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REVIEW

Emerging Roles of Dipeptidyl Peptidase-4 Inhibitors in Delaying the Progression of Type 1 Diabetes Mellitus

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Abstract: Type 1 diabetes mellitus (T1DM) results from the immune cell-mediated destruction of functional pancreatic β-cells. In the presymptomatic period, T1DM is characterized by the presence of two or more autoantibodies against the islet cells in patients without glycemic decompensation. Therapeutic strategies that can modify the autoimmune process could slow the progression of T1DM. Dipeptidyl peptidase-4 (DPP-4) or CD26, a multifunctional serine protease with a dual function (regulatory protease and binding protein), can modulate inflammation and immune cell-mediated β-cell destruction. CD26 is involved in T-cell co-stimulation, migration, memory development, thymic maturation, and emigration patterns. DPP-4 degrades the peptide hormones GLP-1 and GIP. In addition to regulating glucose metabolism, DPP-4 exerts anti-apoptotic, regenerative, and proliferative effects to promote β-cell mass expansion. GLP-1 receptor signaling may regulate murine lymphocyte proliferation and maintenance of peripheral regulatory T-cells. In patients with T1DM, the serum DPP-4 activity is upregulated. Several studies have suggested that the upregulated DPP-4 activity is correlated with T1DM pathophysiology. DPP-4, which is preferentially expressed on the Th1 surface, can promote the polarization of Th1 immunity, a prerequisite for T1DM development. CD26 inhibition can suppress T-cell proliferation and Th1 cytokine production and stimulate tumor growth factor beta-1 (TGF-β1) secretion, which plays an important role in the regulation of autoimmunity in T1DM. Studies on humans or animal models of T1DM have suggested that DPP-4 inhibitors can improve β-cell function and attenuate autoimmunity in addition to decreasing insulin dependence. This review summarizes the emerging roles of DPP-4 inhibitors in potentially delaying the progression of T1DM.

Keywords: CD26, type 1 diabetes mellitus, autoimmunity, autoantibodies, therapeutic targets, prevention

Introduction

Type 1 diabetes mellitus (T1DM), a chronic disease, results from the immune-mediated destruction of functional pancreatic β-cell mass.[1] Insulitis is characterized by an inflammatory response that mainly involves CD8+ T-cells, CD68+ macrophages, CD4+ T-cells, CD20+ B lymphocytes, and CD138 plasma cells. The imbalance among the effector regulatory T-cells contributes to the development of insulitis.[2] Consequently, insulitis leads to the enhanced production of cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNFα) along with the activation of innate immunity and the secretion of other inflammatory factors, such as interleukin 1 beta (IL-1β), induce β-cell death.[3]

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Insulitis was first reported in the 1960s.[4] The correlation of T-cell abnormalities and some human leukocyte antigen alleles with juvenile-onset diabetes was identified in the 1970s. This led to the hypothesis that autoimmunity is the pathophysiological mechanism underlying the development of diabetes in a subgroup of patients.[5]

The identification of islet cell antibody (ICA) provided the first evidence for this hypothesis.[6,7] Subsequently, the concept of a "prediabetic" stage was proposed according to which the production of antibodies precedes the onset of diabetes by several years.[8,9] Various islet autoantibodies, such as insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA) and islet autoantigens, such as tyrosine phosphatase-like insulinoma antigen (IA-2), and zinc transporter 8 (ZnT8) increase the risk of developing clinical type 1 diabetes. Previous studies have reported that most children with multiple islet autoantibodies develop clinical diabetes.[10,11]

The measurement of islet autoantibodies has enabled the prediction of T1DM risk. Clinical trials on the individuals in the prediabetic stage have enabled the identification and quantification of the risk of developing symptoms and the characterization of T1DM into well-defined stages.[12] Stage 1, a presymptomatic stage, is defined as autoimmunity against β-cells (two or more islet autoantibodies) with normoglycemia. The 5-year and 10-year risks of developing the symptomatic disease are approximately 44% and 70% in these patients, respectively.[13] Stage 2 is a presymptomatic stage that is characterized by autoimmunity against β-cells and dysglycemia. The 5-year risk of developing the symptomatic disease at this stage is approximately 75%, while the lifetime risk approaches 100%.[14] Stage 3 is the onset of symptomatic disease.[12]

Recent findings on the cellular and molecular basis of immune-mediated diabetes progression and the characterization of T1DM stages have increased the number of trials that aim to intervene in the early stages of T1DM to prevent or delay progression to the symptomatic stage.[15,16] Additionally, various therapeutic interventions that can potentially modulate the autoimmune process in T1DM have been examined. Dipeptidyl peptidase-4 (DPP-4 or CD26) inhibitors (iDPP-4s), which are widely used to treat patients with type 2 diabetes mellitus (T2DM), are a potential therapeutic for T1DM. In addition to down-regulating the degradation of incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP),[17] DPP-4 is reported to modulate inflammation and immune-mediated β-cell destruction.[18,19] CD26 plays a central role in T-cell co-stimulation, migration, memory development, thymic maturation, and emigration patterns.[20]

T1DM, which is a progressive disease with a high incidence, is associated with high morbidity and mortality. However, the current therapeutic modality for T1DM, which lacks a curative therapy, is the administration of exogenous insulin. Various studies have demonstrated that the strategies to optimally manage diabetes, such as glycemic adjustment, adequate nutrition, and adherence to physical activity have a limited patient compliance.[21,22]

The use of drugs with the potential to prolong the presymptomatic period can reduce the long-term impact of T1DM. iDPP-4s are reported to exert immunomodulatory effects and can potentially delay the progression of T1DM. Thus, there is a need to evaluate the ability of iDPP-4s to prevent, delay, or cure T1DM.

Immunomodulatory Effect of DPP-4 (CD26) in T1DM

Type II transmembrane glycoprotein CD26 or DPP-4 is a multifunctional serine protease that functions as a regulatory protease and a binding protein. DPP-4 is involved in the metabolism of peptide hormones and T-cell immune responses and T-cell activation and proliferation. Both soluble (DPP-4) and membrane-bound forms (CD26) are active in the dimer form.[23,24]

DPP-4 is a member of the prolyl oligopeptidase family, which comprises atypical serine proteinases that can hydrolyze the prolyl bond.[25,26] The levels of DPP-4 are high in the seminal fluid, moderate in the plasma, and low in the cerebrospinal fluid.[27] DPP-4 cleaves X-proline or X-alanine dipeptides from the N-terminus of polypeptides and consequently inactivates several chemokines, growth factors, neuropeptides, and peptide hormones.[23,28]

The peptide hormones GLP-1 and GIP contain an alanine at position 2, which is a substrate for DPP-4-mediated degradation.[29] GLP-1 and GIP, which are secreted from the intestine after ingestion of meals, are involved in glucose metabolism. Incretin hormones promote glucose-dependent insulin secretion from the pancreatic β-cells and suppress excessive glucagon secretion from the α-cells. Additionally, animal and in vitro studies have revealed that GLP-1 and GIP exert anti-apoptotic, regenerative, and proliferative effects to promote β-cell mass expansion.[30] Hadjiyanni et al demonstrated that GLP-1 receptor (GLP-1R) signaling may regulate murine

lymphocyte proliferation and maintain the pool of peripheral regulatory T-cells.[31] The inhibition of DPP-4 activity can downregulate the degradation of GLP-1 and GIP and consequently enhance their therapeutic efficacy.[32]

The enhanced activity of DPP-4 did not result in systemic immune activation. However, enhanced DPP-4 activity was associated with hepatic T-cell activation under various clinical conditions, such as patients with human immunodeficiency virus and hepatitis C virus co-infections exhibiting hepatotoxicity after highly active antiretroviral therapy.[33] Previous studies have reported that the serum DPP-4 levels were upregulated in some autoimmune diseases, such as Graves' disease, Hashimoto thyroiditis, multiple sclerosis, and primary biliary cholangitis. In contrast, the serum DPP-4 levels were downregulated in systemic lupus erythematosus and anti-neutrophil cytoplasmic antibody-associated vasculitis.[34,35]

One study evaluated the serum DPP-4 activity in 48 patients with T1DM (mean T1DM duration: 13.4 ± 9.76 years) and 50 healthy individuals. The fasting serum DPP-4 activity was upregulated in patients with T1DM independent of the presence of the ICA and GADA.[36] Another study involving 76 young Japanese patients with T1DM and 22 healthy volunteers demonstrated that the serum DPP-4 activity was significantly upregulated in patients with T1DM.[37] Iwabuchi et al examining 43 Japanese children with T1DM and 26 age- and sex-matched healthy volunteers also reported that DPP-4 activity was significantly upregulated in the T1DM group without correlation with glycated hemoglobin (HbA1c), blood glucose, GADA status, or diabetes duration, but with an inverse correlation with insulin sensitivity.[38]

Duvnjak et al compared the serum DPP-4 activity within 19 latent autoimmune diabetes of the adult (LADA), 21 T1DM, 26 T2DM and 13 healthy controls patients, demonstrating that individuals with LADA express higher DPP-4 activity than the ones with T1DM and T2DM (mean duration of diabetes 20.3 ± 11.3 years for 3 groups).[39] Once the strong correlation among serum DPP-4 activity, anthropometric parameters and insulin resistance (IR) has been showed,[36,38] the higher DPP-4 activity in LADA patients could be justified by their significantly higher waist circumference than T1DM patients and also by a probably higher IR (represented by a higher insulin dose) than T2DM patients.[39]

The mechanisms underlying the upregulated DPP-4 activity in T1DM and LADA have not been elucidated. Some studies have suggested that hyperglycemia can upregulate DPP-4 activity. Sustained hyperglycemia is reported to enhance the levels of advanced glycation end products (AGEs), which consequently affect the release of DPP-4 from the cell surface and upregulate DPP-4 in T1DM.[40] In patients with T2DM, the serum levels of DPP-4 are correlated with those of AGEs.[41] It was shown earlier that iDPP-4s suppress atherosclerotic vascular injury in diabetic animals by inhibiting the deleterious effects of AGEs.[40,42–45] The use of teneligliptin in T1DM patients as well as in streptozotocin-induced T1DM mice may inhibit foam cell formation and oxidized low-density lipoprotein (ox-LDL) uptake of macrophages via suppression of CD36 and acyl-coenzyme A: cholesterol acyltransferase-1 (ACAT-1) gene expression. Thus, the harmful effects of AGEs are attenuated. In mice, teneligliptin reduced all the damaging effects of AGEs in THP-1 cells and macrophages.[46] The exposure of human glomerular endothelial cells to enhanced glucose level resulted in the upregulation of messenger RNA expression and activity of DPP-4.[47] Similar findings have been reported in the human hepatocyte line HepG2 cells.[48]

However, some studies have suggested that the upregulated activity of DPP-4 is associated with T1DM pathophysiology as it is involved in T-cell immune responses. DPP-4 can modulate in vitro T-cell proliferation and enhance T-cell transendothelial migration.[23,24] The members of the chemokine family are the common DPP-4 substrates for immune function.

CD4+ T-cells can be subclassified into T-helper 1 (Th1) and T-helper 2 (Th2) cells. The Th1 cells predominantly produce IL-2, IFN-γ, and TNF-ß. The Th2 cells secrete cytokines, IL-4, IL-5, and IL-10.[49] A consequence of DPP-4-mediated cleavage of chemokines inhibits the stimulation of Th2 immune responses. Additionally, DPP-4, which is predominantly expressed in the Th1 cells, can shift the chemokine activity toward the stimulation and attraction of Th1 cells. DPP-4 cleaves regulated on activation, normal T-cell expressed and secreted, eotaxin, monocyte-derived chemokine, stromal-derived factor (SDF)-1α, and SDF-1β. The cleavage products of these chemokines trigger Th1-specific chemokine receptors but not Th2-specific chemokine receptors.[50,51] In contrast, the inhibition of DPP-4 increases Th2 cytokine secretion.[52]

Studies on the humans and diabetic animal models have reported that the functional polarization of Th lymphocyte subsets is a potential risk factor for T1DM. The impairment of Th2 function and Th1 immunity are the

prerequisite for disease development.[53,54] Studies on children with a recent diagnosis of T1DM and high-risk (ICA ≥ 20) first-degree relatives of patients with T1DM have revealed that the cellular responses against the islet cell antigen glutamic acid decarboxylase 65 involve the Th1 phenotype.[55,56] Similar results have been reported in the diabetic animal models. Polarized Th function is associated with disease development in non-obese diabetic (NOD) mice and BioBreeding rats.[53,57]

The ability of DPP-4 to modulate the activities of neuropeptides, such as substance P, neuropeptide Y, and endomorphin-2 may contribute to the regulation of interactions between the nervous and immune systems.[27]

Membrane-bound CD26 is expressed in various cells and tissues, such as the T-cells, B-cells, and natural killer cells, melanocytes, epithelia of the renal tubule, endothelial cells, and colonic mucosa. CD26 is critical for the T-cell immune responses as it can modulate T-cell proliferation in vitro and deliver a costimulatory signal for T-cell activation. The resting lymphocytes exhibit minimal levels of CD26. In contrast, the activation of lymphocytes upregulates the expression of CD26. The stimulated T-cells exhibit enhanced expression levels of CD26, which were equivalent to those in the epithelial cells.[23,24] Moreover, the depletion of CD26, a thymic maturation marker, affects the lymphocyte composition, memory T-cell generation, and thymic emigration patterns.[58]

CD26, which serves as a receptor for adenosine deaminase (ADA) on the T-cell surface,[59] can modulate the concentration of local extracellular and intracellular ADA levels.[24,60] The expression levels of ADA inversely regulate cellular proliferation and apoptosis. The binding of ADA to CD26/DPP-4 on the surface of T-cells promotes IL-2 production and secretion.[61,62]

In the antigen-presenting cells, caveolin-1 ligates the CD26 dimers on the T-cell surface, which results in the recruitment of lipid rafts to the plasma membrane and CARMA1 to the cytosolic portion of CD26. This leads to the activation of nuclear factor-κB, T-cell proliferation, and IL-2 production.[63] Furthermore, CD26, regulates adhesion, cytoplasmic dissemination, and migration of T-cells in the intra-plasma membrane by promoting the interaction of chemokine receptors with thrombospondin-1 and CD91.[64]

The inhibition of CD26 is reported to suppress T-cell proliferation and Th1 cytokine production and stimulate tumor growth factor beta-1 (TGF-β1) secretion, which plays an important role in the regulation of autoimmunity in T1DM.[65] TGF-β1 mediates the function of regulatory T-cells and regulates the expansion of Foxp3-expressing CD4+ CD25+ regulatory T-cells.[66] Regulatory T-cells can suppress effector T-cell migration, accumulation, and proliferation in draining lymph nodes and inflamed tissues. Additionally, regulatory T-cells are involved in the maintenance of self-tolerance and the prevention of autoimmune diseases.[67] The CD26-deficient rats are reported to exhibit an enhanced number of regulatory T-cells and a decreased number of memory T-cells.[58]

The upregulation of CD4+ CD25+ Foxp3 regulatory T-cells in the pancreatic lymph nodes ameliorated autoimmunity in NOD mice. Cyclophosphamide-induced exacerbation of diabetes in NOD mice was associated with a decreased pool of CD4+ CD25+ Foxp3 regulatory T-cells.[68,69]

There are contradictory findings on CD26 expression in T1DM. A trial involving 48 patients with T1DM and 50 healthy individuals revealed an upregulated serum DPP-4 activity and a significantly downregulated expression of lymphocyte membrane-bound CD26 without any correlation between serum DPP-4 enzymatic activity and CD26 expression in patients with T1DM.[37] This altered activity of serum DPP-4 and expression of CD26 can be attributed to the secondary change in the entero-insular axis and might be a novel part of the T-lymphocyte regulatory dysfunction observed in T1DM. Caveolin-1 can be a potential downstream target in CD26 signaling and T-cell co-stimulation.[63,70]

Matteucci et al analyzed the proportions of naïve (N), central memory (CM), effector memory, and terminally differentiated effector memory (TEMRA) subsets among CD4+ and CD8+ T-cells expressing CD26 in the peripheral blood of 55 patients with T1DM and 20 healthy volunteers. The authors demonstrated that the T1DM group was associated with decreased proportions and absolute numbers of CM and N cells and increased proportions and absolute numbers of TEMRA cells. The ability of accumulated TEMRA cells in patients with T1DM to elicit life-long upon stimulation by protracted antigen exposure (such as viruses or residual self-antigens) or a homeostatic defect in the regulation/contraction of immune responses is not clear.[20]

Experimental and Clinical Studies with iDPP-4

Several clinical trials have evaluated the safety and efficacy of iDPP-4 in T1DM.[71,72] In vitro, human, and animal

studies have suggested that iDPP-4s could enhance β-cell function and attenuate autoimmunity in T1DM. In 2010, we investigated the ability of iDPP-4 to alleviate new-onset diabetes in NOD mice, modulate the inflammatory response, and stimulate β-cell regeneration. After the diagnosis of new-onset diabetes (non-fasting blood glucose level >250 mg/dL on at least two consecutive measurements), the mice were orally treated with iDPP-4 for 2, 4, or 6 weeks along with insulin if the blood glucose level was >200 mg/dL. Compared with that in the insulin treatment group, diabetes was mitigated (blood glucose levels consistently remaining <200 mg/dL) in 57, 74, and 73% of mice after 2, 4, and 6 weeks of treatment with iDPP-4, respectively. However, long-term remission could not be induced. In NOD mice treated with iDPP-4 for 2 weeks, the mean blood glucose level increased in most mice after discontinuing iDPP-4. Treatment with iDPP-4 for 4 and 6 weeks markedly mitigated new-onset diabetes but could not induce long-term remission. The symptoms of diabetes gradually reemerged after stopping treatment. The disease relapse after stopping the treatment is associated with the reduction in the regulatory T-cell pool. The analysis of rats in remission revealed a marked reduction in insulitis and an enhanced proportion of CD4+ CD25+ Foxp3+ regulatory T-cells among the total CD4+ T-cells. The plasma TGF-β1 and GLP-1 levels were significantly upregulated in the rats in remission. Additionally, the insulin content and the number of insulin and bromodeoxyuridine-positive cells (representing replicated B-cells) in the pancreas significantly increased in the rats in remission. These findings suggest that immune regulation plays a critical role in alleviating new-onset diabetes in iDPP-4-treated NOD mice.[18]

Another study analyzed the effect of sitagliptin treatment for 30 and 90 days in a streptozotocin-induced T1DM experimental animal model. Diabetic mice treated with iDPP-4 exhibited significantly downregulated blood glucose levels, attenuated glycemic response to oral glucose tolerance test, and significantly upregulated GLP-1 serum levels. After 90 days of treatment, iDPP-4-treated diabetic animals exhibited significantly upregulated serum insulin concentrations. Additionally, some mice exhibited a non-significant increase in the number of small pancreatic islets. Furthermore, iDPP-4-treated mice exhibited a decreased proportion of CD4+CD26+ T-cells and an increased proportion of CD4+CD25hiFoxp3+ T-cells in the spleen. iDPP-4 modulated the pancreatic inflammatory profile. Pancreatic lymph nodes from iDPP-4-treated mice exhibited a decreased proportion of CD11b+ cells and decreased levels of inflammatory cytokines in the pancreas, especially IFN-γ.[73]

A previous study reported that two young women with T1DM achieved clinical remission for 4 years after treatment with sitagliptin and vitamin D3. One patient used the oral drugs for approximately 1 month after T1DM diagnosis, while the second patient used them after 10 months. In addition to clinical remission, the two patients exhibited stable C-peptide (CP) levels during this period with early and significantly downregulated GADA levels. However, both patients had factors associated with better outcomes in immunological intervention studies, such as the absence of ketoacidosis at diagnosis, age of more than 14 years, and positive fasting CP levels at the onset of T1DM.[74] Similarly, Lima-Martínez et al described a case of a 19-year-old male who started using sitagliptin (100 mg/day) three days after T1DM diagnosis. The patient exhibited ketoacidosis at the time of T1DM diagnosis and entered remission eight weeks after diagnosis. Additionally, the patient was in remission until the time of the publication (15 months of sitagliptin treatment).[75]

In 2009, a study reported two patients who remained insulin-free for 47 and 43 months after treatment with autologous non-myeloablative hematopoietic stem cell transplants and returned to insulin use. After 4 and 2 months of insulin resumption, 100 mg/day sitagliptin was prescribed. The two patients were insulin-free after 2 months and 1 month of using iDPP-4 for another 5 and 6 months, respectively. Additionally, the patients exhibited upregulated levels of CP.[76]

Recently, a trial conducted by Kumar et al randomized 18 newly diagnosed T1DM cases into the following three groups: group 1, treated with insulin; group 2, treated with insulin and exenatide (5 mg subcutaneously administered twice daily for one month and subsequently 10 mg twice daily); group 3, treated with insulin and sitagliptin (100 mg daily). The insulin requirement of all groups decreased after 12 months of treatment. Compared with that in group 1, the decrease in insulin requirement was higher in groups 2 and 3.[77]

Another study enrolled 20 adults with long-term T1DM and treated them with sitagliptin (100 mg/day), or placebo along with insulin for 4 weeks and then the subjects were crossed over. Sitagliptin significantly improved the parameters of overall glucose control, including postprandial and 24-h glucose levels, and significantly decreased prandial insulin requirements.[78]

A meta-analysis assessed the therapeutic effects of iDPP-4 on T1DM and included patients with both newly diagnosed and long-term disease. The use of iDPP-4 was associated with a reduction in the daily dose of insulin (units/day). The medication was well tolerated. Among the six studies included in the analysis, two patients exhibited self-limited nausea, one patient reported a rash, and one patient had abdominal pain. None of the patients in the six studies developed ketoacidosis. Additionally, the incidence of severe hypoglycemia was not affected.[79]

Another meta-analysis published in 2018 including 253 participants (only 120 CP positive patients) from 5 randomized controlled trials (RCTs) revealed that the addition of iDPP-4 to insulin therapy resulted in a greater, but not significant, reduction in HbA1c levels. A small decrease in postprandial glucose and insulin dose were also noted. Regarding the function of β-cell, from 120 patients with positive CP, the increase in fasting CP (FCP) level could not be showed in the group treated with iDPP-4. However, it is important to note that none of the 5 RCTs have assessed immunological indicators.[80]

Zhao et al evaluated the use of sitagliptin (100 mg/day) in patients with a recent diagnosis (three years or less) of LADA and exhibiting FCP level of ≥200 pmol/L or a 2-h postprandial CP level of ≥400 pmol/L. Thirty patients were randomized into groups treated with insulin with or without sitagliptin 100 mg daily for 12 months. In the sitagliptin group, the 2-h postprandial CP and delta CP levels after 12 months were similar to those at the baseline. However, the levels of 2-h post-prandial CP and delta CP were significantly downregulated in the insulin group. After 12 months of treatment, the GADA titers, insulin dosage, fasting glucose, 2-hour postprandial glucose, and HbA1c levels were not significantly different from that at baseline and after 3, 6, 9, and 12 months of treatment.[19]

Another study comparatively analyzed CP levels in patients with LADA who were treated with linagliptin or glimepiride. Linagliptin preserved β-cell function in patients with LADA during the 2-year study period. The FCP levels increased at weeks 28, 52, and 104 when compared with those at baseline in linagliptin-treated patients but decreased in glimepiride-treated patients. Mean HbA1c levels was similar in both groups.[81] These results suggest that iDPP-4 may have attenuated the rate of decline in CP levels in patients with LADA. These findings also indicated that changes in glucose levels may affect β-cell function.[82] However, glycemic control was similar between groups in both studies. Therefore, the loss of β-cell secretion in iDPP-4-treated patients was not dependent on the glucose levels and the decreased glucotoxicity was not responsible for β-cell preservation.

Regarding general adverse events, iDPP-4 are generally well tolerated. Controversial data has historically associated the use of iDPP-4 with an increased risk of pancreatitis and pancreatic cancer.[83–87] However, an up to date meta-analysis including 165 trials performed on T2DM, with duration ≥ 24 weeks, revealed no association between the use of iDPP-4 and an increased risk of pancreatitis or pancreatic cancer without significant differences across individual molecules in the class.[88] Another meta-analysis that included only T1DM showed no serious side effects clearly related to the iDPP-4 including ketoacidosis and pancreatitis.[80] Furthermore, several metanalyses have shown no differences between iDPP-4 and placebo concerning major cardiovascular events.[89–92]

Conclusion

T1DM, as well as LADA, which are progressive diseases with a high incidence, are associated with high morbidity and mortality. The major therapeutic modality for both, which has no curative therapy, is the administration of exogenous insulin. T1DM and LADA can be effectively managed using iDPP-4s. To the best of our knowledge, this is the first study to review the pathophysiological mechanism underlying the rational use of iDPP-4s, which have the potential to slow the progression of T1DM and LADA. However, this study was limited to a literature review. Among the reviewed studies, some studies had small sample sizes with inadequate reporting of raw participant data and/or standard deviations. Additionally, this review included studies that used different iDPP-4s, dosages, and treatment durations (ranging from weeks to months). However, this study reviewed interesting data that should be considered to design therapeutic strategies for both T1DM and LADA to prevent or delay the onset of symptoms.

Author Contributions

All authors made substantial contributions to conception and design; acquisition, analysis and interpretation of data; took part in drafting the article and revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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