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Chapter

Lipid Peroxidation as a Link between Unhealthy Diets and the Metabolic Syndrome

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Abstract

Unhealthy diets, such as those high in saturated fat and sugar accelerate the development of non-communicable diseases. The metabolic syndrome is a conglomeration of disorders such as abdominal obesity, hypertension, impaired glucose regulation and dyslipidemia, which increases the risk for diabetes and cardiovascular disease. The prevalence of the metabolic syndrome is increasing globally, and dietary interventions may help to reverse this trend. A good understanding of its pathophysiological mechanisms is needed for the proper design of such interventions. This chapter discusses how lipid peroxidation is associated with the development of this syndrome, mainly through the formation of bioactive aldehydes, such as 4-hydroxy-2-nonenal, malondialdehyde, acrolein and glyoxal, which modify biomolecules to induce cellular dysfunction, including the enhancement of oxidative stress and inflammatory signaling. It gives a current understanding of the mechanisms of formation of these aldehydes and how dietary components such as saturated fatty acids promote oxidative stress, leading to lipid oxidation. It also outlines mechanisms, apart from free radical scavenging and singlet oxygen quenching, by which various dietary constituents prevent oxidative stress and lipid oxidation in vivo.

Keywords: Oxidative stress, lipid peroxidation, insulin resistance; metabolic syndrome

1. Introduction

The metabolic syndrome (MS) refers to the occurrence in an individual of multiple physiological disorders related to obesity, hypertension, dysregulated blood glucose and dysregulated blood lipids, and is a risk factor for diabetes and cardiovascular disease [1]. It has been defined more specifically, and in slightly different ways by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III, and by the World Health Organization (WHO). According to the former, MS is characterized by at least three of the following five clinical or biochemical abnormalities: abdominal obesity, arterial hypertension, elevated fasting blood glucose, high plasma triglycerides, and reduced high density lipoprotein cholesterol (HDL-c) [2]. On the other hand, WHO defined it as the occurrence of impaired glucose tolerance or impaired fasting glucose or diabetes and any two of the following: hypertension; elevated trigycerides or low HDL-c; abdominal obesity or obesity as determined by BMI; or microalbuminaria [1].

A proper understanding of the etiology of MS is necessary for its prevention and treatment. This chapter focuses on the role of lipid peroxidation in this pathophysiological process. It begins with a current understanding of the mechanisms of lipid oxidation, with emphasis on the formation of highly reactive lipid oxidation products such as 4-hydroxy-2-nonenal, malondialdehyde, acrolein and glyoxal. This is followed by a discussion of how these aldehydes and other lipid oxidation products contribute to the different MS components. The role of major dietary components in the initiation of oxidative stress and lipid oxidation, as well as mechanisms by which specific dietary components inhibit such undesirable events are also discussed.

2. Mechanisms of lipid peroxidation (LPO) and the formation of bioactive lipid oxidation products

In cells, extensive lipid oxidation and the accumulation of lipid oxidation products occurs under conditions of oxidative stress, when the concentrations of reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide and singlet oxygen increase, and are not matched by an increase in the cellular antioxidant capacity [3]. Electron leakage from the mitochondrial electron transport chain, or the actions of enzymes such as NADPH oxidases and xanthine oxidase generate superoxide anions ($^{\cdot-}O_2$), which are converted by superoxide dismutase to hydrogen peroxide (H_2O_2), which may be converted by ferrous ions (Fe^{2+}) to hydroxyl radicals (·OH) according to the Fenton reaction Eq. (1). Superoxide anion also reacts with nitric oxide (NO), formed by nitric oxide synthases, to form the highly reactive peroxynitrite anion (-OONO), which reacts with H_2O_2 to form singlet oxygen according to Eq. (2), and this is only one of many possible mechanisms of formation of singlet oxygen in biological systems [4–6].

$$\mathrm{HOOH} + Fe^{2+} \rightarrow Fe^{3+} + {}^{-}\mathrm{OH} + HO^{\cdot} \quad (1)$$

$$\mathrm{ONOO^{-}} + \mathrm{HOOH} \rightarrow {}^{1}\mathrm{O_2} + ONO^{-} + \mathrm{H_2O} \quad (2)$$

Lipid peroxidation involves a reaction between unsaturated lipids and oxygen. This may be enzyme-catalysed or non-enzymatic. Non-enzymatic lipid oxidation is either mediated by singlet oxygen, or it may involve free radical oxidation [7]. Singlet oxygen reacts by electrophilic addition to any of the double bonds in an unsaturated fatty acid such as linoleic acid (LA) to form hydroperoxide isomers such as the 10-, 12- and 13-LA hydroperoxides (10-LA-OOH, 12-LA-OOH and 13-LAOOH) as shown in **Figure 1**.

On the other hand, free radical oxidation begins by the abstraction of a hydrogen atom from a fatty acid, for example by the hydroxyl radical, to form a carbon centred radical, which rearranges to form a relatively stable conjugated radical (**Figure 2**). The latter reacts with oxygen to form a peroxyl radical, which abstracts a hydrogen from another fatty acid molecule to form a hydroperoxide and a new carbon centred radical, hence establishing a free radical chain reaction (**Figure 2**).

A fatty acid hydroperoxide can be converted to an alkoxyl radical by Fe^{2+} (**Figure 3**), in analogy to the conversion of H_2O_2 to the hydroxyl radical according to Eq. (1). The alkoxyl radical can be converted to a number of non-aldehydic products, including a hydroxy acid and a keto-acid, or it can cyclize to form an epoxy-allylic radical whose further oxygenation affords a hydroperoxy-epoxide

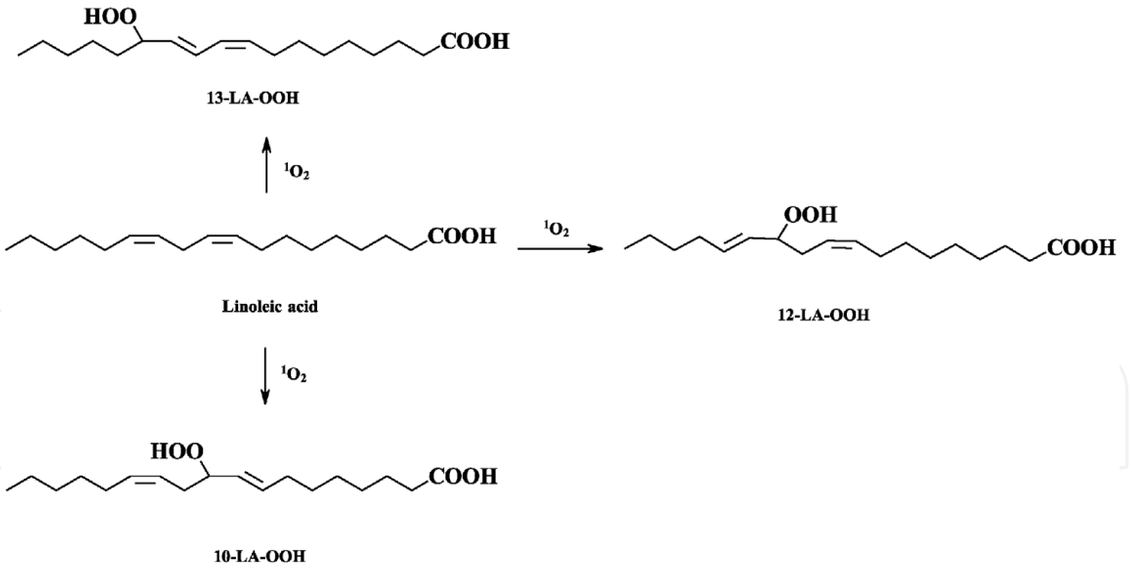

Figure 1.
Formation of different hydroperoxide isomers by the singlet oxygen-mediated oxidation of linoleic acid.

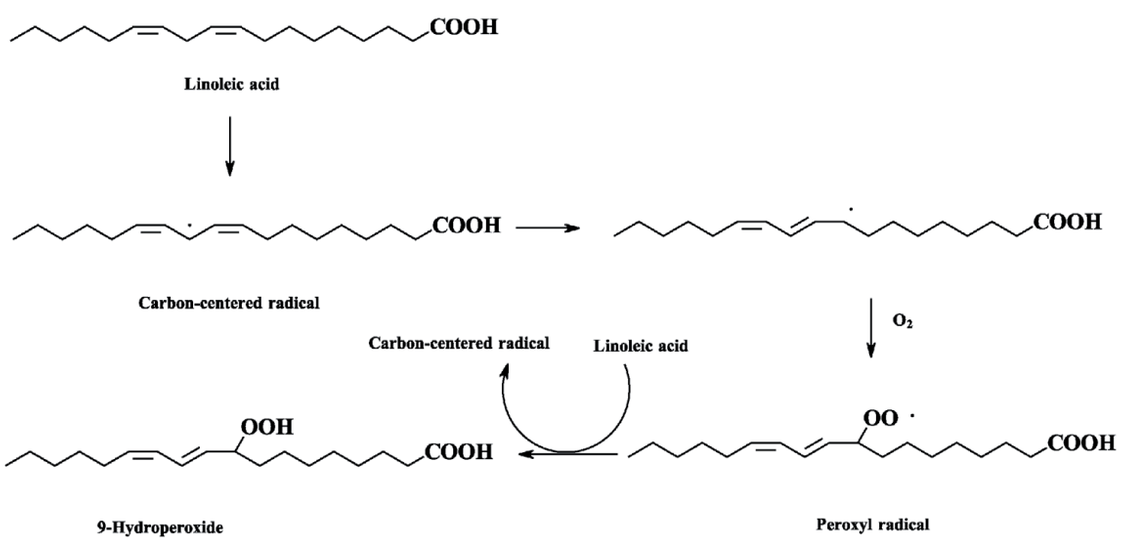

Figure 2.
Free radical peroxidation of linoleic acid showing the formation of one of the two most readily formed hydroperoxides, the 9-hydroperoxide. The other easily formed hydroperoxide is the 13-hydroperoxide (shown in ***Figure 1****).*

(not shown) that can further be converted to various products including epoxy-keto-acids, such as 12,13-epoxy-9-keto-10*E*-octadecenoic acid (**Figure 3**), which contributes to hypertension as discussed in Section 3.2.

An alkoxyl radical can also undergo beta scission (C-C cleavage) to form an aldehyde and a carbon centred radical, and this is only facile if the latter is a resonance stabilized allylic radical, such as would be formed from the 10-LA-OOH (**Figure 4**) or 12-LA-OOH but not 13-LA-OOH [8]. Beta scission is also facile if the carbon bearing the alkoxyl radical occurs next to another oxygen-bearing carbon [9]. Various pathways fulfilling these conditions have been proposed for the formation of the major bioactive lipid-derived aldehydes such as MDA, HNE, acrolein and glyoxal [9, 10].

Acrolein is mainly formed from PUFAS with more than two double bonds, such as arachidonic acid, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) [9]. **Figure 5** shows examples of how MDA, HNE and glyoxal can all be formed from linoleic acid, the most abundant PUFA in most human tissues [3–6]. It starts with the 13-LA-OOH, formed by singlet

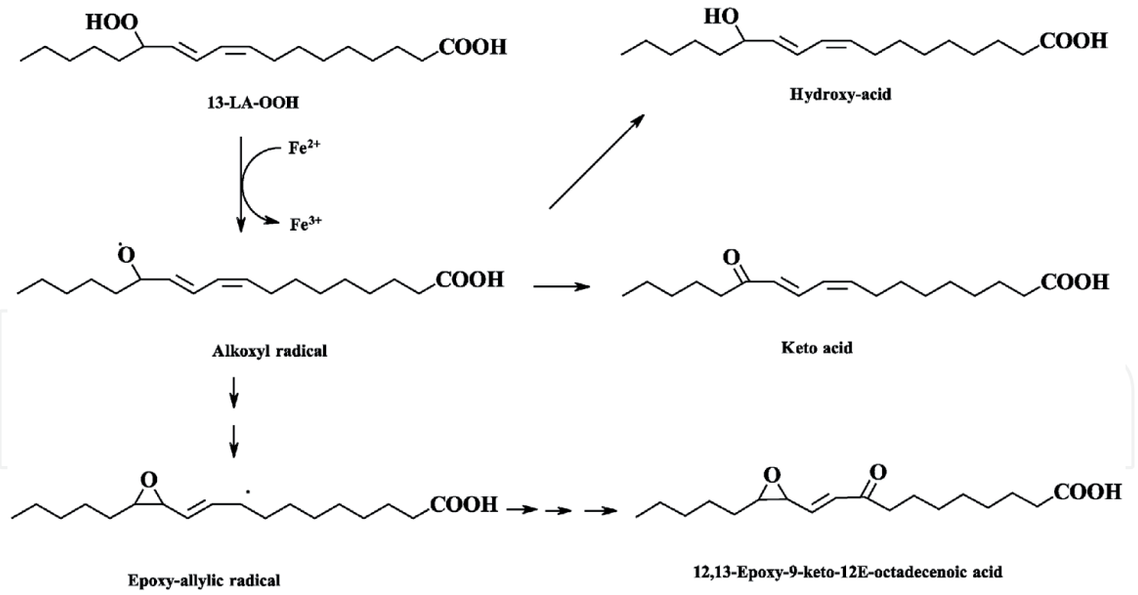

Figure 3.
Conversion of the 13-hydroperoxide of linoleic acid (13-LA-OOH) via the corresponding alkoxyl radical to different types of non-aldehydic products.

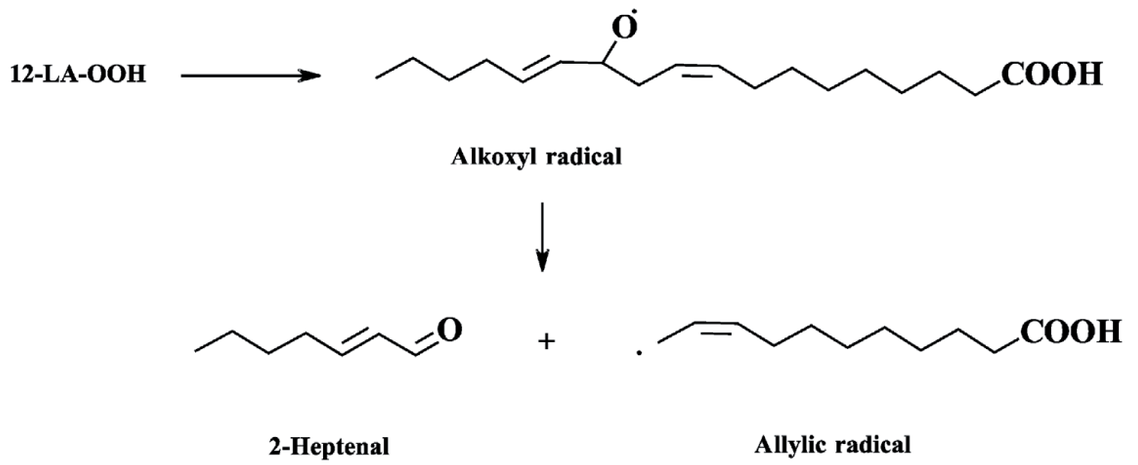

Figure 4.
b-Scission of an alkoxy radical to form an aldehyde (2-heptenal) and an allylic radical. Scission on the other side of the alkoxyl radical to form a vinyl radical and 12-oxo-9-dodecenoic acid is energetically unfavourable.

oxygen -mediated or free radical oxidation, which further reacts with singlet oxygen to form a hydroperoxy-dioxetane (addition of singlet oxygen to a conjugated double bond system forms dioxetanes rather than hydroperoxides). The dioxetane is unstable, and decomposes to form two aldehydes, namely 9-oxononanoic acid and 4-hydroperoxy-2-nonenal (4-HPNE). The former is one of the predominant products of linoleic acid oxidation, and contributes to hypertension through activating phospholipase A2 (Section 3.2). A primary amine (RNH_2) such as lysine or phosphatidylethanolamine may catalyse the conversion of 4-HPNE via a dioxetanyl anion to a dioxetane whose cleavage affords MDA and hexanal (**Figure 5**). While it has long been known that linoleic acid is a precursor of MDA, albeit not as readily as from more highly unsaturated PUFAS, its mechanism of formation from linoleic acid remained elusive [11]. 4-HPNE can alternatively react with another singlet oxygen molecule to form a hydroperoxy-dioxetanyl aldehyde whose decomposition affords glyoxal and 2-hydroperoxy-heptanal (not shown). 4-HPNE can also be converted to an alkoxyl radical, which can abstract a hydrogen to form 4-HNE, or to an epoxy-alkyl radical which can rearrange to an ether radical whose further

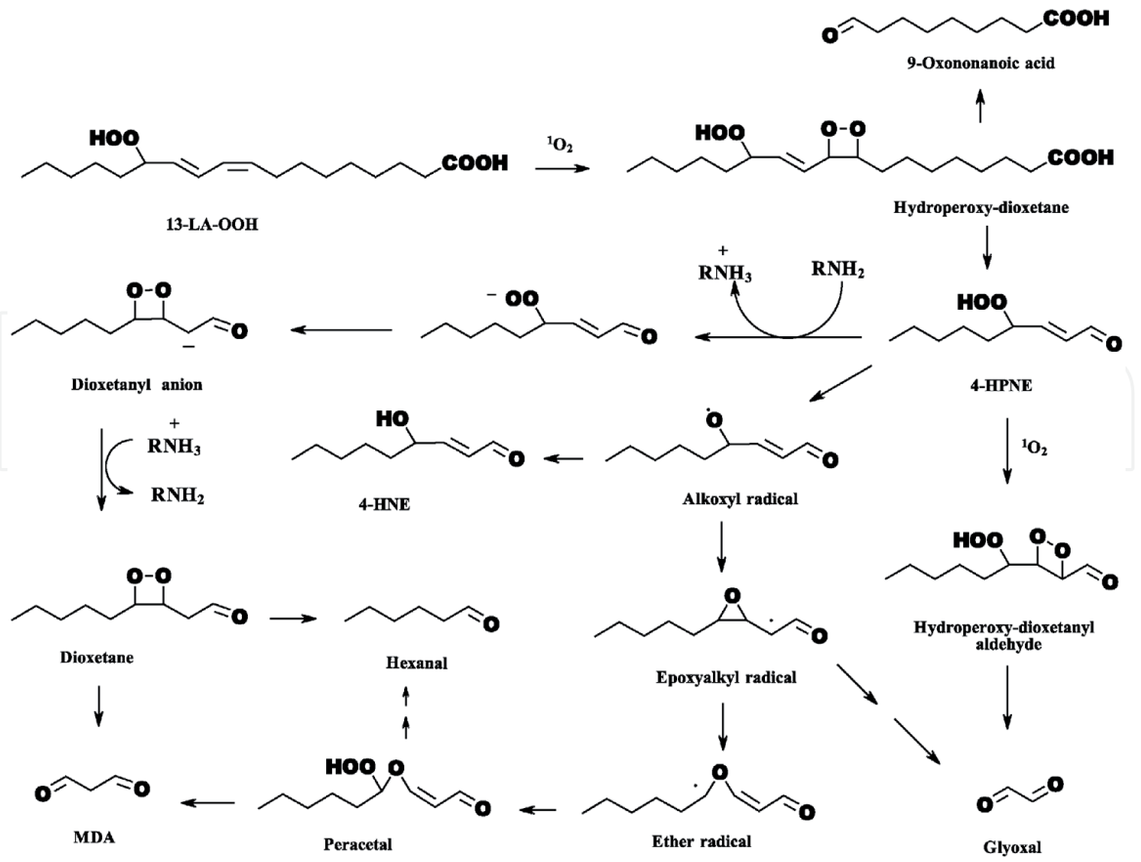

Figure 5.
Mechanisms of the conversion of the 13-hydroperoxide of linoleic acid (LA-OOH) to 4-HNE, MDA, glyoxal, hexanal and 9-oxo-nonanoic acid. Other pathways to these products exist but are not shown.

reaction with oxygen leads to formation of a per acetal that can decompose to MDA and hexane. The epoxy-alkyl radical can also directly react with oxygen to form a hydroperoxy-epoxide whose decomposition affords glyoxal. In the cell, glutathione peroxidase may contribute to the conversion of 4-HPNE to 4-HNE.

3. Lipid peroxidation products contribute to the development of the metabolic syndrome

Lipid oxidation products influence the pathogenesis of metabolic syndrome components such as obesity, hypertension, impaired fasting glucose/diabetes, and dyslipidemia, in various ways [12].

3.1 Obesity

Obesity occurs when adipocytes increase in number and/or size, coupled with increased fat storage and reduced fat oxidation. Adipose tissue (AT) is functionally classified as brown or white (BAT and WAT, respectively). BAT consists of adipocytes specialized for thermogenesis, and hence contribute to reduction of obesity; while WAT, the major type of adipose tissue in humans, has less capacity for fat oxidation, and may contribute to obesity [13]. White adipocytes can exist in or acquire a brown-like (beige or brite) phenotype with higher fat oxidation than ordinary white adipocytes, and a higher number of beige adipocytes reduces an individual's susceptibility to obesity [13]. Expansion of WAT by differentiation of preadipocytes (hyperplasia) into mature adipocytes with adequate lipid filling and fat oxidation

capacity is beneficial for safe storage of fat; but mere expansion of mature adipocytes because of excessive lipid filling and reduced fat oxidation (hypertrophy) is associated with adverse health outcomes.

A certain amount of ROS is required for proper preadipocyte and mature adipocyte physiology. However, oxidative stress and excessive autophagy may inhibit preadipocyte differentiation and promote hypertrophy of mature adipocytes (**Figure 6**) [14]. Likewise, brown or beige adipocytes have many mitochondria for the enhanced fat oxidation, but mitochondrial oxidative stress causes loss of the mitochondria through mitophagy, thus leading to whitening, increased lipid storage and hypertrophy (**Figure 6**) [15]. Adenosine 5-monophosphate kinase (AMPK), sirtuins 1 and 3, protein kinase B (akt), peroxisome proliferator activated receptor gamma and alpha (PPARγ and PPARα, respectively), and PPARγ coactivator-1α (PGC-1α) are among the proteins that reduce oxidative stress and/or promote mitochondrial biogenesis in adipocytes [16, 17]. Both protein kinase A (PKA) and akt are required for PPARγ expression [18], which is required for differentiation of both brown and white adipocytes [19]. PPARγ promotes thermogenesis in mature brown adipocytes through activation of uncoupled protein 1 (UCP-1), and by upregulating glycerol kinase which catalyses glycerol-3-phosphate synthesis, which is required for TG synthesis [20]. While this looks paradoxical, TG synthesis may help reduce the lipotoxicity and oxidative stress induction by free fatty acids (discussed in Section 4), and allow targeted, β-adrenergic signaling-associated release of fatty acids for mitochondrial oxidation. AMPK activates autophagy and induces the transcription factor nrf2; and the latter upregulates antioxidant enzymes such as catalase, glutathione peroxidase, superoxide dismutase and heme oxygenase 1 [21]. Sirt1, which is mainly localized in the nucleus, increases the expression catalase and SOD as reviewed by Iside et al. [22]. In addition, it upregulates autophagy genes, and autophagy defect associated with its inhibition promotes release of exosomes which induce toll-like receptor 4 (TLR4) signaling, downstream activation of nuclear factor kappa B (NF-kB), and NF-kB-mediated upregulation of oxidative stress and inflammation-promoting genes [23].

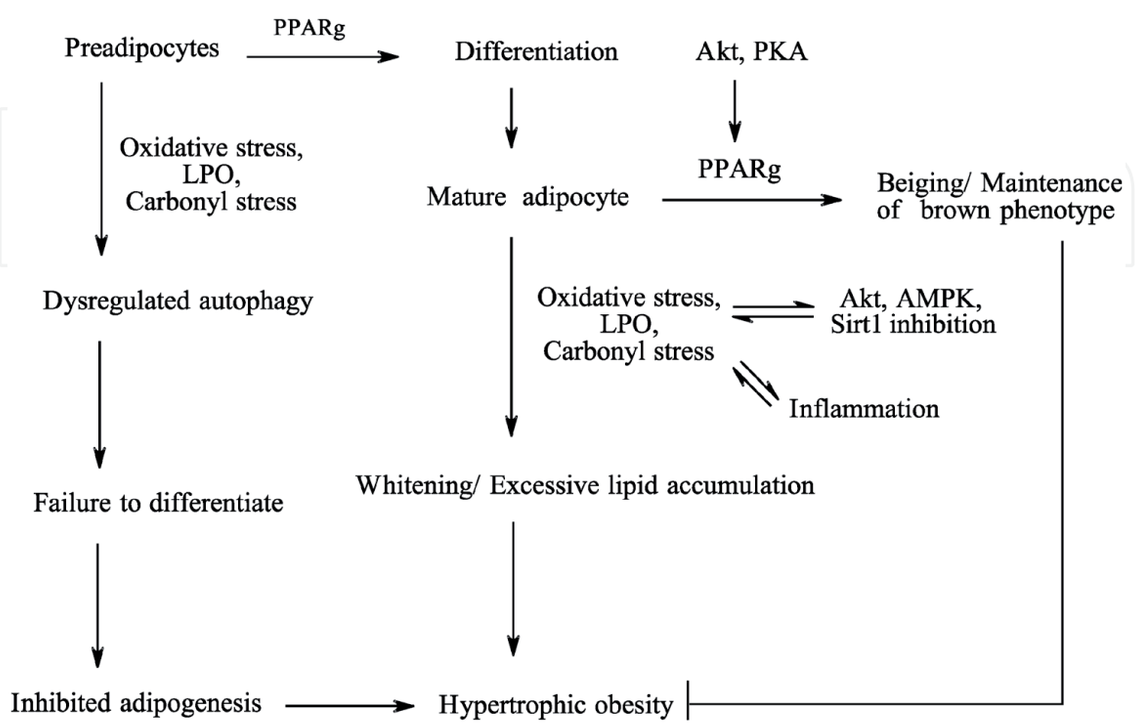

Figure 6.
Role of oxidative stress and lipid oxidation-induced carbonyl stress in the pathogenesis of hypertrophic obesity.

Conditions that promote adipose tissue oxidative stress, including inappropriate diets (Section 4), induce lipid oxidation, and the latter generates carbonyl stress due to formation of various aldehydes as explained in Section 2. These aldehydes, including HNE and acrolein modify and inhibit AMPK and sirt1, thus amplifying oxidative stress and their own formation (**Figure 6**) [24–26]. HNE also carbonylates insulin receptor substrate1/2 (IRS1), leading to degradation and inhibition of the latter, thus inducing insulin resistance and downstream akt inhibition [27]. Thus, insulin resistant obese individuals have lower akt, AMPK ad sirt1 activity, but higher reactive carbonyls and carbonylated proteins [28]. Acrolein and HNE additionally aggravate oxidative stress through readily reacting with, and depleting the antioxidant glutathione [29, 30]. They modify the endoplasmic reticulum calcium pump SERCA, leading to its inhibition and ER stress [3], which aggravates oxidative stress, insulin resistance, sirt1 inhibition, expression of the pro-inflammatory cytokines, TNFα and IL6, and adipocyte whitening [31, 32]. Glutathionylated HNE and other aldehydes released from adipocytes under conditions of oxidative stress promote macrophage infiltration into WAT, and their acquisition of a proinflammatory M1 phenotype [33]. Malondialdehyde reacts with albumin, and the MDA-albumin conjugates promote a proinflammatory phenotype in macrophages and T cells [34]. Cytokines such as interleukin1-β, released from inflammatory macrophages, in turn promote adipocyte oxidative stress and whitening [35].

3.2 Hypertension

Arterial hypertension occurs because of (i) increased renal retention of sodium and water (ii) dysregulation of vasodilators and vasoconstrictors and (iii) arterial stiffness. Obesity is a major risk factor for hypertension [36]. For example, adiponectin inhibits adrenal production of aldosterone, a potent inducer of hypertension [37], but obesity reduces adiponectin secretion and increases circulating aldosterone [38]. Thus, by promoting obesity, lipid peroxidation products indirectly promote hypertension. However, they also induce hypertension independently of obesity. For example, the non-aldehydic linoleic acid oxidation product, 12,13-epoxy-9-keto-10-*E*-octadecenoic acid (Shown in **Figure 3**) also promotes adrenal production of aldosterone to induce hypertension [39].

Aldosterone binds to the renal tubular epithelial cell mineralocorticoid receptor, which, as a transcription factor, upregulates the expression of the epithelial sodium channel, which promotes sodium retention [40]. Independently of gene transcription, aldosterone activates the non-receptor tyrosine kinase cSrc in these cells, probably through the angiotensin receptor type 1 (AT1R), and cSrc activates epidermal growth factor receptor (EGFR) signaling, leading to activation of the mitogen activated protein kinase Erk1/2 [40]. Erk1/2 activates Na^+/K^+ ATPase, which promotes sodium and water retention [41]. Aldosterone-cSrc signaling also induces oxidative stress [40], which induces formation of lipid oxidation products. 4-HNE, inhibits AMPK and sirt1, thus inhibiting eNOS, leading to reduced NO bioavailability, and this causes increased transactivation of EGFR and downstream Erk1/2 [42–44]. Thus, blood HNE levels are increased in hypertension [45], and the latter can be ameliorated by carbonyl quenching [46]. Oxidized low density lipoprotein, which contains oxidatively modified lipids such as HNE, induces oxidative stress in renal tubular endothelial cells, which activates the renal renin-angiotensin system (RAS); whose component, angiotensin 2, overstimulates sodium transporters and thus induces hypertension [47, 48]. Hypertension in turn promotes oxidative stress and LDL oxidation, thereby creating a vicious circle [49].

Inhibition of endothelial cell sirt1, sirt3 and AMPK, which can be mediated by LPO products, causes inhibition of endothelial nitric oxide synthase (eNOS) and

decreases production of NO, the main arterial vasodilator [50–52]. HNE induces endothelial cell insulin resistance, and the associated akt inhibition both inhibits eNOS and upregulates the vasoconstrictor, endothelin [3, 53]. The dysfunctional endothelial cells further produce pro-inflammatory factors such as TNFα, IL-1β, IL-8 and MCP-1 which recruit circulating neutrophils, platelets and monocytes, and the latter differentiate into macrophages [53, 54]. Neutrophils, monocytes and macrophages secrete myeloperoxidase [55]. Myeloperoxidase oxidizes LDL [56]. It also promotes the activation of endothelial cyp4a12a, which catalyzes the formation of 20-hydroxy-eicosatetraenoic acid (20-HETE) from arachidonic acid [57]. 20-HETE upregulates endothelial RAS components including angiotensin 2, a potent vasoconstrictor, which also induces aldosterone secretion [58]. Both angiotensin 2 and aldosterone aggravate endothelial oxidative stress and dysfunction. Androgens promote 20-HETE synthesis, and this may explain the higher occurrence of hypertension in men than women [58].

Stiffness of the coronary artery and other major arteries inhibits their systolic dilatation, and thus promotes systolic hypertension [59]. Degradation of the elastic fiber, elastin, in the walls of the major arteries, and its replacement with collagen fibres is a hallmark of the pathogenesis of arterial stiffness [59]. The myeloperoxidase product, 20-HETE, activates matrix metalloproteinase 12 (MMP-12, macrophage elastase), which degrades elastin [60]. Myeloperoxidase additionally inhibits the elastase inhibitor, α1, and this is antagonized by sulfur compounds such as glutathione [61]. Acrolein and HNE, on the other hand, deplete glutathione [62]. 20-HETE additionally sensitizes vascular smooth muscle cells to stimuli that promote their dedifferentiation and proliferation [58], which contributes to arterial stiffening especially of the muscular arteries [63]. One of the most readily formed aldehydic linoleic acid oxidation products, 9-oxononanoic acid (**Figure 3**) activates phospholipase A2 (PLA_2) leading to generation of eicosanoids and thromboxane A2 in blood [64]. Thromboxane A_2 causes vasoconstriction and the proliferation of smooth muscle cells [65].

Malondialdehyde forms collagen crosslinks that prevent collagen degradation, thus promoting arterial stiffness [66]. Thus, MDA-modified LDL independently predicts arterial stiffness [67]. Glyoxal contributes to arterial stiffness by reacting with collagen to form advanced glycation end products such as GOLA, GOLD, GODIC and carboxymethyl lysine (CML) [68]. CML induces endothelial oxidative stress through the RAGE receptor, which activates components of NF-kB signaling that promote expression of collagen 1 and 2 [69, 70].

3.3 Dyslipidemia

Dyslipidemia in metabolic syndrome is defined by elevated circulating triglycerides (hypertriglyceridemia) or low levels of high-density lipoprotein cholesterol (low HDLc); and hepatic steatosis, a component of non-alcoholic fatty liver disease (NAFLD) is its main risk factor [71]. This is because, in hepatic steatosis, there occurs greater production and secretion of triglyceride-rich very low-density lipoproteins (VLDL), leading to hypertriglyceridemia; as well as higher hepatic lipase activity, which increases the hepatic uptake and degradation of HDL [71]. Hepatocyte oxidative stress, ER stress and associated lipid peroxidation are involved in the development of hepatic steatosis [72, 73], and this makes lipid peroxidation an important factor in the development of dyslipidemia [74].

Low HDLc also occurs in obesity independently of elevated triglycerides, indicating that it occurs even independently of NAFLD [75]. Hypoadiponectinemia, which depends on obesity rather than NAFLD [76], may cause reduced HDLc through increased hepatic lipase activity; reduced

hepatic expression of the HDL protein apo A; reduced expression of the cholesterol export protein ABCA1 which transfers cholesterol to HDL; and upregulated synthesis of LCAT which transfers cholesterol from HDLc to chylomicrons [77]. Obesity is also associated with increased plasma TNFα [78] which suppresses hepatocyte apo AI gene expression via ERK and JNK [79]. HNE contributes to JNK over-activation in hepatocytes [80].

3.4 Prediabetes and diabetes

Diabetes is a state of elevated postprandial and/or fasting blood glucose that, if not controlled, leads to the damage of various organs; while prediabetes refers to an intermediate level of fasting and/or postprandial blood glucose, higher than normal but less than diabetic blood glucose levels [1]. It is an earlier stage toward the development of diabetes, but which can revert to normoglycemia. The major causes of (pre)diabetes are pancreatic alpha and beta cell dysfunctions leading to glucagon over-secretion and insulin under-secretion, respectively; coupled with skeletal muscle, adipose and/or hepatic insulin resistance [81].

Both obesity and hypertension contribute to the pathogenesis of prediabetes, hence the lipid oxidation products that induce obesity and hypertension indirectly promote diabetes thereby. Nevertheless, lipid oxidation products also directly promote (pre)diabetes. For example, malondialdehyde was found to dose-dependently reduce the insulin content in the pancreas and to contribute to beta cell death [82]. HDL prevents beta cell apoptosis and diabetes by promoting cholesterol efflux from these cells, but acrolein- or MDA-modified HDL loses this protective property [83–85]. oxLDL impairs insulin gene expression and causes death of pancreatic beta cells, through induction of oxidative stress and ER stress [86]. As already discussed, lipid oxidation products induce endothelial dysfunction. Pancreatic endothelial cell dysfunction contributes to diabetes, being associated with leukocyte recruitment and increased production of proinflammatory cytokines [87]. Cytokines such as IL-1β and TNFα induce alpha and beta cell oxidative stress [88] and associated lipid peroxidation. Insulin resistance, which can be induced by HNE and acrolein, is part of the alpha cell and beta cell dysfunctions leading to diabetes [81].

4. Role of dietary constituents in inducing tissue oxidative stress, lipid peroxidation and the metabolic syndrome

Diets high in saturated fatty acids, cholesterol, sugar, salt, and red meat, contribute to higher lipid oxidation in the tissues and organs that have a central role in the metabolic syndrome, such as adipose tissue, endothelial tissue, muscle, liver and pancreas.

Although saturated fatty acids do not undergo peroxidation, they contribute to the induction of oxidative stress in cells, which then leads to peroxidation of unsaturated fatty acids. For example, the most abundant saturated fatty acid in the diet, palmitic acid, is a key substrate for the first reaction in ceramide biosynthesis [89]. Ceramides induce oxidative stress, for example by inhibiting components of the electron transport chain [90].

Palmitate also induces oxidative stress and ER stress independently of ceramide. For example, it increases diacylglycerol levels, which is associated with activation of protein kinase C (PKC), which inhibits the Kreb's cycle enzymes aconitase and isocitrate dehydrogenase [91]. Thus, the acetyl COA generated from peroxisomal and mitochondrial fatty acid beta oxidation accumulates in the cell, promoting

acetylation of mammalian target of rapamycin complex (MTORC-1) and high mobility group box-1 (HMGB-1), as has been demonstrated in hepatocytes [92]. Acetylation activates MTORC-1, which inhibits akt and further promotes oxidative stress by upregulating the expression of TLR4, thus upregulating the NF-kB-NADPH oxidase/iNOS axis [92]. Acetylation of HMGB-1 causes its translocation out of the cell, enabling it to induce oxidative stress by interacting with the receptor for advanced glycation end products (RAGE) as well as TLR4, which both induce NF-kB activation [93]. Obesity is associated with increased circulating HMGB-1, which accelerates the pathogenesis of obesity, hypertension and diabetes [72, 73, 94, 95]. TLR2/4 signaling also activates RAS components including angiotensin 2, whose signaling via its receptor AT1R induces NFkB and oxidative stress [3, 96].

PUFAS undergo peroxidation during cooking as well as in the digestive tract [97]. This is more pronounced when they are part of a meal containing meat, especially red meat, which has higher myoglobin content; since iron from the latter promotes lipid oxidation [98]. This leads to a postprandial increase in circulating carbonyls such as malondialdehyde and HNE, which promote oxidative stress, HDL modification and postprandial inflammation [98, 99]. On the other hand, absorbed, unoxidized unsaturated fatty acids including MUFAs and PUFAs reduce palmitate-induced oxidative stress and lipotoxicity in many cell types by promoting the incorporation of palmitate into TGs for safe storage [100–102]. Nevertheless, high concentrations of arachidonic acid also induce deleterious effects. Thus, supplementation of arachidonic acid to a high fat diet led to enhanced obesity in mice [103], which is attributable to the fact that this n-6 fatty acid promotes adipogenesis from preadipocytes, but its cyclooxygenase-mediated oxidation products, prostaglandins E2 and F2a (PGE2 and PGF2a) inhibit browning via ERK activation and associated decrease in UCP-1 expression [104, 105]. These prostaglandins activate NF-kB, diminish adiponectin production, upregulate pro-inflammatory mediators such as TNFα and MCP-1, and thus promote macrophage activation [106]. They promote oxidative stress and lipid oxidation, and the lipid oxidation product HNE in turn induces cyclooxygenase 2 [107]. Adipose inflammation has systemic effects, hence adipose tissue arachidonic acid was found to be independently associated with abdominal obesity, dyslipidemia, hypertension and fasting glucose [108]. Its myeloperoxidase products, 20-HETE is associated with insulin resistance and hyperglycemia [109]. Since humans synthesize arachidonic acid from linoleic acid, the arachidonic acid content in human adipose tissues does not necessarily reflect its dietary intake [110].

Although linoleic acid is a precursor of arachidonic acid, studies of its effects on the metabolic syndrome have given mixed results, with both harmful and protective roles reported [111–113]. The differences are partly due to genetic factors. For example, there are individual and ethnic differences in the expression of fatty acid desaturase 1 and 2 (FADS 1/2); with genotypes favouring greater FADS1/2 activity and arachidonic acid synthesis being associated with greater susceptibility to metabolic dysregulation [114, 115]. Black people and Indians significantly generate arachidonic acid from dietary linoleic acid, unlike people of European origin [114, 116]. A high adipose tissue linoleic: arachidonic acid is inversely associated with cardiovascular mortality and hypertension [112]. Likewise, a low linoleic: arachidonic acid ratio in plasma phospholipids is associated with hypertension [117]. Polymorphisms in the receptor for oxLDL, Lox-1, might also determine differences in the response to increased dietary linoleic acid; since this PUFA increases Lox-1 expression in aortic endothelial cells [118]. The effects of linoleic acid may also be dependent on the overall diet. If the diet is high in other factors that induce oxidative stress such as dietary sugar and salt, the pro-oxidative environment thus created may abrogate potential linoleic acid benefits through its increased

oxidation. This is in analogy to the fact that high glycemic index foods abrogate the anti-obesity effects of fish oil [119]. A high linoleic acid diet may also be unfavourable for people who have already developed some component of the metabolic syndrome and thus have a more pro-inflammatory status.

Oleic acid is the major dietary fatty acid in the Mediterranean diet, which is generally associated with health benefits. This fatty acid is relatively resistant to peroxidation. Besides promoting the safe storage of palmitate in TGs, it induces thermogenesis by upregulating adipose triglyceride lipase and hormone sensitive lipase, which induce lipolysis coupled with fatty acid oxidation [120]. It promotes M2 macrophage phenotype in visceral adipose [121].

The dietary n-3 fatty acids are generally highly susceptible to oxidation because they all contain at least 3 double bonds. Although they are not 4-HNE precursors, decomposition of their hydroperoxides very readily produces acrolein, MDA, glyoxal and methylglyoxal. Despite this, they are largely beneficial, suppressing development of the metabolic syndrome [122]. In adipocytes, their binding to the GPR120/Ffar4 receptor inhibits TLR2 and TLR4 signaling and associated NFkB activation, oxidative stress and inflammation [123]. This receptor also upregulates miR-30b and 378, and induces FGF21 secretion, whose signaling activates AMPK, promotes browning and induces adiponectin [123–126]. The n-3 PUFAs are metabolized by cyclooxygenase to resolvins, protectins, maresins and isoprostanes which help in resolving inflammation [127].

A high dietary n-3: n-6 PUFA ratio has been found to be protective against the metabolic syndrome in some studies but not others [128, 129]. This might be partly due to inter-individual differences in the metabolism of n-6 fatty acids.

High carbohydrate diets promote obesity because excess sugars are stored as lipids. High sucrose or high fructose diets are particularly obesogenic [130]. Fructose metabolism robustly increases palmitate synthesis in adipocytes [131]. Moreover, fructose metabolism is associated with decreased cellular ATP, purine degradation and activation of xanthine oxidase which generates reactive oxygen species and associated lipid peroxidation [132], which is involved in adipocyte whitening and less thermogenesis. Uric acid, a product of purine degradation also induces oxidative stress through increased NADPH oxidase activity and RAS activation [131–134].

High salt (sodium chloride) diets promote obesity, by salt-induced activation of adipocyte Na/K+ ATPase, which is coupled to activation of src, which generates ROS, and transactivates PI3-K-Akt–MTOR and EGFR-ERK/MAPK pathways [135, 136]. This is associated with increased expression of proinflammatory mediators such as TNFα, MCP-1, COX-2, IL-17A, IL-6, leptin, and leptin [136, 137]. Sodium chloride also activates Na+/K+ ATPase and induces oxidative stress in endothelial cells and renal tubular epithelial cells, thereby promoting hypertension [132], and this is also subject to genetic susceptibility [138].

High dietary cholesterol is associated with a high risk of dyslipidemia [139]. Cholesterol-rich chylomicron remnants mainly deliver their cholesterol to the liver, and cholesterol accumulation in hepatocytes strongly induces oxidative stress, by modification of the mitochondrial membrane and limiting import of glutathione into the mitochondria, as well by inducing ER stress and proinflammatory cytokines [140].

The lipopolysaccharide (LPS) component of the walls of gram-negative bacteria is a pro-inflammatory molecule that contributes to metabolic low-grade inflammation (endotoxemia), by signaling through TLR2 and 4 in various cell types, leading to NFkB activation and release of pro-inflammatory cytokines. High sucrose and high saturated fat diets promote the growth of gram-negative bacteria, and thus increase the entry of LPS into the circulation [141].

5. Mechanisms of the antioxidant and metabolic syndrome-suppressing effects of dietary factors

While some food components promote a pro-oxidative and pro-inflammatory state as discussed in the previous section, other dietary factors inhibit oxidative stress and inflammation. They do this through various mechanisms, but the most widely considered mechanisms are those associated with lipid oxidation, including scavenging of free radicals such as peroxyl radicals and alkoxyl radicals, chelation of metal ions that participate in formation of such radicals, and singlet oxygen quenching.

5.1 Free radical scavenging and singlet oxygen quenching

Carotenoids, phenolic substances, tocopherols and ascorbic acid are well known for their antioxidant activities targeting the neutralization of reactive radicals and/or singlet oxygen quenching. Thus, carotenoids reduce oxidative stress and lipid oxidation, resulting in adipocyte beiging and obesity prevention [142]. There is decreased adipose beta carotene in obese subjects, and this was suggested to at least partly be due to their depletion under the high ROS environment [142]. Likewise, tocopherols and tocotrienols have been shown to be protective against all components of the metabolic syndrome [143]. Thus, the high tocotrienol content of palm oil may reduce its potential harm from the high palmitate content [144]. Unfortunately, radical scavenging antioxidants also exhibit pro-oxidant activity, depending on their concentrations and the level of prooxidative factors [145]. Hence, there is need to consider a broad range of dietary factors that prevent oxidative by alternative mechanisms, such as those outlined hereafter. A single molecule can act by multiple mechanisms, and the more mechanisms involved, the greater might be the benefit.

5.2 Insulin-mimicking

Insulin signaling activates akt, which reduces oxidative stress by promoting mitophagy and by activating nrf2 to induce antioxidant enzymes [81, 146]. Moreover, nrf2, via heme oxygenase 1 (HO-1), inhibits NFkB and associated upregulation of NADPH oxidase and iNOS [147]. Quercetin and ferulic acid are examples of molecules that have demonstrated oxidative stress and metabolic syndrome amelioration at least partly through PI3K-akt signaling in various cell types [148–150]. Resveratrol and ferulic acid inhibit LPS- and oxidative stress-induced intestinal barrier injury through this signaling pathway [151, 152].

5.3 AMPK and SIRT1 activation

AMPK and/or sirt1 reduce mitochondrial oxidative stress in adipocytes, pancreatic beta cells, hepatocytes, endothelial cells, and thus are useful in preventing all aspects of the metabolic syndrome. In addition to insulin mimicking, quercetin and ferulic acid, also activate these proteins [153–155].

5.4 Adiponectin and adiponectin receptor enhancement

Compounds that activate AMPK, sirt1 and/or PI3K-akt in adipose tissues limit adipocyte hypertrophy and inflammation, and enhance adiponectin production. Adiponectin has systemic effects in reducing insulin resistance and oxidative stress, because it activates both PI3K-akt and AMPK in insulin target tissues, and also promotes anti-inflammatory polarization of macrophages [156]. Dietary compounds

than ameliorate metabolic syndrome through enhanced adiponectin secretion and/or upregulating adiponectin receptor include n3-fatty acids, sesamin, the citrus derived polymethoxyflavonoids nobiletin and tangeretin, quercetin and resveratrol [157–160].

5.5 Ceramide reduction

Adiponectin signaling increases ceramidase activity, thus reducing ceramide levels [161]. Hence, the adiponectin and adiponectin receptor enhancers should contribute to reducing ceramide-induced oxidative stress. Not much research has been done along this line, but it has been reported that DHA inhibits ceramide biosynthesis [162]. In mice, dietary inulin reduces ceramide synthesis by suppressing neutral sphingomyelinase expression and activity [163].

5.6 Vasodilation

Vasodilation reduces blood pressure, and thus reduces pressure-dependent oxidative stress as well as LDL oxidation and Lox-1 dependent oxidative stress [164]. Thus, for people with prehypertension or hypertension, vasodilation may be a major strategy for reducing oxidative stress and lipid oxidation. Cinnamaldehyde has vasodilatory and antihypertensive activity through effects on smooth muscle contractility [165]. Dietary nitrate achieves vasodilation through NO release, and this is associated not only with pressure regulation, but also other components of the metabolic syndrome including blood glucose and lipid improvement [166]. Adiponectin induces AMPK dependent eNOS activation in endothelial cells, hence adiponectin enhancers such as imperatorin also promote NO synthesis and vasodilatation [167].

5.7 Reactive carbonyl, ALEs and AGEs scavenging

Scavengers of reactive carbonyls such as HNE, acrolein and MDA have been demonstrated to ameliorate oxidative stress, lipid peroxidation and the metabolic syndrome. Examples of compounds with such effects include carnosine, carnosinol, epigallocatechin-3-gallate and the mulberry anthocyanins cyanidin 3-glucoside (C3G) and cyanidin 3-rutinoside (C3R) [46, 168–170]. Aminoguanidine attenuates hypertension by scavenging AGES [171].

5.8 Gut microbiota modulation

Probiotic microorganisms suppress the growth of pathogenic microorganisms. They also produce metabolites such as short chain fatty acids with beneficial effects on the metabolic syndrome. For example, butyrate promotes PI3K-akt signaling to prevent oxidative stress and maintain intestinal barrier integrity [172, 173]. Quercetin, resveratrol and n-3 fatty acids have been demonstrated to positively influence gut microbiota and decrease intestinal barrier permeability in animal studies [153, 174].

6. Conclusions

Lipid peroxidation is a major contributor to the pathogenesis of the metabolic syndrome, especially through highly reactive and bioactive aldehydes such as acrolein, 4-hydroxy-2-nonenal, malondialdehyde and glyoxal. Mechanisms of formation

of these products are now well-understood. For example, this article has highlighted that formation of MDA from linoleic acid may be easier than previously thought. The mentioned aldehydes propagate oxidative stress and inflammation by inducing insulin resistance, inhibiting sirt1 and AMPK, reducing adiponectin secretion, as well as forming AGEs and ALEs that activate the RAGE receptor. Inhibiting LPO and the LPO product-associated oxidative stress and inflammation is necessary for preventing and/or ameliorating progression of the metabolic syndrome. This may not be effectively accomplished by dietary agents that merely scavenge free radicals and/or quench singlet oxygen, but also by those that inhibit the signaling pathways that generate non-lipid ROS, or scavenge the reactive carbonyls, ALEs and AGEs. In addition, saturated fat, sugar, meat, and salt, that fuel the signaling pathways that initiate LPO should be reduced. The metabolic influence of some dietary components such as salt and n-6 PUFAs is particularly influenced by genetics, and this should be duly considered when making dietary recommendations.

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