrossRef]
28. Borissova, A.M.; Tankova, T.; Kirilov, G.; Dakovska, L.; Kovacheva, R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. *Int. J. Clin. Pr.* **2003**, *57*, 258–261.
29. Nyomba, B.L.G.; Auwerx, J.; Bormans, V.; Peeters, T.L.; Pelemans, W.; Reynaert, J.; Bouillon, R.; Vantrappen, G.; De Moor, P. Pancreatic secretion in man with subclinical vitamin D deficiency. *Diabetologia* **1986**, *29*, 34–38. [CrossRef]
30. Wolden-Kirk, H.; Overbergh, L.; Gysemans, C.; Brusgaard, K.; Naamane, N.; Van Lommel, L.; Schuit, F.; Eizirik, D.L.; Christesen, H.; Mathieu, C. Unraveling the effects of 1,25OH2D3 on global gene expression in pancreatic islets. *J. Steroid Biochem. Mol. Biol.* **2013**, *136*, 68–79. [CrossRef]
31. Sergeev, I.N.; Rhoten, W.B. 1,25-Dihydroxyvitamin D3 evokes oscillations of intracellular calcium in a pancreatic beta-cell line. *Endocrinology* **1995**, *136*, 2852–2861. [CrossRef]
32. Doyle, M.E.; Egan, J.M. Pharmacological Agents That Directly Modulate Insulin Secretion. *Pharmacol. Rev.* **2003**, *55*, 105–131. [CrossRef]
33. Gilon, P.; Chae, H.Y.; Rutter, G.A.; Ravier, M.A. Calcium signaling in pancreatic beta-cells in health and in Type 2 diabetes. *Cell Calcium* **2014**, *56*, 340–361. [CrossRef]
34. Altieri, B.; Grant, W.B.; Della Casa, S.; Orio, F.; Pontecorvi, A.; Colao, A.; Sarno, G.; Muscogiuri, G. Vitamin D and pancreas: The role of sunshine vitamin in the pathogenesis of diabetes mellitus and pancreatic cancer. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 3472–3488. [CrossRef]
35. Kjalarsdottir, L.; Tersey, S.A.; Vishwanath, M.; Chuang, J.-C.; Posner, B.A.; Mirmira, R.G.; Repa, J.J. 1,25-Dihydroxyvitamin D(3) enhances glucose-stimulated insulin secretion in mouse and human islets: A role for transcriptional regulation of voltage-gated calcium channels by the vitamin D receptor. *J. Steroid Biochem. Mol. Biol.* **2019**, *185*, 17–26. [CrossRef]
36. De Boland, A.R.; Boland, R.L. Non-genomic signal transduction pathway of vitamin D in muscle. *Cell. Signal.* **1994**, *6*, 717–724. [CrossRef]
37. Johnson, J.A.; Grande, J.P.; Roche, P.C.; Kumar, R. Immunohistochemical localization of the 1,25(OH)2D3 receptor and calbindin D28k in human and rat pancreas. *Am. J. Physiol.* **1994**, *267 Pt 1*, E356–E360. [CrossRef]

38. Morrissey, R.L.; Bucci, T.J.; Richard, B.; Empson, R.N.; Lufkin, E.G. Calcium-Binding Protein: Its Cellular Localization in Jejunum, Kidney and Pancreas. *Exp. Biol. Med.* **1975**, *149*, 56–60. [CrossRef]
39. Wei, Z.; Yoshihara, E.; He, N.; Hah, N.; Fan, W.; Pinto, A.F.M.; Huddy, T.; Wang, Y.; Ross, B.; Estepa, G.; et al. Vitamin D Switches BAF Complexes to Protect beta Cells. *Cell* **2018**, *173*, 1135–1149.e15. [CrossRef]
40. Chen, C.; Luo, Y.; Su, Y.; Teng, L. The vitamin D receptor (VDR) protects pancreatic beta cells against Forkhead box class O1 (FOXO1)-induced mitochondrial dysfunction and cell apoptosis. *Biomed. Pharmacother.* **2019**, *117*, 109170. [CrossRef]
41. Morró, M.; Vilà, L.; Franckhauser, S.; Mallol, C.; Elias, G.; Ferré, T.; Molas, M.; Casana, E.; Rodó, J.; Pujol, A.; et al. Vitamin D Receptor Overexpression in beta-Cells Ameliorates Diabetes in Mice. *Diabetes* **2020**, *69*, 927–939. [CrossRef] [PubMed]
42. Riek, A.E.; Oh, J.; Sprague, J.E.; Timpson, A.; Fuentes, L.D.L.; Bernal-Mizrachi, L.; Schechtman, K.B.; Bernal-Mizrachi, C. Vitamin D Suppression of Endoplasmic Reticulum Stress Promotes an Antiatherogenic Monocyte/Macrophage Phenotype in Type 2 Diabetic Patients. *J. Biol. Chem.* **2012**, *287*, 38482–38494. [CrossRef]
43. Mathieu, C. Vitamin D and diabetes: Where do we stand? *Diabetes Res. Clin. Pr.* **2015**, *108*, 201–209. [CrossRef] [PubMed]
44. Pittas, A.G.; Lau, J.; Hu, F.B.; Dawson-Hughes, B. The Role of Vitamin D and Calcium in Type 2 Diabetes. A Systematic Review and Meta-Analysis. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 2017–2029. [CrossRef] [PubMed]
45. De Boer, I.H.; Tinker, L.F.; Connelly, S.; Curb, J.D.; Howard, B.V.; Kestenbaum, B.; Larson, J.C.; Manson, J.E.; Margolis, K.L.; Siscovick, D.S.; et al. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. *Diabetes Care* **2008**, *31*, 701–707. [CrossRef]
46. Avenell, A.; Cook, J.A.; MacLennan, G.S.; McPherson, G.C. Vitamin D supplementation and type 2 diabetes: A substudy of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing* **2009**, *38*, 606–609. [CrossRef]
47. Ying, W.; Lee, Y.S.; Dong, Y.; Seidman, J.S.; Yang, M.; Isaac, R.; Seo, J.B.; Yang, B.H.; Wollam, J.; Riopel, M.; et al. Expansion of Islet-Resident Macrophages Leads to Inflammation Affecting beta Cell Proliferation and Function in Obesity. *Cell Metab.* **2019**, *29*, 457–474.e5. [CrossRef]
48. Viloria, K.; Nasteska, D.; Ast, J.; Hasib, A.; Cuozzo, F.; Heising, S.; Briant, L.J.; Hewison, M.; Hodson, D.J. GC-Globulin/Vitamin D–Binding Protein Is Required for Pancreatic α-Cell Adaptation to Metabolic Stress. *Diabetes* **2022**, *72*, 275–289. [CrossRef]
49. Kuo, T.; Damle, M.; González, B.J.; Egli, D.; Lazar, M.A.; Accili, D. Induction of alpha cell-restricted Gc in dedifferentiating beta cells contributes to stress-induced beta-cell dysfunction. *JCI Insight* **2019**, *5*, e128351. [CrossRef]
50. Maestro, B.; Campion, J.; Dávila, N.; Calle, C. Stimulation by 1,25-Dihydroxyvitamin D3 of Insulin Receptor Expression and Insulin Responsiveness for Glucose Transport in U-937 Human Promonocytic Cells. *Endocr. J.* **2000**, *47*, 383–391. [CrossRef]
51. Maestro, B.; Molero, S.; Bajo, S.; Dávila, N.; Calle, C. Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3). *Cell Biochem. Funct.* **2002**, *20*, 227–232. [CrossRef]
52. Dunlop, T.W.; Väisänen, S.; Frank, C.; Molnár, F.; Sinkkonen, L.; Carlberg, C. The human peroxisome proliferator-activated receptor delta gene is a primary target of 1alpha,25-dihydroxyvitamin D3 and its nuclear receptor. *J. Mol. Biol.* **2005**, *349*, 248–260. [CrossRef]
53. Liu, Y.; He, Y.; Wang, Q.; Guo, F.; Huang, F.; Ji, L.; An, T.; Qin, G. Vitamin D(3) supplementation improves testicular function in diabetic rats through peroxisome proliferator-activated receptor-gamma/transforming growth factor-beta 1/nuclear factor-kappa B. *J. Diabetes Investig.* **2019**, *10*, 261–271. [CrossRef]
54. Hoseini, R.; Damirchi, A.; Babaei, P. Vitamin D increases PPARgamma expression and promotes beneficial effects of physical activity in metabolic syndrome. *Nutrition* **2017**, *36*, 54–59. [CrossRef]
55. Zhou, Q.G.; Hou, F.F.; Guo, Z.J.; Liang, M.; Wang, G.B.; Zhang, X. 1,25-Dihydroxyvitamin D improved the free fatty-acid-induced insulin resistance in cultured C2C12 cells. *Diabetes/Metab. Res. Rev.* **2008**, *24*, 459–464. [CrossRef]
56. Wright, D.C.; Hucker, K.A.; Holloszy, J.O.; Han, D.H. Ca^{2+} and AMPK Both Mediate Stimulation of Glucose Transport by Muscle Contractions. *Diabetes* **2004**, *53*, 330–335. [CrossRef]
57. George, N.; Kumar, T.P.; Antony, S.; Jayanarayanan, S.; Paulose, C.S. Effect of vitamin D_3 in reducing metabolic and oxidative stress in the liver of streptozotocin-induced diabetic rats. *Br. J. Nutr.* **2012**, *108*, 1410–1418. [CrossRef]
58. Alkharfy, K.M.; Al-Daghri, N.M.; Yakout, S.M.; Hussain, T.; Mohammed, A.K.; Krishnaswamy, S. Influence of Vitamin D Treatment on Transcriptional Regulation of Insulin-Sensitive Genes. *Metab. Syndr. Relat. Disord.* **2013**, *11*, 283–288. [CrossRef]
59. Dong, B.; Zhou, Y.; Wang, W.; Scott, J.; Kim, K.H.; Sun, Z.; Guo, Q.; Lu, Y.; Gonzales, N.M.; Wu, H.; et al. Vitamin D Receptor Activation in Liver Macrophages Ameliorates Hepatic Inflammation, Steatosis, and Insulin Resistance in Mice. *Hepatology* **2020**, *71*, 1559–1574. [CrossRef]
60. Oh, J.; Riek, A.E.; Darwech, I.; Funai, K.; Shao, J.; Chin, K.; Sierra, O.L.; Carmeliet, G.; Ostlund, R.E.; Bernal-Mizrachi, C. Deletion of Macrophage Vitamin D Receptor Promotes Insulin Resistance and Monocyte Cholesterol Transport to Accelerate Atherosclerosis in Mice. *Cell Rep.* **2015**, *10*, 1872–1886. [CrossRef]
61. Marcotorchino, J.; Gouranton, E.; Romier, B.; Tourniaire, F.; Astier, J.; Malezet, C.; Amiot, M.-J.; Landrier, J.-F. Vitamin D reduces the inflammatory response and restores glucose uptake in adipocytes. *Mol. Nutr. Food Res.* **2012**, *56*, 1771–1782. [CrossRef] [PubMed]
62. Lira, F.S.; Rosa, J.C.; Cunha, C.A.; Ribeiro, E.B.; do Nascimento, C.O.; Oyama, L.M.; Mota, J.F. Supplementing alpha-tocopherol (vitamin E) and vitamin D3 in high fat diet decrease IL-6 production in murine epididymal adipose tissue and 3T3-L1 adipocytes following LPS stimulation. *Lipids Health Dis.* **2011**, *10*, 37. [CrossRef] [PubMed]

63. Marziou, A.; Philouze, C.; Couturier, C.; Astier, J.; Obert, P.; Landrier, J.-F.; Riva, C. Vitamin D Supplementation Improves Adipose Tissue Inflammation and Reduces Hepatic Steatosis in Obese C57BL/6J Mice. *Nutrients* **2020**, *12*, 342. [CrossRef] [PubMed]
64. Xu, H.; Barnes, G.T.; Yang, Q.; Tan, G.; Yang, D.; Chou, C.J.; Sole, J.; Nichols, A.; Ross, J.S.; Tartaglia, L.A.; et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Investig.* **2003**, *112*, 1821–1830. [CrossRef]
65. Sadeghi, K.; Wessner, B.; Laggner, U.; Ploder, M.; Tamandl, D.; Friedl, J.; Zügel, U.; Steinmeyer, A.; Pollak, A.; Roth, E.; et al. Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. *Eur. J. Immunol.* **2006**, *36*, 361–370. [CrossRef]
66. Chen, Y.; Kong, J.; Sun, T.; Li, G.; Szeto, F.L.; Liu, W.; Deb, D.K.; Wang, Y.; Zhao, Q.; Thadhani, R.; et al. 1,25-Dihydroxyvitamin D_3 suppresses inflammation-induced expression of plasminogen activator inhibitor-1 by blocking nuclear factor-kappaB activation. *Arch. Biochem. Biophys.* **2011**, *507*, 241–247. [CrossRef]
67. Zhang, Y.; Leung, D.Y.M.; Richers, B.N.; Liu, Y.; Remigio, L.K.; Riches, D.W.; Goleva, E. Vitamin D Inhibits Monocyte/Macrophage Proinflammatory Cytokine Production by Targeting MAPK Phosphatase-1. *J. Immunol.* **2012**, *188*, 2127–2135. [CrossRef]
68. Korhonen, R.; Moilanen, E. Mitogen-Activated Protein Kinase Phosphatase 1 as an Inflammatory Factor and Drug Target. *Basic Clin. Pharmacol. Toxicol.* **2014**, *114*, 24–36. [CrossRef]
69. Giarratana, N.; Penna, G.; Amuchastegui, S.; Mariani, R.; Daniel, K.C.; Adorini, L. A Vitamin D Analog Down-Regulates Proinflammatory Chemokine Production by Pancreatic Islets Inhibiting T Cell Recruitment and Type 1 Diabetes Development. *J. Immunol.* **2004**, *173*, 2280–2287. [CrossRef]
70. Olefsky, J.M.; Glass, C.K. Macrophages, inflammation, and insulin resistance. *Annu. Rev. Physiol.* **2010**, *72*, 219–246. [CrossRef]
71. Narvaez, C.J.; Simmons, K.M.; Brunton, J.; Salinero, A.; Chittur, S.V.; Welsh, J.E. Induction of STEAP4 correlates with 1,25-dihydroxyvitamin D3 stimulation of adipogenesis in mesenchymal progenitor cells derived from human adipose tissue. *J. Cell Physiol* **2013**, *228*, 2024–2036. [CrossRef]
72. Mahajan, A.; Stahl, C.H. Dihydroxy-cholecalciferol stimulates adipocytic differentiation of porcine mesenchymal stem cells. *J. Nutr. Biochem.* **2009**, *20*, 512–520. [CrossRef]
73. Nimitphong, H.; Holick, M.F.; Fried, S.K.; Lee, M.J. 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 promote the differentiation of human subcutaneous preadipocytes. *PLoS ONE* **2012**, *7*, e52171. [CrossRef]
74. Heaney, R.P.; Horst, R.L.; Cullen, D.M.; Armas, L.A. Vitamin D3 distribution and status in the body. *J. Am. Coll. Nutr.* **2009**, *28*, 252–256. [CrossRef]
75. Cianferotti, L.; Demay, M.B. VDR-mediated inhibition of DKK1 and SFRP2 suppresses adipogenic differentiation of murine bone marrow stromal cells. *J. Cell. Biochem.* **2007**, *101*, 80–88. [CrossRef]
76. Kelly, K.A.; Gimble, J.M. 1,25-Dihydroxy Vitamin D3 Inhibits Adipocyte Differentiation and Gene Expression in Murine Bone Marrow Stromal Cell Clones and Primary Cultures. *Endocrinology* **1998**, *139*, 2622–2628. [CrossRef]
77. Sato, M.; Hiragun, A. Demonstration of 1 alpha,25-dihydroxyvitamin D3 receptor-like molecule in ST 13 and 3T3 L1 preadipocytes and its inhibitory effects on preadipocyte differentiation. *J. Cell. Physiol.* **1988**, *135*, 545–550. [CrossRef]
78. Thomson, B.; Ahrens, J.M.; Ntambi, J.M.; DeLuca, H.F.; Clagett-Dame, M. 2-Methylene-19-nor-1alpha-hydroxyvitamin D_3 analogs inhibit adipocyte differentiation and PPARgamma2 gene transcription. *Arch. Biochem. Biophys.* **2007**, *460*, 192–201. [CrossRef]
79. Choi, H.; Myung, K. Vitamin D(3) regulation of body fat, cytokines, and calpain gene expression. *J. Sci. Food Agric.* **2012**, *92*, 632–637. [CrossRef]
80. Duque, G.; Macoritto, M.; Kremer, R. 1,25(OH)2D3 inhibits bone marrow adipogenesis in senescence accelerated mice (SAM-P/6) by decreasing the expression of peroxisome proliferator-activated receptor gamma 2 (PPARgamma2). *Exp. Gerontol.* **2004**, *39*, 333–338. [CrossRef]
81. Narvaez, C.J.; Matthews, D.; Broun, E.; Chan, M.; Welsh, J. Lean Phenotype and Resistance to Diet-Induced Obesity in Vitamin D Receptor Knockout Mice Correlates with Induction of Uncoupling Protein-1 in White Adipose Tissue. *Endocrinology* **2009**, *150*, 651–661. [CrossRef] [PubMed]
82. Weber, K.; Erben, R.G. Differences in triglyceride and cholesterol metabolism and resistance to obesity in male and female vitamin D receptor knockout mice. *J. Anim. Physiol. Anim. Nutr.* **2013**, *97*, 675–683. [CrossRef]
83. Wong, K.E.; Szeto, F.L.; Zhang, W.; Ye, H.; Kong, J.; Zhang, Z.; Sun, X.J.; Li, Y.C. Involvement of the vitamin D receptor in energy metabolism: Regulation of uncoupling proteins. *Am. J. Physiol. Endocrinol. Metab.* **2009**, *296*, E820–E828. [CrossRef] [PubMed]
84. Matthews, D.G.; D'angelo, J.; Drelich, J.; Welsh, J. Adipose-specific Vdr deletion alters body fat and enhances mammary epithelial density. *J. Steroid Biochem. Mol. Biol.* **2016**, *164*, 299–308. [CrossRef] [PubMed]
85. Ni, Z.; Smogorzewski, M.; Massry, S.G. Effects of parathyroid hormone on cytosolic calcium of rat adipocytes. *Endocrinology* **1994**, *135*, 1837–1844. [CrossRef]
86. Thomas, D.M.; Rogers, S.D.; Sleeman, M.W.; Pasquini, G.M.; Bringhurst, F.R.; Ng, K.W.; Zajac, J.D.; Best, J.D. Modulation of glucose transport by parathyroid hormone and insulin in UMR 106-01, a clonal rat osteogenic sarcoma cell line. *J. Mol. Endocrinol.* **1995**, *14*, 263–275. [CrossRef]
87. Cheng, Q.; Boucher, B.J.; Leung, P.S. Modulation of hypovitaminosis D-induced islet dysfunction and insulin resistance through direct suppression of the pancreatic islet renin–angiotensin system in mice. *Diabetologia* **2013**, *56*, 553–562. [CrossRef]

88. Muscogiuri, G.; Chavez, A.O.; Gastaldelli, A.; Perego, L.; Tripathy, D.; Saad, M.J.; Velloso, L.; Folli, F. The Crosstalk Between Insulin and Renin-Angiotensin-Aldosterone Signaling Systems and its Effect on Glucose Metabolism and Diabetes Prevention. *Curr. Vasc. Pharmacol.* **2008**, *6*, 301–312. [CrossRef]
89. Wei, Y.; Sowers, J.R.; Clark, S.E.; Li, W.; Ferrario, C.M.; Stump, C.S. Angiotensin II-induced skeletal muscle insulin resistance mediated by NF-kappaB activation via NADPH oxidase. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *294*, E345–E351. [CrossRef]
90. Leung, P.S. The Potential Protective Action of Vitamin D in Hepatic Insulin Resistance and Pancreatic Islet Dysfunction in Type 2 Diabetes Mellitus. *Nutrients* **2016**, *8*, 147. [CrossRef]
91. Rains, J.L.; Jain, S.K. Oxidative stress, insulin signaling, and diabetes. *Free Radic. Biol. Med.* **2011**, *50*, 567–575. [CrossRef]
92. Chiu, K.C.; Chu, A.; Go, V.L.; Saad, M.F. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am. J. Clin. Nutr.* **2004**, *79*, 820–825. [CrossRef]
93. Forouhi, N.G.; Ye, Z.; Rickard, A.P.; Khaw, K.T.; Luben, R.; Langenberg, C.; Wareham, N.J. Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes: Results from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort and updated meta-analysis of prospective studies. *Diabetologia* **2012**, *55*, 2173–2182. [CrossRef]
94. Deleskog, A.; Hilding, A.; Brismar, K.; Hamsten, A.; Efendic, S.; Östenson, C.G. Low serum 25-hydroxyvitamin D level predicts progression to type 2 diabetes in individuals with prediabetes but not with normal glucose tolerance. *Diabetologia* **2012**, *55*, 1668–1678. [CrossRef]
95. Pittas, A.G.; Harris, S.S.; Stark, P.C.; Dawson-Hughes, B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. *Diabetes Care* **2007**, *30*, 980–986. [CrossRef]
96. Gedik, O.; Akalin, S. Effects of vitamin D deficiency and repletion on insulin and glucagon secretion in man. *Diabetologia* **1986**, *29*, 142–145. [CrossRef]
97. Ljunghall, S.; Lind, L.; Lithell, H.; Skarfors, E.; Selinus, I.; Sørensen, O.H.; Wide, L. Treatment with One-alpha-hydroxycholecalciferol in Middle-aged Men with Impaired Glucose Tolerance-A Prospective Randomized Double-blind Study. *Acta Med. Scand.* **1987**, *222*, 361–367. [CrossRef]
98. Taylor, A.V.; Wise, P.H. Vitamin D replacement in Asians with diabetes may increase insulin resistance. *Postgrad Med.* **1998**, *74*, 365–366. [CrossRef]
99. Alshahrani, F.; Aljohani, N. Vitamin D: Deficiency, Sufficiency and Toxicity. *Nutrients* **2013**, *5*, 3605–3616. [CrossRef]
100. Jorde, R.; Sneve, M.; Emaus, N.; Figenschau, Y.; Grimnes, G. Cross-sectional and longitudinal relation between serum 25-hydroxyvitamin D and body mass index: The Tromsø study. *Eur. J. Nutr.* **2010**, *49*, 401–407. [CrossRef]
101. Afzal, S.; Bojesen, S.E.; Nordestgaard, B.G. Low 25-Hydroxyvitamin D and Risk of Type 2 Diabetes: A Prospective Cohort Study and Metaanalysis. *Clin. Chem.* **2013**, *59*, 381–391. [CrossRef] [PubMed]
102. Scragg, R.; Sowers, M.; Bell, C. Serum 25-Hydroxyvitamin D, Diabetes, and Ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care* **2004**, *27*, 2813–2818. [CrossRef] [PubMed]
103. Knekt, P.; Laaksonen, M.; Mattila, C.; Härkänen, T.; Marniemi, J.; Heliövaara, M.; Rissanen, H.; Montonen, J.; Reunanen, A. Serum Vitamin D and Subsequent Occurrence of Type 2 Diabetes. *Epidemiology* **2008**, *19*, 666–671. [CrossRef] [PubMed]
104. Forouhi, N.G.; Luan, J.; Cooper, A.; Boucher, B.J.; Wareham, N.J. Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: The Medical Research Council Ely Prospective Study 1990–2000. *Diabetes* **2008**, *57*, 2619–2625. [CrossRef] [PubMed]
105. Pittas, A.G.; Sun, Q.; Manson, J.E.; Dawson-Hughes, B.; Hu, F.B. Plasma 25-Hydroxyvitamin D Concentration and Risk of Incident Type 2 Diabetes in Women. *Diabetes Care* **2010**, *33*, 2021–2023. [CrossRef]
106. Song, Y.; Wang, L.; Pittas, A.G.; Del Gobbo, L.C.; Zhang, C.; Manson, J.E.; Hu, F.B. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: A meta-analysis of prospective studies. *Diabetes Care* **2013**, *36*, 1422–1428. [CrossRef]
107. Dalgård, C.; Petersen, M.S.; Weihe, P.; Grandjean, P. Vitamin D Status in Relation to Glucose Metabolism and Type 2 Diabetes in Septuagenarians. *Diabetes Care* **2011**, *34*, 1284–1288. [CrossRef]
108. Robinson, J.G.; Manson, J.E.; Larson, J.; Liu, S.; Song, Y.; Howard, B.V.; Phillips, L.; Shikany, J.M.; Allison, M.; Curb, J.D.; et al. Lack of Association Between 25(OH)D Levels and Incident Type 2 Diabetes in Older Women. *Diabetes Care* **2011**, *34*, 628–634. [CrossRef]
109. Pilz, S.; Hurk, K.V.D.; Nijpels, G.; Stehouwer, C.; Riet, E.V.; Kienreich, K.; Tomaschitz, A.; Dekker, J. Vitamin D status, incident diabetes and prospective changes in glucose metabolism in older subjects: The Hoorn study. *Nutr. Metab. Cardiovasc. Dis.* **2012**, *22*, 883–889. [CrossRef]
110. Oosterwerff, M.M.; Eekhoff, E.M.; Van Schoor, N.M.; Boeke, A.J.P.; Nanayakkara, P.; Meijnen, R.; Knol, D.L.; Kramer, M.H.; Lips, P. Effect of moderate-dose vitamin D supplementation on insulin sensitivity in vitamin D–deficient non-Western immigrants in the Netherlands: A randomized placebo-controlled trial. *Am. J. Clin. Nutr.* **2014**, *100*, 152–160. [CrossRef]
111. Nazarian, S.; Peter, J.V.S.; Boston, R.C.; Jones, S.A.; Mariash, C.N. Vitamin D3 supplementation improves insulin sensitivity in subjects with impaired fasting glucose. *Transl. Res.* **2011**, *158*, 276–281. [CrossRef]
112. Talaei, A.; Mohamadi, M.; Adgi, Z. The effect of vitamin D on insulin resistance in patients with type 2 diabetes. *Diabetol. Metab. Syndr.* **2013**, *5*, 8. [CrossRef]
113. Hanafy, A.S.; Elkatawy, H.A. Beneficial Effects of Vitamin D on Insulin Sensitivity, Blood Pressure, Abdominal Subcutaneous Fat Thickness, and Weight Loss in Refractory Obesity. *Clin. Diabetes* **2018**, *36*, 217–225. [CrossRef]

114. Asemi, Z.; Karamali, M.; Esmaillzadeh, A. Effects of calcium–vitamin D co-supplementation on glycaemic control, inflammation and oxidative stress in gestational diabetes: A randomised placebo-controlled trial. *Diabetologia* **2014**, *57*, 1798–1806. [CrossRef]
115. Pittas, A.G.; Jorde, R.; Kawahara, T.; Dawson-Hughes, B. Response to Letter to the Editor from Dalan: "Vitamin D Supplementation for Prevention of Type 2 Diabetes Mellitus: To D or Not to D?". *J. Clin. Endocrinol. Metab.* **2020**, *106*, 1928–1929. [CrossRef]
116. Zhang, Y.; Tan, H.; Tang, J.; Li, J.; Chong, W.; Hai, Y.; Feng, Y.; Lunsford, L.D.; Xu, P.; Jia, D.; et al. Effects of Vitamin D Supplementation on Prevention of Type 2 Diabetes in Patients with Prediabetes: A Systematic Review and Meta-analysis. *Diabetes Care* **2020**, *43*, 1650–1658. [CrossRef]
117. Krishnamurthy, B.; Dudek, N.L.; McKenzie, M.D.; Purcell, A.; Brooks, A.; Gellert, S.; Colman, P.G.; Harrison, L.C.; Lew, A.; Thomas, H.E.; et al. Responses against islet antigens in NOD mice are prevented by tolerance to proinsulin but not IGRP. *J. Clin. Investig.* **2006**, *116*, 3258–3265. [CrossRef]
118. Nakayama, M.; Abiru, N.; Moriyama, H.; Babaya, N.; Liu, E.; Miao, D.; Yu, L.; Wegmann, D.R.; Hutton, J.C.; Elliott, J.F.; et al. Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. *Nature* **2005**, *435*, 220–223. [CrossRef]
119. Turley, S.; Poirot, L.; Hattori, M.; Benoist, C.; Mathis, D. Physiological beta cell death triggers priming of self-reactive T cells by dendritic cells in a type-1 diabetes model. *J. Exp. Med.* **2003**, *198*, 1527–1537. [CrossRef]
120. Anderson, M.S.; Bluestone, J.A. The Nod Mouse: A Model of Immune Dysregulation. *Annu. Rev. Immunol.* **2005**, *23*, 447–485. [CrossRef]
121. Lieberman, S.; DiLorenzo, T. A comprehensive guide to antibody and T-cell responses in type 1 diabetes. *Tissue Antigens* **2003**, *62*, 359–377. [CrossRef] [PubMed]
122. André, I.; Gonzalez, A.; Wang, B.; Katz, J.; Benoist, C.; Mathis, D. Checkpoints in the progression of autoimmune disease: Lessons from diabetes models. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 2260–2263. [CrossRef] [PubMed]
123. Katz, J.D.; Wang, B.; Haskins, K.; Benoist, C.; Mathis, D. Following a diabetogenic T cell from genesis through pathogenesis. *Cell* **1993**, *74*, 1089–1100. [CrossRef]
124. Burton, A.R.; Vincent, E.; Arnold, P.Y.; Lennon, G.P.; Smeltzer, M.; Li, C.-S.; Haskins, K.; Hutton, J.; Tisch, R.M.; Sercarz, E.E.; et al. On the Pathogenicity of Autoantigen-Specific T-Cell Receptors. *Diabetes* **2008**, *57*, 1321–1330. [CrossRef] [PubMed]
125. Serreze, D.V.; Fleming, S.A.; Chapman, H.D.; Richard, S.D.; Leiter, E.H.; Tisch, R.M. B lymphocytes are critical antigen-presenting cells for the initiation of T cell-mediated autoimmune diabetes in nonobese diabetic mice. *J. Immunol.* **1998**, *161*, 3912–3918. [CrossRef] [PubMed]
126. Greeley, S.A.W.; Katsumata, M.; Yu, L.; Eisenbarth, G.S.; Moore, D.J.; Goodarzi, H.; Barker, C.F.; Naji, A.; Noorchashm, H. Elimination of maternally transmitted autoantibodies prevents diabetes in nonobese diabetic mice. *Nat. Med.* **2002**, *8*, 399–402. [CrossRef]
127. Hu, C.-Y.; Rodriguez-Pinto, D.; Du, W.; Ahuja, A.; Henegariu, O.; Wong, F.S.; Shlomchik, M.J.; Wen, L. Treatment with CD20-specific antibody prevents and reverses autoimmune diabetes in mice. *J. Clin. Investig.* **2007**, *117*, 3857–3867. [CrossRef]
128. Inaba, M.; Nishizawa, Y.; Song, K.; Tanishita, H.; Okuno, S.; Miki, T.; Morii, H. Partial protection of 1α-hydroxyvitamin D3 against the development of diabetes induced by multiple low-dose streptozotocin injection in CD-1 mice. *Metabolism* **1992**, *41*, 631–635. [CrossRef]
129. Mathieu, C.; Laureys, J.; Sobis, H.; Vandeputte, M.; Waer, M.; Bouillon, R. 1,25-Dihydroxyvitamin D_3 prevents insulitis in NOD mice. *Diabetes* **1992**, *41*, 1491–1495. [CrossRef]
130. Mathieu, C.; Waer, M.; Laureys, J.; Rutgeerts, O.; Bouillon, R. Prevention of autoimmune diabetes in NOD mice by 1,25 dihydroxyvitamin D3. *Diabetologia* **1994**, *37*, 552–558. [CrossRef]
131. Gregori, S.; Giarratana, N.; Smiroldo, S.; Uskokovic, M.; Adorini, L. A 1α,25-Dihydroxyvitamin D3 Analog Enhances Regulatory T-Cells and Arrests Autoimmune Diabetes in NOD Mice. *Diabetes* **2002**, *51*, 1367–1374. [CrossRef]
132. Hyppönen, E.; Läärä, E.; Reunanen, A.; Järvelin, M.-R.; Virtanen, S.M. Intake of vitamin D and risk of type 1 diabetes: A birth-cohort study. *Lancet* **2001**, *358*, 1500–1503. [CrossRef]
133. Fronczak, C.M.; Barón, A.E.; Chase, H.P.; Ross, C.; Brady, H.L.; Hoffman, M.; Eisenbarth, G.S.; Rewers, M.; Norris, J.M. In Utero Dietary Exposures and Risk of Islet Autoimmunity in Children. *Diabetes Care* **2003**, *26*, 3237–3242. [CrossRef]
134. Sørensen, I.M.; Joner, G.; Jenum, P.A.; Eskild, A.; Torjesen, P.A.; Stene, L.C. Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. *Diabetes* **2012**, *61*, 175–178. [CrossRef]
135. Zipitis, C.S.; Akobeng, A.K. Vitamin D supplementation in early childhood and risk of type 1 diabetes: A systematic review and meta-analysis. *Arch. Dis. Child.* **2008**, *93*, 512–517. [CrossRef]
136. Vitamin D supplement in early childhood and risk for Type I (insulin-dependent) diabetes mellitus. The EURODIAB Substudy 2 Study Group. *Diabetologia* **1999**, *42*, 51–54. [CrossRef]
137. Gabbay, M.A.; Sato, M.N.; Finazzo, C.; Duarte, A.J.; Dib, S.A. Effect of cholecalciferol as adjunctive therapy with insulin on protective immunologic profile and decline of residual beta-cell function in new-onset type 1 diabetes mellitus. *Arch. Pediatr. Adolesc. Med.* **2012**, *166*, 601–607. [CrossRef]
138. Walter, M.; Kaupper, T.; Adler, K.; Foersch, J.; Bonifacio, E.; Ziegler, A.G. No effect of the 1alpha,25-dihydroxyvitamin D3 on beta-cell residual function and insulin requirement in adults with new-onset type 1 diabetes. *Diabetes Care* **2010**, *33*, 1443–1448. [CrossRef]

139. Bizzarri, C.; Pitocco, D.; Napoli, N.; Di Stasio, E.; Maggi, D.; Manfrini, S.; Suraci, C.; Cavallo, M.G.; Cappa, M.; Ghirlanda, G.; et al. No protective effect of calcitriol on beta-cell function in recent-onset type 1 diabetes: The IMDIAB XIII trial. *Diabetes Care* **2010**, *33*, 1962–1963. [CrossRef]
140. Provvedini, D.M.; Tsoukas, C.D.; Deftos, L.J.; Manolagas, S.C. 1,25-dihydroxyvitamin D_3 receptors in human leukocytes. *Science* **1983**, *221*, 1181–1183. [CrossRef]
141. Provvedini, D.M.; Tsoukas, C.D.; Deftos, L.J.; Manolagas, S.C. 1 alpha,25-Dihydroxyvitamin D3-binding macromolecules in human B lymphocytes: Effects on immunoglobulin production. *J. Immunol.* **1986**, *136*, 2734–2740. [CrossRef] [PubMed]
142. Veldman, C.M.; Cantorna, M.T.; DeLuca, H.F. Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. *Arch. Biochem. Biophys.* **2000**, *374*, 334–338. [CrossRef] [PubMed]
143. Takahashi, K.; Nakayama, Y.; Horiuchi, H.; Ohta, T.; Komoriya, K.; Ohmori, H.; Kamimura, T. Human neutrophils express messenger RNA of vitamin D receptor and respond to 1alpha,25-dihydroxyvitamin D_3. *Immunopharmacol. Immunotoxicol.* **2002**, *24*, 335–347. [CrossRef] [PubMed]
144. Kreutz, M.; Andreesen, R.; Krause, S.W.; Szabo, A.; Ritz, E.; Reichel, H. 1,25-Dihydroxyvitamin-D3 Production and Vitamin-D3 Receptor Expression Are Developmentally-Regulated during Differentiation of Human Monocytes into Macrophages. *Blood* **1993**, *82*, 1300–1307. [CrossRef]
145. Hewison, M.; Freeman, L.; Hughes, S.V.; Evans, K.N.; Bland, R.; Eliopoulos, A.G.; Kilby, M.D.; Moss, P.A.H.; Chakraverty, R. Differential Regulation of Vitamin D Receptor and Its Ligand in Human Monocyte-Derived Dendritic Cells. *J. Immunol.* **2003**, *170*, 5382–5390. [CrossRef]
146. Baeke, F.; Korf, H.; Overbergh, L.; van Etten, E.; Verstuyf, A.; Gysemans, C.; Mathieu, C. Human T lymphocytes are direct targets of 1,25-dihydroxyvitamin D3 in the immune system. *J. Steroid Biochem. Mol. Biol.* **2010**, *121*, 221–227. [CrossRef]
147. Griffin, M.D.; Xing, N.; Kumar, R. Vitamin d and its analogs as regulators of immune activation and antigen presentation. *Annu. Rev. Nutr.* **2003**, *23*, 117–145. [CrossRef]
148. Baeke, F.; Van Etten, E.; Overbergh, L.; Mathieu, C. Vitamin D_3 and the immune system: Maintaining the balance in health and disease. *Nutr. Res. Rev.* **2007**, *20*, 106–118. [CrossRef]
149. Xu, H.; Soruri, A.; Gieseler, R.K.H.; Peters, J.H. 1,25-Dihydroxyvitamin D3 Exerts Opposing Effects to IL-4 on MHC Class-II Antigen Expression, Accessory Activity, and Phagocytosis of Human Monocytes. *Scand. J. Immunol.* **1993**, *38*, 535–540. [CrossRef]
150. Almerighi, C.; Sinistro, A.; Cavazza, A.; Ciaprini, C.; Rocchi, G.; Bergamini, A. 1α,25-Dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in Human Monocytes. *Cytokine* **2009**, *45*, 190–197. [CrossRef]
151. Penna, G.; Adorini, L. 1α,25-Dihydroxyvitamin D3 Inhibits Differentiation, Maturation, Activation, and Survival of Dendritic Cells Leading to Impaired Alloreactive T Cell Activation. *J. Immunol.* **2000**, *164*, 2405–2411. [CrossRef]
152. Berer, A.; Stöckl, J.; Majdic, O.; Wagner, T.; Kollars, M.; Lechner, K.; Geissler, K.; Oehler, L. 1,25-Dihydroxyvitamin D3 inhibits dendritic cell differentiation and maturation in vitro. *Exp. Hematol.* **2000**, *28*, 575–583. [CrossRef]
153. Van Halteren, A.G.S.; van Etten, E.; de Jong, E.C.; Bouillon, R.; Roep, B.O.; Mathieu, C. Redirection of human autoreactive T-cells upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D-3. *Diabetes* **2002**, *51*, 2119–2125. [CrossRef]
154. Pedersen, A.W.; Holmstrøm, K.; Jensen, S.S.; Fuchs, D.; Rasmussen, S.; Kvistborg, P.; Claesson, M.H.; Zocca, M.B. Phenotypic and functional markers for 1alpha,25-dihydroxyvitamin D(3)-modified regulatory dendritic cells. *Clin. Exp. Immunol.* **2009**, *157*, 48–59. [CrossRef]
155. Van Halteren, A.G.; Tysma, O.M.; van Etten, E.; Mathieu, C.; Roep, B.O. 1alpha,25-dihydroxyvitamin D_3 or analogue treated dendritic cells modulate human autoreactive T cells via the selective induction of apoptosis. *J. Autoimmun.* **2004**, *23*, 233–239. [CrossRef]
156. Adorini, L. Tolerogenic dendritic cells induced by vitamin D receptor ligands enhance regulatory T cells inhibiting autoimmune diabetes. *Ann. N. Y. Acad. Sci.* **2003**, *987*, 258–261. [CrossRef]
157. Penna, G.; Roncari, A.; Amuchastegui, S.; Daniel, K.C.; Berti, E.; Colonna, M.; Adorini, L. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4+Foxp3+ regulatory T cells by 1,25-dihydroxyvitamin D3. *Blood* **2005**, *106*, 3490–3497. [CrossRef]
158. Piemonti, L.; Monti, P.; Sironi, M.; Fraticelli, P.; Leone, B.E.; Dal Cin, E.; Allavena, P.; Di Carlo, V. Vitamin D3 Affects Differentiation, Maturation, and Function of Human Monocyte-Derived Dendritic Cells. *J. Immunol.* **2000**, *164*, 4443–4451. [CrossRef]
159. Walker, L.S.K.; von Herrath, M. CD4 T cell differentiation in type 1 diabetes. *Clin. Exp. Immunol.* **2015**, *183*, 16–29. [CrossRef]
160. Emamaullee, J.A.; Davis, J.; Merani, S.; Toso, C.; Elliott, J.F.; Thiesen, A.; Shapiro, A.J. Inhibition of Th17 Cells Regulates Autoimmune Diabetes in NOD Mice. *Diabetes* **2009**, *58*, 1302–1311. [CrossRef]
161. Tian, J.; Lehmann, P.V.; Kaufman, D.L. Determinant Spreading of T Helper Cell 2 (Th2) Responses to Pancreatic Islet Autoantigens. *J. Exp. Med.* **1997**, *186*, 2039–2043. [CrossRef] [PubMed]
162. Boonstra, A.; Barrat, F.J.; Crain, C.; Heath, V.L.; Savelkoul, H.F.J.; O'garra, A. 1α,25-Dihydroxyvitamin D3 Has a Direct Effect on Naive CD4+ T Cells to Enhance the Development of Th2 Cells. *J. Immunol.* **2001**, *167*, 4974–4980. [CrossRef] [PubMed]
163. Mahon, B.D.; Wittke, A.; Weaver, V.; Cantorna, M.T. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. *J. Cell. Biochem.* **2003**, *89*, 922–932. [CrossRef] [PubMed]

164. Tang, J.; Zhou, R.; Luger, D.; Zhu, W.; Silver, P.B.; Grajewski, R.S.; Su, S.-B.; Chan, C.-C.; Adorini, L.; Caspi, R.R. Calcitriol Suppresses Antiretinal Autoimmunity through Inhibitory Effects on the Th17 Effector Response. *J. Immunol.* **2009**, *182*, 4624–4632. [CrossRef]
165. Riachy, R.; Vandewalle, B.; Belaich, S.; Kerr-Conte, J.; Gmyr, V.; Zerimech, F.; D'Herbomez, M.; Lefebvre, J.; Pattou, F. Beneficial effect of 1,25 dihydroxyvitamin D3 on cytokine-treated human pancreatic islets. *J. Endocrinol.* **2001**, *169*, 161–168. [CrossRef]
166. Gysemans, C.; Cardozo, A.K.; Callewaert, H.; Giulietti, A.; Hulshagen, L.; Bouillon, R.; Eizirik, D.L.; Mathieu, C. 1,25-Dihydroxyvitamin D3 Modulates Expression of Chemokines and Cytokines in Pancreatic Islets: Implications for Prevention of Diabetes in Nonobese Diabetic Mice. *Endocrinology* **2005**, *146*, 1956–1964. [CrossRef]
167. Brusko, T.M.; Putnam, A.L.; Bluestone, J.A. Human regulatory T cells: Role in autoimmune disease and therapeutic opportunities. *Immunol. Rev.* **2008**, *223*, 371–390. [CrossRef]
168. Liu, W.; Putnam, A.L.; Xu-Yu, Z.; Szot, G.L.; Lee, M.R.; Zhu, S.; Gottlieb, P.A.; Kapranov, P.; Gingeras, T.R.; de St Groth, B.F.; et al. CD127 expression inversely correlates with FoxP3 and suppressive function of human CD4+ T reg cells. *J. Exp. Med.* **2006**, *203*, 1701–1711. [CrossRef]
169. Jeffery, L.E.; Burke, F.; Mura, M.; Zheng, Y.; Qureshi, O.S.; Hewison, M.; Walker, L.S.K.; Lammas, D.A.; Raza, K.; Sansom, D.M. 1,25-Dihydroxyvitamin D3 and IL-2 Combine to Inhibit T Cell Production of Inflammatory Cytokines and Promote Development of Regulatory T Cells Expressing CTLA-4 and FoxP3. *J. Immunol.* **2009**, *183*, 5458–5467. [CrossRef]
170. Chen, S.; Sims, G.P.; Chen, X.X.; Gu, Y.Y.; Chen, S.; Lipsky, P.E. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J. Immunol* **2007**, *179*, 1634–1647. [CrossRef]
171. Pieńkowska, A.; Janicka, J.; Duda, M.; Dzwonnik, K.; Lip, K.; Mędza, A.; Szlagatys-Sidorkiewicz, A.; Brzeziński, M. Controversial Impact of Vitamin D Supplementation on Reducing Insulin Resistance and Prevention of Type 2 Diabetes in Patients with Prediabetes: A Systematic Review. *Nutrients* **2023**, *15*, 983. [CrossRef]