Vitamin C Physiology:
The Known and the Unknown in Obesity

Büşra Totan[*], Hatice Baygut, Makbule Gezmen Karadağ

Department of Nutrition and Dietetics, Gazi University, Ankara, Türkiye
*Corresponding author: busratotan@hotmail.com

Abstract Vitamin C is effective in strengthening the immune system, capillary blood vessels and protecting the dental health, as well as in the convenient use of iron, calcium, thiamine, riboflavin, folic acid, vitamin A and E in the body. Vitamin C also acts as a cofactor for 15 different enzymes, and shows antioxidant activity as a electron donor reducing agent. It acts as a powerful free radical scavenger by protecting tissues against oxidative stress and reduces inflammation. Obesity is defined as "mild inflammatory disease" due to the increase in inflammatory markers such as C reactive protein (CRP), tumor necrosis factor alpha (TNF) and IL-6. Since antioxidant enzyme activity and serum antioxidant levels decrease in obese individuals, the effect of antioxidant vitamins on weight loss is further investigated. In studies investigating the effectiveness of vitamin C in the treatment of obesity; vitamin C was found to reduce systemic inflammation by inhibiting CRP and TNF alpha pathways, shown to inhibit the hypoxia in adipose tissue with potential for protection against free radicals and decreasing lipid peroxidation. On the other hand, it was shown that vitamin C inhibits mature adipocyte formation and cell growth, inhibits lipolysis, and can be considered as a treatment model for obesity to offer solutions for abnormal fat accumulation. In this review, the action mechanism of vitamin C and its role in dietary treatment were investigated in order to prevent obesity complications and to provide weight loss.

Keywords: obesity, vitamin C, mechanism, inflammation

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1. Introduction

Ascorbic acid is a kind of monosaccharides. In live microorganism, L ascorbic acid is oxidized easily and loses two hydrogens. It is converted to dehydro L ascorbic acid and this reaction is reversible. Vitamin C is absorbed from small bowels in human anatomy [1,2]. It is transported to tissues by the bloodstream and the excess is excreted in the urine from kidneys. Sodium-dependent vitamin C Transporter (SVCT) is transported by specific carriers called 1 and 2. Some ascorbic acid is converted into dehydroascorbic acid after oxidized in the bowels and dehydroascorbic acid is transported by GLUT2 carriers [3,4].

The number of vitamin C in an adult human body is between 1500-3000 mg depending on intake level, and below 900 mg is an undesired level. The normal value of serum vitamin C concentration range is 0.50-1.80 mg/dl [5] and the range between 36.1-79.4 mumol/l is also considered to be normal [6]. Plasma vitamin C concentration depends on dietary intake and its absorption by the gastrointestinal system, its distribution in body fluids, reversible metabolism of vitamin C and factors affecting excretion by kidneys. Diseases, body composition,

genetic factors, affect the metabolism of physical activity [1]. Also, TNF-alpha, an inflammatory cytokine which increases as a result of a disease on the intestinal system affecting the SVCT-1 transporters or an increase in inflammation in the body, may interfere with the absorption by inhibiting the involvement of ascorbic acid in the intestines [7]. The relationship between smoking status, BMI and plasma vitamin C level was shown in CHALICE cohort study [8]. It is foreseen that recommended dietary allowance of vitamin C can change depending on vitamin C transport or metabolism, diseases, smoking status and in obese individuals [1].

According to a guide in the United States and Canada, the recommended dietary allowance of vitamin C (RDA) is 75 mg for women and 90 mg for men (Food and Nutrition Board Panel on Dietary Antioxidants and Related Compounds, 2000). In the study of determining reference values for nutritional intake in Germany, Austria and Switzerland, 110 mg/day for healthy adult men and 95 mg/day for women was recommended. Since smokers have higher metabolic losses than non-smokers and lower plasma vitamin C, the reference value for vitamin C intake was determined 135 mg/day for female smokers and 155 mg/day for male smokers [9]. RDAs for vitamin C is shown in Table 1 for Turkey [10]. Bioavailability of vitamin C decreases rapidly with dose. Current

recommendations suggest the avoidance of doses above 2 g/day to prevent side effects of distention and osmotic diarrhea [10,11].

Table 1. The Recommended Dietary Allowance of Vitamin C (mg)

	Male	Female	Tolerable high level intake
2-3 years old	20	20	400
4-6 years old	30	30	650
7-10 years old	45	45	1200
11-14 years old	70	70	1800
15-17 years old	100	90	1800
Over 18 years old	110	95	2000
Pregnant	-	+ 10	2000
Breastfeeding	-	+60	2000

Vitamin C is effective in enhancing the immune system, strong capillary blood vessels and protecting dental health. It was reported to use iron, calcium, thiamine, riboflavin, folic acid, pantothenic acid with vitamin A and E in the body more conveniently. It is effective in the absorption of nonheme iron and transportation of deposited iron to bone marrow by reducing it [2]. Ascorbic acid is a cofactor for 15 different enzymes. Thus, it plays a role in collagen synthesis and steroid hormone metabolism [1]. The most important function of vitamin C related to obesity is an electron donor, a reducing agent and antioxidant. Antioxidants neutralize free radicals and prevent the damage by giving one or two electrons. Vitamin C in body cells and fluids protects tissues against oxidative stress and is effective in preventing non-enzymatic glycosylation of proteins [12,13]. It is also a powerful free radical scavenger. Under physiological conditions, it functions as preventing DNA mutation, protection against lipid peroxidation, protein integrity protection and elimination of oxidized amino acid residues [13,14]. The antioxidant effects of vitamin C depend on the capacity of the endogenous glutathione antioxidant system, where reversing happens [1,15,16].

2. The Relationship between Vitamin C and Obesity and Potential Mechanisms

Obesity is an increasing public health problem throughout the world. Sedentary lifestyle as a result of high sugar and high saturated fat intake and the global increase in obesity incidence has been a growing issue since 1980's [17]. Obesity is also described as a "low-grade inflammatory disease" due to inflammatory markers increasing with obesity such as C reactive protein (CRP), tumor necrosis factor alpha (TNF) and IL-6 [18,19]. Also, a decrease in antioxidant enzyme activity and serum antioxidant levels have been observed in obese individuals. The relationship between plasma ascorbic acid level and body fat distribution was shown in a previous study [20].

In a previous study conducted with 11592 individuals with BMI higher than 27kg/m^2, it was revealed that serum vitamin C levels were lower in individuals with high BMI regardless of smoking status [21]. Another study on 850

Indian males showed that vitamin C deficiency was positively correlated to abdominal obesity and body fat [22]. Another study showed that plasma ascorbic acid concentration had a negative correlation with body fat, waist circumference and waist-hip ratio regardless of BMI in 19068 individuals aged between 45-79 years [23]. In a study examining dietary habits, it was seen that obese individuals received 51% less vitamin C and serum vitamin C levels were 38% less [24].

On the other hand, the effect of the high antioxidant diet on weight loss was investigated. After 10 weeks of diet program (1500-2000 kcal) on 71 children aged between 7-15 years, it was seen that high antioxidant (vegetable, fruit, vitamin c, folic acid intake) diet was positively correlated to weight loss [25]. In another study, 38 patients were divided into two groups and the group which took 3 grams of vitamin C supplementation for 6 weeks was observed to lose weight more than the other group [26].

Considering all these studies, increasing antioxidant activity impaired by obesity was presented as a solution to provide a decrease in body fat [17]. It was also thought that vitamin C could be a part of the treatment of obesity with several mechanisms provided by its antioxidant activity. These mechanisms are summarized below.

2.1. The Effect of Vitamin C on Oxidative Stress and Systemic Inflammation in the Treatment of Obesity

2.1.1. The Effect of Vitamin C on Oxidative Stress

One of the possible causes of obesity is the increase of reactive oxygen species (ROS) due to the imbalance between ROS and antioxidant defense system and cell injury, necrosis and apoptosis stimulation by the increase in ROS after causing DNA, lipid and protein oxidation. Increased mitochondrial metabolism in obesity, the increase in oxygen consumption and thus increased respiration-induced superoxide radicals and hydrogen peroxide formation also increase oxidative stress [27]. In addition, chronic overnutrition causes oxidative stress with mechanisms such as high-fat-high carbohydrate diet, excessive consumption of saturated fatty acids and trans fats, superoxide formation from NADPH oxidases, oxidative phosphorylation, glyceraldehyde oxidation, protein kinase C (PKC) activity and polyolhexamine pathway. Oxidative stress increases preadipocyte proliferation, adipocyte differentiation and mature adipocyte size [28]. All these are potential inducers for the emergence of metabolic syndrome complications. Vitamin C is an important ROS scavenger, an electron donor, a reducing agent and antioxidant. It neutralizes free radicals and prevents the damage by giving one or two electrons, thus reduces systemic oxidative stress and prevents the occurrence of obesity and related complications [29,30,31].

2.1.2. The Effect of Vitamin C on Systemic Inflammation

Production and excretion of endogenous products due to excessive growth of white fat tissue in obesity turn this tissue into the one with proinflammatory specifications [13,18]. For this reason, fat tissue is not only a triglyceride

storage organ, but previous studies have also shown the role of white fat tissue as a producer of some bioactive substances called adipokine. Adipokines include some inflammatory markers such as TNF-alpha, Interleukin-6 (IL-6), monocyte chemoattractant protein-1. These adipokines induce the production of reactive oxygen species (ROS), known as oxidative stress (OS), and cause systemic inflammation [17]. Also, cell damage caused by the pressure from fat cells due to excessive fat accumulation results in the formation of large amounts of cytokines in adipose tissue. Cytokines increase lipid peroxidation in tissues and produce ROS [32]. Both oxidative stress caused by obesity and the inflammation increased due to the damage in fat tissue caused by oxidative stress are seen as a fundamental factor that accelerates the development of obesity-related diseases such as metabolic syndrome, diabetes, cardiovascular diseases, and cancer, which also trigger each other. It was observed that oxidant markers were healed and antioxidant activity was increased when body fat was reduced [19,33,34]. In reducing body fat, the effectiveness of vitamin C to reduce systemic inflammation is still under investigation.

Vitamin C was observed to inhibit interleukin-1, CRP and TNF alpha pathways. It was also seen to inhibit TNF alpha-induced nf-kb transcriptional activity. Vitamin C also inhibited the activity of IkB kinase a and b in vitro. These two enzymes are also part of the nf-KB signaling pathways and are associated with immunity and inflammation [33,35].

Decreased antioxidant factors and increased tendency of nitric oxide in obesity also increase the tendency to cardiovascular diseases. Vitamin C increases arterial dilatation over nitric oxide release. It reduces lipid peroxidation. Anti-inflammatory effect of vitamin C can be explained with regulation of NF-KB DNA binding activity and decrease in interleukin and tumor factor hepatic mRNA expression [12].

Ford et al. [36] have shown that ROS production the inflammatory process increase as a result of depletion of antioxidants including vitamin C. In a study by Jang et al. [37] on broiler chicks, it was observed that a diet containing 200 mg/kg vitamin C significantly reduced TNF alpha IL6 cytokines and decreased hepatic m-RNA regulation. Peluso et al. [38] found that TNF alpha and interleukin-6 levels decreased when vitamin C-containing fruit juice was given to reduce postprandial stress induced by a high-fat diet.

2.2. The Effect of Vitamin C on Hypoxia in the Treatment of Obesity

Scientific evidence based on cell culture in animals and humans also emphasizes hypoxia in the development of obesity [33,39]. Hypoxia leads to macrophage infiltration and ROS production as the adipose tissue cell number and size grow. And the proinflammatory process starts in this tissue [17].

When a cell becomes hypoxic, the HIF 1-a and HIF 1-b factors of the oxygen homeostasis are induced. Then HIF-1 increases the activation of various hypoxic response elements. It increases the adaptation of the cell to its new

environment. However, this adaptation is impaired when it is hypoxic [35]. Hypoxia in adipose tissue leads to macrophage infiltration and ROS production. And the proinflammatory process starts. Since vitamin C has the potential to protect against oxygen-free radicals, it inhibits hypoxia and stops adipose tissue expansion and reactive oxygen molecule production. It shows this effect by stimulating Bcl-2 and Bcl-xl antiapoptogenic protein upregulation and by inhibiting Bcl-2-related protein X expression. In this way, it can stop the effect of expansion in adipose tissue due to oxygen deficiency [39,40].

2.3. The Effect of Vitamin C on Antioxidant Enzyme Activity and Lipid Peroxidation in Obesity Treatment

The antioxidant enzyme groups associated with obesity are 'paraoxonases (PON)' and 'peroxiredoxins (PRDX)'. Paraoxonases consist of three isozymes; PON1, PON2 and PON3. These enzymes are mainly synthesized in the liver and kidneys and located on the surface of high-density lipoproteins (HDL). PRDX3, which plays an important role in the antioxidant defense system, destroys a significant part (90%) of the H_2O_2 in the mitochondria. It was seen that these enzymes decreased in adipose tissues of obese individuals. PON1 protects against oxidative damage. This prevents inflammatory response in arterial wall cells. In this enzyme activity, dietary antioxidants such as vitamin C, vitamin E and phytochemicals are also effective [41].

Malondialdehyde, the most important of the degradation compounds caused by lipid peroxidation, reacts with the functional groups of various compounds in the cell and causes cell damage. High-fat diet leads to lipid peroxidation. Improvement in malondialdehyde levels were observed in with vitamin C intake in mice fed with high-fat diet [42,43].

2.4. The Effect of Vitamin C on Adipocyte Differentiation and Lipolysis in Obesity Treatment

2.4.1. Preventing Mature Adipocyte Formation and Cell Growth

In animal studies, since glycerol phosphate dehydrogenase (GPDH) enzyme increases its activity in adipose tissue and increases intracellular triglyceride accumulation, preadipocytes are transformed into mature adipocytes. Vitamin C inhibits this transformation by decreasing GPDH enzyme activity [18,44].

When mature adipocytes were exposed to vitamin C intracellularly, the decrease in triglyceride concentration, GPDH activity and mRNA inhibition were observed. Adipocyte cell growth decreased when continuous phosphate ascorbic acid (a sort of higher bioavailability ascorbic acid type) was added [44]. Vitamin C was found to spontaneously stimulate the differentiation of the 3t3-l1 (resistin synthesis) preadipocyte cell pathway [45,46]. In a study on Wistar rats, it was found that vitamin C could provide protection against negative effects of high-fat diet and decrease adipogenesis and

change gene expression related to insulin resistance in the group receiving 750 mg/kg vitamin C for 8 weeks [47].

2.4.2. Inhibition of Lipolysis

It has been found that vitamin C is effective in epididymal adipose tissue by reducing the basal lipolytic rate. In a study on animals, it was observed that vitamin C inhibited glycerol release and isoproterenol-induced lipolysis in mice fed with high-fat diet [44,48].

2.4.3. Effects on cAMP

Vitamin C acts as an inhibitor of adenylate cyclase and plays a role in cellular differentiation by regulating the level of intracellular cyclic adenosine monophosphate (cAMP). It was observed that the cAMP pool decreased by increasing the concentration of ascorbic acid in the cells. It has been indicated that vitamin C is a competitive adenylate cyclase inhibitor. Vitamin C also suppresses the expression of genes under the control of CAMP signaling pathways. While it is known that increased intracellular cAMP concentration supports adipogenesis, vitamin C supplementation inhibits adipogenesis by decreasing intracellular cAMP levels. Thus, it prevents lipid accumulation in mature adipocytes [49,50]. It was observed that 3 g/day vitamin C treatment in mice with high-fat diet inhibited the accumulation of lipids. However, human studies on how it modulates cell signaling are required [50].

2.5. The Relationship of Vitamin C with Obesity over Leptin, Insulin and Glucocorticoids

2.5.1. The Effect of Vitamin C on the Release of Glucocorticoid from Adrenal Glands

Vitamin C supplementation to diet in obese mice provides downregulation of steroidogenesis-related genes, such as steroidogenic acute regulatory protein and hydroxysteroid 11-beta dehydrogenase 2. All these results can be a bridge between weight loss and antioxidant features of vitamin C [48].

2.5.2. The Effect of Vitamin C on Glucose Metabolism and Leptin Inhibition

It was detected that vitamin C competes with glucose in transporting with GLUT 1-3-4 carriers. In a study carried out on mice, its healing effect on insulin sensitivity in adipose tissue was revealed. These results were obtained by the modification of IRS-1/JNK cellular pathways. It has been found that it has an inhibitory effect on leptin release. Improvement in hyperglycemia and its effect on reducing glycosylation on obese diabetic models were observed [46,48,51,52]. The positive effect of mild weight loss with vitamin C supplementation in diabetic patients on lipid and carbohydrate metabolism in patients has also been revealed [53].

Table 2. Some Studies about Vitamin C in the Treatment of Obesity

Source	Country	Characteristics	Outcome measure	Findings
[55]	Denmark	Prospective study 7569 Danish individuals Target biomarker(s): Dietary vitamin C	ΔBW, ΔWC, SNP-score	No statistically significant relationship was found between ascorbic acid intake and ΔBW or ΔWC in general.
[56]	New Zealand	Cross-sectional observational pilot study Individuals aged ≥18 years with: NGT (fasting glucose ≥5.5 mmol/L) (n = 35), prediabetes (fasting glucose ≥5.6 mmol/L) (n = 25), T2DM taking no diabetes medication (fasting glucose ≥7.0 mmol/L) or on a regimen of Metformin only (n = 29) Target biomarker(s): Dietary vitamin C	Fasting Glucose HbA1c Total Cholesterol Triglycerides (mmol/L) Cholesterol (HDL) Cholesterol (LDL) Insulin (pmol/L) hs-CRP (mg/L) Ghrelin (pmol/L) Leptin (ng/mL) Adiponectin (ng/mL) BMI (kg/m^2) Waist-to-Hip Ratio Fat Mass (%)	Adults with a history of smoking, prediabetes, T2DM and/or obesity have higher vitamin C requirements. It should be investigated whether consuming more vitamin C-containing foods and/or receiving vitamin C supplements may be associated with T2DM and/or reduce the risk of complications.
[48]	Spain	Case-control study 30 eight-week-old male Wistar rats Target biomarker(s): Vitamin C supplement	Body-related measurements Food intake measurements Biochemical measurements Hypothalamo-adrenocortical activity indicators	Oral ascorbic acid supplementation has a direct effect on behavioral activity and adipocyte lipolysis in early obesity stages in rats. It shows the protective short-term role of this vitamin against adipocyte caused by chronic high-fat diet consumption.
[57]	Canada	Case-control study 32 four-week-old male C57BL/6 mice Target biomarker(s): Vitamin C supplement	Mass accumulation	It was seen that HF dietary supplementation with the combination of phytosterols and ascorbic acid resulted in reduced mass accumulation with an absolute mass bias between PSAA and HF control.
[8]	New Zealand	Cohort study 404 New Zealand individuals aged 49-51 y Target biomarker(s): Plasma vitamin C	Body Measurements Biochemical measurements Heart Health Mental Health	For this age group, dietary interventions aiming at increasing fruit and vegetable consumption in particular and vitamin C intake in particular were considered to be necessary and plasma vitamin C was found to have a stronger correlation with metabolic health and cognitive deficits than dietary vitamin C.
[58]	Arizona	Cross-sectional study 118 sedentary, non-smoking individuals aged 20-60 y Target biomarker(s): Plasma vitamin C	Plasma adiponectin, plasma insulin, body mass, body fat, waist circumference	Plasma vitamin C, especially in women, was found to be inversely correlated with adiposity markers. It was determined that vitamin C supplementation did not affect circulatory concentration of adiponectin.

In a study by Aeberli et al. on Swedish children, the relationship between dietary consumption of antioxidant vitamins and leptin level was shown [54]. High leptin levels also increase the risk of obesity. It is thought that antioxidant intake in low concentration may cause leptin resistance by affecting leptin gene expression. In a study on mice, glucose lipid metabolism and secretion and expression of various genes were examined by giving vitamin C between 5-1000 mM in culture medium for 72 hours. It was seen that vitamin C decreased glucose intake and lactate production. While a dramatic decrease in leptin secretion was observed, gene expressions inhibiting ırs -3 such as cdkn1a and casp 8 were stimulated with the supplementation of 200 nM vitamin C. Also, it was observed that vitamin C provided insulin regulation by affecting intracellular and extracellular reactive oxygen species [18].

3. Conclusion and Recommendations

Antioxidant treatments in obesity may be therapeutic for systemic oxidative stress complications. Antioxidant supplements can regulate enzyme activities in the control of free radicals, increased ROS and nitric oxide synthesis. Therefore, it was thought that besides weight loss through nutrients and pharmacological treatment, supplementation with antioxidant nutrients such as E, A and C vitamins would help the treatment of obesity by improving the pathological disorders related to oxidative stress [17].

Vitamin C can also be considered as a treatment of obesity to suppress the abnormally secreted cytokines from adipocytes with antioxidant activity and solve abnormal fat accumulation complications by decreasing the level of free radicals [12]. Vitamin C protects against oxidative stress, prevents non-enzymatic glycosylation, increases arterial dilation over nitric oxide release, decreases lipid peroxidation and has anti-inflammatory effect. The role of vitamin C in the treatment of obesity is being investigated with glucose metabolism and its effects on leptin. Re-evaluation of vitamin C requirement may be recommended with the prediction of the increased antioxidant requirement in relation to decreased antioxidant capacity especially in obese individuals with hypertension, diabetes or smoking habits. It is necessary to direct individuals to consume more foods containing vitamin C and it is predicted that supplementation support would reduce the risk of complications and decrease the fat tissue. Further studies are required on this subject. However, although vitamin C can clear ROS, it is clear that the antioxidant effects actually depends on the capacity of the endogenous glutathione antioxidant system in which vitamin C is reversed. It should be considered that excess vitamin C may have prooxidant effect.

As a result, the effects of vitamin C on prevention of obesity complications and providing weight loss should be investigated by prospective randomized controlled trials to recommend vitamin C for obese individuals over RDA. Further studies should be carried out in order to determine the differences between the metabolically healthy and unhealthy obese individuals in the serum vitamin C profile.

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