REVIEW

Nutritional status, genetic susceptibility, and insulin resistance—important precedents to atherosclerosis

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Received: November 29, 2011
Revised: January 18, 2012
Accepted: February 1, 2012

Atherosclerosis is a progressive disease that starts early in life and is manifested clinically as coronary artery disease (CAD), cerebrovascular disease, or peripheral artery disease. CAD remains the leading cause of morbidity and mortality in Western society despite the great advances made in understanding its underlying pathophysiology. The key risk factors associated with CAD include hypercholesterolemia, hypertension, poor diet, obesity, age, male gender, smoking, and physical inactivity. Genetics also play an important role that may interact with environmental factors, including diet, nutritional status, and physiological parameters. Furthermore, certain chronic inflammatory conditions also predispose to the development of CAD. The spiraling increase in obesity rates worldwide has made it more pertinent than ever before to understand the metabolic perturbations that link over nutrition to enhanced cardiovascular risk. Great breakthroughs have been made at the pharmacological level to manage CAD; statins and aspirin have revolutionized treatment of CAD and prolonged lifespan. Nonetheless, lifestyle intervention prior to clinical presentation of CAD symptoms would negate/delay the need for chronic pharmacotherapy in at-risk individuals which in turn would relieve healthcare systems of a costly burden. Throughout this review, we debate the relative impact of nutrition versus genetics in driving CAD. We will investigate how overnutrition affects adipose tissue biology and drives IR and will discuss the subsequent implications for the cardiovascular system. Furthermore, we will discuss how lifestyle interventions including diet modification and weight loss can improve both IR and metabolic dyslipidemia that is associated with obesity. We will conclude by delving into the concept that nutritional status interacts with genetic susceptibility, such that perhaps a more personalized nutrition approach may be more effective in determining diet-related risk as well as response to nutritional interventions.

Keywords:
Atherosclerosis / Diet / Inflammation / Insulin resistance / Nutrigenomics / Obesity

1 Pathogenesis of atherosclerosis

Atherosclerotic lesions begin as fatty streaks underlying the endothelium of large arteries [1, 2]. Recruitment of macrophages and their subsequent uptake of low-density lipoprotein (LDL)-derived cholesterol (LDL-C) results in the formation of "foam-cells", which in turn contribute to lesion bulk [2]. Lipid-laden macrophages are incapable of metabolizing cholesterol and the primary mechanism to relieve the lipid burden is to efflux the acquired cholesterol via the cholesterol transporters ATP-binding cassette transporter subfamily A, member 1 (ABCA1), scavenger receptor-BI (SR-BI), and ATP-binding cassette subfamily G member 1 (ABCG1) onto high-density lipoprotein (HDL) particles. Dysregulation in lipoprotein metabolism with increased levels of LDL and reduced levels/functionality of HDL particles [3, 4] is one of the major mechanisms responsible for the progressive acquisition of cholesterol within the arterial wall. In this review, we will pay particular focus to the causal mechanisms by which dysregulation in lipoprotein metabolism and inflammation-induced coronary artery disease (CAD); the influence of lifestyle and nutritional status on these processes will be discussed later.

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Abbreviations: CAD, coronary artery disease; **CETP**, cholesterol ester transfer protein; **HDL**, high-density lipoprotein; **LDL**, low-density lipoprotein; **MetS**, metabolic syndrome; **MUFA**, monounsaturated fatty acids; **oxLDL**, oxidized LDL; **PUFA**, polyunsaturated fatty acids; **SFA**, saturated fatty acids; **TAG**, triacylglycerides

1.1 LDL-C and atherosclerosis

Increased levels of LDL-C are associated with increased risk of atherosclerosis [3]. LDL particles can be divided into four subclasses ranging from lipid-enriched, largest and most buoyant LDL1, to lipid-depleted, smallest, most dense LDL4 [5, 6]. Small, dense, lipid-poor LDL particles in turn are considered more atherogenic than large LDL particles [6]. These small atherogenic particles have greater susceptibility to modification by oxidation, glycation (in diabetes), or incorporation into immune complexes which is a major cause of injury to the endothelium and underlying smooth muscle cells [7, 8]. Internalization of modified LDL-C by macrophages leads to the accumulation of cholesterol esters, resulting in formation of foam cells [9]. Extensively oxidized LDL (oxLDL) has reduced affinity for hepatic LDL receptors but instead is recognized by scavenger receptors such as CD36 expressed on macrophages and smooth muscle cells, which redirects uptake of oxLDL cholesterol into these cell types contributing to atherosclerotic lesion bulk [2, 9].

1.2 HDL functionality, reverse cholesterol transport (RCT), and CAD risk

HDL-C levels inversely correlate with atherosclerosis [10]. HDL particles have a number of key anti-atherogenic functions, including the capacity to promote RCT and modulate inflammation. HDL particles play a key role in RCT by promoting cholesterol efflux from peripheral cells, including lipid-laden macrophages, and delivering acquired cholesterol to the liver for excretion in the bile and feces, a process that is believed to be atheroprotective [11]. Measurements of HDL-C levels are limited in their capacity to inform on how efficient HDL particles are at facilitating efflux from peripheral cells. A recent study by Khera et al. has demonstrated that measurement of HDL efflux capacity is a stronger predictor of CAD than measurement of plasma HDL-C levels and therefore more intensive interrogation of HDL functions may be warranted to truly define CAD risk [4]. HDL particles also exhibit potent anti-inflammatory functions including the capacity to inhibit oxidation of LDL particles and prevent oxLDL-induced transmigration of monocytes [12]. These anti-inflammatory functions of HDL are negated during the acute phase response [13] and more recently it has been demonstrated that HDL from diabetic cohorts have reduced anti-inflammatory capacity [14]. These findings again highlight the limitations on focusing on HDL particle concentration and the need for greater analysis of functionality.

1.3 Inflammation and CAD paradigm

Chronic inflammation is a classic hallmark of CAD and is thought to play a causal role during its pathogenesis [2, 15–17]. Indeed, certain chronic inflammatory conditions also predispose to the development of CAD including insulin resistance (IR) [18], type 2 diabetes mellitus [19] and arthritis [20]. Some of the earliest features of atherosclerosis include increased expression of adhesion molecules along the endothelium which in turn facilitate the adhesion of inflammatory cells including monocytes and lymphocytes [21]. Epidemiological studies have demonstrated increased vascular risk associated with increased levels of proinflammatory mediators and acute phase proteins such as interleukin (IL)-6, Tumor Necrosis Factor-α (TNF-α), C-reactive protein (CRP), and serum amyloid A [21]. Indeed patients with elevated CRP are at increased risk of clinical events than those with normal CRP [22]. Inflammation is also a critical regulator of lipoprotein metabolism and particularly impacts on HDL functionality [23, 24]. Experimental endotoxemia in vivo reduces HDL efflux capacity [25] and similarly the anti-inflammatory functions of HDL are lost during the acute phase response [13]. HDL composition was also markedly altered during inflammation with increased association of serum amyloid A and dissociation of Apolipoprotein (Apo)-A1 on the particles. These findings suggest that individuals with normal HDL-C levels but elevated systemic proinflammatory cytokines may be at increased risk of atherosclerosis due to reduced functionality of HDL. Endotoxin administration in mice also markedly reduced hepatic expression of key cholesterol transporters ABCG5, ABCG8, and ABCB11 resulting in reduced movement of ^{3}H-cholesterol through the liver to bile and feces [24]. It is thus feasible that in chronic inflammatory states, the liver is the primary target for inflammatory cytokines that alter lipoprotein metabolism pathways.

2 The impact of nutrition on cardiovascular health parameters

2.1 Diet and atherosclerotic risk

There is little doubt that lifestyle, encompassing diet and physical activity, are important determinants of atherosclerotic risk [25, 26], however whether specific macronutrients are associated with enhanced risk is controversial. Many other cardiovascular risk factors are inextricably associated with nutritional status including obesity, hypertension, and hypercholesterolemia making it difficult to extrapolate the direct contribution of dietary components to CAD. In this section, we will review the current literature describing the impact of dietary fat on lipoprotein metabolism and cardiovascular risk. Traditionally low saturated-fat diets are recommended for patients with/at risk of CAD; however the optimal macronutrient replacement for saturated fat is controversial [26]. High-saturated fat diets are associated with modest increases in both LDL and HDL cholesterol levels [27]. A number of mechanisms are likely accountable for these increased cholesterol levels including increased rates of cholesterol synthesis [28] and reduced expression of the LDL-receptor (LDL-R) [29].

Evidence for an adverse role for saturated fat in driving CAD however is incomplete. Recently, a prospective

metaanalysis of 21 independent studies, carried out by Siri-Tarino et al., demonstrated no significant relationship between dietary saturated fat and risk of coronary heart disease, stroke, and cardiovascular disease [30]. The cohort size was 347,747 subjects, 11,006 of which developed CAD or stroke. Furthermore, a study by Krauss et al. demonstrated that a high-fat diet (HFD) (46% dietary energy from fat) in 105 healthy men resulted in an LDL profile that was predominantly comprised of large, buoyant LDL particles. Counterintuitively, when these men were switched to low-fat diet (24% dietary energy from fat) a high proportion of subjects switched to having a more atherogenic LDL profile with smaller, denser LDL particles [31]. Similarly, substitution of saturated fat for carbohydrate in the diet is associated with an elevation in small dense LDL lipoprotein particles and systemic triacylglycerols (TAG), coincident with reductions in HDL-C [5, 31]. Thus the traditional panacea to minimize circulating cholesterol via low-fat, high-carbohydrate diets are not necessarily associated with reduced incidence of cardiovascular events [26, 32].

2.2 Substitution of saturated fatty acid (SFA) for monounsaturated fatty acid (MUFA) and lipid metabolism

Replacement of SFA for the more inert MUFA, as opposed to carbohydrate, has emerged as a potential strategy for cardiovascular risk management, particularly for management of individuals with the metabolic syndrome (MetS) and type 2 diabetes in which improved glycemic control is desired. Indeed consumption of a "Mediterranean" style diet, which is enriched with MUFA and n-3 PUFA, is associated with reduced risk of CAD [33]. It is difficult, however, to extrapolate whether the improvements in cardiovascular risk parameters associated with the Mediterranean diet are solely attributable to changes in dietary macronutrients; indeed it is more probable that the combination of diet and lifestyle modifications, in addition to improved lipid parameters culminate in reduced CAD risk.

Cross-sectional studies suggest that SFA are associated with insulin resistance (IR) [34–36] wherein total fat and particularly SFA has been considered to increase plasma cholesterol concentrations, promote IR, and increase the risk of the MetS [35, 37]. In healthy subjects, isoenergetic substitution of SFA for MUFA or carbohydrates improved insulin sensitivity [38, 39], although Lovejoy et al. [40] showed no effect. A meta-analysis comparing low-saturated, high-carbohydrate diet to high-MUFA diets in type 2 diabetic patients revealed that MUFA diets improve both lipoprotein profiles and glycemic control [41]. MUFA diets were associated with reduced plasma TAG and very low density LDL (VLDL) (−19% and −22%, respectively) and an increase in HDL-C with minimal effect on LDL-C. The DELTA study also compared the exchange of dietary SFA for MUFA in patients with the MetS in a 7-week randomized cross-over study ($n = 52$ men, 33 women) [42]. LDL-C was lower with both complex carbohydrate (−7%) and MUFA (−6.3%) diets. Plasma TAG concentrations were moderately reduced with the MUFA diet but were increased following the high-carbohydrate diets. In the larger scale pan-European LIPGENE study, the effects of isocaloric diets high in either MUFA (38% energy), SFA (38% energy), or low-fat, high complex carbohydrates (LFHCC) on lipid parameters in patients with the MetS ($\sim n = 120$ subjects per group) were investigated over a 12-week intervention period [43]. This study demonstrated little difference in total cholesterol and LDL-C across all diet groups. Plasma levels of HDL-C, however, were significantly increased while plasma TAG levels were decreased with both SFA- and MUFA-enriched diets. A trend toward elevated TAG was evident with the LFHCC diet but HDL-C levels remained constant. These studies argue that replacing SFA for carbohydrates or MUFA is not justified. However cardiovascular risk has been broadly based on basic lipoprotein profiles within these cohorts. Greater interrogation of LDL subparticles (LDL1-4), measurement of LDL modifications, and evaluation of HDL function parameters are justified to gain a greater appreciation of true cardiovascular risk.

2.3 Dietary polyunsaturated fats—the right way forward?

Substitution of SFA for polyunsaturated fat (PUFA) has yielded the most promising results in terms of reducing CAD risk coincident with reductions in circulating LDL-C [44, 45]. The Lyon Diet Heart Study addressed the hypothesis that substitution of a Western-style diet for a Mediterranean diet would improve cardiovascular outcomes. The Mediterranean diet used in the study included increased intake of n-3 PUFA (α-linolenic acid), a reduction in saturated, and a modest increase in fiber and total carbohydrate. Interestingly, despite no change in lipoprotein parameters including plasma TAG, LDL, and HDL levels, there was a 72% reduction in recurrent cardiovascular events in this cohort. Such remarkable effects were maintained at 46 months postcommencement of trial [46, 47]. These findings again demonstrate that lack of difference in crude lipid profiles does not always reflect true cardiovascular risk and justify measurements of functionality. Further beneficial effects of long-chain n-3 PUFA were observed in LIPGENE which incorporated a treatment arm that was assigned to a low-fat, high-complex carbohydrate (LFHCC) diet ± 1.24g/d long-chain (LC) n-3 PUFA for 12 weeks and demonstrated that supplementation with LC n-3 PUFA prevented high-carbohydrate-induced hypertriglyceridemia [43]. These studies give further weight to use of LC n-3 PUFA supplementation as a treatment strategy for dyslipidemia. While systemic cholesterol levels unarguable correlate with CAD, the role/contribution of dietary cholesterol to this phenotype has been rather elusive. In mouse studies, incorporation of cholesterol into an atherogenic diet is essential to drive CAD. However, in humans relative to fatty acid composition, dietary cholesterol has minimal impact on systemic cholesterol levels

[48–50]. Circulating plasma cholesterol is primarily governed by de novo lipogenesis of cholesterol, under control of the rate-limiting enzyme HMG-CoA reductase, which primarily occurs in the liver [51, 52].

2.4 High-protein diets and cardiovascular risk

High-protein diets have received much attention in recent years due to their promising effects on weight loss [53, 54]. In a large-scale intervention study, the effectiveness of low-calorie diets high in protein and low in glycemic index to maintain weight loss were assessed and compared to a low-protein high-glycemic index diet ($n = 773$ participants). Interestingly, fewer participants maintained on the high-protein, low-glycemic index diet dropped out of study compared with individuals on the low-protein high-glycemic index diet indicative of heightened compliance to the high-protein diet. Furthermore, the low-protein high-glycemic index diet was associated with enhanced weight regain compared to high-protein, low-glycemic index group [55]. However, whether substitution of dietary saturated fat for protein has health benefits for cardiovascular disease remains to be fully evaluated. Preliminary studies in hypertensive rats suggests that high-protein diets exacerbate hypertension and renal damage, coincident with increased number of immune cells in the kidney [56] and thus high-protein diets may be contraindicated for cardiovascular disease. Human studies have further demonstrated that amino acid infusion in diabetic individuals increased the glomerular filtration rate (GFR) compared to normal individuals [57]. Furthermore, the Third National Health and Nutrition Examination Survey demonstrated that dietary protein intake correlates with the presence of microalbuminuria, a marker of kidney damage and worsening renal function, in those with diabetes but not in those without diabetes [58]. These findings warrant caution in prescribing high-protein diets to individuals with diabetes given the increased risk of kidney damage [59]. The impact of high-protein diets on atherogenesis, however, is relatively unknown. In the ApoE$^{-/-}$ mouse model of atherosclerosis, intervention with a low-carbohydrate, high-protein (LCHP) diet resulted in greater atherosclerosis compared to mice maintained on standard diet or western diet (with comparable fat and cholesterol content) [60], however such findings remain to be validated in humans.

2.5 The "ideal" diet for minimizing cardiovascular risk

Overall, a rethink of the "ideal" dietary prescription for individuals at risk of developing atherosclerosis is overdue and will be likely tailored to individuals' risk factors that will be particularly relevant for patients with IR and type 2 diabetes. To this end Hu et al. performed a prospective meta-analysis reviewing metabolic, epidemiologic, and clinical trial evidence regarding diet and CAD prevention across 147 original articles and reviews [61]. Findings from this meta-analysis revealed three dietary strategies that improved cardiovascular risk: (i) Substitution of nonhydrogenated unsaturated fats for saturated and trans fats; (ii) increased consumption of n-3 PUFA from fish, fish-oil supplements, or plant sources, and (iii) consumption of a diet high in fruits, vegetables, nuts, and whole-grains and low in refined grain products [61]. In agreement with Siri-Tarino et al., this meta-analysis demonstrated no evidence that lowering percentage dietary fat improved lipid profiles or reduced cardiovascular incidences.

3 Nutritional status, obesity, and metabolic dyslipidemia

While the role of specific dietary macronutrients in development of CAD is still debatable, the association between overnutrition, obesity, and CAD risk is undeniable [62]. Indeed other comorbidities which often coincide with obesity, including IR, hypertension, and type 2 diabetes mellitus [63, 64], result in even greater risk for the development of CAD [65]. The dramatic rise in obesity rates worldwide is extremely worrisome. Specifically, the prevalence of obesity in the USA has increased from 12% in 1991 to 33.8% in 2008 [66, 67]. Likewise, the incidences of type 2 diabetes are also increasing worldwide and approximately 60–90% of cases appear to be directly related to obesity or weight gain [65]. Overwhelming evidence points to a primary role of adipose tissue dysfunction during the development of IR which is a prerequisite to the development of type 2 diabetes. In this review, we will discuss the central role for adipose tissue inflammation in the development of IR and subsequent consequences for the cardiovascular system (see Fig. 1).

3.1 Adipose tissue as an endocrine organ

Adipose tissue, once considered an inert organ responsible for lipid storage and thermogenesis, has emerged as arguably the largest endocrine organ of the body, particularly in the obese state. Adipose-derived cytokines include IL-6, TNF-α, and IL-1-β, chemokines include monocyte chemoattractant protein-1 (MCP1), macrophage migration inhibitory factor (MIF), and fractalkine, and metabolic hormones include leptin, adiponectin, and resistin. During obesity, there is a shift in balance in adipokine secretion with enhanced secretion of proinflammatory cytokines such as IL-1-β, IL-6, and TNF-α and a reduction in secretion of the insulin-sensitizing hormone adiponectin. Indeed adiponectin is often considered a biomarker of adipose tissue "health" with reduced levels associated with IR and enhanced CAD risk [68]. Remarkably, adiponectin significantly correlates with serum HDL-C [69] implicating a role for adipose tissue health in maintenance of cardiovascular health.

3.2 IR and atherosclerosis—mirror images

Chronic inflammation is a classic hallmark of both IR and atherosclerosis. Adipose inflammation is thought to

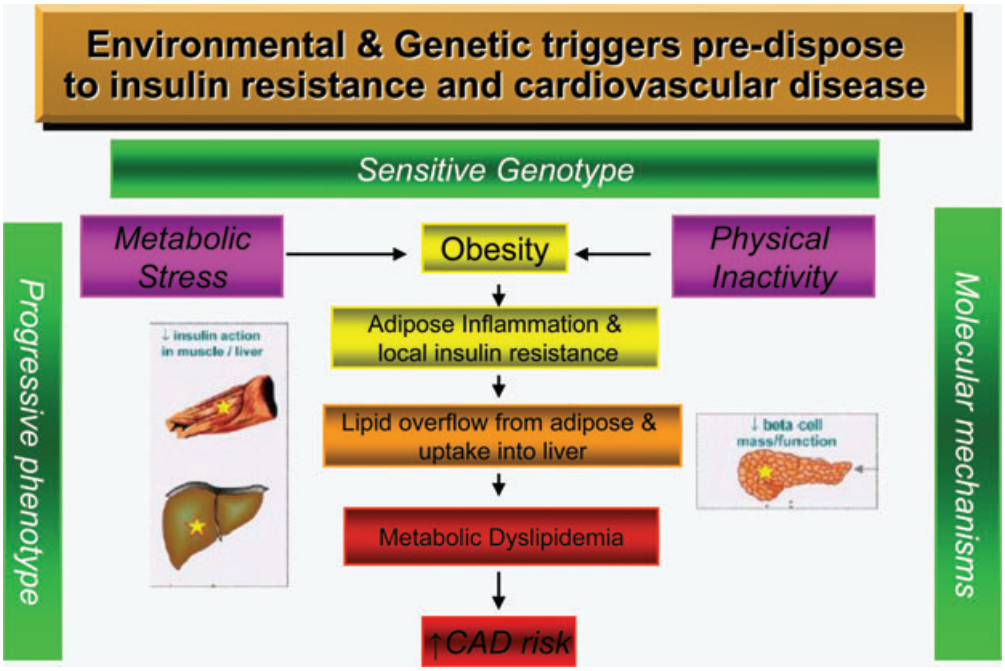

Figure 1. Adipose tissue "health" is a critical determinant of CAD risk. Loss of efficiency of adipocytes to store TAG results in an overflow of fatty acids into circulation and uptake into liver which is a likely critical step in the development of metabolic dyslipidemia and increased cardiovascular risk. The contribution of nutrition status and genetically determined sensitivity to environmental triggers is discussed in this review. *Adapted from* Roche, H. M., *Proc Nutr. Soc.* 64(23), 2005.

be central to the development of IR but whether adipose inflammation also affects atherogenesis is relatively unknown. Lack of either TNF-α [70], IL-1RI [71], or TLR4 [72] signaling in mice has been shown to protect against HFD-induced IR. Similarly, lack of TNF [73], TLR4 [74, 75] and IL-1 [76] protects against development of atherosclerotic lesions. Activation of IL-1 is dependent upon processing from a pro to active form which is facilitated by the NLRP3-caspase-1 inflammasome complex [77]. Lack of NLRP3 inflammasome activation has been shown to protect against HFD-induced IR [78] and is also associated with reduced atherosclerotic lesion formation [79]. Immune cell infiltration into adipose tissue during obesity has been well characterized with initial infiltration of cytotoxic T-cells [80] followed by macrophages [81]. Indeed resident immune cells are thought to be the primary source of adipose-derived cytokines. Similarly, immune cell infiltration into the subendothelial layer of the vasculature is detrimental during atherogenesis [21]. Indeed there are many similarities between these two disease states—the primary core pathology of both states being inflammation.

3.3 Saturated fats—the initiator of adipose tissue inflammation?

The initial trigger that initiates adipose tissue inflammation has been at the center of numerous debates in the obesity field; hypoxia, mitochondrial dysfunction, and lipotoxic free fatty acids (FFA) have all been implicated. Recent data however point to a role for saturated fats in priming the NLRP3 inflammasome complex, and represents a potential mechanism in the initiation of adipose inflammation [82]. Lack of TLR4 has long been known to protect against the development of IR [72] and SFA have been previously shown to interact with and activate TLR4. However, very high doses of SFA are required to drive only very modest inflammatory responses in vitro [72]. Recent data however have shown that saturated fats prime the NLRP3 inflammasome to produce pro-IL-1 [82]; a second signal in turn is required to process pro to active IL-1. The identity of this second signal in adipose is still out for debate; but likely culprits include reactive oxygen species and ATP.

3.4 Metabolic dsylipidema and systemic lipotoxicity—central role for adipose and liver

A major mechanism linking obesity to atherogenesis is metabolic dyslipidemia which encompasses an elevation in levels of small, dense proatherogenic LDL particles, a reduction in HDL-C, and increased levels of circulating TAG [83–86]. This tilting in the balance of LDL:HDL likely accounts for increased manifestation of CAD in obese cohorts. The primary function of adipose is to store FFA, in the form of TAG, and only release these FFA upon energy requirements. During obesity, enlargement of adipocyte size (hypertrophy) and development of IR results in reduced efficiency of adipocytes to store FFA. The net result is increased systemic levels of FFA

and uptake into peripheral organs, in particular the skeletal muscle and liver, and the development of systemic IR. Overflow of lipid from the exhausted adipose tissue into the liver is likely a key step that drives metabolic dyslipidemia and increases CAD risk. The majority of hepatic lipid is derived from nonesterified fatty acids but it is worth noting that de novo lipogenesis and dietary fat do also contribute to the lipid burden [87]. In the past number of years, the incidence of nonalcoholic fatty liver disease (NAFLD) has increased dramatically and the risk of developing NAFLD increases with the degree of obesity [29]. Furthermore, NAFLD has been correlated to increased carotid artery intimal medial thickness [88] independent of other risk factors including obesity and IR. FFA taken up by the liver can be repackaged into TAGs and secreted on VLDL particles. TAGs on VLDL particles in turn can be exchanged for cholesterol esters on HDL particles via cholesterol ester transfer protein (CETP), the activity of which is increased with obesity [89]. TAG enrichment of HDL renders the particles susceptible to cleavage by lipases, such as endothelial lipase which is induced in insulin-resistant chronic inflammatory states [90, 91]. Lipid poor HDL particles in turn are rapidly cleared from circulation [92]. It is thus conceivable that fatty acid infiltration into liver, due to failure of the adipose tissue to adequately lock away deleterious fatty acids, is at the core of metabolic dyslipidemia.

Improving adipose tissue functionality/storage capacity and relieving hepatic lipid burden is an attractive therapeutic target for the treatment of metabolic dyslipidemia. Indeed a recent study from the PERISCOPE trial demonstrated that treatment with the PPAR-γ agonist pioglitazone over 18 months in type 2 diabetic patients was associated with increased HDL-C coincident with reduced levels of TAGs, CRP, and glycated hemoglobin [93]. Furthermore, the improved TAG/HDL ratio correlated with delayed atheroma progression in diabetic patients with CAD. A separate study by Khera et al. examined the effects of pioglitazone treatment on HDL function in patients with the MetS and demonstrated significantly improved efflux capacity of HDL after 12 weeks PPAR-γ intervention [4]. The primary mechanism of PPAR-γ agonists is to enhance storage capacity of adipose tissue and improve adipose insulin sensitivity. Findings from the PERISCOPE study certainly suggest that targeting the adipose tissue to improve metabolic dyslipidemia is a valid therapeutic strategy for reducing CAD risk while findings by Khera et al. demonstrate the added beneficial effects of improving adipose health on HDL efflux parameters.

3.5 Lifestyle strategies for improving metabolic dyslipidemia and IR

The primary strategy to alleviate IR in obese individuals is to promote weight loss through a combination of diet and physical activity [94]. While low-fat diets are recommended for weight loss, they are often replaced by carbohydrates that can result in worsening of metabolic dyslipidemia. At-risk individuals are often advised to consume a low-carbohydrate diet to achieve improved glycemic control and reduce caloric intake to promote weight loss. A study by Kraus et al. demonstrated that low-carbohydrate diets (26% carbohydrate) over a 3-week period reduced TAGs, small LDL particles, and total HDL cholesterol in the absence of weight loss in men [95, 96]. Subsequent induction of weight loss (caloric intake reduced by 1000 kcal/day over 5 weeks) in these individuals resulted in even more pronounced improvement in metabolic dyslipidemia. The LIPGENE intervention study sought to determine whether dietary replacement of SFA for MUFA or consumption of low-fat high-complex carbohydrate (LFHCC) diet (all diets were isocaloric and aimed not to induce weight loss) over 12 weeks would improve systemic insulin sensitivity (Si) in patients with the MetS and after intervention found little effect of macronutrient on Si parameters [43]. Similarly, the RISCK study did not find any justification for replacement of SFA with MUFA or low/high glycemic index carbohydrates on Si measurements [97]. Thus while dietary interventions have the potential to modify lipoprotein parameters, they do not appear to improve insulin sensitivity in the absence of weight loss. Overwhelming evidence supports the concept that weight loss is the best medicine for MetS and in certain incidences can resolve type 2 diabetes and markedly reduce CAD risk [98–100]. Indeed weight loss of 10% of initial body weight is associated with improved glycemic control, improved lipid profiling, and reduced blood pressure in type 2 diabetic cohorts [65]. Weight loss after bariatric surgery (−20%) was also recently shown to improve HDL acceptor functionality via the SR-BI pathway, beyond changes in HDL-C mass [101]. The enhanced efflux capacity of plasma from these individuals was attributed to increased levels of cholesteryl ester-rich HDL2 particles that were coincident with a significant reduction in CETP activity (−15%). Weight loss therefore has a multitude of antiatherogenic effects from resolving metabolic dyslipidemia to improving HDL functionality.

4 Genetic susceptibility and gene nutrient interactions relevant to RCT IR and atherosclerosis

A person's genetic sequence defines the individual but does not directly cause IR or atherosclerosis (apart from the very uncommon monogenic familial forms). Genome-wide association studies fail to explain more than 10–15% of risk for developing obesity, IR, T2DM, or atherosclerosis [102, 103]. The potential interactions between environmental factors, including food intake and other lifestyle factors, add a further layer of complexity which are probably critically important in the pathogenesis and progression of the common polygenic, diet-related diseases. Nutrigenomics provide proof-of-concept wherein dietary factors may interact with sensitive genotypes to increase risk of diet-related diseases and/or determine an individual's response to a dietary intervention

[104–106]. Therefore it may be time to more accurately identify the nutrient sensitive genotypes and to develop a "personalised nutrition" approach, whereby nutrient intake is manipulated/optimized based on an individual's genetic profile to reduce disease risk and/or improve the effectiveness of dietary guidelines/recommendations. Nevertheless, this approach is still in its infancy, progress is hampered by the polygenic nature of IR and atherosclerosis; coupled with the complexity of accurately assessing dietary intake or measuring lifestyle biomarkers; in addition to potentially highly variable degrees of compliance to dietary interventions in free living contexts.

This review will focus on selected genotypes related to HDL metabolism, inflammation, and IR in attempt to illustrate potential proof-of-concept. Notwithstanding this objective it should be noted that we do not yet have a full understanding of which HDL-C genes truly regulate RCT. Costanza et al. determined the relative contribution of genes related to RCT and environment interactions on blood–lipid concentrations [107]. The 11 genes included *ABCA1*, apolipoprotein A1 (*APOA1*), apolipoprotein E (*APOE*), *CETP*, endothelial lipase (*EL*), hepatic lipase (*HL*), lecithin–cholesterol acetyl transferase (*LCAT*), lipoprotein lipase (*LPL*), low-density lipoprotein receptor (*LDLR*), phospholipid transfer protein (*PLTP*), and *SR-BI*. The ten environmental factors were gender, age, education, country of birth, dietary fiber, dietary fat, physical activity, BMI, cigarette smoking, and alcohol intake. Essentially this analysis showed that the RCT pathway genes were weakly associated compared to the more dominating effects of environmental factors in determining blood–lipid concentrations. Thus the authors concluded that environmental factors such as reducing obesity, smoking, and alcohol intake should remain the primary strategies for lipid control. However this bias toward environmental rather than genetic factors may be premature, as this study determined relatively few genes/SNPs related to HDL-C and RCT and we are not fully sure of the true functionality of these variants. Furthermore, it is important to note that the dietary information was relatively crude only focusing on total dietary fat and fiber content, omitting potentially important effects related to more detailed dietary composition.

Within the context of important gene-nutrient interactions, Ordovas et al. investigated the interaction between the -514 C/T polymorphism of *HL*, dietary fat and HDL-related measures in the Framingham Study [108]. HL is a lipolytic enzyme that re-models several lipoproteins and it is regulated by insulin via insulin-responsive elements in the HL promoter. Ordovas et al. demonstrated that the T allele was only associated with higher HDL cholesterol levels and size in subjects consuming a low-fat diet (<30% of energy from fat). When total fat was $\geq$ 30% of energy HDL cholesterol levels were lowest in the TT homozygotes and no difference was observed in the CT and CC individuals. These correlations were observed for SFA and MUFA, but not for PUFA. Thus TT subjects may have an impaired adaptation to higher dietary animal fat intake which could lead to higher cardiovascular risk. Gene–diet interactions between the APOA5 gene variation, obesity, lipoprotein metabolism, and carotid intimal medial thickness, a surrogate measure of atherosclerosis, have been reported [109, 110]. More recently the same group reported that the −1131T/C polymorphism in the APOA5 gene modulates the effect of fat intake on BMI and obesity risk in both men and women in the Framingham Study [111]. The interaction with BMI was dose dependent. In subjects homozygous for the −1131T major allele, BMI increased as total fat intake increased. Conversely, this increase was not present in carriers of the −1131C minor allele. When specific fatty acid groups were analyzed, MUFA showed the highest statistical significance for these interactions with obesity-related measures (BMI, overweight, and obesity). Also, the gene–nutrient concept has been illustrated for *APOE*, a structural component of several lipoproteins and serves as a ligand for the LDL receptor and the LDL receptor-related protein. The *APOE* gene promoter −219G/T polymorphism is associated with coronary heart disease, increased postprandial TRL levels [112], and susceptibility of LDL to oxidative modifications [113], circumstances related to IR. The effect of this polymorphism on peripheral insulin sensitivity was investigated using the insulin suppression test after the consumption of high-MUFA, high-SFA, and high-carbohydrate diets. The steady-state plasma glucose concentration was lower in GG subjects than in GT and TT individuals, irrespective of diet. Significant diet–genotype interactions were found for steady-state plasma glucose and nonesterified fatty acid (NEFA) concentrations. Switching from the SFA-rich diet to the MUFA- or carbohydrate-rich diets decreased the steady-state plasma glucose and NEFA concentrations in GG and GT subjects, but not in TT subjects [114].

Our group has focused on inflammatory genotypes, determining whether these interact with dietary fatty acid composition to affect metabolic health which includes insulin sensitivity and lipid metabolism. Within this context, Phillips et al. showed that compliment component 3 (*C3*), a protein with a central role in the innate immune system, interacted with plasma fatty acid composition to alter risk of metabolic traits associated with the MetS in a prospective case-control LIPGENE cohort [115]. In addition, we replicated our findings in an independent LIPGENE dietary intervention study in a case only MetS cohort ($n = 464$) [43] wherein the "protective" rs11569562 GG genotype was associated with enhanced insulin sensitivity. Furthermore, these GG homozygotes were also more responsive with a much improved lipid profile in response to a low-fat, high-complex carbohydrate diet supplemented with LC n–3 PUFA. While the functional mechanisms conferred by C3 polymorphisms remain to be determined plasma PUFA may modulate susceptibility to IR and inflammation suggesting novel gene–nutrient interactions. Cytokines tend to act synergistically hence we determine the interactive effect between polymorphisms of TNF-α, IL-6, and LTA with plasma fatty acid status. Interestingly, we showed that possession of all three *IL-6*, *LTA*, and *TNF*-α risk genotypes increased risk of the MetS which was further

exacerbated with increasing plasma saturated fat levels, indicating important modulation of genetic risk by dietary fat exposure [116]. These few examples illustrate the potential role of nutrigenomics to rapidly accelerate our understanding of lifestyle and health; providing proof-of-concept that an individual's genetic background partly determines their sensitivity to lifestyle/environmental stressors and their response to lifestyle interventions that are intended to promote health. This approach may be further enhanced by taking a "metabotype approach". Metabotyping reflects a very comprehensive metabolic phenotype that integrates state-of-the-art genetic, clinical, metabolic and molecular profiling (at the gene, transcriptome, proteome, and metabolome levels); that reflects environmental exposures of individuals and populations [117–119]. It is anticipated that a combination of nutrigenomic and metabotype approaches will yield valuable information to further understand the relationship between lifestyle and health.

5 Conclusions and future perspectives

Inflammation is the core pathology which underlies both obesity-induced IR and cardiovascular disease. Furthermore, these disease states often coexist. The mechanisms by which IR increases cardiovascular risk are as yet underappreciated. Much evidence points to a causal role for adipose tissue dysfunction in the development of IR but less is known about the contribution of adipose health to cardiovascular health. Does systemic inflammation that is evident with obesity directly contribute to atherogenesis? Does amelioration of adipose inflammation in the absence of weight loss reduce atherogenesis? What role is there for genetics and how do they interact with environmental factors such as diet, physical activity, and related physiological states in these processes? Nutritional status is ultimately the predominant factor that dictates adipose tissue health. Preventative strategies to limit weight gain and effective lifestyle strategies to promote weight loss will no doubt be at the forefront in the battle against obesity and associated pathologies including CAD.

HMR is funded by Science Foundation Ireland Principal Investigator Award (SFI/PI/1119). FM^{c}G is jointly funded by Science Foundation Ireland, the Health Research Board and the Wellcome Trust (097311/Z/11/Z) under the SFI-HRB-Wellcome Trust Biomedical Research Partnership.

The authors have declared no conflict of interest.

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