

# Considering The Role of Vitamin A in Glucose Metabolism

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## Abstract

Vitamin A as an essential micronutrient is needed for multiple physiological processes. The association between this nutrient and glucose metabolism has been documented in numerous studies with animals and humans. Vitamin A is required for the maintenance of pancreatic  $\beta$  and  $\alpha$  cell mass and for glucose-stimulated insulin secretion. Moreover, the vitamin and its metabolites modulate insulin resistance. Many studies indicate the role of vitamin A in the pathogenesis of type 1 diabetes through its effect on regulation of autoimmune processes and  $\beta$  cell mass as well as in type 2 diabetes through its effect on insulin resistance. Retinol 'family' plays an important role in maintaining the correct glucose metabolism, so it is essential to provide the homeostasis of this nutrients in the body. Awareness of pathophysiology of retinol's impact on the organism is crucial, one of the most costly chronic diseases may be prevented by food fortification and it may result in insertion of newest drugs in diabetology.

**Keywords:** vitamin A; retinol; retinol-binding protein;  $\beta$ -cells; glucose metabolism; diabetes.

## Introduction

Vitamin A is a group of unsaturated nutritional organic compounds which includes retinol, retinal, retinoic acid and pro vitamin A carotenoids. In nature,  $\beta$ -carotene- the most common form of carotene in plants- is a precursor to vitamin A via the action of beta-carotene 15,15'-monooxygenase in the small intestine and liver. In animal source foods, the basic form in which vitamin A occurs is the ester- retinyl palmitate, which undergoes desertification is small intestines to alcohol- retinol. The last one mentioned plays an essential role of Vitamin A. It is transported in bloodstream by retinol binding protein (RBP). RBP4, interacts with two receptors, the Toll-like receptor 4 (TLR4) and the a transmembrane pore STRA6 which transports vitamin A bidirectional between extra- and intracellular compartment leading to the activation of c-Jun N-terminal protein kinase (JNK) pathways and JAK2/STAT5 cascade, respectively. Inside the cell, retinol binds to the cellular retinol binding protein (cRBP), while retinoic acid binds to cellular retinoic acid binding protein (cRABP). Such unified retinoid particles have specific nuclear receptors (retinoic acid receptor (RAR) and retinoid X

receptor (RXR)) which contain DNA- binding domains. Altered BP expression affects retinoid function- for instance by impairing pancreas development, resulting in abnormal glucose and energy metabolism. [1,2,3,4]

Vitamin A is one of the earliest discovered vitamin and researches on this nutrient date back to 19th century. In 1920 Paul Karrer described the chemical structure of vitamin A, in 1932 Holmes and Corbet isolated and crystallized vitamin A and in 1937 the method of vitamin A synthesis has been developed. [5,6,7]

Vitamin A is a fat-soluble nutrient important for vision, reproduction, embryonic development, cell differentiation, epithelial barrier function and adequate immune responses.[8] It is also essential for the regulation of immune functions, including T-cell-mediated immunity. [9]

## Role of vitamin A in glucose metabolism

Vitamin A is an micronutrient crucial for a variety of physiological processes; its role in glucose metabolism, however, has not yet been clearly defined. Studies on rats have shown dependence between glycogen content in the liver and the level of vitamin A. [10,11]

Feeding rodents with vitamin A-deficient diet altered the structure and functions of pancreas by diminishing the islet cells, possibly by inducing cellular stress-mediated apoptosis and reducing SCD1-mediated oleic acid (C18:1) synthesis. It resulted in decreased levels of plasma insulin, glucagon and C-peptide and perturbed the overall cellular metabolism. [12]

Experimental studies have also shown that maternal deficiency of vitamin A during pregnancy affects offspring and leads to decrease of  $\beta$ -cell functions by reducing fetal  $\beta$ -cell replication and impairs glucose-stimulated insulin secretion (GSIS). [13,14]

Vitamin A deficiency causes major reductions in levels of the intracellular binding protein Crbp1 and the retinoic acid-metabolizing enzyme Cyp26a1. There is a reduction in pancreatic islet sizes and the associated aberrant endocrine functions, which shows similarities to the phenotype in advanced type 2 diabetes.

[15] Retinoic acid signaling for maintaining a range of cellular processes, including cell differentiation, proliferation, and apoptosis were described [16] Authors indicate that all-trans-retinoic acid (ATRA) signaling mediated by RARs is required for maintaining  $\beta$ -cell mass and function. In another study, authors decided to evaluate whether treatment with retinoic acid can ameliorate diabetes. All-trans retinoic acid was used to treat Streptozotocin (STZ)-induced diabetic mice. It resulted in improvement of blood glucose levels, which was accompanied by an increase in the amount of  $\beta$  cells. The ATRA-induced production of vascular endothelial growth factor-A from the pancreatic islets was possibly the key factor that mediated the restoration of islet vascularity and recovery of  $\beta$ -cell mass. [17]

Another study by Wang et al. demonstrated that ATRA effectively prevents the progression of T1DM in a murine model of the disease by reducing IFN- $\gamma$  levels and increasing IL-4 levels. [18] Review of results from research on the association between vitamin A and carbohydrate, lipid and protein metabolism in patients with diabetes mellitus were presented by Chen W and Chen G. [19] These studies have clearly shown that vitamin A plays important role in metabolic homeostasis.

### Metabolic effects of vitamin A in diabetic patients

Recently, much attention has been devoted to the role of vitamin A in the regulation of macronutrient metabolism in various disease states, especially obesity, type 2 diabetes and other metabolic disorders. Vitamin A is one of the antioxidant factors, hence the limits of its concentration in the body may play a role in the development of diabetes. [20,21] Diabetes mellitus (DM) and diabetic retinopathy (DR) are associated with oxidative stress and carotenoids- vitamin A precursors- are known to have antioxidant properties. Therefore, the Chinese cross-sectional study aimed to test the relationship between serum carotenoid concentrations and the risk for DM and DR. A total of 747 subjects, consisting of 272 DR patients, 190 diabetic patients without retinopathy, and 285 non-diabetes mellitus healthy controls, were recruited. Levels of  $\alpha$ -carotene were significantly lower in DR patients and  $\beta$ -carotene were significantly lower in DM patients.  $\beta$ -carotene concentration was associated with reduced risk for DM (OR (95%CI): 0.56 (0.34, 0.91),  $P=0.02$ ) and  $\alpha$ -carotene was associated with reduced risk for DR in non-smokers (OR (95%CI): 0.41 (0.17, 0.99),  $P=0.048$ ). No significant association was found between hemoglobin A1c and any carotenoids ( $P>0.05$ ). Authors conclude, that serum  $\beta$ -carotene may have a protective effect on DM and  $\alpha$ -carotene may be a protective factor for DR in non-smokers. [22] Hernández-Pedro study found that the administration of vitamin A partly reverses the damage induced by diabetic neuropathy (DN) has the same therapeutic effect as ATRA on peripheral neuropathy. [23] In addition, ATRA treatment suppressed UAE and TGF- $\beta_1$  synthesis through reductions in PKC activity and ROS production and these results suggest that retinoic acid has a potential therapeutic role for diabetic nephropathy. [24] It was found that retinoic acid, a derivative of vitamin A, may cause increased insulin sensitivity. [25,26] Retinoids have a very important function as antioxidants, while retinol binding protein (RBP) has an important effect on insulin sensitivity, acting as an adipokine. [27] RBP, due to some

studies, is considered to be strongly associated with insulin resistance and for researchers it has become an attractive drug target in type 2 diabetes. [28] Increased concentration of retinol binding protein, particularly of RBP4, leads to low glucose uptake by skeletal muscle and high glucose liver production in mice, with a consequent increase in insulin resistance. [29]

A recent extensive discussion of the potential role of RBP4 in the pathogenesis of insulin-resistant disorders has been presented by the authors of Poland. [30]

Elevated retinol-free RBP4 contributes to insulin resistance in gestational diabetes mellitus in rats. [31]

One study aimed to quantify RBP4 serum standards in 139 women with a wide range of body mass index (BMI) and glucose tolerance level. Although RBP4 have shown lower levels in diabetic and obese, a strong correlation with HOMA-IR leads to conclusion that insulin resistance is growing along with increasing in RBP4 levels. [32] Research by Dutch authors showed that polymorphism in the RBP4 gene is associated with increased risk of type 2 diabetes. [33]

More attention has been recently paid to the role of vitamin A in preventing the development of autoimmune diabetes. It is known that vitamin A is involved in the regulation of autoimmune processes, hence the possibility of its participation in the prevention of type 1 diabetes is considered. [34]

Subsequently, findings establish that holo-RBP and next signaling axis protein- receptor STRA6 are potent regulators of diurnal insulin responses and may represent a novel therapeutic target in type II diabetes. [28] Shidfar et al. investigated effects of combination of zinc and vitamin A supplementation on serum fasting blood sugar (FBS), insulin, apoprotein B and apoprotein A-I in patients with type 1 diabetes (group of forty-eight diabetic patients, 7 to 20-year-old). [35]

They found that combined zinc and vitamin A supplementation can improve serum apoprotein A-I, apoprotein B and the apoprotein B/apoprotein A-I ratio in patients with type 1 diabetes.

A case-control study conducted by Baena et.al aimed to evaluate the effects of type 1 diabetes mellitus (IDDM) on plasma levels of vitamin A (retinol) and serum levels of retinol-binding protein (RBP) and their relationship with the atherogenic indicators. [36] Higher RBP concentrations in IDDM children ( $P=0.05$ ), lower retinol levels ( $P=0.05$ ) and lower vitamin A/cholesterol ratio ( $P=0.02$ ) than in the control group were found. The IDDM children with poor metabolic control face a higher atherogenic risk and vitamin A 'relative deficiency' risk. Relationships between retinol and RBP with atherogenic indicators were found. The results suggest that vitamin A therapeutic supplements in IDDM children may reduce or prevent atherogenic risk.

### Summary- what is known, what can already be done and what are perspectives for the future?

Research on the role of vitamin A in metabolic processes has a long history. Recently, more attention is devoted to the

role of vitamin A in the etiopathogenetic of glucose metabolism disorders and the development of diabetes. [37]

Outcomes of these studies lead to attempts to use this vitamin in the prevention and treatment of diabetes. Danish authors carried out a retrospective study in which they found that mother's extra supplementation with vitamin A during pregnancy reduces the risk of developing type 2 diabetes in their offspring. [38] Recently, vanadium compounds have been prepared and functionalized to decrease the level of hyperglycemia and vitamin A is known to boost beta cell activity. It resulted in synthesis of a new anti-diabetic drug formed from the complexation of a vanadium (IV) salt with vitamin A. The results of the animal studies demonstrate the ability of such complex to act as an anti-diabetic agent, as measured by improvements of lipid profile, antioxidant activity and kidney and liver functions. [39]

Retinoic acid-related orphan receptor  $\gamma$  (ROR $\gamma$ ), due to recent studies, regulates several glucose metabolic genes of the hepatic clock and identifies a novel metabolic function in the diurnal regulation of hepatic gluconeogenesis and insulin sensitivity. Precise molecular mechanisms are not fully understood. ROR $\gamma$  antagonist may provide a novel strategy in the management of metabolic diseases, including type 2 diabetes. [40]

### Presented outcomes give tempting perspective for the future, but nowadays we also can implement some findings to ours and our patients life.

To determine the effects of placebo vs. an encapsulated supplement of fruit and vegetable juice concentrate (FVJC) on serum  $\beta$ -carotene levels, insulin resistance, adiposity, and subclinical inflammation, authors of the study involved thirty age-matched prepubertal boys (9 lean and 21 overweight (OW)). Baseline  $\beta$ -carotene concentrations correlated inversely with HOMA-IR, leptin-to-adiponectin ratio, and abdominal fat mass ( $P \leq .01$ ). A 6-month supplementation with FVJC in the presence of nutritional counselling was associated with an increase in serum  $\beta$ -carotene concentrations and a reduction in adiposity in conjunction with an improvement in insulin resistance in OW boys. [41]

Pistachio is a nut with high polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), polyphenols and carotenoids content, and the synergism between these compounds appears to affect glucose metabolism. In the systematic review authors analyzed studies in which the effect of chronic consumption of pistachio on markers of glucose metabolism was evaluated in pre-diabetic and type 2 diabetics. Four articles were selected, of which three tested the intake of 50 to 57 g of pistachio/day and one 20% of the daily caloric intake, for a period of 1 to 4 months. Studies reported a decrease in fasting blood glucose, insulinemia, HOMA-IR, and fructosamine, with no change in HbA1c. The synergism between PUFA, MUFA, polyphenols and carotenoids present in pistachios can modulate specific miRNA, increasing insulin sensitivity through the PI3K-AKT signalling pathway. [42]

A meta-analysis conducted in 2016 revealed that higher dietary intake of selenium, vitamin C, vitamin E,  $\beta$ -carotene and

$\beta$ -cryptoxanthin was inversely associated with pancreatic cancer risk- the one in which five-year survival rate reaches barely 5%. [43]

### Conclusions

In many experimental studies it has been shown that vitamin A increases the activity of  $\beta$  cells and therefore, the lack of this vitamin plays a role in disorders of glucose metabolism. The results of researches on the role of vitamin A in metabolic processes, including diabetes, will help not only to understand the effect of micronutrients on energy metabolism, but also to develop new pharmaceutical strategies to combat metabolic diseases.

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