



The role of oxidative stress in postprandial endothelial dysfunction

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Abstract

Endothelial dysfunction is a turning point in the initiation and development of atherosclerosis and its complications and is predictive of future cardiovascular events. Ingestion of high-carbohydrate or high-fat meals often results in postprandial hyperglycaemia and/or hypertriacylglycerolaemia that may lead to a transient impairment in endothelial function. The present review will discuss human studies evaluating the impact of high-carbohydrate and high-fat challenges on postprandial endothelial function as well as the potential role of oxidative stress in such postprandial metabolic alterations. Moreover, the present review will differentiate the postprandial endothelial and oxidative impact of meals rich in varying fatty acid types.

Key words: Postprandial hyperglycaemia; Hypertriacylglycerolaemia; Endothelial function; Oxidative stress

The Westernisation of dietary patterns has led to the consumption of more transformed food rich in processed sugars, SFA and *trans*-fatty acids, a higher *n*-6:*n*-3 PUFA ratio, as well as less fruit, vegetables, fish and grains. Moreover, portion sizes and meal frequencies have increased, resulting in individuals spending considerably more time in the postprandial state, identified as being a critical period for atherosclerotic plaque formation⁽¹⁾. Such dietary patterns and overnutrition are linked to obesity, dyslipidaemia and hyperglycaemia, all of which contribute to insulin resistance, diabetes, atherosclerosis, hypertension and CVD. Postprandial endothelial dysfunction represents the common link between these events and could involve oxidative stress⁽²⁾. The objective of the present review is thus to evaluate the role that oxidative stress plays in the postprandial endothelial events following acute hyperglycaemia and hypertriacylglycerolaemia. To meet this objective, we have considered studies evaluating the postprandial impact of oral carbohydrate or fatty acid challenges on *in vivo* oxidative stress and endothelial function in human subjects. Studies evaluating endothelial function by brachial ultrasonography or through markers of endothelial integrity (i.e. adhesion molecules, selectins, von Willebrand factor, endothelial microparticles, etc.) were considered.

General background

Endothelial function

The endothelium lines the inner wall of blood vessels and plays an important role in distributing nutrients and in regulating blood flow, coagulation, inflammation and smooth muscle cell proliferation. It responds to both mechanical stimuli and chemical stimuli that have either vasodilator (i.e. NO, prostacyclins, etc.) or vasoconstrictor (i.e. angiotensin II, endothelin-1, etc.) effect^(3,4). Endothelial function is often evaluated by ultrasonography of the brachial artery and is expressed as a percentage of endothelium-dependent vasodilation in response to transient ischaemia (flow-mediated dilatation)^(5,6). This vasodilatation is principally mediated by NO released from endothelial cells.

Endothelial dysfunction is defined as a reduced response to vasodilatory stimuli and occurs when the normal equilibrium between vasoactive stimuli is disrupted. Endothelial dysfunction also occurs in conjunction with impaired anti-platelet, anti-proliferative and anti-thrombotic activity, transforming the dysfunctional endothelium into a pro-atherogenic environment^(7–9). Endothelial dysfunction is an early step in the setting of CVD (atherosclerosis, hypertension, myocardial infarction and congestive heart failure) and is linked to conditions predisposing to these diseases:

Abbreviations: HMUFAM, high-monounsaturated fat meal; HSFAM, high-saturated fat meal; ICAM, intracellular adhesion molecule; IGT, impaired glucose tolerance; MDA, malondialdehyde; OGTT, oral glucose tolerance test; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus; TBARS, thiobarbituric acid-reactive substance; VCAM, vascular cell adhesion molecule.

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smoking, a sedentary lifestyle, dyslipidaemia, obesity, insulin resistance, type 2 diabetes mellitus (T2DM) and chronic renal failure^(3,4). Endothelial dysfunction is thus predictive of future cardiovascular events in healthy subjects^(10–12) and patients with pre-existing CVD^(4,9,13,14) and has been identified as the ‘ultimate risk factor’ for CVD⁽¹⁵⁾.

Pathophysiology of oxidative stress

In an aerobic state, biological systems utilise O₂ for the majority of processes (i.e. energy substrate oxidation), inevitably resulting in the formation of reactive oxygen species (ROS). Major cellular sources of ROS are the mitochondrial electron transport chain, which specifically produces superoxide anions^(16–18), and the enzyme NADPH oxidase (the main ROS-producing enzyme in the vasculature)⁽¹⁹⁾. In addition to physiological processes, ROS can be increased by lifestyle habits (i.e. smoking, sedentariness or physical activity), diseases (i.e. diabetes and obesity) and nutritional choices (i.e. high-energy, -glycaemic and/or -fat diets and meals), the latter being the focus of the present review^(2,18). In fact, according to current literature, excessive dietary intake of carbohydrates or fatty acids leads to increased oxidative stress levels either directly, since meals often include oxidised nutrients, or through activation of mitochondrial metabolism^(17,20). The latter process begins with postprandial hyperglycaemia and hypertriacylglycerolaemia, which overload the mitochondrial electron transport chain resulting in increased production of ROS^(17,20,21). Glucose and some fatty acids (notably SFA) can also directly activate the ROS-producing NADPH oxidase⁽²²⁾. When produced in excess of antioxidant capacity, ROS lead to oxidative stress⁽²³⁾, which has been defined as an ‘imbalance between oxidants and antioxidants in favour of oxidants, potentially leading to cellular and tissue damage’⁽¹⁷⁾. Oxidative stress is thought to be one of the underlying causes of ageing⁽²⁴⁾ and many important conditions including Parkinson’s⁽²⁵⁾ and Alzheimer’s diseases⁽²⁶⁾, insulin resistance, the metabolic syndrome, T2DM^(2,21,27,28) and atherosclerosis and its complications^(2,21).

In endothelial cells, superoxide anions produced in excess along with NO can rapidly react to form highly unstable peroxynitrite^(20,29–31) or inhibit endothelial and inducible NO synthase resulting in decreased NO bioavailability⁽³²⁾. Therefore, a NO paradox exists whereby the actions of NO are mediated by its concentration and by the redox state of the environment in which it is secreted^(20,29). Dysregulated oxidative stress is therefore believed to play a major role in the development of endothelial dysfunction^(7,17,33,34). Oxidative stress can also induce endothelial activation, resulting in the release of intracellular adhesion molecules (ICAM), vascular cell adhesion molecules (VCAM), selectins and endothelial microparticles that are cytotoxic to endothelial cells, impair NO production and lead to further dysfunction^(23,31,33). These events are also involved in pro-inflammatory processes.

Postprandial endothelial function and oxidative stress: overview of human studies

Hyperglycaemia-induced oxidative stress and endothelial dysfunction

Diabetes, impaired glucose tolerance (IGT) and even hyperglycaemia that is well below the diagnostic threshold for diabetes are invariably associated with atherosclerosis and poorer cardiovascular outcomes, suggesting an impact of hyperglycaemia on endothelial function^(35,36). Moreover, postprandial hyperglycaemia was deemed an important and independent risk factor for CVD in T2DM⁽³⁷⁾ and healthy subjects⁽³⁸⁾. This, and the fact that the diabetic population has increased oxidant and lowered antioxidant levels^(2,39), was the premise for the hypothesis that oxidative stress links postprandial hyperglycaemia and endothelial dysfunction.

Postprandial impact of oral carbohydrate challenges in healthy subjects. The endothelial and oxidative impact of oral carbohydrate challenges has been investigated by several groups (detailed in Table 1). Oral carbohydrate challenges were defined as high-carbohydrate meals (> 65% total meal energy from carbohydrates⁽⁴⁰⁾) and oral glucose tolerance tests (OGTT) although the latter do not represent a physiological situation but rather a commonly used method for the evaluation of glucose metabolism and insulin resistance. Of these, Ceriello *et al.*⁽³⁹⁾ were among the first to show decreased postprandial endogenous antioxidant levels (sulfhydryl groups, uric acid and vitamins C and E) and plasma antioxidant capacity (i.e. plasma total antioxidant content; total radical trapping antioxidant potential (TRAP) method) following an OGTT and to observe increased markers of endothelial damage (ICAM) in healthy and T2DM individuals⁽⁴¹⁾. Similar observations regarding increased endothelial activation markers were also made following OGTT^(42,43). Recently, Watanabe *et al.*⁽⁴⁴⁾ and many others observed that an OGTT significantly decreased endothelial function assessed by ultrasonography that was correlated with postprandial hyperglycaemia ($r = 0.61$; $P < 0.05$) and insulin release ($r = 0.55$; $P < 0.05$). Importantly, some groups have observed no demonstrable increases in postprandial oxidative stress (malondialdehyde (MDA), nitrate/nitrite and H₂O₂ levels) or decreases in plasma antioxidant capacity (i.e. ferric-reducing capacity; ferric-reducing ability of plasma (FRAP) method) or endothelial dysfunction in healthy men following acute glucose or maltodextrin oral loads^(43,45–47).

Studies in which markers of oxidative stress and endothelial function were not measured simultaneously (Table 1) must be interpreted with caution, as they cannot establish a link of causality between these two phenomena. In contrast, studies listed in Table 2 did indeed evaluate both phenomena together and are thus better suited to establish a potential causal link between hyperglycaemia-induced oxidative stress and postprandial endothelial impairment. Ceriello *et al.*⁽³³⁾ observed increased oxidative product

Table 1. Studies evaluating the impact of postprandial hyperglycaemia on markers of oxidative stress or endothelial function

Study	Study population	Intervention	Postprandial oxidative stress	Postprandial endothelial function	Comments
Ceriello <i>et al.</i> (1998) ⁽⁴¹⁾	HS (<i>n</i> 7); T2DM (<i>n</i> 9)	OGTT (75 g glucose)	NA	↑ ICAM	More important for T2DM; prevented by GSH administration
Yngen <i>et al.</i> (2001) ⁽⁴³⁾	HS (<i>n</i> 11)	OGTT (75 g glucose)	NA	= P-selectin and vWF	
Yngen <i>et al.</i> (2001) ⁽⁴³⁾	T2DM (<i>n</i> 11)	OGTT (75 g glucose)	NA	↑ P-selectin = vWF = ICAM, VCAM	
Nappo <i>et al.</i> (2002) ⁽⁴⁷⁾	HS (<i>n</i> 20)	High-CHO meal (144 g CHO, 75% E)	NA	= ICAM, VCAM	
Derosa <i>et al.</i> (2010) ⁽⁴²⁾	HS (<i>n</i> 256); T2DM (<i>n</i> 274)	OGTT (75 g glucose)	NA	↑ ICAM, VCAM and e-selectin	More important for T2DM
Watanabe <i>et al.</i> (2011) ⁽⁴⁴⁾	HS (<i>n</i> 25)	OGTT (75 g glucose)	NA	↓ FMD	
Lewandowski <i>et al.</i> (2011) ⁽¹⁰⁵⁾	HS (<i>n</i> 32)	OGTT (75 g glucose)	NA	↓ MMP-9 = MMP-2	
Ceriello <i>et al.</i> (1998) ⁽³⁹⁾	HS (<i>n</i> 10); T2DM (<i>n</i> 10)	OGTT (75 g glucose)	↓ Plasma antioxidants and TRAP	NA	More important for T2DM
Serin <i>et al.</i> (2007) ⁽⁵⁶⁾	HS (<i>n</i> 35)	OGTT (75 g glucose)	= TBARS	NA	
Serin <i>et al.</i> (2007) ⁽⁵⁶⁾	IGT (<i>n</i> 25); T2DM (<i>n</i> 20)	OGTT (75 g glucose)	↑ TBARS and oxLDL ↓ PON1	NA	
Fisher-Wellman & Bloomer (2010) ^(46,71)	HS (<i>n</i> 10)	2.25 g glucose or maltodextrin/kg body mass	= MDA, NOx, FRAP and H ₂ O ₂	NA	
Bloomer <i>et al.</i> (2010) ⁽⁴⁵⁾	HS (<i>n</i> 9)	OGTT (75 or 150 g)	= MDA and H ₂ O ₂	NA	
Gregersen <i>et al.</i> (2012) ⁽⁷²⁾	HS (<i>n</i> 7); HS with FHD (<i>n</i> 8)	High-CHO meal (182.7 g CHO, 76% E)	↓ Plasma antioxidant capacity, SOD	NA	

HS, healthy subjects; T2DM, type 2 diabetes mellitus; OGTT, oral glucose tolerance test; NA, not available; ↑, increase; ICAM, intracellular adhesion molecule; GSH, glutathione; =, unchanged; vWF, von Willebrand factor; CHO, carbohydrates; E, energy; VCAM, vascular cell adhesion molecule; ↓, decrease; FMD, flow-mediated dilatation; MMP, matrix metalloproteinase; TRAP, total radical trapping antioxidant potential; IGT, impaired glucose tolerance; TBARS, thiobarbituric acid-reactive substance; oxLDL, oxidised LDL; PON1, paraoxonase 1, MDA, malondialdehyde; NOx, nitrate/nitrite; FRAP, ferric-reducing ability of plasma; FHD, familial history of diabetes; SOD, superoxide dismutase.

Table 2. Studies evaluating the link between oxidative stress and endothelial function induced by postprandial hyperglycaemia

Study	Study population	Intervention	Postprandial oxidative stress	Postprandial endothelial function	Comments
Kawano <i>et al.</i> (1999) ⁽⁵⁴⁾ Kawano <i>et al.</i> (1999) ⁽⁵⁴⁾	HS (n 17) IGT (n 24); T2DM (n 17)	OGTT (75g glucose) OGTT (75g glucose)	= TBARS ↑ TBARS*	= FMD ↓ FMD*	Prevented by vitamin C and E co-ingestion
Title <i>et al.</i> (2000) ⁽⁵²⁾	HS (n 10)	OGTT (75g glucose) ± vitamins C (2g) and E (800 IU)	= MDA, GSH, GSHPx and SOD	↓ FMD	Prevented by vitamin E
Lee <i>et al.</i> (2002) ⁽¹⁰⁶⁾	T2DM (n 11)	OGTT (75g glucose)	↑ Superoxide	↓ FMD	Prevented by statin pre-treatment
Ceriello <i>et al.</i> (2002) ⁽⁵¹⁾	T2DM (n 30)	OGTT (75g glucose)	↑ NT	↓ FMD	
Ceriello <i>et al.</i> (2004) ⁽³⁹⁾	HS (n 20)	OGTT (75g glucose)	↑ NT	↑ ICAM, VCAM and e-selectin	
Sampson <i>et al.</i> (2004) ⁽⁵⁵⁾	HS (n 20)	OGTT (75g glucose)	= oxLDL	↑ ICAM and e-selectin = VCAM and MMP	
Sampson <i>et al.</i> (2004) ⁽⁵⁵⁾	T2DM (n 21)	OGTT (75g glucose)	= oxLDL	↓ ICAM, VCAM and e-selectin = MMP	
Ceriello <i>et al.</i> (2005) ⁽⁵⁰⁾	T2DM (n 20)	OGTT (75g glucose)	↑ NT	↓ FMD ↑ ICAM	Prevented by statin pre-treatment
Xiang <i>et al.</i> (2008) ⁽⁵³⁾	IGT (n 42)	OGTT (75g glucose) ± 300mg α-lipoic acid	↑ TBARS*	↑ ICAM ↓ FMD*	Attenuated by α-lipoic acid
Mah <i>et al.</i> (2011) ⁽⁴⁸⁾	HS (n 16)	OGTT (75g glucose)	↑ MDA* and ADMA ↓ FRAP, vitamin C and arginine	↓ FMD*	ADMA inhibits NO production

HS, healthy subjects; OGTT, oral glucose tolerance test; =, unchanged; TBARS, thiobarbituric acid-reactive substance; FMD, flow-mediated dilatation; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; ↑, increase; ↓, decrease; MDA, malondialdehyde; GSH, glutathione; GSHPx, glutathione peroxidase; SOD, superoxide dismutase; NT, nitrotyrosine; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule; oxLDL, oxidised LDL; MMP, matrix metalloproteinase; ADMA, asymmetric dimethylarginine; FRAP, ferric-reducing ability of plasma.
* Significant correlation ($P < 0.05$).

levels (nitrotyrosine) along with endothelial activation (ICAM, VCAM and E-selectin) following an OGTT. An OGTT was also associated with lowered postprandial endothelial function and correlated ($r = 0.80$; $P < 0.05$) with increased lipid peroxidation (MDA)⁽⁴⁸⁾. Acute hyperglycaemic load was also associated with lower total plasma antioxidant capacity (FRAP method), vitamin C and arginine (a precursor of NO) levels, consistent with increased postprandial oxidative stress⁽⁴⁸⁾.

Other studies have evaluated the impact of the co-ingestion or infusion of antioxidants with high-carbohydrate challenges. Ceriello *et al.* found that administration of glutathione or pre-treatment with statins (having antioxidant properties⁽⁴⁹⁾) during an OGTT abolished its oxidative stress-raising and endothelial-impairing properties in healthy and T2DM individuals^(41,50,51). Title *et al.*⁽⁵²⁾ also observed that an OGTT led to attenuated postprandial endothelial function, which was prevented by co-administration of the antioxidant vitamins C and E. Xiang *et al.*⁽⁵³⁾ demonstrated that infusion of α-lipoic acid with a standard OGTT prevented lipid peroxidation (i.e. thiobarbituric acid-reactive substances; TBARS) and the associated decrease in flow-mediated dilatation otherwise observed following the OGTT alone. It is noteworthy that the presence of antioxidants did not influence the extent of postprandial hyperglycaemia and supports the hypothesis that oxidative stress links acute hyperglycaemia to impaired postprandial endothelial function and integrity.

Similarly, the postprandial impact of high-carbohydrate challenges was also investigated in individuals with impaired glucose metabolism such as IGT or T2DM (results shown in Tables 1 and 2). These studies uniformly demonstrated in such populations that high-carbohydrate challenges elevate oxidative stress markers and impair endothelial function to a more prolonged or important extent^(42,43,50,51,54–56). For instance, Kawano *et al.*⁽⁵⁴⁾ observed significant postprandial elevations in TBARS and attenuated flow-mediated dilatation of the brachial artery following an OGTT in subjects with IGT and T2DM while healthy controls were not significantly affected by such challenge. Xiang *et al.*⁽⁵³⁾ observed similar findings in subjects with IGT and, like Kawano *et al.*⁽⁵⁴⁾, observed a positive correlation between postprandial oxidative stress and endothelial dysfunction.

In summary, a strong causative link between acute hyperglycaemia, postprandial oxidative stress and endothelial function in healthy subjects cannot be established due to the lack of studies evaluating these events concomitantly. However, since antioxidant co-ingestion prevents deleterious oxidative and endothelial events following an oral glucose load, it is tempting to hypothesise that acute hyperglycaemia induces the formation of oxidative species impairing endothelial function. Establishing a causal link could be facilitated in higher-risk individuals with impaired glucose metabolism, in which elevated baseline oxidative levels (or impaired antioxidant mechanisms)

could potentially accentuate postprandial insults, making them more easily detectable⁽²⁾.

Hypertriacylglycerolaemia-induced oxidative stress and endothelial dysfunction

Postprandial but not fasting hypertriacylglycerolaemia is associated with an increased risk of atherosclerosis and is now considered an important risk factor for CVD^(57,58). Since dietary fatty acids are a good source of oxidised/oxidisable lipids and can lead to activation of mitochondrial metabolism and to the formation of ROS, it has been proposed that oxidative stress could link postprandial hypertriacylglycerolaemia to vascular damage^(9,20). The second part of the present review will discuss the postprandial impact of acute ingestion of high quantities of different types of fatty acids. High-fatty acid challenges were defined as fatty acid loads or meals providing more than 45% of total energy from fat, which has been recognised as the minimal quantity leading to observable oxidative and endothelial modifications⁽²⁰⁾.

Postprandial impact of high-saturated fat meals. High-saturated fat meals (HSFAM), defined as meals providing more than 10% of total daily energy from SFA (i.e. ≥ 7 g of SFA/meal, based on three meals and 8400 kJ (2000 kcal)/d)⁽⁵⁹⁾, have often been investigated for their hypertriacylglycerolaemic properties and their potential postprandial oxidative and endothelial-impairing properties (Table 3). The majority of these experiments highlighted a significant impairment of postprandial endothelial function following a HSFAM^(60–66). Notably, Vogel *et al.*⁽⁶⁵⁾ and Plotnick *et al.*⁽⁶⁶⁾ in what are recognised today as landmark studies, showed a correlation between the magnitude of postprandial hypertriacylglycerolaemia and the degree of endothelial function impairment. Some also noted that a HSFAM led to increased endothelial microparticle release or to increases in von Willebrand factor and P-selectin^(67–70). Others evaluated the impact of HSFAM-induced hypertriacylglycerolaemia on markers of oxidative stress. The majority of these investigations observed increased postprandial oxidative stress or impaired plasma antioxidant capacity through multiple different markers^(45,71–74). Postprandial hypertriacylglycerolaemia was found to correlate significantly with plasma TBARS (r 0.336; $P < 0.05$)⁽⁷³⁾. These data allow one to conclude that a HSFAM induces transient but significant hypertriacylglycerolaemia that impairs endothelial function and increases oxidative stress and/or lowers antioxidant defences⁽²⁰⁾. However, such studies do not allow the establishment of a firm causal link between postprandial oxidative stress and endothelial dysfunction⁽²⁰⁾.

Table 4 details studies investigating the impact of a HSFAM on endothelial function along with oxidative stress markers. On top of confirming previous observations in which endothelial function was impaired and oxidative stress was increased following a HSFAM, the majority of

these studies correlated postprandial hypertriacylglycerolaemia, oxidative stress and/or endothelial function. Of these, Bae *et al.*⁽⁷⁵⁾ correlated (r -0.78 ; $P < 0.001$) elevated ROS production to endothelial impairments following a HSFAM in healthy subjects. Tushuizen *et al.*⁽⁷⁶⁾ also reported a borderline inverse correlation between postprandial MDA production and endothelial function (r -0.52 ; $P < 0.059$) in healthy subjects. Spallarossa *et al.*⁽⁷⁷⁾ demonstrated that a HSFAM induced activation of myeloperoxidase resulting in a significant elevation in ROS levels, which correlated positively with advanced oxidation protein products (r 0.75; $P = 0.005$) and a loss of endothelial integrity (increased soluble form of CD146 (sCD146): r 0.49, $P = 0.065$; and matrix metalloproteinase-9 (MMP-9): r 0.53, $P < 0.05$).

Individuals with higher cardiovascular risk (i.e. IGT, T2DM and subjects with familial history of T2DM) were also included in some investigations that consistently observed more important and prolonged postprandial hypertriacylglycerolaemia, oxidative stress and/or endothelial dysfunction following a HSFAM^(47,50,51,61,72,73,78–83). Anderson *et al.*⁽⁷⁹⁾ showed that postprandial TBARS were correlated (r 0.72; $P = 0.008$) with decreased endothelial function only in T2DM. Nappo *et al.*⁽⁴⁷⁾ showed that postprandial hyperglycaemia, hypertriacylglycerolaemia and impaired endothelial injuries (increased ICAM and VCAM) were greater in T2DM individuals, while Madec *et al.*⁽⁸⁴⁾ correlated such events with increased oxidative products (nitrotyrosine: r 0.54; $P = 0.0015$) in individuals with familial history of T2DM.

Some investigators also added antioxidant vitamins or compounds to HSFAM to study the oxidative stress-induced postprandial endothelial impairment hypothesis (Tables 3 and 4). Notably, it was demonstrated that co-ingestion of antioxidant vitamins C and/or E or pre-treatment with antioxidant compounds (for example, fruit juices or angiotensin-converting enzyme inhibitors) with a HSFAM prevented postprandial endothelial dysfunction^(65,85,86). The co-ingestion of vitamins C and E with a HSFAM also attenuated postprandial endothelial activation evaluated by ICAM and VCAM⁽⁴⁷⁾. Ventura *et al.*⁽⁷⁴⁾ showed that the addition of red wine to HSFAM reduces postprandial oxidative stress and improves plasma antioxidant potential, observations that were corroborated in a recent review by Covas *et al.*⁽⁸⁷⁾. Burton-Freeman *et al.*⁽⁸⁸⁾ observed that the addition of tomato extract to a HSFAM prevented an increase in oxidised LDL and marginally ameliorated postprandial endothelial function in comparison with a HSFAM alone. Finally, a 3 d vitamin C supplementation in individuals with T2DM attenuated postprandial endothelial alterations and correlated (r 0.42; $P = 0.04$) with lowered ROS production⁽⁷⁸⁾.

It is noteworthy that the addition of antioxidants in the aforementioned studies did not influence the magnitude of postprandial TAG excursion. As such, their protective effects do not appear to be due to effects on TAG



Table 3. Studies evaluating the impact of postprandial hypertriglycerolaemia (HTG) induced by oral high-saturated fat challenges on markers of oxidative stress or endothelial function

Study	Population	Fat composition and % E from fat	Absolute postprandial TAG variation (mmol/l)	Postprandial oxidative stress	Postprandial endothelial function	Comments
Vogel <i>et al.</i> (1997) ⁽⁶⁶⁾	HS (n 10)	14 g SFA; 50% E	1.85*	NA	↓ FMD*	Prevented by co-ingestion of vitamins C and E
Plotnick <i>et al.</i> (1997) ⁽⁶⁵⁾	HS (n 20)	14 g SFA; 50% E	0.6*	NA	↓ FMD*	
Djousse <i>et al.</i> (1999) ⁽¹⁰⁷⁾	HS (n 13)	0.5 g SFA/kg; 48% E	1.0	NA	= FMD	Not affected by red wine ADMA inhibits NO production
Fard <i>et al.</i> (2000) ⁽⁶¹⁾	T2DM (n 50)	52 g SFA; 75% E	3.38	NA	↓ FMD*	
Marchesi <i>et al.</i> (2000) ⁽⁶³⁾	HS (n 10)	40 g SFA/m ² ; 84% E	0.72*	NA	↑ ADMA*	Could be explained by increase baseline artery diameter
Raitakari <i>et al.</i> (2000) ⁽⁹¹⁾	HS (n 12)	55 g SFA; 53% E	1.0	NA	↓ FMD*	
Gokce <i>et al.</i> (2001) ⁽⁶²⁾	HS (n 14)	27 g SFA; 47% E	0.78*	NA	↓ FMD*	Vitamin C and E co-ingestion attenuated endothelial injuries
Nappo <i>et al.</i> (2002) ⁽⁴⁷⁾	HS (n 20); T2DM (n 20)	20 g SFA; 60% E	0.4 (HS)* 1.5 (T2DM)*	NA	↑ ICAM and VCAM (both groups)*	
Ling <i>et al.</i> (2002) ⁽⁸⁵⁾	HS (n 50); CHD (n 74)	5 g SFA; 56% E	1.0 (HS)* 1.4 (CHD)*	NA	↓ FMD*	More important for CHD, prevented by vitamin C co-ingestion
Ferreira <i>et al.</i> (2004) ⁽⁶⁷⁾	HS (n 18)	14 g SFA; 50% E	0.58*	NA	↑ EMP*	Increased baseline artery diameter
Giannattasio <i>et al.</i> (2005) ⁽¹⁰⁸⁾	HS (n 7); HTG (n 16)	83% E	0.30 (HS) 2.47 (HTG)*	NA	= FBF and FMD (HS) ↓ FMD (HTG)*	
Padilla <i>et al.</i> (2006) ⁽⁶⁴⁾	HS (n 8)	16.5 g SFA; 46% E	NA	NA	= FMD	Increased baseline artery diameter
Nicholls <i>et al.</i> (2006) ⁽⁹⁸⁾	HS (n 14)	1 g/kg coco oil (89.6% SFA)	0.31	NA	↓ FMD ↑ ICAM and VCAM	
Rueda-Clausen <i>et al.</i> (2007) ⁽⁹⁹⁾	HS (n 10)	26 g SFA; 91% E	0.12	NA	↓ FMD	Prevented by addition of 540 mg EPA and 360 mg DHA
Harrison <i>et al.</i> (2009) ⁽⁶⁸⁾	HS (n 8)	About 60 g SFA; 60% E	1.45	NA	↑ EMP	
MacEneaney <i>et al.</i> (2009) ⁽¹⁰⁹⁾	HS (n 10); obese (n 8)	About 60 g SFA; 60% E	0.95 (HS) 1.25 (obese)	NA	= ICAM and VCAM	Prevented by addition of 540 mg EPA and 360 mg DHA
Ayer <i>et al.</i> (2010) ⁽⁸⁰⁾	HS (n 11); obese (n 11)	25 g SFA; 54% E	1.1 (HS) 1.0 (obese)	NA	= FMD (both groups)	
Fahs <i>et al.</i> (2010) ⁽⁶⁰⁾	HS (n 20)	13.5 g SFA; 47% E	NA	NA	↓ Normalised FMD	Red wine ameliorated oxidative profile More important for T2DM
Strohacker <i>et al.</i> (2012) ⁽⁷⁰⁾	HS (n 8)	18.5 g SFA; 59% E	0.90	NA	↑ EMP	
Ventura <i>et al.</i> (2004) ⁽⁷⁴⁾	HS (n 15)	14 g SFA; 50% E	0.96	↑ MDA, uric acid ↓ Plasma antioxidant	NA	More important for T2DM
Saxena <i>et al.</i> (2005) ⁽⁷³⁾	HS (n 13); T2DM (n 13)	61 g SFA/m ² ; 81% E	0.29 (HS)* 1.24 (T2DM)*	↑ TBARS*, SOD, GSH	NA	
Devaraj <i>et al.</i> (2008) ⁽¹¹⁰⁾	MetS (n 11)	15.5 g SFA; 50% E	1.02	↑ TBARS, MDA, HNE, peroxide	NA	More important for T2DM
Fisher-Wellman & Bloomer (2010) ⁽⁷¹⁾	HS (n 10)	0.6 g SFA/kg; 1 g fat/kg	0.40*	↑ MDA*, H ₂ O ₂ *, NOx* = Plasma antioxidant capacity	NA	
Bloomer <i>et al.</i> (2010) ⁽⁴⁵⁾	HS (n 9)	20 or 40 g SFA; 100% E	0.28 (33 g SFA) 0.85 (40 g SFA)*	↑ MDA and H ₂ O ₂ (for 40 g SFA only)* = Plasma antioxidant capacity, SOD	NA	More important for T2DM
Gregersen <i>et al.</i> (2012) ⁽⁷²⁾	HS (n 7); HS with FHD (n 8)	27 g SFA; 76% E	1.1		NA	

Oxidative stress and endothelial dysfunction

E, energy; HS, healthy subjects; NA, not available; ↓, decrease; FMD, flow-mediated dilatation; =, unchanged; T2DM, type 2 diabetes mellitus; ↑, increase; ADMA, asymmetric dimethylarginine; ICAM, inter-cellular adhesion molecule; VCAM, vascular cell adhesion molecule; CHD, chronic heart disease; EMP, endothelial microparticles; FBF, forearm blood flow; MDA, malondialdehyde; TBARS, thiobarbituric acid-reactive substance; SOD, superoxide dismutase, GSH, glutathione; MetS, metabolic syndrome; HNE, hydroxynonenal; NOx, nitrate/nitrite; FHD, familial history of type 2 diabetes mellitus.

* Significant correlation ($P < 0.05$).

Table 4. Studies evaluating the link between oxidative stress and endothelial function induced by oral high-saturated fat challenges

Study	Population	Fat composition and % E from fat	Absolute postprandial TAG variation (mmol/l)	Postprandial oxidative stress	Postprandial endothelial function	Comments
Williams <i>et al.</i> (1999) ⁽¹¹¹⁾	HS (n 10)	30 g SFA; 65% E (used or unused oil)	1.29 (unused) 0.82 (used)	= TBARS, lipid peroxidation	= FMD (unused) ↓ FMD (used)	Oil used for deep-frying contained peroxides, no correlation found
Bae <i>et al.</i> (2001) ⁽⁷⁵⁾ Anderson <i>et al.</i> (2001) ⁽⁷⁹⁾	HS (n 11) HS (n 12); T2DM (n 12)	53.4 g SFA; 60% E 80 g SFA	0.59** 0.87 (HS) 5.6 (T2DM)*	↑ ROS production*,** ↑ TBARS* and ROS production = NT (HS) ↑ NT (T2DM)	↓ FMD*,** ↓ FMD*	Significant correlation only in T2DM
Ceriello <i>et al.</i> (2002) ⁽⁵¹⁾	HS (n 20); T2DM (n 30)	47 g SFA; 96% E	NA	= MDA and vitamin E	↓ FMD	Prolonged for T2DM, no correlation calculated
Bae <i>et al.</i> (2003) ⁽¹¹²⁾ Ceriello <i>et al.</i> (2005) ⁽⁵⁰⁾ Anderson <i>et al.</i> (2006) ⁽⁷⁸⁾	HS (n 10) T2DM (n 20) T2DM (n 20)	60% E 47 g SFA; 96% E 80 g SFA; 80% E	0.68* 2.0 0.9*,**	↑ NT and ICAM ↑ ROS production** and TBARS	↓ FMD* ↓ FMD ↓ FMD*	Unknown SFA quantity No correlations calculated Vitamin C supplementation prevented increased ROS and decreased FMD (correlated)
Tushuizen <i>et al.</i> (2006) ⁽⁷⁶⁾	HS (n 17)	30 g SFA; 52% E	0.9**	↑ oxLDL/LDL** and MDA*	↓ FMD* ↑ EMP	
Cortés <i>et al.</i> (2006) ⁽¹¹³⁾	HS (n 12); HC (n 12)	47 g SFA + OO or walnut (ALA and arginine); 63% E	0.93 (HS) 1.37 (HC) Similar for both meals	↓ oxLDL (both meals)	↓ FMD (OO) = FMD (walnut) ↓ ICAM and VCAM (both meals) ↓ e-selectin (walnut) ↓ FMD	No correlations found
Rudolph <i>et al.</i> (2007) ⁽¹¹⁴⁾	HS (n 24)	13.1 g SFA; 37% E	0.47	↑ 8-isoPGF	↓ FMD	No significant correlation found
Spallarasso <i>et al.</i> (2008) ⁽⁷⁷⁾ Armah <i>et al.</i> (2008) ⁽⁸⁹⁾	HS (n 15) HS (n 25)	30 g SFA; 78% E 33 g SFA; 48% E	0.33* 1.04	↑ MPO, ROS* and AOPP*,** ↓ Nitrite = eNOS and <i>Nox-4</i> gene expression	↑ sCD146 and MMP-9** = Endothelial vasodilatation to Ach and SNP	Improved by addition of 2.2 g EPA and 3.2 g DHA
Berry <i>et al.</i> (2008) ⁽¹¹⁵⁾ Lin <i>et al.</i> (2008) ⁽⁶⁹⁾	HS (n 17) HS (n 20)	26.7 g SFA; 53% E 14 g SFA; 50% E	0.40 0.50*	↓ Isoprostane = GSHPx	↓ FMD ↓ FMD* ↑ P-selectin and vWF	No correlations found Prevented by L-Arg co-ingestion
Tsai <i>et al.</i> (2009) ⁽¹¹⁶⁾	HS (n 16)	14 g SFA; 51% E	1.41	↓ GSHPx ↑ PGF2	↓ FMD = ICAM, VCAM	Oxidation and FMD are associated but no correlation calculated
Neri <i>et al.</i> (2005) ⁽⁸⁶⁾ and 2010) ⁽⁸²⁾	HS (n 40), IGT (n 40); T2DM (n 40)	80 g SFA; 49% E	0.68 (HS) 2.9 (IGT) 4.8 (T2DM)*	↑ MDA, HNE, oxLDL, GSHPx	↓ FMD* ↑ ET-1, vWF, VCAM ↓ NO ↑ ICAM*, VCAM**	More important for IGT and T2DM and prevented by antioxidants
Madec <i>et al.</i> (2011) ⁽⁸⁴⁾	HS (n 16); HS with FHD (n 16)	14.25 g SFA; 52% E	0.16 (HS) 0.26 (FHD)**	↑ NT*		In FHD only
Newens <i>et al.</i> (2011) ⁽⁹⁰⁾	HS (n 59)	0.52 g fat/kg; 64% SFA	No significant increase	↓ NOx	↓ FMD = ICAM and ET-1	3.8 g DHA and 0.4 g EPA improved FMD but not NOx
Jenkins <i>et al.</i> (2011) ⁽¹¹⁷⁾	HS (n 10)	30 g SFA; 84% E	0.68	↑ ROS, oxLDL and SOD	= EMP	No significant correlation found

Table 4. Continued

Study	Population	Fat composition and % E from fat	Absolute postprandial TAG variation (mmol/l)	Postprandial oxidative stress	Postprandial endothelial function	Comments
Johnson <i>et al.</i> (2011) ⁽⁸¹⁾	Active HS (<i>n</i> 7); inactive HS (<i>n</i> 7)	16.5 g SFA; 46% E	1.08 (active) 4.08 (inactive)	= TBARS and SOD	↓ FMD only for inactive HS	No significant correlation found
Peairs <i>et al.</i> (2011) ⁽⁸³⁾	Obese (<i>n</i> 11)	59% E	0.23	↓ PGF2	↑ ICAM = VCAM	Unknown SFA quantity, no significant correlation found
Burton-Freeman <i>et al.</i> (2012) ⁽⁸⁸⁾	HS (<i>n</i> 29)	14 g SFA; 46% E	0.62*	↑ oxLDL	= FMD*	Tomato extract prevented oxLDL increase

E, energy; HS, healthy subjects; =, unchanged; TBARS, thiobarbituric acid-reactive substance; FMD, flow-mediated dilatation; ↓, decrease; ↑, increase; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus; NA, not available; NT, nitrotyrosine; MDA, malondialdehyde; ICAM, inter-cellular adhesion molecule; oxLDL, oxidised LDL; EMP, endothelial microparticles; HC, hypercholesterolaemia; OO, olive oil; ALA, α-linolenic acid; VCAM, vascular cell adhesion molecule; MPO, myeloperoxidase; AOPP, advanced oxidation protein product; sCD146, cell-cell adhesion molecule; MMP, matrix metalloproteinase; eNOS, endothelial NO synthase; Ach, acetylcholine; SNP, sodium nitroprusside; GSHPx, glutathione peroxidase; vWF, von Willebrand factor; L-Arg, L-arginine; IGT, impaired glucose tolerance; HNE, hydroxynonenal; ET-1, endothelin-1; FHD, familial history of type 2 diabetes mellitus; NOx, nitrate/nitrite; SOD, superoxide dismutase.

Significant correlation: * $P < 0.05$; ** $P < 0.01$.

metabolism. Rather, they appear to attenuate postprandial hypertriacylglycerolaemia-induced oxidative stress in response to a HSFAM, resulting in lesser endothelial damage. The addition of *n*-3 PUFA to a HSFAM also appears to prevent postprandial endothelial dysfunction independently of the magnitude of hypertriacylglycerolaemia^(60,89,90). Although such investigations are sparse, the effect of co-ingestion of *n*-3 PUFA could be related to improved postprandial NO bioavailability through activation of endothelial NO synthase^(60,89,90).

Postprandial impact of high-monounsaturated or -polyunsaturated fat meals and challenges. Fatty acid types other than SFA may differentially influence postprandial endothelial and oxidative processes. Table 5 lists studies performed with meals rich in MUFA and PUFA. High-monounsaturated fat meals (HMUFAM) are defined as meals providing > 20% of energy from MUFA (≥ 15 g of MUFA and < 5 g SFA based on three meals and 8400 kJ (2000 kcal)/d)⁽⁵⁹⁾. For example, Vogel *et al.* found that 50 g of olive oil on bread impaired postprandial endothelial function while others observed that meals rich in MUFA had neutral effects on endothelial function^(91–94). Although oxidative stress markers were not measured, Vogel *et al.*⁽⁹³⁾ found that co-ingestion of vitamins C and E or balsamic vinegar (antioxidant) prevented postprandial endothelial injury, which again suggests a role for oxidative stress. In contrast, meals with significant amounts of high-oleic safflower-seed oil improved endothelial function in T2DM individuals⁽⁹⁵⁾. These data suggest that HMUFAM may have neutral to beneficial postprandial properties in healthy subjects. Alternatively, the observed differences may reflect differing quantities and sources of MUFA used.

The acute impact of meals containing *n*-3 PUFA or large amounts of *n*-6 PUFA, defined as meals providing > 9% of energy from *n*-6 PUFA (≥ 7 g of *n*-6 PUFA based on three meals and 8400 kJ (2000 kcal)/d), has also been investigated and yields conflicting results⁽⁵⁹⁾. The ingestion of a meal consisting of canned salmon (6 g *n*-3 PUFA) or the addition of either marine or vegetable sources of *n*-3 PUFA to a HMUFAM had no significant impact on postprandial endothelial function^(83,93,95,96). In contrast, the addition of a large quantity of EPA (8.3 g) to a high-fat meal lowered postprandial oxidative stress (improved NO bioavailability) and decreased arterial stiffness⁽⁹⁷⁾. Meals containing high amounts of *n*-6 PUFA from safflower-seed^(94,98), soya-bean^(96,99) or maize⁽⁹⁶⁾ oils have also been evaluated. Safflower-seed oil had a neutral effect on postprandial endothelial function and was associated with decreased markers of endothelial activation^(94,98). Meals rich in soya-bean oil impaired postprandial endothelial-dependent vasodilatation in one instance⁽⁹⁹⁾ and improved hyperaemic forearm blood flow (a marker of endothelial-dependent function) in another⁽⁹⁶⁾. On the contrary, maize oil was shown to impair forearm blood flow⁽⁹⁶⁾.

Table 5. Studies evaluating the link between oxidative stress and endothelial function induced by oral high-monounsaturated or -polyunsaturated fat challenges

Study	Population	Fat composition and % E from fat	Absolute postprandial TAG variation (mmol/l)	Postprandial oxidative stress	Postprandial endothelial function	Comments
Ong <i>et al.</i> (1999) ⁽¹¹⁸⁾	HS (<i>n</i> 16)	38 g MUFA; 59% E	2.4	NA	↓ FMD	
Vogel <i>et al.</i> (2000) ⁽⁹³⁾	HS (<i>n</i> 10)	50 g FA from OO, MO, salmon, OO + vitamins E and C, and OO + vinegar; 50% E	Similar for five meals (from 0.2 to 42 mg)*	NA	↓ FMD (OO)* = FMD (four other meals)	
Rueda-Clausen <i>et al.</i> (2007) ⁽⁹⁹⁾	HS (<i>n</i> 10)	46.2 g MUFA (OO); 31.7 g PUFA (soya); 91% E	0.28 (OO) 0.15 (soya)	NA	↓ FMD (both meals)	No significant correlation found
Raitakari <i>et al.</i> (2000) ⁽⁹¹⁾	HS (<i>n</i> 12)	97 g MUFA; 53% E	1.2	NA	= FMD	Could be explained by increase baseline artery diameter
Nicholls <i>et al.</i> (2006) ⁽⁹⁸⁾	HS (<i>n</i> 14)	0.75 g <i>n</i> -6 PUFA/kg	0.52	NA	= FMD ↓ ICAM and VCAM	No correlation calculated
Williams <i>et al.</i> (2001) ⁽⁹⁴⁾	HS (<i>n</i> 14)	40 g MUFA (OO); 44 g <i>n</i> -6 PUFA (SO); 69% E	0.80 OO 0.55 SO	NA	= FMD for both meals	No correlation calculated
West <i>et al.</i> (2005) ⁽⁹⁵⁾	T2DM (<i>n</i> 18)	32 g MUFA ± ALA or EPA/DHA; 72% E	1.06 (MUFA)* 0.81 (ALA)* 0.81 (EPA/DHA)*	NA	↑ FMD for three meals*	
Tentolouris <i>et al.</i> (2008) ⁽⁹²⁾	T2DM (<i>n</i> 33)	48 g MUFA; 58% E	NA	NA	= FMD	
Berry <i>et al.</i> (2008) ⁽¹¹⁵⁾	HS (<i>n</i> 17)	42.5 g MUFA; 53% E	0.45	↑ Isoprostane	↓ FMD	No significant correlation found
Hall <i>et al.</i> (2008) ⁽⁹⁷⁾	HS (<i>n</i> 17)	43.6 MUFA ± 8.3 g EPA	1.29 for both meals	No change for MUFA ↓ NOx (EPA) ↑ Isoprostane (EPA)	= Arterial stiffness index (MUFA) ↓ Arterial stiffness index (EPA)	No significant correlation found
Tousoulis <i>et al.</i> (2010) ⁽⁹⁶⁾	HS (<i>n</i> 37)	70 g MUFA (OO); 55 g <i>n</i> -6 (maize); 1.6 g <i>n</i> -3 (cod); 55 g <i>n</i> -6 (soya)	NA	= Lipid peroxidation	= RH (OO) ↓ RH (maize) ↑ RH (cod and soya)	No significant correlation found
Peairs <i>et al.</i> (2011) ⁽⁸³⁾	Obese (<i>n</i> 11)	OO ± 2.4 g EPA and 1.6 g DHA; 59% E	0.97 (OO) 0.79 (OO + <i>n</i> -3)	↑ NF-κB (<i>n</i> -3) ↓ PGF2 (two meals)	= ICAM and VCAM (both meals)	Unknown MUFA quantity, no significant correlation found

E, energy; HS, healthy subjects; NA, not available; ↓, decrease; FMD, flow-mediated dilatation; FA, fatty acids; OO, olive oil; MO, maize oil; =, unchanged; ICAM, inter-cellular adhesion molecule; VCAM, vascular cell adhesion molecule; SO, safflower-seed oil; T2DM, type 2 diabetes mellitus; ALA, α-linolenic acid; ↑, increase; NOx, nitrate/nitrite; RH, reactive hyperaemic forearm blood flow; NF-κB, redox-sensitive nuclear transcription factor κB.

* Significant correlation ($P < 0.05$).



Summary. In summary, a single HSFAM is associated with a concomitant increase in postprandial oxidative stress (or decrease in antioxidant protection) and a decrease in endothelial function (or triggered endothelial activation). The causal relationship between these phenomena appears tenuous based upon data in healthy individuals but data from studies in higher-risk individuals are stronger. This could represent the compounding effect of multiple fasting metabolic dysregulations (for example, hyperglycaemia, dyslipidaemia and insulin resistance) and lower antioxidant mechanisms resulting in prolonged hypertriacylglycerolaemia, elevated postprandial oxidative burden and greater endothelial derangements^(39,79,82,100). Some high-risk individuals, being insulin resistant, might also be resistant to the insulin-mediated vasodilatation exacerbating their postprandial endothelial dysfunction⁽¹⁰¹⁾. Studies combining meals rich in carbohydrate and SFA also suggest that hyperglycaemia and hypertriacylglycerolaemia have additive effects on endothelial and oxidative processes^(50,51). Similar postprandial events could be present in healthy subjects but with lesser magnitude and duration owing to more effective metabolic and antioxidant mechanisms making such events harder to observe and thus correlate⁽⁷⁹⁾. Previously described investigations carried out with antioxidant compounds give us insight

and add weight to support a role for oxidative stress in postprandial endothelial dysfunction.

In addition to inter-individual differences in oxidative and endothelial systems, differences in fatty acid absorption and clearance could also contribute to making postprandial responses heterogeneous, thereby weakening correlations. Different components of test meals such as protein, fibre or antioxidants (i.e. polyphenol contents of olive oils) and different sources and thus types of fatty acids (i.e. animal *v.* vegetable sources of SFA) could also explain discrepancies between studies⁽¹⁰²⁾. The postprandial impact of meals rich in MUFA and/or PUFA is less clear and reflects that the SFA:MUFA:PUFA ratio is important in determining postprandial oxidative and endothelial properties of test meals.

Concluding remarks

Postprandial hyperglycaemia and hypertriacylglycerolaemia induced by a high carbohydrate or high SFA intake lead to increased postprandial oxidative stress and impaired endothelial function in the majority of cases (for schematic representation, see Fig. 1), while high MUFA or PUFA intakes have more controversial effects. We believe that oxidative stress has a role to play in postprandial endothelial

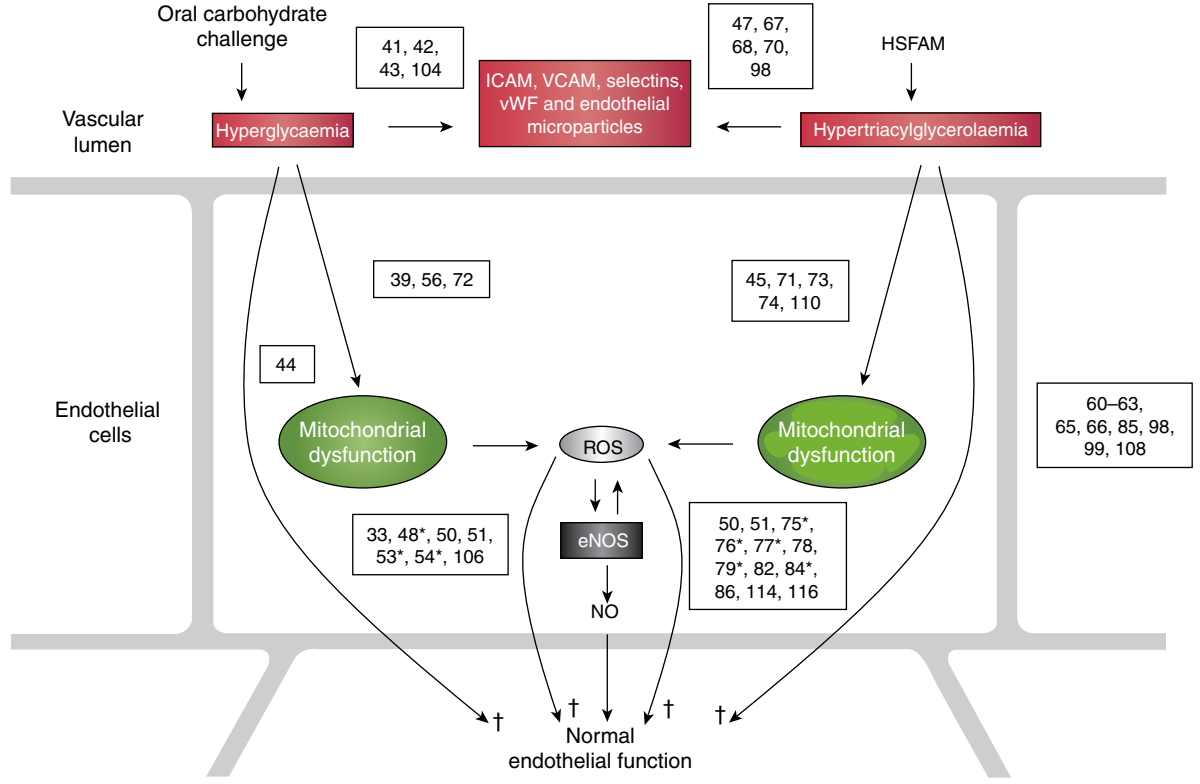


Fig. 1. Schematic representation of oxidative and endothelial postprandial events induced by acute hyperglycaemia or hypertriacylglycerolaemia and reference numbers of studies reporting such events. ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule; vWF, von Willebrand factor; HSFAM, high-saturated fat meal; ROS, reactive oxygen species; eNOS, endothelial NO synthase; VSMC, vascular smooth muscle cell. * Studies reporting significant correlation ($P < 0.05$) between oxidative and endothelial parameters. † Red arrows (grey in print) represent negative effects or impairments. (A colour version can be found online at <http://dx.doi.org/10.1017/S0954422412000182>).

dysfunction but that inter-individual differences contributed to the attenuation of statistical correlation between parameters, particularly in healthy subjects.

One limitation common to most studies is the use of biomarkers assessing different mechanisms taking place in different cellular or biological compartments that might not be relevant to postprandial processes. Wallace *et al.*⁽²⁰⁾ covered this topic in a previous publication and concluded that MDA, oxidised LDL and TBARS are probably unsuitable biomarkers for postprandial studies. In our opinion, markers specifically reflecting the impact of oxidative stress on endothelial processes (myeloperoxidase, NADPH oxidase, nitrotyrosine⁽¹⁰³⁾, nitrate/nitrite, asymmetric dimethylarginine⁽¹⁰⁴⁾) will need to be prioritised in future studies. Different fatty acid types might not affect the endothelium by the same mechanisms and could require different biomarkers to be evaluated properly⁽¹⁰¹⁾. One way to control for inter-individual differences in fatty acid absorption and metabolism would be to characterise postprandial plasma fatty acids (and antioxidants when co-administered) and perform analysis controlled for plasma fatty acid profiles. It is also possible that low-CVD risk populations could not be the most suitable cohorts for mechanistic studies because of their low baseline oxidative stress levels, effective antioxidant and metabolic processes and normal endothelial function compared with higher-risk individuals. Standardisation of oral fat challenges (i.e. standardised homogeneous oral fat load) as was done with OGTT might also need to be implemented to facilitate the understanding of postprandial mechanisms linked to certain fatty acid families. However, complete meals reflecting real-life situations must also be investigated and would provide insight into the cardioprotective mechanism of certain dietary patterns.

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