Dyslipidaemia in Rheumatoid Arthritis: The Role of Inflammation, Drugs, Lifestyle and Genetic Factors

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Abstract: Rheumatoid arthritis (RA) associates with excess cardiovascular morbidity and mortality, resulting in significantly shortened lifespan. Traditional risk factors (e.g. dyslipidaemia and hypertension) and novel risk factors (e.g. systemic inflammation) contribute to the development of cardiovascular disease (CVD) in RA. In the general population, dyslipidaemia has been found to be central to the development of CVD, playing an important role in all stages of atherosclerotic plaque formation. In RA, lipid metabolism may be altered by systemic inflammation, environmental lifestyle factors, drug therapy and several genetic factors. This may result in changes in overall lipid levels, as well as modifications of lipid/lipoprotein structure and function. In this review, we discuss lipid abnormalities specifically in the context of RA and highlight the potential impact of inflammation, genetic factors, lifestyle, and anti-rheumatic drugs on lipid metabolism.

Keywords: Rheumatoid arthritis, dyslipidaemia, inflammation, drugs, genetics, lifestyle, environment.

INTRODUCTION

Rheumatoid arthritis (RA) associates with significantly increased cardiovascular disease (CVD) morbidity and mortality compared to the general population. CVD in RA is multi-factorial arising as a consequence of an interplay between established CVD risk factors (e.g. hypertension, dyslipidaemia, diabetes, smoking) [1], genetic predisposition, and novel disease specific factors, with systemic inflammation being the key player [2]. Several of the traditional risk factors have now been studied in some detail, establishing their role in initiating and perpetuating CVD in RA. Dyslipidaemia is a major factor that requires further investigation specifically in RA.

For decades, abnormalities of the lipid profile such as increased levels of low density lipoproteins (LDL) have been recognised as strong predictors of CVD in the general population. In RA, the lipid profile appears to superficially improve with suppression of components such as LDL and total cholesterol (TC) [3-5]. However, disproportionate suppression of other components of the lipid profile such as high density lipoproteins (HDL), as well intricate modifications of lipids, lipoproteins and enzymes involved in lipid metabolism are likely to increase the risk of CVD in RA [6, 7].

In this review, we discuss lipid abnormalities specifically in the context of RA and highlight the potential impact of inflammation, genetic factors, lifestyle, and anti-rheumatic drugs on lipid metabolism.

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PREVALENCE AND ASSOCIATIONS OF DYSLIPIDAEMIA IN RA

Dyslipidaemia in RA is likely to be governed by many factors, including inflammatory disease activity [8], reduced physical activity secondary to pain and disability [9] as well as drug therapy [7]. Although, collectively these factors are likely to exert a significant influence on the lipid profile of RA patients, the additional potential contribution of genetic factors controlling lipid metabolism has not been addressed. This may explain why the prevalence of dyslipidaemia in RA varies between populations.

Several studies have commented on the prevalence of dyslipidaemia in RA. The first study assessed the prevalence of dyslipidaemia in 87 patients with inflammatory arthritis [10]. According to the United States (US) National Cholesterol Education Program (NCEP) guidelines [11], 55% of inflammatory arthritis patients were dyslipidaemic compared with 8% of controls. Unfortunately, these figures are not specific to RA, but encompass a broad spectrum of inflammatory joint disease, (RA, spondyloarthropathies and undifferentiated inflammatory arthritis) exhibiting varying degrees of inflammation and different disease-specific characteristics. The second study, was carried out on 60 RA males patients [12], thus not reflecting the typical disease population. The investigators reported 68% of patients had serum levels of TC), HDL or LDL that would be considered as risk factors for the development of atherosclerosis according to NCEP criteria. In our own series of 400 patients meeting American College of Rheumatology (ACR) criteria for RA, the prevalence of dyslipidaemia according to the NCEP criteria (TC ≥6.2 mmol/L or LDL ≥4.13 mmol/L or HDL <1.03 mmol/L or TG ≥1.7 mmol/L, or taking lipid lowering therapy) was 51.3% [13].

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Dyslipidaemia appears to be present in RA patients with both early [14] and advanced disease [15]. While the inflammatory burden can be partially blamed for dyslipidaemia in early RA, there is also evidence to suggest that lipid profile may already be altered prior to the onset of disease. One retrospective study performed in the Netherlands on 1078 blood donors, identified 79 patients who later developed RA, and compared their lipid profiles with that of controls from blood samples taken at least 10 years before the onset of RA [16]. Patients who later developed RA were found to have lower levels of HDL, and higher levels of TC, TG and apolipoprotein B (ApoB). This suggests that alterations in the lipid profile may render people more susceptible to the development of RA [17], that RA patients are genetically predisposed to the development of dyslipidaemia or that the transcription of these genes is altered by persistent low-grade inflammation in patients with subclinical RA.

ALTERATIONS IN THE LIPID PROFILE IN RA

In 1963, London *et al.* [18] described a negative association between TC levels and RA disease activity, but no data were produced regarding the effects of inflammation on other lipid parameters. Nevertheless, this study acted as a springboard for future studies to evaluate the contribution of dyslipidaemia to the cardiovascular risk seen in RA. Currently, the most widely reported abnormality of the lipid profile associated with active RA is suppression of HDL levels [14, 19-21]. Although a fall in TC levels has been observed [18], the drop is not as substantial as that seen in HDL levels, thus producing an increased atherogenic index (TC:HDL ratio) [14]. The atherogenic index may be even higher if TC levels increase as claimed by several investigators [19, 22]. There is some controversy over the effects of inflammation on TGs and LDL, some studies show that high disease activity associates with higher TGs [19] while other studies suggest that TGs are reduced [21]. Similar to TGs, the precise relationship between LDL and inflammation also remains unclear [19, 23]. Much of this controversy can be explained by small study size and differences in the populations studied.

To date, the National Health and Nutrition Examination Survey (NHANES III) is the largest study to compare lipid profiles of untreated RA patients with a control group [7]. This study recruited 128 patients with RA, but only 104 patients were untreated with disease modifying anti-rheumatic drugs (DMARDs) or glucocorticoids (GCs) and thus included in the analysis. Although all major components of the lipid profile were analysed, only HDL and ApoA-I levels were found to be lower in the RA patients.

There is growing evidence that ratios of lipid components and apolipoproteins have a higher predictive value of first myocardial infarction than individual components of the lipid profile [24]. Ratios of particular interest include: TC:HDL (discussed above), LDL:HDL and Apo B:Apo A-I. In RA, not only are all these 3 ratios increased [14], but they may offer a more reliable way of assessing the lipid profile by overcoming individual fluctuations in lipids occurring as part of disease flares.

HDL and LDL particles are categorised according to their size and density. This is clinically relevant as small dense LDL particles (LDL3) more readily infiltrate the endothelium and are more prone to oxidative change than their larger counterparts [25, 26], whereas smaller HDL particles (HDL2) are more successful at performing reverse cholesterol transport and thus confer greater cardio-protection [27, 28]. In RA, only 1 small study has assessed the characteristics of lipoprotein sub-fractions [6]. This study, on 31 RA patients, demonstrated significantly higher levels of small dense LDL and lower levels of small HDL particles compared with controls. Interestingly, there were no changes in the levels of basic components of the lipid profile, except LDL levels, which were lower in the RA group.

Lipoprotein (a) [Lp(a)], is a LDL particle in which ApoB-100 is bound to lipoprotein a. Current evidence suggests Lp(a) may be a key factor in the development of atherosclerosis [29-31]. The recognition of Lp(a) as an independent cardiovascular risk factor in the general population [32] has sparked interest into the role of this lipoprotein in RA. Levels of Lp(a) have been found to be increased in RA patients [14, 19, 33]. The significant increases in Lp(a) could be purely as a direct result of inflammation or may be due to increased genetic expression [34]. Irrespective of these findings, it still is unclear whether increased levels of Lp(a) accelerate atherosclerosis in RA. Interestingly, although suppression of inflammation with drug therapy (DMARDs, GCs or biologic agents) can result in the reversal of many of the lipid changes described in active RA, Lp(a) levels appear to remain consistently elevated [33]. Table **1** summarises the findings from all the available studies reporting lipid changes in untreated RA.

RA has been associated with high levels of oxidative stress [35]. The increased oxidative load may contribute to articular tissue damage and perpetuates the inflammatory process [36], but may also be strongly implicated in the pathophysiology of CVD in RA [37, 38]. In RA, it has been shown that LDL within the synovial fluid of an inflamed rheumatoid joint is prone to oxidative modification [39]. More recently it has also been reported that increased levels of oxidised LDL are seen in the plasma of RA patients with ischaemic heart disease [40]. The trigger for LDL oxidation in RA is not fully understood, particularly as a study suggests that inflammation does not play a significant role [41].

In summary, RA patients with active disease develop a pro-atherogenic lipid profile, with low HDL levels and raised atherogenic indices. The additional influence of the other lipid components (LDL and TG), and lipid sub fractions on cardiovascular risk in RA requires further investigation.

RA AND THE METABOLIC SYNDROME

The metabolic syndrome (MetS) is a cluster of traditional cardiovascular risk factors (obesity, glucose intolerance, hypertension, hypertriglyceridaemia, and low levels of HDL), thought to confer cardiovascular risk beyond the sum of its individual components [44]. In RA, several of the individual components of the MetS may be altered through disease specific and inflammation-mediated mechanisms. For example, many RA patients develop rheumatoid cachexia, a condition characterised by an increased fat:muscle mass ratio, while maintaining a constant weight [45]. Thus, it has been suggested that in RA lower cut-off levels should be used to de-

Table 1. Studies of Lipid Profiles in Patients with Untreated Rheumatoid Arthritis

Study	Study Design	TC	HDL	LDL	TG	Lp(a)	Apo A1	TC:HDL Ratio	LDL:HDL Ratio	apoB:apo A1 Ratio
Georgiadis [42]	40 RA <1 yr 45 controls	↑*	↓	↑*	↑*	N/S	↓*	↑*	↑*	N/D
Georgiadis [43]	58 RA <1 yr 63 controls	↑	↓*	↑	↑	N/S	N/S	↑	↑*	N/S
Dursunoglu [19]	87 female RA 50 controls	N/D	↓*	↑	↑*	↑*	N/S	↑*	↑*	N/S
Choi [7]	104 RA age >60 4758 controls	N/D	↓	N/S	N/D	N/S	↓	↑	N/S	N/S
Yoo [8]	184 RA 161 controls	↓* females ↓males	↓females ↓* males	↑* females ↑ males	↑ females ↑ males	↑* females ↑* males	↓females ↓ males	↑ females ↓ males	↑ females ↑ males	↑ females ↑* males
Lee [3]	21 RA 19 controls	↓	↓*	N/D	N/D	↑	N/S	N/D	N/S	N/S
Park [14]	42 RA 42 controls		↓*			↑*	↓*	↑*	↑*	↑*
Seriolo [4]	137 RA 78 controls	↓*	N/D	↓*	N/D	↑*	N/D	N/S	N/S	N/D
Lakator [22]	129 RA (77 GC, 52 NSAID) 1374 controls	↑	↓*	↑*	↓*	N/S	N/S	N/S	N/S	N/S
Svenson [5]	48 RA 21 sero-ve SA	↓	↓*	↓*	↓*	N/S	N/S	N/S	N/S	N/S

*** :** significant change, N/D: no difference between RA and controls, N/S: not studied, SA: spondyloarthropathies, RA: Rheumatoid Arthritis, GC: glucocorticoids, NSAID: non steroidal anti inflammatory drugs, TC: total cholesterol, HDL: high density lipoproteins, TG: trigylcerides, LDL: low density lipoproteins, ApoA: apolipoprotein A, ApoB: apolipoprotein B, yr: years.

fine obesity using the body mass index [46]. In view of such modifications to the individual components, it is not surprising that the MetS has been found to be highly prevalent in RA [47-49]. As inflammation clearly has a central role in the development of the MetS [50], it would be expected that suppression of the inflammatory burden through the use of disease modifying drugs would result in a reduced prevalence of the MetS. Methotrexate has been reported to have cardioprotective properties [51], and more recently has been shown to associate with a lower prevalence of the MetS [49, 52]. Interestingly, recent data would suggest that the 'protective' effects of methotrexate may be due to a drug specific mechanism rather than a generic anti-inflammatory effect [52, 53]. However, this association needs to be explored further in specifically designed longitudinal studies. Long-term GC use associates with many undesirable side effects, including central obesity [54], dyslipidaemia [55], glucose intolerance [56], and hypertension [57]. However, in RA, long-term GC use has not been found to associate with an increased prevalence of the MetS [53].

The rheumatological community is becoming increasingly aware of the need to address cardiovascular risk in RA patients. Tackling the MetS in RA is complex, requiring both suppression of systemic inflammation through the use of DMARD (in particular methotrexate) and GC use, as well as aggressive management of each of the individual components of the MetS e.g. by the use of appropriate antihypertensive therapy for hypertension and/or statins for dyslipidaemia. This is addressed later in this review. However, the importance of lifestyle modification to include weight control and increased physical activity cannot be over-emphasised: this is at least as important in patients with RA as it is in other at risk groups and in the general population.

INFLAMMATION-MEDIATED MECHANISMS CONTROLLING LIPID METABOLISM

The Effects of Inflammation on HDL Metabolism

HDL confers multiple cardiovascular benefits, through its anti-oxidant properties and its ability to perform reverse cholesterol transport [58, 59]. It is now well recognised that high levels of HDL are cardio-protective, whereas low levels act as an independent cardiovascular risk factor [60-63]. Studies in the general population have provided convincing evidence that increasing HDL levels through drug intervention and

lifestyle modification can slow the progression of atherosclerosis and improve cardiovascular outcomes [64-66].

HDL is of particular interest in the context of active inflammation, as its levels can dramatically fall, to a far greater extent than the changes seen in other components of the lipid profile. In acute inflammation, such as infection (bacterial and viral), HDL levels closely correspond to the degree of inflammatory burden, as levels are rapidly suppressed following the onset of infection and their return to normal appears to shadow the patient's recovery [67]. Although, the majority of studies report normalisation of HDL levels within 4 weeks of the onset of infection [67-69], 1 study has shown that the reduced levels persist up to 6 months post infection [70]. In chronic inflammatory conditions, such as RA, HDL levels are persistently low. However, levels may still fluctuate as a consequence of alterations in disease activity [71], drug usage [72, 73] and physical activity levels [9].

The Effect of Acute Phase Proteins of HDL Metabolism

There is accumulating evidence suggesting that many of the anti-oxidant and anti-atherogenic properties of HDL are lost due to direct and indirect effects of inflammation. The inflammatory process triggers the synthesis of many plasma proteins by the liver [74, 75]. Serum amyloid A (SAA) and C-reactive protein (CRP) are 2 of the key plasma proteins whose production is greatly enhanced during inflammation. The net increase in SAA occurs as a result of increased gene transcription [76], and leads to alterations in HDL composition and function. Large amounts of SAA become bound to HDL (mainly HDL3) following the displacement of ApoA-I and ApoAII [77]. The composition of this remodelled acute phase HDL (AP-HDL) is also altered, becoming deplete in cholesterol esters and laden with TG, free cholesterol and fatty acids [78, 79]. The size of AP-HDL is larger than conventional HDL, although the density remains comparable [80]. The modification of the HDL structure to incorporate SAA directly impacts upon its ability to carry out reverse cholesterol transport, as lecithin-cholesterol acyltransferase (LCAT), an enzyme responsible for the esterification of HDL, requires the presence of ApoA-I to be activated. Alongside this, the HDL/SAA structure has an increased affinity for macrophages and a reduced affinity for hepatocytes compared with the unmodified HDL structure [81]. These changes can be partly attributed to alterations in the number of binding sites for the HDL/SAA complex, as inflammation has been shown to increase the number of HDL/SAA binding sites on macrophages and decrease the number on hepatocytes [81]. However, it has been shown that SAA must constitute more than half of the HDL protein in order for cholesterol efflux to become compromised [82].

Interest has also developed around the role of 2 other acute phase reactants, namely, secretory phospholipase A2 (sPLA2), known to possess the capacity to remodel HDL [83], and ceruloplasmin, a copper transporting protein with pro-oxidant properties [84]. Inflammation induces elevations in the plasma concentrations of sPLA2 and this has been linked to smaller HDL particle size, a reduction in HDL cholesterol and apoA-I levels, and an increase in HDL TGs in transgenic mice [85]. Acute phase HDL is also susceptible to enrichment with ceruloplasmin, resulting in a reduced ability to protect LDL against oxidative modification [84, 86]. However, this theory is under scrutiny, as other studies conclude that ceruloplasmin exhibits anti-oxidant properties [87]. The discrepancies regarding the properties of ceruloplasmin may be explained by differences in its structure, as the removal of 1 copper atom appears to alter its function from anti-oxidant to pro-oxidant [88].

Transferrin, a plasma protein involved in iron transport, can be found in association with HDL [89]. It is thought that the usual role of this metal binding protein is to protect LDL against oxidation [89]. However, during inflammation, levels of transferrin fall [90] and thus further predispose the host to a proatherogenic environment.

The Effect of Inflammation-Mediated Enzymatic Change on HDL Metabolism

Several enzymes fundamental to the metabolism of HDL are affected by inflammation. Hepatic lipase (HL), an enzyme expressed primarily in the liver, converts larger HDL particles (HDL2) in to smaller (HDL3) particles, facilitating cholesterol uptake from cells [91]. This process occurs largely due to the hydrolysis of TGs and phospholipids within HDL2. HL also plays a key role in many other aspects of lipoprotein metabolism, including assisting hepatic uptake of HDL and LDL particles by acting as a ligand [92] and aiding reverse cholesterol transport by promoting uptake of HDL cholesterol esters by the scavenger receptor B1 [93]. Animal [94] and human studies [95-97] have shown HL levels to be reduced by the inflammatory process, thus inhibiting its normal functions and the production of a more proatherogenic environment.

Reverse cholesterol transport is a complex cascade of events, which requires the presence of many factors in order for the process to be completed efficiently. Cholesterol ester transfer protein (CETP) plays a pivotal role, providing a pathway for cholesterol esters to be transferred from HDL to lipoproteins rich in ApoB, such as very low density lipoproteins (VLDL) and LDL, allowing cholesterol to ultimately be cleared by the liver [98]. Inflammation has been shown to indirectly impact upon CETP activity by reducing mRNA expression in transgenic mice [99]. However, further studies in this field are required to confirm these findings in the context of chronic inflammation in humans. Phospholipid transfer protein (PLTP) is another key protein required for successful reverse cholesterol transport, whose activity is suppressed by the inflammatory process [100]. The resultant limited activity of PLTP means that essential actions, such as mediating the exchange of cholesterol between TG rich particles and HDL, cannot be carried out. Thus, alterations in PLTP activity can be held partly responsible for lower HDL levels observed during inflammation [101].

Inflammation-mediated variations in the enzymatic content of HDL have also been observed, including reductions of paraoxonase (PON-1) and elevated levels of platelet-activating factor acetylhydrolase (PAF-AH) [86]. Deficiency of PON-1 within HDL renders them susceptible to oxidation and can ultimately convert HDL into a pro-oxidant, pro-inflammatory complex [86, 102]. PAF-AH is found in relation to both LDL and HDL particles. Elevated PAF-AH levels have been observed in a broad spectrum of inflammatory

conditions, including the human immunodeficiency virus (HIV) [103] and RA [104]. However, it remains unclear in humans whether PAF-AH activity is increased during inflammation in both HDL and LDL particles [103, 105]. It is postulated that if PAF-AH activity is increased within HDL particles, this may confer mainly anti-atherogenic properties, as it may protect against the oxidation of LDL, but also produce proatherogenic effects by escalating the production of lysophosphatidylcholine (LPC) [106]. Occasional published reports have demonstrated a negative association between inflammatory burden and PAF-AH levels [107, 108]. However, such studies may lack significant power due to small study size.

It is clear from this evidence that it is not just the reduction in HDL that is an important risk factor for coronary heart disease in heightened inflammatory states, such as RA, but that there are multiple other modifications in its function that may also have an additive effect (Fig. **1**).

The Effects of Inflammation on Triglyceride Metabolism

The relative contribution of elevated TG levels to the development of cardiovascular disease remains controversial. Although there is growing evidence that hypertriglyceridaemia associates with an increased CVD risk [60, 109, 110], it remains difficult to classify it as an independent risk factor, as alterations in the levels occur in conjunction with changes in HDL levels [111].

For many decades, studies have demonstrated dramatic elevations in TG levels in response to infection as well as acute and chronic inflammation [19, 68, 112]. Some studies have reported these changes to be specific to the infective organism (e.g. Gram negative bacteria) [112], whilst others report a significant increase irrespective of the factor triggering the immune activation [68, 96]. TGs are primarily transported in VLDL, therefore hypertriglyceridaemia occurs as a result of either overproduction or impaired clearance of VLDL. The inflammatory process interferes with the normal metabolism of TGs through the release of multiple cytokines and alterations in enzymatic activity (see below).

The Effects of Cytokines on TG Metabolism

Numerous cytokines released during inflammation may hinder TG metabolism. TNF-α is released in vast quantities during active inflammation. Elevations in TNF-α levels may disturb lipoprotein metabolism by decreasing lipoprotein lipase (LPL) activity, reducing liver metabolism [113] and modifying the composition of lipoprotein particles [114]. Studies in rats have clearly demonstrated that the administration of exogenous TNF-α results in doubling of baseline plasma TG levels [115]. Subsequent studies in humans have produced data confirming a positive correlation between TNF-α and TG levels. However, much of this data has been generated from studies carried out on healthy subjects [116] and patients without active inflammation [117]. Although studies assessing this correlation on the background of

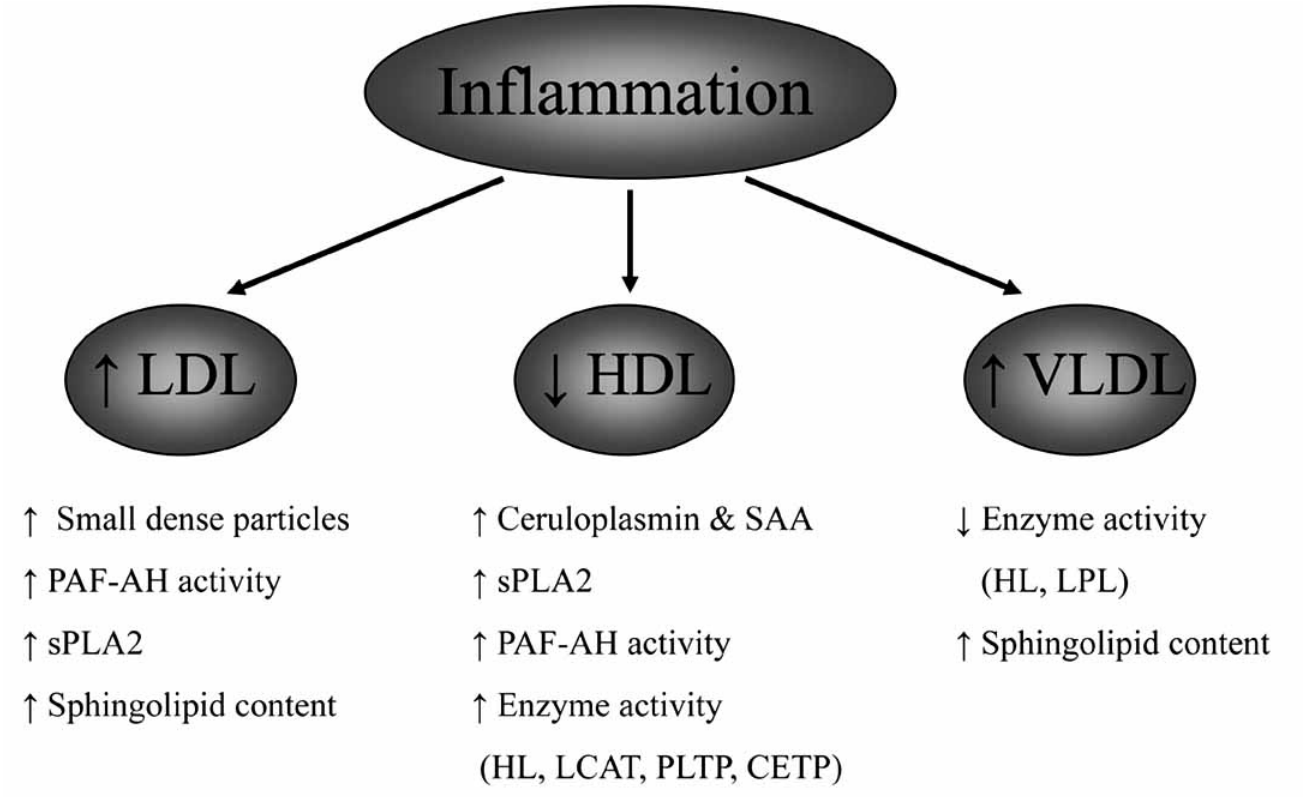

Fig. (1). The effects of inflammation on the structure, composition and function of lipids.

chronic inflammation are few, the available data confirm a striking positive association in patients with systemic lupus erythematosus (SLE) [118].

In RA, the advent of new biologic therapies specifically designed to target TNF-α has enabled this issue to be addressed from another angle. Interestingly, there is no convincing evidence to support the reverse association, (i.e. that as levels of TNF-α fall or TNF-α is inactivated, levels of TG also reduce). The precise effects of anti-TNF agents on TG levels are an issue of much debate. However, the vast majority of current published data indicates that treatment either does not impact upon TG levels [4, 119, 120] or may actually result in a paradoxical rise [121, 122]. These unexpected findings may be explained by small study size, inadequate adjustment for other potential confounders or by an unknown mechanism. Further large-scale studies are required to elucidate the exact effects of anti-TNF agents on cardiovascular risk factors, such as dyslipidaemia.

Over recent years, interest in the inflammatory cytokine IL-6 has escalated, due to the recognition of its atherogenic properties [123], and its potential as a therapeutic target both in cardiovascular diseases and in RA [124, 125]. A growing bank of evidence indicates that IL-6 levels influence lipoprotein metabolism [126], generating particular effects on the concentrations of TGs and HDL. IL-6 levels correlate positively with TG, and negatively with HDL levels [127, 128]. These findings may be particularly important in the context of the metabolic syndrome (MetS) [129], as emerging research indicates a potential role for IL-6 in the development of the MetS [130, 131]. Despite the strong evidence to support a positive relationship between cytokine exposure and TG levels, there are also a few studies demonstrating a negative association [132].

Drug therapy again offers a further insight in to the relationship between IL-6 and TG levels, as lipid lowering therapies such as statins display a dual mode of action by lowering TG levels and suppressing IL-6 through their anti-inflammatory properties [133]. The future use of new monoclonal antibodies specifically targeting IL-6 [125] in chronic inflammatory diseases such as RA, will allow this issue to be addressed in more detail.

The Effects of Inflammation-Mediated Enzymatic Change on TG Metabolism

LPL is an intravascular enzyme specifically found in endothelial cells. It is a multifunctional enzyme, displaying the ability to mediate lipoprotein uptake and to catalyse the hydrolysis of TGs within circulating VLDL and chylomicrons [134]. The explosive release of cytokines such as TNF-α and IL-6 occurring during inflammation leads to a reduction in the levels of LPL and HL *via* down regulation of gene expression at the transcriptional level [135, 136], which ultimately leads to a reduced clearance of TG-rich particles. The net result of these modifications takes some time to accrue. Thus, such changes only contribute to hypertriglycerideamia in the setting of persistent chronic inflammation [137].

Peroxisome proliferator-activated receptors (PPAR) are ligand-activated transcription factors, important in several aspects of lipid metabolism. Of particular interest is PPAR-α, regulating lipid metabolism both at the intracellular and extracellular level [138]. LPL has been shown to activate PPARs, through a preferential action on TG-rich particles (VLDL) [139]. Therefore, inflammation-mediated suppression of LPL levels inhibits PPAR activation and ultimately contributes to hypertriglyceridaemia [136]. The pathway of PPAR activation has long been used as a lipid lowering therapeutic target. Fibrates are PPAR-α agonists, used to treat dyslipidaemia by reducing TG levels and increasing HDL levels [140]. HDL levels increase with fibrate therapy due to PPAR activated up-regulation of ApoA-I and ApoA-II gene transcription [141, 142].

The Effects of Inflammation on LDL Metabolism

Epidemiological studies have shown elevated LDL levels to be one of the strongest predictors of coronary artery disease [143]. To combat this risk, guidelines have been developed, with LDL as the primary focus for lipid lowering therapy [11, 144]. Several large scale studies in the general population have demonstrated that intensive lipid lowering therapy confers greater CV benefits than moderate therapy [145-147]. Furthermore, such studies demonstrate continued clinical benefit even when LDL levels are lowered below the current recommended treatment goals [146]. Over the last 50 years a steady decline in LDL levels has been observed amongst Americans, according to the NHANES [148]. These changes may have occurred secondary to an increased prescription of lipid lowering medication and an overall more aggressive approach to the management of dyslipidaemia.

Inflammation lowers LDL levels [20, 149]. Superficially, this appears to produce a less atherogenic environment. However, by delving deeper it becomes apparent that inflammation mediated structural/oxidative changes may promote atherogenesis *via* the development of pro-inflammatory, atherogenic LDL particles [150, 151]. In fact, persistent inflammation such as that seen in RA, may fuel a vicious circle of oxidation and inflammation (Fig. **2**).

Inflammation-Mediated Structural Changes of LDL

Low-density lipoproteins are sub-classified according to size and density. A predominance of small dense LDL particles is associated with a 3-5 times increased risk of CHD (the Quebec cardiovascular study) [152]. Studies in patients affected by inflammatory disorders, including psoriatic arthritis [153], the acquired immunodeficiency syndrome (AIDS) [154] and RA [6] have demonstrated a preponderance of small dense LDL particles compared with control groups. At present, information regarding the precise mechanisms behind these changes is limited and further research in this area is required.

Inflammation-Mediated Oxidative Changes of LDL

During inflammation there is release of reactive oxygen species (ROS) from activated leucocytes. Elevated ROS levels overwhelm the host's usual antioxidant mechanisms, resulting in damage to cells and lipid peroxidation [155]. The alterations in LDL composition have been blamed almost entirely for the accelerated oxidative modification during inflammation. In animal models, inflammation induced by the introduction of lipopolysaccharide (a major component

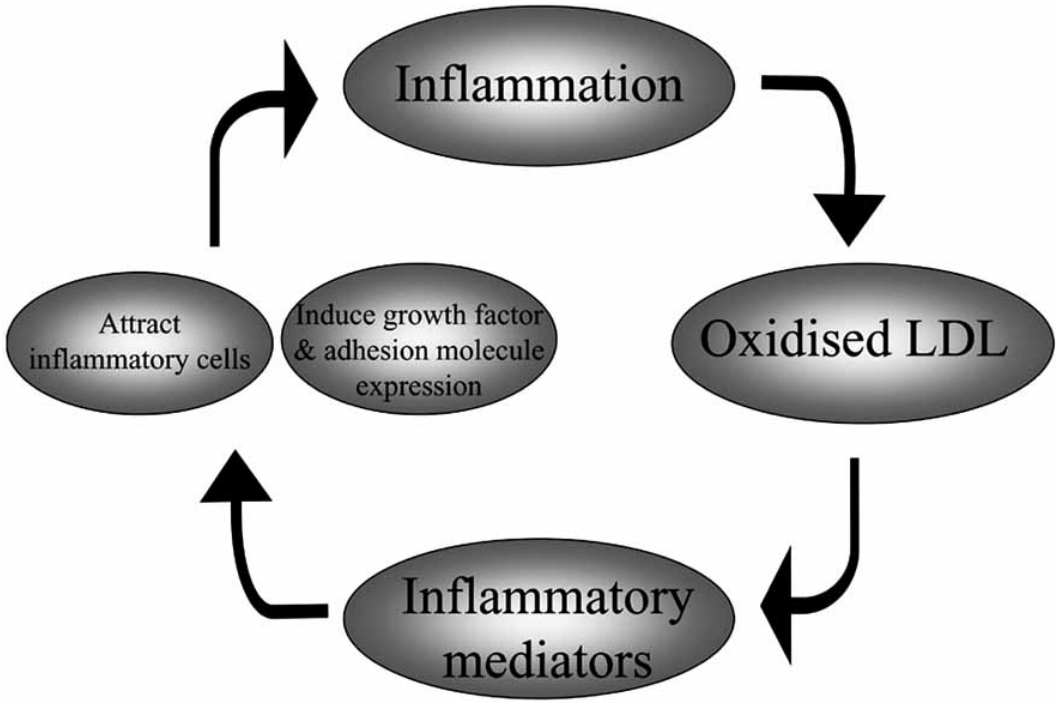

Fig. (2). The vicious cycle of inflammation and oxidised LDL.

of the cell wall of gram negative bacteria), has been shown to increase markers of lipid peroxidation [156]. Other studies carried out in human subjects with inflammatory disorders have confirmed similar elevations in markers of lipid peroxidation and an increased oxidative susceptibility of LDL [157]. Conflicting results are reported by Paredes *et al.*, who found no differences in lipid peroxidation between patients with active RA and the control group [158]. This discrepancy may be explained by the small study size, the degree of inflammatory burden or by the methods used to identify oxidative change.

The Effects of Acute Phase Proteins on LDL Metabolism

The pro-atherogenic properties of LDL are enhanced by CRP and sPLA2 during inflammation [159]. The inflammation mediated increase in sPLA2 activity produces small dense LDL particles that have a surface layer relatively deficient in phospholipids [160]. Such changes in the outer-most layer of LDL increase its ability to interact with arterial proteoglycans, perhaps further enhancing its uptake into the arterial wall and the formation of atherosclerotic plaques. sPLA2 may also indirectly promote LDL oxidation, through the production of fatty acids. Fatty acids are prone to oxidative change, and may subsequently induce oxidation of LDL [161]. Once oxidised, LDL is readily taken up by macrophages, and an abundance of CRP is recognised to facilitate this process, and promote subsequent foam cell formation [162].

The Effects of Inflammation-Mediated Enzymatic Change on LDL Metabolism

Endothelial lipase (EL) is a newly identified member of the triglyceride lipase family [163]. Apart from its role in HDL homeostasis, EL may enhance lipid uptake into the vascular endothelium *via* its bridging function [164]. Although, it is widely accepted that EL is up-regulated during inflammation [165, 166], the exact effect that this has on LDL is still a matter of debate. One of the earliest studies to address this issue was carried out in LDL receptor deficient mice and demonstrated that hepatic expression of EL leads to a reduction in serum LDL levels [163]. In contrast, a later study in EL knockout mice has reported a massive increase (90%) in LDL cholesterol levels [167]. Two further studies, have also tried to identify the role of EL in LDL metabolism. The first failed to demonstrate any effect of EL on LDL levels in the mouse model [168], while the second demonstrated that EL promotes LDL uptake by macrophages [169].

EFFECTS OF ENVIRONMENTAL LIFESTYLE ON THE LIPID PROFILE

Variations in lifestyle and exposure to environmental factors can significantly alter the lipid profile. In RA, some of these factors may be modified as a consequence of complications of the disease. For example, regular physical activity has been shown to produce a less atherogenic lipid profile [170]. However, many RA patients have a limited capacity for physical activity due to the functional limitations produced by joint deformity and pain, and/or organ involvement (breathlessness from lung disease, or cardiac involvement). In this section we discuss the impact of environmental and lifestyle factors on the the lipid profile and address how these are further altered by the presence of RA (see Fig. **3**)

Seasonal Variation

Studies have demonstrated both biological variation (i.e. normal day to day variation) [171] and cyclical seasonal variation in plasma lipid and lipoprotein levels [172, 173]. Within patient biological variation is in the order of 6-7% for TC and HDL, 8-10% for LDL and 20-30% for TG [171,

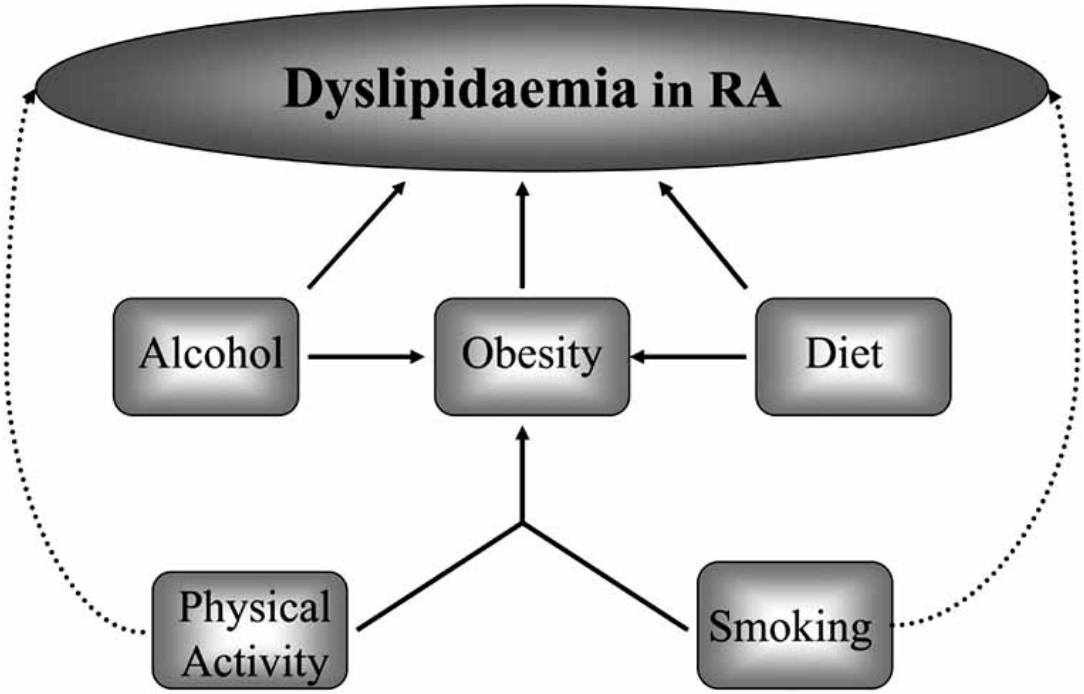

Fig. (3). The potential interplay of lifestyle factors in the development of dyslipidaemia in RA.

174]. The most widely reported seasonal changes are elevations in TC and LDL levels in winter [175], with peak levels being reached during January [173, 176]. Apolipoprotein levels also demonstrate seasonal fluctuations, with ApoA-I and A-II levels markedly elevated in the summer [177]. These findings have been shown to be independent of country of origin, ethnicity, age, sex and baseline lipids. Interestingly LDL demonstrates an increased susceptibility to oxidation during winter (January) and a reduced susceptibility during summer (June/July) [178]. Some studies also report winter elevations in HDL and TG levels [176, 179]. The precise mechanisms controlling these changes remain elusive. However, several hypotheses have been put forward. These include: (a) a haemodilution effect due to secondary mobilisation of fluid from the interstitial to the intravascular compartment due to heat acclimatization [180], occurring during the summer months as a result of a combination of increased environmental temperature and physical activity (b) seasonal variations in physical activity levels [176], although some studies would argue against the second hypothesis, as seasonal variations are still present after adjustment for physical activity [176, 177].

Currently, there are no studies to address the effects of biological/seasonal variation of lipids in RA patients. The lack of studies is not surprising as several other factors associated with disease activity display similar fluctuations, such as morning joint stiffness, and disease activity worse in colder weather. Thus, it would be difficult to distinguish between the effects of the disease itself on lipid parameters and those occurring as a result of 'normal' variation.

Menopause

Female sex hormones have been shown to exert a protective effect against the development of CVD. A hormonal deficiency, such as that observed with the menopause, leads to an increased risk of CVD [181]. This may be partially explained by accelerated proatherogenic changes in the lipid profile occurring independent of increasing age [182]. Postmenopausal women experience a deterioration in their lipid profile, with significant increases in LDL, TC, TG and HDL3 [182-184], with some studies reporting a worse lipid profile than age-matched male counterparts [185]. It has been suggested that genetic mechanisms that control individual variation of lipids, in particular HDL, may differ between premenopausal and postmenopausal women [186]. Relative correction of the hormonal profile through the use of hormone replacement therapy (HRT) can produce beneficial changes in the lipid profile by elevating HDL2 and reducing LDL levels [187]. However, despite these findings, we do not consistently see a decrease in vascular risk with HRT [188]. In addition, there is some evidence that CRP levels increase following the use of certain HRT products [189, 190].

In RA, postmenopausal status has been associated with significantly higher TC, TG, TC:HDL ratio, ApoB, Lp(a) and LDL:HDL ratio than those observed in premenopausal RA patients [8]. Postmenopausal RA women have also been shown to have higher TG and Lp(a) and a lower TC than healthy postmenopausal women [8].

Physical Activity

Regular long-term exercise promotes many health benefits, ranging from improved bone density to a reduction in cardiovascular risk. Much of the reduction in cardiovascular risk can be attributed to modification of conventional risk factors, including a reduction in blood pressure [191], improvement of the lipid profile [9, 42] and weight reduction.

In the general population, exercise is recommended as a lifestyle change for all patients with dyslipidaemia or estab-

lished cardiovascular disease [11]. Supporting this recommendation are several studies and meta-analyses demonstrating significant improvements in the lipid profile in patients adhering to a regular exercise programme [170, 191, 192]. The most significant changes observed with moderate exercise are elevations in HDL levels, lower TC:HDL ratio and lower TG levels [170, 191, 193, 194]. The scale of change appears to be influenced by the mode of exercise taken, with endurance exercise training proving to be substantially more effective than resistance training [195, 196]. Furthermore, age also seems to influence the degree of alteration in the lipid levels seen following exercise [197]. Older patients have been shown to lower the TC levels to a greater extent, but also appear to more readily enhance their HDL levels [197]. Unfortunately, the majority of exercise studies have been conducted in normolipidaemic subjects. Thus, there is a relative lack of available data on the effects of exercise training in dyslipidaemic patients.

Many of the improvements in the lipid profile require several months for the benefits to accrue. However, there is some evidence to suggest that changes in the lipid profile occur following a single episode of exercise [198]. Single exercise sessions appear to result in rapid increases in HDL levels occurring 18-24 h post-exercise that can persist for up to 72 h [199, 200]. Although the minimum amount of exercise required to improve blood lipids is not known, the United Kingdom government recommendations suggest at least 30 min of continuous exercise 5 days a week are required for a healthy lifestyle. However, continuous exercise is not required for alterations in the lipid levels to occur, as changes have been reported in patients whose exercise time is broken up throughout the day [201].

As HDL is one of the key components of the lipid profile to be modified by exercise, some interest has been generated around the effects of exercise on HDL sub fractions. A large proportion of studies assessing the influence of short term exercise on HDL sub fractions has shown significant increases in both HDL-2 (low density) and HDL-3 (high density) [202, 203]. The relative increases in the HDL sub fractions differ between studies with some demonstrating similar increases in both HDL-2 and HDL-3 [203], and others demonstrating a disproportionate increase in HDL-2, resulting in an increase in the HDL-2/HDL-3 ratio [204]. These discrepancies can be explained by differences in the subjects studied (athletes *vs* healthy men), the number of subjects involved, the mode and length of exercise, and advice regarding other lifestyle modifications. Evidence to support similar changes in HDL sub fractions among subjects adhering to longer-term exercise programmes, or in dyslipidaemic subjects is lacking.

The mechanism by which exercise mediates positive effects on HDL can be partly attributed to the alterations in the enzymes responsible for HDL metabolism [205]. Two of the key enzymes whose function may be altered are LPL and hepatic HL. One study demonstrated large increases in the activity of LPL and a significant reduction in HL activity in endurance trained individuals *vs* sedentary controls [206]. The enhanced enzyme activity of LPL may escalate lipid transfer to HDL, and simultaneous decreases in HL activity may result in reduced clearance of HDL.

In RA, traditionally patients and rheumatology healthcare professionals have been cautious regarding exercise, due to a widely held but unfounded fear that it would trigger aggravation of disease or damage the joints. These preconceptions resulted in exercise restriction and may, in part, account for the inactive lifestyle of many RA patients [207]. Indeed, physical activity has been shown to directly associate with CVD risk factors in patients with RA [208]. However, over recent years well designed physical exercise programmes have been shown not only to be safe in RA but also to promote prolonged improvements in morning stiffness, Stanford arthritis self-efficacy scale (SES) and other disease outcomes [209, 210]. The beneficial effects of exercise on disease parameters and well-being have been observed in all RA patients irrespective of disease duration [211] or activity [212, 213]. Although regular exercise as part of an individually designed programme is now recommended as an integral part of RA treatment, and has been included in the ACR treatment guidelines, there are no specific trials addressing the effects of exercise on CVD risk factors (e.g. dyslipidaemia) in RA. Specific well-designed studies are required to address this issue in RA, as the inflammatory burden in these patients may have already modified conventional cardiovascular risk factors (abnormal lipid profile, changes in body fat: muscle ratio etc), and thus the beneficial effects of exercise on CVD may be even greater than those seen in the general population.

Obesity

The classical pattern of dyslipidaemia in overweight and obese subjects is characterised by elevated levels of TG, TC, ApoB-100 and small LDL particles, and decreases in HDL levels [214, 215]. The dyslipidaemia of obesity has become one of the fundamental criteria for diagnosing the MetS [216-219]. Insulin resistance (IR) is often found in conjunction with both obesity and the MetS, and plays a key role in the development of dyslipidaemia. One of the primary obesity-associated defects in lipid metabolism is the overproduction of VLDL [220]. This phenomenon may be a consequence of a cascade of events occurring in the insulin resistant state, resulting in hepatic steatosis [221]. Furthermore, there is a delayed clearance of VLDL particles, due a reduction of the LDL receptor activity that occurs in conjunction with IR [143]. The low HDL levels seen in obese states are likely to be triggered by several mechanisms. Firstly HDL clearance is enhanced in insulin resistant states, due to stimulation of hepatic lipase and the resultant production of smaller HDL particles [222]. Secondly, transfer of apolipoproteins and phospholipids from TG-rich lipoproteins to HDL is reduced. Thirdly, the delayed clearance of TG-rich lipoproteins facilitates the CETP mediated exchange between cholesterol esters in HDL and triacylglycerols in VLDL [223].

RA associates with profound changes in body composition, partly as a result of the process of rheumatoid cachexia. This is an abnormal metabolic response leading to loss of lean body mass, which, in the case of RA patients, is often replaced by fat [224]. As a result, commonly used body mass index (BMI) thresholds for overweight and obesity in the general population, do not apply in RA [225]. Obesity in RA, has been linked to physical inactivity and worse RA

outcomes [46, 226], but also to a worse CVD risk factor profile [208]. Its exact association with lipid changes has not been studied in RA.

Smoking

Smoking reduces life expectancy, through multiple detrimental effects on health [227]. Much of the associated morbidity and mortality can be attributed to the carcinogens contained within the cigarette smoke, resulting in an increased risk of developing cancer (especially lung cancer) [228] or increased rates of CVD [229]. The mechanism by which smoking promotes CVD still needs to be elucidated. However, it has been suggested that smoking induced alterations in the lipid profile may contribute to this susceptibility [230]. Several large studies confirmed that smoking exposure associates with a pro-atherogenic lipid profile, with elevated TC, LDL, TG levels, and the TC:HDL ratio, and an associated reduction in HDL levels [231-234]. Data produced from such studies has to be interpreted with caution, as it is difficult to control for other lifestyle factors, such as weight changes, diet, alcohol consumption and physical activity. The relationship between smoking and lipid levels appears to be dose dependant [234] and readily reversible on cessation [235]. Cigarette smoke is known to create a pro-oxidative state in the circulation [236], and disturb endothelial function [237]. The smoking-induced oxidative burden induces lipid peroxidation [238], thus further accelerating atherosclerosis.

Smoking has been linked to a 2-4 fold increased risk of developing RA [239], and may also influence the severity of the disease [240], functional status [241] and and other parameters such as body weight and muscle mass [242]. However, a recent study has produced conflicting findings suggesting that cigarette smoke does not accelerate RA disease progression. In fact, the study demonstrated that heavy smoking may be associated with reduced radiographic progression and improvement in functional scores [243]. The effect of smoking in RA varies due to the length of exposure, with acute exposure resulting in immuno-stimulatory effects and chronic exposure resulting in immunosuppressive effects [244]. Although, it is clear that smoking may influence the development and pathogenesis of RA, no specific studies have addressed the effects of smoking on lipid metabolism in RA.

Alcohol

Moderate alcohol intake associates with a lower risk of CVD [245-247]. The reduction in CVD risk of moderate drinkers compared with those who abstain has been shown to lie between 10 and 40% [247]. The cardio-protective effect of alcohol has been linked to beneficial changes in both the lipid profile [247-249] and haemostatic parameters [250, 251]. By far the most common and well-reported change in the lipid profile is an increase in HDL concentrations [234, 247, 252, 253]. The precise mechanisms contributing to the quantitative change in HDL are still being scrutinised, however, current proposals include: (a) increased hepatic production or increased transport rate of apoA-1 and apoA-II [254, 255] (b) increased cholesterol efflux from macrophages to HDL mediated by ABCA1 [256] (c) alcohol-induced reduced activity of CETP [257]. However, a recent study failed to demonstrate any relationship between CETP activity and HDL levels among moderate alcohol consumers compared with abstinent controls [258]. Furthermore, the study demonstrated alcohol-induced alterations in LPL activity.

A degree of controversy exists regarding the relative contributions of HDL subfractions, to the elevation of HDL levels seen with moderate alcohol intake. Virtually all studies demonstrate an increase in both HDL-2 and HDL-3 subfractions [253, 259]. However, the effects on the HDL-2:HDL-3 ratio varies between studies [259, 260]. One study assessing the effects of habitual alcohol consumption has demonstrated that the changes in HDL subfractions may differ between genders, with males experiencing a rise in both HDL-2 and HDL-3, but females only experiencing an isolated significant rise in HDL-2 [253]. A recent study, evaluated the qualitative changes of HDL observed during exposure to varying degrees of alcohol in 279 healthy men [259]. The investigators confirmed that alcohol consumption results in a shift from HDL-3 to predominantly HDL-2a, and a significant phospholipid enrichment of all HDL subfractions.

Hypertriglyceridaemia has long been associated with regular alcohol use [261]. A meta-analysis of 42 studies has confirmed a positive relationship between moderate alcohol consumption and TG levels, reporting a 0.19 mg/dl increase per g of alcohol consumed per day [247]. The impact of alcohol exposure on the other components of the lipid profile including LDL and TC levels have been addressed in comparatively fewer studies. However, the majority of these demonstrate a modest inverse correlation of both TC and LDL with alcohol [248, 262]. LDL particle size may be reduced in patients with alcohol-induced hypertriglyceridaemia, resulting in a subsequent increased susceptibility to oxidation [263].

Potential predisposing factors in the development of RA have been debated for decades [264]. The onset of disease is thought to be the result of a complex interaction of environmental agents with genetic factors [265]. Epidemiological studies indicate that alcohol consumption correlates with a reduced risk of developing RA [266, 267]. Unfortunately, post diagnosis data to assess the effects of alcohol on disease parameters and the lipid profile are lacking. Studies to address this issue are likely to be hampered by ethical and safety issues regarding interactions with disease modifying anti-rheumatic drug (DMARD) therpy, in particular, patients are actively discouraged from drinking alcohol when they are receiving therapy with methotrexate, which is currently by far the most commonly used DMARD for the treatment of RA.

Diet

It is well established that dietary intake has far reaching health implications. An unhealthy diet rich in saturated fats and sugars has been linked to an increased risk of CVD [268], whereas diets high in unsaturated fats and anti-oxidants such as the Mediterranean diet are linked to a reduced CVD risk [269]. There are multiple individual dietary components that impact upon the lipid profile. Fish oils are rich in omega-3 polyunsaturated fatty acids which lowers plasma TG levels [270, 271], red yeast rice has been shown

to reduce TC and LDL levels [272] and olive oil raises HDL-cholesterol and reduces levels of oxLDL [273]. In RA, data regarding the impact of diet on the lipid profile is sparse. One randomised study on 66 active RA patients, demonstrated that patients treated with a gluten-free vegan diet had lower LDL and oxLDL levels [274].

THE EFFECTS OF DRUGS ON THE LIPID PROFILE

The impact of recent therapeutic advances in the management in RA on cardiovascular risk is not clear. However, several recent studies suggest that therapeutic intervention and control of disease activity may reduce cardiovascular risk [42, 43, 275]. A large cross sectional study (QUEST) of over 4,000 RA patients, suggested a reduced cardiovascular risk with prolonged use of DMARDs, glucocorticoids (GCs) or anti-tumour necrosis factor therapy (anti-TNF) [275]. These findings should be interpreted with caution as the study is limited by its cross sectional design and therefore causality can not be assumed. Despite this, a further prospective study has confirmed significant improvements in cardiovascular risk factors following treatment with methotrexate and GCs [42]. Part of these obsereved effects may be governed through drug-induced changes in the lipid profile. In this section we will summarise the effects of DMARDs, GCs, and biologic agents (anti-TNF, rituximab and tocilizumab) on the lipid profile in RA.

The use of statins in RA is escalating at an exponential rate due to the increased awareness of the importance of tackling CVD in RA. Statins classically produce a less atherogenic lipid profile by lowering TC, LDL and TG and increasing HDL levels. However, in RA statins have been shown to exert additional anti-inflammatory properties [276], resulting in suppression of disease activity [277]. Thus, it is possible that statins produce their effects on the lipid profile in RA both through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A and through suppression of the inflammatory load.

The pleiotropic effects of statins are far reaching. Statins have anti-inflammatory properties, which have been shown to have a modest beneficial impact on the clinical signs and symptoms of RA [277, 278] and other forms of inflammatory arthritis [279, 280]. Statin use has been reported to produce a statistically (though not clinically) significant reduction in the number of swollen joints and disease activity scores (DAS) [277, 281]. In addition, suppression of biochemical markers of inflammation have been observed [277, 282], with statin therapy suppressing CRP and ESR levels by as much as 50% and 28%, respectively [277]. This suggests that although statins are unlikely to produce clinically significant anti-rheumatic effects on their own, they may be useful adjuncts to standard anti-rheumatic drug therapy. Also, although they are likely to act primarily act on the lipid profile to reduce CVD risk, in RA they have been shown to reduce other markers of vascular dysfunction, including arterial stiffness [283], and flow mediated dilatation [284]: it remains unclear whether this is mediated through lipid effects, anti-inflammatory effects, or is due to other direct effects on the vasculature. There are however no hard CVD end-point statin trials in RA. In fact, RA patients have been systematically excluded from all large statin trials in the general population. Such trials are required in patients with RA due to the multitude of factors that may contribute to vascular damage in this disease, which make it difficult to predict whether the effect of statins will be of the same magnitude as that seen in the general population.

Statins may also improve manifestations of extra-articular disease in RA patients, such as renal dysfunction. Renal dysfunction is very common in RA with around two thirds of all RA patients reported to have a mild renal impairment and a further 10-15% to have moderate renal impairment [285]. The renal dysfunction seen in RA patients may occur as the result of inflammation-mediated vascular damage, drug therapy (e.g. non-steroidal anti-inflammatory drugs), and the presence of other associated comorbidities e.g. glucose intolerance and hypertension. Interestingly, poor renal function has been found to associate with an excess cardiovascular mortality in the general population [286], with end stage kidney disease patients approximately twenty times more likely to die from CVD [287]. Although no studies have directly assessed the effects of statins on renal function in RA, data from studies performed in the general population suggest that statins may slow renal function decline [288, 289]. The diverisity of the potential beneficial effects of statins, makes them an attractive choice for both CVD risk reduction and for symptom control in RA [290].

The precise effects of statins on dyslipidaemia, disease activity and severity, as well as hard CVD end-points in RA are currently being investigated in the largest, prospective, double-blind, randomised controlled trial ever conducted in RA (the TRACE RA trial) [291].

Glucocorticoids (GCs)

GCs have long been recognised to have beneficial effects in RA [292, 293]. However, in current rheumatological practice GC use has been curbed due to adverse effects. They are used increasingly as a short term measure to induce a rapid reduction in disease activity while awaiting the effects of slower acting DMARD therapy [294]. The long term use of GCs is controversial due to loss of efficacy over time, and the undesirable side effect profile [293].

For many years it has been widely assumed that GC use associates with a more atherogenic lipid profile (raised TC, TG and HDL levels) regardless of the indication for use [295]. However, many of these early studies were performed on renal transplant patients. Thus, they may have been confounded by other lipid influencing variables, such as the underlying disease process, co-morbid conditions and concomitant medications [296, 297]. Over more recent years, conflicting data has been produced from several prospective studies, indicating that GC may actually improve the lipid profile by increasing HDL and lowering the TC:HDL ratio [298, 299]. In 2005, a large study involving 15,004 participants demonstrated differences in the lipid profile in patients receiving GCs according to their age [300, 301]. In patients over the age of 60, GC use was associated with higher HDL and Apo-A1 levels, and lower TC:HDL and ApoB:ApoA-I ratios. No association was noted between GC use and HDL levels, TC levels or TC:HDL ratio among subjects below the age of 60. A potential limitation of this study was the difference in the indication for GC use between the age groups,

and thus the underlying effects of the individual disease processes on the lipid profile. Unsurprisingly, studies assessing the effects of GCs on lipid metabolism in healthy individuals are sparse. A small study on 8 normolipidaemic healthy men treated with prednisolone for 14 days demonstrated a significant increase of VLDL-TG, VLDL-cholesterol, HDL-cholesterol, Apo A-I and ApoE, with normalisation of the lipid profile to baseline levels 2 weeks after discontinuation of prednisolone [7, 301]. A further study on 8 normolipidaemic healthy men examined the relationship between GC exposure and HDL sub fractions [302]. This demonstrated a rapid change in the lipid profile following initiation of 30 mg oral prednisolone, with elevations seen in HDL within 2 days of commencement. Within the HDL subclass, GC exposure induced redistribution of HDL particles, resulting in increased levels of HDL2 and a reduction of HDL3.

A systematic review of the literature was performed to identify if GC use alters the lipid profile in RA. The search criteria included 'rheumatoid arthritis', 'lipid', 'lipids', 'dyslipidaemia', 'steroids', 'prednisolone' and 'glucocorticoids' Following restriction of the search criteria (age >19, human, English, title/abstract), a total of 10 papers were identified. Of these, only 6 papers mentioned the effects of GCs on the lipid profile in RA. However, the majority did not set out to assess this relationship as their primary objective. Thus, the number of patients included that were actually receiving GCs in the majority of studies was very small. The results of some of the studies may have also been affected by potential confounders, such as concurrent changes in DMARD therapy [303]. The largest and most robust study to comment on the effect of GCs on the lipid profile was reported by Boers *et al.* [304]. This was a randomised controlled trial in which 76 RA patients were randomised to take combination therapy of methotrexate (stopped at 40 weeks), sulphasalazine and a reducing dose of prednisolone (initially 60 mg/day prednisolone, tapered in 6 weekly steps to 7.5 mg/day and stopped after 28 weeks) and 79 RA patients who were allocated to take sulphasalazine alone. Both arms of the study were well matched according to age, disease duration and disease activity. The study reported a significant increase in TC and HDL levels, and a reduction in the TC:HDL ratio in both study arms. However, the greatest improvements were observed in the combination therapy arm, with the corrective effect on the lipid profile occurring far more rapidly. The lipid changes were far more significant in the combination therapy arm up until 28 weeks and then all lipid parameters returned to levels similar to those seen in the sulphasalazine only arm, indicating that the changes in the lipid profile may be more specific to GC use (stopped at 28 weeks) rather than the additive effects of the 3 combination therapy drugs.

In RA, the limited available data addressing the relationship between GC exposure and the lipid profile, demonstrate a corrective effect on the altered lipid profile seen in active RA. The most widely reported changes include an increase in both TC and HDL levels [299, 304]. However, HDL appears to increase at a proportionately higher rate compared with TC, thus generating a more favourable atherogenic index [15]. Much of the witnessed normalisation of TC and HDL levels with GC use in RA has been attributed to the suppression of disease activity through their anti-inflammatory actions [15, 304]. Data produced regarding changes in TG levels is not so clear and has only been specifically looked at in 3 out of the 6 studies identified. Although, 2 studies have shown an increase in TG levels with GC use [5, 305], another study failed to demonstrate any change [303]. This discrepancy may be attributed to differences in the populations studied including disease characteristics, drug use, and the power of the individual studies. Further large studies are required in order to fully elucidate the effects of GCs on TG levels. However, as part of a recent cross sectional study examining the effects of GCs on the presence of the MetS we have demonstrated that although TG and HDL levels increase with GC use, this does not associate with an increased prevalence of the MetS [53].

All studies demonstrating the effects of glucocorticoids on the lipid profile in patients with RA are summarised in Table **2**.

Hydroxychloroquine

Hydroxychloroquine (HCQ) is an anti-malarial medication that also exhibits disease modifying and anti-inflammatory actions when prescribed for RA or SLE. In the 1980's Beynen noted a reduction in cholesterol synthesis with low dose chloroquine [307]. A subsequent study confirmed these initial observations and demonstrated reductions in cholesterol and TG levels in those prescribed chloroquine [5]. In the 1990's Wallace *et al*. carried out a study to assess whether HCQ exhibited similar lipid lowering properties as its parent drug, chloroquine [305]. The study involved 150 patients with RA or SLE who were randomised to take HCQ alone, GCs alone, HCQ and GCs, or no drug. HCQ use resulted in a reduction in cholesterol, LDL and serum TG levels, which appeared to be independent of changes in weight and diet. Later studies demonstrate that HCQ produces a less atherogenic lipid profile, by increasing HDL levels by approximately 15% [308].

The mechanism underlying the lipid lowering effects of HCQ and chloroquine are still disputed. However, some plausible modes of action have been described in studies analysing the interaction of chloroquine. Potential reasons include: (a) *via* the inhibitory actions on VLDL secretion by the liver [309] (b) inhibition of cholesterol synthesis by blockage of a site distal to hydroxymethlyglutaryl coenzyme A (HMGCoA) reductase [310], and, (c) inhibition of proteolysis of internalise cholesterol esters leading to increased LDL receptor values [307, 311].

Ciclosporin

Since the first reported use of ciclosporin A (CyA) for the management of RA in 1979 [312], the drug has been used both as monotherapy or in combination with other DMARD therapy, such as methotrexate [313, 314]. Chronic CyA administration has been shown to adversely affect the lipid profile. However, much of this data has been generated from small studies on transplant patients [315, 316]. A study of 65 post renal transplant patients, demonstrated elevations in TG and Lp(a) levels, and suppressed HDL levels in those treated with CyA monotherapy compared with azathioprine and prednisolone [317]. The reduction in HDL levels may be

Table 2. Studies Assessing the Impact of Glucocorticoid Use on the Lipid Profile in Patients with RA

Study	Number of Patients	Other Drugs Used	Follow Up	Patient Demographics	Lipid Changes
Peters *et al.* Ann rheum dis 2007 [15]	80 RA (35 on pred)	Infliximab	48 wks	Age 56 DD: 10 yrs Female 77 %	Pred ↑ TC and HDL levels and ↓ TC:HDL ratio
Dessein *et al.* J.Rheumatol 2004 [303]	92 RA (37 had pred in past) (18 currently on pred ≤ 4mg) No controls	At enrolment 17 patients taking DMARDs by completion 84 patients on DMARDs	6 mths	Female 80% Age 56 yrs DD: 11 yrs	No changes in LDL, HDL or TGs
Boers *et al.* Ann rheum dis 2003 [304]	155 early active RA	Patients randomised to either MTX& SLZ & pred (76) or SLZ alone (79)	56 wks	Age 50 yrs DD: 4 months Female 59%	↑ TC, HDL and ↓ TC:HDL ratio in both group but greater in combination therapy group.
Dessein *et al.* Arthritis res 2002 [306]	79 RA (10 on pred) 39 age/sex matched OA controls (6 on pred)	Median dose of pred 5 mg	Cross-sectional	Age 52 yrs Female 83% DD: 8.5 yrs	No significant differences between RA patients taking and not taking steroids.
Wallace *et al.* Am J med 1990 [305]	108 SLE, 47 RA (14 HCQ, 8 pred, 4 HCQ & pred, 21 neither drug) 108 SLE	HCQ	Cross-sectional	Age 46.6 yrs	Pred alone have ↑ TC, HDL and TG but ↓ LDL compared to those not on treatment. (unable to distinguish between effects in RA and SLE patients)
Svenson *et al.* Arch intern med 1987 [5]	33 (only 4 treated with just pred)	Pred & AZA or Pred & cyclo or Pred alone	9 mths	Age 49 yrs	↑ TC, TG, HDL and LDL in all groups including pred only arm.

TC: total cholesterol, TG: triglycerides, HD: high-density lipoproteins, LDL: low-density lipoproteins, Pred: prednisolone, MTx: methotrexate, SLZ: sulphasalazine, AZA: azathioprine, HCQ: hydroxychloroquine, cyclo: cyclophosphamide, OA: osteoarthritis, SLE: systemic lupus erythematosus, DD: disease duration, RA: rheumatoid arthritis, DMARDs: disease modifying anti-rheumatic drugs, yrs: years, wks: weeks, mnths: months.

explained by the inhibitory actions of CyA on ABCA1-mediated lipid efflux [318]. Despite these findings in transplant patients, further studies are required to address the potential effects of CyA on the already altered lipid profile seen in RA.

Gold

Gold is one of the oldest treatments for RA, and was first used in the late 1920s [319]. Its use has diminished over recent years with the advent of newer more effective DMARDs and biologic therapies. Gold therapy has many adverse effects including dermatitis, stomatitis, post injection reactions, haematuria and proteinuria. However, not much has been reported about its effects on the lipid profile. Munro *et al.* reported that gold use may have the net effect of producing a more atherogenic profile by increasing TG levels and reducing HDL levels [308]. No further studies have directly looked at the influence of gold on lipid levels.

Anti-Tumour Necrosis Factor Agents

The identification of TNF-α as a key cytokine in the pathogenesis of RA has resulted in the development of specific biologic therapies designed to target TNF-α with the net effect of inhibiting its inflammatory properties [320]. The introduction of anti-TNF agents in 2000, has revolutionised the treatment of RA with better disease control and dramatic improvements in quality of life [321]. Despite the overwhelming benefits of anti-TNF therapy, a number of complications and adverse effects have been noted [322]. By far the most common complication of anti-TNF therapy is infection [323]. However, there is expanding evidence to suggest that these agents may also interact with other metabolic parameters, such as the lipid profile [73].

To date, 3 anti-TNF agents have been licensed for use in RA, Infliximab, Adalimumab and Etanercept. The structure and mode of action of the 3 agents varies. Infliximab is a chimeric monoclonal antibody, adalimumab is a fully humanised monoclonal antibody and etanercept is a soluble TNF-α receptor fusion protein. The underlying characteristics of these molecules may be key to their mode of action and effects on the lipid profile.

A systematic review of the literature was carried out to address the effect of the 3 anti-TNF agents on the lipid profile. A PubMed search was conducted with specified search criteria: 'rheumatoid arthritis', 'lipid', 'lipids', 'dyslipidaemia', 'anti-tumour necrosis factor', 'infliximab', 'etanercept'

and 'adalimumab. The limites applied to the search included: age >19, human, English and title/abstract. The search identified a total of 19 papers, of these 16 studies were found to address the impact of anti-TNF agents on the lipid profile. Overall, the studies recruited relatively small populations and had a short duration of follow up, with several studies only looking at a handful of patients over a 6 week period [324-326]. The largest study enrolled 97 RA patients who were prospectively followed up for 1 year [327]. The study was limited by the lack of a control group and only reported changes in HDL and TC. Twelve of the fifteen studies did not include a control group for comparison.

Multiple studies have produced information on the short-term effects of anti-TNF agents on the lipid profile [328-330], but there are relatively few addressing the longer term effects [15, 121]. In the short term studies, duration of treatment ranged from 6 weeks to 6 months, and the majority only assessed the effects of infliximab [122, 328, 329, 331]. Irrespective of their duration, these studies demonstrate similar findings with a universal increase in TC, and a large proportion confirming an increase in HDL, but no overall change in the atherogenic index (TC:HDL ratio). Although TG levels were not looked at in all studies, the available data tends to show an increase in TG levels up until 6 months in patients treated with infliximab [122, 328]. Saiki *et al.*, have shown the most convincing evidence of a relationship between anti-TNF and an increase in TG levels [332]. The study compared TC and TG levels among 32 patients with refractory RA treated with infliximab, to 32 age- and sex-matched control patients with active RA treated with methotrexate over a 6 month period. A significant and persistent elevation in TG levels was observed from 2 weeks in the infliximab arm but no change was seen among those treated with methotrexate, thus indicating that changes in TG levels are likely to be due a drug-specific mechanism rather than a 'blanket' anti-inflammatory effect.

Published data regarding the effects of the other 2 anti-TNF drugs is limited. The short term effects of etanercept and adalimumab have only been studied in 2 studies [4, 330]. However, due to study design and small number of patients enrolled, they only reported on the generic effect of anti-TNF on the lipid profile rather than the effect of the individual drugs. Seriolo *et al.*, reported similar findings to the studies performed solely on patients receiving infliximab (increased TC and HDL) [4], whereas the other study reported no effect of anti-TNF on the lipid profile [330]. The effect of etanercept and adalimumab on the lipid profile needs to be addressed in further large scale studies, particularly as differences in their molecular structure, mode of action and half-life may alter how they affect the lipid profile.

The effects of anti-TNF therapy on Lp (a) levels were addressed in only 3 studies [4, 324, 330]. None of the studies demonstrated a significant change in Lp(a) levels. However, this may be the result of a lack of power due to small study size, with the largest recruiting a population of 34 RA patients [4]. Unfortunately, 2 of these studies attempted to look at the effects of all 3 anti-TNF agents, thus making the results difficult to interpret, as Lp(a) levels may be affected differently by each TNF agent e.g. cancelling each other out in the reported results.

A summary of all studies addressing the effects of anti-TNF agents on the lipid profile in patients with RA is shown in Table **3**.

Rituximab

Rituximab, an anti-CD20 monoclonal antibody, is used to treat patients with active RA unresponsive to DMARDs and/or 1 anti-TNF agent. Rituximab was originally developed for the treatment of B cell lymphoma, but has since been found to be useful in other conditions including RA, with significant reductions in disease activity and functional improvement [333, 334]. Although rituximab is now widely used, relatively little is known about the effects of the drug on the lipid profile, structure or function. To date, there has been 1 prospective study of 6 RA patients treated with rituximab for 6 months [335]. The investigators report minor lipid changes at 2 weeks. However, the changes in the lipid profile are most likely to have been induced by the concomitant infusions of methylprednisolone (given to reduce side effects) rather than the rituximab per se [336]. The lipid profile returned to baseline and no significant differences were reported after 6 months of treatment. However, this study had a primary objective of assessing endothelial function and not lipid parameters and therefore it was unclear whether potential confounders such as statin use were taken into consideration.

Tocilizumab

Tocilizumab is an interleukin-6 (IL-6) receptor antagonist, offering a different mode of action to all other currently available biologic therapies. Although data from clinical trials have shown tocilizumab to be effective at controlling disease activity in RA [125, 337], concerns have arisen regarding its effects on the lipid profile. Available evidence demonstrates a significant increase in TC, HDL, TG and LDL levels following treatment with tocilizumab [125, 337, 338]. The relative changes in each of these levels and the impact this has on atherogenic indices such as TC:HDL ratio is less clear, with some studies reporting an increase in the TC:HDL ratio [125], while others failed to demonstrate a change [337]. It has been hypothesized that the elevations in lipid levels occurs as part of a 'corrective' phenomenon of treatment by reversing the effects of high-grade inflammation on the lipid profile. Although studies do demonstrate both suppression of inflammatory markers (ESR and CRP) and elevations in lipid levels, no direct correlations have been reported to confirm an association. Further studies are therefore required to not only address this issue, but also to establish the effects of tocilizumab treatment on other lipid parameters such as apolipoproteins, Lp(a), lipoprotein structure and function, which may also confer CVD risk.

GENETIC REGULATION OF LIPID METABOLISM

ATP Binding Cassette Transporter Gene (ABCA1) Polymorphisms

The ATP binding cassette transporter protein is primarily involved in the transport of phospholipids and cholesterol from cells to intracellular acceptors, including lipid-free ApoA1. Polymorphisms of the ABCA1 gene lead to alterations in protein function. In the most severe form, patients

Table 3. The Effects of Anti- Tumour Necrosis Factor Agents on the Lipid Profile in Patients with Rheumatoid Arthritis

Study	Type of Anti-TNF	Number of Patients	F/U	Changes in Lipid Profile				
				TC	HDL	TC/HDL	TG	Lp(a)
Garces *et al.*, Ann.Rheum.Dis 2008	Inflix Etan	**30 RA, 29 AS, 6 PsA** Inflix= 44 Etan= 21	**1yr**	↑ **inflix** N/C Etan	**N/C inflix** ↑ Etan	**NS** NS	**NS** NS	**NS** NS
Nishida *et al.* Endocrine J 2008 [327]	Inflix	**97**	**1 yr**	↑	↑	NS	NS	NS
Soubrier *et al.* Joint bone spine 2008 [330]	All	**Etan =6** Inflix =11 Adal = 12	**14 wks**	N/C	N/C	N/C	N/C	N/C
Oguz *et al.* Acta Clin Belg 2007 [326]	Inflix	**7**	**9 mths**	**N/C**	**N/C**	**NS**	**NS**	**NS**
Popa *et al.* Ann Rheum Dis 2007 [73]	Inflix	**55**	**55=6 mths 31=1 yr**	↑	↑	↑	NS	NS
Peters *et al.* Ann Rheum Dis 2007 [15]	Inflix	**80**	**48 wks**	↑ **at 6 wks, by 48 wks baseline**	↑ **at 6 wks, by 48 wks** baseline	↑**at 6 wks, by 48 wks back to baseline**	NS	NS
Saiki *et al.* J. Rheumatol 2007 [332]	Inflix	**43 refractory RA** 32 age/sex matched RA controls on MTX 32 healthy controls	**6 mths**	↑ **from 2 wks**	NS	NS	↑ **from 2 wks**	NS
Tam *et al.* Clin Rheumatol 2007 [328]	Inflix	**19**	**14 wks**	↑	↑	N/C	↑	NS
Allanore *et al.* Clin Chim Acta 2006 [119]	Inflix	**59 refractory RA** 56 RA controls not on anti-TNF	**30 wks**	↑	↑	**N/C**	↑	NS
Dahlqvist *et al.* Scand J Rheu-matol 2006 [121]	Inflix (41 also MTx, 13 other DMARD 28 Pred)	**52 RA on infliximab** 70 early RA controls	**2 yrs**	↑ **initial,** then ↓ by 6 month	↑**initial**, then ↓ by 6 month	↑	**NS**	NS
Kiortis *et al.* J Rheumatol 2006 [122]	Inflix	**82** (50 = RA 32 = AS)	**6 mths**	↑	N/C	N/C	↑	NS
Seriolo *et al.* Ann NY Acad Sci 2006 [4]	All **(plus MTX & pred)**	**Etan = 16** Inflix = 14 Adal =4	**48 wks**	↑	↑	**N/C**	**N/C**	**N/C**
Spanakis *et al.* J Rheumatol 2006 [331]	Inflix	**60** (24=RA 26=AS 10=PsA	**6 mths**	↑ **(1st month only**	↑	↓ **(at 3 months)**	NS	NS
Vis *et al.* J Rheumatol 2005 [329]	Inflix	**69**	**6 wks**	↑	↑	N/C	NS	NS

(Table 3) contd….

Study	Type of Anti-TNF	Number of Patients	F/U	Changes in Lipid Profile				
				TC	HDL	TC/HDL	TG	Lp(a)
Irace *et al.* Atherosclero 2004 [325]	Inflix	**10**	**6 wks**	↓ only after 1st infusion	↓	NS	N/C	NS
Cauza *et al.* Wien Klin Wochenschr 2002 [324]	Inflix	**7**	**6 wks**	N/C	↓	NS	↑	N/C

Anti-TNF: anti- tumour necrosis factor, Inflix: infliximab, Etan: etanercept, Adal: adalimumab, MTX: methotrexate, Pred: prednisolone, DMARD: disease modifying anti-rheumatic drugs, RA: rheumatoid arthritis, AS: ankylosing spondylitis, PsA: psoriatic arthritis, wks: weeks, mths: months, N/C: no change, NS: not significant, yrs: years, wks: weeks, mths: months.

develop Tangier disease, characterised by reduced HDL in heterozygotes or clinically absent HDL in homozygotes [339]. To date, a number of single nucleotide polymorphisms (SNPs) have been identified and their association with plasma lipid levels and cardiovascular risk addressed in general population studies [340-342]. Patients carrying the K allele of the rs2230806 (R219K) SNP appear to be significantly protected from developing CVD, and a variety of studies report that it assocaites with lower TG levels and higher HDL levels [343-345]. Other polymorphisms including the I883M (rs4149313) and V771M (rs2066718) have been associated with an increased CVD risk [341, 346, 347], but demonstrate inconsistent effects on lipid parameters [348, 349]. R1587K (rs2230808) and E1172D (***rs33918808***) have also both been associated with an increased CVD risk [341, 350]. ABCA1 polymorphims and their association with CVD have not been studied in RA.

Cholesterol Ester Transfer Protein (CETP) TaqIB Polymorphism

The cholesterol ester transfer protein (CETP) is key to the transfer of cholesterol esters and triglycerides between lipoproteins. It aids reverse cholesterol transport and HDL metabolism, by transferring cholesterol esters from HDL to VLDL and LDL. Variations in CETP levels can occur as a result of a SNP in intron 1 of the CETP gene (TaqIB), located on chromosome 16. The presence of a B2 allele confers lower CETP levels than the presence of the more common B1 allele. Thus, patients homozygous for the B2 allele often have significant elevations in their HDL-C levels compared with B1 homozygous patients [351]. Based on these findings, it is rather unsurprising that the B2 allele has also been associated with a lower CVD risk in the general population [352, 353]. A meta-analysis of 113,833 patients has demonstrated further changes associated with inheriting the B2 allele, including lower CETP mass and activity, lower levels of LDL-C, apoB, and TGs and increased levels of ApoAI [354]. Interestingly, the presence of the B2 allele may also enhance clinical benefit from statin therapy among patients with significant coronary artery disease, with a net effect of reducing cardiovascular events [355]. The worldwide frequency of the minor allele (B2 allele) is 42%. This was reported to be identical among East Asian and white populations [354]. The genotypic and allelic frequencies of the CETP TaqIB and the influence this may have on the lipid profile or CVD risk has not been studied in RA.

Apolipoprotein E (ApoE) Polymorphisms

ApoE is a major component of VLDL and chylomicrons. It is essential for the catabolism of TG-rich lipoprotein constituents, and facilitates the uptake of VLDL and chylomicrons into the liver [356]. ApoE may further regulate lipid metabolism *via* enhancing effects of LPL and HL [357]. Three isoforms of ApoE exist as a result of 2 SNPs, ApoE2, ApoE3 and ApoE4. ApoE3 is considered as the parent form, occurring in more than 60% of the population [358] and the other 2 as mutations. ApoE2 is produced due to a base change (arginine to cysteine) at residue 158, whereas ApoE4 is the consequence of a base change (cysteine to arginine) at residue 112. Such changes alter the structure and function of the protein, resulting in a significantly reduced binding affinity of ApoE2 to the liver receptors [359], a subsequent delay in the removal of dietary fat from the blood [360] and the development of type III hyperlipidaemia [361]. ApoE4 predisposes to atherosclerosis through mechanisms that are still being elucidated [358]. However, some studies indicate that the lipoprotein distribution of ApoE4 differs from the parent form, and that particles containing ApoE4 are prone to catabolism, which ultimately leads to further alterations in lipoprotein metabolism with the end result of increasing LDL, TC and TG levels [362, 363]. ApoE polymorphisms may also partially account for variations observed in atherosclerotic plaques, with differences being observed in carotid intima-media thickness [364]. The prevalence and contribution of the ApoE genotypes to the development of CVD in RA have not yet been studied.

Lipoprotein Lipase (LPL) Polymorphisms

The LPL gene is located on chromosome 8p22 and is responsible for the production of LPL. The enzyme plays a key role in the mobilisation of non-esterified fatty acids and monoglycerol molecules for energy utilisation and storage by cells *via* the hydrolysis of the triacylglycerol component of VLDL and chylomicrons. Thus, a deficiency of this enzyme can result in an accumulation of both plasma chylomicrons and TGs, as seen in the autosomal recessive condition – familial LPL deficiency [365]. To date several SNPs of the

LPL gene have been associated with lipid abnormalities and CVD [366]. Four SNPs including D9N (rs1801177), N291S (rs268), S447X (rs328) and hindIII (rs320) have been shown to significantly alter plasma levels of TG and HDL [366]. Available data, from several independent studies have demonstrated an increased CVD risk with LPL mutations (S447X, *Pvu*II (rs285)) [367-369], and this association has recently been confirmed in a large meta-analysis [366]. The HuGE association review and meta-analysis demonstrated an increased odds ratio (OR) for myocardial infarction and coronary stenosis with G188E (OR=2.8), D9N (OR=1.33) and T-93G (OR=1.22). However, the remaining 4 SNPs (N291S, PvuII, HindIII, S447X) analysed were not found to associate [366]. The frequency and impact of such genetic polymorphisms have not been studied in RA.

Apolipoprotein (A1/C3/A4/A5) Gene Cluster

The long arm of chromosome 11 is home to the regulatory gene cluster that encodes for proteins ApoA1, ApoC3, ApoA4 and ApoA5. Interestingly, not only have the genes responsible for these proteins been found to be close in their chromosomal proximity, but the proteins produced by each gene have been found to have inter related functions involved in the metabolism of TG-rich lipoproteins and HDL [370, 371], a phenomenon that may be attributed to linkage disequilibrium. ApoA1 is the main protein component of HDL and plays an important regulatory role in reverse cholesterol transport. ApoC3 is found in association with VLDL and HDL, and primarily acts as an inhibitor of LPL [372], thus slowing the rate of catabolism of triglyceride rich particles. Due to the inhibitory effects of this protein an inverse relationship between ApoC3 levels and TG levels exists. ApoA4 is a major constituent of chylomicrons, and is thought to be involved in TG metabolism [373], along with ApoA5 [374-376]. An extensive array of SNPs has been identified within the genes responsible for the production of each of these proteins, which have been linked not only to alterations in lipid metabolism and but also to CVD. For example, around 20 SNPs of the ApoA5 gene have been identified, with around half of these found to be associated with disorders of TG metabolism [377], and others associated with excess CVD risk [374, 378]. ApoC3 M455, ApoA4 T347S, ApoA5 S19W may be particularly interesting in the context of the lipid abnormalities described in RA, but have not been studied yet in this condition. ApoC3 M455 is associated with HDL levels, with the presence of the C allele shown to significantly reduce levels [379]. The Apo A4 S347T is associated with an increased risk of CVD [380], and apo A5 S19W with significantly elevated TG levels [381, 382].

CONCLUSIONS

Dyslipidaemia in RA is the consequence of the complex interaction of multiple factors, with inflammation fundamental to most. Although our overall understanding of the role of inflammation in dyslipidaemia can help us to understand the lipid changes seen in RA, further studies are required specifically in RA as there may be disease specific phenomena occuring. The contribution of genetic factors to dyslipidaemia in RA requires further investigation in large-scale studies, particularly in the context of gene-environment interactions. In addition, the precise contribution of dyslipidaemia to the excess CVD risk seen in RA remains to be elucidated, providing scope for future research.

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DECLARATION OF INTEREST

The authors declare they have no conflicts of interests.

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