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Review

Role of vitamin A in type 2 diabetes mellitus biology: Effects of intervention therapy in a deficient state

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ABSTRACT

Diabetes has emerged as the biggest pandemic of our times, growing parallel to obesity. Insulin treatment regimens have been unable to completely inhibit protein glycation, which is responsible for the development of increased oxidative stress in diabetic tissues. Coupled with recent evidences that highlight the role of reactive oxygen species in the onset and progression of type 2 diabetes mellitus (T2DM), the antioxidants have taken prime focus as a possible intervention strategy. Studies have established a role of antioxidant vitamins C and E in improving patient condition in the past. Vitamin A, in addition to its role as an antioxidant, boasts a pleiotropic role in cell regulation through its action on gene regulation, maintenance of epithelial cell integrity, and resistance to infection. Studies have also ascribed a role to vitamin A in up-regulating the antioxidant enzyme functions in the body. Additionally, a link has been found between diabetes and deficient vitamin A levels indicating vitamin A supplementation may have a role in T2DM biology. This review therefore focuses on the vitamin A intervention in T2DM patients having deficient in vitamin A.

Introduction

Over the past 20 years, world population diagnosed with diabetes has more than doubled. The current estimates suggest a further increase in numbers, with a frequency that will affect 552 million people globally by 2030 [1], making diabetes a high-priority disease of the present times.

Broadly, diabetes mellitus is classified as type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) based on the body's ability to either produce or use insulin, respectively. Of the two, the latter comprises 90% of people suffering from diabetes and therefore poses a greater health concern. T2DM is largely a result of excess body weight and physical inactivity that contributes to increased insulin resistance [2]. The onset of T2DM involves both genetic and environmental elements that affect β-cell function and tissue (muscle, liver, adipose, and pancreas) insulin sensitivity resulting in hyperglycemia [3] (Fig. 1). Genetically, diabetes is polymorphic and many genes are involved, with mutations or polymorphism in each making its contribution to an increased probability of disease onset, for example, *ABCC8* (sulphonylurea receptor), *SLC2* (GLUT), *INS* (insulin), and so on [4]. Family history of diabetes increases the susceptibility to T2DM with mature onset diabetes of young accounting for 2% to 5% of all patients with T2DM [5]. Risk also increases with age, which is synonymous with the accumulation of β-cell damage and oxidative insult. This is exemplified by the fact that majority of the population suffering from T2DM lies above the 45-y age group, although recent studies indicate a downward shift in this class [2].

More recently, studies have linked T2DM pathogenesis with mitochondrial dysfunctions owing to its role in insulin release and energy homeostasis [6]. Aging-associated loss of mitochondrial function was found to predispose older individuals to intramyocellular lipid accumulation resulting in insulin resistance. Low density of mitochondria has been consistently reported in patients with T2DM [7]. Additionally, reactive oxygen species (ROS), which is heavily implicated in the pathogenesis of the disease [8], is principally produced as a result of incomplete electron transport in mitochondria. The increased oxidative stress then drives the diabetes progression and may account for various associated complications [6]. A number of pathways are involved in ROS production due to persistent hyperglycemia [8] for example, polyol pathway, nonenzymatic

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glycation of proteins, and activation of protein kinase C (PKC; Fig. 2). All these proposed mechanisms ultimately act via mitochondria, resulting in increased generation of ROS [6,9,10].

Cellular antioxidant systems are critical in neutralizing ROS. However, owing to the oxidative insult in uncontrolled diabetes, their levels are often found to be altered [11]. The deficient antioxidant status of patients with T2DM is thought to contribute to cardiovascular complications [12,13]. Exogenous supplementation of antioxidants has been shown to relieve stress in this regard [14]. Because β cells are deficient in antioxidants, dietary intake of antioxidants has been employed as an intervention strategy to improve longevity in patients with T2DM [15]. Most vitamins, known to have a variable degree of antioxidant activity, are routinely employed as an intervention in T2DM therapy. Previously, vitamins C and E were ascribed a protective function in diabetes as a result of their role in controlling ROS production, albeit with inconsistent results [16,17]. Despite the highest antioxidant potential among all the known vitamins [18], the use of vitamin A as a therapeutic intervention in T2DM is still in its infancy.

Reduced serum vitamin A levels have been routinely reported in patients with T1DM. However, the data regarding serum vitamin A levels in patients with T2DM is ambiguous [19]. Although, several studies have reported against changes in vitamin A status in patients with T2DM [19,20]; research now provides evidence for a reduced vitamin A status in most of the people suffering from T2DM. It was further reported that all the malnourished diabetes patients suffered from a condition of vitamin A deficiency compared with the malnourished control population [21].

Vitamin A has been ascribed a role in islet regulation and pancreas development [22]. In obese mice, vitamin A supplementation resulted in reduced hyperglycemia and hyperlipidemia [23]. Its importance in disease biology is therefore clearly highlighted and necessitates an exploration of the molecular mechanism involved in therapy.

Review of literature for the present study included a PubMed and Google search of the role of vitamin A or retinol in T2DM biology. All the papers consulted were of English language.

Vitamin A metabolism

Vitamin A (retinol) is a lipid soluble, pale yellow crystalline solid [24] that is obtained from animal sources as an ester, primarily retinyl palmitate. Plants are devoid of retinol and contain carotenoids such as β-carotene that serve as provitamins [24]. Once absorbed in the intestinal mucosa, both retinyl esters and carotenoids are converted to retinol, which is stored in the liver [25]. The stored retinol can either be converted to the aldehyde form, retinal, or further oxidized to yield retinoic acid (RA). Retinal has important functions in the visual cycle, whereas RA is involved in controlling the expression of multiple genes (>500) via binding and activating the members of the nuclear hormone receptor family, retinoic acid receptors (RAR) and retinoid X receptors (RXR) [26,27]. These receptors are capable of forming heterodimers by binding with other nuclear hormone receptors; chiefly the vitamin D receptors (VDRs) and peroxisome proliferator-activated receptors (PPARγ) [28].

Vitamin A deficiency is associated with decreased immunity and night blindness. The daily average requirement of vitamin A for adults has been estimated as 500 μg for women and 625 μg for men [17].

High intake of provitamin carotenoids, such as β-carotene does not cause hypervitaminosis due to regulated formation of the active metabolites of vitamin A [29]. Consumption of preformed retinol is associated with vitamin A toxicity, possibly in part due to its antagonistic action on vitamin D-mediated cellular processes [25,30] (Fig. 3). The upper level of intake for adults is therefore set to 3000 μg/day (10,000 IU) and in patients with dyslipidemia or hyperlipoproteinemias, the maximal dosage should be restricted to <5000 units/day [17]. This review, however, discusses the deficiency of vitamin A in T2DM disease biology.

Interestingly, vitamin A deficiencies have been noted in the Asian developing countries and in lower income groups in the United States, where diabetes is on the rise [31]. An increased concentration of both cellular retinol binding protein (CRBP) and cellular RA binding protein (CRABP) in the islets results from a deficiency of vitamin A and may impair insulin release. Retinoic acid has been recently identified as a regenerator of rat insulinoma cell line. It is also reported to increase glucokinase activity in RINmF5 cell line as well as fetal islets and differentiated adult islets boasting of a role in regulation of islet function and insulin release [32,33]. Vitamin A has also emerged to play a role in energy homeostasis through its actions on PKC. The formation of PKC–retinol complex ensures an enhanced flux of pyruvate into the krebs cycle via signaling through the pyruvate dehydrogenase complex, thereby acting as a nutritional sensor [34]. A reduced baseline response was observed in vitamin A-deficient lecithin:retinol acyl transferase knockout mice, which increased to normal levels within 3 h by an intraperitoneal injection of vitamin A, suggesting its importance in energy homeostasis [35].

T2DM represents a state of altered oxidation reduction as a consequence of insulin insensitivity that leads to cell damage and an eventual loss of β-cell activity. Research provides evidence of vitamin A-mediated regulation of insulin release and energy homeostasis. This review therefore aimed to explore the potential therapeutic impact of vitamin A supplementation in vitamin A-deficient disease pathophysiology.

Potential mechanisms through which vitamin A can impact T2DM

Chelation of oxide radicals

Diabetes is characterized by hypoxia and retinol serves as a better lipoperoxyl radical scavenger at low partial pressures of oxygen [35]. During lipid oxidation, retinol is consumed through self-oxidation reactions and is oxidized to 5,6-retinol epoxide, thereby quenching the excess free radicals produced [36].

In the pancreatic islets opening of K^+/adenosine triphosphate (ATP) channel is a prerequisite for insulin secretion and is determined by the ATP/adenosine diphosphate (ADP) ratio. Mitochondrial dysfunction causes changes in the ATP/ADP ratio and is thought to affect the glucose-induced insulin secretion response. ROS, in addition to causing nonspecific damage to the biomolecules, also results in the loss of mitochondrial membrane potential. This is believed to uncouple the respiratory chain with a consequent leakage of superoxide anions and hydrogen peroxide from the electron transport chain presumably amplifying the redox stress until damage becomes irreversible [37].The site of ROS generation in mitochondria is very close to mitochondrial DNA and hence accounts for the loss of function. Furthermore, activation of uncoupling protein 2 (UCP-2) by superoxide radical also decreases the ATP/ADP ratio and thus reduces the insulin secretory response. The chelation of ROS