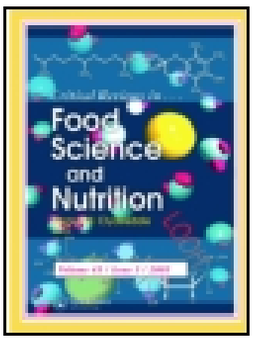

Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

Association between Vitamin Deficiency and Metabolic Disorders Related to Obesity

Samanta T. Valdés, Maria das Graças V. Tostes, Pamella C. Anunciação, Bárbara P. da Silva & Helena M. Pinheiro Sant'Ana

To cite this article: Samanta T. Valdés, Maria das Graças V. Tostes, Pamella C. Anunciação, Bárbara P. da Silva & Helena M. Pinheiro Sant'Ana (2016): Association between Vitamin Deficiency and Metabolic Disorders Related to Obesity, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2015.1117413

To link to this article: http://dx.doi.org/10.1080/10408398.2015.1117413

Accepted author version posted online: 08 Jan 2016.

Association between vitamin deficiency and metabolic disorders related to obesity

Samanta T. Valdés[1], Maria das Graças V. Tostes[2], Pamella C. Anunciação[3,*], Bárbara P. da Silva[3] and Helena M. Pinheiro Sant'Ana[3]

[1]Universidad de Talca, Talca, Chile

[2]Center of Agrarian Sciences, Universidade Federal do Espírito Santo, Alegre, Espírito Santo, Brazil.

[3]Department of Nutrition and Health, Universidade Federal de Viçosa, Viçosa, Minas Gerais, Brazil.

[*]Corresponding author: Department of Nutrition and Health, Universidade Federal de Viçosa, Avenida PH Rolfs s/n, 36570-900, Viçosa -- MG, Brazil. Tel.: +55 31 3899 1684 Fax: +55 31 3899 2541, E-mail: nutripamella@gmail.com

Abstract

Inappropriate food behavior contributes to obesity and leads to vitamin deficiency. This review discusses the nutritional status of water- and fat-soluble vitamins in obese subjects. We verified that most vitamins are deficient in obese individuals, especially the fat-soluble vitamins, folic acid, vitamin B_{12} and vitamin C. However, some vitamins have been less evaluated in cases of obesity. The adipose tissue is considered a metabolic and endocrine organ, which in excess leads to changes in body homeostasis, as well as vitamin deficiency which can aggravate the pathological state. Therefore, the evaluation of vitamin status is of fundamental importance in obese individuals.

Keywords

obesity, vitamin deficiency, metabolic disorders, fat-soluble vitamins, water-soluble vitamins.

1. Introduction

Obesity is defined by the World Health Organization as a body mass index (BMI) of 30 kg/m^2 or more, and constitutes a growing health problem worldwide. In 2014, 39% of adults aged 18 years and over were overweight, and 13% were obese (WHO, 2015). In Brazil, the overweight and obesity prevalence increased for both sexes and all age groups, with childhood obesity exceeding international standards for this age group (IBGE, 2010). Approximately 52.5% of Brazilians are overweight and 17.9% of the population is obese (Ministério da Saúde, 2014).

Some environmental and behavioral factors may be indicators of obesity by influencing food choices, intake and energy expenditure. Caloric intake in excess of caloric expenditure leads to a positive energy balance with consequent weight gain (Hill, 2006). Additionally, an obesogenic environment favors weight accumulation and genetic factors associated with poor nutrition can exacerbate obesity (Foss, 2009).

The study of obesity emphasizes the relationship between the metabolism of macronutrients and increased risk of development of chronic diseases associated with weight gain. However, an association between obesity and vitamin deficiency has been postulated. Overweight individuals are more predisposed to vitamin deficiency, due to differences in intake of dietary fruit, vegetable, and energy by overweight and obese individuals as compared to individuals of normal weight. These associations may also result from alterations in the physiology of micronutrient metabolism, with greater fat mass leading to increased sequestering of lipophilic vitamins in adipose tissue (Landrier *et al.*, 2012).

Fat-soluble vitamins are required for various body functions such as bone metabolism, blood coagulation, immune response, antioxidant activity and other actions needed for the prevention of many diseases (Institute of Medicine, 2001). Water-soluble vitamins are essential to metabolism, participating in several metabolic pathways and are involved in the reactions of energy production, redox reactions and the transfer of carbon units (Institute of Medicine, 1998).

Recent research has linked deficient serum vitamin levels and their intake to obesity. Nevertheless, we found no reviews in the literature compiling and evaluating this area of research.

A search was performed in the databases Pubmed, Scielo, Lilacs, Scopus and Science Direct for articles published between 2001 and 2015 related to obesity and water- and fat-soluble vitamins using the following keywords: obesity, adipokines, inflammatory process, supplementation associated with carotenoids, vitamins A, D, E and K, thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), folate (B_9), cobalamin (B_{12}), vitamin C and respective isomers. Abstracts of all articles encountered were carefully read and those presenting a relationship between vitamin status and obesity development were included.

2. Fat-soluble vitamin deficiency and obesity

There appears to be a correlation between increase in adipose tissue and decrease in serum fat-soluble vitamin levels. The main studies linking obesity and fat-soluble vitamins are described in Table 1.

2.1. Vitamin A and carotenoids

Vitamin A and carotenoids are essential in human nutrition since they prevent certain diseases (Neuhouser *et al.*, 2001). Food intake and lifestyle can influence serum concentrations of these

nutrients, especially low intake of fruits and vegetables containing vitamin A and its precursors (Van Het Hof *et al.*, 2000; Bermudez e Tucker, 2003). Studies demonstrated that obese individuals present vitamin A deficiency and low serum levels of carotenoids (Wallström *et al.*, 2001; Galan *et al.*, 2005; Switzer *et al.*, 2005; Silva *et al.*, 2007; Vioque *et al.*, 2007; Botella-Carretero *et al.*, 2010). However, it has not yet been determined if this deficiency is due to a poor diet or to other factors, such as oxidative stress and inflammatory processes that result from obesity.

To identify the relationship between vitamin A and carotenoids intake and their serum levels, adolescents were evaluated regarding to serum concentrations of retinol, α-carotene, β-carotene, β-cryptoxanthin, lycopene and lutein + zeaxanthin. The authors verified that serum concentrations of carotenoids did not differ between genders, although there was a greater consumption of vitamin A ($p < 0.05$) by males (960 RE/ day) than by females (752 RE/ day). The obese participants had serum concentrations 2 to 10% lower for α-carotene, β-carotene, β-cryptoxanthin and lycopene as compared to those with normal weight, although the intake of these nutrients was similar between different BMI ranges (Neuhouser *et al.*, 2001).

Silva et al. (2007) verified lower serum levels of retinol and carotenoids ($p < 0.05$) in overweight and obese children as compared to normal weight children. In adults, the β-carotene intake differed between the genders: women presented higher intake of this nutrient (2.2 mg/1000 kcal) than men (1.7 mg/1000 kcal) ($p < 0.05$); younger women (<45 years) had lower serum β-carotene (0.6 mol/L) and BMI was inversely associated with serum concentrations of β-carotene in both men and women ($p < 0.05$) (Galan *et al.*, 2005). Other studies demonstrated the inverse relationship between BMI and serum concentrations of β-carotene (Wallström *et al.*,

2001), β-cryptoxanthin (Switzer *et al.*, 2005), retinol (Botella-Carretero *et al.*, 2010), and other carotenoids (α-carotene and lutein + zeaxanthin) (Vioque *et al.*, 2007). Although carotenoids intake were similar in subjects with different BMI ranges, these studies showed that obese subjects presented lower serum levels of vitamin A precursors. Gunanti et al. (2014) verified that higher concentrations of serum α-carotene, trans-β-carotene, cis-β-carotene were associated with a reduced risk of childhood overweight or obesity, whereas increased retinol concentrations were associated with an increased risk. Similarly, serum concentrations of α-carotene, trans-β-carotene and cis-β-carotene, were inversely associated with overall fat mass.

A mechanism that may be responsible for the inverse associations found between serum carotenoids and adiposity would be differences in dietary fruit, vegetable, and energy intakes between obese and non-obese subjects. Even though obese subjects may consume an excess of energy foods, they may not be meeting all of their micronutrient needs (Gunanti *et al.*, 2014). In addition, a person with higher fat mass would have a larger portion of ingested β-carotene absorbed by fat tissue than would a lean person and thus would have reduced serum carotenoid concentrations when compared with lean individuals.

In an animal model, Jeyakumar et al. (2005) observed that obese rats with vitamin A supplementation (129 mg vitamin A/kg diet for 2 months) showed a reduction ($p \leq 0.05$) in the adiposity index and retroperitoneal adipose tissue weight while a marginal reduction was observed in lean rats. However, this treatment resulted in an increase ($p \leq 0.05$) of retroperitoneal adipose tissue apoptotic index, with under expression of anti-apoptotic protein and over expression of pro-apoptotic protein (proteins Bcl2 and Bax, respectively) in the lean rats. The

authors concluded that vitamin A supplementation regulates adipose tissue mass in the lean and obese rats by different mechanisms.

Vitamin A supplementation also improved hepatic retinol stores ($p \leq 0.05$) for lean and obese rats without affecting serum free retinol levels, but did not change the expression levels of mRNA uncoupling protein1 (UCP1) on brown adipose tissue (Jeyakumar *et al.*, 2006). On the other hand, rats fed a vitamin A deficient diet had increased adiposity and body weight gain (Bonet *et al.*, 2000; Ribot *et al.*, 2001). These studies showed that vitamin A intake has some degree of influence on energy metabolism in animals.

In vitro research has pointed to the relationship between retinoids metabolism and the activity of differentiation and functionality in the adipose tissue, as *all*-trans-retinol (RA) appears to inhibit cell differentiation in adipocyte cell culture (Ahuja *et al.*, 2003). The administration of pharmacological doses of RA increases lipolysis in adipocytes, decreases the expression of leptin and resistin (Ribot *et al.*, 2001; Berry e Noy, 2009), activates thermogenesis by uncoupling proteins (UCPs) (Mercader *et al.*, 2006) and improves oxidative metabolism (Amengual *et al.*, 2008). Pro-vitamins A (β, β-carotene) decrease the peroxisome proliferator-activated receptor gamma (PPARγ) activity, depressing the cell differentiation of pre-adipocytes to adipocytes, and reduces the storage capacity of lipids in the adipocytes due to the action of monooxygenase enzyme-1 β, β-carotene (Lobo *et al.*, 2010).

In vitro assays and animal experiments demonstrated an important role of vitamin A and carotenoids in oxidative metabolism modulation and in the reduction of cell differentiation, which could help in the treatment of obesity. The effect of vitamin A deficiency and carotenoids insufficiency in obesity may increase the risk of fat deposition and chronic inflammation

associated with obesity. It is necessary to establish the mechanism ruling this relationship in humans in order to help in treating this disorder.

2.2. Vitamin D

Vitamin D deficiency is characterized by plasma levels of circulating 25-hydroxy vitamin D [25(OH)D] below 20 ng/mL (Holick, 2009) and is associated with some chronic diseases, such as insulin resistance, metabolic syndrome (Aarts *et al.*, 2011), atherosclerosis (Freedman *et al.*, 2010) and obesity (Cheng *et al.*, 2010). The endogenous production of vitamin D is the main source of this vitamin as a result of skin exposure to sunlight (Holick, 2009), because few foods contain this vitamin and always in small amounts (Ross *et al.*, 2011). Possible reasons for low vitamin D status during obesity are a lower intake of vitamin D by obese individuals (Wortsman *et al.*, 2000), less physical activity, which results in less exposure to sunlight (Brock *et al.*, 2010), and decreased intestinal absorption of the nutrient vitamin D in individuals underwent bariatric surgery (Aarts *et al.*, 2011). Individuals residing in high latitudes also have low exposure to the sun, and relationship between low endogenous vitamin D synthesis and higher rates of obese and overweight individuals has been verified (Macdonald *et al.*, 2008). The relationship between vitamin D metabolites [25(OH)D and $25(OH)_2D$] and seasonal variations and BMI was also verified; both metabolites decreased during winter in subjects with higher BMI (Moan *et al.*, 2009).

An inverse association between serum 25(OH)D concentrations and waist circumference, BMI (even in lean subjects with BMI $<25 kg/m^2$), and subcutaneous and visceral adipose tissue volumes was observed in 1882 subjects. The prevalence of vitamin D deficiency was three times higher in subjects with high fat concentration in subcutaneous and visceral tissues than in those

with lower fat accumulation in these tissues (Cheng *et al.*, 2010). Other studies corroborate these findings (Wortsman *et al.*, 2000; Looker, 2005; Aasheim *et al.*, 2008; Lu *et al.*, 2009; Ortega, López-Sobaler, *et al.*, 2009; Beydoun *et al.*, 2010). It appears that the higher the degree of obesity, the more severe the vitamin D deficiency (Antolín *et al.*, 2010).

There is controversy regarding ethnic variables related to vitamin D deficiency and high BMI, because some differences were observed among Caucasians, African-Americans and Hispanic-Americans (Mckinney *et al.*, 2008; Gemmel *et al.*, 2009), while other studies did not verify this relationship among Hispanic- and African-Americans (Parikh *et al.*, 2004; Young *et al.*, 2009). However, González et al. (2015) in a clinic-based sample of Hispanic adults observed that those with higher BMI, waist circumference, and waist-to-height ratio had a significantly lower vitamin D status.

The factor that may result in significant differences between ethnic groups regarding vitamin D status is the degree of obesity. Ethnic groups with higher BMI presented greater potential to sequester vitamin D due to the greater mass and volume of adipose tissue, presenting more severe hypovitaminosis D caused by its deposit. The Recommended Dietary Allowances (RDA) established for vitamin D, for subjects between 1-70 years, both genders, recommends the intake of 15 µg/day of cholecalciferol, under the assumption of minimal sunlight exposure (Ross *et al.*, 2011). Sun exposure variable should be considered since these groups, ranging from 1 to 70 years old may have different degrees of exposure to sunlight. However, it is difficult to determine the absolute percentage of circulating 25(OH)D from the cutaneous synthesis and / or oral intake of vitamin D in the free-living population.

Children and adolescents showed an increase on adiposity associated with vitamin D deficiency. Children with insufficient vitamin D intake (daily intake <70 IU) presented higher body weight, BMI, waist circumference and waist/hip ratio (Rodríguez-Rodríguez *et al.*, 2010). Adolescents showed the same relationships (Alemzadeh *et al.*, 2008; Dong, Stallmann-Jorgensen, *et al.*, 2010), but no increase in parathyroid hormone (PTH) concentrations, as opposed to other findings (Wortsman *et al.*, 2000; Valiña-Tóth *et al.*, 2010). It appears that the relationship between vitamin D deficiency and adiposity in adolescents results from metabolic factors for this age group, mainly due to hormonal changes (Lenders *et al.*, 2009).

Since vitamin D is fat-soluble, it can be stored in the adipose tissue (Wortsman *et al.*, 2000) and with a large concentration of adipose tissue, there is a decrease in vitamin D bioavailability (Valiña-Tóth *et al.*, 2010). Researchers suggested that when more subcutaneous fat is available (e.g., in obese individuals), more vitamin D is sequestered there, resulting in less circulating 25(OH)D levels (Wortsman *et al.*, 2000; Blum *et al.*, 2008). According to Lenders et al. (2009), a decrease of 0.5 ng/mL of 25(OH)D in adolescents was related to 1% increment in body fat mass, whereas a decrease of 0.8 pg/mL of PTH resulted in 1% increase on visceral adipose tissue. The authors explained that the fat distribution could be associated with vitamin D status, but this relation may be dependent on metabolic factors.

Regarding levels of supplementation, care must be taken when using doses of vitamin D supplementation since the recommended daily intake for adults is 15 μg/day (Hathcock *et al.*, 2007). Salehpour et al. (2012) observed that the supplementation with vitamin D_3 (25 μg/day as cholecalciferol) decreased ($p<0.001$) body fat mass in obese subjects with vitamin D (-2.7±2.1 kg) as compared to obese subjects with placebo (-0.5±2.1 kg), but body weight and waist

circumference did not change in both groups. However, not all studies showed a positive effect of vitamin D on weight loss (Sneve *et al.*, 2008; Gallagher *et al.*, 2013). Gallagher et al. (2013) analyzed seven doses of vitamin D supplementation (400-4800 IU/d) in women with normal weight and obesity. The group with BMI <25kg/m^2 developed higher levels of serum 25(OH)D after vitamin D supplementation, as compared to those with BMI >25kg/m^2. However, all obese women reached adequate levels of serum 25(OH)D while women with normal weight reached much higher levels of 25(OH)D. The authors suggested that differences in serum 25(OH)D levels between normal and obese women may be due to differences in volume dilution and the response to vitamin D supplementation is dependent on body weight. In both groups, there was no significant change in total body fat mass after treatment with vitamin D.

Saliba et al. (2013) concluded that BMI was inversely associated with the increase in serum 25(OH)D levels in response to vitamin D supplementation. Other study showed that a higher vitamin D serum status was negatively associated with adiposity and was able to inhibit the differentiation of pre-adipocytes, contributing to decrease adiposity (Dong *et al.*, 2010). Some hypotheses can explain the inverse relationship between increased adiposity and plasma vitamin D deficiency. A possible mechanism for increased lipogenesis is associated with moderate or severe vitamin D deficiency, which is responsible for elevating the secretion of PTH. This substance promotes a greater influx of calcium into the adipocyte, stimulating lipogenesis (Mccarty e Thomas, 2003).

Vimaleswaran et al. (2013) analyzed the relationship of 12 established single nucleotide polymorphisms (SNPs) with body mass index (BMI) and four typical vitamin D related SNPs in 42024 patients. The results showed that each unit increase of BMI was associated with a 1.15%

decrease of 25(OH) D. The study revealed obesity as a causal risk factor for vitamin D deficiency, which accounts for approximately one third of vitamin D deficiency.

Other association between obesity and vitamin D is the modulation of adipogenesis exerted by 1,25(OH)D through the inhibition of the vitamin D-dependent receptor. It decreases the activity of PPARγ and vitamin D receptor-dependent (VDR) on the inhibition of cytidine-cytidine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding protein alpha (C/EBPα). Both components are involved in the maturation of pre-adipocytes to adipocytes (Wood, 2008). In the case of vitamin D deficiency, this differentiation can occur in a higher extent due to increased activity of PPARγ and C/EBPα receptors, increasing the volume of the adipose tissue, which may accept larger accumulation of fat.

Some metabolic parameters related to vitamin D status may be improved with supplementation. Addition of 83 mg/day of vitamin D to the diet increases 25(OH)D (+185%) and calcitriol (+45%) concentrations, as well as decreases PTH (-26.5%), triglycerides (-13.5%) and inflammatory markers, such as the tumor necrosis factor (TNF-α) (-10.2%) when compared to the placebo. Low-density lipoprotein cholesterol (LDL-c) was elevated with vitamin D supplementation (+5.4%) ($p < 0.001$) (Zittermann *et al.*, 2009) because when increasing circulating vitamin D there was a higher absorption of calcium from the intestine, decreasing fecal excretion of calcium salts with insoluble fats, especially saturated fats. Thus, there is an increase in the synthesis of LDL-c (Major *et al.*, 2007). Consequently, if a vitamin D supplementation in obese individuals is necessary, calcium should be considered, since both are metabolically related.

Studies established the association of vitamin D deficiency in obese individuals, a higher accumulation of vitamin D in adipose tissue for its storage and a lower intake of vitamin D. The status of vitamin D seems to be associated with an improvement in inflammatory processes and this relation should be studied further.

2.3. Vitamin E

Obesity is associated with increased oxidative stress, which is related with low serum antioxidant levels, which in turn may increase the risk of coronary heart disease. The decrease in serum levels of antioxidants such as α- and γ-tocopherol relates to increased oxidation of low density lipoproteins (Keaney *et al.*, 2003), certain types of cancer and insulin resistance (Shah *et al.*, 2007), increasing the risk of atherosclerosis in obese subjects. Vitamin E is an antioxidant that can protect cell membranes from damage caused by lipid peroxidation, inhibit cell proliferation, platelet adhesion and formation of nitrous compounds (Azzi e Stocker, 2000). Studies confirmed an association between increases of abdominal adiposity in obese individuals and vitamin E deficiency (Tungtrongchitr *et al.*, 2003; Molnar *et al.*, 2004; Vajro *et al.*, 2004). Low serum vitamin E may also be associated with higher rates of lipoprotein high-density lipoprotein cholesterol (HDL-c) oxidation (Keaney *et al.*, 2003). An inverse relationship between serum levels of α-tocopherol and plasma lipids is also seen among obese children (Morinobu *et al.*, 2002).

Neuhouser et al. (2001) observed that serum α-tocopherol levels were approximately 10% lower in obese adolescents, as compared to those with normal weight, although the average intake did not differ among groups of adolescents. Dietary intake was a determinant of serum α-tocopherol and explained only 28% of the variability in serum.

A comparison between serum α-tocopherol levels of men and women showed that serum values of vitamin E were associated with dietary intake of the vitamin, gender, age, smoking and alcohol consumption (Galan *et al.*, 2005), but no inverse association between BMI and serum vitamin E were verified.

A study with children showed that obese children with metabolic syndrome presented lower serum levels of α-tocopherol (2.4±3.1 μmol/mmol) when compared to obese children (3.7±0.9 μmol/mmol) and normal weight children (3.8±0.7 μmol/mmol) (Molnar *et al.*, 2004).

Vitamin E supplementation in obese animals increased the serum levels of mRNA and protein expression related to adiponectin, as well as increased mRNA expression of leptin (Shen *et al.*, 2010). Another study verified that vitamin E supplementation in obese animals suppressed interleukin-6 produced by epididymal adipose tissue (Lira *et al.*, 2011). These results demonstrate that vitamin E may also act in the treatment of obesity by stimulating the production of anti-inflammatory adipokines (adiponectin), as well as in the expression of modulating factors of food intake (leptin) and by suppressing pro-inflammatory cytokines (IL-6), which are factors that further hinder the control of obesity.

Studies are contradictory regarding the association between vitamin E and obesity. However, among other fat-soluble vitamins, vitamin E has the greatest antioxidant potential and its isomers may be important for oxidative stress control and damage caused by some underlying diseases, typical in obese individuals.

2.4. Vitamin K

Few studies related vitamin K status and obesity. There is no consensus regarding this nutrient and weight gain. There is no evidence that this vitamin relates to obesity or exacerbation

of its symptoms. Supplementation of 500 mg/day of phylloquinone (K_1) for 36 months showed a positive effect on insulin resistance, but did not change weight and BMI for both genders (Yoshida *et al.*, 2008). A hypothesis considered is that vitamin K could exert a positive effect on insulin receptors or this vitamin could help the production of some adipokines involved in insulin resistance.

In a study that compared body fat percentage with circulating vitamin K isomers, fat percentage inversely associated with K_1 plasma in women. The highest percentages of fat in both men and women were associated with elevated circulating levels of decarboxylated prothrombin, which is an indicative of reduced hepatic vitamin K utilization in obese subjects (Levin *et al.*, 2010; Shea *et al.*, 2010).

Other study observed that vitamin K intake was higher in older individuals (55-64 years) with lower BMI ($<25 kg/m^2$) and nonsmokers. There was a trend of decreased vitamin K intake over the years, verified mainly by decreasing cooked green vegetable consumption, which accounted for 23% of vitamin K consumption. Thus, it appears that plasma concentrations of K_1 relate to gender, age, seasonality and intake. BMI did not relate directly to K_1 serum concentrations (Thane *et al.*, 2006).

3. Water-soluble vitamin deficiency and obesity

The most common water-soluble vitamins evaluated in obese subjects are thiamin (B_1), pyridoxine (B_6), folate (B_9), cobalamin (B_{12}) and vitamin C. The main studies relating water-soluble vitamin deficiency to obesity show that the deficiency is quite prevalent in obese individuals (Table 2).

3.1. Thiamin (B_1)

Thiamin is a coenzyme involved in many biochemical pathways necessary for proper tissue and organ function. Deficiency of this vitamin leads to the lactate and pyruvate accumulation and to a decrease in the levels of alpha-keto-glutarate, acetate, citrate, and acetylcholine (Carrodeguas *et al.*, 2005). Obese patients should be closely monitored to detect cardiovascular and neurologic manifestations, and adequate therapy should be used to prevent irreversible outcomes because alteration of these compounds can be responsible for several damages (Carrodeguas *et al.*, 2005).

Few studies evaluated the serum concentration of thiamin in obesity. In subjects undergoing bariatric surgery, the high surgical demand associated with rapid weight loss and absorptive area may induce a more severe thiamin deficiency. In this case, it is essential to assess the individual before surgery and correct the deficiency if necessary (Carrodeguas *et al.*, 2005; Flancbaum *et al.*, 2006). A study observed a prevalence of thiamin deficiency of 15.5% in 303 patients on pre-operative bariatric surgery (Lira *et al.*, 2011). In another study with 379 patients this prevalence was 29% (n = 110) (Flancbaum *et al.*, 2006). However, preoperative thiamine level was recorded retrospectively and thiamine intake was not evaluated in these patients.

Patrini et al. (2004) reported reduced plasmatic thiamine levels in obese women. Moreover, erythrocyte thiamin had lower concentrations in obese women (16.3 pmol/mg) as compared to normal weight women (20.0 pmol/mg).

Tea intake containing a mixture of thiamine, arginine, caffeine and citric acid compared to a placebo (only tea) did not decrease adipose tissue weight (-3.8%; $p < 0.05$), hepatic triglyceride content (150 mg/dL; $p < 0.05$) and plasma insulin concentration (77.0 IU/dL; $p < 0.05$) in mice. Thiamine was added due to its importance in energy metabolism (Muroyama *et*

al., 2003). However, it was a mixture of nutrients and these results may not be attributed to thiamine intake.

The intake and control of serum levels of thiamin is essential because this vitamin acts as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids. A difference around 10% in the average thiamin requirements for men and women is assumed based on mean differences in body size and energy utilization (Institute of Medicine, 1998). Obese individuals may have different requirements for thiamin, so the recommended daily intake does not consider their higher body weight. There is no consensus regarding thiamin supplementation for obese individuals and it may be a crucial factor for improvement of metabolism in obesity treatment.

3.2. Pyridoxine (B_6)

Pyridoxine is an underlying cofactor that participates in a wide range of reactions, including metabolism of homocysteine and sulfur-containing amino acid (Nachtigal *et al.*, 2005).This vitamin acts as a cofactor for the enzyme glycogen phosphorylase, used to break down glycogen (stored glucose) to produce energy. In addition, vitamin B_6 is a cofactor for transamination and decarboxylation to produce γ-aminobutyric acid and serotonin, which may affect weight by an indirect mechanism (Nachtigal *et al.*, 2005).

Vitamin B_6 deficiency has been associated with inflammatory diseases, such as cardiovascular disease, rheumatoid arthritis, inflammatory bowel disease and diabetes, resulting from impairment of enzymes involved in the structural integrity of the arterial wall, in altering platelet function, and interfering with cholesterol metabolism (Sakakeeny *et al.*, 2012). Patients with vitamin B_6 deficiency showed higher levels of C-reactive protein, an acute-phase reactant that is characteristic of inflammatory condition (Aasheim *et al.*, 2008). A cohort database

showed that plasma pyridoxine is inversely associated with systemic markers of inflammation, including acute phase reactants, cytokines, adhesion molecules, and oxidative stress, attributed to functional deficiency of pyridoxine (Sakakeeny *et al.*, 2012).

Despite the influence of vitamin B_6 status on inflammatory processes, we found few studies with obese individuals.

Tungtrongchitr et al. (2003) verified adequate serum levels of vitamin B_6 in 149 overweight or obese adults as compared to 113 normal weight adults. However, Aasheim et al. (2008) observed vitamin B_6 deficiency in severe obese subjects (110 patients), and a negative association between serum vitamin B_6 and BMI.

A long-term study analyzed the association of nutritional supplements administration with weight change over 10 years among individuals 53 to 57 years old, and verified that overweight or obese individuals who used vitamin B_6 supplementation presented lower weight gain ($p < 0.05$) (Nachtigal *et al.*, 2005). It is possible that the effect of vitamin B_6 on energetic metabolism helps weight control.

In another study, obese or overweight individuals had a negative correlation between serum levels of folic acid and vitamin B_6 between men and women (Tungtrongchitr *et al.*, 2003), because these nutrients share common metabolic pathways, and the deficiency of one can change the operation of the other or can mask a deficiency, making it important to evaluate both nutrients. The relationship between folate and vitamin B_6 may be critical, and the control of homocysteine levels which is discussed in the next topic.

Pyridoxine is a vitamin involved in energy metabolism and there are evidences that it can influence the inflammatory process presented in obesity. Hence, this vitamin should be more studied and considered in obesity handling.

3.3. Folate (B_9)

Folate is an essential nutrient involved in many crucial functions in the body, and its deficiency relates to an increase in serum levels of homocysteine. Increased total plasma homocysteine concentration is associated with cardiovascular disease. Epidemiological studies identified an inverse association between blood folate concentrations, folate intake and cardiovascular events, which are more frequent amongst obese individuals (Moat *et al.*, 2004).

Obese individuals showed inadequate folate levels (Mahabir *et al.*, 2008; Ortega, Lopez-Sobaler, *et al.*, 2009; Schweiger *et al.*, 2010). Ortega et al. (2009) verified that obese women have a greater risk of inadequate folate status, even with similar folate intake to non-obese individuals. Mahabir et al. (2008) observed that increased body fat percentage correlated to lower folate serum level. Serum folate was 22% lower in obese individuals and 12% lower in those overweight when compared to women with normal weight. In another study, BMI higher than 50 kg/m² correlated with a major likelihood of folate deficiency (Schweiger *et al.*, 2010). Abnormal levels of folate are common in obese patients in both pre- and post-operative of bariatric surgery, and it is essential a prior evaluation and correction of pre-existing disabilities (Madan *et al.*, 2006).

An analysis using population data from 16191 subjects (NHANES III) found that obese or overweight individuals were more likely to have low folate serum levels (Kimmons *et al.*, 2006). Other authors also analyzed data from NHANES (NHANES 1988-1994 and NHANES

1999-2000), and showed that an increase of BMI in women of childbearing age is related to lower serum folate (Mojtabai, 2004). These results led to questions like whether obese women would have higher nutritional requirement than adequate weight women would at childbearing age, and whether there is a larger requirement for monitoring pregnancy in obese women due to the further risk of neural tube defects and other complications caused by folate deficiency.

Bradbury et al. (2014) reported a 1% decrease in serum folate concentration associated with every increase of one unit in BMI. Bird et al. (2015) demonstrated that BMI values exceeding the desirable range are positively associated with red blood cell folate concentrations in adults, but inversely associated with serum folate concentrations. In obesity, low serum folate may stimulate folate uptake by red blood cells (Bird *et al.*, 2015). Regardless of some studies had pointed an inverse relation between folate and BMI, Aasheim et al. (2008) and Reitman et al. (2002) did not identify differences between folate levels in obese adult men and women, as compared to non-obese individuals. The low serum folate status associated with obesity may be due to a volumetric dilution of the blood in obese subjects and/or low folate intake in the obese population. Another explanation may be that adiposity influences folate uptake by the intestinal epithelium (Bird *et al.*, 2015).

Folate is essential to endothelial function. Hyperhomocysteinemia is a risk factor for atherosclerosis and associates with endothelial dysfunction. Folic acid supplementation can lower plasma homocysteine concentrations safely and inexpensively (Moat *et al.*, 2004). Folic acid supplementation for 1 year was associated with an increase of plasma folate levels and a decrease of homocysteine levels ($p < 0.05$) among healthy adults with hyperhomocysteinemia. It seems that long-term folic acid supplementation may improve arterial endothelial function and

can be a factor for prevention of atherosclerosis in hyperhomocysteinemic adults (Woo *et al.*, 2002).

Obese adults showed deficient levels of folate and high homocysteine levels (Tungtrongchitr *et al.*, 2003; Zhu *et al.*, 2006). Ortega et al. (2009) observed that weight loss higher than 5% was associated with higher folate and lower homocysteine levels, probably because hypocaloric diets lead to an increase in fruits and vegetables intake, which are sources of folate.

An experimental assay with hypertensive rats has shown that folate deficiency can promote oxidative stress and multiple features of the metabolic syndrome that are associated with increased risk for diabetes and cardiovascular disease (Pravenec *et al.*, 2013). An *in vitro* assay demonstrated that the principal circulating metabolite of folate (5-methyltetrahydrofolate) can increase nitric oxide production, which is the major endogenous relaxing factor of the endothelium, and it may scavenge superoxide radicals, which could help the handling of progressive endothelial damage, which is common in obese subjects (Gao *et al.*, 2012).

Studies have shown that folic acid supplementation may improve insulin resistance, another aggravating feature presented on obesity. Folic acid supplementation (5 mg/day) decreased homocysteine plasma level and insulin resistance, improved the glycemic control, and increased serum folate and B_{12} in 48 overweight and obese men with type 2 diabetes under metformin treatment (at least 1500 mg daily) (Gargari *et al.*, 2011). The possible mechanism may be that homocysteine thiolactone (active form of homocysteine) can inhibit tyrosine phosphorylation insulin-stimulated of β-subunit insulin receptor and its substrates, and decrease the p85 regulatory subunit of phosphatidylinositol 3-kinase activity, including a reduction in

insulin-stimulated glycogen synthesis (Gargari *et al.*, 2011). Another possible mechanism may be ameliorating endothelial dysfunction induced by elevated homocysteine, converting L-arginine to nitric oxide and L-citrulline, which scavenge reactive oxygen species such as $O2^{-}$ and peroxynitrite, and maintaining a coupled endothelial nitric oxide synthase reaction, and prevent nitric oxide synthase dysfunction (Gargari *et al.*, 2011).

Folate deficiency may aggravate obesity by different ways. This vitamin may be a crucial adjuvant nutrient in obesity management and the safety levels of supplementation for obese subjects must be evaluated..

3.4. Cobalamin (B_{12})

Vitamin B_{12} is a cofactor in the synthesis of methionine to homocysteine; therefore, deficiency of vitamin B_{12} can lead to hyperhomocysteinemia. As described above, hyperhomocysteinemia is correlated with insulin resistance and with the development of cardiovascular disease (Pinhas-Hamiel *et al.*, 2006). Therefore, the concerns reported for folate deficiency are similar for vitamin B_{12} deficiency, and it is essential to assess the nutritional status of obese individuals to avoid potential complications.

Obese children and adolescents aged 6 to 19 years (n = 164) showed lower average concentration of serum vitamin B_{12} when compared to those with normal weight (n = 228) (Pinhas-Hamiel *et al.*, 2006). Vitamin B_{12} deficiency was also observed by Madan et al. (2006) in 13% of patients evaluated in pre-operative bariatric surgery. Schweiger et al. (2010) observed only 3.6% of vitamin B_{12} deficiency in 114 patients referred to bariatric surgery. Another research conducted with post-menopausal women identified decreased levels of vitamin B_{12} followed by increased BMI (Mahabir *et al.*, 2008). Gunanti et al. (2014) also verified that serum

concentrations of vitamin B_{12} were inversely associated with BMI in children. However, some studies have shown no deficiency of vitamin B_{12} in obese subjects (Reitman *et al.*, 2002; Zhu *et al.*, 2006; Aasheim *et al.*, 2008; Mahabir *et al.*, 2008).

A long-term (10 years) supplementation of vitamin B_{12} was associated with lower levels of weight gain in overweight or obese individuals ($p < 0.05$) (Nachtigal *et al.*, 2005). This effect may be related to vitamin B_{12} as a cofactor of methylmalonyl CoA mutase leading to succinyl CoA (an intermediate of the Krebs cycle) which helps the control of caloric expenditure and energy availability. The contribution to red blood cell production is also important since vitamin B_{12} deficiency can result in anemia, which leads to fatigue and a lack of desire to exercising (Nachtigal *et al.*, 2005).

A group of 100 diabetic patients was randomly assigned to receive either an oral dose of daily B-group vitamins (1.7 mg of folic acid, 1.7 mg of vitamin B_2, 20 mg of vitamin B_6, 0.134 mg of vitamin B_{12}) and antioxidant vitamins (221 mg of α-tocopherol and 167 mg of vitamin C) or placebo daily for 90 days. This supplementation reduced homocysteine levels in the intervention group compared to the placebo group, as well as improving antioxidant status and exhibiting anti-inflammatory effect in obese diabetic patients (Gariballa *et al.*, 2013).

The assessment of vitamin B_{12} in obese individuals is important due to its interference in energy metabolism, its relation with homocysteine levels and its possible effect on weight gain. However, more studies are necessary to determine the security level of vitamin B_{12} intake for obese subjects.

3.5. Vitamin C

Vitamin C is required for the post-translational modification of pro-collagen polypeptides to form the resilient, cross-linked collagen molecule. Defective collagen synthesis is one of the most common symptoms attributed to scurvy because scurvy leads to fatigue (Kypreos *et al.*, 2001), which reduces the willingness to practice exercises and contributes to the recrudescence of obesity. Vitamin C is also required for carnitine biosynthesis, which is responsible for shuttling long chain fatty acids across the mitochondrial membrane for β-oxidation and subsequent fat oxidation (Reda *et al.*, 2003). Carnitine transport in muscle is dependent of γ-butyrobetaine (synthesized by a vitamin C-dependent process) (Reda *et al.*, 2003), so when there is a depletion of vitamin C plasma carnitine concentration increases and, consequently, β-oxidation decreases. Johnston (2005) demonstrated this relation, since he verified a raised level (30%) of oxidized lipids during moderate exercise for individuals with adequate levels of vitamin C, as compared to overweight or obese adults. It seems that individuals with vitamin C deficiencies may be more resistant to weight loss.

Higher BMI values associated with lower serum vitamin concentration in obese individuals (Riess *et al.*, 2009). Aasheim et al. (2008) corroborate with this results in a comparison between subjects with severe obesity recommended for bariatric surgery and normal weight individuals. Johnston (2005) observed an inverse relationship between plasma concentrations of vitamin C, BMI and waist circumference in overweight or obese adults.

Inadequate eating behavior must be the main cause of lower vitamin C levels in obese individuals because this vitamin has a wide availability of fresh fruits and vegetables, besides being a common antioxidant added to many processed foods (Riess *et al.*, 2009). This relation is verified in studies where fruits consumption associated with higher ascorbic acid concentrations

in obese individuals (Riess *et al.*, 2009) and low vitamin C intake, associated with larger central adiposity in 926 women between 40 to 60 years old (Azadbakht e Esmaillzadeh, 2008).

Ascorbic acid reduced weight gain and decreased total body weight and adipose tissue of rats fed a high fat diet. This reduction associated with low expression of genes involved in adipogenesis, adipocyte differentiation and metabolism of glucocorticoids (Campion *et al.*, 2006; Campión *et al.*, 2008; Boque *et al.*, 2009). In an *in vitro* assay, it was observed that vitamin C inhibited glucose uptake and lactate production, and reduced glycerol release and caused a consistent fall of leptin secretion in a dose-dependent manner. Moreover, vitamin C modified the expression of some important obesity-related proteins. The decreased glucose uptake could be due to transport competition between vitamin C and glucose that possibly leads to leptin secretion inhibition, which could result in inhibition on lipolysis. The authors also verified effects of vitamin C on reactive oxygen species modulations, with an important decrease in its extracellular content (Garcia-Diaz *et al.*, 2010). These results showed different pathways through which vitamin C could improve glucose and fat metabolism in primary culture rat adipocytes.

Vitamin C supplementation reduced the levels of C-reactive protein in 75% of obese subjects (Block *et al.*, 2009). In this case, vitamin C could improve the endothelial dysfunction caused by oxidative stress. In obese subjects (24 men and 13 women), the infusion of vitamin C increased the impaired vasodilation in response to acetylcholine, showing a protective effect on the endothelial dysfunction of these individuals (Perticone *et al.*, 2001).

There is a consistent association between antioxidant deficiency and obesity. It is important to evaluate the occurrence of vitamin C deficiency in order to improve the treatment of obesity and verify a potential impact of supplementation for obese subjects.

3.6. Other water-soluble vitamins

Few studies evaluated riboflavin, niacin, pantothenic acid and biotin in obese subjects, but some studies have shown a possible link with obesity. In the study performed by Aasheim et al. (2008), obese subjects presented adequate riboflavin levels. Apelt et al. (2009) analyzed the activity of erythrocyte glutathione reductase (a common indicator used to assess the status of riboflavin) and verified that glutathione reductase activity was inversely correlated with some cardiovascular risk factors such as systolic arterial pressure ($p < 0.001$), total cholesterol levels ($p = 0.018$), and LDL-c levels ($p = 0.039$), which can be exacerbated in obese subjects. Therefore, riboflavin intake could help in oxidative stress control and in the prevention of cardiovascular disease.

Niacin is an anti-lipolytic agent that can inhibit lipolysis by decreasing free fatty acids and very-low-density lipoprotein cholesterol (VLDL-c) production in the liver, and by lowering the levels of circulating triglycerides (Langin, 2006). Niacin as a drug is potent in raising HDL-c and in reducing the incidence of myocardial infarction (Joy e Hegele, 2008). Niacin can also act on the expression profile of adipokines. Niacin-treated subjects showed improvement in the cytokine profile with increased adiponectin and decreased resistin secretion, and authors observed decreased HDL-c and total triglycerides serum levels (Westphal *et al.*, 2006). An *in vitro* assay conducted by Wang-Fisher et al. (2002), observed that the administration of a drug similar to niacin induced the release of leptin in isolated rat adipocytes.

The prevalence of obesity and diabetes in the last 50 years in the US population increased parallel to per capita consumption of niacin, thiamin or riboflavin. It was due to grain

fortification with vitamins. However, no evidence indicated that these vitamins related to glucose intolerance or insulin resistance (Zhou *et al.*, 2010).

Cereals and flours fortification have led to a high intake of niacin in recent years in the U.S., and a higher intake of niacin related to increased obesity in children (Da Li *et al.*, 2010). These authors supplemented niacin in healthy subjects and concluded that niacin caused hyperinsulinemia followed by hypoglycemia, suggesting that postprandial hypoglycemia leads to increased hunger and increased food intake, causing obesity (Da Li *et al.*, 2010). However, this study included only five individuals and proposes a model to explain the effects found, requiring further evaluation to extrapolate this theory as a potential determinant of obesity.

Pantothenic acid supplementation facilitates the metabolism of fatty acids and their use as energy. In a study evaluating pantothenic acid supplementation in rats and its effects on mitochondrial oxidation, the authors verified that the compounds phosphopantothenate, pantotenin and pantothenol increased oxidative phosphorylation of pyruvate and fatty acids, where pantothenol increased the activity of carnitine palmitoyltransferase (Naruta *et al.*, 2003). The importance of pantothenic acid in lipid metabolism cannot be discarded since this nutrient can present strong correlation with obesity. However, studies are needed to describe this association.

Biotin increases mitochondrial biogenesis via enzyme activation in this synthesis route, thus avoiding the consequent development of insulin resistance presented in obesity (Liu *et al.*, 2009). Moreover, acetyl CoA carboxylase is a lipogenic enzyme, which acts in the synthesis of long chain fatty acids and is biotin-dependent. Inhibition of this enzyme inhibits adipogenesis, suggesting that this enzyme can be targeted to control obesity (Levert *et al.*, 2002). In an

experimental study, biotin supplementation decreased the weight of adipose tissue, triglycerides and the expression of lipogenic genes in the liver and adipose tissue (Larrieta *et al.*, 2010). Further clarification of the role of biotin is needed regarding its relationship with obesity, as well as additional studies in the obese population to assess serum levels of this vitamin.

4. Conclusion

In general, obese individuals have low levels of both soluble- and water-soluble vitamins, as compared to non-obese. Vitamins have several body functions and their deficiency may bring undesirable consequences, especially in obese patients. These individuals present changes in their metabolism because adipose tissue is an endocrine and metabolic organ, which may secrete inflammatory adipokines. Thus, the increase in adipose tissue leads to an inflammatory condition of low intensity and other serious health consequences. Vitamin deficiencies may exacerbate this situation, especially when involved in homocysteine metabolism due to their atherogenic potential. Is not known whether obese individuals have a higher requirement of these nutrients or obesity itself can lead to reduced plasma levels of the vitamin. Thus, it is unclear whether vitamin deficiency is a cause or an effect of obesity.

There should be a greater awareness of both professionals and patients regarding the importance of vitamins in the diet, particularly in obesity, giving more attention to these micronutrients and not just the energetic nutrients and caloric value of food directly related to weight increase. Therefore, because most vitamins are below the normal blood levels in obese individuals, it is necessary to assess the nutritional needs of obese subjects. Also, is essential to evaluate the need for new dietary recommendations, to verify whether the food intake meets the nutritional requirements and to examine the necessity of vitamin supplementations for these

subjects. Further studies are necessary to assess the mechanisms by which the vitamins are related to obesity.

Acknowledgment

The authors are grateful to Prof. Dr. Rinaldo Cardoso dos Santos for the English review.

5. References

Aarts, E. et al. (2011). Vitamin D absorption: consequences of gastric bypass surgery. *European Journal of Endocrinology*.164(5):827-832.

Aasheim, E. T. et al. (2008). Vitamin status in morbidly obese patients: a cross-sectional study. *The American journal of clinical nutrition*.87(2):362-369.

Ahuja, H. et al. (2003). The retinoid X receptor and its ligands: versatile regulators of metabolic function, cell differentiation and cell death. *Journal of biological regulators and homeostatic agents.*17(1):29-45.

Alemzadeh, R. et al. (2008). Hypovitaminosis D in obese children and adolescents: relationship with adiposity, insulin sensitivity, ethnicity, and season. *Metabolism*.57(2):183-191.

Amengual, J. et al. (2008). Retinoic acid treatment increases lipid oxidation capacity in skeletal muscle of mice. *Obesity.*16(3):585-591.

Antolín, S. H.; Martínez, M. D. C. G.; De Frutos, V. Á. (2010). Concentraciones deficientes de vitamina D en pacientes con obesidad mórbida. Estudio de caso-control. *Endocrinología y nutrición.*57(6):256-261.

Apelt, N. et al. (2009). ACP1 genotype, glutathione reductase activity, and riboflavin uptake affect cardiovascular risk in the obese. *Metabolism*.58(10):1415-1423.

Azadbakht, L.; Esmaillzadeh, A. (2008). Dietary and non-dietary determinants of central adiposity among Tehrani women. *Public health nutrition.*11(05):528-534.

Azzi, A.; Stocker, A. (2000). Vitamin E: non-antioxidant roles. *Progress in lipid Research*.39(3):231-255.

Bermudez, O. I.; Tucker, K. L. (2003). Trends in dietary patterns of Latin American populations. *Cadernos de Saúde Pública.*19:S87-S99.

Berry, D. C.; Noy, N. (2009). All-trans-retinoic acid represses obesity and insulin resistance by activating both peroxisome proliferation-activated receptor β/δ and retinoic acid receptor. *Molecular and cellular biology.*29(12):3286-3296.

Beydoun, M. et al. (2010). Associations among 25-hydroxyvitamin D, diet quality, and metabolic disturbance differ by adiposity in adults in the United States. *The Journal of Clinical Endocrinology & Metabolism.*95(8):3814-3827.

Bird, J. K. et al. (2015). Obesity is associated with increased red blood cell folate despite lower dietary intakes and serum concentrations. *J Nutr.*145(1):79-86.

Block, G. et al. (2009). Vitamin C treatment reduces elevated C-reactive protein. *Free Radical Biology and Medicine.46*(1):70-77.

Blum, M. et al. (2008). Vitamin D3 in fat tissue. *Endocrine*.33(1):90-94.

Bonet, M. L. et al. (2000.) Opposite effects of feeding a vitamin A-deficient diet and retinoic acid treatment on brown adipose tissue uncoupling protein 1 (UCP1), UCP2 and leptin expression. *J Endocrinol*.166(3):511-7.

Boque, N. et al. (2009). Some cyclin-dependent kinase inhibitors-related genes are regulated by vitamin C in a model of diet-induced obesity. *Biological and Pharmaceutical Bulletin*, *32*(8), 1462-1468.

Botella-Carretero, J. I. et al. (2010). Retinol and α-tocopherol in morbid obesity and nonalcoholic fatty liver disease. *Obesity surgery.*20(1):69-76.

Bradbury, K. E. et al. (2014). Estimation of serum and erythrocyte folate concentrations in the New Zealand adult population within a background of voluntary folic acid fortification. *J Nutr.*144(1):68-74.

Brock, K. et al. (2010). Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large US sample of healthy middle-aged men and women. *The Journal of steroid biochemistry and molecular biology*.121(1):462-466.

Campion, J. et al. (2006). Diferential gene expression and adiposity reduction induced by ascorbic acid supplementation in a cafeteria model of obesity. *Journal of physiology and biochemistry.*62(2):71-80.

Campión, J. et al. (2008). Vitamin C supplementation influences body fat mass and steroidogenesis-related genes when fed a high-fat diet. *International journal for vitamin and nutrition research.*78(2):87-95.

Carrodeguas, L. et al. (2005) Preoperative thiamine deficiency in obese population undergoing laparoscopic bariatric surgery. *Surgery for obesity and related diseases.*1(6):517-522.

Cheng, S. et al. (2010). Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. *Diabetes*.59(1):242-248.

Da Li, W.-P. S. et al. (2010). Chronic niacin overload may be involved in the increased prevalence of obesity in US children. *World journal of gastroenterology*.16(19):2378.

Dong, Y. et al. (2010). Low 25-hydroxyvitamin D levels in adolescents: race, season, adiposity, physical activity, and fitness. *Pediatrics*.125(6):1104-1111.

Dong, Y. et al. (2010). A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. *The Journal of Clinical Endocrinology & Metabolism*.95(10):4584-4591.

Flancbaum, L. et al. (2006). Preoperative nutritional status of patients undergoing Roux-en-Y gastric bypass for morbid obesity. *Journal of Gastrointestinal Surgery*.10(7):1033-1037.

Foss, Y. J. (2009). Vitamin D deficiency is the cause of common obesity. *Med Hypotheses*.72(3):314-21.

Freedman, B. I. et al. (2010). Vitamin D, adiposity, and calcified atherosclerotic plaque in African-Americans. *The Journal of Clinical Endocrinology & Metabolism*.95(3):1076-1083.

Galan, P. et al. (2005). Serum concentrations of β-carotene, vitamins C and E, zinc and selenium are influenced by sex, age, diet, smoking status, alcohol consumption and corpulence in a general French adult population. *European journal of clinical nutrition*.59(10):1181-1190.

Gallagher, J. C.; Yalamanchili, V.; Smith, L. M. (2013). The effect of vitamin D supplementation on serum 25OHD in thin and obese women. *The Journal of steroid biochemistry and molecular biology*.136:195-200.

Gao, L. et al. (2012). Role of Uncoupled Endothelial Nitric Oxide Synthase in Abdominal Aortic Aneurysm Formation Treatment With Folic Acid. *Hypertension*.59(1):158-166.

Garcia-Diaz, D. F. et al. (2010). Vitamin C inhibits leptin secretion and some glucose/lipid metabolic pathways in primary rat adipocytes. *Journal of Molecular Endocrinology*.45(1):33-43.

Gargari, B. P.; Aghamohammadi, V.; Aliasgharzadeh, A. (2011). Effect of folic acid supplementation on biochemical indices in overweight and obese men with type 2 diabetes. *Diabetes research and clinical practice*.94(1):33-38.

Gariballa, S. et al. (2013). Oxidative damage and inflammation in obese diabetic Emirati subjects supplemented with antioxidants and B-vitamins: a randomized placebo-controlled trail. *Nutr. Metab.*10:21-28.

Gemmel, K. et al. (2009). Vitamin D deficiency in preoperative bariatric surgery patients. *Surgery for Obesity and Related Diseases.*5(1):54-59.

González, L. et al. (2015). Vitamin D status is inversely associated with obesity in a clinic-based sample in Puerto Rico. *Nutrition Research.*35(4):287-293.

Gunanti, I. R. et al. (2014). Low serum concentrations of carotenoids and vitamin E are associated with high adiposity in Mexican-American children. *J Nutr.*144(4):489-95.

Gunanti, I. R. et al. (2014). Low Serum Vitamin B-12 and Folate Concentrations and Low Thiamin and Riboflavin Intakes Are Inversely Associated with Greater Adiposity in Mexican American Children. *The Journal of Nutrition. 144*(12), 2027-2033.

Hathcock, J. N. et al. (2007). Risk assessment for vitamin D. *The American journal of clinical nutrition*.85(1):6-18.

Hill, J. O. (2006). Understanding and addressing the epidemic of obesity: an energy balance perspective. *Endocr Rev*.27(7):750-61.

Holick, M. F. (2009). Vitamin D status: measurement, interpretation, and clinical application. *Annals of epidemiology*.19(2):73-78.

Institute of Medicine. (1998). *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline.* Washington, DC: The National Academies Press.

Institute of Medicine: Food And Nutrition Board. (2001). *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: The National Academies Press.

Instituto Brasileiro de Geografia e Estatística. (2010). *Pesquisa de Orçamentos Familiares 2008-2009.* Brasil: Ministério do Planejamento, Orçamento e Gestão.

Jeyakumar, S. M.; Vajreswari, A.; Giridharan, N. V. (2006). Chronic dietary vitamin A supplementation regulates obesity in an obese mutant WNIN/Ob rat model. *Obesity*.14(1):52-9.

Jeyakumar, S. M. et al. (2005). Vitamin A supplementation induces adipose tissue loss through apoptosis in lean but not in obese rats of the WNIN/Ob strain. *J Mol Endocrinol*.35(2):391-8.

Johnston, C. S. (2005). Strategies for healthy weight loss: from vitamin C to the glycemic response. *Journal of the American College of Nutrition*.24(3):158-165.

Joy, T.; Hegele, R. A. (2008). Is raising HDL a futile strategy for atheroprotection? *Nature reviews Drug discovery.*7(2):143-155.

Keaney, J. F. et al. (2003). Obesity and systemic oxidative stress clinical correlates of oxidative stress in the Framingham Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*.23(3):434-439.

Kimmons, J. E. et al. (2006). Associations between body mass index and the prevalence of low micronutrient levels among US adults. *Medscape General Medicine*.8(4):59.

Kypreos, K. E. et al. (2001). Type V collagen regulates the assembly of collagen fibrils in cultures of bovine vascular smooth muscle cells. *Journal of cellular biochemistry*.80(1):146-155.

Landrier, J. F.; Marcotorchino, J.; Tourniaire, F. (2012). Lipophilic micronutrients and adipose tissue biology. *Nutrients*.4(11):1622-49.

Langin, D. (2006). Adipose tissue lipolysis as a metabolic pathway to define pharmacological strategies against obesity and the metabolic syndrome. *Pharmacological Research.*53(6):482-491.

Larrieta, E. et al. (2010). Pharmacological concentrations of biotin reduce serum triglycerides and the expression of lipogenic genes. *European journal of pharmacology*.644(1):263-268.

Lenders, C. M. et al. (2009). Relation of body fat indexes to vitamin D status and deficiency among obese adolescents. *The American journal of clinical nutrition*.90(3):459-467.

Levert, K. L.; Waldrop, G. L.; Stephens, J. M. (2002). A biotin analog inhibits acetyl-CoA carboxylase activity and adipogenesis. *Journal of Biological Chemistry*.277(19):16347-16350.

Levin, S. M. et al. (2010). A worksite programme significantly alters nutrient intakes. *Public health nutrition.*13(10):1629-1635.

Lira, F. S. et al. (2011). Supplementing alpha-tocopherol (vitamin E) and vitamin D3 in high fat diet decrease IL-6 production in murine epididymal adipose tissue and 3T3-L1 adipocytes following LPS stimulation. *Lipids Health Dis.*10:37.

Liu, J. et al. (2009). Targeting mitochondrial biogenesis for preventing and treating insulin resistance in diabetes and obesity: Hope from natural mitochondrial nutrients. *Advanced drug delivery reviews.*61(14):1343-1352.

Lobo, G. P. et al. (2010). β, β-carotene decreases peroxisome proliferator receptor γ activity and reduces lipid storage capacity of adipocytes in a β, β-carotene oxygenase 1-dependent manner. *Journal of biological chemistry.*285(36):27891-27899.

Looker, A. C. (2005). Body fat and vitamin D status in black versus white women. The *Journal of Clinical Endocrinology & Metabolism.*90(2):635-640.

Lu, L. et al. (2009). Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. *Diabetes care*.32(7):1278-1283.

Macdonald, H. M. et al. (2008). Vitamin D status in postmenopausal women living at higher latitudes in the UK in relation to bone health, overweight, sunlight exposure and dietary vitamin D. *Bone*.42(5):996-1003.

Madan, A. K. et al. (2006). Vitamin and trace mineral levels after laparoscopic gastric bypass. *Obesity surgery.*16(5):603-606.

Mahabir, S. et al. (2008). Measures of adiposity and body fat distribution in relation to serum folate levels in postmenopausal women in a feeding study. *European journal of clinical nutrition.62*(5):644-650.

Major, G. C. et al. (2007) Supplementation with calcium+ vitamin D enhances the beneficial effect of weight loss on plasma lipid and lipoprotein concentrations. *The American journal of clinical nutrition.*85(1):54-59.

Mccarty, M.; Thomas, C. (2003). PTH excess may promote weight gain by impeding catecholamine-induced lipolysis-implications for the impact of calcium, vitamin D, and alcohol on body weight. *Medical hypotheses.*61(5):535-542.

Mckinney, K.; Breitkopf, C. R.; Berenson, A. B. (2008). Association of race, body fat and season with vitamin D status among young women: a cross-sectional study. *Clinical endocrinology.*69(4):535-541.

Mercader, J. et al. (2006). Remodeling of white adipose tissue after retinoic acid administration in mice. *Endocrinology*.147(11):5325-5332.

Ministério da Saúde. (2014). *Vigitel Brasil 2014. Vigilância de Fatores de risco e Proteção para doenças crônicas por inquérito telefônico***.** Brasil**:** 37 p.

Moan, J. et al. (2009). Seasonal variation of 1, 25-dihydroxyvitamin D and its association with body mass index and age. *The Journal of steroid biochemistry and molecular biology*.113(3):217-221.

Moat, S. J. et al. (2004). Folate, homocysteine, endothelial function and cardiovascular disease. *J Nutr Biochem.*15(2):64-79.

Mojtabai, R. (2004). Body mass index and serum folate in childbearing age women. *European journal of epidemiology*.19(11):1029-1036.

Molnar, D.; Decsi, T.; Koletzko, B. (2004). Reduced antioxidant status in obese children with multimetabolic syndrome. *International journal of obesity*.28(10):1197-1202.

Morinobu, T. et al. (2002). Nutritional status of beta-carotene, alpha-tocopherol and retinol in obese children. *International journal for vitamin and nutrition research*.72(3):119-123.

Muroyama, K. et al. (2003). Anti-obesity effects of a mixture of thiamin, arginine, caffeine, and citric acid in non-insulin dependent diabetic KK mice. *Journal of nutritional science and vitaminology*.49(1):56-63.

Nachtigal, M. et al. (2005). Dietary supplements and weight control in a middle-age population. *Journal of Alternative & Complementary Medicine*.11(5):909-915.

Naruta, E. et al. (2003). The influence of panthotenic acid mitochondrial oxidation and oxidative phosphorylation in liver of rats with alimentary obesity. *Voprosy pitaniia.*73(4):3-7.

Neuhouser, M. L. et al. (2001). Serum concentrations of retinol, alpha-tocopherol and the carotenoids are influenced by diet, race and obesity in a sample of healthy adolescents. *J Nutr.*131(8):2184-91.

Ortega, R. M. et al. (2009). Folate status in young overweight and obese women: changes associated with weight reduction and increased folate intake. *Journal of nutritional science and vitaminology*.55(2):149-155.

Ortega, R. M. et al. (2009). Vitamin D status modification by two slightly hypocaloric diets in young overweight/obese women. *International journal for vitamin and nutrition research.*79(2):71-78.

Parikh, S. J. et al. (2004). The relationship between obesity and serum 1, 25-dihydroxy vitamin D concentrations in healthy adults. *The Journal of Clinical Endocrinology & Metabolism*.89(3):1196-1199.

Patrini, C.; Griziotti, A.; Ricciardi, L. (2004). Obese individuals as thiamin storers. *International journal of obesity*.28(7):920-924.

Perticone, F. et al. (2001). Obesity and Body Fat Distribution Induce Endothelial Dysfunction by Oxidative Stress Protective Effect of Vitamin C. *Diabetes*.50(1):159-165.

Pinhas-Hamiel, O. et al. (2006). Obese children and adolescents: a risk group for low vitamin B12 concentration. *Archives of pediatrics & adolescent medicine*.160(9):933-936.

Pravenec, M. et al. (2013). Folate deficiency is associated with oxidative stress, increased blood pressure, and insulin resistance in spontaneously hypertensive rats. *Am J Hypertens.*26(1):135-40.

Reda, E. et al. (2003). The carnitine system and body composition. *Acta diabetologica.*40(1):s106-s113.

Reitman, A. et al. (2002). Low plasma antioxidants and normal plasma B vitamins and homocysteine in patients with severe obesity. *IMAJ-RAMAT GAN-*.4(8):590-593.

Ribot, J. et al. (2001). Changes of adiposity in response to vitamin A status correlate with changes of PPARγ2 expression. *Obesity research.*9(8):500-509.

Riess, K. P. et al. (2009). Ascorbic acid deficiency in bariatric surgical population. *Surgery for Obesity and Related Diseases.*5(1):81-86.

Rodríguez-Rodríguez, E. et al. (2010). Associations between abdominal fat and body mass index on vitamin D status in a group of Spanish schoolchildren. *European journal of clinical nutrition.*64(5):461-467.

Ross, A. C. et al. (2011). The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *The Journal of Clinical Endocrinology & Metabolism.*96(1):53-58.

Sakakeeny, L. et al. (2012). Plasma pyridoxal-5-phosphate is inversely associated with systemic markers of inflammation in a population of US adults. *The Journal of nutrition.*142(7):1280-1285.

Salehpour, A. et al. (2012). A 12-week double-blind randomized clinical trial of vitamin D3 supplementation on body fat mass in healthy overweight and obese women. *Nutr J.*11(1):78.

Saliba, W.; Barnett-Griness, O.; Rennert, G. (2013). The relationship between obesity and the increase in serum 25 (OH) D levels in response to vitamin D supplementation. *Osteoporosis International.*24(4):1447-1454.

Schweiger, C. et al. (2010). Nutritional deficiencies in bariatric surgery candidates. *Obesity surgery*.20(2):193-197.

Shah, S. et al. (2007). Oxidative stress, glucose metabolism, and the prevention of type 2 diabetes: pathophysiological insights. *Antioxidants & redox signaling*.9(7):911-929.

Shea, M. K. et al. (2010). Adulthood obesity is positively associated with adipose tissue concentrations of vitamin K and inversely associated with circulating indicators of vitamin K status in men and women. *The Journal of nutrition*.140(5):1029-1034.

Shen, X.-H. et al. (2010). Vitamin E regulates adipocytokine expression in a rat model of dietary-induced obesity. *Experimental biology and medicine*.235(1):47-51.

Silva, L. D. S. V.; Veiga, G. V.; Ramalho, R. A. (2007). Association of serum concentrations of retinol and carotenoids with overweight in children and adolescents. *Nutrition*.23(5):392-397.

Sneve, M.; Figenschau, Y.; Jorde, R. (2008). Supplementation with cholecalciferol does not result in weight reduction in overweight and obese subjects. *European Journal of Endocrinology*.159(6):675-684.

Switzer, B. R. et al. (2005). Plasma carotenoid and vitamins A and E concentrations in older African American women after wheat bran supplementation: effects of age, body mass and smoking history. *Journal of the American College of Nutrition.*24(3):217-226.

Thane, C. W.; Wang, L. Y.; Coward, W. A. (2006). Plasma phylloquinone (vitamin K1) concentration and its relationship to intake in British adults aged 19--64 years. *British journal of nutrition*.96(06):1116-1124.

Tungtrongchitr, R. et al. (2003) The relationships between anthropometric measurements, serum vitamin A and E concentrations and lipid profiles in overweight and obese subjects. *Asia Pacific J Clin Nutr*.12(1):73-79.

Tungtrongchitr, R. et al. (2003) Serum homocysteine, B 12 and folic acid concentration in Thai overweight and obese subjects. *International journal for vitamin and nutrition research*.73(1):8-14.

Vajro, P. et al. (2004). Vitamin E treatment in pediatric obesity-related liver disease: a randomized study. *Journal of pediatric gastroenterology and nutrition*.38(1):48-55.

Valiña-Tóth, A. L. B. et al. (2010). Relationship of vitamin D and parathyroid hormone with obesity and body composition in African Americans. *Clinical endocrinology*.72(5):595-603.

Van Het Hof, K. H. et al. (2000). Carotenoid bioavailability in humans from tomatoes processed in different ways determined from the carotenoid response in the triglyceride-rich lipoprotein fraction of plasma after a single consumption and in plasma after four days of consumption. *The Journal of nutrition*.130(5):1189-1196.

Vimaleswaran, K. S. et al. (2013). Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS medicine*.10(2):e1001383.

Vioque, J. et al. (2007). Plasma concentrations of carotenoids and vitamin C are better correlated with dietary intake in normal weight than overweight and obese elderly subjects. *British journal of nutrition*.97(05):977-986.

Wallström, P. et al. (2001). Serum concentrations of β-carotene and α-tocopherol are associated with diet, smoking, and general and central adiposity. *The American journal of clinical nutrition*.73(4):777-785.

Wang-Fisher, Y.; Han, J.; Guo, W. (2002). Acipimox stimulates leptin production from isolated rat adipocytes. *Journal of endocrinology.*174(2):267-272.

Westphal, S. et al. (2006). Adipokines and treatment with niacin. *Metabolism*.55(10):1283-1285.

Woo, K. S. et al. (2002). Long-term improvement in homocysteine levels and arterial endothelial function after 1-year folic acid supplementation. *The American journal of medicine.*112(7):535-539.

Wood, R. J. (2008) Vitamin D and adipogenesis: new molecular insights. Nutrition reviews.66(1):40-46.

World Health Organization. (2015). Obesity and overweight. Available in: < http://www.who.int/mediacentre/factsheets/fs311/en/ >. Acess in: July, 28.

Wortsman, J. et al. (2000). Decreased bioavailability of vitamin D in obesity. *The American journal of clinical nutrition.*72(3):690-693.

Yoshida, M. et al. (2008). Effect of vitamin K supplementation on insulin resistance in older men and women. *Diabetes Care*.31(11):2092-2096.

Young, K. A. et al. (2009). Association of plasma vitamin D levels with adiposity in Hispanic and African Americans. *The Journal of Clinical Endocrinology & Metabolism*.94(9):3306-3313.

Zhou, S.-S. et al. (2010) B-vitamin consumption and the prevalence of diabetes and obesity among the US adults: population based ecological study. *BMC Public Health.*10(1):746.

Zhu, W. et al. (2006). Elevated plasma homocysteine in obese schoolchildren with early atherosclerosis. *European journal of pediatrics.*165(5):326-331.

Zittermann, A. et al. (2009). Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *The American journal of clinical nutrition*.89(5):1321-1327.

Table 1 - Relationship between fat-soluble vitamin deficiency and obesity.

Vitamin	Reference	Study design	Results
Vitamin A and carotenoids	Neuhouser et al. (2001)	285 adolescents	Obese individuals with serum α-and β-carotene, β-cryptoxanthin and lycopene from 20 to 10% lower.
	Morinobu et al. (2002)	93 obese children	Lower levels of β-carotene in obese children.
	Galan et al. (2005)	3128 adults	BMI was inversely related to β-carotene.
	Switzer et al. (2005)	39 women	BMI inversely correlated with serum β-carotene and β-cryptoxanthin.
	Silva et al. (2007)	471 children and adolescents	Overweight children have 10% prevalence of retinol deficiency and 55.8% of carotenoids than non-obese children.
	Botella-Carretero et al. (2010)	80 preoperative patients for bariatric	BMI was inversely related to serum concentrations of

		surgery	retinol.
	Gunanti et al. (2014)	1154 children and adolescents	Inverse associations between serum carotenoids and adiposity, but serum retinol were positively associated with adiposity.
Vitamin D	Looker (2005)	6042 women	Inverse relationship between 25(OH)D and body fat percentage.
	Aasheim et al. (2008)	110 patients with severe obesity compared to 58 normal-weight	Lower concentrations of 25(OH)D in obese subjects.
	Alemzadeh et al. (2008)	127 children and adolescents	Inverse relationship between vitamin D and BMI, insulin resistance.
	McKinney et al. (2008)	800 individuals	Inverse relationship between serum 25(OH)D, BMI and fat percentage, positive association between intake and serum 25(OH)D.

	Cheng et al. (2009)	1882 individuals	Inverse relationship between serum 25(OH)D and WC, serum insulin, BMI, subcutaneous adipose tissue volume and visceral.
	Lu et al. (2009)	3262 individuals	Vitamin D deficiency associated with increasing age, levels of 25(OH)D inversely associated with metabolic syndrome and insulin resistance.
	Ortega et al. (2009)	61 young people with overweight and obesity	Diet enriched with vitamin D led to greater weight loss.
	Young et al. (2009)	917 individuals Hispanic-American and 439 African-American	Vitamin D inversely correlated with BMI, visceral and subcutaneous adipose tissue.
	Beydoun et al. (2010)	7996 individuals	Central obesity in adults associated with low serum 25(OH)D.
	Dong et al. (2010)	559 adolescents	Inverse relationship

			between vitamin D and fat.
	Rodríguez-Rodríguez et al. (2010)	102 children	Deficiency of 25(OH)D associated with increased body weight, BMI, WC and waist / hip ratio.
	González et al. (2015)	797 adults	Inverse correlation between 25(OH)D and BMI, waist circumference, and waist-to-height ratio.
Vitamin E	Morinobu et al. (2002)	275 individuals	Serum α-tocopherol was 10% lower in the obese.
	Neuhouser et al. (2001)	93 obese children	Correlation between serum α-tocopherol and plasma lipids without relation to severe obesity.
	Galan et al. (2005)	58 women with adequate weight	A positive association between serum vitamin E intake and lack of association with BMI.
	Switzer et al. (2005)	3128 adults	A positive association between visceral adiposity and body with γ-tocopherol.

	Botella-Carretero et al. (2010)	39 women	Relationship between increased BMI and adiposity with low plasma vitamin E concentration.
Vitamin K	Thane et al. (2006)	3339 individuals	BMI was not related to serum phylloquinone.
	Yoshida et al. (2008)	355 individuals supplemented	No change in weight and BMI in both genders.
	Shea et al. (2010)	443 obese	An inverse association between fat percentage and K1 women plasma.

BMI: body mass index; 25(OH)D: circulating 25-hydroxy vitamin D; WC: waist circumference.

Principal studies linking obesity to fat-soluble vitamins. Studies show deficient serum and accumulation in adipose tissue of fat-soluble vitamins.

Table 2- Relationship between water-soluble vitamin deficiency and obesity.

Vitamin	References	Study design	Results
Thiamine	Patrini et al. (2004)	10×10 obese women with normal weight	Low levels of thiamine in plasma and higher levels of erythrocyte thiamin.
	Carrodeguas et al. (2005)	303 obese	15.5% with thiamine deficiency.
	Flancbaum et al. (2006)	379 obese	29% with thiamine deficiency.
Folate	Mojtabai et al. (2004)	Population data from NHANES 1988--1994 e NHANES 1999--2000	Increased BMI in women of childbearing age related to lower serum folate.
	Kimmons et al. (2006)	Population data from NHANES III	Obese or overweight individuals are more likely to have low levels of folate.
	Madan et al. (2006)	100 individuals with severe obesity indicated for bariatric surgery	6% of folate deficiency before surgery and 11% one year after surgery.

	Mahabir et al. (2008)	51 postmenopausal women	Serum folate 22% lower in obesity and 12% lower in overweight individuals.
	Schweiger et al. (2010)	14 subjects with severe obesity	24% of folate deficiency.
	Bradbury et al. (2014)	4721 participants aged ≥15 y	1% decrease in serum folate concentration associated with every increase of 1 unit in BMI.
	Bird et al. (2015)	3767 adults from the NHANES (2003-2006)	Obesity is associated with decreased serum folate, which parallels decreased folate intakes.
Vitamin B_6 and B_{12}	Aasheim et al. (2008)	110 severely obese individuals x 58 individuals with normal weight	Deficiency of vitamin B_6 in obese subjects.
	Zhu et al. (2006)	41 obese and 27 normal weight	Levels of homocysteine, vitamin B_{12} and folate elevated in obesity.
	Pinhas-Hamiel et al. (2006)	164 children and adolescents (6-19	Serum vitamin B_{12} lower in subjects with obesity.

		years) compared with 228 obese normal weight	
	Madan et al. (2006)	100 individuals with severe obesity	13% had vitamin B_{12} deficiency.
	Schweiger et al. (2010)	114 individuals with severe obesity	3.6% had vitamin B_{12} deficiency.
Vitamin C	Kimmons et al. (2006)	Population data from NHANES III	Obese or overweight were more likely to have low levels of vitamin C.
	Azadbakht et al. (2007)	926 woman	Low intake of vitamin C associated with increased central adiposity.
	Aasheim et al. (2008)	110 patients x 58 severely obese patients with normal weight	Low concentrations of vitamin C.
	Riess et al. (2009)	266 patients before bariatric surgery	36% vitamin C levels below recommended levels.

BMI: body mass index; NHANES: National Health and Nutrition Examination Survey.

Principal studies relating water-soluble vitamins to obesity. Studies show that water-soluble vitamin deficiency is quite prevalent in the obese population.

