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REVIEW

Obesity, cardiovascular disease, and role of vitamin C on inflammation: a review of facts and underlying mechanisms

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Abstract Obesity means the accumulation of excessive fat that may interfere with the maintenance of optimal state of health. Obesity causes cardiac and vascular disease through well-known mediators such as hypertension, type-2 diabetes mellitus, and dyslipidemia, but there are evidences for other mediators such as chronic inflammation, oxidative stress, and thrombosis. The decreased levels of antioxidants factors and nitric oxide predispose to further cardiovascular adverse events. To reduce the risks, antioxidants can help by neutralizing the free radicals and protecting from damage by donating electrons. Having the capacity, vitamin C protects from oxidative stress, prevention of non-enzymatic glycosylation of proteins, and enhances arterial dilation through its effect on nitric oxide release. It also decreases lipid peroxidation, and alleviates inflammation. The anti-inflammatory property of vitamin C could be attributed to ability to modulate the NF-$_k$B DNA binding activity and down-regulation in the hepatic mRNA expression for the interleukins and tumor factors.

Keywords Obesity · Cardiovascular disease · Metabolic syndrome · Inflammation · Oxidative stress · Thrombosis · Nitric oxide · Antioxidant · Vitamin C · Ascorbic acid

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Abbreviations

BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CRP	C reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
FFAs	Free fatty acids
HDL	High density lipoprotein
HT	Hypertension
IGT	Impaired glucose tolerance
IL	Interleukin
LDL	Low density lipoprotein
MCP-1	Macrophage chemoattractant protein-1
MDA	Malondialdehyde
MI	Myocardial infarction
NF-$_k$B	Nuclear factor $_k$B
NHANES	National Health and Nutrition Examination Survey
NO	Nitric oxide
PAI-1	Plasminogen activator inhibitor-1
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SNPs	Single-nucleotide polymorphisms
T2DM	Type-2 diabetes mellitus
TC	Total cholesterol
TG	Triglyceride
TNF-α	Tumor necrosis factor alpha
WC	Waist circumference

Obesity facts

Obesity is defined as an excess of body adiposity (increased body weight). Adiposity could be determined by using the body mass index (BMI), which commonly uses cut-points for overweight BMI $\geq$ 25 to <30 and obesity BMI $\geq$ 30, for both men and women. BMI is calculated by using height and weight, it is also classified internationally according to National Heart, Lung, and Blood Institute task force, along with the associated disease risk with increasing BMI as shown in Table 1 (National Institutes of Health 1998), and it is measured using the following formula:

$$\text{BMI}\left(\text{kg/m}^2\right) = \text{Weight}\,(\text{kg})/\text{Height square}\left(\text{m}^2\right)$$

However, it is recognized that the associated BMI with mortality and morbidity risk may vary in several ethnic groups (Weng et al. 2006). New recommendations from the Asia-Pacific population suggested that a BMI of more than 23 means overweight and more than 25 for obesity, which opposes the usual limits used internationally (Anuurad et al. 2003).

Overweightness and obesity are the fifth leading risk of global deaths, and usually means the accumulation of abnormal or excessive fat that may interfere with the maintenance of optimal state of health. In fact, almost 2.8 million adults succumb to death every year owing to their overweight or obese status (World Health Organization 2014).

Another parameter that is used to detect obesity is Waist Circumference (WC) which is used to determine the excess of body fat in the abdomen. According to the *National Institute for Health and Clinical Excellence* (NICE) protocol (Centre for Public Health Excellence at NICE 2006), WC measurement is taken at the level of the superior border of the iliac crest and parallel to the floor (Ross et al. 2008). Table 2 illustrates the ranges of WC for males and females.

The *WHO Stepwise Approach to Surveillance* (STEPS) provides a simple standardized method for collecting, analysing and disseminating data based on ethnic differences in WHO member countries. The WHO STEPS protocol for measuring WC instructs that the measurement be made at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest (World Health Organization 2011). Table 3 provides a view about WC measurements according to WHO.

Table 1 Classification of obesity by Body Mass Index

BMI (kg/m^2)	Classification pattern
Less than 18.5	Underweight
From 18.5 to less than 25	Normal
From 25 to less than 30	Overweight (pre-obesity status)
From 30 to less than 35	Obese class I
From 35 to less than 40	Obese class II (very obese)
From 40 and more	Obese class III (morbid obese)

Table 2 Waist circumference classification according to NICE guidelines

Sex	Waist circumference (WC)	Classification
Male	Less than 102 cm	Normal
	More than or equal 102 cm	High risk for metabolic complications
Female	Less than 88 cm	Normal
	More than or equal 88 cm	High risk for metabolic complications

Table 3 Waist circumference classification according to WHO recommendations

Country or ethnic groups	Gender	Measurements (cm)
Europid, International	Men	>94
	Women	>80
South Asia, China, Japan	Men	>90
	Women	>80

Review of obesity indices

A report of European Prospective Investigation into Cancer and Nutrition, with a data from 97,942 subjects and 7 cohorts reported that BMI was involved to predict the prevalence of obesity and the escalating trends of obesity in 2015 in European populations (von Ruesten et al. 2011). Sikorski et al. (2012) used a cross-sectional approach in German study based on telephone representative sample to investigate obesity prevention support in general public by determined BMI.

Wang and Beydoun (2007) defined adult overweight and obesity using BMI cut-points of 25 and 30 kg/m^2; respectively, to illustrate the epidemic of obesity in the United States and its relationship with gender, age, socioeconomic status, ethnicity, and geographic characteristics. Differently, Warraich et al. (2009) used the modified BMI criterion for Asian populations which consider the 23 and 25 kg/m^2 of BMI's as overweight and obese; respectively, to determine the prevalence of obesity and malnutrition in school-going children from grades 6th to 8th of Karachi, Pakistan. BMI $\geq$ 31 kg/m^2 was used to investigate the somatic morbidity, including fatal morbidity, throughout adulthood in men starting adult life as obese, among Danish young men who were examined for military service between 1943 and 1977 (Zimmermann et al. 2011).

However, BMI classification misses subjects with increased cardiometabolic risk factors related to elevated

adiposity (Gómez-Ambrosi et al. 2012). Therefore, the assessment of obesity required more than one parameter. As a part of the Geelong Osteoporosis Study, Pasco et al. (2012) used BMI and WC as anthropometric measures for 1467 men and 1076 women aged 20–96 years, and were assessed during the period 2001–2008; to determine the prevalence of obesity, and to examine the relationship between the BMI and body fat through population-based cross-sectional study. Furthermore, a cross-sectional study was used to determinate the prevalence of obesity in the Maracaibo City in Venezuela involved 2108 individuals who were interrogated for anthropometric measurements by WHO criteria for BMI and WC from the adult treatment panel no. 3 (ATP-III) statements (Bermúdez et al. 2012). In another study, BMI and WC were used to assess the obesity of 5267 Chinese children, who were selected from 30 primary schools of 5 provincial capital cities in order to identify the relation of dietary patterns with obesity and related cardio-metabolic risk factors (Shang et al. 2012). Sardinha et al. (2012) compared the relationship of weight classes with educational level, the prevalence of overweight, obesity, and abdominal obesity were determined by BMI and WC among 9447 Portuguese adults aged 18–103 years.

To describe the patterns and trends in WC and abdominal obesity for 7129 men and 9244 women aged 70–89 in England during 1993–2010, Howel (2012) agreed that the best ways of estimating the obesity and abdominal obesity are by using BMI and WC. Recio-Rodriguez et al. (2012) conducted cross-sectional study to analyse the relationship between abdominal obesity and general obesity with subclinical atherosclerosis, arterial stiffness, and wave reflection in healthy, diabetics, and hypertensive subjects, BMI and WC were used on 305 individuals.

In previous studies, part of them used BMI as a unique indicator of obesity, while in rest the BMI and WC were used together to determine the obesity in general, and abdominal obesity in particular. As a measure of adiposity, BMI does not distinguish fat mass from lean body mass, and its validity varies by age, sex and ethnicity (Hu 2008). WC should be superior over BMI for predicting metabolic disorders due to: (1) most studies indicated a high correlation (0.8–0.9) between WC and BMI, which makes it difficult to separate general from abdominal obesity; (2) using BMI and WC identify the abdominal obesity, while using BMI indicate an overall obesity (Hu 2008).

Insights into the causes of weight gain

In USA, obesity prevalence increased from 13 to 32% between the 1960s and 2004. Currently, 66% of adults are overweight or obese; 16% of children and adolescents are overweight and 34% are at risk of becoming overweight (Wang and Beydoun 2007). It is well known that food-related behaviour is complex and is determined by the interplay of many factors, including physiological factors, socio-demographic factors such as income, education, occupation, behavioural and lifestyle factors such as physical activity, smoking, knowledge and attitudes related to diet and health (Al-Hazzaa et al. 2012). Moreover, a high intake of energy-dense macronutrient-poor foods, heavy marketing of energy dense foods and fast food outlets, sugar sweetened soft drinks and fruit juices, adverse social and economic conditions, all are considered to be risk factors for obesity (Swinburn et al. 2004).

Excessive caloric intake and insufficient physical activity are the primary factors of weight-gain (Gellman and Turner 2012). Basically, weight-gain results from a sustained positive energy balance; that is, expending energy less than consumed over an extended period of time. Weight-gain results from a complicated overlap between biological, environmental, genetic, and psychosocial factors that impact satiety, appetite, and storage of food as body fat (Gellman and Turner 2012).

Biologic influences

Biological system complexity has a big effect on energy balance, this system balances the amount of body fat by regulating the unconscious drive to eat, which is adaptive in times of food shortage, but has become problematic given the relative plenty of dense-caloric foods and limited physical activity participation (Friedman 2009).

Different biological factors have managed energy expenditure. Ghrelin is a novel gut peptide that has been isolated from human stomach tissues (Kojima et al. 1999). There is evidence to suggest that ghrelin could be involved in energy homeostasis, specifically in the regulation of food intake and substrate oxidation (Wortley et al. 2004). St-Pierre et al. (2004) found that higher levels of ghrelin are associated with low levels of resting and postprandial thermogenesis, which is independent of individual differences in fat-free mass and fat mass. Although speculative, serum ghrelin may play a role in the regulation of energy homeostasis by acting as a hormonal marker of increased energy efficiency.

Genetic contributors

Escalated obesity is not based on genetic origin; genes interplay with environmental factors to elevate risk incidence of obesity. Assessing the participation of genes in obesity; the percentage of variability due to genetic factors is about 75%, indicating that genetics play a clear role in vulnerability to increased obesity (Walley et al. 2009). The single gene mutations are responsible for rare forms of

monogenic obesity [leptin (LEP), leptin receptor (LEPR), melanocortin-4 receptor (MC4R), and pro-opiomelanocortin (POMC)]. However, there is growing evidence that common genetic variants or single-nucleotide polymorphisms (SNPs) may play an important role in the obesity epidemic. These SNPs have modest effects on an individual susceptibility to common forms of obesity, but due to their high frequency, they can have a large contribution to obesity on the population level (Nguyen and El-Serag 2010).

Perinatal influences and social networks

Children are more likely to be obese if their mothers had severe obesity; this fact highlights the significance of gene-environment interactions (Kral et al. 2006). From Framingham Heart Study, person's risk of becoming obese increased by 57% if a friend became obese, also, the risk of becoming obese increased by 40 and 37% if a person had a sibling or spouse who became obese, respectively (Christakis and Fowler 2007).

Environmental factors

Obesogenic environment means promoting excess eating and physical inactivity (Al-Hazzaa et al. 2012). Energy expenditure has decreased in the developed world, majorly due to sedentary work of employment, limited physical exertion by energy-saving devices, and minor physical requirements for transportation. With physical inactivity, desire for inexpensive fast foods has increased dramatically; these foods contain high amounts of fat and sugar "caloric dense". Indeed, the food marketing promotes consumption of these foods through aggressive advertising (Kumanyika et al. 2008). Other studies have demonstrated aspects of the buildings environment (such as homes, schools, and shopping malls) that contributes to the prevalence of obesity. Residents of communities with ready access to healthful foods tend to have healthier diets and lower incidence of obesity. Low income can contribute to higher levels of obesity (Sallis and Glanz 2009), and obesity tends to be more prevalent among people who are less educated or earn lower incomes than people who are more educated or earn higher incomes (Robert Wood Johnson Foundation 2008).

Severity of obesity

Adams et al. (2006) mentioned that a modest increase in weight may reduce lifespan, and increased substantial associated costs. This cohort study reported mortality rates through 10 years for about a half-million Americans aged between 50 and 71 years in the National Institutes of Health-American Association of Retired Persons. The results demonstrated that 20–40% increase in mortality in all subjects (both men and women) who were overweight in midlife, and a two to threefold increased risk of mortality among obese individuals.

The complications of obesity were studied extensively, obesity was related to cancer, cardiovascular disease (CVD), increased mortality and metabolic consequences, and reduced quality of life. The relationship between obesity and CVD especially coronary heart disease (CHD) has been analysed in more than 100 prospective studies, three meta-analyses worldwide including about 92 prospective studies, they have specified the association between obesity components and CHD mortality and incidence. Obesity can progress to metabolic syndrome by exerting a state of chronic low-grade inflammation, which may explain the development of the obesity-related pathologies, such as CVD and type-2 diabetes mellitus (T2DM) (Hu 2008). Additionally, it plays an important role in the development of insulin resistance that triggers the comorbidities of metabolic syndrome, such as dyslipidemia, hypertension (HT), hyperglycaemia, prothrombotic state, and atherosclerosis (Boura-Halfon and Zick 2009).

In Asian Pacific Cohort, 33 cohort studies from Japan, Singapore, New Zealand, Australia, China and other countries with more than 300,000 participants have analysed, who were adjusted for age, sex, and smoking habit. The analysis found a strong linear relationship of BMI with CHD and stroke. It was stated that as; each 2 kg/m^2 increment of BMI would increase the risk of ischemic stroke by 12% (95% CI 9–15%) and 11% increase of CHD (95% CI 9–13%). The main findings of this analysis were more than 3000 incidents of stroke, and more than 2000 incidents of CHD (Ni Mhurchu et al. 2004).

The diverse Populations Collaboration analysed about 26 cohort studies from the United States with more than 380,000 participants adjusted for smoking and stratified analysis by age. The analysis found Relative Risks (RRs) for CHD mortality, for obese groups relative to normal-weight group were 1.51 (95% CI 1.36–1.67) for males and 1.62 (95% CI 1.46–1.81) for females (McGee and Collaboration 2005).

Likewise, Bogers et al. (2007) analysed about 31 cohorts from the United States and Europe with about 390,000 participants adjusted for age, sex, and smoking. The main finding was the incidence of CHD significantly increased with higher levels of BMI. Obesity was associated with relative risks of 1.69 (95% CI 1.44–1.99) compared to normal weight.

In addition to producing illness, obesity has the ability to reduce functional capacity. Alley and Chang (2007) evaluated the relationship between obesity and disability during the period of 1998–2004. They used NHANES data to

examine the association of changes in weight and the prevalence of disability. Disability is defined as impaired activities of daily living and/or functional impairment. The study found that, the prevalence of disability among obese subjects grew relative to that seen in normal-weight subjects, 42.2% of obese subjects reported some degree of functional impairment compared with 26.6% in normal-weight subjects. For impairment of activities of daily living, 5.5% was reported in obese people compared to 3.5% in normal-weight individuals.

Furthermore, there is a consensus agreement on increased blood pressure (BP) with increased weight or BMI in both males and females. Weber et al. (2004) stated that high BMI was associated with HT, and considered as a primary cause of elevated BP. El Bcheraoui et al. (2014) screened the association of socio-demographic factors with overweightness and obesity; they found BP increased with increasing weight among Saudis adults, and Abd Elaziz et al. (2014) found the level of BP increased with overweightness and more for obese adults in Cairo, Egypt.

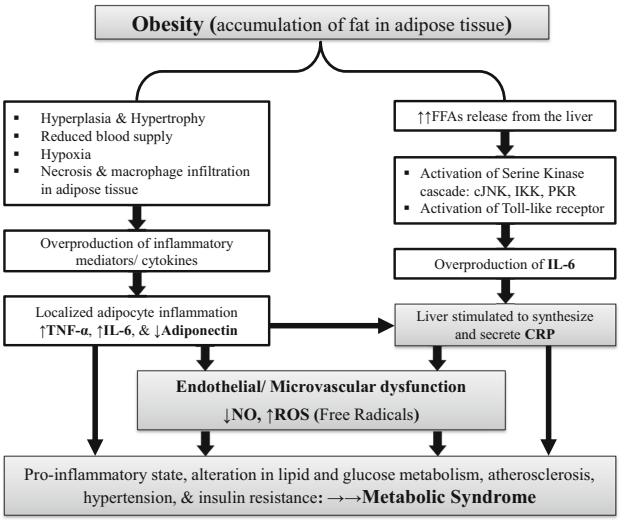

Fig. 1 Mechanisms linking obesity and metabolic syndrome via inflammatory mediators and oxidative stress mechanisms (Ellulu et al. 2016a). *TNF-α* tumor necrosis factor alpha, *IL-6* interleukin 6, *NO* nitric oxide, *ROS* reactive oxygen species, *cJNK* c-jun N-terminal kinase, *IKK* inhibitor of k kinase, *PKR* protein kinase R

Mechanisms linking obesity and cardiovascular disease

Obesity is increasingly recognized as a serious health problem, there are still many unanswered questions about how the multiple disorders associated with excess weight gain interact to cause cardiovascular and renal diseases. Although, there is a growing evidence suggests that obesity initiates a cascade of disorders including HT, diabetes, atherosclerosis, and chronic renal disease. Abnormal kidney function, caused by increased renal tubular reabsorption, initiates volume expansion and increased BP during excess weight gain, and the HT and metabolic abnormalities associated with obesity, in turn, contribute to chronic renal disease. Obesity causes cardiac and vascular disease through well-known mediators such as HT, T2DM, and dyslipidemia, but there is evidence for less well-characterized mediators such as chronic inflammation, oxidative stress, and thrombosis (Hall et al. 2002).

Indeed, in recent years, metabolic syndrome has associated with global epidemic of obesity and diabetes, which reported as **diabesity** (Zimmet et al. 2001). The state of metabolic syndrome increases the risk not only for developing diabetes but also for CVD (Grundy et al. 2004). In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study involving European men and women, non-diabetic persons with the metabolic syndrome had an increased risk of death from all causes as well as from CVD. After adjustment for age, blood cholesterol levels, and smoking, the overall hazard ratios for all-cause and CVD mortality in persons with the metabolic syndrome as compared with persons without it were 1.44 and 2.26 in men and 1.38 and 2.78 in women (Hu et al. 2004).

As a major cause of insulin resistance, obesity can be complicated by metabolic dysregulation including HT and dyslipidemia (high levels of triglycerides and circulating fatty acids originating from the diet or accelerated lipolysis in adipocytes), thus results in diabetes, and progresses to CVD (Bilan et al. 2009). Figure 1 was adapted from Ellulu et al. (2016a) has reported the link between the obesity status and metabolic syndrome via inflammatory and oxidative stress mechanisms.

Obesity and inflammation

Inflammation is considered a characteristic feature of metabolic syndrome (Bassuk et al. 2004), characterized by secreting inflammatory adipokines usually from adipose tissue, such as leptin, interleukin (IL-6), tumor necrosis factor alpha (TNF-α), macrophage chemoattractant protein-1 (MCP-1), and resistin (Lafontan 2004).

There are positive associations between different measures of obesity and plasma adipokines levels (Straub et al. 2000). It has been calculated that one-third of total circulating concentrations of IL-6 originate from adipose tissue (Fontana et al. 2007). In fact, there exists increased evidence that obesity constitutes a low-grade inflammatory state, and it was represented in metabolic processes regulation (Scheller et al. 2011).

The overexpressed pro-inflammatory cytokines in obesity is considered the link between obesity and

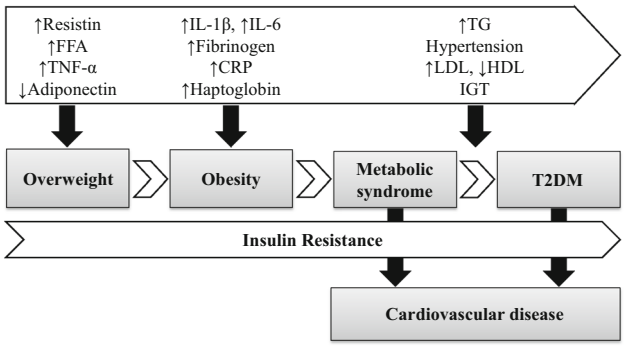

Fig. 2 The relationship of inflammatory markers and disease factors to specific stages pathologic continuum from overweight to T2DM and CVD (Badawi et al. 2010). Depicted are the increases or decreases in relative values of various inflammatory markers and disease factors that take place as overweight progresses towards T2DM. *CRP* C reactive protein, *FFA* free fatty acids, *IGT* impaired glucose tolerance, *IL* interleukin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *TG* triglycerides, *T2DM* type-2 diabetes mellitus

inflammation (Hotamisligil 2006). Adipose tissue responds to stimulation of extra nutrients via hyperplasia and hypertrophy of adipocytes. The nature of adipose tissue is heterogeneous; including endothelium, immune cells, and adipocytes (Halberg et al. 2008). With progressive adipocyte enlargement and obesity, the blood supply to adipocytes may be reduced, leading to consequent hypoxia (Cinti et al. 2005).

Hypoxia is proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to production of inflammatory mediators. This result in a localized inflammation in adipose tissue that propagates an overall systemic inflammation associated with the development of obesity-related comorbidities (Trayhurn and Wood 2004). Amongst inflammatory mediators, three are produced by macrophages: TNF-α, IL-6, and adiponectin (Karastergiou and Mohamed-Ali 2010). IL-6 strongly stimulates hepatocytes to produce and secret the C reactive protein (CRP) indicating a state of inflammation (Zhang et al. 2009).

Moreover, in obesity, accumulation of free fatty acids activates pro-inflammatory serine kinase cascades, such as I_kB kinase and c-JunN-terminal kinase, which in turn promotes adipose tissue to release IL-6 that triggers hepatocytes to synthesize and secrete CRP (Rocha and Libby 2009). For simple illustration, Fig. 2 adapted and modified from Badawi et al. (2010) explains the relationship of inflammatory markers and disease factors to specific stages pathologic continuum from overweight to T2DM and CVD.

Overweight as indicated in Fig. 2 sets the stage for low-grade chronic inflammation, with adiponectin levels decreasing while resistin, free fatty acids (FFAs) and TNF-α increase. As overweight progresses to obesity, continued inflammation further leads to elevated CRP, fibrinogen, IL-6, IL-1β and haptoglobin. Obesity can be complicated by metabolic dysregulation (metabolic syndrome) to develop frank T2DM where low density lipoprotein (LDL) cholesterol and triglyceride levels increase, high density lipoprotein (HDL) cholesterol levels deceases and HT and impaired glucose tolerance (IGT) manifest (Dandona et al. 2003). Throughout the pathologic continuum from overweight to T2DM, insulin resistance increases progressively and the risk of CVD elevates. Metabolic syndrome is associated with about twofold increased susceptibility to CVD whereas T2DM is linked to fourfold higher risk (Lüscher et al. 2003).

Other factor can link obesity with inflammation, the bacterial lipopolysaccharide derived from gut microbiota acts as a trigger for systemic inflammation through binding with CD14 receptors (DiBaise et al. 2008). Growing evidence has described the microbiome as an integral part of physiology; microbiome can contribute to obesity via increasing dietary energy harvest, promoting fat deposition, triggering systemic inflammation, perhaps modifying locomotor activity, and having central effects on satiety (Tsai and Coyle 2009).

Obesity and oxidative stress

Reactive oxygen species (ROS) are a byproduct of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis. An imbalance between ROS production and the cellular antioxidant defense system leads to oxidative stress (Ellulu et al. 2016b). Environmental factors and genetic interactions play key roles in oxidative stress mediated pathologies (De Marchi et al. 2013). ROS can originate from different subcellular sources, but mitochondria are generally considered the primary source of ROS generation (Adam-Vizi and Chinopoulos 2006).

In stress conditions, ROS levels increase and, because of their high reactivity, participate in a variety of chemical reactions. They are involved in cell damage, necrosis, and apoptosis via oxidation of lipids, proteins, and DNA (Elahi et al. 2009), and provoke also endothelial dysfunction, infiltration, and activation of inflammatory cells (Hulsmans et al. 2012). Smoking, diabetes, and obesity are independently associated with increased oxidative stress in both sexes (Keaney et al. 2003).

In addition to serving as a storage depot for lipid energy, adipose tissue is a metabolically active endocrine organ. Obesity is a chronic inflammatory state, total and abdominal obesity are significantly and positively associated with serum CRP levels, which is largely regulated by IL-6 (Heinrich et al. 1990). Inflammation is a source of

Table 4 The mechanisms of formation of free radicals during obesity

Title	Mechanism
Adipose tissue	Obesity oxidative stress resulted from the increased release adipocytes inflammatory mediator like TNF-α, IL-1, and IL-6; these cytokines are potent stimulators for the production of ROS and nitrogen by macrophages and monocytes. Moreover, adipocytes secrete angiotensin II, that stimulates NAD(P)H oxidase leading to major formation of ROS production in adipocytes
Fatty acid oxidation	Mitochondrial oxidation of fatty acids are capable of producing free radicals in liver and, therefore, oxidative stress, which could result in mitochondrial DNA alterations in the oxidative phosphorylation that occurs in mitochondria, causing structural abnormalities and overproduction of ROS
Overconsumption of oxygen	Obesity increases the mechanical load and myocardial metabolism; therefore, oxygen consumption is increased. The increased oxygen consumption produces ROS as superoxide, hydroxyl radical, and hydrogen peroxide derived from the increase in mitochondrial respiration, and from the loss of electrons produced in the electron transport chain
Accumulation of cellular damage	Excessive fat accumulation can cause cellular damage due to pressure effect from fat cells. Cellular damage in turn leads to high production of cytokines such as TNF-α, which generates ROS in the tissues, increasing the lipid peroxidation rate
Type of diet	Consumption of diets high in fat may alter oxygen metabolism. Fatty deposits are vulnerable to suffering oxidation reactions. If the production of these ROS exceeds the antioxidant capacity of the cell, oxidative stress resulting in lipid peroxidation could contribute to the development of atherosclerosis

TNF-α tumor necrosis factor alpha, *IL* interleukin, *ROS* reactive oxygen species, *NAD(P)H* nicotinamide adenine dinucleotide phosphate

oxidative stress, which is also implicated in the development of atherosclerosis. Consistently, elevated levels of oxidative stress markers like malondialdehyde (MDA) and F_2-isoprostanes have been found in a number of inflammatory diseases (Dworski et al. 2001) (F_2-isoprostanes are prostaglandin-like products of the free radical-catalyzed peroxidation of arachidonic acid. They are formed in situ esterified to phospholipids and are released into plasma by phospholipases. Both MDA and F_2-isoprostanes are established biomarkers of lipid peroxidation in vivo) (Morrow et al. 1992). Increased production of ROS may also enhance the inflammatory response by activating redox-sensitive nuclear transcription factors such as nuclear factor $_k$B (NF-$_k$B). These transcription factors are essential for the inducible expression of genes associated with immune and inflammatory responses, including cytokines, inducible NO synthase, and resulting in the increased expression of adhesion molecules on the surface of endothelial cells and vascular smooth muscle cells, resulting in an inflammatory state in adipose tissue, endothelial dysfunction, and, ultimately, atherogenesis (Lastra et al. 2006). Thus, the pro-inflammatory and pro-oxidant effects of increased adiposity represent a potential link between obesity and CVD (Lavrovsky et al. 2000).

Another oxidative stress marker is the urinary levels of 8-iso Prostaglandin $F_2\alpha$, which are positively related with obesity and insulin resistance, and negatively associated with plasma concentration of adiponectin, the anti-inflammatory adipokine. ROS including free radicals are etiologically involved in the development CVD including atherosclerosis, arrhythmia, cardiomyopathy, congestive heart failure, and ischemic heart disease (Zalba et al. 2001). Table 4 adapted from Fernández-Sánchez et al. (2011) have summarized the mechanisms of formation of free radicals during obesity.

Obesity and thrombosis

Adipose tissue is metabolically active organ through secreting hormones, cytokines and growth factors that act in an autocrine, paracrine or endocrine manner. These moieties influence and help control energy homeostasis, glucose and lipid metabolism, and vascular homeostasis. Factors released from adipose tissue involved interleukins, leptin, resistin, adiponectin, fibrinogen, tissue factor (TF), Factor VII and VIII, and plasminogen activator inhibitor-1 (PAI-1) (Darvall et al. 2007).

Fibrinogen promotes arterial and venous thrombosis through increased fibrin formation, platelet aggregation and plasma viscosity; and promotes atherosclerosis through vascular smooth muscle and endothelial cell proliferation (Reiner et al. 2001). The coagulation cascade is initiated when TF is exposed to blood and binds with factor VIIa. Obese patients' exhibit increased TF-mediated coagulation, with raised adipocyte and monocyte TF expression secondary to elevated levels of CRP, TNF-α, angiotensin II and insulin (Visser et al. 1999). Furthermore, high factor VII and factor VIII levels correlate with measures of obesity, and an increased risk of CHD and stroke in many studies. High triglycerides and low HDL cholesterol, the most common lipid disturbances found in obesity, are also found with high factor VII and VIII levels (Woodward et al. 1997). Indeed, obesity has the potentiality to develop cardiac and vascular diseases through interrelated

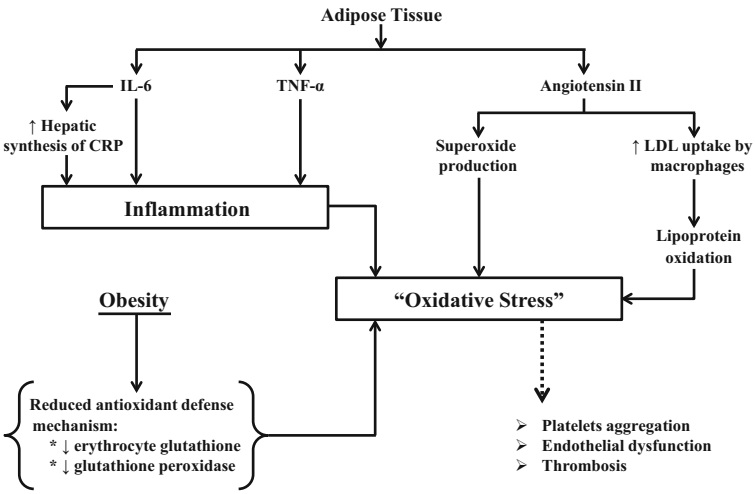

Fig. 3 Oxidative stress and obesity: the relationship between obesity, inflammation, oxidative stress, endothelial dysfunction and thrombosis (Darvall et al. 2007). *TNF*-α tumor necrosis factor alpha, *IL-6* interleukin 6, *CRP* C reactive protein, *LDL* low density lipoprotein

mechanisms involving inflammation, oxidative stress, and thrombosis. Figure 3 adapted and modified from Darvall et al. (2007) explained the relationship between obesity, oxidative stress, endothelial dysfunction and thrombosis.

Further mechanisms linking obesity and cardiovascular disease

Obesity develops CVD not only by generating inflammation, oxidative stress, and thrombosis. As shown in Fig. 3, if obesity lasts for a long time, the antioxidant defense factors could be depleted, as represented by decreasing the activity of enzymes like superoxide dismutase, glutathione peroxidase, and catalase. It was approved that obese individuals are significantly lower in circulated antioxidant enzymes, having implications for the development of obesity-related health problems (Ozata et al. 2002). In addition, levels of serum antioxidants, such as vitamin A, vitamin E, vitamin C, and β-carotene, as well as glutathione, are decreased in obesity, and ROS decreases the expression of adiponectin (Furukawa et al. 2004).

Nitric oxide (NO) is a physiological regulator of diverse functions in several tissues. NO is an important anti-atherogenic agent and it inhibits platelet activation and aggregation, leukocyte chemotaxis, and endothelial adhesion. Endothelium-dependent vasodilation of NO is impaired under condition of obesity, which is observed equally in the presence of hypercholesterolemia (DeSouza et al. 2005).

Furthermore, obesity increases cardiovascular risk through risk factors such as increased fasting plasma triglycerides, high LDL cholesterol, low HDL cholesterol, elevated blood glucose and insulin levels and high BP. Novel lipid dependent, metabolic risk factors associated to obesity are the presence of the small dense LDL phenotype, postprandial hyperlipidemia with accumulation of atherogenic remnants and hepatic overproduction of apoB containing lipoproteins. All these lipid abnormalities are typical features of the metabolic syndrome and may be associated to a pro-inflammatory gradient which in part may originate in the adipose tissue itself and directly affect the endothelium. The link between obesity, the metabolic syndrome and dyslipidemia, observed in the development of insulin resistance in peripheral tissues leading to an enhanced hepatic flux of fatty acids from dietary sources, intravascular lipolysis and from adipose tissue resistant to the antilipolytic effects of insulin (Klop et al. 2013).

Obesity and cardiovascular disease

Increased body weight in healthy people leads to metabolic syndrome development. Metabolic syndrome is associated with the development of diabetes and CVD. As independent risk factor, obesity and particularly abdominal obesity are associated with CVD irrespective of races or sex differences (Yusuf et al. 2004). The majority of hypertensive patients are obese subjects, each 10 kg higher body weight is associated with a 3.0 mmHg higher systolic and 2.3 mmHg higher diastolic BP (Flegal et al. 1998). These increases translate into an estimated 12% increased risk for CHD and 24% increased risk for stroke (National Institutes of Health 1998).

The prevalence of sleep-disordered breathing and sleep disturbances rises dramatically in obese subjects, meaning that obesity is the most important modifiable risk factor for sleep disordered breathing (Bearpark et al. 1995). Each 1-unit increase in BMI was associated with a multiple adjusted increase of 4% in the risk of ischemic stroke and 6% for hemorrhagic stroke (Kurth et al. 2002), also, obesity considered as independent risk factor for developing coronary artery diseases due to fatty streak and advanced lesion (fibrous plaques and plaques with calcification or

ulceration); as evidenced by Framingham Heart Study (Poirier et al. 2006).

Furthermore, elevated BMI predisposes to congestive heart failure by promoting HT, T2DM, and CHD. It is estimated that there is an increase in the risk of CHF of 5% for men and 7% for women for each increment of 1-unit of BMI with the existence of a continuous gradient without evidence of a threshold (Kenchaiah et al. 2002). Finally, weight-stable obese subjects have an increased risk of arrhythmias and sudden death for both genders, even in the absence of cardiac dysfunction (Kannel et al. 1988).

Effect of vitamin C

The term "Vitamin C" refers to the chemical compound ascorbic acid. There are two forms of ascorbic acid; namely, D and L-ascorbic acid. The principal natural compound with vitamin C activity is *L-ascorbic acid* (Rekha et al. 2012). Vitamin C is a reducing agent or antioxidant due to its characteristic of donating an electron, and probably all of its metabolic roles can be accounted for this function. Antioxidant neutralizes free radicals and protects from damage by donating one or two electrons (Wilson 2005). In body cells and fluids, vitamin C protects tissues from oxidative stress and thus plays an important role in preventing diseases (Wilson 2005). Vitamin C is structurally similar to glucose and can replace it in many chemical reactions, and thus is effective in the prevention of non-enzymatic glycosylation of proteins (Afkhami-Ardekani et al. 2003). A possible mechanism for the beneficial effect of plasma vitamin C on heart failure may be related to the fact that vitamin C enhances arterial dilation through its effect on nitric oxide release (Plantinga et al. 2007).

Vitamin C deficiency occurs when vitamin C storage decreases to half of its optimal size (lacking vitamin C from diet for more than a month), scurvy symptoms begin to appear. Two signs of a vitamin C deficiency illustrate its role in maintaining the integrity of blood vessels; the gums bleed easily around the teeth, and capillaries under the skin break spontaneously, producing pinpoint haemorrhage (Whitney and Rolfes 2008).

Many other signs may take place as a result of inadequate intake of vitamin C, like; haemorrhaging, rough, brown, and dry skin due to inadequate collagen synthesis, the inability to form scar tissue resulting in failure of wounds to heal. Anaemia, infections, and fracture of long bones are also common due to inadequate intake of vitamin C (Whitney and Rolfes 2008). Hypovitaminosis C is associated with depression in hospitalized patients (Zhang et al. 2011), Alzheimer's disease (von Arnim et al. 2012), lipid and blood sugar abnormalities (Afkhami-Ardekani and Shojaoddiny-Ardekani 2007).

Therapeutic use of vitamin C

Vitamin C has various therapeutic uses; it reduces risks associated with smoking, such as improving pulmonary function (McEvoy et al. 2014), reduces myocardial injury due to smoking (Das et al. 2012), decreases lipid peroxidation (Kuiper et al. 2011), and alleviates inflammation (Block et al. 2004). It also protects against cancer through decreasing the incidence of oral premalignant lesions as provided by Maserejian et al. (2006), and help against gout (Choi et al. 2009). Moreover, the effects of vitamin C also include improving the mood (Zhang et al. 2011), and protect against neural damage (Tveden-Nyborg et al. 2009).

Khajehnasiri et al. (2013) used RCT to identify the role of vitamin C (250 mg/twice a day) and/or LC n-3 PUFAs (180 mg EPA/120 mg DHA) on inflammatory markers among 136 shift workers with a depression score $\geq$10 in 21-item Beck Depression Rating Scale for 60 days. This study showed that supplementation of EPA/DHA plus vitamin C was associated with a decrease in depression score ($p < 0.05$).

Effect of vitamin C on blood pressure and heart diseases

Large epidemiological studies have reported that dietary intake of antioxidants inversely correlates with hypertension (Salonen et al. 2003; Myint et al. 2008). Similarly, treatment with ascorbic acid significantly improved systolic blood pressure (SBP) and diastolic blood pressure (DBP) in mild-to-moderate hypertensive patients (Duffy et al. 1999). In experimental models of hypertension, vitamin C alone or in combination with vitamin E increased the synthesis of nitric oxide and reduced BP (Sherman et al. 2000; Xu et al. 2000). In addition, the antioxidant rich diet was shown to relieve hypertension and reduces renal immune cell infiltration (Rodriguez-Iturbe et al. 2003).

Wannamethee et al. (2013) examined prospectively the associations between plasma levels of both vitamin C and E, dietary intakes of vitamin C and incident heart failure (HF) of 3919 men aged 60–79 years with no prevalent HF followed up for a mean period of 11 years, in whom there were 263 incident HF cases. Higher plasma vitamin C was associated with a reduced risk of HF in older men with or without MI.

Juraschek et al. (2012) reviewed randomized controlled trials to assess the association between vitamin C and BP. A total of 29 studies have been reviewed with minimum dose of 500 mg, and median duration of 8 weeks, in the results showed that short term administration of vitamin C can reduce BP, but more evidence is needed for long

duration intake. Pfister et al. (2011) examined the prospective association of plasma vitamin C concentrations with incidents of fatal and nonfatal heart failure in apparently healthy men and women, aged 39–79 years participating in the "*European Prospective Investigation into Cancer and Nutrition*". As plasma level of vitamin C increased the incidence of heart failure decreased. Every 20 ± 1.0 μmol/L, the increase in plasma vitamin C concentration was associated with a 9% relative reduction in risk of HF.

Block et al. (2008) used a cross-sectional study to examine the association between plasma ascorbic acid concentration and BP in 242 women aged 18–21 years. After adjusting for race, BMI, education, and fat and sodium intake, the level of ascorbic acid was classified into four groups. Subjects in the highest level of the plasma ascorbic acid distribution had 4.66 mmHg lower SBP (95% CI 1.10–8.22 mmHg, $p = 0.005$) and 6.04 mmHg lower DBP (95% CI 2.70–9.38 mmHg, $p = 0.0002$) than those in the lowest level of plasma ascorbic acid.

Kim et al. (2002) organized a double blinded RCT to investigate the long-term effect of vitamin C supplementation on BP; two groups were supplemented with 50 or 500 mg vitamin C for 5 years in Japan. Before supplementation, neither SBP nor DBP was significantly related with the serum vitamin C concentration. After adjusting for age, BMI, and alcohol intake, or stratification for gender, SBP was increased in the both high dose and low dose vitamin C groups 5.88 mmHg increase (95% CI 3.11–8.65), and 5.73 mmHg increase (95% CI 2.62–8.83); respectively. There was no change of DBP, and the conclusion is that there is no reduction in BP with long-term moderate doses (500 mg/day) of vitamin C supplementation.

Effect of vitamin C on diabetes

Park et al. (2015) conducted a study to assess whether the intake of vitamin A, vitamin C, fruits, or vegetables was negatively associated with metabolic syndrome in Korean adults aged 20 years by using a cross-sectional study of 27,656 adults who participated in the 2007–2012 Korean National Health and Nutrition Examination Survey. The results showed twofold increase in total vitamin C intake among women, indicating a decrease of 6.7% in metabolic syndrome.

Ellulu et al. (2015) recruited 64 HT and/or T2DM patients in a parallel RCT; the supplementation of 1.0 g of vitamin C for 8 weeks was effectively changed the inflammatory and metabolic markers. CRP and IL-6 were reduced significantly (from 14.86 ± 9.20 to 7.74 ± 4.53 mg/L, $p < 0.05$; from 2.20 ± 0.75 to 1.40 ± 0.53 pg/mL, $p < 0.05$; respectively). Similarly, fasting blood glucose (FBG) and triglyceride (TG) were also reduced significantly after 8 weeks of vitamin C intervention (from 188.13 ± 81.24 to 126.16 ± 34.06 mg/dL, $p < 0.05$; and from 223.81 ± 87.88 to 155.10 ± 48.12 mg/dL, $p < 0.05$; respectively).

Montero et al. (2014) reviewed 10 RCTs systematically, and quantified the effect of antioxidant vitamin E and/or C supplements on endothelial function in T2DM subjects. Post-intervention standardized mean difference (SMD) in endothelial function did not reach statistical significance values (0.35; 95% CI −0.17 to 0.88; $p = 0.18$). In a subgroup analysis, post-intervention endothelial function significantly improved in T2DM subgroups, with BMI ≤ 29.45 kg/m^2 (SMD = 1.02; $p < 0.05$), but not in T2DM subgroups with BMI > 29.45 kg/ m^2, indicating that prolonged antioxidant vitamin E and/or C supplementation could be effective in improving endothelial function in non-obese T2DM.

Siavash and Amini (2014) enrolled 50 patients of T2DM in three groups, the first one received 1.0 g vitamin C, the second received 600 mg gemfibrozil, and the last one got a combination of both to find out the change in lipid profile and FBG. Vitamin C had similar results to gemfibrozil in elevating HDL cholesterol, but no effects were detected in FBG or other lipid biomarkers.

Gaur and Dixit (2012) assessed the comparative effects of vitamin C supplementation on lipid profiles in 60 healthy male and female human subjects, 30 individuals were given 500 mg vitamin C tablets one daily basis for 30 days, and the control group of 30 individuals were given placebo capsules (glucose 500 mg). Vitamin C caused significant reduction in total cholesterol (TC) and LDL cholesterol.

Dakhale et al. (2011) examined the effect of oral vitamin C with metformin on FBG, HbA1c, and plasma ascorbic acid level with T2DM, using a double-blinded RCT for 12 weeks. Two groups consisting of 35 patients each, one group received a placebo with metformin and the second received vitamin C with metformin. In conclusion, oral supplementation of vitamin C with metformin reversed ascorbic acid levels in blood, reduced FBG and improved HbA1c.

Jariyapongskul et al. (2007) studied the role of vitamin C in protecting against diabetic retinopathy in rats induced by streptozotocin (STZ) injection. After dividing the rats into two groups; one fed vitamin C supplements (1.0 g per 1 l water), and the other was not fed vitamin C. Significant correlation was observed between a decreased plasma level of vitamin C and blood glucose level in both groups. Furthermore, Sargeant et al. (2000) examined the cross-sectional association between plasma vitamin C level, and HbA1c in self-reported DM patients. The mean plasma of vitamin C levels were significantly higher in individuals with HbA1c levels <7%.

Effect of vitamin C on inflammation

Ford et al. (2003) stated that the inflammatory process increased production of ROS, which may deplete stores of antioxidants including vitamin C. As an antioxidant, vitamin C increases extracellular collagen production that is important for immune cells function (Ottoboni and Ottoboni 2005). Use of vitamin C in treating inflammations associated with diseases has been considered, it can be used with depression (Khajehnasiri et al. 2013), cancers (Du et al. 2012; Mikirova et al. 2013), gastritis (Aditi and Graham 2012), lung diseases and asthma (Sexton et al. 2013).

The mechanisms of anti-inflammatory properties of vitamin C with antioxidant capacity have been attributed to their ability to modulate the NF-$_k$B-DNA binding activity (Carcamo et al. 2002; Choi et al. 2004). The activation is primarily promoted by oxidative stress and lead to cytokine-induced expression of cell adhesion molecules (CAM) molecules in the vascular endothelium and to TNF-α and IL-6 induced production of CRP by the liver (Wu and Schauss 2012). Jang et al. (Jang et al. 2014) showed vitamin C rich diet can improve the pro-inflammatory cytokines including TNF-α, and IL-6 by a significant down-regulation in the hepatic mRNA expression.

Peluso et al. (2014) used mixed fruit-juice drink and vitamin C to reduce postprandial stress induced by a high fat meal (HFM) providing 1334 kcal in healthy overweight subjects using a cross-over RCT. Ingestion of HFM in the placebo group led to an increase in circulating levels of TC, TG, FBG, insulin, TNF-α and IL-6. Ingestion of HFM in the trial group significantly reduced plasma levels of TC and TG, and decreased inflammatory response mediated by TNF-α and IL-6.

Aguiló et al. (2014) found that an intake of vitamin C (500 mg/day) did not reduce the level of IL-6 induced by exercise after 15 days of supplementation in a placebo RCT study. Zhang et al. (2013) aimed to elucidate the effect of oral vitamin C supplementation on inflammatory status in maintenance haemodialysis patients with low vitamin C level, and high CRP level. 100 Patients were divided into two groups. In group 1 ($n = 48$), patients were orally administered with 200 mg/day vitamin C in the first 3 months, and then the vitamin C supplementation was withdrawn in the next 3 months. In group 2 ($n = 52$), patients were not given vitamin C in the first 3 months, and then they were orally administered with 200 mg/day in the next 3 months. The study concluded that inflammation in patients with vitamin C deficiency and high levels of CRP could be partially improved by long-term oral administration of small doses of vitamin C.

Ma et al. (2013) conducted an RCT on Japanese population with atrophic gastritis in an area of high stomach cancer incidence between 1995 and 2000. Daily doses of 50 or 500 mg vitamin C were given, and 120 and 124 participants completed the 5-year study, respectively. Although serum ascorbic acid was higher in the high-dosage group (1.73 ± 0.46 mg/L) than in the low-dosage group (1.49 ± 0.29 mg/L), $p < 0.001$, at the end of the study, no significant difference ($p = 0.63$) was observed for CRP between the low- and high-dosage groups 0.39 (95% CI 0.04–4.19) and 0.38 (95% CI 0.03–4.30) mg/L, respectively.

Mikirova et al. (2013) summarized data of potentially therapeutic plasma ascorbate concentrations can be achieved with intravenous infusion of vitamin C (IVC). Evidence suggests that IVC may be able to modulate inflammation by reducing CRP, which in turn might improve outcomes for cancer patients. As well, Wannamethee et al. (2013) found that the plasma level of vitamin C is associated with a significant reduction in the risk of heart failure (HF) in both men with and without pre-existing MI. The inverse association between plasma level of vitamin C and HF in men was explained by traditional risk factors involving reduction of CRP.

Block et al. (2009) investigated whether vitamins C or E could reduce CRP on 396 healthy non-smokers. They randomized participants into three groups: 1000 mg/day vitamin C, 800 IU/day vitamin E, or placebo, for a period of 2 months. Median baseline CRP level was low, 0.85 mg/L. However, a significant interaction was found, indicating that treatment efficiency depends on baseline CRP concentration. Among participants with CRP indicative of elevated cardiovascular risk (≥1.0 mg/L), vitamin C reduced median CRP by 25.3% compared to placebo ($p = 0.02$). The median reduction in the vitamin C group for CRP was 0.25 mg/L (about 16.7%).

Wannamethee et al. (2006) examined the cross-sectional associations between dietary and plasma vitamin C, and markers of inflammation for subjects free of diabetes or heart diseases. Dietary and plasma vitamin C were inversely and significantly correlated with CRP ($r = -0.10$, $p < 0.001$; $r = -0.16$, $p < 0.001$; respectively). Furthermore, Block et al. (2004) determined the effect of vitamin C in reducing plasma CRP in active and passive smokers. Participants were randomized to receive a placebo or vitamin C (515 mg/day) adjusted by BMI. The supplementation of vitamin C yielded 24.0% reduction (95% CI −38.9 to −5.5%, $p = 0.036$) compared to control in plasma CRP. Finally, Ford et al. (2003) examined the relationship between CRP and vitamin C level in the blood through cross-sectional study, CRP was significantly and inversely associated with vitamin C level.

Conclusion

Accumulation of fat in adipose tissues has active role on metabolism, which linked the obesity with CVD due to imbalanced release of adipokines. Inflammation and

oxidative stress have featured by endothelial and microvascular dysfunction predisposing to HT, thrombosis, atherosclerosis, and metabolic syndrome. Moreover, obesity develops CVD by reducing and depleting the antioxidant defense factors like vitamins and specific enzymes including superoxide dismutase, glutathione peroxidase, and catalase. The reduced nitric oxide and obesity-associated dyslipidemia have associated also with CVD development. The major cardiovascular adverse events, which are obesity-related, included serious complications, which lead to affect the quality of life or even death such as CHD, stroke, congestive heart failure, and arrhythmia. On the other hand, having antioxidant capacity, vitamin C neutralizes free radicals and protects from damage by donating electrons. It protects from oxidative stress, prevention of non-enzymatic glycosylation of proteins, and enhances arterial dilation through its effect on nitric oxide release. It also reduces the risk of smoking via improving pulmonary function, decreases lipid peroxidation, and alleviates inflammation. Epidemiological studies reported that antioxidants involving vitamin C could improve BP, and reduce the risks of heart failure. Among diabetic patients, the appropriate levels of vitamin C or adequate supplementations have decreased the incidence of metabolic syndrome, endothelial dysfunction, improved blood sugar and lipid profile, and reduced the inflammatory markers. Vitamin C can improve inflammation by reducing the inflammatory and pro-inflammatory markers such as CRP, IL-6, and TNF-α. The anti-inflammatory property of vitamin C attributed to their ability to modulate the NF-$_k$B DNA binding activity and down-regulation in the hepatic mRNA expression for the interleukins and tumor factors.

Compliance with ethical standards

Conflict of interest There are no significant competing professional or personal interests that might influence the performance or presentation of the work described in this manuscript.

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