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Positive evidence for vitamin A role in prevention of type 1 diabetes

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Abstract

Type 1 diabetes mellitus (T1DM) as one of the most well-known autoimmune disease, results from the destruction of β -cells in pancreas by autoimmune process. T1DM is fatal without insulin treatment. The

expansion of alternative treatment to insulin is a dream to be fulfilled. Currently autoimmunity is considered as main factor in development of T1DM. So manipulation of the immune system can be considered as alternative treatment to insulin. For the past decades, vitamin A has been implicated as an essential dietary micronutrient in regulator of immune function. Despite major advantage in the knowledge of vitamin A biology, patients who present T1DM are at risk for deficiency in vitamin A and carotenoids. Applying such evidences, vitamin A treatment may be the key approach in preventing T1DM.

Key words: Diabetes; Autoimmune; Pancreas; Insulin; Vitamin A

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Core tip: Diet modification and vitamin supplementation is a practical treatment approach for autoimmune diseases. However few broadly studies have been conducted on the use of vitamin A in the treatment of type 1 diabetes. Our objective is to consolidate the current literature to better delineate the vitamin A on immune pathway involved in formation of type 1 diabetes.

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a well-known autoimmune disease that is characterized by a state of T cell-mediated selective deficiency of absolute or relative insulin-producing β -cells^[1-4]. Despite modern medical management, T1DM is still one of the most

common chronic childhood diseases^[5]. T1DM eventually ends up in several disorders including renal failure, ketoacidosis, heart disease, stroke and visionless^[1]. It is estimated that T1DM affects 497100 children under 15 years globally^[5]. Currently administration of exogenous insulin has been the core strategy of treatment for patient with T1DM^[4,6]. However it is not without complications. So, alternative preventive and treatment approaches to insulin are required. It has been shown that manipulation of the immune system with altering the course of the disease can be consider as alternative preventive and treatments approach to insulin^[7]. The effects of vitamin A on immune system have been studied more than any other nutrients^[8]. The concept of modulation of immune system by vitamin A dates back to the early twenties and the work of Green *et al*^[9,10] who reported that vitamin A and β -carotene have "anti-infective" properties. Today, dietary vitamin A and its derivatives are recognized as crucial agents for normal immune system function and regulation^[11].

Interestingly, recent studies have demonstrated that vitamin A deficiency leads to defects in glucose-stimulated insulin secretion^[12]. In addition presence of relatively high levels of cellular retinol binding protein (RBP), cellular retinoic acid (RA) binding proteins, transthyretin (TTR) and RBP in pancreatic rat islets have been documented^[13-15]. Despite major advantage in the knowledge of vitamin A biology, patients who present T1DM are at risk for deficiency in vitamin A and carotenoids^[16,17]. It has been shown that bioavailability and plasma concentrations of vitamin A, TTR, retinol, and RBP fall in children and adults with T1DM^[18-22].

The action of vitamin A to control immune response has led to a growing hypothesis of potential role of vitamin A in T1DM as an autoimmune disease. This review highlights new information regarding to vitamin A and RA in regulation of immune responses in patient with T1DM. So, the purpose of the current study was to thoroughly review the function of vitamin A in the immunology of T1DM.

RESEARCH

We performed a comprehensive literature search of the subject using MEDLINE and PubMed, for "vitamin A", OR "retinoic acid" OR "retinol" AND "type 1 diabetes mellitus" OR "T1DM". All papers fulfilling the above criteria were considered. All papers obtained in the search were fully discussed by the authors. References lists of all original published articles were scanned to find additional eligible studies.

VITAMIN A/RA METABOLISM AND SIGNALING

Vitamin A is an essential nutrient that can be acquired from the diet either as preformed vitamin A [primarily as retinyl ester (RE), retinol, and in much smaller amount

as RA] or provitamin A carotenoids^[23]. This vitamin has been well known for its critical function in embryonic development, vision and the nervous system, as well as in regulation and development of the immune system^[24]. Both dietary vitamin A as vegetable and fruit-derived carotenoids and REs from animal sources are converted to retinol within the lumen of the small intestine or the intestinal mucosa and then enzymatically re-esterified with long-chain fatty acids within the enterocyte to form RE^[23,25-27]. REs are packaged into chylomicrons together with other dietary lipids and secreted into the lymphatic system^[27]. The liver is the primary organ for storage of vitamin A, where the retinol form of vitamin is esterified by lecithin: Retinol acyl transferase and stored as a RE^[28,29]. To meet the tissue vitamin A needs, retinol released into the circulation from liver and bound to its specific transport protein, retinol-binding protein (RBP or RBP4)^[30,31].

In the liver and the peripheral stream, vitamin A is mainly in the form of retinol and REs. Although the function of vitamin A is applied in its metabolite form RA^[28]. So, its precursors must be converted to RA by a two-step process^[32]. First, retinol is hydrolyzed into retinal by ubiquitous alcohol dehydrogenase, and then irreversible hydrolysis reaction allows the formation of RA^[33]. Regulation of gene expression by RA, and the discovery of RA receptor and retinoic acid X receptor which are specific receptors for the active metabolites of vitamin A such as all trans and 9-cis-retinoic acids, provided fundamental documents for the understanding retinoids effects on immune function^[34-36]. RA is inactivated by CYP26A1, CYP26B1 and CYP26C1^[28,29].

PREDIABETES STAGE

Type 1 diabetes is an autoimmune disease, which result from development of islet autoantibodies against proteins in insulin producing beta cells and immune-mediated destruction of insulin producing beta cells in the pancreas^[37]. These individuals with antibody positive within many years are at risk of developing T1DM^[38-40]. Progressive autoimmune β -cell damage usually precedes the clinical onset of diabetes, and occurs years before any clinical symptom of T1DM^[41,42]. This long pre-diabetes phase making T1DM as a predictable disease, and provides an opportunity to prevent individuals with active insulinitis from developing clinical disease^[37].

So T1DM will be a preventable disease by the intervention targeting the manipulating of immune system. In this context one approach is the trimolecular complex, including a self-reactive CD4 T cell, insulin, and HLA molecule^[43].

TYPE 1 DIABETES AND INNATE IMMUNE RESPONSES

The body's first defense system against microorganism invasion is the innate immune system^[44]. Unlike the

adaptive immunity, the response mounted by the innate immune system is relatively nonspecific, that mediated primarily by macrophages, dendritic cells (DCs), and granulocytes, basically functioning as phagocytes and APCs^[45].

The innate immune response depends on the recognition of the microbial-associated molecular patterns (MAMPs), through special cell receptors called pattern recognition receptors (PRRs)^[46,47]. PRRs enable innate immune system to sense and recognize specific microbial compounds known as MAMPs^[46]. PRRs comprise at least three distinct families: RA-inducible gene-I-like helicases, nucleotide oligomerization domain-like receptors (NLRs), and Toll-like receptors (TLRs)^[48].

The TLR family, best known and characterized in mammals, is composed of 13 receptors, which when activated cause activation of the immune system^[49]. TLRs are able to recognize extracellular and endocytosed ligands^[50]. Activation of TLR starts a cascade of pro-inflammatory reactions that leads to increased expression of specific cytokines, chemokines, and co-stimulatory molecules^[51]. In type 1 diabetes, it has been demonstrated that TLRs, as the result of autoreactive processes directed against self antigens, may be priming an unwarranted adaptative immune response^[52]. According to a study of Devaraj *et al.*^[53] the monocytes attained from type 1 diabetic patients expressed TLR2 and TLR4 more than the control group. Furthermore shown in these patients the TLRs activity as well as the targets of the downstream TLR signaling including nuclear factor- κ B (NF- κ B), MyD88, and TIR-domain-containing adapter-inducing interferon (IFN)- β were all respectively more expressed. So, TLR2 and TLR4 signaling may have significant role in development of type 1 diabetes^[54]. However, TLR3 is not required for onset of autoimmune diabetes, while TLR9-deficient compared to TLR9 heterozygotes mice showed a significantly decreased incidence of diabetes^[55].

NLRs and C-type lectin receptors have not been reported to be directly related to autoimmunity. However, they may trigger autoimmune responses or initiate the adaptive immune system by autoimmune mechanisms^[56].

Macrophage

The early studies indicated the role of macrophages in the pathogenesis of T1DM^[57]. It has been reported that the islet infiltrates of young non-obese diabetic (NOD) mice contain macrophages and if the influx of these cells into the pancreas is inhibited, development of type 1 diabetes is prevented^[58]. In addition, according to animal models macrophages produce proinflammatory cytokines such as tumor necrosis factor (TNF)- α and interleukin (IL)-1 β which could be pathogenic for B cells^[59,60]. Cytotoxic T cells are activated in the presence of macrophages, which subsequently destroy pancreatic β -cells^[61]. Overall, the current evidence supports a pathogenic role for macrophages in initiation and development of T1DM.

DCs

DCs, a group of diverse intrinsic effectors which have

two main actions relevant to T cell immune system controlling, including: Presentation of antigens to T cells and determining the nature of T cell response^[62]. *In vivo*, as compared to healthy controls, DCs were located around the pancreatic islets in type 1 diabetic patients^[63]. DCs present in the pancreatic islets of type 1 diabetic patient which suggests that these cells have a direct or indirect role in β -cell destruction^[63]. In T1DM, DCs function as important APCs, DCs degrade the T cell response to antigen presentation^[63]. Together, these studies support a diabetogenic role for DCs in the initiation steps of this disease.

Natural killer cells

Natural killer (NK) cells can recognize and kill virus-infected cells through a number of different mechanisms; in addition NK cells have a critical role in immune regulation^[64]. Data on NK cells in patients with T1DM are inconclusive^[1]. Following stimulation by pro-inflammatory cytokines, NK cells generate a large quantity of cytokines such as IFN- γ , TNF- α , and granulocyte macrophage-colony-stimulating factor (GM-CSF)^[65]. According to animal models, NK cells can play a consequential role in the development of T1DM; however human studies accomplished in this field are rare. Evidence from animal model and man have shown that NK cells are potentially involved both in progression and protective of type 1 diabetes, thus suggesting a dual role for these cells in type 1 diabetes pathogenesis^[66]. NK cells shown differently role in different stages of diseases to the disease pathogenesis^[66]. These cells are the main source of IFN- γ , and therefore, they regulate the intensity of the immune attack in diabetes and also the progression of insulinitis to diabetes^[67].

The NK receptors consist of two main families including NKG2A, for HLA E molecules, and the killer cell immunoglobulin-like receptors (KIR), for the recognition of HLA A, B, and C molecules^[68]. Increased frequency of KIR gene haplotypes has been observed in patients with type 1 diabetes^[68].

In the blood of diabetic patients and in lymphoid tissues of NOD mice NK cell function has been impaired. Also, in type 1 diabetic patients a slight decrease of NKG2D expression has been observed. However animal studies suggested that NK cells activity was detected only in the early pre-diabetic infiltrates^[1]. Most pancreatic NK cells of NOD mice became hypo-responsive during the later stages of diabetes development, as it is detected by lower cytokine secretion and a higher tendency for degranulation as a reaction toward antibodies which are distinct for receptor activation^[69].

According to the available evidence, NK cells can exhibit protective functions in β -cell autoimmunity conceivably by the down-regulation of T-cell lymphocytes and by the generation of IFN- γ .

Neutrophils

Neutrophils are a part of the immune system which do

not act specifically. These cells have a key role in the host immune system against different bacterial infections during the early host response to infection^[1]. Neutrophils express many chemokine receptors, including CXCR1 and CXCR2, which respond to early chemokines released by macrophages. Neutrophils also express chemotactic receptors for complement, lipid mediators, and bacterial products^[70,71]. So, neutrophils react to different chemo-attractants including lipid mediators, complement fragments and bacterial products^[72,73].

Many studies for the roles of neutrophils in the pathogenesis of diabetic complications have been carried out and ended with many controversies. According to previous studies, neutrophil dysfunction in chemotaxis, phagocytosis, killing bacteria and the release of superoxide in type 1 diabetic patients and animal models are not a cause but an effect of disease^[74-77].

VITAMIN A AND INNATE IMMUNE SYSTEM

Macrophage

The available evidence has introduced retinoids as important regulators of monocytic/macrophages function^[78-81]. According to RA effect on monocytic/macrophages, it is shown that RA restrains the secretion of cytokines that promote the production of Th1-type cells and also it increases the secretion of cytokines that promote the production of Th2-type cells^[82]. Macrophages secrete cytokines like TNF and nitric oxide (NO) under activation conditions^[83]. RA affects the secretion of major cytokines generated by macrophages, including TNF- α , IL-1, IL-6, and IL-12^[81]. A number of studies have shown that all-trans-RA extremely reduced the mRNA levels of TNF, regulates NO production, and increases IL-1 generation^[82].

Kim *et al.*^[84] studied the impact of RA on a mouse model macrophage and its oblique effect on T cells. In their study they pretreated the macrophages with RA and precedingly activated them with lipopolysaccharides. In regard to the previous study, it was shown that RA inhibited the production of pro-inflammatory mediators (IL-12 production) by activating macrophages and the macrophages treated with RA when applied as antigen presenting cells (APCs) decreased the T-cell production of IFN- γ and increase the generation of IL-4. Collectively RA signaling seems to set up a Th2-Treg non-inflammatory base^[84,85]. Using RA-treated macrophages as APCs in co-cultures, result in IL-12 reduction and also T cell-derived IFN- γ and IL-4 levels down-regulated and up-regulated, significantly^[86]. Supplementation with vitamin A at 6500 IU/d for 6 mo in 6 patients with common variable immunodeficiency, who had low serum retinol concentrations, decreased the TNF- α level in comparison to onset levels^[87]. The overall results show that supplementing with the preformed vitamin A may decrease the production of particular proinflammatory cytokines [monocyte-derived DCs (MoDCs), TNF- α and IL-6] by macrophages^[8] (Figure

1).

DCs

DCs, the primitive guardian cells which activate the development of adaptive immunity, can act as APCs and establish immune responses^[88]. Therefore, RA's influence on this kind of cell could have a major role in initiating the adaptive immunity^[79]. Apoptosis was induced by retinoids in immature MoDCs, this is inhibited by the secretion of cytokines like TNF- α and IL-1 β . Also, retinoids enhanced the up-regulation of MHC-II and CD86 expression on MoDCs^[79]. IL-4 and RA act synergistically on some populations of DCs and reduce the production of proinflammatory cytokines^[89,90]. Furthermore RA could regulate the immunosuppressive properties of human tolerogenic DC and also mediate the transformation of B cells into B-regs^[91] (Figure 1).

NK cells

NK cells, part of the innate immune system, are critical in the first line of defense against tumors and viral infections^[92]. These cells play an immune-regulatory role in antibody production and cell-mediated immunity through their production of various cytokines^[93]. Previous investigations reported that vitamin A deficiency has a fundamental effect on NK cell lytic activity in young rodents^[94]. Deficiency of vitamin A reduces the activity of NK cells and the ability of spleen cells to produce IFN after mitogen stimulation^[95,96]. According to *in vitro* and *in vivo* studies, using physiologic or high concentrations of retinoids result in an enhancement of NK cell activity^[97-99]. However, the mechanism for this stimulation is not fully clear^[99]. A U-shaped relationship between vitamin A and NK cells has suggested which both low and high doses of vitamin A may have deleterious effects on NK cell hematopoiesis, differentiation or function^[100]. In addition there is an interesting progressive relationship between the degree of vitamin A deficiency and the observed immune-suppression^[101] (Figure 1).

Neutrophils

The importance of the neutrophils is recognized in animals with neutropenia or a deficiency of any key neutrophils enzymes^[102,103]. In these animals, mild infections can be life threatening^[102,103]. The neutrophils differentiates requires the oxidized form of retinol, RA^[104,105]. The development of neutrophils in the bone marrow is controlled by the genes that are modulated by RA receptors, and RA in cultures accelerates maturation of neutrophils^[106,107]. According to previous studies, treatment with RA or vitamin A could restore the level of neutrophils and the capacity of superoxide-production in calves and rats significantly^[108,109]. Vitamin A deficient rats had significantly higher numbers of hyper-segmented neutrophils (67%) relative to those in the control rats^[103]. However the data on the relationship between vitamin A and neutrophils function in humans are sparse and inconclusive^[8] (Figure 1).

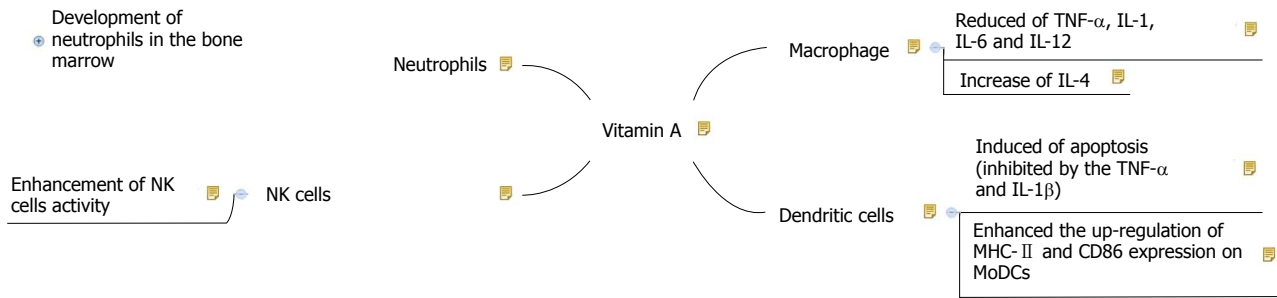


Figure 1 Schematic diagram for the pathways of vitamin A effects on innate immune system. NK: Natural killer; TNF: Tumor necrosis factors; IL: Interleukin; MoDCs: Monocyte-derived dendritic cells.

TYPE 1 DIABETES AND ADAPTIVE IMMUNE RESPONSES

The adaptive immune system, which is the body's second defense system against pathogens, functions by its antigen-specific structure which distinguishes foreign molecules by their antigens which is mediated by the interaction between T cells and APCs. It generates long-term response by using immunological memory. T cells and T cell receptor are the essential section in the adaptative immune system^[1].

It is currently accepted that T cells play an important role in type 1 diabetes pathogenesis^[110]. These cells are the most important players in the autoimmune attack of β -cells^[110]. Anti-islet T cells, including both: CD4 and CD8 T cells have been observed in patients with T1DM^[111]. It has been shown that transfer of anti-islet specific CD4 or CD8 T cells can lead to diabetes, as follows; insulinitis and diabetes can be adoptively transferred by T cells from diabetic mice into non-diabetic mice, whereas B cells are not needed^[111-113]. In fact insulinitis seen in T1DM is induced by diabetogenic T cells that then recruit heterogeneous mixture of cells^[114].

CD8 T cells directly attack β -cells by MHC type 1 expressed on pancreatic β -cells, therefor in the absence of beta-2 microglobulin which reduces MHC type 1 or in the status of beta-restricted MHC type 1 deficiency, it is adequate to stop diabetes development and to avoid β -cell demolition in NOD mice^[115,116].

CD4 T cells are activated by β -cell APCs, and they mainly provide cytokines such as IL-21 to help both B cells and CD8 T cells, which is required for the development of T1DM in NOD mice. CD4 T cells secrete IFN- γ , stimulating macrophages to release other cytokines, such as IL-1 β , TNF- α , and free radicals, which are toxic to β -cells^[44].

Lymphocytes can kill β -cells directly through a cytotoxic process or by the secretion of proinflammatory cytokines, such as IL-1 β , IFN- γ ; they also release free radicals, which destructs the pancreatic β -cells. Cytokines induce the production of inducible NO synthase which results in NO production and NO synthesis influences the β -cell death^[117]. Free radicals can induce, in turn, apoptosis and necrosis of β -cells^[118].

In the disease progression phase, both T and B lymphocytes can be activated against self antigens in

an islet lesion and trigger an immunological response that leads to the destruction of pancreatic β -cells^[119,120] (Figure 2).

VITAMIN A AND ADAPTIVE IMMUNE RESPONSES

A study by Iwata *et al.*^[121] for the first time described the role of RA in the biology of T cells. Recently evidenced T-cell immune-competence can be affected by vitamin A deficiency^[8].

Transforming growth factor (TGF)- β which is a suppressor of Th1 and Th2 differentiation and the inducer of transforming T-cells to Tregs or to Th17, mediates RA in the process of formation, differentiation and inhibition or activation of Th1, Th2, Th17 and Treg lymphocytes^[122]. The main impact of RA in lymphocyte differentiation by TGF- β is the transformation of Th17^[123,124]. RA has a two way affected on Th17 which on one hand it promotes its differentiation and on the other hand it downregulates it^[125]. Th17 appears to be the example of customized immunity for special types of pathogens, but the abnormal Th17 responses could be involved in an exceeding number of autoimmune dysfunctions^[126]. In some types of irregular immune responses, the defective form of RA *via* a genetic or an environmental mechanism intermediates the complex regulation of Th17^[127].

A growing number of evidence indicates that vitamin A is involved in the modulation of IL-10 production. IL-10, secreted by Th2-helper T cells, restricts the production of pro-inflammatory Th1-type cytokines, such as IFN- γ and IL-2, in both T and NK cells. This is a major mechanism in reducing the inflammatory responses to some defects^[128].

A recent review demonstrated that in the status of vitamin A deficiency, Th1-cells mediate immune responses and when vitamin A is supplemented it induces Th2 immune responses^[129]. Results from a number of studies that investigated the effect of vitamin A on infections that lead to one of the two immune responses, Th1 or a Th2 response, intimate that the immunological functions of vitamin A are specific for every pathogene and may involve other parts of the immune system other than Th1 or a Th2. Further studies are needed to examine the mechanism of vitamin A

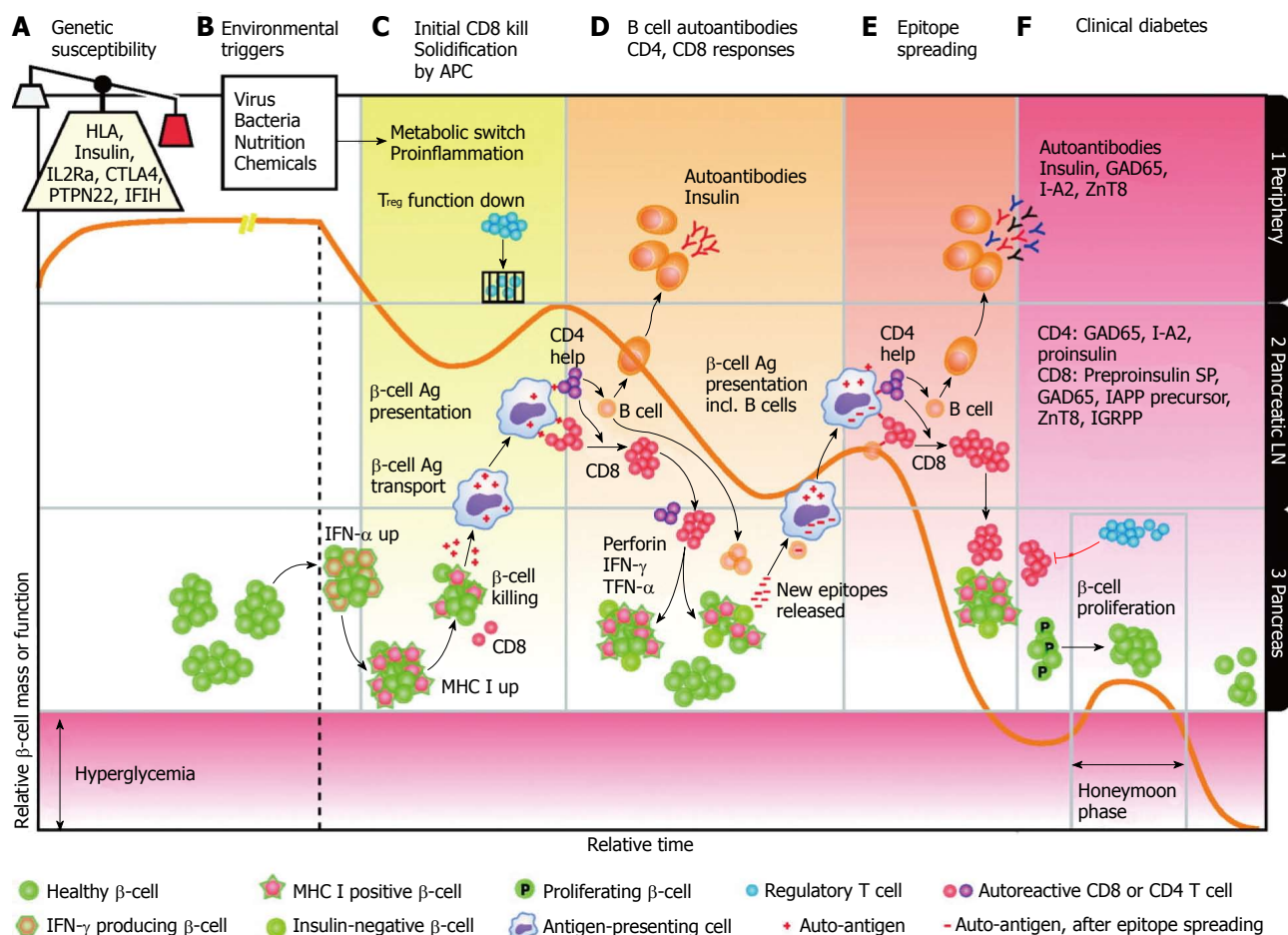


Figure 2 Immunology of type 1 diabetes^[115]. TNF: Tumor necrosis factors; IL: Interleukin; MoDCs: Monocyte-derived dendritic cells; APCs: Antigen presenting cells; IFN: Interferon; HLA: Human leukocyte antigen.

supplementation on differential of Th1/Th2 responses comparing to the baseline vitamin A status in humans and the specific pathogens that cause disorders^[8].

Overall, there is no exact evidence to state for a direct role of vitamin A supplementation on cytokine secretion or lymphocyte production. One principle reason for the wide range of results in studies is the specific immune response toward each pathogen which may affect the impact of vitamin A on T-cell function. Also, vitamin A may have momentary effects on intermediary factors of T-cell-dependent immunity which may not have been noticed in some population studies. Few randomized clinical trials have been accomplished on the topic of vitamin A supplementation on the proliferation or activation of B lymphocytes^[8].

REVIEWS ON T1DM AND VITAMIN A

In the status of lack of balance between different subtypes of T-cells, autoimmune diseases occur^[130]. For instance, IFN- γ -producing CD4 or CD8T effectors (Teff) cells activation and expansion and/or reduction of the number or function of CD4T regulatory (Treg) cells, can result in autoimmune diseases^[130-134]. Present evidence showed that both CD4⁺ and CD8⁺ Teff cells

are related in the initiation and further development of type 1 diabetes^[135-137]. CD4⁺ and CD8⁺ Teff cells which are typically reactive with antigens on the β -cells in the pancreas can cause type 1 diabetes, an autoimmune disease^[138]. Recent studies introduced IL-17-producing CD4 Th17 cells as a new generation of Teff cells that trigger potent inflammatory responses resulting in autoimmune disorders^[139]. These results suggest that the establishment of effective *in vivo* immune-tolerance can be considered as practical strategy to treat autoimmune diseases such as type 1 diabetes. However this approach requires simultaneous targeting of more than one T-cell population subset. Therefore, immune tolerance induced by clinically relevant agents or methods affecting various T-cell subtypes could demonstrate an effective way for treating human autoimmune disorders^[140].

Vitamin A and its derivatives are potent immune tolerance agents by its ability to transform Th1 to Th2 lymphocytes^[138,140]. Vitamin A regulates the adaptive and innate immune responses by different mechanisms for example, its high-level can diminish development of Th1 and promote development of Th2 responses^[141]. Vitamin A supplementation results in a decrease in serum pro-inflammatory cytokines, such as TNF- α and IFN- γ , and an increase in the immunosuppressive cytokine

IL-10^[87,142]. Such immune modulation by vitamin A could decrease the development risk of autoimmune diseases^[143]. Present evidence reported high level of dietary vitamin A may have major effects on down regulating inflammatory immune cells and reducing the damage caused by oxidation in the islets that contribute to dysfunction of β cells. An animal study conducted by Zunino *et al.*^[138] showed that intervention with a diet rich in vitamin A inhibited the development of type I diabetes in mice by reducing or delaying of the infiltration of immune cells in to the islets.

Furthermore vitamin A plays a role in the release of insulin and glucagon hormones^[12], and therefore has profound effects throughout the body in the regulation of glucose homeostasis^[12,13]. Vitamin A in active form has an important role in the secretion and release of insulin in the langerhans islets cells. The presence of RA binding proteins in pancreatic islet cells could probably explain the significance of vitamin A for optimal islet function^[12]. Furthermore RA may be involved in regulation of the hormones released by the islet cells^[12]. Deficient islet cells were defective in hormone release when exposed to graded levels of glucose^[12,13]. Vitamin A deficiency results in change in pancreatic tissue quality, which could conceivably increase digestion with the collagenase^[144].

In an animal study, NOD mice were divided into 3 groups and treated with 250 IU of vitamin A per gram of their daily food or treated with 1% freeze-dried grape powder in their diet or a control diet for 7 mo. After 7 mo, in the control group 71% of the mice had a blood sugar level more than 13.9 mmol/L (full-blown T1DM) whereas only 25% of the mice in the vitamin A group and 33% of the grape powder group reached the above blood sugar level. Furthermore TNF- α , an inflammatory marker in T1DM patients, in the vitamin A and grape powder groups was respectively lower compared to the control group^[145]. These results suggested that polyphenols or vitamin A in the diet protect beta-cell islets against autoimmune inflammatory attacks and have the potency to decrease the formation of autoimmune diseases such as type 1 diabetes^[146].

In addition it has been showed that all-trans retinoic acid (ATRA), a potent derivative of vitamin A treatment restricted both CD4⁺ and CD8⁺ IFN- γ producing cells without affecting CD4⁺ IL-17-producing cells. ATRA treatment also affects the function and activation status of CD8⁺ T-cells^[140]. Macrophages generate less TNF- α which in return reduces the production of chemokines which promote the recruitment of immune cells in to the islets including IP-10, RANTES, and MIP-1b, and also intracellular adhesion molecule-1^[147,148]. According to histological studies, non diabetic animal treated with ATRA did not have insulinitis, indicating that ATRA may have also inhibited T-cells trafficking to and infiltration in to islets, thus preventing diabetes. Furthermore, recently *in vitro* and *in vivo* trials indicated that ATRA treatment may result in upregulation of Foxp3⁺ Treg cells and reduction of Th1 and Th17 cell differentiation^[125,141,149]. Protective effects of ATRA are impairing in the status

of inadequacy of donors Foxp3⁺ CD4⁺ Treg cells^[140]. Overall, these evidences support the idea that vitamin A and its derivatives exerted its autoimmune-protective effect, at least in part, by inhibiting both CD4⁺ and CD8⁺ IFN- γ -producing Teff cells with no effects on IL-17-producing Teff cells, and inducing the production of Treg cells. However despite the fact that ATRA treatment inhibited the *in vitro* differentiation of Th17 cells did not alter the Th17 cell population^[125,141,149,150]. Although Th17 cells are important players in pathogenesis of some autoimmune diseases including experimental autoimmune encephalitis and autoimmune arthritis, its function in type 1 diabetes is not yet discovered^[151-153]. Expression of granzyme B was suppressed by ATRA. In addition ATRA efficiently inhibits infiltration of T-cells into islets, and precluded the progression of insulinitis and diabetes. A study conducted by Van *et al.*^[140] showed that defect less islets or pre-insulinitis were detected in ATRA-treated mice, even after 17 wk of the cell transfer while the control group developed severe destructive insulinitis at 2 wk after cell transfer with CD4 CD25.

CONCLUSION

This review reported that both vitamin A and ATRA effectively induced immune tolerance that inhibited islet inflammation and progression to diabetes. In this review, as fully mentioned previously we showed that ATRA treatment had a dual effect, the inhibition of Teff cells and inducing Treg cell proliferation in therapeutic of type 1 diabetes. Nonetheless, the protective effect of ATRA is inhibited when CD4CD25 T-cells, thus a majority of Foxp3 Treg, are drawn down in donor splenocytes. In prediabetic NOD mice with initiated insulinitis, ATRA treatment can inhibit the development of T1DM. Nevertheless, the mechanisms demonstrating the role of vitamin A or ATRA treatment in inducing immune tolerance and prevention of autoimmune diseases is not yet clear^[138,142,154-156]. So, to further validate and establish the potential of using ATRA for therapy, further studies are needed to evaluate its relative contribution in modulating type 1 diabetes and to show the mechanisms by which vitamin A and ATRA may inhibit the development of autoimmune disorders. Overall, it seems that the use of vitamin A and ATRA *via* induction of immune tolerance provides an effective method in inhibiting type 1 diabetes.

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Neuroendocrine hormone amylin in diabetes

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Abstract

The neuroendocrine hormone amylin, also known as islet amyloid polypeptide, is co-localized, co-packaged and co-secreted with insulin from adult pancreatic islet β cells to maintain glucose homeostasis. Specifically, amylin reduces secretion of nutrient-stimulated glucagon, regulates blood pressure with an effect on renin-angiotensin system, and delays gastric emptying. The physiological actions of human amylin attribute to the conformational α -helix monomers whereas the misfolding instable oligomers may be detrimental to the islet β cells and further transform to β -sheet fibrils as amyloid deposits. No direct evidence proves that the amylin fibrils in amyloid deposits cause diabetes. Here we also have performed a systematic review of human amylin gene changes and reported the S20G mutation is minor in the development of diabetes. In addition to the metabolic effects, human amylin may modulate autoimmunity and innate inflammation through regulatory T cells to impact on both human type 1 and type 2 diabetes.

Key words: Amylin; Neuroendocrine hormone; Diabetes

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Core tip: This is a systematic review to describe amylin as a neuroendocrine hormone. Besides the glucose homeostasis and cytotoxicity of amylin, we tried to perform that the S20G mutation of human amylin is also minor in the pathogenesis of diabetes. In addition to the metabolic effects, human amylin may have impact on autoimmunity, implicating a potential as the immunosuppressor to improve autoimmunity conditions in the future therapy of diabetes, allergic diseases and immune rejection.

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INTRODUCTION

Amylin, or islet amyloid polypeptide (IAPP), is a neuroendocrine hormone co-localized, co-secreted and co-packaged with insulin from pancreatic β cells^[1,2]. Abnormalities in human amylin folding, secretion and action have detrimental effects on islet function and glucose regulation by islet amyloidosis and β cell dysfunction in type 2 diabetes (T2D)^[3-5]. The molecules of amylin polypeptide fold to form the α -helix monomers and oligomers and the β -sheet fibrils. The amylin-aggregated amyloid fibrils are thought to form through smaller cell toxic intermediates and deposited amyloid disrupts normal islet architecture^[6]. However, amylin plays a critical role in metabolism homeostasis^[7] as a neuroendocrine hormone that carries a targeted signal to the brain. Several actions of amylin that impact glucose regulation have been identified, including the effects on nutrient-stimulated glucagon secretion^[8], on nutrient delivery from the stomach to the small intestine for absorption^[9], on renin-angiotensin system (RAS)^[10] and on food intake by delaying gastric emptying^[11].

FUNCTIONAL AMYLIN

Amylin functions as part of the neuroendocrine pancreas and contributes to glucose homeostasis with other two pancreatic islet hormones insulin and glucagon. The amylin and insulin is a pair of synergistic partner genes co-expressed by a common promoter^[12], and regulates the levels of glucose by complex endocrine and neuronal pathways. In physiological state, the simultaneous release of amylin and insulin from the secretory granules results in a parallel pattern in the islet β -cells in response to glucose stimulation^[13]. However, concentration of plasma amylin and insulin decreased in advanced T2D^[7]. Glucagon commonly increases blood glucose when nutrients are not available; while insulin and amylin primarily decrease the post-meal glucose by stimulating the uptake of glucose from circulation into muscle and fat cells for storage and by inhibiting the endogenous glucose output from liver. Complimentary to insulin, amylin regulates postprandial glycaemia by suppressing postmeal glucagon secretion from islet α -cells^[8], which is possibly mediated by signals from the vagus nerve at the pancreatic islets. Amylin and insulin also coordinate storage of carbohydrate to transfer triglyceride into muscle glycogen in skeletal muscles^[14] probably by phosphorylase activation^[15] (Table 1 and Figure 1).

As a neuroendocrine hormone, amylin also acts in the central nervous system to produce satiety through brainstem-localized receptors, which have been found at several locations in the brain, including the nucleus accumbens, the dorsal raphe and the area postrema in rat brain^[16]. The area postrema may be an important

Table 1 Physiological actions of amylin

Neuroendocrine effects
Inhibiting insulin secretion in a high concentration
Inhibiting glucagon secretion at mealtime
Delaying nutrient delivery from stomach to the small intestine
Reducing food intake by a signal from the central nervous system
Metabolic effects
Co-regulating glucose with insulin and glucagon
Inhibiting muscle glycogen synthesis ^[15]
Stimulating oxidative responses and low density lipoprotein uptake in insulin-producing cells
Inhibiting bone resorption
Lipolytic-like effects
Renal effects
Renin \uparrow
Angiotensin II \uparrow
Regulating renal growth
Regulating water-sodium homeostasis
Haemodynamic effect
Aldosterone \uparrow
Hypocalcaemia
Vasodilation

site for amylin action. This area does not have a blood brain barrier and allows access to circulatory peptides. Lesioning studies have indicated that some of amylin's actions are mediated at this site. The suppression of neuronal amylin on food intake and gastrointestinal motility^[17] to slow down the absorption and to limit the rate at which glucose enters the circulation^[18] has been found in human. Gastric emptying is considered to be a typical pathological phenomenon and a crucial reason for the postprandial hyperglycemia in T1D. It is believed that most of amylin deficiency in T1D may be pathogenically significant in the gastric behavior^[19]. Thus, high plasma amylin concentration in young with newly-diagnosed T1D^[20], which may result in a delay in gastric emptying that markedly improved postprandial glucose excursions in new T1D patients^[19]. Amylin deficiency significantly affects the lack of delay in gastric emptying in response to hyperglycemia in T1D^[19], and is further supported by the highly potent protective effects of amylin on glucose homeostasis^[21].

Furthermore, a physiological effect of amylin on the RAS has been implicated in the hemodynamic regulation of blood pressure^[22] and kidney function^[10]. Inhibition of angiotensin-converting enzyme (ACE) is associated with the reducing density of amylin binding in the renal cortex^[10]. Pharmacokinetics pattern of amylin closely resembles that of C-peptide^[23-25]. Excreted in the urine, when glomerular filtration decreases, amylin cumulates in the blood stream. Therefore, patients with renal failure may have high levels of circulating amylin^[26]. These patients also have a higher than normal prevalence of islet amyloid in the absence of diabetic symptoms^[27] (Table 1 and Figure 1).

KINETICS OF AMYLIN

Human amylin is derived from a larger precursor

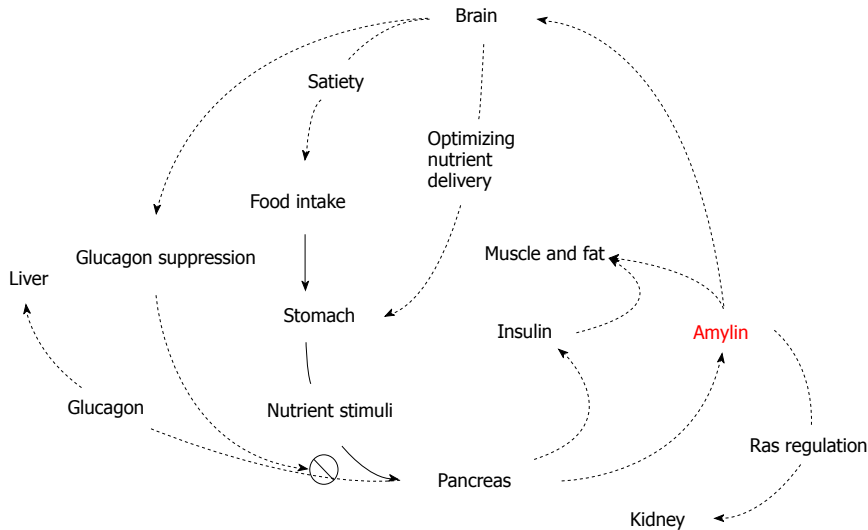


Figure 1 Overview of physiological actions of amylin. (1) Amylin suppresses glucagon secretion from islet alpha cells at mealtime and thus, inhibits glucagons-induced glucose release from the liver; (2) Amylin delays nutrient delivery from the stomach to the small intestine for absorption; (3) Amylin reduces food intake by a signal mediated through the central nervous system; (4) Renal amylin may stimulate Renin-Angiotensin System; and (5) Amylin and insulin coordinate storage of carbohydrate.

proamylin, coding sequence with 89 amino acids residue. The flanking peptides at N-terminal and C-terminal of mature amylin are removed by a proteolytic enzyme, which is also responsible for proinsulin to insulin conversion in the β cells^[28]. The prohormone convertases PC2 and PC3 involved in processing proinsulin are likely responsible for amylin processing as well^[5].

Measuring the concentration of circulating amylin is challenging. The minimum detectable concentration of amylin in 50 mL plasma is 0.5 to 2 pmol/L, and the dynamic range is 2 to 100 pmol/L^[29]. The basal plasma concentrations of amylin in human in the 2-15 pmol/L range, with an insulin/amylin ratio of 10-100:1^[30,31]. In healthy subjects, circulating amylin rises in response to the glucose challenge^[32]. The amylin to insulin molar ratio is similar at all time points despite of high-frequency oscillations and inter-race differences in circulating amylin concentrations^[33,34].

Circulating amylin levels are increased in individuals with obesity, hypertension, positive family history of insulin resistance in line with hyperinsulinaemia^[35-37]. An exaggerated amylin response has been documented in subjects with obesity and impaired glucose tolerance^[32,36]. Moreover, the amylin to insulin ratio is consistent in insulin-resistant persons at all time points, although large interindividual variations (0.2% to 1.6%) in amylin/insulin secretory ratios have been documented^[35]. Thus, hyperamylinemia due to insulin resistance precedes the occurrence of T2D^[36]. However, in later-stage T2D, the secretion of both amylin and insulin becomes deficient^[32]. In diabetic patients on insulin treatment, amylin/insulin is detectable but the response to the glucose challenge is negligible, reflecting functional failure of the islet β cells^[38]. Interestingly, diabetes is also characterised by an excess of glucagon, in particularly after mealtimes. The net effect of insulin and amylin deficiency and glucagon excess is an increased postmeal glucose level. Furthermore, prolonged exposure of pancreatic islets to hyperglycaemia favours selective amylin secretion, increasing the risk of islet amyloid formation and β cell

apoptosis^[39,40].

AMYLIN-DERIVED AMYLOIDOSIS

Amyloidosis is a generic term for aggregation state of amyloid polypeptide with β -sheet conformation that bounds to each other by certain chemical bonds^[41]. Amylin is encoded by calcitonin mRNA from a gene made up of three introns on the 12th chromosome^[42]. Besides amylin, more than 25 proteins in human are known by their fibrillate aggregation^[43,44]. Many of them have similar protein structures with amyloid-like properties and characteristic occurrences in metabolic disturbances, such as amylin, amyloid light-chain and β -amyloid^[45,46]. In the islet of T2D patients, amylin fibrils commonly contribute to the form of islet amyloid. In addition, amylin is also found to deposit in brain^[16], plays the potential role in the development of Alzheimer's disease (AD) and cerebrovascular disease (CVD) pathology with β -amyloid, or might impair brain function independently of β -amyloid pathology^[47].

Certain gene mutations, amino acid sites in amylin protein and minor components are more or less associated with amyloid deposits. It has been reported some mutations in the human amylin gene leading to amino acid substitutions, such as S20G. S20G is an important amylin gene mutation resulting in a glycine for serine substitution at position 20 of the mature IAPP molecule (Figure 2A). *In vitro* studies indicate that the S20G mutation amylin is more cytotoxic in forming amyloid and inducing apoptosis in COS-1 cells^[48]. A low prevalence (< 5%) of the S20G has been reported in T2D Japanese^[49-51], Hong Kong Chinese^[52,53], Taiwanese^[54], and Mainland Chinese. All the cases with the mutation S20G are heterozygous. Although the heterozygous mutation S20G is more common in diabetic patients than in normal control (2.6% vs 0.9%, $P < 0.0001$), linkage analysis reveals that mutation in or near amylin gene is unlikely a major course of T2D^[55] (Table 2).

Many molecular chaperones, like apolipoprotein E

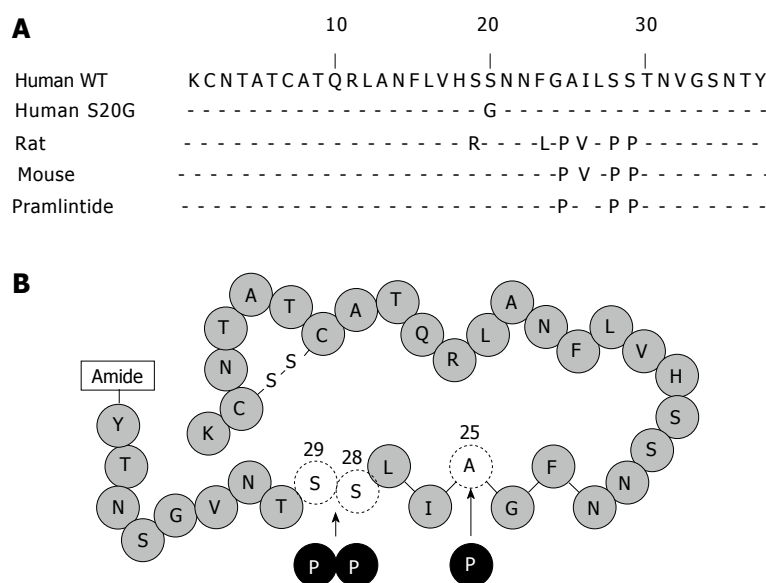


Figure 2 Amino acid sequence and diagrammatic representations of human amylin and pramlintide. A: Amino acid sequence alignment of human (WT, S20G), rat, mouse amylin and pramlintide. Only the amino acids that differ are shown. The sequence between amino acids 20 to 29 represents the amyloidogenic domain; B: The synthetic amylin analog pramlintide differs from human amylin at three amino acid sites (proline at 25, 28, and 29) and this molecule overcomes these disadvantages of human amylin.

(apoE) and heat shock protein (HSP) family, may relate to amylin deposits^[56-58], and is generally considered as a major genetic modulator of β -amyloid deposition and risk of AD^[59,60]. The apoE ϵ 4 allele particularly affects the increased risk for atherosclerosis^[61], brain plaque^[61] and islet amyloidosis. In T2D, apoE plays a critical role in lipid metabolism, amylin fibril formation^[62] and is a probable link to atherosclerosis^[57]. HSP is identified within highly purified β cell granules derived from INS-1E islet β cells such as insulin and amylin^[63]. Vita demonstrates the existence of direct functional interactions involved HSP70, can suppress the misfolding of human amylin^[58], which is also proved to limit the toxicity of β -amyloid^[64]. These chaperones may contribute the AD-diabetes link at the pathophysiological level, including the interactive amyloid of β -amyloid and human amylin^[65,66].

CONFORMATIONS OF AMYLIN

The conformation of amylin is considered a significant factor in that abnormal accumulation of amylin fibrils in organs may lead to amyloidosis in T2D. Human amylin is subtyped into three different conformations: Monomers, oligomers and fibrils (Figure 3). Monomers are unfolded random-coiled peptides physiologically. These molecules can be misfolding with α -helix structures, and aggregated into the pathologic oligomers, the soluble amyloid intermediates, which include spherical particles of 2.7 to 4.2 nm in diameter^[67]. Amylin fibrils formation is a self-driven process accumulating the misfolded oligomeric proteins with a β -sheet fibrillar structure into insoluble islet amyloid deposits. Islet amylin-amyloid is the pathologic hallmark of most individuals with T2D^[22,68].

In physiological state, the toxic oligomers can be rescued into amyloid fibrils by chaperones or eliminated by the ubiquitin-proteasome system^[69]. Concentration of amylin fibrils in the intracytoplasmic organelles of human beta cells far exceed the *in vitro* concentration

required for amyloid formation, so there must be an underlying mechanism in normal beta cells to induce the aggregation of amylin monomers into fibrils. Mechanisms that may associate with amylin-amyloid include an acid pH^[70], the presence of chaperon proteins (HSP), or the presence of other proteins^[58]. Then these possible factors for amylin aggregation may derive from hyperglycaemia, high-fat diet, or low-grade chronic inflammation^[3], which are considered as the cardinal symptoms of T2D. The amylin monomer has its special function in endocrine system, or further polymerise to amyloid fibrils, which may play an important role in cell informational transfer, memory and survival prolonging^[71].

Mature fibrillar aggregate of amylin has been considered to be nontoxic, and even these small amyloid deposits seen widely located in islets or other organs in T2D, may not have significant contribution to organs damage. Therefore, the formation of fibrils from cytotoxic oligomers can be considered as a protective mechanism of transforming a dynamic protein into inert amyloid. Here we have to be curious whether this process of fibrillar formation initially acts as a rescuer in the pathway of cell failure^[71].

The amino acid sequence of amylin derived from islet amyloid in T2D is identical to that present in healthy humans, and amylin from human insulinoma tissue. Moreover, amylin structure exhibits close sequence homology among all species in both the amino terminal (residues 1 to 19) and the carboxy terminal (residues 20 to 29) regions. In contrast, residues 20 to 29 show considerable divergence among species and have been implicated in the conversion of the peptide's secondary structure from a predominantly α helical one to a β sheet structure^[72]. This assignment is based on the comparison of the sequences of human amylin, which is highly amyloidogenic, with those of cat amylin, which is moderately amyloidogenic, and with rat and mouse amylin, which does not aggregate to form amyloid^[72,73].

Table 2 Prevalence of the amylin gene mutation S20G in Asian populations (%) *n*

	Ref.	Type 2 diabetes	Impaired glucose tolerance	Type 1 diabetes	Control
Japanese	Seino <i>et al</i> ^[50]	2.6 (1538)	-	-	0.8 (1108)
Japanese	Yamada <i>et al</i> ^[51]	4.7 (86)	-	-	1.6 (182)
Japanese	Sakagashira <i>et al</i> ^[49]	4.1 (294)	-	0 (59)	0 (187)
Hong Kong Chinese	Ng <i>et al</i> ^[53]	1.5 (462)	-	-	0 (126)
Taiwanese	Chuang <i>et al</i> ^[54]	1.6 (182)	4.2 (24)	1.6 (122)	4.4 (99)
Mainland Chinese	Lee <i>et al</i> ^[52]	2.1 (94)	-	-	0 (106)

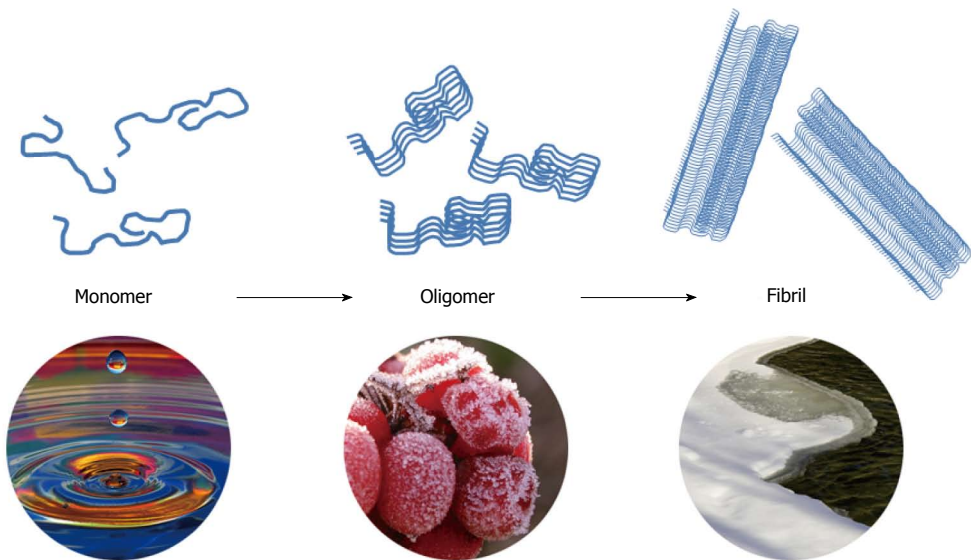


Figure 3 Three conformations of human amylin. Monomers of amylin with physiological functions mainly contribute to glucose and lipid homeostasis and tend to misfold into the cytotoxic oligomers. A self-driven process is accumulating the misfolded oligomers into insoluble nontoxic amylin fibrils with a β -sheet structure.

AMYLIN TOXICITY

Mechanisms of islet β cell depletion by amyloid include mechanical replacement, apoptosis, necrosis and β cell membrane damage. Human amylin has been clearly shown toxic to insulin-producing β cells of the adult pancreas of rats and humans^[74]. The cytotoxic action of amylin in insulin-producing cells is paralleled by increased oxidative responses and low density lipoprotein (LDL) uptake, suggesting that cytotoxic mechanisms of amylin in insulin-producing cells involve changes in pathways of cellular oxidative stress systems and lipid homeostasis^[75].

Soluble oligomer of amylin is recently reported to contribute the primary toxicity in T2D but not insoluble fibril in the amyloid diseases^[76-78]. Different misfolded oligomers of amylin with a conformation-dependent structure suggest that they share a common mechanism of pathogenesis^[79]. Like oligomer of β amyloid protein playing an important role in the pathogenesis of AD and CVD^[80], oligomeric amylin is also a central subject in the risk of the islet β -cell lesion in T2D through formation of toroidal (ion-leaking) pores inserted into membranes^[81,82].

THERAPEUTIC APPLICATION AND PROSPECTIVE

Human amylin has a tendency to aggregate, form

insoluble particles and stick to surfaces. Learnt from non-amyloidogenic rat amylin, the peptide structure is broken by substituting the positions 25 alanine, 28 and 29 serines into proline residues (Figure 2B). This analog of human amylin, named "pramlintide", is used for the potential prevention of complications of T1D as an adjunct with insulin and a single agent for T2D^[2]. This soluble, stable synthetic analog amylin avoids aggregation of amyloid relating the development of β -cell dysfunction^[83]. Like wild-type human amylin, pramlintide can adjust postprandial glucagon release and gastric emptying rate in individuals with T1D and T2D^[84-87]. In clinical therapy of diabetes, pramlintide as an assistant treatment of insulin usually decreases postprandial glucose without rising insulin level^[88,89]. In T1D, pramlintide therapy significantly reduced 4.4-6.6 mmol/mol haemoglobin a1c at 26 wk vs placebo^[90,91]. And mean body weight was significantly reduced (-0.8 to -1.3 kg at week 26 or 29) vs placebo^[90-92]. Then in T2D, pramlintide therapy resulted in significant reductions in haemoglobin a1c (-7.7 to -8.7 mmol/mol after 16 or 26 wk) and mean body weight (-1.4 to -1.6 kg after 16 or 26 wk) vs placebo^[93-95]. According to these functions, the pramlintide is manufactured and designed as injection in pen injector. Since the pH value of pramlintide buffer is incompatible with most insulin products, pramlintide is recommended not to mix with insulin in the same syringe (shown in Symlin[®] Package Insert). This analog

has the same functions of blood glucose regulation and gastric emptying delay as wild-type human amylin.

Human amylin no doubt plays a significant role in neuroendocrine contribution to glucose homeostasis. Treatment with non-fibrillar pramlintide improves glycaemic control and weight management without adverse events of severe hypoglycaemia in T1D and T2D^[96]. However, whether the toxicity of fibrillar amylin contributes significantly to pathogenesis of diabetes is yet unconvincing. Studies data indicate that microscopically evident fibrillar amylin is neither necessary nor sufficient to cause diabetes, but rather that it is positively correlated with protection^[97,98].

It is worth noting that amylin may regulate the inflammatory response and immune factor secretion^[99,100]. Mouse amylin was reported that can trigger a broad autoimmune response by CD4⁺ effector T cells in NOD mice^[101]. Recent study shows that human amylin can induce CD4⁺CD25⁺FoxP3⁺ Regulatory T cells and reduce risk of autoimmune diabetes^[102]. It firstly demonstrates autoimmune inhibition by human amylin. All these findings suggest a novel approach to restore glucose homeostasis and improve autoimmunity conditions such as autoimmune diseases, allergic diseases, immune rejection of organ transplantation and graft vs host reaction (GVHR).

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