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Postprandial Triglycerides, Oxidative Stress, and Inflammation

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Abstract

Among the most common non-communicable diseases are obesity, cardiovascular disease, and diabetes, which are responsible for the major cardiometabolic phenotypes. Together with mitochondrial alterations, oxidative stress and inflammation are key molecular mechanisms that contribute to the onset and development of these conditions. Meal consumption is a recurring daily activity that is directly linked to oxidative stress and inflammation. Acute increases in lipids, notably triglycerides, during the postabsorptive period have been suggested to induce a state of inflammation with stimulation of adhesion molecules, cytokines, oxidative stress, and leukocyte activation. Not only lipids but also meal-induced elevations in glucose have also been linked to postprandial oxidative stress and inflammation. The impact of postprandial hypertriglyceridemia and hyperglycemia on oxidative stress and inflammation is not only independent but may be cumulative. It is our hypothesis that, in a system that could not maintain homeostasis to continuous changes of the environment, repeated exposures to meals that provide modest doses of fat and glucose could potentially elicit abnormal responses that contribute to the onset and development of chronic cardiometabolic phenotypes.

Keywords: postprandial triglycerides, oxidative stress, inflammation, hypertriglyceridemia, hyperglycemia, cardiometabolic phenotypes

1. Introduction

Non-communicable diseases refer to chronic conditions that are non-infectious and non-transmissible and include obesity, cardiovascular disease, diabetes, cancer, as well as respiratory and neurological diseases. They represent the most common cause of death and disability in developed as well as developing countries [1]. In addition to age-related mitochondrial alterations, oxidative stress and inflammation are key mechanisms in the onset and development of these conditions [2].

Lipids, in particular esterified lipids such as triglycerides (TG), phospholipids, and cholesteryl esters are essential metabolites for energy, cell membrane integrity as well as regulatory hormones. Reactive oxygen species (ROS) are produced by normal physiological processes and play an important role in cell signaling and tissue homeostasis. In view of their high content of polyunsaturated fatty acids (PUFA), lipids transported in plasma lipoproteins as well as those in cellular membranes are especially susceptible to ROS damage, i.e. lipid

peroxidation. An imbalance between the formation and detoxification of ROS can lead to the oxidative stress and the nonenzymatic modification of biomolecules, such as proteins, carbohydrates, nucleic acids and lipids. Lipid peroxidation damages surface phospholipids directly and delivery of oxidized fatty acids to the cells play an important role in many inflammatory diseases and can mediate proinflammatory changes [3]. With meal consumption, the intermittent influx of newly absorbed dietary fat in the form of TG-rich chylomicrons is associated with delayed clearance of plasma lipids. This delay is further exacerbated in individuals with metabolic syndrome, type 2 diabetes as well as in obese individuals resulting in greater ROS damage.

Chronic hyperglycemia in diabetes is associated with concomitant increase in the level of ROS and a reduction in enzymatic and nonenzymatic cell antioxidant defenses [4, 5]. In vitro study has demonstrated that intermittent exposure to high glucose environment could stimulate superoxide production and enhance endothelial cell apoptosis to a greater extent than exposure to constant high glucose [6]. In vivo study also noted that intermittent meal-induced elevations in plasma glucose could also play a role in inducing inflammation and oxidative stress [7]. Ingestion of glucose has been reported to result in increased production of tumor necrosis factor alpha (TNF α) and interleukin-6 (IL-6) by peripheral blood mononuclear cells, and increased formation of ROS [8, 9]. Furthermore, addition of glucose to a fatty meal delays the metabolism of intestinal chylomicrons in healthy subjects, thus enhancing lipid peroxidation. In fact, there is ample evidence that the impact of postprandial hyperlipidemia and hyperglycemia on inflammation and oxidative stress is independent and cumulative [10].

2. Lipoprotein-associated oxidative stress and inflammation

Oxidative stress refers to an imbalance between the generation of reactive oxygen/nitrogen species (ROS/RNS) and the capacity of antioxidative protection systems to counteract them. All substrates in the cells are potential targets of ROS with lipids being most susceptible to undergo oxidative modification, in particular polyunsaturated fatty acids (PUFA) with the multiple double bonds [11]. Peroxidation of PUFA leads to the formation of isoprostanes [12] and their levels are considered to accurately reflect the oxidative status of the environment [13]. Oxidative modification of lipids can also result in the formation of reactive aldehydes, such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE) [14]. MDA and HNE modified metabolites can be detected in plasma [15].

Serving as both a source of energy and structural components of cells, lipids are transported in the circulation by a network of globular particles of varying in size (from 5 to 1200 nm in diameter) and composition. Independent of the size, these so-called lipoproteins consist of a hydrophilic outer layer and a hydrophobic inner core [16]. The surface of lipoproteins consists of an amphipathic phospholipid bilayer stabilized by non-esterified cholesterol and specific proteins known as apolipoproteins. The inner core includes nonpolar lipids such as triglycerides and cholesteryl esters in various amounts. The key lipoproteins are the triglyceride-rich lipoproteins (TRL), the cholesterol-rich atherogenic lipoproteins, low-density lipoproteins (LDL), and the protective, anti-oxidative, anti-atherogenic lipoproteins, high-density lipoproteins (HDL). TRL are responsible for the delivery of TG to peripheral tissues can be of intestinal origin, chylomicrons, or of hepatic origin, very-low density lipoproteins (VLDL). While chylomicrons which carry dietary fats are present only in the postprandial state, VLDL are constantly being produced by the liver to transport endogenous triglycerides and are metabolic precursors of

LDL which are delivered to peripheral tissues as cholesterol-rich particles [16]. In addition to their anti-inflammatory and anti-oxidative properties, HDL serves as the primary vehicle for reverse cholesterol transport [16].

In the circulation, very-low density lipoproteins (VLDL) are triglyceride-rich (TG-rich) lipoproteins synthesized in the liver for the export of new formed TG to peripheral tissues [17]. VLDL unloads their cargo of triglycerides via interactions with lipoprotein lipase that is anchored to the endothelium via heparan sulfate proteoglycans [18]. As part of this process, lipoprotein particles form tight junction with the endothelium allowing released free fatty acids and monoglycerides to be delivered to the underlying cells. The neutral and oxidized free fatty acids released by the hydrolysis of TG-rich lipoproteins can induce endothelial inflammation [19]. In the same process, excess ROS generated by activated macrophages in the arterial wall can attach themselves to lipoproteins in the circulation (**Figure 1**). Plasma lipoproteins are thus seeded with oxidants that can initiate the propagation of oxidative damage, unless the oxidative epitopes are quenched by antioxidant mechanisms [17, 20].

Following meal consumption, newly absorbed dietary fats are packaged in the intestine and secreted into the circulation as chylomicrons which contain over 90% TG by mass and range in diameter from 100 to 1200 nm [16]. These intestine-derived TG-rich lipoproteins compete with hepatic VLDL for interactions with lipoprotein lipase to deliver TG to peripheral tissues. Depending on the TG contents in the meal as well as the capacity of the lipolytic system, retention times for both VLDL and chylomicrons at the endothelium could be significantly extended. The net result is a greater propensity for plasma lipoproteins to be seeded with ROS generated in the arterial wall, especially when the endothelium is under chronic inflammation. Indeed using immunoassay for IgG specific for oxidative epitopes we have reported acute reduction in circulating IgG levels following meal consumption in patients with documented coronary artery disease [21]. Furthermore, this transient reduction was observed only when the meal was enriched in polyunsaturated fatty acids which are most susceptible to modification by ROS [22].

With the hydrolysis of VLDL and chylomicron TG to free fatty acids and glycerol, smaller lipoprotein particles are formed relatively enriched in cholesterol, the so-called VLDL and chylomicron remnants. While most chylomicron remnants are cleared by the liver via receptor-mediated uptake, only 50% of the VLDL remnants are directly removed from plasma. The remaining 50% are converted to cholesterol-rich low-density lipoproteins (LDL), the major cholesterol carrying lipoproteins in normal human plasma [23–25]. If the oxidative epitopes transferred from the arterial wall to the TG-rich VLDL are not efficiently removed or quenched, we have suggested that this could represent an alternate pathway for the formation of oxidatively modified LDL (**Figure 1**) [20]. This is different from the traditional concept which postulates that LDL oxidation must take place in the arterial wall [26]. The presumption is that plasma lipoprotein lipids are well protected by inherent antioxidant defenses in particular, LDL itself contains most of the antioxidant α -tocopherol in plasma [26]. Recent data would suggest that under certain conditions, oxidative modification of plasma lipoproteins could be initiated in the circulation. By using the *in vitro* assay described by Esterbauer et al. [27] to assess the oxidative susceptibility of plasma LDL, we can show that, while LDL isolated from fasting plasma would undergo oxidative modification only in the presence of Cu^{++} as a catalyst, LDL isolated from non-fasting plasma was susceptible to auto-oxidation in the absence of Cu^{++} (**Figure 2A**) [28]. Furthermore, in some patients with metabolic syndrome, auto-oxidation of fasting LDL could be prevented following management with ABT-335 (choline salt of fenofibric acid) (**Figure 2B**) [28].

While endothelial cells are continuously exposed to high concentrations of free fatty acids in the fasted state generated by the hydrolysis of hepatic VLDL,

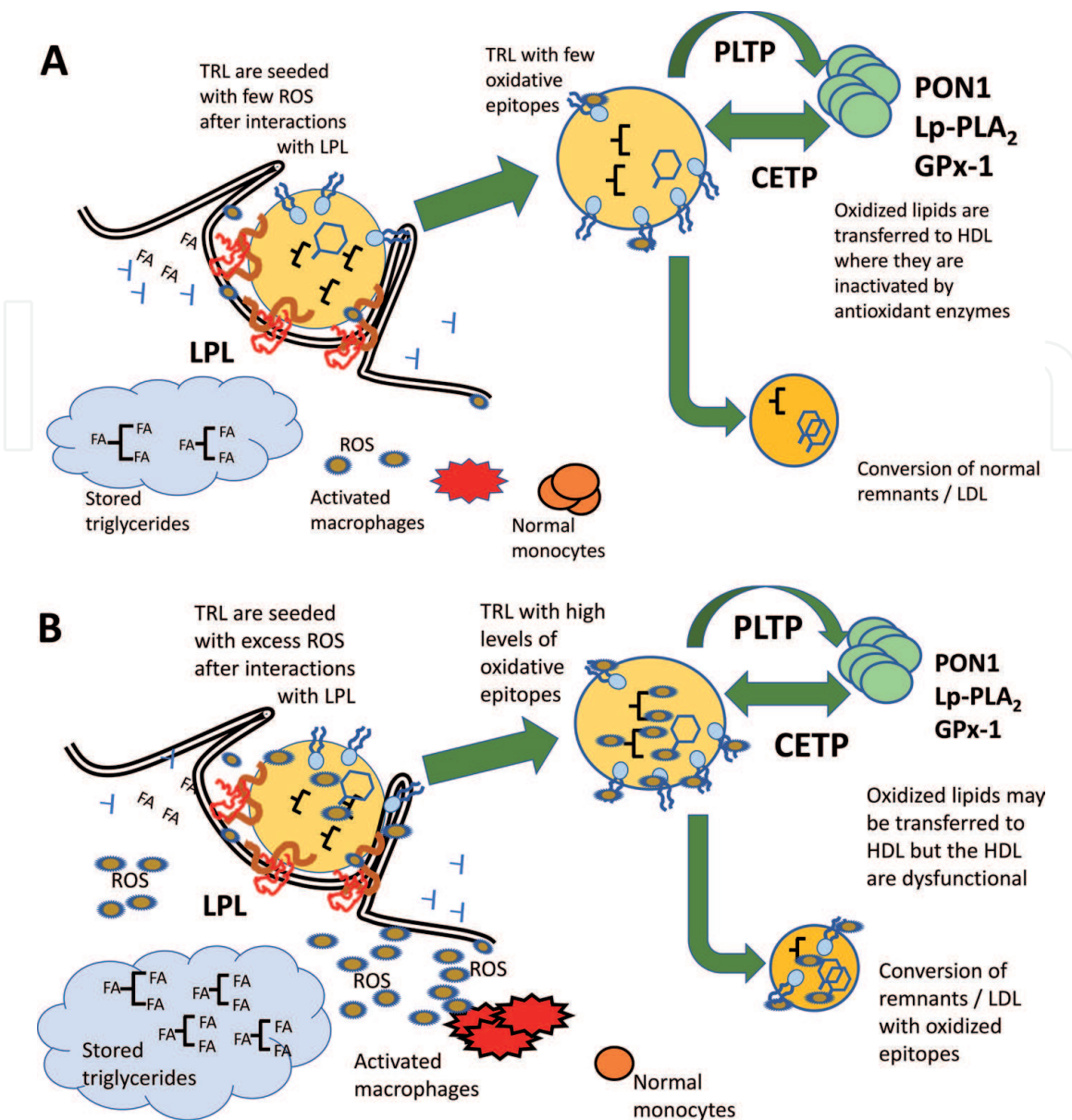


Figure 1.

Interactions of TG-rich lipoproteins with the endothelium. (A) In the case of the healthy endothelium, as TG-rich lipoproteins (TRL) are attached to the arterial wall via heparan sulfate proteoglycans, lipoprotein lipase (LPL) hydrolyzes TG into free fatty acids (FA) and monoglycerides that can penetrate the endothelium and be reconstitute as stored TG. With modest quantity of activated macrophages, only minimal amount of ROS is generated to seed plasma lipoproteins. In the circulation, lipoproteins undergo remodeling via the action of phospholipid transfer protein (PLTP) and cholesteryl ester transfer protein (CETP) with the transfer of oxidized lipids to high-density lipoproteins (HDL) where they are inactivated by antioxidant enzymes, including paraoxonase (PON-1), lipoprotein-associated phospholipase A2 (Lp-PLA₂) and glutathione peroxidase (GPx-1). With the depletion of TG, TG-rich lipoproteins are converted to normal chylomicron remnants and LDL. (B) In the case of the inflamed endothelium, there are excess generation of ROS by increasing number of activated macrophages. Together with impaired hydrolysis by LPL and greater flux of TG-rich lipoproteins, the retention time of TRL along the arterial wall is increased resulting to a greater opportunity for ROS to seed plasma lipoproteins. In the circulation, while oxidized lipids may still be transferred to HDL, the antioxidative properties of HDL have been reduced. The net result is the generation of chylomicron remnants and LDL with significant number of oxidative epitopes that could undergo spontaneous auto-oxidation.

intermittent entries of intestinal chylomicrons carrying dietary fats can further increase this concentration. Depending on the type of fat, interactions of these free fatty acids with endothelial cells could have deleterious effect on endothelial function [29, 30]. In vitro studies with human aortic endothelial cells have demonstrated that high levels of the polyunsaturated fatty acid linoleic acid increase endothelial cell permeability [31] whereas increased levels of the saturated fatty acid palmitate and the monounsaturated fatty acid oleate tend to decrease the activity of

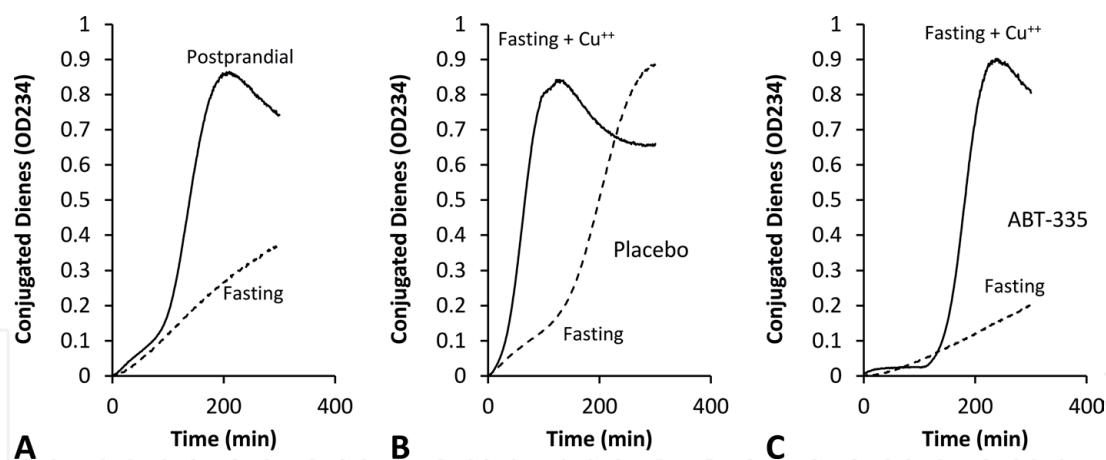


Figure 2. Continuous monitoring of in vitro oxidation of LDL from two patients with metabolic syndrome. (A) In the absence of the catalyst Cu^{++} , LDL isolated from Patient A at 4 h after meal undergoes spontaneous auto-oxidation while LDL isolated from fasting plasma does not. (B) During the placebo period, fasting LDL isolated from Patient B undergoes spontaneous auto-oxidation in the absence of Cu^{++} and the lag time is significantly reduced in the presence of Cu^{++} . (C) After 8 weeks of therapy with ABT-335, fasting LDL from Patient B no longer undergoes auto-oxidation in the absence of Cu^{++} and demonstrates the typical oxidation kinetics in the presence of Cu^{++} .

endothelial nitric oxide synthase [32]. However, if these newly released free fatty acids have been previously oxidized, they can elicit additional pro-inflammatory responses in endothelial cells. Oxidized free fatty acids can have direct effect on toll-like receptors, insulin resistance, upregulation of NF- κ B, expression of adhesion molecules and macrophage cytotoxicity [33, 34].

In addition to the free fatty acids released as part of the hydrolysis of TG-rich lipoproteins, LDL is direct product of the metabolism of TG-rich VLDL [17]. The presence of oxidized phospholipids on the surface of plasma lipoproteins can also contribute to oxidative and inflammatory status [35–37]. As illustrated (**Figure 1**), a number of intrinsic enzymes on circulating HDL can blunt the deleterious effect of oxidized phospholipids, namely paraoxonase-1, lipoprotein-associated phospholipase A2 and glutathione peroxidase-1 [38]. However, in individuals with hypertriglyceridemia, excess generation of LDL with oxidized phospholipids [26, 39] and impaired anti-oxidant enzymes on HDL may exacerbate the oxidative process.

3. Glucose-associated oxidative stress and inflammation

Exposure to elevated plasma glucose in patients with type 2 diabetes mellitus is associated with both an increased level of ROS and a drop in cell antioxidant defense, enzymatic as well as non-enzymatic [4, 5]. In addition to serving as a barrier to control movements of fluid, solutes and cells between blood and tissue, the endothelial layer also play a key role in regulating vascular tone and inflammatory processes [40]. While the impact of hyperglycemia on endothelial cell metabolism is beyond the scope of this presentation it should be noted that, at normal fasting plasma glucose concentrations (4–6 mM, 72–108 mg/dL), the glucose transporter GLUT-1 is already functioning at saturation level [41]. GLUT-1 is the primary glucose carrier responsible for the uptake of glucose by endothelial cells [42]. In vitro studies with human umbilical vein endothelial cells have indicated that exposure to high concentration of glucose is associated with increased oxidative stress as assessed by increased levels of nitrotyrosine and 8-hydroxy-2'-deoxyguanosine [6]. In fact, the increase in oxidative stress was even more pronounced when endothelial cells were exposed intermittently to high and low glucose concentrations [6]. It has also been demonstrated that high

glucose levels stimulate ROS production through protein kinase C (PKC)-dependent activation of NAD(P)H oxidase [43, 44]. The net result of constant and intermittent hyperglycemia is enhancement of endothelial cell apoptosis [6, 44].

In both normal and type 2 diabetic patients, intermittent hyperglycemia has been demonstrated to be more deleterious to endothelial cell metabolism and oxidative stress than constant elevations in plasma glucose [45]. In fact, reduction in the mean amplitude of glycemic excursion with dipeptidyl peptidase-IV inhibition in patients with type 2 diabetes is associated with reduction in oxidative stress and biomarkers of inflammation [46].

In addition to the stimulation of ROS production, exposure to high glucose concentrations can also lead to nonenzymatic modifications of proteins with the formation of glycated proteins or advanced glycation end-products (AGE) [47]. Glycation of specific proteins can severely alter their function as in the case of glycated hemoglobin C with increased affinity for oxygen and subsequent decreased oxygen delivery to tissues [48]. Glycation of plasma LDL by methylglyoxal, a side product of glycolysis, results in enhanced delivery of these pro-atherogenic particles to the arterial wall leading to increased risk for atherosclerosis in patients with type 2 diabetes [49]. Glycation of insulin has also been suggested to contribute to insulin resistance leading to more severe hyperglycemia [50].

4. Meal-induced oxidative stress and inflammation

The fat content of a typical Western meal ranges from 20 to 40 g of fat which corresponds to between 5 and 8 times the total pool of TG in plasma. In a healthy individual with normal metabolism, plasma TG level reaches peak level by 2 h after meal and returns to pre-meal level by 6 h. As many individuals customarily consume 3 meals a day, they spend the majority of their day in the postprandial state. Several processes contribute to the increased oxidative stress and inflammatory state associated with meal consumption [51]. The magnitude and timing of postprandial inflammatory response to a high-fat meal may depend on fat content, caloric intake, body-mass index [52] as well as age of the individual [53, 54].

Firstly, as noted in earlier section, the intermittent secretion of intestinal chylomicrons after each meal has a direct effect on the metabolism of circulating hepatic VLDL. While this may not be the case for individuals with normal TG levels, the lipolytic system may be saturated in individuals with elevated TG as in the case of obesity and diabetes. The net result is a delayed clearance of TG-rich lipoproteins, prolonged interactions of TG-rich particles with the endothelium, and greater potential for the transfer of ROS from the arterial wall to circulating plasma lipoproteins (**Figure 1B**). Treatment of peripheral blood mononuclear cells with lipolysis products of postprandial TG-rich lipoproteins resulted in increased expression of TNF α , IL-1b, and IL-8 [55].

Secondly, the meal-induced change in free fatty acids can contribute to the deleterious impact on the endothelium not only with respect to the increased concentrations but also to the type of free fatty acids. In patients with insulin resistance, the impact of postprandial free fatty acids is further exacerbated by the failure of postprandial insulin to inhibit the activity of hormone-sensitive lipase (HSL) in tissues. In the normal individuals, the increase in insulin concentration during postprandial lipemia would inhibit the activity of HSL and shut off the mobilization of free fatty acids from peripheral tissues [56–58]. With insulin resistance, HSL remains active during postprandial lipemia and continues to mobilize free fatty acids from intracellular stores contributing to even higher plasma free fatty acid concentrations.

Thirdly and most importantly is the independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on oxidative stress and inflammation [10]. In both normal and diabetic individuals, compared to high fat meal, the inclusion of a glucose dose equivalent to an oral glucose tolerance test resulted in greater increase in nitrotyrosine and circulating adhesion molecules, including E-selectin, ICAM-1, and VCAM-1 [59]. Management with simvastatin in the short term (3 days) did not affect lipids but reduced the effect on nitrotyrosine and adhesion molecules. Extended therapy with simvastatin (3 months) blunted the meal-induced hypertriglyceridemia as well as the post-prandial responses in nitrotyrosine and adhesion molecules [10, 59]. In patients with type 2 diabetes, meal-induced increases in TG and glucose were attenuated by prandial + basal insulin [60]. Post-meal increased in C-reactive protein (hs-CRP), IL-6, and TNF α were also reduced [60] with the addition of prandial insulin.

5. Future directions

In view of the fact that individuals are in a postprandial state throughout the day, assessment of oxidative and inflammatory status in the fasted might not provide an accurate snapshot. It is important to understand the processes that affect oxidative stress and inflammatory status in a non-fasted state [61]. Additional research is needed to understand how nutrients, with respect to quality, quantity, and frequency, could be managed to attenuate the deleterious effect of postprandial hypertriglyceridemia and hyperglycemia on oxidative stress and inflammation [62]. Blunting the acute daily fluctuations in plasma glucose and triglycerides may be a novel mode of management to reduce oxidative stress and inflammation in high-risk individuals. Furthermore, special attention should be placed on the timing of antioxidant ingestion in relation to meal consumption as that might have a direct impact on the time course of postprandial response [63].

6. Conclusions

Assessment of oxidative and inflammatory status in the fasted state may not provide an accurate picture of the metabolic status of an individual. Intermittent elevations in plasma triglycerides and glucose associated with meal consumption throughout the day may be associated with considerable increase in oxidative stress and inflammation depending on the quantity and quality of the meals.

Abbreviations

AGE	advanced glycated end-products
CRP	(hs-CRP) high-sensitive C-reactive protein
FFA	free fatty acid
HDL	high-density lipoproteins
IL	interleukin
LDL	low-density lipoproteins
LPL	lipoprotein lipase
HSL	hormone sensitive lipase
ROS	reactive oxygen species
TG	triglycerides
TRL	TG-rich lipoproteins
VLDL	very-low density lipoproteins

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