

Taking a Daily Vitamin to Prevent Type 1 Diabetes?

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Type 1 diabetes is an autoimmune disorder characterized by genetic susceptibility associated with a growing number of loci, including major histocompatibility complex (MHC), which provides a strong influence (1). While the number of susceptibility genes and loci is numerous, an even larger list of environmental agents has long been noted to influence, in either a positive or negative fashion, the risk for or progression to type 1 diabetes (2). Unfortunately, studies examining genetic and environmental influences on type 1 diabetes are remarkably complex in terms of study design, performance, and data analysis. Large study populations are also required for identifying minor influences of genetic loci or environmental agents, yet these efforts often result in the identification of candidates with relatively small odds ratios (i.e., a small influence on disease risk). In addition, type 1 diabetes is quite heterogeneous in its presentation, form, and characteristics when examined from either a metabolic or an immunologic perspective. It is also probable that some degree of complexity arises from geographical clusters wherein specific gene-environment interactions for a particular region yield different answers to the question of what causes type 1 diabetes (3).

What is evident is that an increase in type 1 diabetes is occurring globally, yet, as previously emphasized, many hypotheses exist as to the cause for this observation (4). Of those thought to be environmental in nature, vitamins have gained particular attention of late, the most notable perhaps being vitamin D. This is based on epidemiologic-, therapeutic-, and genetic-based studies for this molecule in type 1 diabetes (5–7). At the same time, vitamin A, another fat-soluble vitamin with immunomodulatory effects, has been ascribed as being relatively deficient in subjects with established type 1 diabetes (8). Indeed, recent studies outside the type 1 diabetes arena have noted vitamin A as a major “agent of influence” in the development of what is widely referred to as “oral tolerance” to dietary agents, as well as in the regulation of immune responses, in general, as shown in Fig. 1 (9). However, an immediate intellectual conflict arises when attempting to associate these vitamins collectively with type 1 diabetes risk in that vitamin A deficiency is largely considered a problem in the developing world, whereas vitamin D deficiency is both dietary and latitude influenced. Therefore, it remains to be seen if deficiencies of either of these vitamins actually lead to increased cases of

type 1 diabetes in a uniquely genetic and geographical way.

Animal studies of type 1 diabetes involving NOD mice have shown beneficial results with either vitamin A or vitamin D therapy (10–13). When testing therapeutic interventions in NOD mice, most studies to date have loosely been divided into early prevention (in 4- to 8-week-old mice), late prevention (in 10- to 12-week-old mice), intervention (at diabetes onset), or reversal (in established diabetes). Broadly speaking, a large number of agents have shown efficacy in both forms of prevention, with fewer in intervention, and so far only islet transplantation has realistically been translated from mice to humans as a means to intervene in type 1 diabetes (14).

In this issue of *Diabetes*, Van et al. (15) provide evidence that a derivative of vitamin A, all-trans retinoic acid (ATRA), inhibits diabetes formation in NOD mice. This was essentially demonstrated in two ways. First, the authors used an accelerated disease model where spleen cells from already diabetic mice were adoptively transferred into a strain of mice normally resistant to type 1 diabetes development (i.e., NOD.scid), a system whereby diabetes is consistently transferred into the recipient mice. These recipient NOD.scid mice are naturally type 1 diabetes resistant in that while they have the same genetic background as NOD mice, they have also a mutation that has rendered them immunodeficient (i.e., no T- or B-lymphocytes). This makes this strain of animals particularly useful for transferring various cell populations in order to dissect out contributions of specific facets of the immune system to type 1 diabetes progression. Van et al. (15) demonstrate that by treating NOD.scid recipients with ATRA, the transfer of diabetes by diabetogenic splenocytes could be markedly suppressed. Their second means of ascribing efficacy involved demonstration in a “late prevention” protocol (i.e., using ATRA to treat 10-week-old NOD mice). In these latter efforts, intraperitoneal injection of ATRA significantly delayed the progression to type 1 diabetes in treated animals.

Armed with these beneficial therapeutic observations, these authors took their research a step further by pursuing identification of the mechanism(s) underlying these observations, efforts that directed them to notations regarding the influence of ATRA on immunoregulatory pathways. In short, they found decreased effector T-cell function and increased regulatory T-cell activities in association with ATRA treatment. Of further interest, they did not find an effect of ATRA on so-called “Th17 cells,” a population of cells recently implicated in other (i.e., non-diabetic) autoimmune disorders (16–18). These Th17 cells are thought by some (19) to represent the prime mediators of inflammation. Here, it is important to note that while Van et al. (15) found in vitro evidence that ATRA attenuated Th17 differentiation, the failure to demonstrate this in vivo requires further investigation. The authors also correctly point out that in terms of therapy, future studies in

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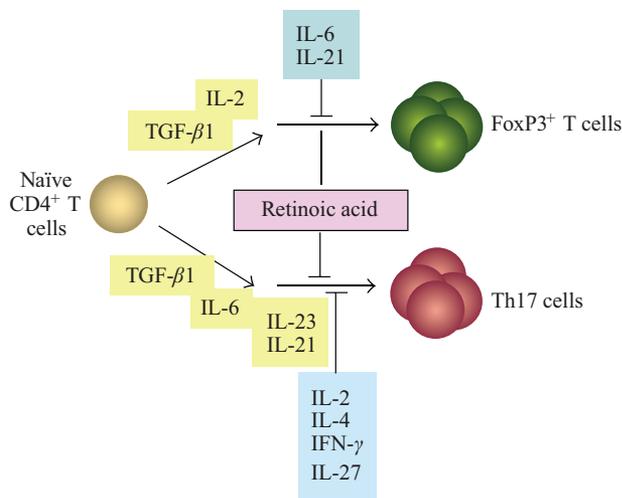


FIG. 1. A central role for vitamin A has been proposed in the reciprocal regulation of inflammatory versus regulatory T-cells. Within this schema, vitamin A suppresses the polarization of Th17 cells while promoting the induction of T regulatory cells in the context of the noted cytokines. (Reproduced with permission from *Clin Dev Immunol* [DOI 2008:416910], © 2008.)

recent-onset NOD mice as well as in animals with established type 1 diabetes must be performed.

So, what does this all mean in terms of human type 1 diabetes? First, the NOD model has been useful in many investigations, but we have yet to fully translate a prevention or intervention treatment modality from the NOD mouse to man (note: promising agents do exist but do not yet form a standard of care). For this reason, it would have been helpful for Van et al. to have treated the animals with an oral dose (rather than intraperitoneal injection) that would approximate tolerable human doses to avoid hypervitaminosis A. Also, this would fall under the category of a “safe” treatment, with the aforementioned proviso that vitamin A is toxic in high doses. Finally, both vitamin A and D are fat soluble and found in fish oil supplements. Epidemiological evidence suggests that increased consumption of n-3 fatty acids and fish oil (which contain various amounts of vitamin A and D) is associated with reduced type 1 diabetes-associated autoantibody conversion (20). This raises the intriguing possibility that a combination of vitamins A and D, in safe pharmacologically formulated doses rather than the usual daily recommended dose, might be of benefit in the treatment of those at increased risk for type 1 diabetes. Clearly, more studies in animal models as well as in humans are required to validate or disprove this notion.

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