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Review

Combination of vitamin D and dipeptidyl peptidase-4 inhibitors (VIDPP-4i) as an immunomodulation therapy for autoimmune diabetes

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ABSTRACT

Type 1 diabetes (T1D) and latent autoimmune diabetes in adults (LADA) represent the most common types of autoimmune diabetes and are characterized by different age of onset, degrees of immune-mediated destruction of pancreatic beta cells and rates of disease progression towards insulin dependence. Several immunotherapies aimed to counteract autoimmune responses against beta cells and preserve beta-cell function are currently being investigated, particularly in T1D. Preliminary findings suggest a potential role of combination therapy with vitamin D and dipeptidyl peptidase-4 (DPP-4) inhibitors (VIDPP-4i) in preserving beta-cell function in autoimmune diabetes. This manuscript aims to provide a comprehensive overview of the immunomodulatory properties of vitamin D and DPP-4 inhibitors, as well as the rationale for investigation of their combined use as an immunomodulation therapy for autoimmune diabetes.

1. Introduction

Autoimmune diabetes is a highly heterogeneous disease which can occur at any age [1]. Type 1 diabetes (T1D) and latent autoimmune diabetes in adults (LADA) represent the most common types of autoimmune diabetes, although other rare forms or subgroups of autoimmune diabetes have also been described, such as fulminant T1D and checkpoint inhibitor-associated autoimmune diabetes [2,3].

1.1. Type 1 diabetes (T1D)

T1D is an organ-specific autoimmune disease characterized by the immune-mediated destruction of insulin-secreting pancreatic beta cells, which ultimately results in lifelong dependence on exogenous insulin [4]. Even though beta-cell-targeted autoimmune responses are known to occur in T1D, the exact aetiology and pathological mechanisms are still not clear [5]. T1D is a complex multifactorial disease in which both genetic susceptibility and environmental factors promote the autoimmune responses against beta cells [5]. Several environmental risk factors have been suggested as candidate triggers of islet autoimmunity, including certain viruses (particularly enteroviruses), higher birthweight, infant weight gain, dysbiosis of the gut microbiota and various dietary factors (e.g., vitamin D deficiency, omega-3 fatty acid deficiency, high milk consumption) [6–10].

Although T1D onset usually occurs in children or young adults, the disease can occur at any age [5]. The process of pancreatic islet infiltration by immune cells (also known as "insulitis") represents the histological hallmark of the autoimmune destruction of beta cells within the pancreatic islets [11]. Even though CD8+ cytotoxic T lymphocytes are the most frequent amongst the islet infiltrating immune cells, CD4+ T lymphocytes (also known as T helper cells or Th cells), B lymphocytes and macrophages are also found, especially in young children [5,12].

Autoreactive CD8+ T cells recognize major histocompatibility complex (MHC) class I-restricted islet autoantigens on beta-cell surface and exert cytotoxic effects through a number of effector mediators, particularly cytokines released by T helper type 1 (Th1) cells such as interferon (IFN)-γ [5,13]. Evidence also suggests an important role of Th17 cells and follicular helper T cells in T1D pathophysiology [14]. Furthermore, several studies demonstrated that patients with T1D exhibit defects in the ability of regulatory T cells (Tregs) to suppress the activity and proliferation of autoreactive CD4+ and CD8+ T cells [15–18].

The starting point in the natural history of T1D is represented by genetic susceptibility to the disease, which is subsequently followed by three distinct stages, namely:

- stage 1 (islet autoimmunity): this stage is characterized by the development of beta-cell autoimmunity, as evidenced by the presence of at least two islet autoantibodies among glutamic acid decarboxylase autoantibodies (GADA), zinc transporter 8 autoantibodies (ZnT8A), insulin autoantibodies (IAA), insulinoma-associated antigen-2 autoantibodies (IA-2A); during this stage, subjects remain normoglycemic and asymptomatic.
- stage 2 (abnormal glucose tolerance): subjects maintain multiple islet autoantibody positivity and remain asymptomatic, but display dysglycemia, as evidenced by impaired fasting glucose levels, abnormal oral glucose tolerance test, or glycated hemoglobin (HbA1c) ≥ 5.7%
- stage 3 (symptomatic disease): this stage is characterized by the onset of clinical T1D, which is often accompanied by symptoms such as polyuria, polydipsia, fatigue, weight loss, and diabetic ketoacidosis [19].

Shortly after the clinical onset of the disease and the initiation of insulin therapy, most subjects with T1D (approximately two-thirds) experience a transient and partial spontaneous remission phase (also referred to as "honeymoon phase"), which is accompanied by a marked reduction in exogenous insulin requirements and near-normal glycemic control [20–23]. Conversely, complete remission (characterized by near-normal glucose control without need for insulin therapy) seldom occurs, being described in approximately 2–12% of young T1D subjects in some population-based cohort studies [21]. Overall, duration of remission phase varies widely between individuals, with an average of approximately 7 months [24]. It has been suggested that both immune and metabolic factors contribute to the beta-cell recovery observed during the honeymoon phase, including transient development of antigen-specific adaptive immune tolerance, optimized glucose control, improved insulin sensitivity, as well as reduced glucotoxicity following the initiation of insulin therapy [20,25].

1.2. Latent autoimmune diabetes in adults (LADA)

LADA is a distinct form of autoimmune diabetes characterized by an older age of onset, a less severe immune-mediated destruction and functional deterioration of beta cells, and a slower progression towards insulin dependence compared to T1D [1]. Assessment of the pathology of pancreata obtained from LADA patients revealed that this disease represents a milder and more slowly progressing form of autoimmune diabetes compared to T1D. This is strongly suggested by various findings, such as increased beta-cell proliferation capacity, increased anti-inflammatory capacity (as documented by the increase of interleukin [IL]-10 gene expression), reduced beta-cell proapoptotic signaling, and predominance of IL-1β in the immune cell infiltrate as compared to the predominance of tumor necrosis factor (TNF)-α observed in T1D pancreata [26].

Current criteria for diagnosing LADA include: i) adult age of onset (greater than 30 years); ii) presence of any islet cell autoantibody; and iii) absence of insulin requirement for at least 6 months after diagnosis [1,27,28]. Compared to T1D, LADA displays a greater clinical

heterogeneity and shares clinical and metabolic features with both T1D and type 2 diabetes (T2D). In fact, patients with LADA exhibit a remarkable variability in the rate of beta-cell destruction, different degrees of insulin resistance and heterogeneous patterns of islet autoimmunity, probably due to differences in genetic and immune factors [1]. For these reasons, LADA is often diagnosed and treated as T2D, potentially resulting in a more rapid progression towards insulin dependence. This aspect has relevant clinical implications, since optimal glucose control is critical to preserve beta-cell function and reduce the risk of chronic diabetes complications [1,29].

2. Pathophysiology of autoimmune diabetes: Beyond the beta cell

Although T1D has long been conceived as an autoimmune disease arising from the immune-mediated destruction of pancreatic beta cells, accumulating evidence over the last years has showed that T1D pathophysiology is more complex and involves also other relevant aspects, such as dysfunction of glucagon-secreting alpha cells and histological abnormalities of the exocrine pancreas. Notably, T1D patients often exhibit a dysregulated glucagon secretion by pancreatic alpha cells, consisting in: i) impaired ability of these cells to secrete glucagon in response to hypoglycemia, and/or ii) excessive postprandial glucagon secretion [30,31]. These alterations can substantially contribute to the occurrence of hyperglycemic and hypoglycemic episodes. Several factors account for the alpha-cell dysfunction occurring in T1D, including lack of beta-cell signaling, sympathetic islet neuropathy, as well as alterations in transcription factors constituting alpha-cell identity [30,32,33]. It has been shown that insulin-negative islets in subjects with T1D are dominated by glucagon-positive cells that often lack the alpha-cell transcription factor ARX, while instead expressing PDX1, which is normally only expressed in beta cells, suggesting a process of beta-cell dedifferentiation into alpha cells [34]. However, beta-cell neogenesis from alpha cells emanating from endocrine progenitor cells that reside within or adjacent to the ductal epithelium has also been suggested as a possible mechanism aimed to compensate for beta-cell loss in T1D. Therefore, it is challenging to establish whether the intermediate cell type (exhibiting some characteristics of alpha cells and some characteristics of beta cells) arises from beta-cell dedifferentiation or beta-cell neogenesis [34].

Histological abnormalities of the exocrine pancreas are common in patients with T1D. In particular, acinar atrophy, intralobular and interacinar fibrosis, leucocytic infiltration, fatty infiltration, pancreatic arteriosclerosis and focal lesions of acute pancreatitis are all frequently observed [35]. Vascular events and hemorrhages within pancreatic islets also occur in patients with T1D [36]. Periductal accumulation of leukocytes and fibrosis (the end stage of inflammation) might negatively affect islet neogenesis from endocrine progenitor cells residing within the periductal area [36]. Recently, it has been shown that patients with T1D exhibit a lower number of acinar cells and a greater degree of fibrosis within the pancreatic exocrine tissue [37]. The loss of pancreatic exocrine mass accounts for the smaller pancreas volume observed in patients with T1D compared to non-diabetic subjects [35,37]. Noteworthy, 25% to 75% of adult subjects with T1D show pancreatic exocrine dysfunction [35]. Various putative causal factors for such histological abnormalities have been proposed, such as: i) impaired secretion of insulin, glucagon, somatostatin and pancreatic polypeptide; ii) global pancreatic inflammation; iii) autoimmune responses targeting the exocrine pancreas; iv) vascular and neural abnormalities; and v) involvement of pancreatic stellate cells [35]. In light of these remarks, therapeutic strategies aimed to restore the disordered glucagon secretion and the histological abnormalities of the exocrine pancreas would be highly desirable interventions in the setting of autoimmune diabetes.

3. Heterogeneity of autoimmune diabetes

The canonical notion that T1D results from the complete loss of beta cells leading to an absolute insulin deficiency [38] has recently been overcome. Indeed, emerging evidence shows that many patients with long-standing T1D exhibit the persistence of insulin-containing pancreatic islets and maintain some degree of endogenous insulin secretion even many decades after the diagnosis [39–42]. In this regard, it is worth considering that T1D is a highly heterogeneous disease in terms of immunopathological and clinical features [43]. Age at diagnosis is one of the main variables associated with the heterogeneous rate of decline in insulin secretion among subjects with T1D. In particular, younger age at onset of T1D is accompanied by lower residual beta-cell function [44,45], greater decline in endogenous insulin secretion [46,47] and lower occurrence of the honeymoon phase [20,24]. Recently, Leete et al. [48] demonstrated the existence of two histologically distinct endotypes of T1D that correlate with age at diagnosis. By using pancreas samples recovered soon after T1D onset (<2 years) from young people diagnosed at different ages (<7 years, 7–12 years and ≥ 13 years), authors found that the younger group exhibited more pronounced aberrant proinsulin processing within insulin-containing islets, lower C-peptide levels and higher median proinsulin to C-peptide ratio compared to the group diagnosed at ≥ 13 years [48]. These distinct patterns of residual insulin secretion appear to align with the previously described immune phenotypes (immunotypes) of T1D [12,49]. Similar findings have also been observed in patients with LADA. In this context, the LADA China Study 8 investigated whether age of onset of LADA contributes to the clinical heterogeneity of the disease by comparing clinical, metabolic and immunogenetic characteristics between elderly and young patients [50]. Interestingly, the study found that elderly LADA group (age of onset ≥ 60 years) exhibited a better residual beta-cell function and a higher degree of insulin resistance compared to young LADA group (age of onset < 60 years). Elderly LADA patients showed more proportion of low titre GADA and lower GADA titres compared to young LADA patients aged < 40 years. Elderly LADA group also showed a clinical and genetic profile more similar to that of age-matched subjects with T2D [50].

All the aforementioned remarks have important implications in the setting of immune interventions for autoimmune diabetes. Retention of residual endogenous insulin secretion has been associated with improved glucose control, reduced risk of hypoglycemia, lower glucose variability and fewer chronic diabetes complications in T1D [51–54]. Therefore, protection against immune-mediated beta-cell destruction and preservation of residual beta-cell mass and function (as measured by C-peptide, which is secreted from beta cells at an equimolar ratio to insulin) represent critical goals of clinical trials investigating the efficacy of disease-modifying agents and immunotherapies for autoimmune diabetes, including T1D and LADA [1,55,56]. So far, several immunotherapies have been investigated in new-onset T1D, although they have mostly showed no effect or only a transient beneficial effect in counteracting the progressive decline in beta-cell function [56]. Hence, the use of immunotherapeutic agents in a combination therapy approach is worth being tested in future clinical trials. Targeting multiple pathways involved in beta-cell loss and dysfunction (e.g. innate immunity, adaptive immunity, regulatory immunity, glucotoxicity) may represent a successful immune intervention for autoimmune diabetes [57]. Moreover, the clinical and immunopathological heterogeneity of autoimmune diabetes accounts, at least in part, for the interindividual variability in the response to different immunotherapies [58]. This aspect should be taken into account in future studies to facilitate the selection of targeted immunotherapies aimed to halt beta-cell autoimmunity and disease progression in selected subsets of individuals with autoimmune diabetes.

Over the last few years, our group and other authors showed a potential therapeutic role of dipeptidyl peptidase-4 inhibitors (DPP-4i) and/or vitamin D in prolonging the clinical remission phase and preserving the residual beta-cell function in patients with autoimmune diabetes [59–69]. This review aims to provide a comprehensive overview of the anti-inflammatory and immunomodulatory properties of vitamin D and DPP-4i, as well as their potential synergistic effects in preserving residual beta-cell function in autoimmune diabetes, including both T1D and LADA. In the text, we will use the term VIDPP-4i when referring to the combination therapy with vitamin D and DPP-4i.

4. Vitamin D and immune system

Vitamin D is a term that refers to a group of fat-soluble secosteroids, namely: i) ergocalciferol (vitamin D2), which is produced in response to ultraviolet irradiation of the phytosterol ergosterol found in fungal sources such as mushrooms and yeast, and ii) cholecalciferol (vitamin D_3), which is synthesized in the human skin upon ultraviolet-B (UVB) light irradiation of the precursor 7-dehydrocholesterol (7-DHC). Although vitamin D is primarily produced in the skin upon sunlight exposure, it can also be obtained from a few external sources, such as fungal sources or animal foods containing ergocalciferol and cholecalciferol, respectively [70,71]. Once produced in the skin or ingested and absorbed through foods or dietary supplements, vitamin D_3 is transported in the blood by vitamin D binding protein (DBP) to the liver, where it is converted into 25-hydroxyvitamin D_3 [25(OH)D_3, also known as calcifediol] by the action of vitamin D-25-hydroxylase enzyme. Then, 25(OH)D_3 is transported to the kidneys, where 1-α-hydroxylase enzyme catalyzes its conversion into 1,25-dihydroxyvitamin D_3 [1,25(OH)2D3; also referred to as calcitriol], which is the biologically active metabolite of vitamin D [70]. 25(OH)D is the major circulating form of vitamin D and its serum levels represent the most reliable biomarker of vitamin D status [72,73].

Over the last years, a growing body of evidence showed that vitamin D exerts pleiotropic effects [74–78] other than the well-known regulation of calcium and bone homeostasis [79,80]. Remarkably, several preclinical and experimental studies demonstrated that calcitriol plays an important role in the regulation of innate and adaptive immune responses [74,77,81,82]. The first hint of the role of vitamin D in the maintenance of immune homeostasis came from the evidence that immune cells are both vitamin D targets and local producers of vitamin D. Vitamin D acts through a specific receptor known as vitamin D receptor (VDR), which is a member of the nuclear receptor/steroid hormone receptor superfamily. The actions of vitamin D are classified into: i) genomic, through the VDR-mediated transcriptional effects in the cell nucleus, and ii) non-genomic, when the VDR located on the cell membrane and/or cytoplasm induces rapid signaling pathways [83]. Functional VDR has been identified in almost all immune cells, including neutrophils, T lymphocytes and antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages [84,85]. On the other hand, it has been shown that several immune cells (e.g., macrophages, DCs, T- and B-lymphocytes) express the vitamin D-activating enzymes 25- and 1α-hydroxylase [86–90]. Therefore, inactive vitamin D metabolites can be converted into the active form calcitriol within a local immunological milieu [81]. Importantly, calcitriol has been shown to exert several effects on innate and adaptive immune system, resulting in the activation of anti-inflammatory and immunomodulatory pathways and induction of immune tolerance. Calcitriol promotes monocyte and macrophage antimicrobial activity by inducing the production of antimicrobial peptides, such as cathelicidin and defensin β2 [91–93]. Indeed, observational evidence suggests that vitamin D deficiency may be involved in the pathophysiology of various infectious diseases [81,94–96].

On the other hand, calcitriol reduces macrophage surface expression of MHC class II molecules, resulting in reduced macrophage antigen presentation ability and T-cell stimulatory capacity [88,97]. Calcitriol favours the shift of macrophage polarization from M1 phenotype (proinflammatory phenotype) towards M2 phenotype (anti-inflammatory phenotype) [98], resulting in the up-regulation of IL-10 and down-regulation of inflammatory stimuli (e.g., IL-1β, IL-6, TNF-α, RANKL,

COX-2) [82,99]. Calcitriol also modulates the morphology, differentiation and function of DCs, rendering them more adherent spindle-shaped, less mature and more tolerogenic, thereby reducing their antigen presentation ability [82]. In DCs, calcitriol has been shown to downregulate IL-6 and IL-12, upregulate IL-10, and decrease the expression of MHC class II molecules and co-stimulatory molecules CD80 and CD86 [100]. With regard to vitamin D effects on adaptive immune system, it has been shown that calcitriol: i) inhibits the production of Th1 cytokines (e.g., IL-2, IFN-γ), Th9 cytokines (e.g., IL-9) and Th17 cytokines (e.g., IL-17, IL-21) [81,82,101], ii) upregulates Th2 cytokines (e.g., IL-4, IL-5) [82], iii) induces IL-10-producing Tregs [82,101], and iv) affects Th cell balance by increasing Th2 cells and inhibiting Th1 and Th17 cell differentiation, thus leading to a shift of T cells from an effector (pro-inflammatory) phenotype towards a regulatory (anti-inflammatory) phenotype [74,82,102,103]. A direct effect of calcitriol on CD8+ T cell hyperactivation has also been reported and consists in the calcitriol ability to reduce the secretion of IFN-γ and TNF-α and increase the synthesis of anti-inflammatory cytokines IL-5 and transforming growth factor beta (TGF-β) by these cells [104]. Notably, the effects of calcitriol on T cells are mediated by both direct actions and indirect actions on innate immune cells, such as DCs [82]. In human T cells, T-cell antigen receptor (TCR) signaling via p38 leads to subsequent induction of VDR and phospholipase C-gamma 1 (PLC-γ1), which are required steps for classical TCR signaling and T-cell activation [105]. In another study conducted on human T cells, calcitriol was able to promote the differentiation of Tregs, inhibit Th17 cell proliferation, suppress IL-17 production and significantly upregulate PLC-γ1 expression, which then induced the expression of the anti-inflammatory cytokine TGF-β1 [106]. These results suggest that calcitriol indirectly modulates the differentiation of human Treg/Th17 cells by affecting the VDR/PLC-γ1/TGF-β1 pathway. Finally, calcitriol has been shown to exert a direct effect on B cells by inhibiting the generation of plasma cells and post-switch memory B cells, thus inhibiting the proliferation of activated B cells and inducing their apoptosis [90].

5. Role of vitamin D in autoimmune diabetes: T1D and LADA

Over the last years, vitamin D deficiency has been increasingly suggested as a risk factor for several autoimmune diseases [74,107–111], including T1D [112–115]. Several studies showed that incidence of T1D is directly correlated with latitude and inversely correlated with ultraviolet radiation [116–120]. A number of observational studies showed that subjects with new-onset and established T1D exhibited significantly lower levels of 25(OH)D compared to healthy controls [121–130]. Other studies documented the existence of a significant seasonality in the incidence of T1D, consisting of a higher percentage of incident cases observed during winter, early spring and late autumn compared to late spring and summer months [131,132].

Since vitamin D deficiency is highly prevalent in autoimmune diseases, several studies have also investigated the therapeutic value of vitamin D supplementation in such diseases, including T1D [111]. It has been suggested that higher serum vitamin D levels and vitamin D intake during infancy and early childhood may have a role in reducing the risk of T1D later in life [112,133,134]. Moreover, pre-clinical evidence suggests a potential role of vitamin D in the regulation of beta-cell function and insulin synthesis and secretion [112,135]. Indeed, human pancreatic beta cells express both 1α-hydroxylase [136–138] and VDR [139], and a vitamin D response element (VDRE) has been found in the human insulin gene promoter [140]. In addition, vitamin D has been found to be capable of promoting beta-cell survival through a VDR-dependent transcriptional program enhancing anti-inflammatory responses [141]. A number of studies conducted in non-obese diabetic (NOD) mice (an animal model of T1D) demonstrated that calcitriol and its analogs can prevent or halt the progression of autoimmune diabetes and insulitis [112]. Moreover, transgenic mice overexpressing VDR in beta cells are protected against streptozotocin-induced diabetes and

exhibit preserved beta-cell mass, along with reduced islet inflammation [142]. Interestingly, a recent study [143] showed that DBP is highly expressed in murine and human alpha cells, and loss of DBP gives rise to alterations in alpha-cell number and size, electrical activity and glucagon secretion *in vitro* and *in vivo*. Additionally, authors found reduced expression levels of DBP in islets of donors with late-onset or long-standing T1D [143].

Studies conducted in subjects with T1D suggest that vitamin D can exert direct effects on T cells. Gabbay et al. [61] showed that vitamin D_3 administration in patients with new-onset T1D (at a dose of 2000 IU/day and in addition to insulin therapy) led to a significant increase in the percentage of Tregs at 12 months compared to placebo. Thereafter, Treiber et al. [144] showed that vitamin D_3 supplementation for 12 months in patients with new-onset T1D (at a dose of 70 IU/kg body weight/day) was associated with a significant improvement in Treg suppressor capacity compared to placebo. In a study conducted in 12 children positive for islet autoantibodies, calcitriol administration (at a dose of 0.25 μg/day) led to negativization of GADA and IAA after a median time of 6 months [145].

However, intervention studies and randomized controlled trials investigating the efficacy of vitamin D as an adjuvant immunomodulatory agent aimed to preserve residual beta-cell function and improve glucose control in recent-onset T1D have yielded inconclusive results [112]. Several reasons may underlie the discrepancies in results observed across these studies, including the heterogeneity of study duration, vitamin D formulations (e.g., cholecalciferol, calcifediol, calcitriol, alfacalcidol) and vitamin D doses, timing and schedule of administration [112]. Thus, the heterogeneous study design across the studies limits, at least in part, the interpretation of these results. Moreover, most studies only assessed fasting C-peptide level as a marker of residual beta-cell function, without evaluating stimulated C-peptide. In addition, clinical outcomes were mostly evaluated solely in relation to the administered vitamin D dose, whereas serum 25(OH)D levels at baseline and/or during follow-up were not reported. Indeed, individual serum response to a given vitamin D dose is markedly variable and depends upon multiple factors, such as baseline vitamin D status, body fat percentage, seasonal variations, ethnicity, genetics (e.g., gene polymorphisms), use of certain medications and different types of vitamin D formulations [146,147]. This aspect is particularly relevant in the setting of autoimmune diseases. In fact, immunomodulatory effects of vitamin D may be achieved *in vivo* upon attainment of serum 25(OH)D concentrations above those required for bone health (e.g., 40–60 ng/mL vs. 30–40 ng/mL, respectively). It is also worth noting that achievement of serum 25(OH)D levels ≥ 40 ng/mL after vitamin D_3 supplementation (at a dose of up to 10,000 IU/day) has proven to be safe over a short-term period in otherwise healthy vitamin D-deficient subjects [148]. High dose vitamin D supplementation has also proven to be safe in long-term hospitalized patients [149]. Interestingly, a small study investigated the immunomodulatory effects of calcifediol administered for 12 months in children with new-onset T1D [150]. The study was designed to achieve and maintain serum 25(OH)D levels above 50 ng/mL during the follow-up period. Target serum 25(OH)D levels were safely reached and maintained. Peripheral blood mononuclear cell (PBMC) reactivity against GAD-65 and proinsulin decreased significantly upon 25(OH)D_3 replenishment, and this reduction was inversely correlated with serum 25(OH)D concentrations. Fasting C-peptide levels remained stable after one year of calcifediol administration [150].

On the other hand, only a few studies have investigated the role of vitamin D in LADA. Du et al. [151] found a higher surface expression of CD14 and Toll-like receptor 4 (TLR4) on monocytes collected from LADA patients, as compared to controls. The authors showed that calcitriol was able to modulate the increase in IL-1β and TNF-α production by monocytes in response to lipoteichoic acid and lipopolysaccharide [151]. A Swedish case-control study found that ≥ 1 serving per week consumption of fatty fish (a food source containing high amounts of vitamin D) may reduce the risk of LADA [152]. With regard to

intervention studies, Li et al. [68] showed that 12-month treatment with the vitamin D analog alfacalcidol (at a dose of 0.5 µg/day) in addition to insulin therapy resulted in a partial preservation of beta-cell function in patients with LADA. Notably, authors showed steady fasting and stimulated C-peptide levels in the alfacalcidol plus insulin group, whereas fasting C-peptide levels decreased in the insulin alone group during the 12-month intervention period. Moreover, LADA patients with a shorter duration of the disease (<1 year) exhibited a better response to alfacalcidol in terms of preservation of fasting- and stimulated C-peptide levels, as compared to patients who received insulin therapy alone [68]. Therefore, future prospective intervention studies investigating the efficacy of vitamin D supplementation as an adjuvant immunomodulatory strategy in patients with T1D and LADA are warranted.

6. DPP-4 and immune system

Dipeptidyl peptidase-4 (DPP-4) - a serine exopeptidase also known as cluster of differentiation 26 (CD26) - is a cell surface antigen (DPP-4/CD26) expressed ubiquitously in several cells and tissues including kidney, intestine, liver, lung, endothelia, pancreatic duct and islet cells, as well as in immune cells such as DCs, monocytes, macrophages, T cells, activated B cells and activated natural killer (NK) cells [153–155]. DPP-4/CD26 is a type II transmembrane, homodimeric glycoprotein anchored to the membrane by its signal peptide. However, CD26/DPP4 also exists in a soluble form, which still maintains its enzymatic activity and is thought to be released from the cell membrane into the bloodstream [153].

Upon activation, approximately 50% of human B cells express DPP-4/CD26, and selective suppression of DPP-4 activity reduces B-cell activation and DNA synthesis in a dose-dependent manner [153]. DPP-4/CD26 plays important co-stimulatory T-cell functions: it is expressed only on a fraction of resting T cells, whereas it becomes markedly upregulated upon T-cell activation [153]. As a lymphocyte cell surface protein, CD26 has three main functions, all of which can affect T-cell proliferation and chemotaxis, namely: (a) adenosine deaminase (ADA) binding, (b) peptidase activity, and (c) extracellular matrix binding [156].

Interaction of ADA-CD26 complexes on T-cell surface induces co-stimulatory effects on T-cell activation which are independent of dipeptidyl peptidase and deaminase activities [157]. This co-stimulatory signal results in a marked increase in the production of Th1 and pro-immflamatory cytokines IFN-γ, TNF-α and IL-6 [157]. Also, it has been demonstrated that caveolin-1 is a co-stimulatory ligand for CD26, and caveolin-1/CD26 interaction induces T-cell proliferation and nuclear factor kappa B (NF-kB) activation with subsequent co-stimulation of TCR/CD3 [158]. With regard to CD8+ T cells, CD26-mediated co-stimulation of CD8+ T cells appears to exert a cytotoxic effect mainly via granzyme B, TNF-α, IFN-γ and Fas ligand [159]. Moreover, CD26-costimulation pathways in CD8+ CD26^{high} T lymphocytes are mediated by EGR2 (early growth response 2) and IL-10, and are therefore distinct from those of CD8+ CD28^{high} T cells [160].

In addition, it has been shown that DPP-4/CD26 is a negative selection marker for human Tregs [161,162], while human Th17 cells exhibit high levels of enzymatically active DPP-4/CD26 [163]. Phenotypic analysis of human CD4+ T cells conducted by Bengsch et al. [163] showed that CD26 expression is highest on Th17 cells producing type 17 cytokines (e.g., IL-22, IL-17, TNF) compared to Th1, Th2, and Tregs. In particular, the lowest CD26 expression levels identified for IL-10-producing CD4+ T cells and CD25^{hi} CD127^{-} FOXP3^{+} regulatory T cells suggest suppressive effects exerted by CD26 on these cells [163]. Similar findings have recently been observed by Zhao et al. [164], who investigated the role of CD26 in T-cell differentiation *in vitro* by analyzing CD26 expression in different subsets of human peripheral blood T cells after solid-phase immobilized specific monoclonal anti-CD3 antibody stimulation. Authors found that the percentages of cells secreting Th1 cytokines (IL-2 and IFN-γ) and Th17 cytokines (IL-6, IL-17, and IL-22) or

expressing Th17 typical biomarkers (CD161, CD196, and IL-23 receptor) in the CD26^{high} group were substantially higher compared to the CD26^{low} group. Furthermore, fluorescence microscopy revealed a co-expression of CD26 with IL-2, IFN-γ, IL-17, IL-22, and IL-23R in lymphocytes [164]. These findings provide evidence that the high expression of CD26 is accompanied by the differentiation of T cells into Th1 and Th17 subsets, further indicating that CD26 plays a pivotal role in the regulation of immune responses.

CD26 binds to caveolin-1 on APCs and upregulates the co-stimulatory molecule CD86, resulting in the engagement with CD28 on T cells and subsequent antigen-specific T cell activation [165]. CD26 also acts as a binding protein for ADA, anchoring it to the cell surface and reducing the local concentrations of adenosine [166]. ADA is an enzyme which downregulates the biologic effects of adenosine in situ by catabolizing adenosine to its metabolite inosine. The surface-aligned CD26/ADA complex deaminates adenosine and prevents its binding to the adenosine receptor A2A on immune cells. As a result, effector T cells can escape from adenosine-mediated suppression, thus promoting inflammation [167]. Thus, blockade of surface-bound ADA activity favours exogenous adenosine access to A2A receptors on effector T cells and promotes adenosine-mediated suppression in these cells. As previously mentioned, CD26 expression is absent or negligible in Tregs; hence, Tregs cannot efficiently anchor ADA to their membranes, leading to reduced ADA activity and subsequent extracellular adenosine accumulation which ultimately results in suppressive effects on effector T cells.

In keeping with the aforementioned findings, our group previously demonstrated that the DPP-4 inhibitor sitagliptin exerts immunomodulatory properties in human lymphocytes through several mechanisms, including: i) dose-dependent inhibition of PBMC proliferation and decreased PBMC CD26 expression; ii) decreased production of IL-6 and IFN-γ; iii) reduction in the percentage of CD4^{+}/IL-17^{+} and CD4^{+}/IFN-γ^{+} T cells, and iv) increase in TGF-β1 concentrations [168]. Altogether, these findings suggest DPP-4 inhibition as a valuable therapeutic option in chronic inflammatory and autoimmune diseases.

7. Role of DPP-4 inhibitors in autoimmune diabetes: T1D and LADA

DPP-4 substrates are polypeptides with an alanine or a proline at the second position from the N-terminal side. DPP-4 cleaves off amino-terminal dipeptides from several substrate hormones, neuropeptides, chemokines and growth factors, thus influencing the biological activity of such molecules [153]. In this regard, DPP-4 was identified as a therapeutic target in T2D due its ability to cleave and inactivate the gut hormones (incretins) known as gastric inhibitory polypeptide (GIP, also referred to as glucose-dependent insulinotropic polypeptide) and glucagon-like peptide-1 (GLP-1), which are secreted by enteroendocrine K and L cells, respectively [153]. GIP and GLP-1 are secreted from gut enteroendocrine cells upon meal ingestion and promote insulin secretion in a glucose-dependent manner [169,170]. DPP-4 inhibition blocks incretin degradation and increase endogenous levels of incretins by prolonging their half-life, thus extending the insulinotropic effect of such hormones, lowering fasting and postprandial glucose concentration, suppressing glucagon secretion and reducing hepatic glucose production [171,172]. Recently, it has also been shown that DPP-4 inhibition can modulate insulin secretion via GLP-1-independent mechanisms, such as the regulation of intra-islet peptide YY (PYY) [173].

DPP-4 inhibitors (DPP-4i), also known as gliptins, have proven to be effective in enhancing endogenous insulin secretion and impoving glucose control in patients with T2D [172]. Since 2006, several DPP-4i have become available as oral antihyperglycemic agents for the treatment of T2D, including sitagliptin, vildagliptin, linagliptin, saxagliptin and alogliptin [172]. Pre-clinical evidence and experimental studies also suggest that DPP-4i can exert pleiotropic effects beyond their glucose-

lowering properties, conferring protection against cardiovascular disease and microvascular diabetes-related complications through both GLP-1-dependent and GLP-1-independent mechanisms [174,175]. In addition, several studies suggest that DPP-4i exert anti-inflammatory and immunomodulatory effects *in vitro* and *in vivo* [176–181]. In short-term randomized controlled trials conducted in patients with T2D, sitagliptin has been shown to increase the expression of IL-10 (an anti-inflammatory cytokine) and to reduce the expression of different markers of low-grade inflammation, pro-inflammatory cytokines and cell adhesion molecules, such as C-reactive protein, IL-6, IL-18, TNF-α, secreted phospholipase-A₂, serum amyloid A-LDL complex, soluble intercellular adhesion molecule-1 (sICAM-1) and E-selectin [176,177,181]. These effects may provide a further advantage in the prevention and management of diabetes-related proatherogenic comorbidities. Furthermore, a recent large retrospective cohort study involving more than 750,000 patients with T2D found that DPP-4i are associated with lower risk of autoimmune disorders, particularly for the younger patients and the lesser duration of diabetes diagnosed [182].

Given their anti-inflammatory/immunomodulatory properties and their ability to increase circulating levels of incretins, DPP-4i have the potential to exert multiple positive effects on pancreatic beta cells leading to the preservation of beta-cell mass and function, namely: i) improvement of glucose-stimulated insulin secretion (GSIS); ii) reduction of gluco-, lipo- and cytokine-toxicity; iii) stimulation of insulin gene expression and biosynthesis; iv) suppression of beta-cell apoptosis; and v) stimulation of beta-cell proliferation, survival and neogenesis from endocrine progenitor cells within islet and extra-islet pancreas tissue, as it has been demonstrated in animal models of diabetes and isolated human islets [176,178,183–188].

Therefore, the use of DPP-4i has been suggested as a valid treatment option in patients with autoimmune diabetes [189]. Animal studies conducted in NOD mice showed that DPP-4i were able to prevent or delay the onset of diabetes and even reverse the established disease after the onset of overt hyperglycemia by modulating the inflammatory and autoimmune responses against pancreatic beta cells and thereby protecting beta-cell mass [190–194]. In such animal models of autoimmune diabetes, DPP-4i: i) reduce insulitis, ii) stimulate beta-cell proliferation, iii) increase CD4+ CD25+ FOXP3+ regulatory T cells, and iv) reduce migration of splenic and lymph node CD4+ T-cells [190–194]. A recent animal study conducted in a streptozotocin-induced T1D experimental model demonstrated that treatment with sitagliptin was able to improve metabolic control, decrease pancreatic inflammatory profile and increase systemic regulatory T cell frequency [195].

Case reports and small pilot studies conducted in patients with autoimmune diabetes have found that DPP-4i, alone or in combination with other agents, significantly improved glucose control and reduced insulin requirements, with a favourable tolerability profile [189]. However, studies investigating the use of DPP-4i in T1D led to inconclusive results in terms of improvement of glucose control, reduction of daily insulin requirements, as well as preservation or increase of endogenous insulin production [189,196–199]. The inconsistent findings observed across studies may be explained by a number of factors, such as the small sample size and the heterogeneous diabetes duration at enrollment. For instance, the inclusion of T1D subjects with long-standing disease and only marginal residual beta-cell function may reduce the potential benefits of DPP-4 inhibition in this population. The 12-month randomized, placebo-controlled, phase 2 trial REPAIR-T1D showed lack of efficacy of combination therapy with sitagliptin plus the proton-pump inhibitor lansoprazole in preserving beta-cell function in patients with new-onset T1D [200]. These findings differ from those observed in NOD mice [201]. However, the use of a lower sitagliptin dose (50 mg/day) in patients younger than 18 years may have not been adequate to achieve the *in vivo* anti-inflammatory effects of sitagliptin. It is also worth noting that serum DPP-4 activity is higher in both children and adults with T1D compared to healthy controls [202–205] and subjects with T2D [205]. Duvnjak et al. [206] showed that LADA patients

exhibited a significantly higher serum DPP-4 activity compared to subjects with T1D and T2D. In the multinomial regression analysis, DPP-4 activity remained significantly associated with both LADA and T1D, whereas it did not show an association with T2D [206]. Interestingly, it has also been suggested that increased DPP-4 activity mediates the impairment in insulin sensitivity driven by TNF-α in T1D [207]. Additionally, patients with T1D using bolus rapid-acting insulin analogues exhibit lower postprandial GLP-1 levels following ingestion of test meal [208]. Altogether, these findings may partly explain the inability of several participants to achieve adequate GLP-1 levels in the REPAIR-T1D study [200]. In fact, authors found a slight trend towards C-peptide preservation in a subgroup who produced increased concentrations of GLP-1 and gastrin while receiving the treatment [200]. These findings appear to suggest that the dose of DPP-4i administered in clinical studies may significantly affect the study outcomes. In this regard, our group previously showed that sitagliptin-mediated inhibition of human PBMC proliferation is dose-dependent [168]. Of note, sitagliptin was able to modulate the differentiation of Th1 and Th17 cells into TGF-β1-producing regulatory cells and to markedly reduce the expression of IFN-γ, IL-6 and IL-17 [168]. Similar findings have also been observed in animal models of diabetes [194,209]. Thus, future studies investigating the role of DPP-4i in preserving beta-cell mass and function in new-onset T1D should consider the administered dose and the disease duration as factors able to significantly affect the study outcomes. Moreover, assessing serum DPP-4 activity and CD26 expression on lymphocytes may be useful in the attempt to establish a minimum DPP-4i dose able to effectively inhibit DPP-4 activity, increase GLP-1 levels and subsequently modulate innate and adaptive immune responses *in vivo*. It would also be worth taking into account potential differences existing between distinct DPP-4i molecules in terms of pharmacokinetics and anti-inflammatory/immunomodulatory actions. Although it has been demonstrated that different DPP-4i have a similar safety and efficacy profile as oral antihyperglycemic agents for the treatment of T2D [210], the existence of differential effects on immune system exerted by distinct DPP-4i cannot be excluded due to the peculiarity of each molecule in terms of pharmacokinetic and pharmacodynamic characteristics, binding modes of DPP4i in the active site of DPP-4 and ability to interfere with CD26 dimerization [211,212]. The use of DPP-4i as an adjuvant therapeutic strategy to preserve beta-cell function has also been investigated in patients with LADA. An open-label, randomized controlled study first showed that 12-month treatment with sitagliptin (at a dose of 100 mg/day) in addition to insulin preserved C-peptide secretion better than insulin alone in patients with recent-onset LADA (duration of diabetes ≤ 3 years) [213]. Another open-label, prospective, randomized controlled trial conducted in patients with LADA in the stage of non-insulin-dependency suggested that sitagliptin (at a dose of 50 mg/day, titrated up to 100 mg/day to achieve the established target for glucose control) may be more effective in preserving beta-cell function compared to insulin therapy for at least 4 years [214]. A recent 24-month randomized controlled trial conducted in LADA patients (with a disease duration of ≤ 3 years) demonstrated that sitagliptin (at a dose of 100 mg/day) in addition to insulin led to significantly higher changes in the updated homeostatic model assessment of beta-cell function (HOMA2-B) from baseline, and significantly improved the first-phase insulin secretion (during the hyperglycemic clamp test) and insulin sensitivity (during the hyperinsulinemic euglycemic clamp test) as compared to insulin intervention alone [215]. A 1-year open-label randomized controlled trial conducted in LADA patients also found that sitagliptin (100 mg/day) in addition to insulin ameliorated glucose control and altered the phenotype of T cells by increasing the percentage of protective Th2 cells and reducing the percentage of pathogenic Th17 cells [216]. However, a 21-month randomized trial conducted in LADA patients with < 3 years of known diabetes found that sitagliptin (at a dose of 100 mg/day) did not lead to significant differences in beta-cell function as compared to insulin therapy [217]. An exploratory analysis of a 2-year double-blind, randomized controlled study conducted in

patients diagnosed with T2D and HbA1c values of 6.5%-10% while on metformin (who were randomized to additional once-daily linagliptin 5 mg or glimepiride 1–4 mg) suggested that linagliptin may attenuate the rate of decline in C-peptide levels among patients with LADA [69]. A post hoc analysis of data pooled from five randomized, placebo-controlled studies found that saxagliptin was effective in reducing blood glucose levels and appeared to improve beta-cell function in GADA-positive patients [218]. In a recent consensus statement from an international expert panel providing recommendations for the management of patients with LADA, DPP-4i have been suggested as oral antihyperglycemic agents able to improve glucose control and potentially preserve residual insulin secretory capacity in this population, although larger randomized studies are warranted to draw definitive conclusions in this direction [29].

8. VIDPP-4i combination therapy for treatment of autoimmune diabetes

In light of the aforementioned findings and evidence deriving from studies conducted in other clinical settings [219,220], vitamin D and DPP-4i may exert synergistic effects on immune system by virtue of their anti-inflammatory and immunomodulatory properties. When vitamin D and DPP-4i are administered together, such combination therapy may exert anti-inflammatory and immunomodulatory actions to a greater extent than vitamin D or DPP-4i administered alone. Emerging evidence suggests that combination therapy with vitamin D plus DPP-4i (VIDPP-4i) has the potential ability to preserve beta-cell function in autoimmune diabetes [64]. Herein, we discuss the current evidence for the existence of synergistic effects of vitamin D and DPP-4i and the consequential implications for the treatment of autoimmune diabetes.

8.1. Synergistic anti-inflammatory and immunomodulatory effects of vitamin D and DPP-4 inhibitors: Mechanistic evidence

Evidence for synergistic anti-inflammatory and immunomodulatory effects of vitamin D and DPP-4i primarily comes from recent studies conducted in patients with T2D. A study conducted by Mahabadi-Ashtiyani et al. [221] on PBMCs collected from T2D patients and healthy controls revealed that the addition to the culture of sitagliptin plus vitamin D_3 was more effective in reducing IL-6 and TNF-α production in both patients and controls, as compared to cultures treated with sitagliptin or vitamin D_3 alone. The same group recently demonstrated the *in vitro* ability of sitagliptin and vitamin D_3 to effectively suppress the increased T helper cell proliferation and inflammatory responses in patients with T2D [222]. Of note, the addition of sitagliptin or vitamin D_3 to the cultures led to decreased proliferation of CD4+ T cells and non-CD4+ cells isolated from both T2D patients and healthy controls. Sitagliptin in combination with vitamin D_3 was also more effective in suppressing cell proliferation, decreasing IL-17 production and enhancing the expression of the anti-inflammatory cytokine IL-37 by PBMCs [222].

In a study conducted in 54 nephropathic and 57 non-nephropathic T2D patients, Telikani et al. [223] demonstrated that, as compared to healthy control, the production of IFN-γ and IL-17 was increased and FOXP3 expression was decreased in T2D subjects who did not receive sitagliptin and vitamin D_3. On the other hand, VIDPP-4i (vitamin D_3 1000 IU/day plus sitagliptin 100 mg/day) was associated with decreased IFN-γ, IL-17 and IL-21 production, downregulated expression of RORγt (a marker for Th17 cells) and BCL6 (a marker for T follicular helper cells), along with upregulated expression of IL-37 and FOXP3, which are well-known markers for Tregs [223]. Similar results have been observed in another study from the same group, showing that treatment with sitagliptin plus vitamin D_3 reduced the levels of IFN-γ and IL-17 in both non-nephropathic and nephropathic T2D patients compared to untreated patients [224]. IL-37 levels were enhanced in patients treated with sitagliptin or sitagliptin plus vitamin D_3 compared

to untreated patients. Moreover, treatment with sitagliptin plus vitamin D_3 increased IL-4 levels in non-nephropathic T2D patients. Overall, these findings suggest that treatment with sitagliptin plus vitamin D_3 is more effective in reducing the upregulation of the pro-inflammatory cytokines IFN-γ and IL-17 in patients with T2D [224]. According to the synergistic anti-inflammatory actions of vitamin D and DPP-4i, a recent study conducted in a rat model of fructose/salt-induced insulin resistance showed superadditive renoprotective effects evoked by the combined use of vitamin D_3 and vildagliptin, which reversed hyperuricemia and exerted a plethora of renal anti-inflammatory, antioxidant, anti-apoptotic and anti-fibrotic effects [225].

Interestingly, studies conducted in transplant setting shed light on the rationale for combined use of vitamin D and DPP-4i. Vitamin D deficiency is highly prevalent following solid organ transplantation [226]. Pre-clinical studies showed that vitamin D and its analogs have beneficial effects in terms of islet graft survival and prevention of allograft rejection and recurrence of autoimmunity in animal models of syngeneic and allogeneic islet transplantation [227]. Therefore, vitamin D supplementation has been suggested as a valid therapeutic strategy to reduce opportunistic infections and prevent allograft rejection after solid organ and cell transplantation [226,227]. In this regard, Zhou et al. [228] found that vitamin D deficiency represents an independent risk factor for acute cellular rejection after liver transplantation. Accordingly, the incidence of acute cellular rejection and bacterial and fungal infections was reduced in patients receiving vitamin D supplementation. Moreover, vitamin D supplementation was associated with increased numbers of Tregs and decreased numbers of T naïve cells and CD8+ CD28+ T cells, suggesting that vitamin D may favour immune tolerance towards the liver allografts [228].

Likewise, DPP-4 inhibition before and after islet transplantation decreased the effect of beta-cell autoimmunity and led to prolongation of islet graft survival in NOD mice, partially by reducing the homing of CD4+ T-cells into pancreatic beta cells [191]. DPP-4 inhibition has recently been suggested as a potential strategy to prevent chronic allograft dysfunction following solid organ transplantation (such as lung transplantation) by inducing an anti-inflammatory cytokine profile [229]. Also, a recent study demonstrated that treatment with a murine anti-CD26 monoclonal antibody (begelomab) induced over 60% responses in steroid refractory acute graft-versus-host disease (SR-aGVHD), thus suggesting a role of CD26+ T cells in tissue damage in the context of GVHD [230]. Accordingly, a recent phase 2 clinical trial showed that sitagliptin (administered orally at a dose of 600 mg every 12 h starting the day before transplantation until day 14 after transplantation) in addition to a standard immunosuppressive regimen of sirolimus and tacrolimus resulted in a markedly low incidence of grade II to IV acute GVHD by day 100 after myeloablative allogeneic hematopoietic stem-cell transplantation [231,232].

Overall, these findings suggest that the combined use of vitamin D and DPP-4 inhibition (through the use of gliptins or anti-CD26 monoclonal antibodies) may represent a valuable therapeutic option worth being investigated in future studies involving transplant recipients. In fact, VIDPP-4i may modulate T-cell differentiation and promote immune tolerance by selectively inhibiting effector T cells and upregulating Tregs, potentially allowing for reduction of immunosuppressant dose and immunosuppression-related toxicity. In this context, the use of DPP-4i may also be advantageous in terms of reduced glucotoxicity and preservation of beta-cell function among patients with T1D who underwent kidney, pancreas or islet transplantation, and patients with post-transplant diabetes [233].

Finally, current mechanistic evidence suggests that vitamin D and DPP-4i exert synergistic anti-inflammatory and immunomodulatory effects on immune system via shared signaling pathways, which result in: i) reduced antigen presentation ability and T-cell stimulatory capacity by APCs; ii) reduced differentiation and activation of Th1 and Th17 cells; iii) enhanced differentiation of Th2 cells and Tregs; iv) reduced differentiation of CD8+ T cells; v) decreased expression of pro-

inflammatory cytokines, such as IFN-γ, TNF-α, IL-6 and IL-17; vi) increased expression of anti-inflammatory cytokines, such as TGF-β1, IL-4, IL-5, and IL-37; vii) decreased activation of B cells and reduced islet autoantibody titres. Fig. 1 illustrates the mechanisms underlying the synergistic anti-inflammatory and immunomodulatory effects exerted by vitamin D and DPP-4i, as well as their protective effects on pancreatic islets and beta cells.

8.2. VIDPP-4i as an immunomodulation therapy for autoimmune diabetes: Clinical evidence

Case reports and pilot studies conducted in patients with autoimmune diabetes showed potential protective effects of VIDPP-4i on beta-cell function (Table 1). We first reported a markedly prolonged clinical remission phase (up to 4 years), accompanied by decreased GADA titres and preserved beta-cell function in two T1D patients who received VIDPP-4i with sitagliptin 100 mg/day plus vitamin D_3 5000 IU/day

[59]. In a subsequent study involving a larger sample size (n = 34; 17 T1D patients and 17 controls), we showed that the same VIDPP-4i regimen in addition to insulin therapy was associated with a prolonged clinical remission phase (from 1 to 5 years; mean: 27.1 ± 18.9 months), accompanied by a significant reduction in CD8+ CD26+ T cell count compared to T1D patients treated with insulin alone [64,234]. In a study conducted on a cohort of 19 patients with new-onset T1D, we recently showed that this combination therapy was associated with residual beta-cell function and a median remission phase (as assessed by an IDAA1c value of ≤ 9) of 10 months (ranging from 6 to 87 months) [65].

Similar findings have been observed in patients with LADA. Of note, Rapti et al. [67] first reported the case of a 31-year-old patient with LADA who received VIDPP-4i with sitagliptin 100 mg/day plus vitamin D_3 2000 IU/day (in addition to metformin) shortly after the onset of the disease. The patient maintained insulin independence and exhibited normalization of GADA titre levels and HbA1c values over a 2-year
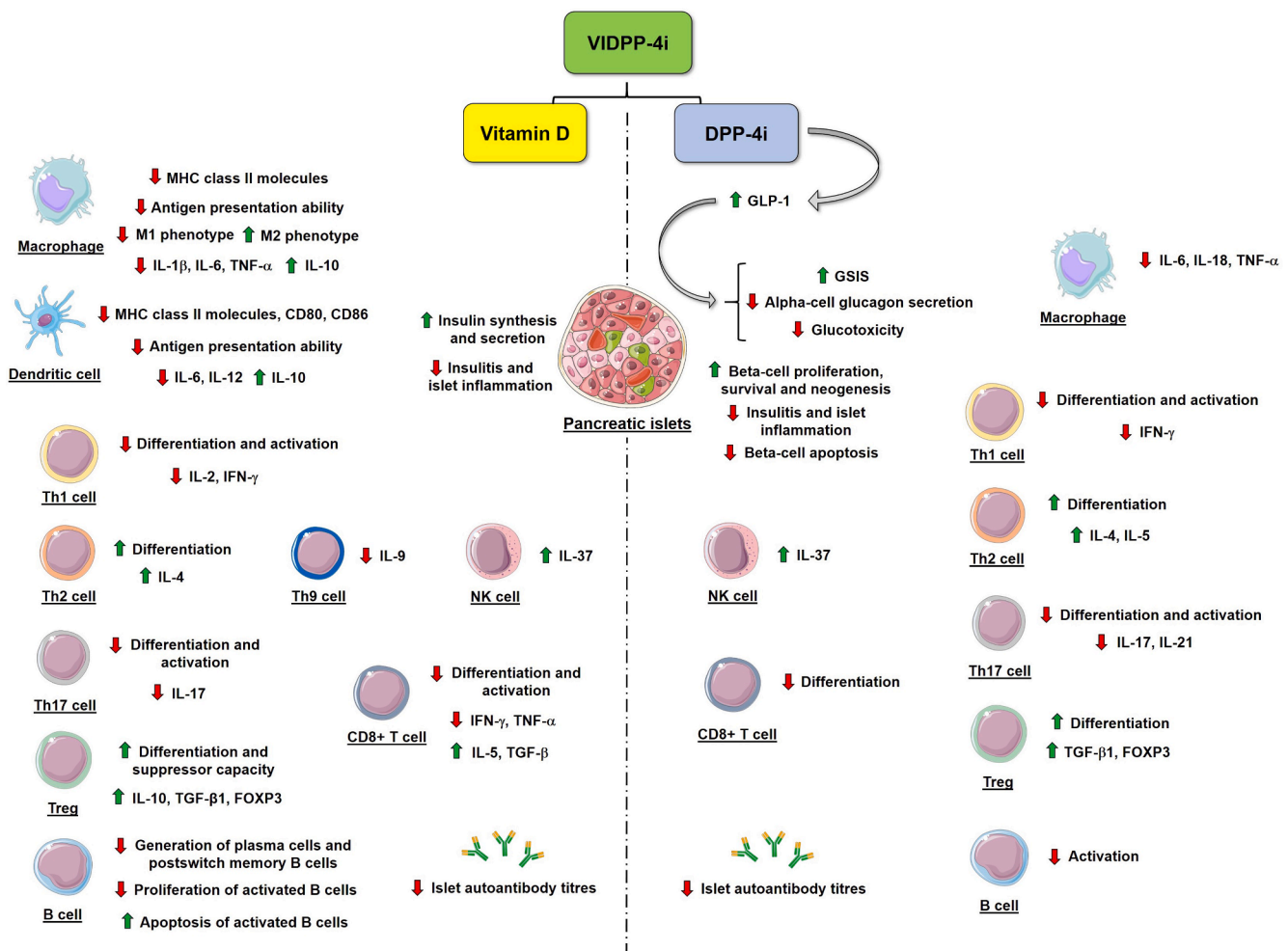

Fig. 1. Mechanisms underlying the synergistic anti-inflammatory and immunomodulatory effects of vitamin D and DPP-4 inhibitors in autoimmune diabetes. Studies conducted *in vitro* and in animal models of autoimmune diabetes showed that vitamin D and DPP-4 inhibitors promote the activation of anti-inflammatory and immunomodulatory pathways, resulting in protective effects on pancreatic islets and beta cells. Notably, vitamin D and DPP-4 inhibitors (VIDPP-4i) exert synergistic effects on innate and adaptive immune system via shared signaling pathways, which primarily result in: i) reduced antigen presentation ability and T-cell stimulatory capacity by antigen-presenting cells; ii) reduced differentiation and activation of Th1 and Th17 cells; iii) enhanced differentiation of Th2 cells and Tregs; iv) reduced differentiation of CD8+ T cells; v) decreased expression of pro-inflammatory cytokines, such as IFN-γ, TNF-α, IL-6, IL-17; vi) increased expression of anti-inflammatory cytokines, such as TGF-β1, IL-4, IL-5, and IL-37; vii) decreased activation of B cells and reduced islet autoantibody titres. In addition, DPP-4 inhibitors exert well-known GLP-1-mediated protective effects on beta cells, by promoting glucose-stimulated insulin secretion, suppressing glucagon secretion and reducing glucotoxicity. The term vitamin D refers to the active metabolite calcitriol. Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; GSIS, glucose-stimulated insulin secretion; IFN-γ, interferon-gamma; IL, interleukin; MHC, major histocompatibility complex; NK cell, natural killer cell; TGF-β1, transforming growth factor beta 1; Th, T helper cell; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell; VIDPP-4i: combination therapy with vitamin D and DPP-4 inhibitors.

Table 1
Summary of the main studies on the use of combination therapy with vitamin D and DPP-4 inhibitors (VIDPP-4i) in patients with autoimmune diabetes (T1D and LADA).

Study Design	Study Population	Study Treatment	Main Findings	References
Case series	N = 2 young adults with T1D Patient #1: 20-year-old woman Patient #2: 21-year-old woman T1D duration at VIDPP-4i initiation: patient#1, 1 month; patient #2, 10 months.	Sitagliptin 100 mg/day plus vitamin D_3 5000 IU/day, with or without insulin	Both patients experienced clinical remission of T1D, as evidenced by a daily insulin requirement of < 0.5 IU/kg/day, HbA1c values below 6% and fasting C-peptide levels above 0.90 ng/mL. Both patients showed an early and significant decrease in GADA titres, which remained below the baseline levels throughout a 48-month follow-up period. Patient #1: complete clinical remission (without need for insulin therapy) maintained during a 4-year follow-up period. Patient #2: partial clinical remission maintained during a 4-year follow-up period. Both patients maintained normal serum levels of calcium and 25(OH)D. No side effects related to VIDPP-4i have been reported.	Pinheiro et al. (2016) [Ref. [59]]
Cross-sectional study	N = 17 children and adults with T1D (receiving insulin in combination with sitagliptin and/or vitamin D_3) vs. 17 controls	10 T1D subjects (age range: 16–43 years, 7F/3M) were treated with insulin alone; 5 T1D subjects (age range: 20–47 years, 3F/2M) were treated with insulin and sitagliptin 100 mg/day plus vitamin D_3 5000 IU/day; 2 subjects with new-onset T1D (13 and 15 years, 1F/1M) were treated with sitagliptin 100 mg/day and vitamin D_3 5000 IU/day. Eight healthy donors (age range: 19–34 years, 6F/2M) and 9 women (age range: 15–39 years) with Hashimoto's thyroiditis served as control group.	VIDPP-4i regimen in addition to insulin therapy was associated with a prolonged clinical remission phase (from 1 to 5 years; mean 27.1 ± 18.9 months), accompanied by a significant reduction in CD8+ CD26+ T cell count compared to T1D patients treated with insulin alone (p-value = 0.022). No side effects related to VIDPP-4i were reported.	Pinheiro et al. (2017); Pinheiro et al. (2018) [Ref. [234,64]]
Case series	N = 19 children and adults (7F/12 M; median age 15 years [6–39]) with new-onset T1D	Sitagliptin 100 mg/day plus vitamin D_3 5000 IU/day (in addition to insulin therapy)	The use of VIDPP-4i was associated with residual beta-cell function, along with a median remission phase (as assessed by an IDAA1c value of ≤ 9) of 10 months (ranging from 6 to 87 months). Mean fasting C-peptide levels at baseline were 0.86 ± 0.47 ng/mL, whereas last follow-up mean C-peptide levels were 0.89 ± 0.57 ng/mL. No side effects related to VIDPP-4i were reported.	Pinheiro et al. (ATTD 2020 Invited Speaker Abstracts, 2020) [Ref. [65]]
Case report	31-year-old Caucasian male with LADA	Sitagliptin 100 mg/day plus vitamin D_3 2000 IU/day administered in addition to metformin (1700 mg/day) shortly after the onset of the disease	2 years after the diagnosis of LADA, the patient showed normalization of HbA1c values (5.2% vs 9.6%), as well as negativization of GADA titres (4.1 U/mL vs 32 U/mL; normal values < 5 U/mL). VIDPP-4i was well tolerated.	Rapti et al. (2016) [Ref. [67]]

Table 1 (*continued*)

Study Design	Study Population	Study Treatment	Main Findings	References
Multicenter, randomized-controlled study	N = 60 patients with LADA Age: between 18 and 70 years Duration of diabetes: <4 years	Participants were randomized to receive for 12 months: conventional therapy with metformin (1–1.7 g/day) and/or insulin treatment (group A, n = 21); saxagliptin (5 mg/day) plus conventional therapy (group B, n = 20); or vitamin D_3 (2000 IU/day) plus saxagliptin and conventional therapy (group C, n = 19).	During the 12 month-follow-up period, the levels of fasting C-peptide, 2-hour postprandial C-peptide and C-peptide index were maintained in group C. In group B, fasting C-peptide levels at 12 months were significantly lower than those at baseline (p-value = 0.005), whereas no significant differences in postprandial C-peptide index levels were found during treatment. In group A, fasting C-peptide index levels were significantly reduced at 12 months compared to baseline (p-value = 0.022), while they showed no significant differences in either group B or group C at 6 months and 12 months. The levels of postprandial C-peptide index decreased continually from 95.64 ± 72.21 pmol/L to 82.75 ± 74.03 pmol/L at 6 months (p-value = 0.161) and 74.20 ± 56.84 pmol/L (p-value = 0.049) at 12 months in group A. In contrast, postprandial C-peptide index levels in group C continued to increase from 91.31 ± 63.21 pmol/L to 116.28 ± 97.09 pmol/L (p-value = 0.087) at 6 months and 118.14 ± 108.07 pmol/L (p-value = 0.213) at 12 months. The levels of GADA titres in group C significantly decreased compared to those at baseline (p-value < 0.05), but no significant differences in levels of GADA titres were observed in group A and group B. No significant differences were observed among the three groups in levels of fasting C-peptide, postprandial C-peptide, C-peptide index or GADA titres. Insulin dose was significantly higher in group C than in group A or group B at baseline; however, the insulin dose showed no significant differences at 6- or 12-month follow-up. Insulin, metformin, saxagliptin and vitamin D_3 were well tolerated. No severe hypercalciuria or hypercalcemia was observed in group C, and no severe hypoglycemic episodes, liver or renal dysfunction or other side effects were reported in any group.	Zhang et al. (2020) [Ref. [66]]

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; F, females; GADA, glutamic acid decarboxylase autoantibodies; HbA1c, glycated hemoglobin; IDAA1c, insulin-dose adjusted A1c; LADA, latent autoimmune diabetes in adults; M, males; T1D, type 1 diabetes; VIDPP-4i, combination therapy with vitamin D and DPP-4 inhibitors.

follow-up period [67]. Recently, Zhang et al. [66] conducted a 12-month multicenter, randomized controlled study in 60 LADA patients (disease duration < 4 years) to explore the protective effects on beta-cell function of VIDPP-4i with vitamin D_3 and saxagliptin in addition to conventional therapy with metformin and/or insulin. Participants were randomized to receive: i) conventional therapy with metformin (1–1.7 g/day) and/or insulin treatment; ii) saxagliptin (5 mg/day) plus conventional therapy; or iii) vitamin D_3 (2000 IU/day) plus saxagliptin and conventional therapy for 12 months. In participants who received VIDPP-4i, levels of fasting C-peptide and fasting C-peptide index (CPI, calculated as the ratio of serum C-peptide to plasma glucose) were not significantly different at 12 months compared to those at baseline, whereas postprandial C-peptide index levels increased (although not significantly) during the follow-up period. However, insulin dose showed no significant differences at 6 and 12 months. On the other hand, postprandial C-peptide index levels declined significantly at 12 months in participants who received conventional therapy alone. Even more surprisingly, participants who received saxagliptin in addition to conventional therapy without vitamin D_3 exhibited significantly decreased fasting C-peptide levels at 12 months compared to those at baseline [66]. Additionally, patients on VIDPP-4i showed a significant reduction in the GADA titre levels at 12 months compared to those at baseline, whereas no significant changes in GADA titres were reported in the other two groups after 12 months of treatment. VIDPP-4i was safe and well tolerated, with no side effects reported throughout the follow-up period [66]. These findings seem to suggest that saxagliptin alone cannot fully reverse glucotoxicity and/or exert anti-inflammatory and immunomodulatory effects to preserve and maintain beta-cell function in autoimmune diabetes. By contrast, adding vitamin D_3 to saxagliptin might have the potential to better protect beta-cell function, as a likely consequence of the synergistic effects exerted by vitamin D and DPP-4i on immune system and inflammatory pathways.

9. Discussion and conclusion

Over the last years, several studies showed that vitamin D and DPP-4i can exert pleiotropic actions beyond their well-established role in the regulation of bone and glucose homeostatis, respectively. Emerging preclinical evidence supports the existence of synergistic anti-inflammatory and immunomodulatory properties of vitamin D and DPP-4i, which result in the reduction of pro-inflammatory and autoimmune responses against pancreatic beta cells in animal models of autoimmune diabetes. Preliminary findings also suggest that VIDPP-4i therapy has the potential ability to preserve beta-cell function in patients with autoimmune diabetes, including T1D and LADA.

To date, immunotherapies have mostly showed no effect or only a transient beneficial effect in reducing the decline in beta-cell function that occurs over time in autoimmune diabetes. Therefore, the use of immunotherapeutic agents in a combination therapy appears to be a valid approach to obtain better results in terms of preservation of beta-cell mass and function. In particular, targeting multiple pathways involved in beta-cell loss and dysfunction (e.g. innate immunity, adaptive immunity, regulatory immunity, glucotoxicity) may represent a successful immune intervention for autoimmune diabetes. In this context, combination therapy with vitamin D and DPP-4i may be an attractive choice in the treatment of T1D, LADA, other forms of autoimmune diabetes or other autoimmune diseases. Indeed, vitamin D and DPP-4i co-administration may substantially enhance the efficacy of each of these compounds as immunomodulatory agents compared to their use as monotherapy (vitamin D alone or DPP-4i alone). Vitamin D may promote anti-inflammatory responses, exert immunomodulatory effects, induce immune tolerance and potentially stimulate insulin synthesis and secretion. On the other hand, DPP-4i have been shown to exert similar actions on innate and adaptive immune system. Moreover, DPP-4i are known to effectively improve glucose control and reduce glucotoxicity by suppressing glucagon secretion and promoting GSIS through GLP-1-

dependent and GLP-1-independent mechanisms. Also, the use of vitamin D and DPP-4i has proven to be safe in the context of diabetes (including autoimmune diabetes) and both these agents are relatively inexpensive.

In conclusion, large-scale, long-term, prospective randomized controlled trials are therefore required to confirm the aforementioned preliminary findings and determine the ability of VIDPP-4i to counteract beta-cell autoimmunity, improve glucose control, preserve beta-cell mass and function, prolong clinical remission phase, sustain insulin independence stage, and slow down or delay the progression of autoimmune diabetes. Randomized controlled trials are particularly warranted in the context of LADA, given the scarcity of studies investigating the efficacy of immune interventions in this population [29]. As a matter of fact, LADA represents an ideal model for exploring the combined effects of vitamin D and DPP-4i on autoimmunity and beta-cell function, because this disease is typically associated with a slower and less severe immune-mediated beta-cell destruction compared to T1D. Therefore, LADA offers a wider window to test immune interventions that may slow down beta-cell failure.

Additionally, it would be interesting to investigate the use of VIDPP-4i as an immune intervention aimed to prevent the onset of clinical diabetes in subjects with genetic susceptibility to T1D or during the pre-symptomatic stages of the disease. Likewise, the use of VIDPP-4i may also be investigated in the context of solid organ or cell transplantation, particularly in T1D subjects who received kidney, pancreas or islet transplantation, in order to assess whether this combination therapy is able to reduce immunosuppressant dose and immunosuppression-related toxicity, reduce glucotoxicity, improve glucose control and prolong allograft survival or prevent graft dysfunction. However, several aspects still remain to be addressed, such as: i) the identification of optimal doses and target circulating levels of vitamin D and DPP-4i required to achieve and maintain the anti-inflammatory and immunomodulatory effects of such molecules *in vivo*; and ii) the interindividual heterogeneity of response to vitamin D and DPP-4i, which can be related to a number of factors (e.g., genetic or environmental factors). Future mechanistic studies and clinical trials will certainly help to answer these questions.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationship that could have influenced the work reported in this paper.

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