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Vitamin A: a missing link in diabetes?

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Abstract

Vitamin A has a critical role in embryonic development, immunity and the visual cycle. In recent years, evidence has demonstrated that vitamin A can also regulate metabolic pathways implicated in the pathogenesis of obesity and diabetes. This has increased interest in the possible antiobesity and antidiabetic properties of natural and synthetic vitamin A derivatives. However, whether vitamin A deficiency or aberrations in vitamin A metabolism contribute to the pathogenesis of diabetes is not known. This perspective article will review what is currently known and new data regarding the link between vitamin A and the clinical manifestations of common and atypical forms of diabetes.

Keywords

β cells; diabetes; dietary nutrient; glucose metabolism; insulin; islets; pancreas; retinoic acid; retinol; vitamin A

Vitamin A refers to a family of compounds, also called retinoids, that exhibits structural and biochemical similarity to retinol, the form of dietary vitamin A absorbed from animal and plant sources[1]. For over 100 years studies have demonstrated a critical role for vitamin A in embryonic development, immunity, and the visual cycle[2,3]. In the past four decades synthetic analogs of vitamin A, known as retinoids, have been extensively developed and used for clinical treatment of dermatological disorders and a number of cancers[2]. In recent years, a growing body of evidence has demonstrated that vitamin A can also regulate metabolic pathways implicated in the pathogenesis of obesity and diabetes[4]. This has increased interest in the possible antiobesity and antidiabetic properties of natural and synthetic vitamin A derivatives[5]. However, a fundamental question is whether vitamin A deficiency (VAD) or aberrations in vitamin A metabolism can contribute to the pathogenesis of diabetes. Whether or not aberrations in vitamin A signaling play a role in the onset of diabetes is not known, so we will review both what is currently known and new data suggesting a possible link between the lack of vitamin A and the clinical manifestations of common and atypical forms of diabetes.

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Vitamin A & Type 2 diabetes

Type 2 diabetes (T2D) is a global health crisis affecting more than 350 million adults and children worldwide[6]. Global projections estimate that there will be more than 439 million cases by 2030, with more than 90% T2D[6]. Diet and obesity are major risk factors for the development of T2D[7], so over the past two decades, numerous studies have examined the role of individual dietary components (e.g., carbohydrate, fats, vitamins), including vitamin A, to determine if any specific dietary factors may be linked to obesity driven T2D[8,9]. Starting in 1991, a number of small human studies reported that serum vitamin A levels were elevated in children and adults with frank T2D or clinical manifestations of T2D, such as obesity and impaired glucose tolerance[10–12]. Yet other human studies, and a number of larger epidemiological studies, have reported contradictory findings on the relationship between vitamin A status and diabetes or its symptoms[13,14].

Some demonstrated that serum vitamin A or intakes of provitamin A carotenoids, such as β -carotene, protect against insulin resistance[13,15]; data from over 15,000 adults collected in the National Health and Nutrition Examination Survey in the USA showed that total serum vitamin A (retinol and retinyl esters) is associated with a reduced risk of metabolic syndrome[14]. Other studies, including the landmark α -tocopherol β -carotene (ATBC) trial of 29,000 Finnish smokers, found either no relationship[16–19], or an elevated risk of diabetes associated with higher serum vitamin A or β -carotene[20,21]. The contradictory findings from these studies, coupled with the inherent limitations of both small and largescale human diet and epidemiological studies, such as food recall and self-selection bias, made it difficult to determine if vitamin A was either protective or prodiabetic. A further challenge is determining if any anti-T2D effects of provitamin A carotenoids, such as β -carotene, are due to their vitamin A activity, as there are a number of enzymatic pathways which tightly regulated their conversion to active form of vitamin A[22]. Until there is a better understanding of the relationship between dietary carotenoids and their potential to modulate T2D risk as provitamin A molecules, consuming high doses of carotenoid supplements may be ill advised, as data from the ATBC trial suggest this could be harmful to humans[23], possibly due to disruptions to vitamin A metabolism and signaling[22].

In 2006, Kahn and colleagues demonstrated that obesity and insulin resistance in mice and humans led to elevations in serum levels of RBP4[24,25]. RBP4 is synthesized in the liver and is the primary carrier of serum vitamin A (retinol)[1]. Other researchers also reported an association between elevated serum RBP4 levels and T2D[26]; however, subsequent studies failed to detect this relationship[27,28]. Human, experimental animal and cell culture studies eventually demonstrated that the prodiabetic effect of RBP4 is not related to vitamin A or RBP4's role as a vitamin A carrier[29–31]. In fact, it is now accepted that the elevations of RBP4 detected in T2D are largely from adipose tissue and not liver, further supporting a nonvitamin A role for any prodiabetic properties of RBP4[25,32]. Despite increasing data on the molecular mechanisms responsible for the prodiabetic effects of RBP4[29], little is known regarding the biological functions of RBP4 outside of its role as the major serum vitamin A carrier. Nevertheless, anti-T2D therapies that block RBP4 are being developed[25]. However, as RBP4 is the major carrier of serum vitamin A, a thorough understanding of how these therapeutic approaches might affect vitamin A metabolism is

essential, as anti-RBP4 therapies can compromise vitamin A status in rodents and humans[33–35].

Based on findings from human studies, it remains unclear if and how vitamin A deficiency is involved in the pathogenesis of T2D. Studies from our laboratory are in agreement with others that vitamin A can favorably regulate metabolic pathways central to the pathogenesis of T2D, such as pancreatic β -cell mass and function[36,37], obesity[38] and lipid metabolism[39]. Therefore it is our opinion that further research is warranted to determine if compromised vitamin A status may negatively affect these pathways and increase risk for the development of T2D.

Vitamin A & Type 1 diabetes

Type 1 diabetes (T1D), an autoimmune disease characterized by T-cell-mediated destruction of insulin producing β cells, makes up approximately 10% of all diabetes cases[40]. T1D has a strong genetic component[40], but the incidence of T1D is rising, suggesting interactions between disease susceptibility genes and the environment[41]. Unlike T2D, where overnutrition and lifestyle are well-established risk factors[8], the environmental risks that drive T1D remain elusive. Vitamin A is essential for the regulation of immune functions, including T-cell-mediated immunity[42,43]. Therefore, one long held hypothesis is that impaired vitamin A metabolism can affect autoimmunity and the onset of Type 1 diabetes[44]. Human studies examining this hypothesis have been few in number and with small cohorts, but all have demonstrated that, compared with nondiabetics, individuals with T1D have decreased circulating levels of vitamin A or RBP4[10,21,45]. Experimental models of T1D in rodents have been largely in agreement with human studies. Basu *et al.* [21] demonstrated, in both experimentally induced T1D in mice and in biobreeding (BB) rats which spontaneously develop T1D, that serum vitamin A, hepatic levels of the major storage form of vitamin A, retinyl-palmitate (RP) and retinyl-ester hydrolase, the enzyme responsible for mobilization of hepatic vitamin A stores, are reduced[44,46–48]. High doses of dietary vitamin A failed to increase serum vitamin A in BB rats, suggesting that a defect in vitamin A metabolism, rather than increased vitamin A turnover or catabolism, is associated with T1D[48]. However, in a study in BB rats VAD protected against T1D and dietary vitamin A, in the form of RP, promoted T1D[49]. It is not clear why these various studies show contradictory results.

In contrast to studies examining if VAD promotes T1D, the data that vitamin A, in its more bioactive form, all-*trans* retinoic acid (RA), diminishes the characteristics of T1D are more consistent. Pharmacological administration of RA to non-obese diabetic (NOD) mice, which like BB rats spontaneously develop a T1D phenotype with autoimmune destruction of β cells, delayed the onset and severity of T1D and protected from the loss of β -cell mass[50]. Two studies convincingly demonstrated that RA prevented the immunodestruction of β cells in NOD mice by increasing the numbers of tolerogenic immunosuppressive Treg cells, which suppressed CD4⁺ and CD8⁺ T-effector cells[51,52]. The destruction of insulin producing β cells in T1D is largely the result of defects in tolerance toward self-antigens[53]. The capacity of RA to enhance immunotolerance[54], coupled with preclinical data in models of T1D, have brought attention to RA as a potential treatment for T1D[55].

To determine if VAD is involved in the onset of T1D requires more vigorous studies with larger cohorts. However, based on decades of studies of the effects of VAD in humans and rodents, it is largely accepted that even marginal or subclinical VAD (defined as normal serum vitamin A levels, but depleted liver vitamin A stores) leads to compromised immune responses and increased mortality[56–58]. This raises a fundamental question of whether individual variations in vitamin A metabolism and subclinical VAD might contribute to the complicated interplay among genetics, environment and T1D. As rodent models suggest that T1D is associated with impaired vitamin A availability[48], individuals with T1D resulting from compromised vitamin A metabolism could potentially be treated with vitamin A therapies which enhance endogenous vitamin A availability.

Vitamin A & pancreatic endocrine function

Vitamin A is essential for development of the pancreas and insulin producing β cells[59,60]. There are also data suggesting that vitamin A is essential for maintenance of pancreatic β -cell function and mass in adults[36]. Chertow *et al.* showed that vitamin A compromised pups, born from mothers with marginal VAD, exhibited hyperglycemia, diminished glucose stimulated insulin secretion and reduced pancreatic levels of crbp1[61]. Administration of dietary vitamin A, either as RP or RA, restored euglycemia and normalized pancreatic insulin secretion[61]. This study by Chertow *et al.* did not address whether the effects of vitamin A on pancreatic endocrine function resulted from VAD during fetal development or in the adult, as the model used by Chertow also impaired fetal pancreatic development[62]. Gudas and colleagues addressed this question by inducing marginal versus severe VAD in adult mice by using wild-type mice and mice with a genetic predisposition for VAD. The researchers showed that marginal VAD leads to marked reductions in pancreatic vitamin A levels, hyperglycemia and to a 30–40% increase in β -cell death[36]. In parallel with the marked loss of β cells, marginal VAD reduced the pancreatic levels of the vitamin A binding protein, crbp1[36]. Crbp1 (RBP1) is crucial for the utilization and storage of dietary vitamin A[63], so these data suggest that even marginal VAD results in decreased β -cell utilization of vitamin A. Hyperglycemia and loss of β -cell mass were even more pronounced in the severely VAD adult mice, and unlike the situation in marginally VAD mice, severe VAD altered islet composition by increasing the numbers of pancreatic glucagon secreting α -cells[36]. The pancreatic endocrine aberrations from VAD were not permanent, as dietary vitamin A restored euglycemia and β -cell mass in VAD mice. Taken together, data from Trasino *et al.*[36], point to a major role of vitamin A in maintaining β -cell numbers and β -cell functions in the adult pancreas. Consistent with this, Brun *et al.*[37], demonstrated that pancreatic vitamin A signaling through RA receptors is essential for maintaining normoglycemia, β -cell mass and insulin secretion in mice[37]. Interestingly, VAD had no effect on peripheral insulin sensitivity[36], a critical pathological feature of early T2D, but instead VAD recapitulated some of the pancreatic endocrine profiles of individuals with advanced T2D and some features of T1D (e.g., marked β -cell apoptosis and increased presence of glucagon producing α cells)[64,65]. Beginning with the studies by Martin *et al.* [59], these data collectively demonstrate a key role for vitamin A in maintaining the functions of pancreatic endocrine β cells, both in the fetal and adult pancreas.

Vitamin A & atypical diabetes mellitus

It is unclear if the similarities in the pancreatic endocrine profiles between VAD mice and those seen in advanced T2D and T1D suggest a unifying mechanism for β -cell death across both forms of diabetes. This is less likely as the mechanisms for β -cell loss between T1D and T2D are quite different[66]. It is more probable that aberrant vitamin A metabolism or signaling is involved in the pathogenesis of one or more subsets of diabetes, which is increasingly being recognized as a more heterogeneous group of diseases than previously thought[67]. One atypical form of diabetes, malnutrition-related diabetes mellitus (MRDM), is often diagnosed in African countries where VAD is endemic[68–70]. MRDM is exclusively a pancreatic driven malady, and frequently presents with hyperglycemia, loss of pancreatic mass, no insulin resistance and no islet autoimmunity typical of T1D[68–70]. The etiology of MRDM is currently unknown and a number of dietary and genetic factors have been proposed[71,72]. The clinical manifestation of MRDM is strikingly similar to the metabolic profile of vitamin A deficient mice, which are hyperglycemic, have marked loss of pancreatic β -cell mass, but do not develop insulin resistance[36]. Our studies demonstrate that vitamin A is essential for the maintenance of pancreatic β -cell mass[36], therefore the similar pancreatic driven metabolic profiles of MRDM and VAD mice suggest that deficits in β -cell mass and function in MRDM may be uniquely due to compromised vitamin A status or VAD. Determining if vitamin A is specifically involved in the etiology of MRDM would be difficult given the complex and numerous health consequences of under nutrition disorders[70]. The striking overlap between the metabolic profiles MRDM and VAD mice does raise the question of whether oral vitamin A therapy would mitigate hyperglycemia and pancreatic β -cell deficits in individuals with MRDM. However, until there is a better understanding of whether VA status is linked to MRDM, targeted interventions for MRDM should prioritize addressing the numerous health conditions driven by the underlying malnutrition. Developing animal models that recapitulate MRDM could be useful in determining the role of vitamin A in the pathogenesis of this rare form of diabetes.

Another atypical form of diabetes, which has long been recognized and is now gaining more attention, is diabetes-associated tuberculosis (TB)[73]. For more than 85 years, there have been observations that patients with diabetes have two- to three-times increased risk of developing tuberculosis[73], and for reasons that are unclear, that risk is highest for individuals with poor glycemic control[73,74]. While cases of TB predominately occur in developing countries[73], the incidence of diabetes-associated TB is similar in both developing and developed countries[73]. Diabetes leads to numerous hormonal and neurological complications, including increased risk for infection[75], but it is neither clear how diabetes specifically increases risk of TB, nor how TB itself might exacerbate diabetes, as there is evidence to support the latter[76].

Vitamin A's vital role in immunity[77] and evidence for a role of VAD in diabetes[36,44] might provide important links between TB and diabetes. VAD leads to compromised T cell and innate immune responses involved in combating TB infection[77–79]; and TB, as one of the most common lower respiratory tract infections associated with severe VAD, is mitigated by oral vitamin A therapies[80–84] by enhancing macrophage antimicrobial responses[85,86]. First, this raises the possibility that the severity of VAD itself might be a

risk factor for developing diabetes-associated TB, if, as some data suggest[73,76], TB itself promotes diabetes. If TB infection promotes or exacerbates diabetes, there is also reason to hypothesize that clinical manifestations of diabetes (e.g., hyperglycemia, impaired glucose tolerance) would improve with oral vitamin A therapy in individuals with diabetes and TB. However, there is increasing consensus that diabetes compromises immune responses and increases risk for TB[73,75]. If the latter is true, there still remains a rationale to determine the vitamin A status and the effects of oral vitamin A therapy in populations with diabetes-associated TB, given the compelling evidence of a role of vitamin A in glycemic control and diabetes[36–37,44].

Nevertheless, if a nexus between VAD and diabetes-associated TB exists, examining this would be a formidable challenge, as it is well known that infections, including TB, antagonize vitamin A metabolism and promote VAD[81,87]. This is further complicated by data showing that even subclinical infections in humans lead to diminished vitamin A levels[88] and that anti-TB therapy can correct VAD[82]. The double burden and complex interactions between vitamin A metabolism and infections like TB, lead to a typical cycle of infection and VAD[58], making it difficult to examine the impact of vitamin A and VAD on diabetes-associated TB. Still, as worldwide cases of diabetes-associated TB are predicted to increase at an alarming rate[73], with the majority of these cases occurring in developing countries with the highest burden of diabetes[89], there is an urgent need for programs that aim to identify populations at high risk for developing diabetes-associated TB in regions where VAD and TB are endemic. Recognizing the vital interplay between vitamin A status and TB infection, in 2012, a promising initiative began screening for randomized controlled clinical trials of vitamin A supplementation in cases of diabetes-associated TB in China[90], which is facing a growing diabetes health crisis[91].

Although the incidence of severe VAD has not been documented in developed countries for many decades[92], there is evidence of decreased dietary vitamin A intake and marginal VAD in some developed populations that were previously thought to have adequate vitamin A status[93,94]. This, coupled with evidence that diabetes-associated TB equally affects populations from both developed and developing countries[73], raises the possibility that individuals with marginal VAD might be at increased risk for diabetes-associated TB.

Vitamin A, pancreatic fetal developmental program & diabetes

Loss of β -cell function and mass is a defining feature of both forms of diabetes, T1D and T2D[65]. This has led to a strong clinical interest in developing β -cell replacement therapies for diabetes using either new sources of transplantable insulin producing β cells or small molecules to activate pancreatic endocrine progenitors to repopulate islets with new β cells[95,96]. Vitamin A, in the form of RA, and RA receptors are essential for pancreatic β -cell development[60,97]. RA is also an essential component of *in vitro* chemical protocols that direct embryonic stem cells to differentiate into insulin-producing β cells[98], in part because RA regulates the mRNA expression of a number of fetal transcription factors (TFs) involved in endocrine cell and β -cell specification, including *Pdx1*, *Ngn3* and *NeuroD*[98–101]. Many of these β -cell-specific fetal TFs, which are regulated by vitamin A during pancreatic development, have now emerged as important proteins in maintaining adult β -cell

pools, and mutations or loss of expression of some of these TFs is associated with loss of β -cell mass in advanced T2D[102]. There is also evidence that pancreatic centroacinar and ductal cells are pancreatic progenitor cells and are highly enriched in the enzyme Aldh1a1 (Raldh1), which synthesizes RA from vitamin A (retinol)[103]. In response to injury, centroacinar and ductal cells express pancreatic fetal developmental genes known to be regulated by RA, such as *Sox9*, and differentiate to insulin producing endocrine cells[103]. This points to RA as an important signaling molecule in replacing β cells in response to pancreatic injury, which is consistent with the degree of loss of β cells observed in advanced T2D.

Our studies[36] are in agreement with this and further demonstrate that even in the absence of pancreatic injury, vitamin A is essential to maintain steady state pools of β cells[36]. Given that, even marginal VAD in wild-type adult mice decreased pancreatic vitamin A levels and resulted in a loss of β -cell mass and insulin responses[36], we propose that marginal VAD and reduced pancreatic vitamin A levels alter the expression of some of the 'fetal' β -cell TFs required for maintaining β cells in adult mice[36].

Conclusion & future perspective

The incidence of diabetes is growing at an alarming rate. We have outlined some of the current research examining the relationship between vitamin A and both the common and some rare forms of diabetes. The experimental data suggest that vitamin A and related synthetic retinoids could be new drugs for the treatment of diabetes. However, more rigorous and comprehensive studies are required to determine if VAD is a risk factor for the development of diabetes and to assess the safety and efficacy of oral vitamin A therapies for diabetes. Nonetheless, as oral and topical RA therapies have been used for decades in the treatment of a number of cancers and dermatological disorders[2,104–105], development of retinoids as novel antidiabetic agents will benefit from the large body of clinical and basic research on the safety and therapeutic uses of vitamin A.

In light of the known metabolic modulating properties of vitamin A and the body of human data suggesting that low vitamin A is a possible independent risk factor for diabetes, we would currently recommend that dietary vitamin A intakes and serological levels of vitamin A be recorded in individuals participating in clinical trials of antidiabetic agents or epidemiological studies of nutrients and diabetes risk. Such efforts could aid in determining possible confounding effects of vitamin A status on the efficacy of antidiabetic agents and would provide vital information for scientists and health policy makers to determine if populations at high risk for diabetes require higher vitamin A intake levels.

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Practice points

- Human evidence is inconclusive on the relationship between vitamin A and Type 2 diabetes.
- The robust antidiabetic properties of vitamin A warrant further animal and human studies on the role of vitamin A and etiology of Type 2 diabetes.
- Data are lacking on whether vitamin A deficiency increases risk for onset of Type 1 diabetes.
- There is compelling evidence that vitamin A can modulate T-cell mediated immunity involved in the etiology of Type 1 diabetes.
- Determining vitamin A status of individuals newly diagnosed with Type 1 diabetes could provide insight into any relationship between vitamin A status and risk for Type 1 diabetes.
- Vitamin A is involved in maintaining pancreatic β -cell mass.
- Natural or synthetic analogs of vitamin A should be studied as β -cell modulating agents.
- Less common forms of diabetes might be linked to vitamin A given the prevalence of these forms of diabetes in populations with high risk of vitamin A deficiency.
- Loss of endocrine mass in Type 2 diabetes involves proteins regulated by vitamin A during pancreatic development.
- Therefore, studies should determine if reduction in pancreatic vitamin A levels and signaling lead to reductions of these proteins and endocrine mass in Type 2 diabetes.