Review

Vitamin C in the Treatment and/or Prevention of Obesity

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Summary Obesity has emerged as one of the major health threats worldwide. Moreover, an excessive body fat accumulation, which defines this disease, could lead to several associated clinical manifestations such as cardiovascular events, type 2 diabetes, inflammation, and some types of cancer. The appearance of these co-morbidities has often been related to an unbalanced oxidative stress. Therefore, antioxidant-based treatments could be considered as interesting approaches to possibly counteract obesity fat accumulation complications. In this context, it has been observed that vitamin C intake (ascorbic acid) is negatively associated with the occurrence of several conditions such as hypertension, gallbladder disease, stroke, cancers, and atherosclerosis, and also with the onset of obesity in humans and animals. Among the possible beneficial effects of ascorbic acid on obesity-related mechanisms, it has been suggested that this vitamin may: (a) modulate adipocyte lipolysis; (b) regulate the glucocorticoid release from adrenal glands; (c) inhibit glucose metabolism and leptin secretion on isolated adipocytes; (d) lead to an improvement in hyperglycemia and decrease glycosylation in obese-diabetic models; and (e) reduce the inflammatory response. Possibly, all these features could be related with the outstanding antioxidant characteristics of this vitamin. Thus, the present article reviews the up-to-date evidence regarding in vitro and in vivo effects of vitamin C in obesity and its co-morbidities.

Key Words ascorbic acid, antioxidant, body weight, oxidative stress

Obesity: Overall Characteristics

One of the issues that importantly affect the daily living of each individual is body weight increment and specifically fat accumulation (1). Despite the fact that human beings require the presence of adipose tissue in the organism, when this tissue enlarges excessively several harmful consequences occur (2, 3). Obesity has become a spotlight worldwide, emerging among the main global health threats that nowadays affect our society’s well being (1). Indeed, it is well known that an excessive body fat deposition, the feature that defines this disease, is a triggering factor for several associated clinical manifestations such as type 2 diabetes (T2D), metabolic syndrome features, cardiovascular events, inflammation, and arthritis (3). The increase in the consumption of meals with high sugar/high saturated fat content, in combination with a sedentary lifestyle, is dictating the vertiginous global increase of obesity incidence that has been observed from the ‘80s (4). Over the past twenty years, the prevalence of this condition has been tripled in areas like USA, England, Eastern Europe and the Middle East, and even a more drastic rise has been observed in developing countries (5).

This disease is defined as a rise in the fuel reservoir in the organism by means of increased fat content, accompanied by larger total body weight due to a positive imbalance between energy intake and energy expenditure (6). This mass increment has been related specifically with the increase of white adipose tissue (WAT) deposits. Indeed, WAT is, in addition to energy storage, an endocrine organ able to secrete a large number of molecules involved in a wide variety of physiopatholog-
Table 1. Evidence regarding VC prevention and/or treatment of obesity and its co-morbidities.

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<td>(85)</td>
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In obesity, WAT overgrowth leads to a dysregulated production of these endogenous products (3), many of which have pro-inflammatory activity (8) and may also modulate mitochondrial status (9). Indeed, it has been reported that several inflammatory products derived from this tissue, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), monocyte chemotactrant protein-1 (MCP-1), and inducible nitric oxide synthase (iNOS), are correlated with increased body adiposity (10). In addition, it has been found that inflammatory-related pathways are activated in obesity and insulin-resistance states (11, 12). Besides the secretion of these pro-inflammatory cytokines, the adipose tissue produces other substances that also have important local and systemic effects (13). Among these molecules, leptin, which controls food intake and energy expenditure (14), and adiponectin, which has been related with significant insulin-sensitivity improvements (15), are metabolically relevant.

### Evidence Summary

<table>
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CVD, cardiovascular disease; DHA, dehydroascorbic acid; GPDH, glycerol-3-phosphate dehydrogenase; GSH, reduced glutathione; HFD, high fat diet; HIF-1α, hypoxia-inducible factor alpha; hsCRP, high sensitive C-reactive protein; IKK, IκB kinase; IRS-1, insulin receptor substrate 1; IRS-3, insulin receptor substrate 3; JNK, c-Jun N-terminal kinase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; NF-κB, necrosis factor kappa B; NO, nitric oxide; ROS, reactive oxygen species; T2D, type 2 diabetes; VC, vitamin C; VE, vitamin E; WAT, white adipose tissue.
levels of several WAT adipokines are directly implicated in obesity-associated ROS overproduction. This feature links the pathogenic secretion pattern of WAT with an enhanced oxidative stress status (20).

In this sense, antioxidant-based treatments are emerging as an interesting approach to possibly counteract obesity fat accumulation complications, which are often accompanied by an increased systemic oxidative stress (21). The beneficial antioxidant effects of vitamin supplementation are attributed to their ability to scavenge free radicals, control nitric oxide (NO) synthesis and release, inhibit ROS generation, and upregulate antioxidant enzyme activities (22). In this regard, the intake of vitamin C (VC) has been positively associated with serum antioxidant status (23) and negatively related with the occurrence of hypertension, gallbladder disease, stroke, cancers, and atherosclerosis (24). Interestingly, VC has proven to exert positive effects in obesity in animal and human studies (25–27). Among the possible beneficial effects of this vitamin on obesity-related mechanisms, it has been suggested that VC may: a) modulate adipocyte lipolysis (28–31), b) regulate the glucocorticoid release from adrenal glands (32), c) inhibit glucose metabolism and leptin secretion on isolated adipocytes (33), d) lead to an improvement in hyperglycemia and decrease glycosylation in obese-diabetic models (34), e) reduce the inflammatory response mediated by necrosis factor kappa B (NF-κB) (35, 36), and f) regulate behavioral activity (29) (Table 1 and Fig. 1).

**Vitamin C**

Vitamin C (VC, ascorbic acid) is a water soluble vitamin characterized by a six-carbon monosaccharide structure, very similar to the glucose molecular structure...
Most mammal species synthesize VC de novo; that is, they endogenously produce VC through biosynthesis, implying specifically the enzyme l-gulono-gamma-lactone oxidase. However, guinea pigs, primates, and humans absolutely depend on the external supply of this molecule due to an inactivation of this enzyme by mutation (38). Moreover, VC is needed in relatively high quantities, since ascorbic acid is not retained nor accumulated in the body and the excess is immediately eliminated through urine (39). VC is absorbed from the intestine lumen and renal tubules by enterocytes and renal epithelial cells, respectively, and subsequently distributed throughout the organism by the bloodstream.

Several relevant functions have been ascribed to VC: wound healing, iron absorption collaboration, collagen biosynthesis participation, and hemoglobin activation (40). Besides, this vitamin acts as an enzymatic cofactor for the biosynthesis of collagen, carnitine, catecholamines, and peptide neurotransmitters (41). However, the most acclaimed feature of this molecule relies on its antioxidant properties, since it has been reported that plasma and cell VC acts as a potent oxygen and nitrogen free radical scavenger (37). Intracellular VC is involved in oxidation and degradation reactions and could prevent cell death and inhibit nucleotide mutations due to oxidative damage.

When VC loses electrons in biosynthetic or antioxidant reactions, an oxidized ascorbic radical (with a very short lifespan) is generated (42). This radical presents a low potential reduction as compared to every reactive species of nitrogen and oxygen. Thus, ascorbate is a highly efficient electron donor for several redox reactions, since it is able to replace highly damaging free radicals with a low reactive ascorbate radical. This unstable intermediate is then converted into dehydroascorbic acid (DHA), which is the oxidized form of VC. It is known that DHA and VC induce differential effects in cellular function (43).

VC transport occurs by two main mechanisms: 1) VC enters the cells through a specific family of transporters (sodium vitamin C transporters 1 and 2) in a process mainly driven by sodium gradient (44) and 2) the oxidized form of VC, DHA, is transported inside the cell more rapidly than its reduced form, entering by facilitated diffusion through the 1, 3, and 4 isoforms of the glucose transporter GLUT (45–47). Once inside the cell, DHA is reduced to its original form, ascorbate. This fact contributes to the intracellular accumulation of VC in its reduced form. This process allows many tissues to accumulate VC at a millimolar level, against concentration gradient, and to maintain redox status balance to a more reduced intracellular environment.

**Vitamin C against Obesity Development**

Oxidative stress induces important modifications and impairments in cellular functions. Wide efforts have been undertaken in order to delay or prevent the onset and/or progression of diseases related to this etiopathogenesis, e.g., by trying to identify specific molecules with therapeutic potentials (48). In this sense, approaches using antioxidant supplementation/administration have been used since they are able to reduce and eliminate ROS, lowering the risk of presenting this wide range of chronic diseases, including obesity (49).

**a) Body weight modulation**

Animal studies have demonstrated that oral VC supplementation improves insulin sensitivity in hyperglycemic ob/ob mice without affecting body weight (34). Moreover, VC supplementation has also been associated with body weight reduction in guinea pigs (50) and with a massive reduction in the adipocyte number in rats after direct injection in fat deposits (31). Positive effects on diet-induced obesity models have also been described. For example, Campion et al. found that eight weeks of VC supplementation in a cafeteria model of obesity protected rats against diet-induced adiposity and hyperleptinemia (25), a process in which several steroidogenic genes (51, 52), as well as adipokines such as apelin and leptin (26), could be involved. This dietary model shares common western diet features and has the ability to induce metabolic syndrome conditions (53–55) such as adiposity, hyperinsulinemia, hyperleptinemia, and liver oxidative stress in rodents (18).

On the other hand, it is widely accepted that diets rich in fruits, vegetables, legumes, and other antioxidant-rich plants are associated with a lower incidence of various chronic diseases including obesity (56). Several studies have been performed searching for the beneficial effects of VC enriched-diets and/or supplementation on body weight modulation in humans. In this context, an inverse relationship between the presence of this antioxidant in plasma and body mass has been observed (57). Subjects with adequate levels of VC burn 30% more fat during moderate exercise compared to subjects with low levels. Besides, low VC levels in plasma have been related with high central adiposity measurements, such as waist-to-hip ratio, in obese subjects (58, 59) and with an increase in heart attack risk, especially in hypertensive and overweight subjects (60). Moreover, after a 10-wk diet program, a positive association between weight loss and the antioxidant capacity of the diet (that is, diets rich in fruits, vegetables and legumes) has been described (61). Furthermore, a wide body of evidence in humans has proven that VC supplementation induces beneficial effects related to a slight weight loss (62) and to lipid and carbohydrate metabolisms in T2D patients (63). Finally, antioxidant-rich diets including VC have been associated with a lower prevalence of overweight and obesity (64) and with the prevention of weight and abdominal fat gain along a 3-y follow-up in adults (58).

Hence, diverse scientific evidence indicates that VC nutritional status or supplementation could be effectively involved in the modulation of body weight and adiposity.

**b) Oxidative stress**

Obesity is characterized by presenting mitochondrial dysfunction and ROS overproduction, as well as by an association between oxidative stress and insulin-resistance (65, 66). Besides, the oxidative stress present in an excessively enlarged VAT comprises a potential inducer
factor for the appearance of metabolic syndrome complications (17). Among the functions of antioxidant vitamins, it is important to highlight their capacity for reducing free radical levels, regulating NO synthesis and liberation, inhibiting ROS production, and inducing enzymes in charge of the antioxidant defense of the organism (22). Regarding VC, an important ROS-scavenging capacity has been described (37, 67).

Studies in animals have reported that an antioxidant cocktail, containing VC, has important ameliorating effects on insulin-resistance and on redox imbalance in adipose tissue from HF-fed rats (68). These insulin-sensitizing features were driven through insulin receptor substrate-1 (IRS-1)/c-Jun N-terminal kinase (JNK) pathway modulation. In rats fed a high fat diet (HFD) supplemented with VC, a slight amelioration of malondialdehyde hepatic levels was observed, as compared to animals fed HFD alone (26). Finally, in vitro studies have pointed out that VC treatment reduced ROS intracellular and extracellular levels on isolated adipocytes from lean animals (33).

Several investigations have also addressed positive outcomes of VC in humans. For example, when children with severe obesity consumed a low-calorie diet with mandarin juice, they experienced a significant decrease in malondialdehyde and carbonyl groups levels in plasma, together with an increase in blood antioxidants such as VC (69). Furthermore, it has been observed that a vitamin E (VE)/VC supplementation induces a reduction of both high sensitive C-reactive protein plasma levels and cobalt–albumin binding score as measures of oxidative stress, indicating anti-atherogenic effects in humans (70). It has also been reported that an antioxidant supplementation (including VC) for 4 mo modulates redox balance in obese children and adolescents (71). This supplementation improved oxidative stress markers such as antioxidant status (antioxidant levels) and 8-iso-prostaglandin F2α,β. In another study, a separate VC and VE supplementation evidenced a reduction in lipid peroxidation, measured as F2-isoprostane levels, where oxidative stress markers were related with higher BMI of individuals (72). Moreover, it has been described that VC exerted protective effects over endothelial dysfunction induced by oxidative stress in obesity, inducing improvements in impaired acetylcholine-stimulated vasodilatation (67). An antioxidant supplementation (VC, VE, and carotene) was able to reduce exercise-induced oxidative stress in young overweight adults, displaying improvements in blood lipid hydroperoxide, C-reactive protein, IL-6, cholesterol, and the antioxidant status (73). Finally, VC levels were negatively correlated with free radicals and positively correlated with reduced glutathione (GSH) levels in plasma, after a chronic VC administration (63).

Based on all this information, it is highly plausible that many of the beneficial effects of VC reported on obesity features could be due to its associated high antioxidant potential.

c) Adipocyte differentiation and lipolysis

Regarding VC effects in adipocytes in vitro, several authors have demonstrated this vitamin can act on differentiation, triglyceride accumulation, and lipolysis, although with controversial results (74, 75). Specifically, it has been observed that VC stimulates the “spontaneous” differentiation of the 3T3-L1 preadipocytes cell line (74, 76), consequently increasing the activity of the glycerol phosphate dehydrogenase (GPDH) enzyme and the intracellular accumulation of triglycerides, both of which are markers of conversion of pre-adipocytes into mature adipocytes. Contrarily, it has been described that VC inhibits the differentiation process in this same cell line by reducing the activity of GPDH (75). Moreover, when mature adipocytes were exposed to VC, the intracellular triglyceride concentration was decreased (30) and GPDH activity and mRNA expression were significantly inhibited (30, 33). Finally, it has been reported that a continuous addition of phosphate ascorbic acid (which has the advantage of being a VC derivative with prolonged bioavailability) stimulated cellular growth of adipocytes (74, 75).

Regarding lipolysis, in a study performed on lean animals, ascorbic acid decreased the lipolytic effect of catecholamines and enhanced the basal lipolytic rate of epididymal adipose tissue (28). Furthermore, in a diet-induced obesity model, it has been shown that rats fed a HFD supplemented with VC presented a decreased isoproterenol-induced lipolysis as compared to rats fed a HFD alone (29). Besides, VC inhibited glycerol release in primary-cultured adipocytes from lean and obese animals (33, 66).

Regarding all this evidence, a clear role of VC over triglyceride accumulation remains elusive. Thus, the possible benefits of this molecule over metabolic syndrome features associated with obesity could be due to combined effects over, e.g., carbohydrate and lipid metabolism.

d) Glucocorticoid metabolism

A close relationship between energy balance and glucocorticoids exists. Adipocytes present diverse types of adrenergic receptors that are closely related with fat modulation (lipolysis). Thus, targeting the glucocorticoid metabolism could be of interest in relation to fat accumulation. In this sense, it has been reported that VC possesses inhibitory effects on steroidogenesis in guinea pigs (77). High doses of this vitamin can affect glucocorticoid secretion by adrenal glands (32). In this sense, inhibition of glucocorticoid actions could drive a protective effect over body weight rise, as found in a rodent obesity model (53). According to a microarray experiment, some genes related to steroidogenesis, such as steroidogenic acute regulatory protein and hydroxysteroid 11-beta dehydrogenase 2, are downregulated when diet-induced obese rats are supplemented with VC (55). All these outcomes can constitute a bridge between weight reduction and VC antioxidant features (25).

e) Glucose metabolism

As described before, it has been observed that an antioxidant cocktail (including VC) induced significant improvement in insulin-sensitivity in the adipose tissue of HFD-fed rats (68). These outcomes were related
with improvements in cellular insulin signaling by modification of the IRS-1/JNK cellular pathway. Thus, VC appears to exert some effects on insulin resistance induced by an obese state.

Oxidative stress induces a decrease in GLUT4 expression by inhibiting the binding of transcription factors, such as nuclear factor 1, to response elements in the promoter of this gene (78). This feature leads to a decreased insulin-induced glucose uptake. Therefore, the antioxidant activity of this vitamin could be implicated in insulin resistance derived from obesity. On the other hand, it has been reported that DHA competes with glucose for the GLUT-1 and GLUT-3 transporters in the basal state and for the GLUT-4 transporter under insulin stimuli (79), to enter cells. This evidence could indicate that the supplementation/incubation with VC could carry out effects on glucose metabolism by interfering with glucose uptake. In this sense, it has been demonstrated that a VC treatment inhibits glucose metabolism on isolated adipocytes from both lean and obese animals (33, 66) and modulates the expression of insulin receptor substrate-3 (IRS-3) on isolated adipocytes from lean animals (33), of apelin on isolated adipocytes from both lean and obese animals (66), and on a co-culture murine model of adipocyte-macrophage crosstalk (80).

Regarding animal models, VC supplementation on a HFD induced a slight insulin-sensitivity improvement measured as glucose and insulin plasma levels and HOMA index in rats (26). Moreover, this supplementation induced gene expression modulation of transcripts that are directly related with insulin resistance, such as apelin and IRS-3, in the WAT of these animals (26). Furthermore, a trend to a reduction of glucose, insulin, and HOMA levels was reported in rats fed a HFD supplemented with VC for 2 wk compared to HFD-fed animals (29). This finding suggests an insulin sensitization effect of VC at early stages of obesity development. In this regard, it has been observed that VC (in antioxidant cocktails) protected β-cells from glucose toxicity, suppressing apoptosis and stimulating proliferation in rodents (81). On the other hand, it is known that lipid accumulation in adipocytes enhances lipolysis, resulting in higher plasma free fatty acid levels, and consequently may lead to systemic insulin resistance (82). In a study described before, VC supplementation inhibited isoproterenol-induced lipolysis of isolated adipocytes from retroperitoneal fat deposits of rats fed a HFD for 2 wk, versus HFD alone. Thus, VC supplementation could be involved in mechanisms that lower circulatory free fatty acid levels, reducing chances of insulin-resistance development in peripheral tissues. This outcome was also supported by correlations observed between HOMA index and lipolysis rates of isolated adipocytes (29).

Concerning humans, diabetes mellitus is one of the most prevalent endocrine diseases associated with high oxidative stress (83). Indeed, hyperglycemia leads to an oxidative stress increase, which in turn diminishes antioxidant defense systems. Therefore, several studies have focused on the potential role of antioxidants, including VC, in the treatment of this disease. It has been suggested that VC supplementation can decrease fasting and postprandial oxidative stress, preventing T2D (83). A 3-mo supplementation with this vitamin significantly reduced blood glucose and increased the activity of some glucose metabolism-related enzymes that could reduce insulin resistance by lowering oxidative stress parameters (84). VC has also been significantly and inversely associated with glycosylated hemoglobin levels and with both fasting and postprandial glycemia (85). Moreover, it has been reported that a chronic VC administration improved whole body glucose disposal and non-oxidative glucose metabolism (63). Besides, additional positive effects of VC on these carbohydrate metabolism markers have been demonstrated in patients following pharmacological treatments in comparison with those in the placebo group, suggesting a possible use of this vitamin in combination with drugs (86).

This considerable amount of literature indicates that VC plays a positive role in glucose metabolism by reducing oxidative stress, modulating insulin production at the pancreas level and this hormone signaling at target tissue levels, modulating glucose transport, regulating fatty acids systemic levels, and ameliorating inflammation.

f) Locomotive behavior

In experimental animal models, cafeteria diet intake has been proved to induce a significant decrease in the locomotive behavior (29). A decreased locomotive activity might be associated with the increase in body weight, contributing to the persistence of diet-induced obesity (87, 88). However, when animals were fed a HFD supplemented with VC for 2 wk, they were significantly more active than those fed a HFD alone, without presenting differences in body weight or adiposity (29). This effect on locomotive behavior was specifically observed for the rearing frequency. As a matter of fact, different studies have shown that physical activity is not always affected by HFD consumption, although it could depend on the dietary exposure duration (26, 29), on the diet fat composition (89), and on sexual differences (90). In this sense, a delayed onset of amphetamine-induced locomotion and rearing by ascorbate (91) and a reduced locomotor activity induced by ethanol and dopamine agonist in rodents (92) has been reported, presenting VC as a neuromodulator factor antagonizing the physiological and behavioral effects of the dopamine system (92, 93). Thus, VC could be involved in the induction of a weight loss behavior, prior to obesity onset.

g) Inflammatory response

Obesity is often accompanied by a low-grade inflammation condition in the adipose tissue (94). Indeed, adipokines, cytokines, and other factors produced by this tissue could be responsible for this process (13). This situation could lead to macrophage infiltration, consequently aggravating the obesity state (20). The crosstalk between inflammatory macrophages and adipocytes may influence insulin resistance, since macrophages contribute to the development of insulin resistance in obese patients, while weight loss reduces macrophage
infiltration and the expression of inflammation-related factors in adipose tissue (95, 96). Thus, several inflammatory products derived from this tissue, such as TNF-α, IL-6, MCP-1, leptin, and NO, correlate with increased body adiposity (10) and appear to participate in the induction and maintenance of the chronic inflammatory state associated with obesity (97). Therefore, a reduction in the inflammatory status based on antioxidant/anti-inflammatory agents could constitute a potential treatment to improve insulin sensitivity and to avoid adverse obesity-associated consequences (98). Among these agents, VC has been claimed as one of the most important natural antioxidants due to its well-known ROS-scavenging properties (67, 99).

Regarding VC, this molecule seems to inhibit the activation of NF-κB by diverse stimuli, including the interleukin-1 and TNF-α pathways, which has been observed in HUVEC primary cultures (100) and in human cell lines such as ECV304, HeLa, monocyctic U937, myeloid leukemia HL-60, and breast MCF7 (35, 100). Furthermore, another work demonstrated that DHA exposure results in an inhibition of transcriptional activity of NF-κB induced by TNF-α (35). DHA has been described as directly inhibiting the activity of IkB kinases α and β (IKKα and IKKB), in vitro. Both enzymes are key components in the signaling pathway of NF-κB and are involved in innate immunity and inflammation (101). Hence, these data suggest a dual-action mechanism of VC regarding NF-κB function: 1) as antioxidant, scavenging ROS and 2) following oxidation to DHA, exerting a direct function through inhibition of IKK enzymes.

In obese individuals, peripheral blood mononuclear cells are encountered due to a pro-inflammatory state, as suggested by an increment in intracellular activity of NF-κB, by a decrease in iKKB, and by the enhancement of pro-inflammatory genes that are regulated by NF-κB (102). Furthermore, it has been described that obese animals fed a HFD supplemented with VC presented lowered leptin mRNA levels in WAT compared to animals fed a HFD alone (26). Regarding in vitro studies, there has been observed a dose-dependent inhibition of leptin expression and secretion from lean-rat isolated adipocytes incubated with insulin (33), and in adipocytes isolated from either lean or HFD-fed animals (66). Moreover, an in vitro VC treatment reduced the expression and/or secretion of several inflammatory markers that were induced by the co-culture between adipocytes and macrophages (a technique used to emulate inflammatory cell-to-cell crosstalk in obesity) (80). VC treatment improved cell viability, and inhibited NO secretion, MCP-1 mRNA expression, and protein secretion induced by the direct contact of murine adipocytes and macrophages. Improved cell viability in adipocytes isolated from WAT of lean and obese rats has also been observed after VC treatment (66).

All this body of evidence suggests that VC could be involved in the inhibition of obesity-related inflammatory status onset, and therefore eventually participating in the prevention of obesity-related comorbidities.

h) Hypoxia

When a cell becomes hypoxic, protein hypoxia-inducible factors α and β (HIF-1α and HIF-1β) bind together in the nucleus constituting HIF-1, which is the master regulator of oxygen homeostasis. Subsequently, HIF-1 promotes the activation of several hypoxic response elements for the cell to adapt to its new environment. However, this adaptation can be disrupted when the hypoxic environment becomes chronic. This is the case of obesity, where established hypoxia occurs at the adipose tissue level (due to adipose tissue expansion in cell number and size) causing several alterations, such as macrophage infiltration and generation of ROS, that lead to a pro-inflammatory state within that tissue (103–106). Today, strong scientific evidence based on cell culture, animal, and human studies support that hypoxia plays a fundamental role in the initiation and development of obesity (107–109).

Several studies have determined the ability of VC for counteracting the adverse effects caused by a hypoxic environment in different cell types. Indeed, VC reacts with oxygen free radicals and has the potential to protect both cytosolic and membrane components of cells from oxidative damage under hypobaric hypoxic stress (110). Moreover, Kim et al. demonstrated that VC was able to reduce apoptosis in bovine ovarian cortex (111). In the same line, inhibition of hypoxia-induced damage and apoptosis pathways in adult rat cardiomyocytes and ischemic hearts was observed upon VC treatment (112). In this elegant study, the authors demonstrated that VC, in its oxidized form DHA, decreased apoptosis with the inhibition of BCL2-associated X protein (Bax) expression, caspase-3 activation, and cytochrome c translocation into the cytoplasm, and induced an upregulation of the antiapoptotic proteins B-cell lymphoma 2 and Bcl-xl (Bcl-2 and Bcl-xl). DHA treatment also inhibited the dephosphorylation of the prosurvival signaling protein Akt in the ischemic myocardium and increased the signal transducer and activator of transcription 3 (STAT3) phosphorylation, both in vivo and in hypoxic cardiomyocyte cultures. In addition, inhibition of ROS and ligand-receptor-induced STAT5b phosphorylation by DHA treatment has also been demonstrated in other cellular systems (113). Finally, it has been shown that a VC treatment prevented the stabilization of HIF-1α induced by NO in HUVEC cells (114) and reduced ROS production and HIF-1α activity in hypoxic endothelial cells (115).

Based on the positive effects that VC seems to exert in a hypoxic environment in different conditions and cell types, it could be suggested that this vitamin may ameliorate the adverse effects caused by the lack of oxygen observed in an expanded adipose tissue.

Conclusion

According to the evidence presented here, VC could be implicated in diverse mechanisms that are involved in the onset, development, and further consequences of body weight increase. These mechanisms could be related to oxidative stress prevention, intracellular fat
accumulation modulation, glucocorticoid release inhibition, insulin-sensitizing improvement, inflammation amelioration, and counteraction of hypoxic-related injury. All these data indicate a direct effect of VC on important obesity-related mechanisms and contribute substantially to the general knowledge regarding the potential of dietary antioxidants over triglyceride accumulation by a chronic intake of a fat-rich diet.

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