



Role of ascorbic acid in diabetes mellitus: A comprehensive review

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Abstract

Diabetes mellitus (DM) is a multifactorial disease with no one specific drug available to treat. The main causes of DM Type 2 are insulin resistance and decreased insulin production. Oxidative damage to beta cells due to reactive oxygen species is a trusted cause of DM2. Vitamins are a class of nutrients required in miniscule quantity. Vitamin C is one of the most powerful dietary antioxidant available, closest in structure to carbohydrate. Vitamin C and glucose competitively inhibit each other to penetrate the cell membrane by the tunneling mechanism. Clinical trials have suggested that mega doses of vitamin C reduce the microvascular complications of DM2 such as retinopathy, nephropathy, and diabetic foot. Apart from this, there is another biological significance of vitamin C. Vitamin C in higher dose reduces the (glycosylated hemoglobin concentration) levels and low-density lipoproteins. Role of vitamin C as an adjunct in the treatment of DM2, atherosclerosis has been significantly contributory. This review paper presents the different biological roles of vitamin C, in particular DM2.

Introduction

Diabetes mellitus (DM) is clinically and genetically a heterogeneous metabolic disease which is characterized by abnormally elevated blood glucose and dysregulation of carbohydrate, protein and lipid metabolism. The primary cause of DM2 is either insulin resistance or decrease in insulin production. Insulin is the principal regulatory hormone of glucose. Insulin primarily increases the facilitated transport of glucose into the cell, thus reducing blood glucose.^[1] At a biochemical level, insulin has an inhibitory effect on the gluconeogenic enzyme phosphoenolpyruvate kinase and a stimulatory effect on glycolytic enzymes such as glucokinase, pyruvate kinase, phosphofructokinase, and fructose 2,6 bisphosphatase.^[2] One of the major causes of beta cell dysfunction in DM2 is the influence of oxidative stress. Oxidative stress is mediated by reactive oxygen species (ROS) produced due to advanced glycation end formation, glucose autoxidation, glucosamine production, and oxidative phosphorylation.^[3]

Vitamin C is a water-soluble vitamin and a powerful dietary antioxidant. It is also a generous donor of electrons, thus helping in the scavenging mechanism. Mega doses of vitamin C in DM2

helps to reduce the blood glucose, reduces capillary fragility in diabetics, reduces glycosylation and decreased the production of Sorbitol.^[4] Although the mechanism of action of vitamin C in lowering the blood glucose appears promising and convincing, but its use in regular practice remains disappointing. There are limited clinical trials exploring the therapeutic benefits of using vitamin C in DM2.

Metabolism of Vitamin C

Vitamin C, also known as ascorbic acid is a water-soluble antioxidant which was first isolated in 1928 by Hungarian biochemist and Nobel prize winner Szant-GyorGyi. Human body is completely dependent on the exogenous source of vitamin C due to complete absence of L-gulonolactone oxidase in the liver. The major dietary sources of vitamin C are citrus fruits, green chillies, and tomatoes. The minor sources being dairy products. The biological viability of vitamin C reduces over time.^[5]

The metabolism of vitamin C starts from the oral buccal mucosa by means of passive diffusion. In the gastrointestinal system, the absorption is through an energy expenditure and carrier-mediated transport mechanism. The same mechanism

of absorption applies to the renal system. Hence, the saturation point of vitamin C is reached rapidly. Thus, it is advised to take vitamin C in smaller doses. The maximum absorption of vitamin C is in the gastrointestinal tract (70%). With an oral intake of 90-150 mg/day, a maximum of 68-86 mol/L of vitamin C in plasma is reached. The available vitamin C is used in 2 h, and the estimated excretion in blood is within 3-4 h. The maximum concentration of vitamin C is reached and kept is 20 mg/kg body weight, above which it is rapidly excreted in urine. Vitamin C is abundantly found in the lymphocytes, thus its levels reduce during infection and inflammation.^[6]

Vitamin C occurs in two isomeric forms, namely, L-xylo ascorbic acid and D-xylo ascorbate. The L-form is oxidized to L-dehydroascorbic acid, which is an active form of vitamin C. L-dehydroascorbic acid is further oxidized to 2-3 diketo-L-gulonic acid.^[7]

Biological Functions of Vitamin C

Following are the biological functions of vitamin C:^[8]

1. Metabolism of tyrosine, folic acid, and tryptophan.
2. Synthesis of amino acid such as carnitine and catecholamines.
3. Aids in absorption of iron and breakdown of histamine. Here iron implies the non-heme variety of iron found in plants and drinking water.
4. Ascorbic acid helps in the formation of the neurotransmitter serotonin, norepinephrine from dopamine.
5. Formation and maintenance of collagen. Vitamin C increases the level of procollagen messenger RNA.
6. Vitamin C works as a coenzyme to convert proline and lysine to hydroxyproline and hydroxylysine.
7. Ascorbic acid promotes growth, development, and maintenance of osteoblasts and delaying osteoporosis.
8. Ascorbic acid combats free radical damage by neutralizing hydroxyl and superoxide radical.
9. Vitamin C can rejuvenate vitamin E by preventing its oxidation to tocopherol radical. Thus, it provides protection of protein thiol group against oxidation.
10. Vitamin C protects the sperm from oxidative damage and helps in detoxification of the body from harmful environmental pollutants like hydrocarbons.
11. Ascorbic acid enhances lymphocyte function and lowers the bacteriological activity.

Oxidative Stress and Antioxidants

Oxygen becomes a damaging component of the cellular system when it begins to generate reactive species. Oxidative stress is defined as a disturbance in the balance between oxidants and antioxidants due to different factors such as aging, drugs, and toxicity. The ROS causes necrosis, organ damage, and ultimately death. When the antioxidant levels are limited, the damage due to oxidative stress can become debilitating and cumulative leading to several diseases. Antioxidants are natural substances that may prevent or delay cellular damage. Vitamin C, vitamin

E, and beta-carotene are the naturally occurring antioxidants. These antioxidants are biomarkers of oxidative stress. These antioxidants are either exogenous or endogenous which are either chain breaking or preventive. The various biological antioxidants include glutathione, vitamin C, E, and cysteine.^[9]

Role of Oxidative Stress in DM

Oxidative stress is increased in DM Type 2. The cause of oxidative stress is glucose autooxidation, redox imbalance, reduced antioxidant defenses including reduced activity of antioxidant enzymes. The other cause of increased oxidative is elevated levels of pro-oxidants such as ferritin and homocysteine.^[10]

AGE products are formed in chronic hyperglycemia due to the interaction of glucose with specific amino acids on proteins. Glycation of proteins alters the protein and cellular function. This leads to change in the binding of AGE to their receptors which lead to modification in cell signaling and further produces free radicals. Vascular complications in diabetes are caused due to oxidative stress. The tissues are more susceptible to ROS leading to vascular complications of DM2. The biological markers of oxidative stress in DM2 are proteins, lipids and vitamins, enzymatic, and nonenzymatic antioxidants.^[11]

Alpha-lipoic acid is an antioxidant which is known to reduce the oxidative stress *in vivo*. It enhances glucose utilization in Type 2 DM and reduces complications of DM. Alpha-lipoic acid prevents lipid peroxidation by scavenging free radicals or by increasing the antioxidant enzyme activity. Alpha-lipoic acid restores the redox status by modulating glutathione. Vitamin C lowers the levels of oxidative markers. Vitamin C and E act synergistically to prevent the effect on vitamin E by preventing its oxidation to tocopherol radical.^[12]

Role of Vitamin C in DM2

The role of vitamin C in DM2 is explained by the pathway glucose ascorbate antagonism. Both glucose and ascorbate require help from insulin before they can penetrate cell membranes using special pumps. Vitamin C and glucose helps in insulin-mediated tunneling mechanism into cells through the cell membrane. High levels of glucose obstruct vitamin C entry into the cell. Insulin pumps are present more in the WBC. This explains that vitamin C and glucose compete with each other. The three mechanism present by which vitamin C protect end organ damage in diabetes are:^[13]

1. Vitamin C functions as an antioxidant.
2. Vitamin C inhibits the intracellular accumulation of sorbitol.
3. Vitamin C reduces the glycosylation of protein.

Vitamin C is structurally similar to glucose and may, therefore, compete with glucose for transportation into the cell. In the presence of hyperglycemia, the uptake of vitamin C into cells appears impaired.

Clinical Studies Using Vitamin C in DM Type 2

There are various dosages of vitamin C which have been tried on diabetics to lower the blood glucose.

The primary outcome of all these studies was fasting blood glucose (FBG), postprandial blood glucose (PPBG), and glycosylated hemoglobin (HbA1c). There was a significant reduction in the FBG and PPBG after oral supplementation of vitamin C. The success in reduction of FBG and PPBG depends on the dose of vitamin C and the duration, for which it was taken.

Author	Year	Dosage of Vitamin C	Results
Jayesh K. Bhat	2012	500 mg/day for 3 months	Reduced FBS, PPBS, HbA1c, BUN
Ganesh N. Dakhale	2011	1000 mg/day for 3 months	Reduced FBS, PPBS, HbA1c
Parisa Ghaffani	2015	800 mg for 2 months	Reduced plasma insulin and plasma TGL
Ashraf Kotb	2015	1000 mg for 3 months	Reduced FBS, PPBS, HbA1c
Rekha Nayak	2011	1000 mg for 2 months	Reduced FBS, PPBS
Amin <i>et al.</i>	2016	500 mg for 2 months	Reduced FBS, HbA1c
Sahkouri	2011	200 mg OD	Reduced FBG, PPBS
Delvarian	2008	500 mg for 2 months	Reduced FBS, PPBS

FBS: Fasting blood sugar, PPBS: Postprandial fasting blood sugar, HbA1c: Glycosylated hemoglobin, TGL: Triglyceride lipase, BUN: Blood urea nitrogen, FBG: Fasting blood glucose

Recommended Dietary Allowance (RDA) of Vitamin C

The dietary requirement of vitamin C is a meager 60 mg/day. The proposed RDA is 200 mg/day which would be adequate enough keeping in view the pharmacokinetics of vitamin C. Higher levels of vitamins, i.e., >1000 mg/day results in better bioavailability.^[14]

Vitamin C Toxicity

Toxicity of vitamin C is very rare at dosage of 1000-1500 mg. Atrophic gastritis occurs at dosage of 3 g. Since vitamin C is water soluble, it is excreted in urine and gives a false positive test for sugar. Vitamin C should be avoided by patients having chronic kidney disease as there is the formation of oxalates which forms renal stones. However, some research suggests that the urine undergoes a transformation at the later stage.^[15]

Conclusion

This review emphasized the role of oxidative stress in DM and role of antioxidants in ameliorating the damage caused by the free radicals. Increase in the levels of oxygen and nitrogen free radicals is related to lipid peroxidation, nonenzymatic glycation of proteins, and oxidation of glucose which contributes to DM2. Vitamin C is a powerful dietary antioxidant available abundantly which competes with glucose to penetrate the cell membrane. This is facilitated by insulin. Hence, besides dietary intake of vitamin C, it should also be supplemented synthetically for better control of diabetes.

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