REVIEW

Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus

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insulin resistance, dyslipidemia, β-cell dysfunction, impaired glucose tolerance and ultimately leading to T2DM. Chronic oxidative stress, hyperglycemia and dyslipidemia are particularly dangerous for β-cells from lowest levels of antioxidant, have high oxidative energy requirements, decrease the gene expression of key β-cell genes and induce cell death. If β-cell functioning is impaired, it results in an under production of insulin, impairs glucose stimulated insulin secretion, fasting hyperglycemia and eventually the development of T2DM.

Key words: Insulin resistance; Dyslipidemia; Type 2 diabetes mellitus; Oxidative stress

Core tip: Oxidative stress is underling in the development of cardiovascular disease, type 2 diabetes mellitus (T2DM) and diabetic complications. Increased oxidative stress appears to be a deleterious factor leading to insulin resistance, dyslipidemia, β-cell dysfunction, impaired glucose tolerance and ultimately leading to T2DM.

Abstract

Oxidative stress is increased in metabolic syndrome and type 2 diabetes mellitus (T2DM) and this appears to underlie the development of cardiovascular disease, T2DM and diabetic complications. Increased oxidative stress appears to be a deleterious factor leading to

INTRODUCTION

Aerobic life uses oxygen to oxidize (metabolism) food substrates (carbon- and hydrogen-rich) to obtain the heat energy and chemical essential for life. When we oxidize molecules with oxygen, the oxygen molecule itself becomes reduced and forms intermediates.
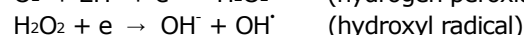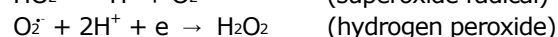
In eukaryotic cells, reactive oxygen species (ROS) are always produced as the consequence of regular physiological metabolism[1]. These ROS (pro-oxidants) productions are counter-balanced by cellular antioxidant defense mechanisms in the normal physiological conditions. ROS define as diverse chemical that have reactive properties are capable to accommodate or donate electrons (e-) to the broad range of biological molecules. Normally, the production and neutralization of ROS are balance with antioxidants in a living system and does not cause any oxidative damage, determines as physiological state[2]. The imbalance between these prooxidants and antioxidants in the living organism system to determine as oxidative stress state, brings to cellular disruption and damage[3]. The free-radical can attack polyunsaturated fatty acids oxidation in physiological systems known as lipid peroxidation. Lipid peroxidation is an autocatalytic free radical mediated destructive process whereby poly-unsaturated fatty acids in cell membranes undergo degradation to form lipid hydroperoxides[4,5]. By-products of lipid peroxidation such as conjugated dienes and malondialdehyde (MDA) are increased in the patients with obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM). Carbohydrates, lipids, proteins and DNA are the targets of oxidative stress modification biomolecules generally as the principal of ROS induced cellular damage. Therefore, these ROS modified biomolecules are used as oxidative stress markers both *in vivo* and *in vitro* measurement. Recent study suggests that ROS may act as the mechanical link of salt sensitive hypertension, over nutrition and high fat diet, metabolic syndrome and T2DM animal models[6]. ROS levels are increased in obesity, especially in abdominal obesity which is the major component of metabolic syndrome and it can be reduced by weight loss[7]. Many studies demonstrated that increased oxidative stress is associated with insulin resistance pathogenesis by insulin signals inhibition and adipokines dysregulation[8,9]. In animal studies, oxidative stress enhances insulin resistance. The evidence suggested that angiotensin Ⅱ (Ang Ⅱ) infused rats required the increased glucose load to maintain normal glucose levels during hyperinsulinemic clamp to stimulate ROS production[10]. Thus, ROS may also contribute and accelerate the insulin resistance development in insulin-targeted organs of the over nutrition and the excess salt individuals.

In the large general population studies demonstrated that insulin resistance is multifactorial[11,12] and the genetic component[11,13,14]. Insulin resistance most often precedes in many years before the onset of T2DM. Insulin resistance and the consequence of declined of insulin secretion are the principle of the T2DM pathogenesis[11,12,15,16]. The late complications of diabetes have been associated and implicated in their etiology with oxidative stress[17-19]. The influence of oxidative stress on insulin resistance, dyslipidemia, abnormal lipoprotein production and the pathophysiology of T2DM by using *in vivo*, *in vitro* and animal models data on these effects were also included in this review.

ROS

Oxygen exists in air known as oxygen molecule (O_2) or dioxygen. Oxygen on the surface of earth appeared in significant amounts approximately 2.5×10^9 years ago. It was created by the photosynthetic activity of plants and microorganisms (blue green algae). Increased atmospheric oxygen concentration was followed by the ozone layer formation in the stratosphere. Both oxygen and ozone layer were filters against the solar ultraviolet radiation reaching surface of the Earth. In eukaryotic cells, ROS is produced as the consequence of the normal aerobic physiological metabolism[1]. These ROS levels are counter-balanced with the cellular antioxidants in the normal physiological conditions. ROS define as diverse chemical that have reactive properties are capable to accommodate or donate electrons (e-) to the broad range of biological molecules. These species includeinstability radicals arise from an unpaired e-. Existence of the presence of oxygen and the aerobic organisms on the earth is possible[20].

$$O_2 + e + H^+ \rightarrow HO_2^{\cdot} \quad \text{(hydroperoxyl radical)}$$
$$HO_2^{\cdot} \rightarrow H^+ + O_2^{\cdot-} \quad \text{(superoxide radical)}$$
$$O_2^{\cdot-} + 2H^+ + e \rightarrow H_2O_2 \quad \text{(hydrogen peroxide)}$$
$$H_2O_2 + e \rightarrow OH^- + OH^{\cdot} \quad \text{(hydroxyl radical)}$$

However, these molecules are also played an adverse role in the biological systems as oxidative stress. At the steady state of the living systems, oxygen metabolism always produce oxygen-derived free radicals such as superoxide $O_2^{\cdot-}$, hydroxyl $OH^{\cdot}$, alkoxyl $RO^{\cdot}$, peroxyl $RO_2^{\cdot}$, peroxynitrite $ONOO^-$ and oxygen-derived non-radicals such as hydrogen peroxide H_2O_2, hypochlorous acid $HOCl$ and hypobromous acid $HOBr$. Both free radicals and non-radicals groups are the important factors of the oxidative stress mediated cellular damages[21]. Normally, the neutralization of ROS productions by cellular antioxidant defense mechanisms are determine as the physiological state and do not cause any oxidative damage[2]. The imbalance of the ROS production and antioxidants defense system in the living systems caused oxidative stress brings to cellular function disruption and damage[3].

This imbalance occurs due to over production of ROS and reduction of the antioxidant defense mechanisms. The electron transport chain in mitochondrial, peroxisomes and cytochrome P450 system are the most important sources of ROS production (involves in $O_2^{\cdot-}$ production)[22]. Moreover, various enzymes can be accelerated ROS production such as cyclooxygenases[23,24], xanthine oxidase[25], uncoupled nitric oxide synthases (NOS)[26-28] and NADPH oxidases[29]. Drugs such as doxorubicin[30,31], cisplatin, acetaminophen[32-34] and nimesulide[35]. Heavy metals (Fe, Cd, Pb, Hg) as the toxic substances[36-39], acrolein, chloroform, carbon tetrachloride[40], tertiary butyl hydroperoxide[41-44], environmental pollutants (oxides of
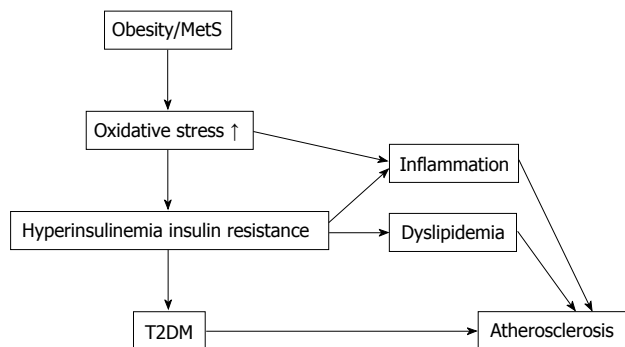
Figure 1 Summarized of obesity and metabolic syndrome elevate in oxidative stress. T2DM: Type 2 diabetes mellitus; MetS: Metabolic syndrome.

Figure 2 Increased oxidative stress by xanthine oxidase. NADH: Nicotinamide adenine dinucleotide.

nitrogen, SO_2, CO_2), xenobiotics, UV irradiation and the other factors induce ROS overproduction.

In metabolic disorders assist the increased ROS production in the physiological system such as obesity, insulin resistance and diabetes mellitus[45-48]. In Figure 1 summarized of obesity and metabolic syndrome elevate in oxidative stress. Superoxide radical ($O_2^{\cdot-}$), hydroxyl radical (OH•) and hydrogen peroxide (H_2O_2) are the three major ROS in physiological organisms[49]. Superoxide radical ($O_2^{\cdot-}$) acts as the parent ROS molecules caused from the one electron reduction of oxygen molecule by electron transport chain enzymes in mitochondrial such as enzymes in cytochrome P450, cyclooxygenase and NADPH oxidase. Various reactions of enzymes and non-enzymes system further convert these ROS molecules to hydroxyl radical (OH•), peroxynitrite ion ($ONOO^-$) and hyperchlorous acid (HOCl). For example superoxide dismutase converts $O_2^{\cdot-}$ to H_2O_2 by the dismutase reaction[50,51].

Elevated ROS molecules caused the cellular macromolecules damage such as lipids[52], proteins[53] and nucleic acids[54]. In the anti-oxidants system of the living system, possess own antioxidant defense mechanisms[55] includes enzymes and non-enzyme molecules such as SOD, catalase (CAT) and glutathione peroxidases (GPx). Enzyme SOD catalyzes $O_2^{\cdot-}$ conversion to H_2O_2, while CAT converts H_2O_2 to H_2O and O_2. For reduction of two peroxide molecules use non-enzymatic glutathione (GSH; reduced and oxidized forms), reduced glutathione (GSH) and GPx catalyze to produce oxidized glutathione (GSSG) and water[56]. Various enzymes play the important combination roles in the series of antioxidant defense systems such as glutathione reductase, glutathione S-transferase, and glutathione disulfide (GSSG).

ROS production is identified as endogenous and exogenous source. UV exposure and xenobiotic agents has been shown to generate these ROS[57]. In fact, dietary is the major source of these oxidant compounds, especially in animal fat as the source of high lipid peroxides[58]. ROS may also be derived from the general biochemical reactions in living organism to generate ROS as by-products or end products. In the transition heavy metals such as iron (Fe^{2+}) and copper (Cu^+) are pose the oxidative stress production, especially in
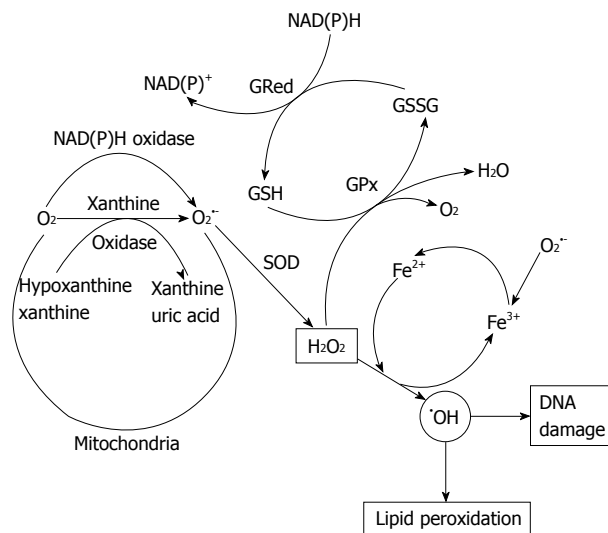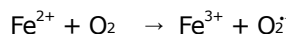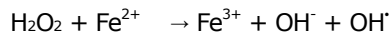
Fe^{2+} may cause autooxidation to cause $O_2^{\cdot-}$ generation and/or interaction with H_2O_2 can generate OH• via the Fenton and Harber Weiss reactions[59]. Fenton chemical reaction may also causes lipid peroxides generation and propagation[60].

Auto oxidation of Fe^{2+}:

$$Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2^-$$

Fenton reaction:

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^- + OH^{\cdot}$$

Haber-Weiss reaction:

$$H_2O_2 + O_2^- \xrightarrow{Fe} O_2 + OH^- + OH^{\cdot}$$
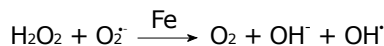
The major cellular oxidative stress is come from mitochondrial respiration. Heart, brain, kidney, liver and skeletal muscle are the effective oxygen consumption organs is converted oxygen to $O_2^{\cdot-}$, approximate releasing 0.1%-0.2% while the liver is converted oxygen to $O_2^{\cdot-}$, approximately releasing 2%[61]. Electron transport chain complex of the mitochondrial has been sourced to $O_2^{\cdot-}$ generation and have been estimated upto 107 ROS molecules per mitochondria per day[62].

In the enzymatic systems of xanthine oxidase generated via xanthine dehydrogenase, which utilize oxygen molecule as e- acceptor during catabolism of xanthine. Xanthine oxidase is the generator of $O_2^{\cdot-}$, H_2O_2[63] and OH• producer[64], highly expressed in epithelial, injured and diseased tissues as shown in Figure 2. Xanthine oxidase has been involved to peroxynitrite ($OONO^-$) and nitric oxide (NO) productions through nitrite reduction[65,66]. Intracellular nitric oxide synthases (NOS) catalyze L-arginine to form citrulline and NO. Endothelial NOS and neuronal NOS are activated by calcium-induced calmodulin binding to produce NO levels[67]. Inducible NOS (iNOS) has also calmodulin bound molecule. It may rapid and chronic expression in many cell types such as smooth muscle cells, hepatocytes and macrophages. INOS is induced by the many inflammatory cytokines

Fatty acid with 3 double bond

RH   Hydrogen abstraction

$H^{\cdot}$

$R^{\cdot}$ Conjugated diene with UV absorbance at 234 nm

Molecular rearrangement

$R^{\cdot}$ Peroxylradical: abstracted H^+ from another fatty acid causing an autocatalytic chain reaction
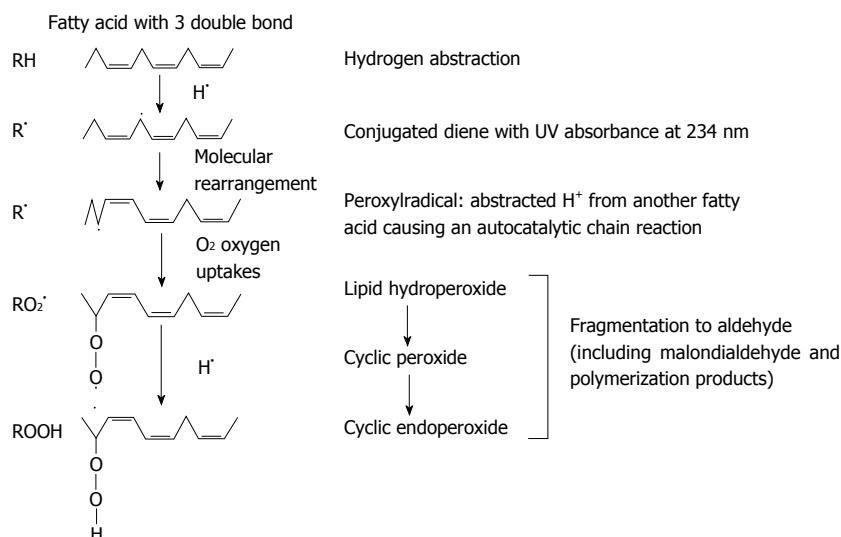
O_2 oxygen uptakes

$RO_2^{\cdot}$ Lipid hydroperoxide

O
O
$H^{\cdot}$ Cyclic peroxide   Fragmentation to aldehyde (including malondialdehyde and polymerization products)

ROOH   Cyclic endoperoxide

O
O
H

Figure 3 The chain reaction of lipid peroxidation.

[tumor necrosis factor-α (TNF-α), interleukin-6 and growth factors] regulation at the transcriptional level, results in micromolar NO production[67]. INOS can poduce $O_2^{\cdot-}$ and OONO$^-$ when lower in L-arginine substrate[68].

LIPID PEROXIDATION

Fats and oils oxidized with characteristic changes in texture, color, taste and odor. This process, known as rancidity, was chemically defined in the 1940s as an autoxidative free-radical chain reaction[69]. The most powerful oxidant formed in biological systems is hydroxyl radical. It can attack any biological molecule. The initiation step of lipid peroxidation occurred when hydroxyl radicals attack to polyunsaturated fatty acids, to cause the free-radical polyunsaturated fatty acids oxidation in biological systems. Lipid peroxidation is autocatalytic lipid hydroperoxides radical production mediated poly-unsaturated fatty acids in cell membranes destruction and degradation process[4,5]. Conjugated dienes and MDA, by-products of lipid peroxidation are increased in the circulation of obesity, metabolic syndrome and T2DM patients.

First-peroxidation chain initiation, results from the attack by any species to reduce a hydrogen atom from methylene (-CH₂-) group of polyunsaturated fatty acid or membrane. Because one hydrogen atom contains one electron, reduction leaves an unpaired electron on the carbon of -CH-, double bond in the fatty acid weakens the C-H bonds on the carbon atom adjacent to the other double bond and facilitates it removal. Then, the polyunsaturated fattyacid chains in lipids membrane are sensitive to cause lipid peroxidation. The carbon-centered radical forms a conjugated diene by the molecular rearrangement (Figure 3), which combines with oxygen to form a peroxyl radical that able to reduce a hydrogen atom from another fatty acid to start a chain reaction. Peroxidation continues to use up the polyunsaturated fatty acid substrate unless

the chain-breaking antioxidant (vitamin E) agent is added to terminate the chain reaction. The three stages of lipid peroxidation are initiation, propagation and termination. Hydroxyl radical ($^{\cdot}$OH), alkoxyl radical (RO$^{\cdot}$), peroxyl radical (ROO$^{\cdot}$), and HO$_2^{\cdot}$ species can abstract the first hydrogen atom of polyunsaturated fatty acid but not H_2O_2 or $O_2^{\cdot-}$[70]. Variety of lipid hydroperoxides and cyclic peroxides are the end products of the chain reaction. Lipid peroxides are stable molecules in the physiological temperatures. Lipid peroxides decomposition is catalyzed by transition heavy metals. For example, iron ion-active complexes present in circulating can participate in the Fenton reaction to promote lipid peroxide decomposition. Hemoglobin and the cytochromes molecules can also facilitate peroxide decomposition, although they do not directly catalyze Fenton chemistry. However, hemeproteins can release chelatable iron that can participate in Fenton chemistry[71]. Ferritin and hemosiderin are effective at stimulating lipid peroxidation and catalase is weakly effective, caused problems to use catalase as a probe for H_2O_2 in lipid peroxidation systems[72].

Reduced heavy metal [Fe^{+2}, Cu$^+$] react with lipid peroxides (LOOH) to alkoxyl radical or Cu$^+$ react with LOOH to alkoxyl radical.

$$LOOH + M^{n+} \rightarrow LO^{\cdot} + M^{(n+1)+} + OH^-$$

In the reaction oxidized-heavy metals [Fe^{+3}, Cu^{+2}] slowly react with LOOH to produce alkoxyl and peroxyl radicals. Both peroxyl and alkoxyl radicals initiate the chain reaction by reducing hydrogen atoms (Figure 3). The fixed oxidation metals ions can affect the rate of lipid peroxidation (Ca^{2+}, Pb^{2+} and Al^{3+} ions). Lipid peroxidation accelerates by the iron salts stimulation result in the membrane structure changes and important implications for environmental toxicology[73].

Rawls et al[74] demonstrated that singlet O$_2^{\cdot}$ is formed during the lipid peroxidation degradation and might contribute to cause more initiation in the chain

reaction. Initiation in the first-chain initiation should be used as lipid peroxide decomposition reactions to start the new chain reaction. Iron ions and ferrous ions are free radicals[55], can act in electron transfer reactions with oxygen molecule. Then, the presence of iron ions can promote the hydroxyl radicals formation by Fenton reaction. Bielski et al[75] demonstrated that the ·OH radical production in any source can initiate lipid peroxidation reaction.

$$LH + OH^\cdot \rightarrow L^\cdot + H_2O$$
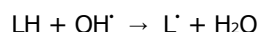
Superoxide-dependent Fenton reaction (superoxide resulting H_2O_2 and reducing Fe^{3+} to Fe^{2+}) did not demonstrate any substantial involvement of the hydroxyl radical in liposomal peroxidation systems as detected by the scavengers action[76]. Hydroxyl radicals in the systems can be measured by spin trapping[77] or deoxyribose degradation measurements[76] but do not contribute to the lipid peroxidation rate[76]. The addition of iron ion in any preparations can stimulate peroxidation reaction by lipid hydroperoxide degradation to generate peroxyl ($LO_2^\cdot$) and alkoxyl ($LO^\cdot$) radicals.

$$2LOOH \xrightarrow[\text{complexes}]{Fe} LO^\cdot + LO_2^\cdot + H_2O$$
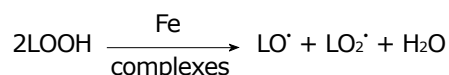
The rate constant of the reaction when ferrous ions are reacted as 1.5×10^3 /mol/L per second[78], which is higher than the rate reaction constant of ferrous ions with H_2O_2 reaction (76 /mol/L per second)[79]. The iron ions stimulate lipid peroxidation by the lipid degradation reactions from the present of abundant hydroperoxide.

Iron or copper in a biological system attach to biological molecules at the specific location of OH radicals formation to cause lipid, protein and DNA damage. On lipid membrane, the propagation step of lipid peroxidation reactions does not proceedes further until the reaction reach the protein portion. Thus, lipid peroxidation *in vivo* causes proteins membrane damage[80,81]. This damage has more biologically important than those lipids membrane damage. Cells also contain mechanisms for recognizing and removing oxidative modified proteins[80,81].

OXIDATIVE STRESS

Oxidative stress occurs at the molecular level as the cellular event when increased ROS overwhelm the antioxidant defense capabilities systems. Oxidative stress was defines as the increasing ROS production, vary in intensities, the different cellular locations and may be occurred either acutely or chronically[82]. Oxidative damage to macromolecules including carbohydrates, proteins, lipids and DNA typically viewed as increased ROS induced cellular damage to cause the irreversible macromolecules modifications. Therefore, the by-products of these oxidative modified biomolecules are used as oxidative stress biomarkers *in vivo* and *in vitro*. Many research studies demonstrated the association of oxidative stress and the pathogenesis

of insulin resistance *via* insulin signals inhibition and adipocytokines dysregulation[8,9]. Oxidative stress biomarkers included MDA[83], 4-hydroxy-2-nonenal and isoprostanes species[84], protein carbonyls, 3-nitrotyrosine, hydroperoxides, protein oxidation products[85], glycation end products, carbohydrate modifications[86] and 8-hydroxy-2′-deoxyguanosine (8-OH-dG), an oxidized DNA product[84].

Assaying lipid peroxidation
The lipid peroxidation contributes to the pathogenesis of atherosclerosis. It is occurred in the blood vessel walls and does not occur from low density lipoproteins (LDL) in circulation[87,88]. LDL can enter to the blood vessel walls. The modified LDL (oxidized LDL) may escape from the scavenger recognition receptors and back to the circulation. Therefore, this circulating LDL peroxidation is a potentially useful biomarker of lipid peroxidation in circulation. Indeed, this assay is used for the demonstration of *in vivo* antioxidants inhibit the effects of lipid peroxidation[89,90].

Thiobarbituric acid-reactive substance
MDA from the oxidative polyunsaturated fatty acids (PUFA) degradation is determined by the reaction of thiobarbituric acid (TBA) with MDA to generate the stable end product of MDA-TBA adduct[91-95]. This MDA free radical has been demonstrated as a causative of the atherosclerosis pathogenesis[96,97], aging[98], cancer[99] and Alzheimer's disease[100,101]. Serum MDA levels have been used as the lipid peroxidation biomarker and indicator of free radical damage[37,83,102]. MDA, the three-carbon dialdehyde, can exist in many forms in the aqueous circulation. This method was used the reaction of MDA with TBA and heated under acidic conditions but the TBA can react with many chemical species such as proteins, phospholipids, aldehydes, amino acid and nucleic acids[103,104]. One MDA molecule reacts with TBA two molecules to form a stable pink to red chromophore that absorbs maximally at 532 nm[105] or fluorescence detection. This chromophore is termed thiobarbituric acid reacting substances. Elevated MDA levels in T2DM patients are associated with cardiovascular disease risk[83].

Isoprostanes
The most valuable of lipid peroxidation biomarker in the biological system is the isoprostanes, elevated from the PUFA peroxidation[106-113]. Isoprostanes identified as free form and the most are esterified to lipids in circulation. Isoprostanes can be analyzed by mass spectrometry techniques, so that can easily be detected in human body fluids[108,109,112,113]. Isoprostanes appear to turn over rapidly in metabolized and excreted[108,109]. Isoprostanes and their metabolites detection in urine may be the useful biomarker for lipid peroxidation[113]. Isoprostanes assay have focused on the F_2-isoprostanes measurement, which elevate from the arachidonic acid peroxidation[109]. Elevation of F_2-isoprostanes levels have
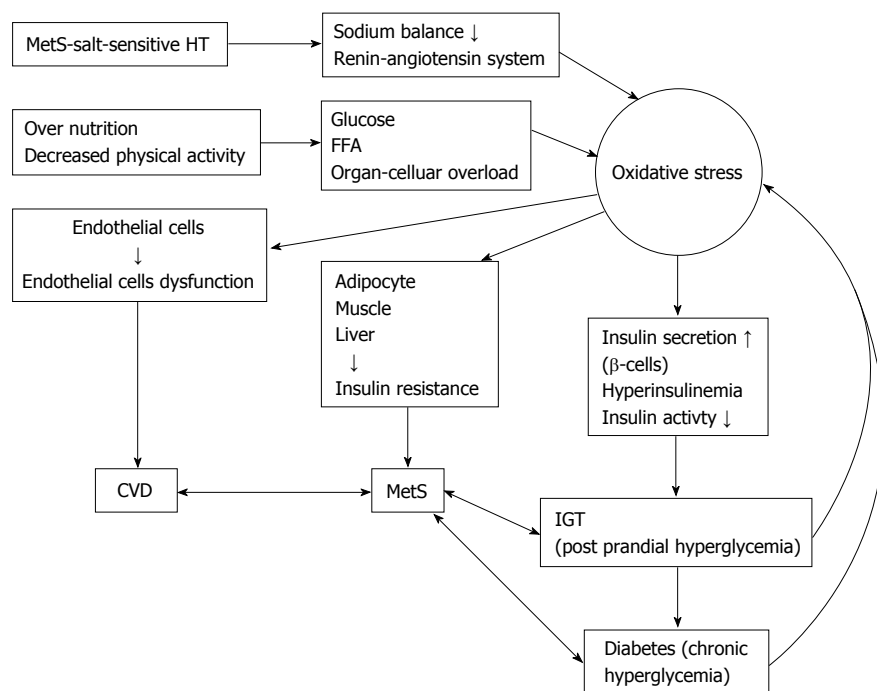
Figure 4 Summarized the increasing reactive oxygen species in obesity, metabolic syndrome and salt sensitive hypertension. FFA: Free fatty acid; MetS: Metabolic syndrome; HT: Hypertension; IGT: Impaired glucose tolerance.

been shown in conditions of the cardiovascular disease, diabetes development[114,115], cigarette smoking[111,116,117], hyperhomocysteinaemia[118] and hypercholesterolaemia[110,119]. F2-isoprostane levels have also been shown to decrease by antioxidants supplementation both in animal models and humans subjects[120-124].

Oxidative stress in metabolic syndrome
The components of metabolic syndrome consist with abdominal obesity, dyslipidemia, hypertension and diabetes[125,126]. It is the major modern lifestyle complication cause from physical inactivity and overeating and associated with the increased risk of cardiovascular diseases, hypertension and T2DM that summarized in Figure 4.

Over nutrition and oxidative stress: In metabolism of glucose through glycolysis and tricarboxylic acid (TCA) cycle to generate nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2) as the electron donors. In over nutrition, the excessive glucose occur and a large amount of glucose is oxidized in the glycolysis and TCA cycle to increase NADH and FADH2 generation in electron transport chain of mitochondrial and increased superoxide generation[127]. The excessive of free fatty acids (FFAs) leads to increase FFA-oxidation and acetyl coenzyme A (CoA) oxidation in TCA cycle generate the NADH and FADH2 electron donors as glucose oxidation results in mitochondrial ROS overproduction[127]. Furthermore, NADPH oxidase in the plasma membrane can convert oxygen molecule to superoxide radical and involve in ROS nutrient-based generation. In adipocytes, ROS is generated by in fused

with FFAs, treatment with NADPH oxidase inhibitor can block this ROS generation. This indicates that NADPH oxidase involves in fatty acids ROS generation[8]. Palmitate can activate diacylglycerol synthesis and protein kinase C (PKC) leading to activate NADPH oxidase[128]. Thus, over accumulated fat result in the increased fatty acids oxidation and lead to activate NADPH oxidase (in local or remotely cells) to cause ROS over production in over nutrition or obesity (Figure 4). Conversely, calorie restriction may be associated with normal physiological system[129] and may involve in normal cellular redox state[130]. In aged animals models treated with antioxidant agents or hypocaloric diets led to ameliorate in oxidative stress status and tissue function[131,132]. Treatment with resveratrol, a polyphenol reduced atherosclerosis and diabetes development[133]. These studies demonstrate that nutrition is associated with increased or decreased redox status and over nutrition result to increase oxidative stress to contribute pathogenesis of atherosclerosis, cancer and other diseases.

Oxidative stress in adipose tissue: Increased fat accumulation in human has been associated with oxidative stress biomarkers[134]. Similarly, obese mice were significantly higher oxidative stress levels in circulation[8]. Moreover, lipid peroxidation and H2O2 levels were increased in adipose tissue[8]. These mean that adipose tissue may the major source of ROS production and can be released to the circulation potentially affecting various distance organs functions and damage (Figure 4).

Increased NADPH oxidase expression in adipose

tissue associated with increased oxidative stress levels. Increased mRNA expression was found in adipose tissue of obese mice[8]. Increased ROS generation in lipid accumulation and further elevating ROS generation with FFA treatment were found in 3T3-L1 adipocytes cultured[8]. These ROS generation processes can be blocked by NADPH oxidase inhibitors, apocynin or diphenyleneiodonium. Many studies suggest that NADPH oxidase induces adipocytes ROS production[8]. Moreover, obese mice ameliorated hyperinsulinemia, hypertriglyceridemia, hyperglycemia and hepatic steatosis by supplementation with apocynin[8]. These data demonstrate that NADPH oxidase increase ROS production in obesity and metabolic syndrome may play the important roles in the atherosclerosis, T2DM and cancer pathogenesis. Adipose tissue tries to increase antioxidant enzymes levels to against ROS over production. However, these antioxidant enzymes activity and expression are decreased in adipose tissue[8,135-137]. Then, increased ROS-production enzymes and decreased antioxidant enzymes may cause oxidative stress in obese and metabolic syndrome.

Oxidative stress and salt-sensitive hypertension:
As in mention above, ROS levels are increased in obesity and can be ameliorated by weight loss[7]. Obese rats induced by refined sugar or high fat diet leading to ROS overproduction and increase oxidative stress[6,138]. Many research evidences suggest that metabolic syndrome was associated with the salt-sensitive hypertension. ROS play the roles as mechanical link of metabolic syndrome and salt-sensitive hypertension[125,126], which itself leads to ROS overproduction[139-142]. Salt restriction in hypertensive obesity was more effective reduction in blood pressure than in hypertensive non-obesity patients, and weight loss in obesity and salt sensitive hypertensive patients caused the successful of blood pressure reduction[143]. Salt-sensitive hypertensive patients were significantly more prevalent in metabolic syndrome patients than without metabolic syndrome[144]. Oxidative stress in abdominal adipocytes due to increase adipocytokines secretion such as TNF-α, angiotensinogen, non-esterified fatty acids[126]. Interestingly, infused Ang II-rats disturbed sodium balance to cause ROS overproduction in salt-sensitive rats[139-141]. Moreover, in salt-sensitive hypertensive patients are also increased 8-isoprostane levels[142]. Thus, ROS may the underling pathogenesis of diseases in metabolic syndrome, obese and non-obese intake excessive salt as the salt-sensitive hypertensive patients.

In high-renin patients (non-modulating salt sensitive hypertension) had elevated the homeostasis model assessment of insulin resistance (HOMA-IR) levels[145]. Insalt-sensitive hypertensive non-obesity patients had significantly lower insulin sensitivity than in non-salt-sensitive hypertensive patients[146]. Insulin resistance caused salt-sensitive hypertensive obesity and/or metabolic syndrome patients[125]. Increased renal ROS overproduction may increase the salt sensitive hypertension[147]. Then, increased renal oxidative stress may contribute to cause salt-sensitive hypertension development. Moreover, ROS overproduction in vascular endothelial cells suppresses the NO-dependent vaso-dilation[148] and may play the role in the salt-sensitive hypertension development.

Oxidative stress in type 2 diabetes
Many research studies demonstrated that T2DM patients have increased ROS production-induced higher oxidative damage in the circulation and also have reduced antioxidant defenses mechanisms[149-152]. Increased ROS production in T2DM patients is thought to activate many detrimental pathways including hexosamine pathways, advanced glycation end-products (AGEs) formation, and PKCβ1/2[127]. Hyperglycemia condition can induce oxidative stress by several mechanisms such as glucose autoxidation, polyol pathway, AGE formation and PKCβ1/2 kinase. Elevated free fatty acids, leptin and other circulating factors in T2DM patients may also contribute to cause ROS overproduction. Figure 5 demonstrates the association of increased ROS production with atherosclerosis and sources of ROS generations in T2DM patients.

Glucose autoxidation
Hyperglycemia due to cause increased glucose metabolism leading to increase NADH and FADH$_2$ overproduction, which are used by the electron transport chain of mitochondria to generate ATP[153]. NADH overproduction can cause the higher proton gradient production in mitochondria. These electrons are transferred to oxygen to produce higher superoxide[154]. The NADH dehydrogenase of the complex I ubiquinone oxidoreductase and complex III cytochrome c reductase are the two main site of superoxide production *via* the electron transport chain[155].

The polyol pathway
Oxidative stress increased in circulation of T2DM patients from the polyol pathway. ROS was generated by two enzymes: (1) Aldose reductase in the reaction use NADPH to change glucose to sorbitol. Sorbitol production is a minor reaction in normal physiological conditions. However, 30%-35% of glucose in T2DM conditions is metabolized by polyol pathway[156]. In the condition of sorbitol overproduction, the availability of NADPH is reduced this reflect to reduce glutathione regeneration and NOS synthase activity to cause increased oxidative stress[153]; and (2) Sorbitol dehydrogenase in the second step oxidizes sorbitol to fructose concomitant with NADH overproduction. Increased NADH may be used by NADH oxidases to increase superoxide production[157] include in mitochondrial over superoxide production.

PKCβ1/2
Many structures and biochemical components changed in the circulation of T2DM patients were caused from PKCβ1/2 activation *via* diacylglycerol leading to cause dysfunction in endothelial contractility and permeability,
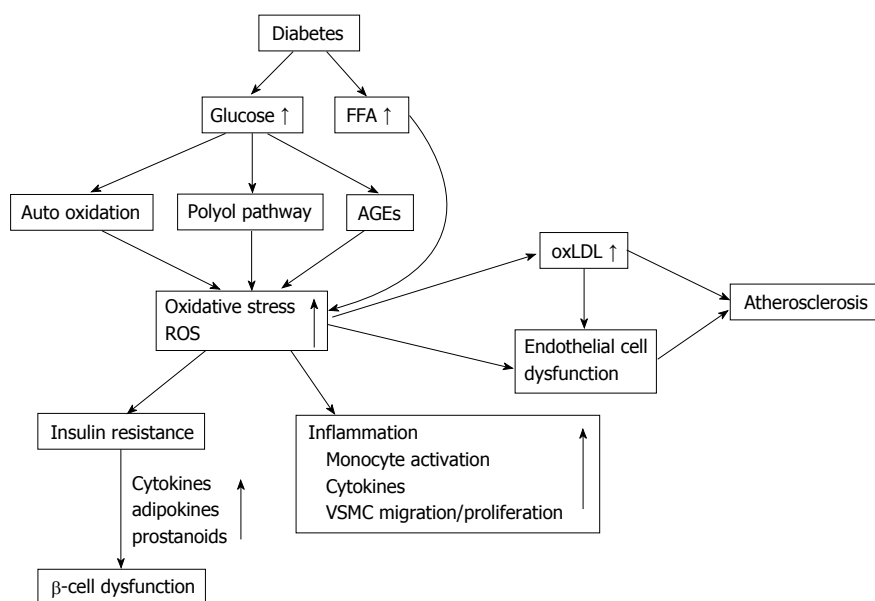
Figure 5 Summarizes the reactive oxygen species associations with atherosclerosis and sources of reactive oxygen species production in type 2 diabetes. oxLDL: Oxidized low density lipoprotein; FFA: Free fatty acids; AGEs: Advanced glycation end-products; VSMC: Vascular smooth muscle cells; ROS: Reactive oxygen species.

hemodynamics (retinal blood flow) changes, extracellular matrix protein synthesis, VEGF production and intracellular signaling in the vascular[128,158,159].

Non-enzymatic glycation

Glycation end-product is the binding of ketone or aldehyde groups of glucose with the free amino groups of proteins leading Schiff bases formation without enzymes, then to form the Amadori product and rearrangements of the structure to the irreversible AGEs in the final[160,161]. AGEs has been demonstrated in atherosclerotic lesions and their tissue of T2DM patients and increased AGEs levels associated with severity of the diseases[162]. Moreover, binding of AGEs to specific cell surface receptor for AGE can activate intracellular redox signaling and subsequent to activate the expression of redox-sensitive transcription factors and inflammatory mediator[163-165].

Inflammation

Oxidative stress is the major factor underlying in the CVD, insulin resistance and T2DM pathogenesis. These may explain by the presence of the inflammation conditions. Now, inflammation recognized as the one manifestation of oxidative stress[166] and can be generate the inflammatory mediators including adhesion molecules and interleukins to induce oxidative stress[166]. The concept of atherosclerosis is an inflammatory disease now well established. This chronic inflammation may be involved in the insulin resistance and T2DM pathogenesis[167]. Recent clinical research indicates that sub-clinical inflammation may impact in the development and progression of diabetic complications[165,168]. Moreover, excessive FFA and glucose induce inflammation effect through oxidative stress and reduced antioxidants[169]. Interestingly, the subclinical pro-inflammatory state

observed in many pathogenesis conditions such as atherosclerosis, aging, T2DM and cancer, is caused from mitochondrial ROS overgeneration[170].

Other sources of oxidative stress in diabetes

Non-esterified FFAs are elevated in T2DM patients[171]. These excessive FFAs enter the citric acid cycle to generate acetyl-CoA to receive NADH overproduction to cause mitochondrial superoxide over production. In humans, infused FFA has been shown increased lipid peroxidation by elevated isoprostanes marker levels[172,173]. Adipocytokine, leptin is secreted from the adipocytes to act on the central nervous system to decrease food intake. It reflects all effects on the vascular smooth muscle cells, endothelial cells, macrophages and monocytes[174]. Leptin levels are increased and associated with cardiovascular disease in T2DM patients[175-177]. In culture of endothelial cells incubated with leptin to cause ROS production[178,179].

Antioxidants

Regulation of the cellular redox status is depends on the rate of ROS counterbalance and elimination from the enzymatic and/or non-enzymatic antioxidants. Superoxide is converted by SOD to H_2O_2 and O_2 molecule. There are 3 isoforms of SOD such as cytosolic Cu/Zn SOD (SOD1), mitochondrial Mn-SOD (SOD2) and extracellular SOD (SOD3). Catalase, the heme metalloenzyme is expressed in peroxisomes, mitochondria, cytoplasm and nucleus. H_2O_2 is catalyzed by catalase to oxygen and water[180]. While glutathione peroxidase the selenoprotein, was found in both intracellular and extracellular. Glutathione peroxidase has a highly sensitive function for lipid peroxides degradation, converses H_2O_2 to water by using the thiol group of glutathione[181]. Their H_2O_2

detoxification plays the important roles to prevent lipid peroxidation production and regulation of the cellular redox status[182]. The glutathione system, thioredoxin peroxidase is key enzyme to regulate the cellular levels of thiol/disulfide while the production of antioxidant enzymes is regulated by the redox-cellular transcription factors[183]. For example, the expressed transcription factor NF-E2 related factor in the cytosolic is interrupted binding with Keap-1 as the responsible to increase oxidative stress and translocate to the nucleus for initiation of the transcription of the various antioxidant enzymes[184] as the strategy to develop many class of antioxidant, anti-inflammatory, and anticancer agents. Reduction in non-enzymatic antioxidants, thiol glutathione and thioredoxin are the major dysregulation of the cellular redox status[185]. The cellular redox status is reflected by the reduction of glutathione (GSH), oxidized glutathione (GSSG) ratio (or GSH:GSSG ratio), ascorbic acid, tocopherols and methionine and cysteine amino acids. Exogenous herbal antioxidants compounds in dietary foods include flavanoids, anthocyanins and polyphenolics act as ROS scavenging[186,187]. The direct interaction of ROS with non-enzymatic antioxidants is based on chemical structure properties. In free radicals participate in 1e- oxidation while non-radical species was 2e- oxidation. For example, $O_2^{\cdot-}$ and OH• radicals react with the ascorbic acid and thiols. While the OH• more activity and instability react with methionine and tocopherols. H_2O_2 and the non-radical may react with thiols and methionine, and the $OONO^-$ discriminate to react with thiols, ascorbic acid, tocopherols and methionine[188].

Oxidative stress induces insulin resistance

Oxidative stress plays the major role in the association with the insulin resistance pathogenesis by insulin signals disruption and adipocytokines dysregulation[8,9]. In rat models, oxidative stress enhances insulin resistance. The evidence suggested that Ang Ⅱ infused rats required the increased glucose infusion to maintain euglycemia during hyperinsulinemic clamp to stimulate ROS production[10]. For this example, Ang Ⅱ-infused rats were caused insulin resistance from the suppression on insulin-induced glucose uptake in skeletal muscle and increased in oxidative stress biomarkers in this animal experiment. In experimental model, superoxide dismutase and tempol can reduce the insulin resistance. Many evidences indicated that ROS overproduction may induce insulin resistance and confirmed by the supplementation of antioxidant tempol to cause insulin resistance amelioration in Ren-2 transgenic rats[189]. Insulin-target organs of the obese and diabetic KKAy mice were stimulated and caused ROS over production (skeletal muscle, liver and adipose tissue)[8] and to cause insulin resistance in these organs. High fat-fed mice found ROS overproduction in liver and adipose tissue of these obese mices to induce insulin resistance[190]. Many research studies suggested that antioxidant agents decreased plasma insulin, glucose, triglycerides levels and ameliorate insulin resistance in KKAy mice

with no weight loss[8]. Antioxidant coenzyme Q10 supplementation can ameliorate the increased insulin levels in circulation of SHR/cp rats[191]. As mention above, in over nutrition, the excessive glucose occur and a large amount of glucose is metabolized in the glycolysis and TCA cycle leading to increased NADH and FADH2 production in electron transport chain of mitochondrial and increased superoxide production[127]. In aged animals models treated with antioxidant agents or hypocaloric diets led to ameliorate in oxidative stress status and tissue function[131,132].

Insulin resistance

In general population, insulin resistance precede in many years before onset of T2DM and it is also multi-factorial[11,12] such as genetic component[11,13]. Insulin resistance and reduction in insulin production are the major characteristics of the T2DM pathogenesis[11,12,14-16]. Modern lifestyle, physical inactivity, abdominal obesity and excessive of adipokines can cause insulin resistance[11,15]. In early stage, normal glucose tolerance is preserved by compensation hyperinsulinemia. About 25% of non-diabetic subject cause insulin resistance in the same ranges that found in T2DM patients[12]. Insulin resistance continuous increases and/or decreases in insulin secretory compensation responses, the deterioration into impaired glucose tolerance occurred. Increased glucose, FFA and insulin levels lead to ROS overproduction, increased oxidative stress and activate stress transduction factor pathways. This can cause insulin activity inhibition and secretion to accelerate the onset of T2DM as shown in Figure 6.

Oxidative stress has been demonstrated the implication and association in the late complications of diabetes mellitus[17,18] as in the schematic of Figure 5. Many studies have demonstrated ROS overproduction and increased oxidative stress to insulin resistance[192-194]. Both in vitro studies and in animal models demonstrated that α-lipoic acid (LA), antioxidant agent increase insulin sensitivity[194-196]. In clinical trials, supplementation with vitamin C, vitamin E, glutathione increases insulin sensitivity in both insulin-resistance and T2DM patients[197,198]. LA act as insulin sensitizer agent, it increased insulin sensitivity about approximately 25% and approximately 20% higher than metformin and rosiglitazone, respectively[199,200]. Oral supplementation with LA formulation for 6 wk decreased circulating fructosamine levels[201] and increase insulin sensitivity[202] in T2DM patients and the other studies have confirmed 2.5 mmol/L of LA to cause GLUT4 activation and translocation[203-205].

Because insulin resistance occurred before chronic hyperglycemia development[12], that difference from insulin resistance in the pre-diabetic state result from oxidative stress activation by increased glucose levels. However, obesity demonstrated the strong association with insulin resistance. In this regard, the mediator of oxidative stress-induced insulin resistance of the pre-diabetic state might be from the adipocyte-derived
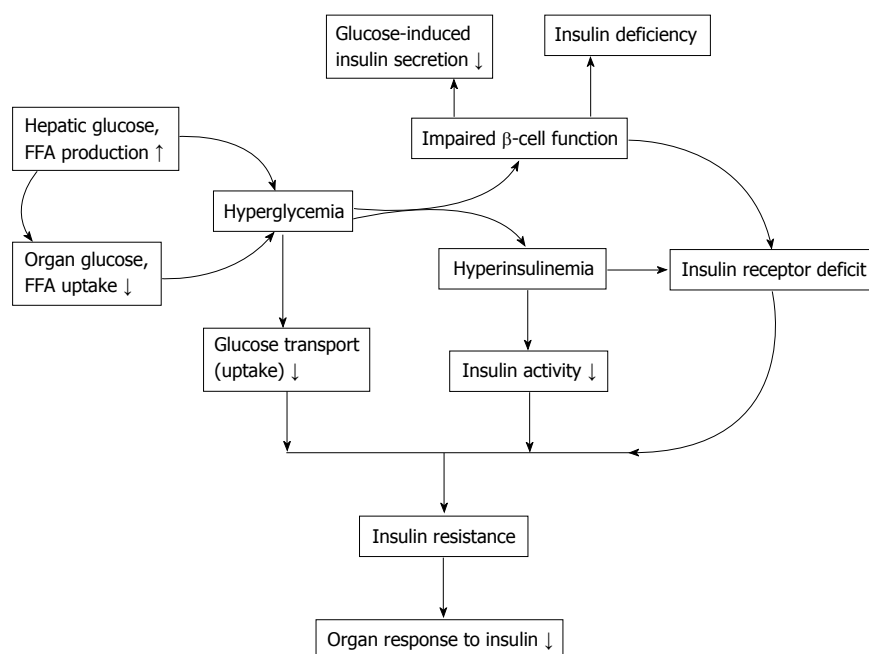
Figure 6 Insulin resistancedevelopment and consequence of β-cell dysfunction. FFA: Free fatty acid.

factor such as TNF-α[206], leptin[207], FFAs[208-210] and resistin[211]. However, the FFAs elevations are associated with insulin resistance and obesity[208,209,212]. Many studies found that increased FFA levels decrease insulin sensitivity, as in the Randle hypothesis[210] and insulin-signaling inhibition[212]. The increased fasting FFA levels are significantly correlated with decreased reduced/oxidized glutathione ratio in T2DM patients[190]. Elevated FFA concentrations cause mitochondrial dysfunction such as uncouplers of oxidative phosphorylation in mitochondria[213] and increased superoxide production[214]. These caused the exacerbated situation from FFAs induce oxidative stress and reduce intracellular glutathione caused impaired endogenous antioxidant defenses[190,215,216]. Supplementation with glutathione improves insulin sensitivity and β-cell function by the restoration of redox status in T2DM patients and healthy subjects[217].

FFA mediated the nuclear factor-κB (NF-κB) activation, as the consequence of FFAs increased ROS overproduction and glutathione reduction[216,218-220] and also linked to FFA-activated PKC-θ[221] to caused NF-κB activation[222]. Vitamin E supplementation inhibits the FFA-induced NF-κB activation[216] indicated that FFAs act as pro-inflammatory agent effects the alteration of the cellular redox status.

The HOMA-IR was proposed by Matthews *et al*[223] that can be used to estimate insulin resistance and insulin sensitivity in individuals. HOMA-IR is easy to calculate and no more laborious technique. HOMA-IR method derives from the mathematic calculation from fasting plasma insulin and glucose concentrations.

Oxidative stress and β-cells dysfunction
Increased circulating glucose levels stimulate the β-Cells

function by sensing and secreting of insulin in appropriate amount[224] and as the target of oxidative stress. The processes are complex and depend on many factors[16]. The critical glucose metabolism in mitochondrial is the importance linking stimulus the insulin secretion[224-226]. Therefore, mitochondria damage and markedly blunt insulin secretion is also occur by the ability of oxidative stress (H_2O_2)[226]. Many studies in T2DM patients have suggested that chronic exposure to high glucose and/or high FFA levels impaired β-cells function and β-cells dysfunction[16,227]. Because β-Cells are lower in antioxidant enzymes levels (superoxide dismutase, catalase and glutathione peroxidase) and higher sensitive to oxidative stress[228]. Oxidative stress exposure to β-cells activated the increased p21 cyclin-dependent kinase inhibitor production, decreased insulin mRNA, ATP and calcium flux reductions in mitochondria and cytosol to cause apoptosis[226]. Glucose or methyl succinate can stimulate insulin secretion and inhibit by response to K^+ within 30 min[226]. The results indicate that mitochondria in β-cells involved in the processes of glucose induced insulin secretion are affected by increased oxidative stress. Lipid peroxidation, oxidative stress products exposed to islets, inhibited insulin secretion and also caused glucose oxidation[229]. Conversely, antioxidants can protect β-cell against the toxicity of oxidative stress, AGEs production and inhibit NF-κB activation[230-234]. These antioxidants are N-acetyl cysteine (NAC), α-phenyl-tert butylnitrone, aminoguanidine and zinc. Recent research study evaluated β-cells function after over expression of glutamine. Hexosamine over production resulted from the deterioration of insulin signaling of glucose-stimulated insulin secretion. Fructose-6-phosphate amidotransferase is the rate-limiting enzyme increase in hexosamine pathway[235], coincident with increased

H_2O_2 production[235] that can ameliorate by NAC supplementation.

β-cells glucose-induced toxicity

West[19] demonstrated that insulin secretion in T2DM patients improved by the reduction of hyperglycemia with diet, insulin or sulfonylureas. On the other hand, in healthy normal, high glucose infused as a clamp reduces insulin secretion[236]. In the study of long term culture of HIT-T15 and/or βTC-6 cells demonstrated that increased glucose levels cause decreased insulin secretion, insulin mRNA and decreased binding of transcription factors[237,238]. Thus, glucose toxicity, the concept of the condition of hyperglycaemia itself can decrease insulin secretion which implies the irreversible damage to cellular components of β-cells[239]. Generally in β-cells, excessive glucose oxidation and metabolism will always cause to ROS over production. Superoxide dismutase and catalase are normally as the detoxified antioxidant enzymes. β-Cells are low amount of these antioxidant enzymes and also low in glutathione peroxidase, a redox-regulating enzyme[240]. Then, hyperglycaemia condition leads to increase ROS production and accumulation in β-cells and subsequent of cellular components damage. Pancreas duodenum homeobox-1 is an insulin promoter activity regulator was loss leading to β-cell dysfunction[240]. Supplementation with NAC and/or aminoguanidine can ameliorate the glucotoxic effects on insulin gene activity[230], reduced insulin levels and increased insulin mRNA and insulin sensitivity[230].

β-cells lipid-induced toxicity

Lipotoxicity to β-cells concept, elevation of non-esterified fatty acids concentrations in diabetic and non-diabetic obese patients, result of the enhanced adipocyte lipolysis. In the presence of the excessive fatty acid oxidation in β-cells is caused increased long-chain acyl CoA accumulation leading to inhibit β-cells function[241]. This process is as an integral part of the normal insulin secretory function. This long-chain acyl CoA can inhibit the insulin secretory function by opening β-cell K+-sensitive ATP channels. In the second mechanism, in long-term culture of β-cells formulas with FFAs can effect the potential reduction on mitochondrial membrane and uncoupler proteins-2 over expression to cause the K+-sensitive ATP channels opening which lead to decreased ATP production and insulin secretion[242,243]. Third mechanism, β-cells apoptosis might possess from triglyceride or fatty acid induced ceramide synthesis and/or nitric oxide production. Thus, impaired insulin secretion and β-cell dysfunction strongly associated with the FFA-stimulated ROS overproduction[244].

β-cells combined glucose/lipid toxicity

Elevation of glucose and FFA levels are the major characteristic of T2DM patients. This combination is the major β-cells toxicity and require the maximize protection. In culture cells of islets or HIT cells were exposed to high concentrations of glucose and FFA levels. There was decrease in insulin-gene activity and insulin mRNA[245]. In the study of islets co-culture with high glucose and palmitate levels caused impaired insulin signaling of the glucose-stimulated insulin secretion[244]. Recent studies have confirmed that β-cells lipotoxicity is the concurrent status as the amplifying effect mediated by glucose toxicity in hyperglycemia condition[246,247].

Dyslipidemia

Insulin resistance and T2DM are characterized by dyslipidemia one major risk factor for cardiovascular disease. Lipid triad is the complex metabolic milieu associated with dyslipidaemia[248] comprise with hyper-triglyceridemia, low levels of high-density lipoprotein cholesterol (HDL-C) and the appearance of small, dense, LDL (sdLDL) - and caused excessive post prandial lipemia[249,250]. Diabetic dyslipidemia caused from the disturbance of lipid metabolism, an early event cardiovascular complications development and was preceded in T2DM patients by several years[249-253]. Indeed, insulin resistance status in both with and without T2DM patients was display qualitatively similar lipid abnormalities[250]. The different components of diabetic dyslipidemia are closely linked to each other metabolically[249-253] and are initiated by the elevation of triglyceriderich very LDL (VLDL) from hepatic over production[249,251]. It is the key importance mechanisms to elucidate the over production of VLDL involved in diabetic dyslipidemia[249].

In insulin resistance state, decrease insulin function and lack of insulin inhibits lipolysis leads to increase FFAs generation of and lower lipoprotein lipase activity. This occurs after meal consumption, generates a chylomicron remnant rich in TG[254], caused elevated hepatic FFAs and VLDL TG-rich particles secretion. These processes affects HDL-C metabolism through the interchange with TG-rich lipoproteins via cholesteryl ester transfer protein to produce HDL particles containing high TG concentrations. These HDL-TG particles were hydrolyzed with hepatic lipase to TG and HDL. This HDL becomes smaller and less antiatherogenic activity, easily to remove from the circulation by the kidneys. Moreover, insulin resistance in T2DM patients associated with endothelial dysfunction led to increase risk of CVD[255]. The most atherogenic subfractions of sdLDL are elevated in circulation of obesity individuals, as a key feature in association with elevated triglyceride and low HDL cholesterol. Elevated sdLDL concentrations are also founded in abdominal obesity subjects and demonstrated greater myocardial risk.The mechanisms are related to excess accumulation of abdominal adipose tissues, elevated total cholesterol and LDL-C and related to high saturated-fat consumption, weight gain and obesity.

Dyslipidemia is commonly occurred in T2DM patients and might play the major role in accelerated

macrovascular atherosclerotic disease and increased CVD risk in T2DM patients[256]. Dyslipidemia in T2DM patients as lipids triad is characterized by increased insulin levels, hypertriglyceridemia, low HDL-C levels and increased sdLDL-particles (independent of LDL-cholesterol) and increased TG-rich remnant lipoprotein (TGRLs) concentrations[257,258]. In this manner, low HDL-C levels associated with hyperinsulinemia or insulin resistance and insulin signaling for insulin-mediated glucose disposal[259] characterized by higher fasting plasma glucose and insulin levels. Then, these major changes associated with the insulin resistance syndrome are increased TGRLs and decreased HDL-C levels. Thus, in dyslipidemia, using the lipoprotein concentration ratios are associated with insulin resistance and increased CVD risk conditions. Lipoprotein ratios might be useful to identify insulin resistance individuals even different in fasting glucose or insulin levels. Obesity, metabolic syndrome, and T2DM may also show the same dyslipidemia characteristic[12,257,259] and measuring TG, HDL-C, TC/HDL-C and TG/HDL-C ratio in circulation may also use as insulin resistance estimation. For example, these TG, HDL-C, TC/HDL-C and TG/HDL-C ratio are independently associated with insulin levels, insulin resistance and CVD risk[258,260,261].

Lipoprotein ratios: In description above, the major change is increased TGRLs and decreased HDL-C levels are associated with insulin resistance syndrome. Insulin plays the important role in TG metabolism, in normal condition TGRLs particles reduces synthesis by the distinct pathways when compared with VLDL particles synthesis[249,258]. Insulin fails to suppress VLDL particles synthesis[262]. Insulin resistance is significantly associated with increased lipid synthesis in the liver, increased FFAs flow to the liver and decreased VLDL particles clearance resulting in increased VLDL levels in the circulation[251]. Thus, dyslipidemia (as lipoprotein ratios) may associate with insulin resistance and increased CVD risk. On this basis, waist circumference, LDL-C, TG levels, insulin resistance and the CVD risk are estimated[263]. The major features of dyslipidemia are determined by hypertriglyceridemia, low HDL-C levels and slightly high or normal LDL-C levels with altered composition. Hypertriglyceridemia is indicate as elevated atherogenic chylomicron and VLDL remnant and associated with increased CVD risk[264,265]. These phenomenons demonstrated the problems of VLDL and HDL levels but not the LDL levels and concurrent with increased insulin levels. Low HDL-C level is associated with the hyperinsulinemia and/or insulin resistance and insulin signaling for insulin-mediated glucose disposal[259]. All of these features are associated with coronary heart disease risk in obesity, metabolic syndrome and T2DM patients. The TC/HDL-C, TG/HDL-C ratios and non-HDL-C (as TC - HDL-C) were used as surrogate markers for insulin levels and insulin resistance estimation. In Tangvarasittichai et al[258] study suggests that TC/HDL-C, TG/HDL-C ratios and non-

HDL-C can be used as markers of insulin levels, insulin resistance and CVD risk factor[258,263]. The highest % sensitivity and % specificity cut-off points corresponding to the TC/HDL-C, TG/HDL-C ratios and non-HDL-C are 3.58, 2.48 and 130.4, respectively[258]. Because of TC/HDL-C, TG/HDL-C ratios and non-HDL-C are easily calculated and ordered with every lipid profiles available to the clinician and no costs addition. The cut-off value of these ratios in Tangvarasittichai et al[258] study was lower than the results from Western populations[266-268]. Then, insulin resistance was significantly predicted by these markers. For atherosclerotic risk assessment in obesity, metabolic syndrome and T2DM patients requires more attention to lipid screening.

Development of T2DM from insulin resistance
Insulin resistance often occurs with T2DM but is insufficient for the T2DM development. β-cells dysfunction are important event for the T2DM development and progression. In early stage of insulin resistance, β-cells increase the secretory function try to compensate and control hyperglycemia. In Pima Indian population study caused acute insulin response dysfunction or decreased β-cell responses was found during the normal glucose tolerance state in individuals who eventually progressed from normal glucose tolerance to impaired glucose tolerance or T2DM when compared with individuals who persisted in the state of normal glucose tolerance[269]. There was evidence of early defects in glucose disposal by decreased insulin sensitivity before the development of glucose intolerance state, although output of circulating glucose did not increase until the progression from impaired glucose tolerance to T2DM revealed. Interestingly, individuals who demonstrated transient glucose intolerance but were able to recover and to reach normal glucose tolerance and did not show the early secretory defect observed in progressed individuals[269]. β-cells failure or dysfunction occurred as the results of the combination of increased oxidative stress, glucose and lipids accumulation to cause glucotoxicity and lipotoxicity to β-cells to progress increased apoptosis and loss of the insulin granule secretory components expression[270].

T2DM
The World Health Organization updated the prevalence of T2DM estimated by the year 2025 those 30.3 million people in the United States and total of 380 million people worldwide will be diagnosed as DM[271]. By the year 2050, those 45.6 million Americans will be diagnosed as DM[272]. T2DM is associated with obesity, sedentary lifestyle and lack of exercise in the aging population. There are a number of gene abnormalities related to T2DM, that showed significant differences exist in the abnormalities gene associated with T2DM among the various ethnic populations, such as African Americans, Asians and Europids[273,274]. The contribution of any one of these genes to T2DM is small and total

Table 1 Type 2 diabetes mellitus and glucose levels for diagnostic criteria[1]		
Glucose management test	**Range**	**Diagnosis**
Fasting plasma glucose (mg/dL) (at least 8 h fast)	≥ 126	Diabetes mellitus
	100-125	Impaired fasting glucose
	≤ 99	Normal
2-h oral glucose tolerance test of 75 g glucose load (mg/dL) WITH	≥ 200	Diabetes
Random screening with common symptoms of diabetes (polyuria, polydipsia, weight loss, *etc*.)	140-199	Impaired glucose tolerance
	≤ 139	Normal
Hemoglobin A1c (%)	≥ 6.5	Diabetes
	5.7-6.4	Prediabetes/high risk
	≤ 5.7	Normal

[1]All tests in diabetes range must be repeated after 24 h, to be confirmed diagnosis.

aggregate of all described genes accounts for < 15% of the predisposition[273,275]. It is typically diagnosed in patients older than 30 years with overweight or obesity and positive in family history of T2DM. However, insulin resistance may occur and develop in many years before diagnosed as T2DM[276]. Figure 7 summarized the etiology of the T2DM pathogenesis.

Patients are diagnosed as T2DM when plasma glucose levels reach at the diagnostic criteria (Table 1). These T2DM patients are at high risk for microvascular complications (*e.g.,* nephropathy, retinopathy and neuropathy) and macrovascular complications (*e.g.,* peripheral vascular disease, cerebrovascular disease and cardiovascular disease). T2DM patients with good controlled plasma glucose levels demonstrated to delay the progression of microvascular and macrovascular complications[271,277].

MANAGEMENT OF DYSLIPIDEMIA AND HYPERGLYCEMIA IN T2DM PATIENTS

Fasting serum lipids profile should be determined annually in T2DM patients as in the recommendation by the American Diabetes Association (ADA)[278]. ADA recommended for the satisfied lipids profile level as low-risk by LDL-C < 100 mg/dL (2.6 mmol/L), triglycerides < 150 mg/dL (1.7 mmol/L) and HDL-C > 50 mg/dL (1.3 mmol/L)[276].

Treatment
Lifestyle interventions: The American Diabetes Association and the American Heart Association recommend that increased physical activity and lifestyle modifications should be advised for all T2DM patients[278,279]. Combination with such interventions included nutrition therapy or supplementation, weight loss and non-smoking. These have been help T2DM patients to receive better controlled their lipid concentrations. Nutrition interventions and supplementations should be designed according to the condition of T2DM individuals such as diabetes status,
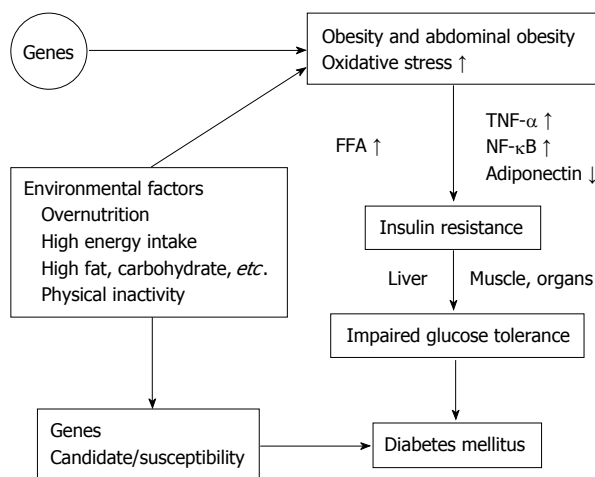

Figure 7 Summarized the etiology of the type 2 diabetes mellitus pathogenesis. FFA: Free fatty acid; NF-κB: Nuclear factor-κB; TNF-α: Tumor necrosis factor α.

age, other comorbidities and avoidance to intake transfat, saturated fat, cholesterol and should increase intake of fiber (fiber in oats, legumes, citrus), omega-3 fatty acids and plant stanols/sterols[278]. Glycemic control can also modify circulating triglycerides levels, especially in T2DM patients with hypertriglyceridemia and poor glycemic control[278].

Pharmacological interventions of dyslipidemia
There are many pharmacological classes available for dyslipidemia treatment.

Statins: Statins inhibit enzyme 3-hydroxy-3-methyl-glutaryl CoA reductase suppress cholesterol synthesis and increase number and activity of LDL-receptor. Statins are effective drug for lowering LDL-cholesterol, raising HDL-C and reducing TG levels. There are seven pharmaceutical forms of statins including lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin available in the market. Statins also have the other pharmacodynamic actions such as vascular inflammation reduction, immune suppression, improved endothelial function, platelet aggregability, enhanced fibrinolysis, antithrombotic action, increase neovascularization in ischemic tissue and stabilization of atherosclerotic plaques[280].

Fibrates
Fibrates control the lipid metabolism by mediated through peroxisome proliferator-activated receptors-α activation, stimulation of β-oxidation of fatty acids in peroxisomes and mitochondria to cause lowering fatty acid and triglycerides levels in circulation. The first drug of this class is Clofibrate. Eventually, the revolution in lipid-lowering drugs research discover of many other fibrate drugs such as fenofibrate, bezafibrate, gemfibrozil and ciprofibrate. These drugs demonstrated the adverse effect to cause hepatomegaly and tumor formation in the liver of rodents. Then, they had restricted for the widely

use in humans. Gemfibrozil and fenofibrate are Food and Drug Administration (FDA)-approved for lipid lowering drugs due to milder effect on peroxisome proliferation.

Nicotinic acid

Long term study of the coronary drug project demonstrated that niacin is the effective drug to increase HDL-C levels and reduced CVD events[281] in a non-diabetic subjects. Niacin cause adverse effects on the glycemic control levels in T2DM patients. In high doses treatment with niacin may increase blood glucose levels. The modest doses of 750-2000 mg/d of niacin are significantly increased HDL-C levels and decreased LDL-C, triglyceride levels and accompanied with modest changes in glucose levels for diabetes therapy[282,283]. However, there is no evidence for the CVD outcomes reduction with niacin supplementation in T2DM patients.

Antihyperglycemic drugs: The standard care for T2DM patients is mainly in controlled blood glucose levels by using glycemic lowering drugs and concomitant with controlled diet and increased physical activity. With proper controlled and managed these contributors such as circulating glucose levels, hemoglobin A1c, lifestyle modifications, these can be effectively controlled and reduced the progression and complications disease. In general, only approximately 50% to 60% of T2DM patients have achieved their glycemic goals[284]. There are many reasons for poor control of T2DM including medication efficacy, adverse effects, access to medications and health care education, poor adherence, lack of lifestyle changes and no physical activity. Now a day, more pharmacologicals for T2DM treatment have been approved for use. There are 12 classes of antihyperglycemic drugs FDA-approved in the United States[285] such as sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, biguanides, sodium glucose transporter 2 inhibitors, α-glucosidase inhibitors, amylin analogues and glucagon-like peptide-1 (GLP-1) receptor agonists. These are insulin analogues. Metformin is one of the most commonly prescribed medications for T2DM management. Metformin treatment ameliorate the insulin resistance especially in liver and skeletal muscle but less effect in adipose tissue[286,287], decreased inflammatory response, improved glycemic control[288,289] and enhance β-cell function in T2DM patients by increased insulin sensitivity and glucotoxicity reduction[290]. Metformin reduces fatty acid oxidation in adipose tissue[291], increased GLUT4 translocation in muscle and adipose tissues by activated enzyme adenosine monophosphate kinase and reduced gluconeogenesis in liver[292-295]. There are many developed non-conventional drugs to improve glycemic control such as Cycloset is used together with diet and exercise to treat type 2 diabetes. Cycloset is not for treating type 1 diabetes. Welchol is a non-absorbed, polymeric form, lipid-lowering and glucose-lowering agent for oral administration. Welchol is a high-capacity bile acid-binding molecule. Afrezza Inhalation Powder is the FDA approved the inhalation form of insulin. The new drug is not a substitute for long-acting insulin and use as the combination with conventional long-acting insulin drug for both types of diabetes and many drugs are in the late clinical trials state.

There are new medications and treatments were identified from the FDA, they are in the clinical trials or waiting for approval treatment in dyslipidemia, obesity and T2DM[296]. Recent research study reports that metformin treatment cause metabolic effects to increase GLP-1 concentration in the circulation[297,298]. GLP-1 is an incretin generated from the transcription product of the proglucagon gene. Incretin is a signaling polypeptide contained with 30-amino acid. GLP-1 secretion by ileal L-cells is not depend on the presence of nutrients in the small intestine and responsible for stimulated insulin secretion to limit glucose elevations with the higher efficacy at high glucose levels[276,299]. Elevated GLP-1 secretion might possibly cause increased glucose absorption in the distal segments of small intestine.

Incretins are the gastrointestinal hormone secreted from the intestine and stomach responsible for oral food intake and stimulated the secretion of insulin during meals in healthy peoples[276]. Two major incretin molecules are (1) GLP-1; and (2) Glucose-dependent insulinotopic peptide knows as gastric inhibitory polypeptide (GIP) and to neutralize stomach acid to protect the small intestine and no therapeutic efficacy in T2DM. GLP-1 has lower glucose levels by stimulated insulinproduction and increased glucose metabolism in adipose tissue and muscle. GLP-1 promote the pancreatic β-cells proliferation, reduce apoptosis, increase cardiac chronotropic, inotropic activity, decreases glucagon secretion, reduces glucose production, increase appetite suppression for food intake reduction and slow gastric emptying[271,276,299]. GLP-1 is degraded by enzyme DPP-4 and this enzyme does not inhibit by metformin[298]. The prevention of GLP-1degradation by DPP-4 is one method to increase the effects of GLP-1. DPP-4 inhibitor drugs inhibit the glucagon secretion which in turn increases secretion of insulin to decrease blood glucose levels and decreases gastric emptying. The FDA-approved the DPP-4 inhibitor drugs including sitagliptin (Januvia), alogliptin (Nesina), saxagliptin (Onglyza), linagliptin (Tradjenta), anagliptin, vildagliptin, teneligliptin, gemigliptin and dutogliptin. The adverse effects are dose-dependent to cause headache, vomiting, nausea, nasopharyngitis, hypersensitivity and other conditions. Other side effects of exenatide (GLP-1 agonist) note for abdominal pain, acid stomach, diarrhea, altered renal function, weight loss, dysgeusia, belching and cause pruritus, urticaria and rash reactions at the injection site.

CONCLUSION

In this present review has described the detrimental effects from chemicals and biochemicals reaction, metals, medications, over nutrition, obesity and diseases in oxidative stress, insulin resistance development and
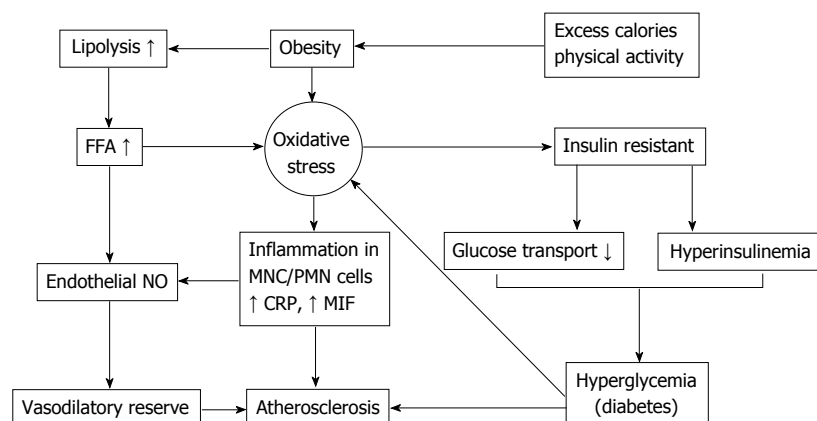
Figure 8 Connection between life style, oxidative stress, insulin resistance, inflammation and atherosclerosis. FFA: Free fatty acid; NO: Nitric oxide; MNC: Mononuclear cells; PMN: Polymorpho nuclear cells; CRP: C-reactive protein; MIF: Migration inhibitory factor.

the progression of T2DM and the progression of diabetic complications and organ dysfunctions. Oxidative stress played underling associated with the pathogenesis of diseases, leading to increases risk of insulin resistance, dyslipidemia, elevated blood pressure, metabolic syndrome, inflammation and endothelial dysfunction. This reviewed support the oxidative stress contribution of the multifactorial etiology of oxidative stress and insulin resistance in the whole body. ROS act as the signal transduction factor and plays the important role in oxidative stress-mediated downstream signaling pathways and enhances the cell death. Furthermore, risk for several chronic diseases development associated with oxidative stress and metabolic syndrome including T2DM, hypertension, arthritis, congestive heart failure, chronic renal failure, cancer and Alzheimer's. These diseases may be substantially reduced by dietary modifications, increased physical activity and antioxidant drugs ameliorated oxidative stress. The therapeutic approaches target on oxidative stress may delay or prevent the progression and onset of diseases. Then, antioxidants supplementation may curtail the progression and onset of the metabolic disease complications. Antioxidant interventions, an importance goal of future clinical investigations should be implementation and to improve oral bioavailability targeted to the oxidant overproduction site. Lifestyle change remains the best prevention and therapeutic approach to oppose the increasing epidemic of cardiovascular diseases, obesity, hypertension, dyslipidemia and T2DM. Finally, the connection between oxidative stress, insulin resistance, dyslipidemia, inflammation, life style, atherosclerosis and diabetes as demonstrated in the schematic in Figure 8.

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