PERSPECTIVE

Diabetes Management

Vitamin A: a missing link in diabetes?

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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.

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.

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

KEYWORDS

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

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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.

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 counties [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.

Financial & competing interest disclosure

Portions of the research discussed in this article were supported by Weill Cornell funds and by NIH grants, R01CA043796 and R01DE010389 to LJ Gudas, and T32 grant CA062948 to SE Trasino. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 D'ambrosio DN, Clugston RD, Blaner WS. Vitamin A metabolism: an update. *Nutrients* 3(1), 63–103 (2011).

2 Gudas LJ. Emerging roles for retinoids in regeneration and differentiation in normal and disease states. *Biochim. Biophys. Acta* 1821(1), 213–221 (2012).

3 Gudas LJ, Roberts A, Sporn M. *Cellular Biology and Biochemistry of the Retinoids.* Raven Press, NY, USA (1994).

4 Brun, PJ, Yang KJ, Lee SA, Yuen JJ, Blaner WS. Retinoids: potent regulators of metabolism. *Biofactors* 39(2), 151–163 (2013).

• **Thorough review of the metabolic-modulating properties of vitamin A.**

5 Villarroya F, Iglesias R, Giralt M. Retinoids and retinoid receptors in the control of energy balance: novel pharmacological strategies in obesity and diabetes. *Curr. Med. Chem.* 11(6), 795–805 (2004).

6 Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res. Clin. Pract.* 87(1), 4–14 (2010).

7 Maggio CA, Pi-Sunyer FX. Obesity and Type 2 diabetes. *Endocrinol. Metab. Clin. North Am.* 32(4), 805–822, viii (2003).

8 Khazrai YM, Defeudis G, Pozzilli P. Effect of diet on Type 2 diabetes mellitus: a review. *Diabetes Metab. Res. Rev.* 30(Suppl. 1), 24–33 (2014).

9 Kaur B, Henry J. Micronutrient status in Type 2 diabetes: a review. *Adv. Food Nutr. Res.* 71, 55–100 (2014).

10 Krempf M, Ranganathan S, Ritz P, Morin M, Charbonnel B. Plasma vitamin A and E in Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) adult diabetic patients. *Int. J. Vitam. Nutr. Res.* 61(1), 38–42 (1991).

11 Basualdo CG, Wein EE, Basu TK. Vitamin A (retinol) status of first nation adults with non-insulin-dependent diabetes mellitus. *J. Am. Coll. Nutr.* 16(1), 39–45 (1997).

12 Tavridou A, Unwin NC, Laker MF, White M, Alberti KG. Serum concentrations of vitamins A and E in impaired glucose tolerance. *Clin. Chim. Acta* 266(2), 129–140 (1997).

13 Ylönen K, Alfthan G, Groop L, Saloranta C, Aro A, Virtanen SM. Dietary intakes and plasma concentrations of carotenoids and tocopherols in relation to glucose metabolism in subjects at high risk of Type 2 diabetes: the botnia dietary study. *Am. J. Clin. Nutr.* 77(6), 1434–1441 (2003).

14 Beydoun MA, Shroff MR, Chen X, Beydoun HA, Wang Y, Zonderman AB. Serum antioxidant status is associated with metabolic syndrome among U.S. Adults in recent national surveys. *J. Nutr.* 141(5), 903–913 (2011).

15 Sluijs I, Cadier E, Beulens JW, Van Der A DL, Spijkerman AM, Van Der Schouw YT. Dietary intake of carotenoids and risk of Type 2 diabetes. *Nutr. Metab. Cardiovasc. Dis.* 25(4), 376–381 (2015).

16 Kataja-Tuomola M, Sundell JR, Männistö S *et al.* Effect of alpha-tocopherol and

beta-carotene supplementation on the incidence of Type 2 diabetes. *Diabetologia* 51(1), 47–53 (2008).

17 Reunanen A, Knekt P, Aaran RK, Aromaa A. Serum antioxidants and risk of non-insulin dependent diabetes mellitus. *Eur. J. Clin. Nutr.* 52(2), 89–93 (1998).

18 Abahusain MA, Wright J, Dickerson JW, De Vol EB. Retinol, alpha-tocopherol and carotenoids in diabetes. *Eur. J. Clin. Nutr.* 53(8), 630–635 (1999).

19 Liu S, Ajani U, Chae C, Hennekens C, Buring JE, Manson JE. Long-term beta-carotene supplementation and risk of Type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 282(11), 1073–1075 (1999).

20 Arnlöv J, Zethelius B, Risérus U *et al.* Serum and dietary beta-carotene and alpha-tocopherol and incidence of Type 2 diabetes mellitus in a community-based study of Swedish men: report from the Uppsala Longitudinal Study of Adult Men (ULSAM) Study. *Diabetologia* 52(1), 97–105 (2009).

21 Basu TK, Tze WJ, Leichter J. Serum vitamin A and retinol-binding protein in patients with insulin-dependent diabetes mellitus. *Am. J. Clin. Nutr.* 50(2), 329–331 (1989).

22 Eroglu A, Harrison EH. Carotenoid metabolism in mammals, including man: formation, occurrence, and function of apocarotenoids. *J. Lipid Res.* 54(7), 1719–1730 (2013).

23 The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N. Engl. J. Med.* 330(15), 1029–1035 (1994).

24 Yang Q, Graham TE, Mody N *et al.* Serum retinol binding protein 4 contributes to insulin resistance in obesity and Type 2 diabetes. *Nature* 436(7049), 356–362 (2005).

25 Graham TE, Yang Q, Blüher M *et al.* Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. *N. Engl. J. Med.* 354(24), 2552–2563 (2006).

26 Cho YM, Youn BS, Lee H *et al.* Plasma retinol-binding protein-4 concentrations are elevated in human subjects with impaired glucose tolerance and Type 2 diabetes. *Diabetes Care* 29(11), 2457–2461 (2006).

27 Promintzer M, Krebs M, Todoric J *et al.* Insulin resistance is unrelated to circulating retinol binding protein and protein C inhibitor. *J. Clin. Endocrinol. Metab.* 92(11), 4306–4312 (2007).

28 Von Eynatten M, Lepper PM, Liu D *et al.* Retinol-binding protein 4 is associated with components of the metabolic syndrome, but not with insulin resistance, in men with Type 2 diabetes or coronary artery disease. *Diabetologia* 50(9), 1930–1937 (2007).

29 Moraes-Vieira PM, Yore MM, Dwyer PM, Syed I, Aryal P, Kahn BB. RBP4 activates antigen-presenting cells, leading to adipose tissue inflammation and systemic insulin resistance. *Cell Metab.* 19(3), 512–526 (2014).

30 Erikstrup C, Mortensen OH, Nielsen AR *et al.* RBP-to-retinol ratio, but not total RBP, is elevated in patients with Type 2 diabetes. *Diabetes Obes. Metab.* 11(3), 204–212 (2009).

31 Aeberli I, Biebinger R, Lehmann R, L'allemand D, Spinas GA, Zimmermann MB. Serum retinol-binding protein 4 concentration and its ratio to serum retinol are associated with obesity and metabolic syndrome components in children. *J. Clin. Endocrinol. Metab.* 92(11), 4359–4365 (2007).

32 Gavi S, Stuart LM, Kelly P *et al.* Retinol-binding protein 4 is associated with insulin resistance and body fat distribution in nonobese subjects without Type 2 diabetes. *J. Clin. Endocrinol. Metab.* 92(5), 1886–1890 (2007).

33 Cioffi CL, Dobri N, Freeman EE *et al.* Design, synthesis, and evaluation of nonretinoid retinol binding protein 4 antagonists for the potential treatment of atrophic age-related macular degeneration and stargardt disease. *J. Med. Chem.* 57(18), 7731–7757 (2014).

34 Baglietto L, Torrisi R, Arena G *et al.* Ocular effects of fenretinide, a vitamin a analog, in a chemoprevention trial of bladder cancer. *Cancer Detect. Prev.* 24(4), 369–375 (2000).

35 Dimitrov NV, Meyer CJ, Perloff M *et al.* Alteration of retinol-binding-protein concentrations by the synthetic retinoid fenretinide in healthy human subjects. *Am. J. Clin. Nutr.* 51(6), 1082–1087 (1990).

36 Trasino SE, Benoit YD, Gudas LJ. Vitamin A deficiency causes hyperglycemia and loss of pancreatic β-cell mass. *J. Biol. Chem.* 290(3), 1456–1473 (2015).

•• **First study to demonstrate that the vitamin A deficiency in adult mice leads to a metabolic phenotype with similarities to advanced Type 2 diabetes.**

37 Brun PJ, Grijalva A, Rausch R *et al.* Retinoic acid receptor signaling is required to maintain glucose-stimulated insulin secretion and β-cell mass. *FASEB J.* 29(2), 671–683 (2015).

38 Berry DC, Noy N. All-*trans*-retinoic acid represses obesity and insulin resistance by activating both peroxisome proliferation-activated receptor beta/delta and retinoic acid receptor. *Mol. Cell. Biol.* 29(12), 3286–3296 (2009).

39 Amengual J, Ribot J, Bonet ML, Palou A. Retinoic acid treatment enhances lipid oxidation and inhibits lipid biosynthesis capacities in the liver of mice. *Cell. Physiol. Biochem.* 25(6), 657–666 (2010).

40 Pociot F, Akolkar B, Concannon P *et al.* Genetics of Type 1 diabetes: what's next? *Diabetes* 59(7), 1561–1571 (2010).

41 Knip M, Simell O. Environmental triggers of Type 1 diabetes. *Cold Spring Harb. Perspect. Med.* 2(7), a007690 (2012).

42 Raverdeau M, Mills KH. Modulation of T cell and innate immune responses by retinoic acid. *J. Immunol.* 192(7), 2953–2958 (2014).

43 Hall JA, Grainger JR, Spencer SP, Belkaid Y. The role of retinoic acid in tolerance and immunity. *Immunity* 35(1), 13–22 (2011).

44 Basu TK, Basualdo C. Vitamin A homeostasis and diabetes mellitus. *Nutrition* 13(9), 804–806 (1997).

45 Krill D, O'leary L, Koehler AN *et al.* Association of retinol binding protein in multiple-case families with insulin-dependent diabetes. *Hum. Biol.* 69(1), 89–96 (1997).

46 Tuitoek PJ, Ziari S, Tsin AT, Rajotte RV, Suh M, Basu TK. Streptozotocin-induced diabetes in rats is associated with impaired metabolic availability of vitamin A (retinol). *Br. J. Nutr.* 75(4), 615–622 (1996).

47 Chen M, Thomson AB, Tsin AT, Basu TK. The hepatic retinyl ester hydrolase activity is depressed at the onset of diabetes in BB rats. *Br. J. Nutr.* 89(2), 231–238 (2003).

48 Lu J, Dixon WT, Tsin AT, Basu TK. The metabolic availability of vitamin A is decreased at the onset of diabetes in BB rats. *J. Nutr.* 130(8), 1958–1962 (2000).

49 Driscoll HK, Chertow BS, Jelic TM *et al.* Vitamin A status affects the development of diabetes and insulitis in BB rats. *Metabolism* 45(2), 248–253 (1996).

50 Juang JH, Van YH, Kuo CH, Lin MY, Liu YH, Chang HY. Prevention and reversal of diabetes by all-*trans* retinoid acid and exendin-4 in NOD mice. *Int. J. Endocrinol.* 2014, 435481 (2014).

51 Van YH, Lee WH, Ortiz S, Lee MH, Qin HJ, Liu CP. All-*trans* retinoic acid inhibits Type 1 diabetes by T regulatory (Treg)-dependent suppression of interferon-gamma-producing T-cells without affecting Th17 cells. *Diabetes* 58(1), 146–155 (2009).

52 Di Caro V, Phillips B, Engman C, Harnaha J, Trucco M, Giannoukakis N. Involvement of suppressive B-lymphocytes in the mechanism of tolerogenic dendritic cell reversal of Type 1 diabetes in NOD mice. *PLoS ONE* 9(1), e83575 (2014).

53 Jeker LT, Bour-Jordan H, Bluestone JA. Breakdown in peripheral tolerance in Type 1 diabetes in mice and humans. *Cold Spring Harb. Perspect. Med.* 2(3), a007807 (2012).

54 Strober W. Vitamin a rewrites the ABCs of oral tolerance. *Mucosal Immunol.* 1(2), 92–95 (2008).

55 Wasserfall C, Atkinson MA. Taking a daily vitamin to prevent Type 1 diabetes? *Diabetes* 58(1), 24–25 (2009).

56 Kaufman DR, De Calisto J, Simmons NL *et al.* Vitamin a deficiency impairs vaccine-elicited gastrointestinal immunity. *J. Immunol.* 187(4), 1877–1883 (2011).

57 Sommer A, WHO. *Vitamin A Deficiency and its Consequences: A Field Guide to Detection and Control.* (3rd). WHO, Geneva, Switzerland. (1995).

•• **A pioneer and authority on oral vitamin A therapy for treatment of vitamin A deficiency-associated ocular disease. This publication highlights the need for novel biomarkers for determining subclinical vitamin A deficiency.**

58 Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhea in children with preexisting mild vitamin a deficiency. *Am. J. Clin. Nutr.* 40(5), 1090–1095 (1984).

59 Martín M, Gallego-Llamas J, Ribes V *et al.* Dorsal pancreas agenesis in retinoic acid-deficient RALDH2 mutant mice. *Dev. Biol.* 284(2), 399–411 (2005).

• **Demonstrates the vital role of vitamin A in pancreatic development.**

60 Oström M, Loffler KA, Edfalk S *et al.* Retinoic acid promotes the generation of pancreatic endocrine progenitor cells and their further differentiation into beta-cells. *PLoS ONE* 3(7), e2841 (2008).

61 Chertow BS, Blaner WS, Baranetsky NG *et al.* Effects of vitamin A deficiency and repletion on rat insulin secretion *in vivo* and *in vitro* from isolated islets. *J. Clin. Invest.* 79(1), 163–169 (1987).

62 Matthews KA, Rhoten WB, Driscoll HK, Chertow BS. Vitamin A deficiency impairs fetal islet development and causes subsequent glucose intolerance in adult rats. *J. Nutr.* 134(8), 1958–1963 (2004).

63 Ghyselinck NB, Båvik C, Sapin V *et al.* Cellular retinol-binding protein I is essential for vitamin A homeostasis. *EMBO J.* 18(18), 4903–4914 (1999).

64 Henquin JC, Rahier J. Pancreatic alpha cell mass in european subjects with Type 2 diabetes. *Diabetologia* 54(7), 1720–1725 (2011).

65 Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with Type 2 diabetes. *Diabetes* 52(1), 102–110 (2003).

66 Cnop M, Welsh N, Jonas JC, Jörns A, Lenzen S, Eizirik DL. Mechanisms of pancreatic beta-cell death in Type 1 and Type 2 diabetes: many differences, few similarities. *Diabetes* 54(Suppl. 2) S97–S107 (2005).

67 Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. *Lancet* 383(9922), 1084–1094 (2014).

68 Bhatia E, Baijal SS, Kumar KR, Choudhuri G. Exocrine pancreatic and beta-cell function in malnutrition-related diabetes among north Indians. *Diabetes Care* 18(8), 1174–1178 (1995).

69 Al-Amin AN, Ahrén B. Relation between malnutrition and development of diabetes mellitus. *Int. J. Pancreatol.* 26(3), 125–130 (1999).

70 Mcmillan DE. Tropical malnutrition diabetes. *Diabetologia* 29(2), 127–128 (1986).

71 Sanjeevi CB, Kanungo A, Samal KC. Immunogenetic studies on malnutrition-modulated diabetes mellitus. *Ann. NY Acad. Sci.* 958, 144–147 (2002).

72 Ekoé JM, Zimmet P, Williams DRR. *The Epidemiology of Diabetes Mellitus: An International Perspective.* Wiley, Chichester, UK (2001).

73 Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect. Dis.* 9(12), 737–746 (2009).

74 Leung CC, Lam TH, Chan WM *et al.* Diabetic control and risk of tuberculosis: a cohort study. *Am. J. Epidemiol.* 167(12), 1486–1494 (2008).

75 Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. *Diabetes Metab.* 18(3), 187–201 (1992).

76 Alisjahbana B, Van Crevel R, Sahiratmadja E *et al.* Diabetes mellitus is strongly associated with tuberculosis in indonesia. *Int. J. Tuberc. Lung Dis.* 10(6), 696–700 (2006).

77 Semba RD. Vitamin A, immunity, and infection. *Clin. Infect. Dis.* 19(3), 489–499 (1994).

78 Stephensen CB, Jiang X, Freytag T. Vitamin A deficiency increases the *in vivo* development of IL-10-positive Th2 cells and decreases development of Th1 cells in mice. *J. Nutr.* 134(10), 2660–2666 (2004).

79 Brown CC, Noelle RJ. Seeing through the dark: new insights into the immune regulatory functions of vitamin A. *Eur. J. Immunol.* 45(5), 1287–1295 (2015).

80 Mathur ML. Role of vitamin A supplementation in the treatment of tuberculosis. *Natl Med. J. India* 20(1), 16–21 (2007).

81 Hanekom WA, Potgieter S, Hughes EJ, Malan H, Kessow G, Hussey GD. Vitamin A status and therapy in childhood pulmonary tuberculosis. *J. Pediatr.* 131(6), 925–927 (1997).

82 Kassu A, Ota F, Nhien NV *et al.* Deficient serum retinol levels in HIV-infected and uninfected patients with tuberculosis in gondar, ethiopia. *Nutr. Res.* 2(27), 86–91 (2007).

83 Pakasi TA, Karyadi E, Wibowo Y *et al.* Vitamin A deficiency and other factors associated with severe tuberculosis in Timor and Rote Islands, East Nusa Tenggara Province, Indonesia. *Eur. J. Clin. Nutr.* 63(9), 1130–1135 (2009).

84 Sinclair D, Abba K, Grobler L, Sudarsanam TD. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst. Rev.* (11), CD006086 (2011).

85 Wheelwright M, Kim EW, Inkeles MS *et al.* All-*trans* retinoic acid-triggered antimicrobial activity against mycobacterium tuberculosis is dependent on NPC2. *J. Immunol.* 192(5), 2280–2290 (2014).

86 Yamada H, Mizuno S, Ross AC, Sugawara I. Retinoic acid therapy attenuates the severity of tuberculosis while altering lymphocyte and macrophage numbers and cytokine expression in rats infected with mycobacterium tuberculosis. *J. Nutr.* 137(12), 2696–2700 (2007).

87 Campos FA, Flores H, Underwood BA. Effect of an infection on vitamin A status of children as measured by the relative dose response (RDR). *Am. J. Clin. Nutr.* 46(1), 91–94 (1987).

88 Thurnham DI, Mccabe GP, Northrop-Clewes CA, Nestel P. Effects of subclinical infection on plasma retinol concentrations and assessment of prevalence of vitamin A

deficiency: meta-analysis. *Lancet* 362(9401), 2052–2058 (2003).

89 Alwan A, WHO. *Global Status Report on Noncommunicable Diseases 2010.* WHO, Geneva, Switzerland (2011).

90 Wang Q, Ma A, Bygbjerg IC *et al.* Rationale and design of a randomized controlled trial of the effect of retinol and vitamin D supplementation on treatment in active pulmonary tuberculosis patients with diabetes. *BMC Infect. Dis.* 13, 104 (2013).

91 Chan JC, Zhang Y, Ning G. Diabetes in China: a societal solution for a personal challenge. *Lancet Diabetes Endocrinol.* 2(12), 969–979 (2014).

92 Black RE. Global distribution and disease burden related to micronutrient deficiencies. *Nestle Nutr. Inst. Workshop Ser.* 78, 21–28 (2014).

93 Agarwal S, Reider C, Brooks JR, Fulgoni VL. Comparison of prevalence of inadequate nutrient intake based on body weight status of adults in the United States: an analysis of NHANES 2001–2008. *J. Am. Coll. Nutr.* 34(2), 126–134 (2015).

94 Whatham A, Bartlett H, Eperjesi F *et al.* Vitamin and mineral deficiencies in the developed world and their effect on the eye and vision. *Ophthalmic Physiol. Opt.* 28(1), 1–12 (2008).

95 Guo T, Hebrok M. Stem cells to pancreatic beta-cells: new sources for diabetes cell therapy. *Endocr. Rev.* 30(3), 214–227 (2009).

96 Jun HS. *In vivo* regeneration of insulin-producing beta-cells. *Adv. Exp. Med. Biol.* 654, 627–640 (2010).

97 Pérez RJ, Benoit YD, Gudas LJ. Deletion of retinoic acid receptor β (RARβ) impairs pancreatic endocrine differentiation. *Exp. Cell Res.* 319(14), 2196–2204 (2013).

98 Micallef SJ, Janes ME, Knezevic K, Davis RP, Elefanty AG, Stanley EG. Retinoic acid induces PDX1-positive endoderm in differentiating mouse embryonic stem cells. *Diabetes* 54(2), 301–305 (2005).

99 Vetere A, Marsich E, Di Piazza M, Koncan R, Micali F, Paoletti S. Neurogenin3 triggers beta-cell differentiation of retinoic acid-derived endoderm cells. *Biochem. J.* 371(Pt 3), 831–841 (2003).

100 Micallef SJ, Li X, Janes ME *et al.* Endocrine cells develop within pancreatic bud-like structures derived from mouse ES cells differentiated in response to BMP4 and retinoic acid. *Stem Cell Res.* 1(1), 25–36 (2007).

101 Gu C, Stein GH, Pan N *et al.* Pancreatic beta cells require NeuroD to achieve and maintain functional maturity. *Cell Metab.* 11(4), 298–310 (2010).

102 Guo S, Dai C, Guo M *et al.* Inactivation of specific β cell transcription factors in Type 2 diabetes. *J. Clin. Invest.* 123(8), 3305–3316 (2013).

103 Rovira M, Scott SG, Liss AS, Jensen J, Thayer SP, Leach SD. Isolation and characterization of centroacinar/terminal ductal progenitor cells in adult mouse pancreas. *Proc. Natl Acad. Sci. USA* 107(1), 75–80 (2010).

104 Tallman MS, Andersen JW, Schiffer CA *et al.* All-*trans* retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. *Blood* 100(13), 4298–4302 (2002).

105 Baldwin HE, Nighland M, Kendall C, Mays DA, Grossman R, Newburger J. 40 years of topical tretinoin use in review. *J. Drugs Dermatol.* 12(6), 638–642 (2013).