Ethnicity and Inflammatory Pathways – Implications for Vascular Disease, Vascular Risk and Therapeutic Intervention

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Abstract: Cardiovascular disease remains the most common cause of death worldwide, yet there is a wide variation in disease prevalence between different ethnic groups. One's individual risk is not entirely explained by 'traditional' risk factors and this, along with the observation that endogenous and lifestyle risk factors appear to cluster in the same individuals has led to the idea that there may be a common mechanism underlying this disease. It has been postulated that inflammatory pathways may be important. Results from our own and other studies have demonstrated that there may be ethnic differences in the level of circulating inflammatory markers which may be partially related to demographic, lifestyle or genetic factors. Before it is possible to add inflammatory markers to global risk scores it is imperative that a clear understanding of their function, normal range and major determinants in different ethnic groups is established. To date the ethnic research in this area has been very sparse and further work is urgently required. The usefulness of these inflammatory markers in the diagnosis and prognosis of disease in these different populations also needs to be investigated before therapeutic strategies can be fully developed.

Keywords: Inflammation, ethnicity, cardiovascular disease, cytokines, innate immunity, cardiovascular risk.

BACKGROUND

Ethnic Differences in Cardiovascular Disease (CVD)

The study of change in patterns of health and disease across populations has been of interest since Thomas Malthus in 1798 argued that 'population growth will always tend to outrun the food supply' and that 'betterment of the lot of mankind is impossible without stern limits on reproduction' [1]. Since then, the theories on the health of populations in transition have developed with the groundbreaking contribution given to public health by Abdel Omran [2]. In his essay of 1971 Omran conceptualizes the theory of epidemiological transition in which degenerative and man-made diseases displace pandemics of infection as the primary causes of morbidity and mortality. In societies around the world we now observe two main distinct phenomena: first, a rapidly growing movement of populations between locations where there are large differences in health indicators or where there are differences in the nature and practice of health care; second, that migration and mobility of populations are responsible for health differentials between origin and destination [3].

CVD remains the most common cause of death worldwide yet there is a wide variation in disease prevalence and in particular, of coronary heart disease (CHD) between different ethnic groups [4]. Individuals of African origin, both in Africa and when migrated to the Caribbean or to Europe, have a much lower prevalence of CHD [5]. This apparent protection however is not observed in African-Americans [6]. By comparison, the mortality from CHD in UK Indian Asians is at least 40% higher than that for European whites [4,7].

An intriguing aspect of the epidemiology of vascular disease around the world is the consistent report that stroke is an important cause of morbidity, disability, and death in adults of black African origin, whether living in Africa, the Caribbean, US, or the UK [8]. The study of trends in stroke mortality in the US among African-Americans suggests stages of evolution of patterns of CVD among black people of sub-Saharan African origin [8]. This evolution is characterized by advancing acculturation, urbanization, and affluence with a progressive increase in salt intake, smoking habit, and saturated fat intake. This theory suggests that in the absence of high fat intake atherosclerosis is absent and is predominantly due to high blood pressure. With affluence, urbanisation and ensuing increases in cholesterol (and later obesity and diabetes) atherosclerosis develops and CHD becomes prevalent.

Ethnicity, Novel Risk Factors and CVD Risk Estimates

Despite a widely held belief that 'traditional' risk factors such as smoking, blood pressure and serum lipids account for up to 90% of an individual's CVD risk [9], the search for novel risk factors has nevertheless been extensive and new risk factors such as C-Reactive Protein (CRP) have emerged as potential contenders. If this is the case then it could be argued that there might be little to be gained from the pursuit of novel risk factors. However, we, like many others, believe that there are several reasons why these factors should still be pursued. Firstly, it still has not been possible to attribute the ethnic differences in CHD prevalence to known ethnic differences in CHD risk factors, such as serum lipid levels [5], diabetes [5,10-12], hypertension [5,10-11], smoking [5,10-11] or homocysteine levels [13]. Secondly, 35% of CHD occurs in individuals whose cholesterol is less than 5.4mmol/L [14]. Thirdly, an understanding of such risk factors may lead to a better understanding of the underlying disease aetiology. This in turn may lead to the development of improved preventive and therapeutic interventions.

There is an increasing awareness that inflammation, and possibly infection, may contribute to CVD development and discussions regarding the addition of CRP, an inflammatory marker, to global risk scores are ongoing [15-17]. However, it is important that the clinical usefulness of such markers is fully evaluated. They need to be able to predict CVD independently of established risk factors [18-23]. The magnitude of the relationship needs to be considered and the measurements need to be reliable, reproducible and cost effective. However, even the existing risk scores are not equally applicable to all groups of individuals and, in particular, those from different ethnic backgrounds. Adjusted 'traditional' risk estimates for certain groups are therefore required [24,25]. We believe that a similar predicament might exist for the application of risk scores to inflammatory markers. Furthermore, there is a need to

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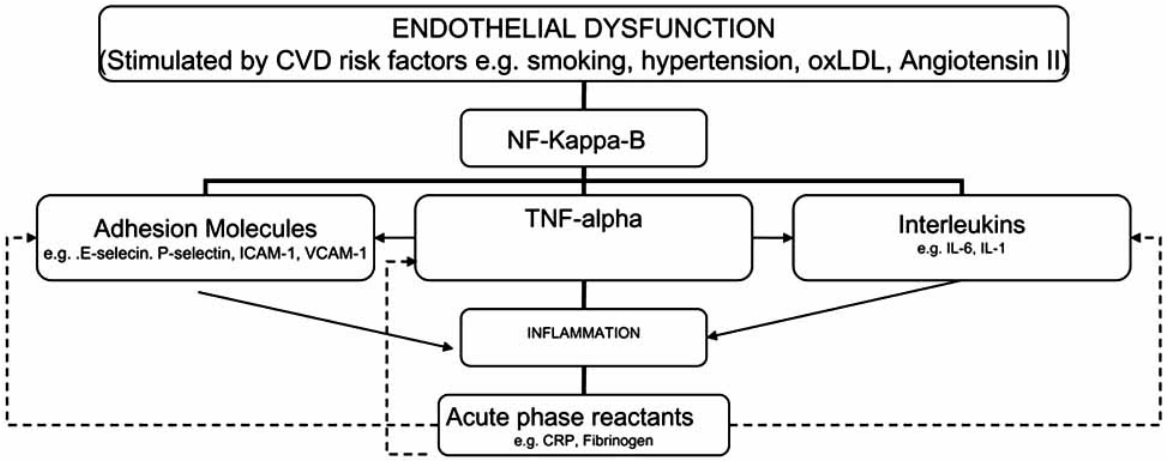

Fig. (1). Inflammatory cascade.

understand and fully evaluate any other factors which might lead to an elevation of the level of these markers.

In this review we highlight some of the known ethnic differences in new inflammatory CVD risk factors; we discuss factors which may be responsible for each of these differences and finally, we discuss the importance of understanding ethnic variations in circulating levels with regard to the application of risk scores and development of novel treatment regimes.

Inflammatory Hypothesis for CHD

The existence of clusters of endogenous and lifestyle risk factors in the same individuals has led to the idea that there may be a common mechanism underlying their ability to influence the development of these diseases. Moreover as one's individual risk is not entirely explained by these 'traditional' risk factors and monocytes were observed in atherosclerotic plaques, the idea that inflammatory pathways may be important in the development of CHD was proposed [26]. Monocytes, along with inflammatory cytokines, which accumulate in atherosclerotic plaques, are released when plaques are disrupted. A number of these inflammatory markers, including CRP have shown strong relationships with CHD development [27-29] Fig. (**1**).

As well as the endothelial dysfunction, studies have also highlighted the potential importance of adipose tissue in relation to inflammatory burden in CVD, describing the expression and secretion of both pro-inflammatory and protective factors, collectively termed adipocytokines [30]. These factors include tumour necrosis factor alpha (TNF-α), which is a key mediator of the acute phase response. Resistin has been proposed as a potential link between obesity and inflammation, although the aetiology for this is unclear [31, 32]. Other factors involved in inflammation include IL-1β, IL-6, IL-8, IL-10, TGF-β as well as factors involved in the acute-phase response (serum amyloid A, plasminogen activator inhibitor-1 (PAI-1)) [33]. Angiotensin II (ANG II) is also produced by adipose tissue and this and PAI-1 are important in the fibrinolytic and thrombotic pathways [34,35]. Adiponectin, which is unique in its known protective abilities, exhibits both insulin sensitising and anti-inflammatory properties with serum levels reduced in both type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) [36, 37].

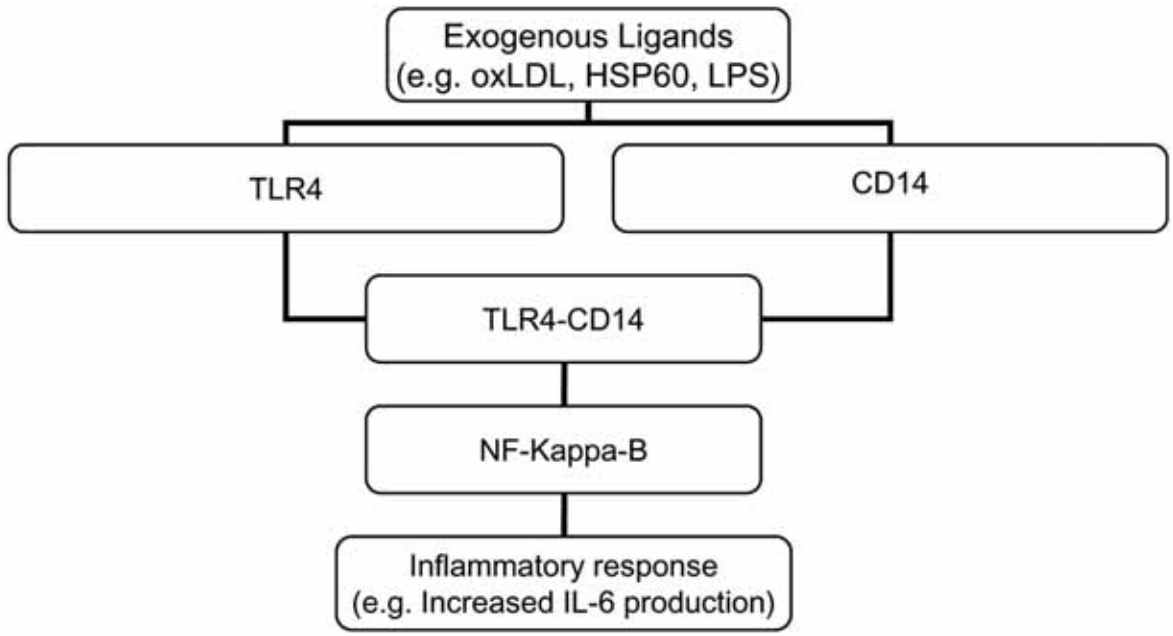

Fig. (2). TLR4 inflammatory pathway.

Whilst adipose tissue increases the production of pathogenic adipocytokines in obesity, it is hypothesised that 'macrophage recruitment' into adipose tissue may contribute to the pathogenic response by enhancing the inflammatory response and release of cytokines [38, 39].

Toll-Like Receptor Pathway and Oxidation

Toll-like receptors (TLRs) are evolutionary conserved innate immune receptors that are shared by the IL-1 receptor signalling pathways. As shown in Fig. (**2**), these receptors combine with the pattern recognition molecule CD14 to form a complex (TLR4-CD14), which activates the NF-κB pathway that mediates adhesion molecule expression and inflammatory cytokine production Fig. (**1**) [40]. TLR ligation therefore induces expression of a wide variety of genes, such as those encoding proteins involved in leukocyte recruitment, production of reactive oxygen species and phagocytosis [41]. Activation of TLRs also elicits the production of cytokines that augment local inflammation [40]. TLR ligation may also induce apoptosis which is probably an important first line defence mechanism against microbial compounds.

Ethnic Differences in Inflammatory Markers

In this review, we have focused on white individuals of Caucasian origin (whites) living in the UK or America; Indian individuals of South Asian origin living in the UK and finally both individuals of African origin (both African and Caribbean individuals) living in the UK as well as individuals of African origin living in America (African Americans). Although, individuals of African origin in the UK and in Africa are at high risk of CVD and stroke they are at a low risk of CHD. This protection from CHD however, is not evident in African Americans. This highlights the importance of environmental and lifestyle factors as well as possible genetic factors in the determination of CHD risk. Some studies may have included other groups of individuals and in which case the values for these may have been reported but they are not the main focus of this review.

This review has examined the components of the pathway outlined in (Fig. (**1** & **2**). We searched the electronic Medline database using Pub Med up until early December 2006. We used ethnicity and race and the molecule/component of the pathway of interest. Furthermore, we reviewed the reference list of original and review articles to search for more articles. We focused on studies of individuals of African, white and South Asian origin. Only studies that were published in English and full articles were included.

For many of the components of the pathway of interest ethnicity data is either unavailable or relatively scarce and hence the review therefore is focused on specific adhesion molecules, interleukins, matrix metalloproteinase's and C-reactive peptide. The data for CRP however, is increasing exponentially. An overview of the latter data is included in this review but a more comprehensive and separate review of ethnic differences in CRP may soon be warranted.

1) CD14, TLRs, Oxidation and the Response to Infectious Agents

Risk factors for atherosclerosis, including oxidative stress / oxidation (oxLDL) and raised soluble heat shock proteins, lead to the activation of transcription factor and inflammatory response [42]. Activation of monocytes by the CD14 receptor induces intracellular changes, which result in increased monocyte-endothelial adhesion and thus initiate the adhesion pathway described in Fig. (**1**). Recent evidence suggests that gene-gene and gene-environment interactions are important in this pathogenic pathway [43] and CD-14 expression is increased in acute coronary syndrome (ACS) and is associated with a 2.4 time increase in TNF-α following an infectious stimulus (Lipopolysaccharide (LPS)) [44]. There have been suggestions that nonspecific infections (periodontal infections, respiratory tract infections) may be linked to CVD [44] and, some studies have linked specific infectious agents (e.g. *Helicobacter pylori and Chlamydia pneumoniae*) to arterial disease [45]. Gram-negative bacteria have a LPS complex associated with their outer membrane, which contains endotoxin and this complex elicits a variety of inflammatory responses. The evidence linking infectious agents with CHD and arterial disease is often weak and inconclusive and, therefore further studies are required. The burden of infectious disease is also different in different countries and populations. Full evaluation of these markers in these different population settings is required to see if the potential for a marker to predict CVD can be universally applied.

The inflammatory response to such infectious agents is thought to occur through TLRs and a given individual's response to such pathogens may greatly influence the atherosclerotic process [46]. A crucial role in the response to infectious agents may be played by interleukin-10 (IL-10) [47]. It has been suggested that patients with increased CD14 expression may have an enhanced inflammatory response to LPS or other gram negative products [46]. We have found that there are clear ethnic differences in plasma LPS levels (Miller, M.A.; McTernan, P.G.; Harte, A.L.; Fernandez da Silva, N.; Strazzullo, P.; Alberti, G.M.M.; Kumar, S; Cappuccio, F.P (unpublished observation)) and we are currently investigating possible ethnic differences in CD14 levels.

It has been suggested that insulin may act directly on the gastro-intestinal adsorption of endotoxin (LPS), independently of circulating glucose concentrations [48]. Ethnic difference in insulin resistance may therefore play a role in this pathway. Polymorphic variation in both the CD14 promotor is associated with a higher prevalence of ACS in CAD patients [49] and a functional polymorphism in the TLR (TLR4 Asp 299Gly) has been linked to the development of cardiovascular events [50] and efficacy of pravastatin [51]. However, the frequency of these polymorphisms and the relationship to CVD in different ethnic groups remains to be established.

2) NF-Kappa B

Nuclear factor kappa-B (NF-κB) is a transcription factor, which is present in an inactive form in monocytes, endothelial cells and smooth muscle cells and adipose tissue. It is activated, possibly through a mechanism involving TLRs, by classic CVD risk factors such as hypertension, hypercholesterolemia, smoking, oxidized LDL and angiotensin II. Activated NF-κB in turn activates adhesion molecules, TNF-α and interleukins (e.g. interleukin-1 (IL-1) and interleukin-6 (IL-6)). Activated TNF-α production has further stimulatory effects on adhesion molecule expression and promotes further induction of IL-6. This inflammatory cascade in turn leads to the production of acute phase reactants such as CRP and fibrinogen Fig. (**1**). Ritchie *et al.* [52], demonstrated that there is significant and specific activation of NF-κB in patients with unstable angina pectoris. Furthermore, this activation precedes a clinical event and may possibly be involved in plaque disruption [52]. There are no studies to date that have examined ethnic differences in NF-κB activation. Interestingly, a recent animal study has suggested that prolonged expression of genes induced by NF-κB might be anti-atherogenic rather than pro-atherogenic [53].

3) Adhesion Molecules (ICAM-1, VCAM-1, E-Selectin, P-Selectin)

In the formation of an atheromatous lesion and subsequent development of CHD the adhesion molecule pathway is activated and adhesion molecules are expressed [54]. Expressed

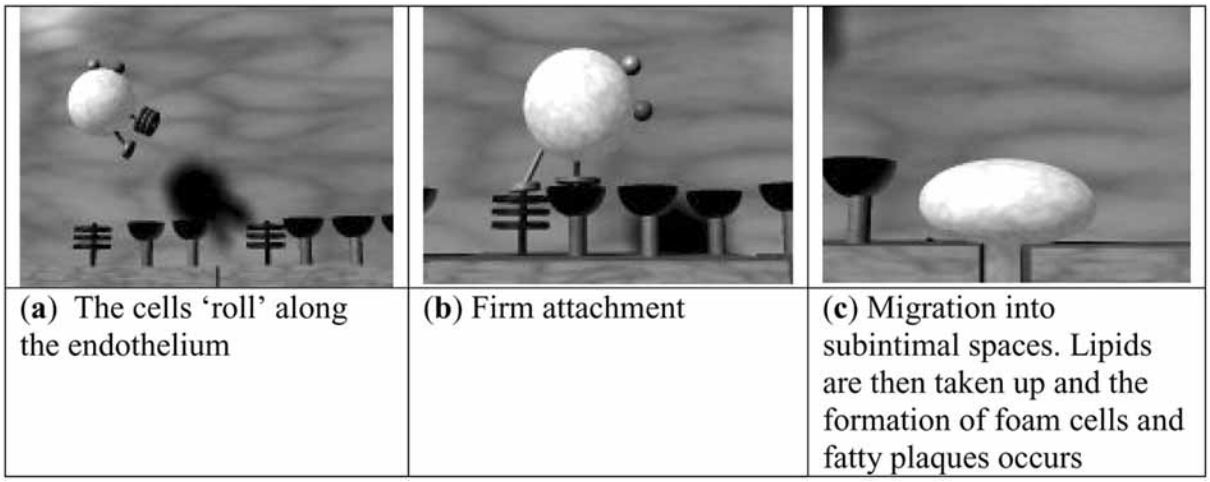

Fig. (3). Schematic diagram showing attachment of a leukocyte *via* endothelial adhesion molecules and their receptors.

adhesion molecules attract leukocytes to the endothelium Fig. (**3**). The cells 'roll' along the endothelium (**a**), become firmly attached to it (**b**) and migrate into the subintimal spaces where they take up lipids and become foam cells and form fatty plaques (**c**).

Table 1. Ethnic Differences in Circulating Soluble Adhesion Molecule Levels

Study (Author and Ref)	Subjects	Molecule	Key Outcomes
Lutsey [66]	Cross-sectional study from the Multi-Ethnic Study of Atherosclerosis (MESA).	ICAM-1	Men (n=1145): White (285); black (252); Hispanic (282); Chinese (233); p<0.0001 Women (n=1469): Whites (288); black (255); Hispanic (287); Chinese (229); p<0.0001.
Miller [65]	261 white (120 females), 188 African origin (99 females), 215 South Asian (99 females) individuals from the UK.	ICAM-1	No difference between whites and South Asians. Lower levels in people of African origin than white individuals. Values are means (95% CI) Whites: 274(263 to 286)ng/mL v African origin 189 (180 to 199)ng/mL v South Asians 268 (255 to 280) ng/mL; p<0.001.
Hwang [58]	272 patients with carotid artery atherosclerosis (CAA), and 316 control subjects from Atherosclerosis Risk In Communities (ARIC) study.	ICAM-1	White (n=243) v blacks (n=69) controls (244.2 (+/-70.8) ng/mL v 190.0 (+/-100.0) ng/mL p=0.0001: (+/-SD).
Miller [65]	261 white (120 females), 188 African origin (99 females), 215 South Asian (99 females) individuals from the UK.	VCAM-1	No difference between whites and South Asians. Lower levels in people of African origin than white individuals. Whites 432 (418 to 446)ng/mL v African origin 386 (372 to 401)ng/mL v South Asians 439 (424 to 455) ng/mL; p<0.001.
Hwang [58]	272 patients with carotid artery atherosclerosis (CAA), and 316 control subjects from Atherosclerosis Risk In Communities (ARIC) study.	VCAM-1	White (n=240) v blacks (n=72) controls (460.9 (+/-138.6)ng/mL v 415.1 (+/-153.1) ng/mL); p=0.002.
Makin [67]	234 patients (80% white, 7% Indo-Asian, 13% Afro-Caribbean) with confirmed peripheral artery disease.	P-Selectin	187 Whites 51(+/-18)ng/mL v 30 Afro-Caribbean 45(+/-15)ng/mL v 17 Indo Asian 46 (+/-18)ng/mL; p=0.176. Means +/- SD.
Miller [65]	261 white (120 females), 188 African origin (99 females), 215 South Asian (99 females) individuals from the UK.	P-Selectin	No difference between whites and South Asians. Lower levels in people of African origin than white individuals. Whites 72(69 to 75)ng/mL v African origin 57 (55 to 61)ng/mL v South Asians 72 (68 to 75)ng/mL; p<0.001.
Lutsey [66]	Cross-sectional study from the Multi-Ethnic Study of Atherosclerosis (MESA).	E-Selectin	Men (n=426): Whites (57.0 ng/mL); black (61.8 ng/mL); Hispanic (56.9 ng/mL); Chinese (50.8 ng/mL): p=0.2298. Women (n=570): Whites (45.8 ng/mL); black (55.3 ng/mL); Hispanic (59.1 ng/mL); Chinese (49.8 ng/mL): p<0.0001.
Miller [65]	261 white (120 females), 188 African origin (99 females), 215 South Asian (99 females) individuals from the UK.	E-Selectin	No ethnic differences in levels observed. Whites 45.4(43.9 to 47.8) ng/mL v African origin 46.4 (43.8 to 49.3) ng/mL v South Asians 46.5 (43.9 to 49.2)ng/mL; p=0.790.
Lawrence [68]	125 normoglycaemic control women (90 European, 19 South Asian and 16 Afro-Caribbean).	E-selectin	European: 57 (43–75) ng/ml; South Asian: 74 (58–97) ng/ml; Afro-Caribbean: 80 (67–97) ng/ml); ns.
Hwang [58]	272 patients with carotid artery atherosclerosis (CAA), and 316 control subjects from Atherosclerosis Risk In Communities (ARIC) study.	E-Selectin	White (n=241) v blacks (n=68) controls (32.8 (+/-15.2) ng/mL v 36.5 (+/-16.9) ng/mL); ns.

Adhesion molecules from the selectin family members are involved in the adhesion of leukocytes to the activated endothelium. They are also responsible for the observed cell 'rolling' whereas two different adhesion molecules intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are involved in the extravasation of leukocytes into the surrounding tissue. The expression of adhesion molecules can be induced by pro-inflammatory cytokines such as TNF-α and CRP. The latter is produced by the liver in response to IL-6 [55]. Oxidative processes may also be important in the initiation and development of atherosclerosis.

Soluble adhesion molecules (sCAMs), which lack cytoplasmic and membrane spanning domains, are present in the circulation [56]. Increased levels of soluble P-selectin (sP-selectin) and soluble E-selectin (sE-selectin) are found in ischemic heart disease [57-59]. Raised levels of soluble ICAM-1 (sICAM-1) are found in both CAD [58-60] and peripheral artery disease [61] and although soluble VCAM-1 (sVCAM-1) does not appear to be raised in CAD [58], the levels are raised in some forms of peripheral atherosclerosis [62] (see also Reviews [63-64]).

In our study in which we investigated possible ethnic differences in adhesion molecule levels between apparently healthy untreated individuals, we did not find any differences in the levels of circulating sICAM-1 or sVCAM-1 levels between South Asian and white individuals [65]. By contrast, we found that the levels of sICAM-1 and sVCAM-1 were lower in individuals of African origin compared to whites Fig. (**4**). These differences were maintained following the multiple adjustments shown in Fig. (**4**), as well as following adjustment for homocysteine and Social class, Waist-to Hip ratio instead of BMI, HDL instead of triglycerides and diastolic blood pressure instead of systolic blood pressure (see online supplement Miller [65]. Hwang *et al.* [58] have also demonstrated that levels of sICAM-1 and sVCAM-1 are lower in African Americans compared to white Americans despite the higher CHD rate of African Americans. In a recent study Lutsey *et al.* [66], confirmed that both male and female black African American individuals have significantly lower levels of sICAM-1 compared to whites and that this difference is maintained following adjustment for age, education, individuals income, study site, smoking, current alcohol. BMI, Leisure physical activity, sedentariness score, diabetes status, hypertension status, statin use, and current hormone replacement therapy use among women (Table **1**).

Unlike the results from the smaller study of Makin *et al.* [67], we demonstrated that the level of sP-selectin was significantly lower in individuals of African origin [65]. The level in West African individuals was also significantly lower than that in individuals of Caribbean origin Fig. (**4**) [65]. In

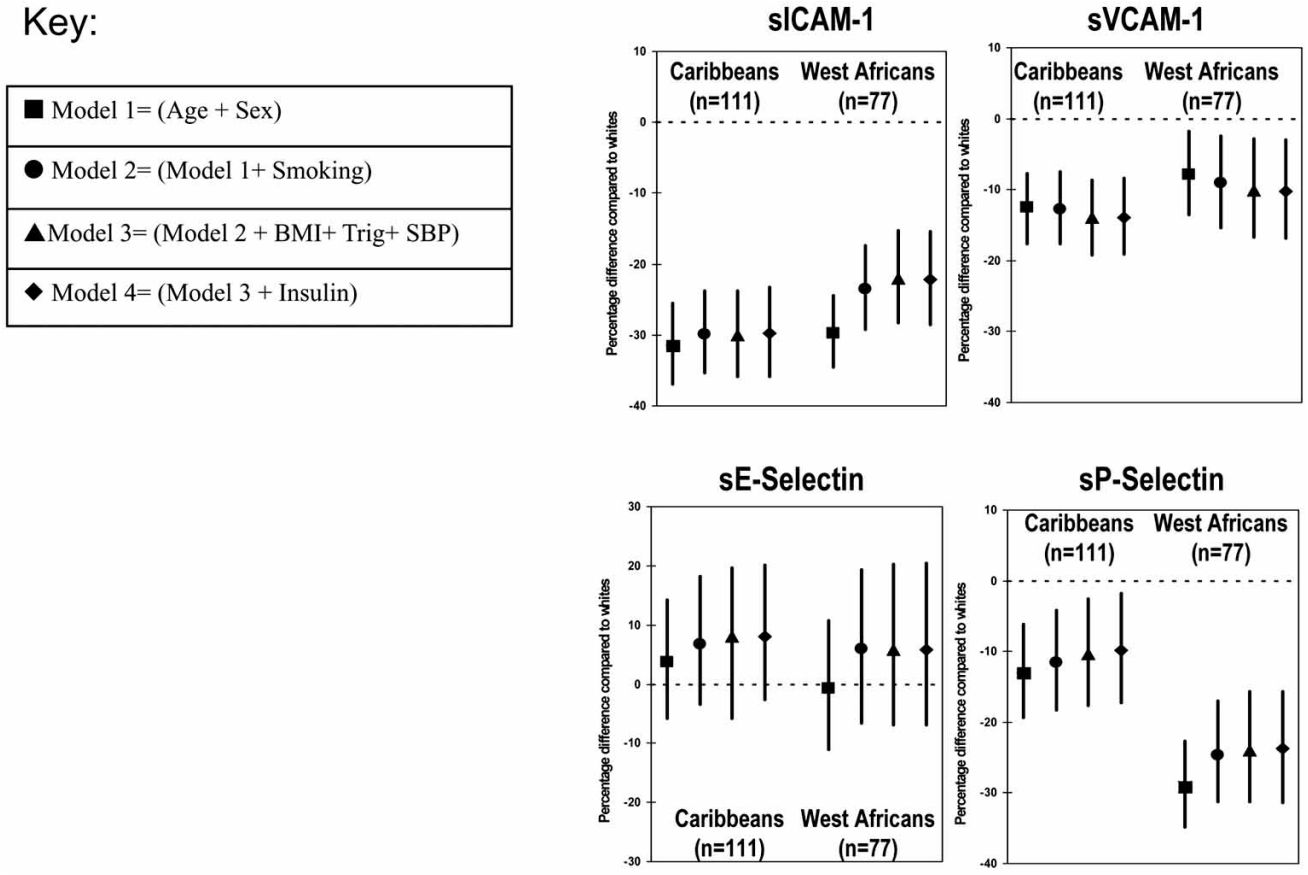

Fig. (4). Fig. (4). Multiple regression of adhesion molecules as dependent variables. Percentage difference in adhesion molecules in Caribbeans and West Africans compared to whites (Adapted from Miller *et al.* [65]).

agreement with Hwang *et al.* [58] and Lawrence *et al.* [68] we did not find any ethnic differences in sE-selectin levels [65]. Although, in a recent study Lutsey *et al.* [66] found that the level of sE-selectin was higher in black women compared to white women, this difference was abolished following the multiple adjustments previously described for in their study. Although Lawrence *et al.* found that the sE-selectin levels were lower in European women than South Asians of Africans the differences were not significant [68]. However, it may be of interest to note that in a cross-sectional survey of men and women from an Aboriginal community in Western Australia that the mean level of sE-selectin appeared to be very high (119ng/mL 111-128ng/mL) [69].

(i) Genetic Factors

The expression of inflammatory markers may be altered by polymorphisms in the regulatory regions of these genes and may have important effects on disease susceptibility, progression and prognosis.

Selectins are glycoproteins, which have both an amino terminal lectin-like domain and an epidermal growth factor like domain. The lectin-like domain plays an important role in mediating cell binding through interaction with cell surface carbohydrate ligands [70, 71]. A polymorphism at codon 128 in the epidermal growth factor-like domain of E-selectin, which results in an amino acid exchange from serine (S) to arginine (R) [72] has a frequency which varies with age. The 128Arg allele has been linked to the prevalence of atherosclerosis and increased restenosis following coronary angioplasty [72,73].

The frequency of this polymorphism is lower in people of African origin [74]. It is unclear, however, whether [74-76] the polymorphism is related to sE-selectin levels. This polymorphism is in the coding region of the gene and is therefore unlikely to affect gene expression but it may be linked to other E-selectin mutations. Wenzel *et al.* [73] found a correlation between the Ser128Arg polymorphism and the G98T mutation. Zheng *et al.* [77] noted that 16% of patients with premature CAD had both mutations compared with 4% of controls. It is likely that relatively healthy individuals would have a low frequency of the G98T mutation and hence, in these individuals, any association between these polymorphisms and plasma levels would be difficult to detect. Even if this polymorphism is not associated with circulating sE-selectin levels it may still be important as it has been shown to be associated with a decreased binding specificity, increased affinity for additional ligands [78] and with an extension in leukocytes recruitment [79]. These potentially deleterious effects may provide a mechanistic link between this polymorphism and inflammatory disease and it is of interest that the frequency of this polymorphism is reduced in individuals of African origin who have a lower incidence of CHD than whites or South Asians.

The P-selectin gene, which is highly polymorphic, is located on chromosome 1q21 to 1q24 [80]. The Thr715Pro (A/C) polymorphism is located in the consensus repeat (CR9) domain of exon 13, which is adjacent to the transmembrane domain [81,82]. It substitutes a polar amino acid for a non-polar one at position 715 [80]. A lower frequency of the Pro715 (C) allele has been found in patients with myocardial infarction (MI), suggesting that this polymorphism may be protective for MI [80]. The results from our study demonstrate that the levels of circulating sP-selectin vary according to genotype [83]. In whites, the C allele reduced sP-selectin levels in a dose-dependent way suggesting an additive model of expression. However, despite this association and the reduced frequency of the 'protective' C allele in South Asians, there was no difference in sP-selectin levels between whites and South Asians. More surprisingly, given that sP-selectin levels are significantly lower in individuals of African origin, we did not find the expected excess of the C allele in these individuals. However, these results are consistent with the ECTIM (Etude cas-temoin de l'infarctus myocarde) study, in which the Pro715 allele was more frequent in individuals with a higher risk of MI in Belfast than those at lower risk from France [80]. Although this polymorphism contributes to sP-selectin levels in whites and South Asians it is unlikely to be responsible for the observed ethnic differences in sP-selectin levels.

A large number of common polymorphisms have been identified in the ICAM-1 gene, however few studies have investigated their relationship either with soluble forms or with CAD and the number of individuals studied is often small (see Review Blankenberg *et al.* [63]). A single-base polymorphism at codon 241 in exon 4 of the ICAM-1 gene is associated with circulating ICAM-1 levels in the Stanillas cohort [84]. In that healthy population of both children and adults the R241 allele was significantly associated with lower sICAM-1 levels and explained 3.4% and 1.9% of the sICAM-1 variability in that population. Differences in frequency of this but not the E469K ICAM-1 polymorphism have been noted between Korean [85], Jordanian and Palestinian [86], and Italian individuals [87] with the highest frequency being found in European individuals.

VCAM-1 is not expressed in baseline conditions but it is rapidly induced by pro-atherosclerotic conditions. Likewise, it does not appear to be a risk factor in healthy individuals but emerges as a strong risk predictor in individuals with disease. Although, SNPs have been identified in the VCAM-1 gene [88] there is no data on their frequency in different populations or their association with circulating levels.

(ii) Other Factors that Could Affect Adhesion Molecule Levels

Factors that can determine the level of circulating adhesion molecule and cytokine levels need to be adjusted for confounding factors before examining ethnic differences in circulating levels. These factors include age, sex, smoking status, socio-economic status, blood pressure, insulin and serum lipids [57,58,65,89-90]. Indeed, many of these associated factors including serum lipids show ethnic variations and may provide a potential mechanism for the ethnic difference in CHD risk. HDL is low in individuals of African origin [10] and high-density lipoprotein (HDL)-cholesterol has been shown to inhibit the cytokine-induced expression of endothelial cell adhesion molecules [91]. It is negatively associated with adhesion molecule levels [65]. There are associations between serum triglycerides and soluble adhesion molecule levels, which may be adhesion-molecule-specific [57-59]. Ethnic differences in adhesion molecule levels are still maintained following adjustment for ethnic differences in serum lipid levels [65].

Other factors that may be important include the rate of cell-surface shedding or clearance of these molecules. Assay method, sample type (e.g. Serum vs. plasma), handling, storage-time and storage temperature also need to be considered when comparing different studies.

4) Interleukins (IL-1, IL-6, IL-10)

The term IL-1 is generally used to describe IL-1α and IL-1β, both of which exercise the same biological effects. IL-1 is considered to be a prototypical proinflammatory cytokine but its functions are not restricted solely to inflammation. It exerts its effects when it binds to specific cell receptors.

Plasma concentrations of IL-1β and its receptor (IL-1Ra) have been determined in black and white patients with inflammatory bowel diseases (IBD) and compared with control individuals [92]. Significantly increased levels of IL-1Ra in black South African patients compared with white South African

patients (P=0.0006) and black South African controls (P=0.0008) have been demonstrated. No difference in IL-1β levels was reported. This is consistent with the findings of Elkind *et al.* [93] who reported no difference in the unadjusted levels. Whereas, Albandar *et al.* [94] have demonstrated that black American individuals have significantly lower IL-1β levels than whites (24%); P=0.05 (Table **2**). However, it is of interest to note that the number of individuals in these studies was very small and that the level of IL-1β varied considerably between studies.

Interlukin-6 (IL-6) is produced apostrophe mainly by activated monocytes and smooth muscle cells. It's action causes the de novo hepatic synthesis of acute phase reactants such as CRP. IL-6 may play a role in CHD development through a variety of mechanisms [95]. IL-6 increases the release of adhesion molecules from the endothelium, it increases the release of fibrinogen by the liver, it increases basal glucose uptake and affects insulin sensitivity. It also affects platelet aggregation. IL-6, along with TNF-α and CRP, has been associated with the metabolic syndrome. Increased circulating concentrations of IL-6 have been demonstrated in patients with unstable, but not stable, angina [96]. Results from the Rural Health Study have shown that total CVD mortality over a 5-year follow-up period is predicted by high IL-6 levels. Furthermore, the association is independent of prevalent vascular disease, smoking and traditional risk factors and it is additive too, but stronger, than CRP [97].

Possible ethnic variation in IL-6 levels has not been widely investigated. Elkind *et al.* [93] and Hong *et al.* [98] failed to demonstrate any difference in basal circulating IL-6 levels in American black and white individuals. Whereas Kalra [99] found that UK Afro-Caribbean individuals has slightly higher levels than whites (p=0.04). In the latter study there was no significant difference between the demographic and most of the metabolic characteristics between the two groups. Fasting insulin levels however were significantly lower in the Caucasian individuals (p=0.03) [99]. A lack of power may explain the reason for this discrepancy. The number of individuals in the first two studies was approximately half that in the latter and the difference observed was small. Alternatively, it may reflect differences in the UK and American African population environments. Furthermore, in some studies it is unclear whether any ethnic differences in metabolic variables were present between the individuals of different ethnic origin [93,98]. In a separate study, Petersen *et al.* [100] examined non-smoking individuals who had similar daily activity levels and similar dietary composition. They found that the levels in Asian-Indians were significantly higher than in whites (p<0.001) Table (**3**). Although these individuals were also well matched for BMI the fasting glucose and insulin concentrations were significantly increased in the Asian Indians compared to the whites [100].

Little is known about the role of anti-inflammatory factors in atherogenesis. Anti-inflammatory cytokines such as IL-10 may play an important role in the modulation of the inflammatory response [101]. IL-10 is a prototypical pleiotrophic anti-inflammatory cytokine produced by Th-2 sub-type of T-cells, B-cells monocytes and macrophages [102] and exhibits a broad array of immune functions. Animal studies have demonstrated that increased IL-10 production is associated with a significant decrease in endothelial NF-κB activation and an increase in endothelial expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule–1 (ICAM-1). IL-10 also reduces the production of matrix metalloproteinases by monocytes and therefore may be important in atheromatous plaque stabilization. Increased IL-10 serum levels are associated with improved systemic endothelial vasoreactivity in patients with elevated CRP serum levels, demonstrating that the balance between pro- and anti-inflammatory mediators is a major determinant of endothelial function in patients with CAD [103].

There is no direct evidence to suggest that there are ethnic differences in circulating IL-10 levels. However, one study has suggested that there may be ethnic differences in levels in response to a stimulus of Interferon (IFN), which is the primary treatment for hepatitis C virus (HCV). The long-term success rate is low particularly for African Americans relative to whites. Kimball *et al.* [47] compared the production of cytokines from stimulated peripheral blood in African Americans and white individuals. They found ethnic differences in the production of some but not all cytokines. Healthy African Americans produced less IL-10 (P = 0.05) than healthy white individuals but, by contrast, IFN-gamma and TGF-β levels were equivalent. They concluded that ethnicity may contribute to variable immune responses and therapeutic outcome. They suggested that the cytokine profile among African Americans indicates a more robust immune response, which may complicate therapy with IFN. However, basal levels of these cytokines in the

Table 2. Ethnic Differences in Inflammatory Markers

Study (Author and Ref)	Subjects	Molecule (assay details)	Key Outcomes
Mwantembe [92]	Black controls n= 7; White controls n=10.	IL-1 Ra	Whites: 486.1 +/-341pg/mL v blacks: 764.7+/-545pg/mL.
Elkind [93]	Whites n= 48; blacks n=47.	IL-1β	Whites: 0.23 +/-0.43pg/mL v blacks: 0.35 +/- 0.59pg/mL; ns.
Albandar [94]	Total n=124: 24 white; 17 Hispanic; 83 black.	IL-1β	White 28.4pg/mL (SE=5.09); Hispanic 34.7pg/mL (SE=6.05), black 21.7pg/mL (SE=2.74). Blacks had significantly lower IL-1beta concentration than Hipanics (55%) and whites (24%); p=0.05.
Mwantembe [92]	Black controls n= 10; White controls n=10.	IL-β	Whites: 1.99 +/-1.88pg/mL v blacks 2.69+/-2.58pg/mL; ns.
Petersen [100]	22 Asian Indian and 107 Whites.	IL-6	Whtes: 0.78 (0.67 to 0.91)pg/mL v Asian-Indian: 1.60 (1.16 to 2.21)pg/mL; p<0.001.
Kalra [99]	78 Afro-Caribbeans and 82 matched Whitess with no vascular disease or medication.	IL-6.	Whites: 1.5pg/.L v Afro-Caribbean 2.3pg/mL; p=0.04.
Hong [98]	Total group n= 70: 20 white men, 16 black men, 20 white women, 14 black women.	IL-6	The average level of IL-6 was 1.36 (+/- 0.80)pg/mL. No differences with gender or ethnicity.
Elkind [93]	Whites n= 48; blacks n=47.	IL-6	Whites 1.15 +/-1.08pg/mL v blacks 1.36 +/- 1.51pg/mL; ns.

different ethnic groups were not determined and it is clear that 'basal' levels of immune parameters may differ between different ethnic groups and the appropriate evaluation of reference levels is required.

Factors Responsible for Ethnic Differences in Interleukin Levels

(i) Genetic Factors

Mwantembe *et al.* [92] investigated the allelic frequencies of TaqI, PstI, and variable number of tandem repeat (VNTR) polymorphisms of the IL-1β, IL-1 receptor (IL-1Re), and IL-1 receptor antagonist (IL-1Ra). They demonstrated that the IL-1Re PstI(-) allele was significantly more frequent in black South African patients compared with white patients. The frequency of the IL-1Ra 240-bp allele was lower in black South African compared with white South African controls and that the 410-bp allele was more frequent in black compared with white controls. It is possible that these genetic polymorphisms may in part be responsible for the difference in the level of IL-1Ra in black patients compared with white patients and black controls.

Studies have shown that polymorphic variations in the IL-6 gene influence circulating levels and that there are large ethnic variations in allele frequencies, which could therefore lead to ethnic differences in gene expression and circulating levels.

A G/C promoter region polymorphism has been identified in the 5' flanking region of the IL-6 gene at position -174. In healthy UK men and women the frequency of the C allele was 40.3% and was found to be associated with significantly lower levels of plasma IL-6 [104]. The frequency of this polymorphism is much lower in a Korean population [105, 106] and there is heterogeneity in the frequencies of the cytokine polymorphisms even amongst different white populations such as Italian, German and UK populations [107]. A low frequency of this polymorphism has also been reported in black and Asian individuals [108]. A recent study has demonstrated that this mutation is functional, in that, individuals with the G genotype have a significantly higher IL-6 response to vaccination with *Salmonella typhii* [109]. The observed ethnic differences in allele frequencies underline the importance of a 'local' reference population when evaluating the clinical relevance of cytokine gene polymorphisms. Whether the observed ethnic differences in allele frequency are associated with ethnic differences in circulating IL-6 levels or have an effect on disease incidence and progression in different population's remains to be elucidated.

The production of IL-10 is dependent upon many factors including an individual's genotype [110-112]. Different gene variants (single-nucleotide polymorphisms (SNPs) have been shown to be associated with different IL-10 expression. The promoter region of the gene contains three distinct SNPs at the nucleotide positions -1082 (G to A), -819 (C to T) and -592 (C to A). Furthermore, the presence of three major haplotypes in most populations has been identified (GCC, ACC, ATA) [110,112-120]. In the majority of studies the GG genotype of the -1082 SNP is linked with high genotype expression. Likewise for the haplotypes the GCC seems to be associated with high production, the ACC with intermediate levels and the ATA with low [118, 119]. In a recent study Rady *et al.* [120] have recently demonstrated that within the IL10 promotor SNPs there are significant differences in allelic frequencies and haplotype rates according to ethnicity. In particular, African Americans and Hispanics have a lower rate of high-producer and higher rate of low-producer IL-10 producer SNPs when compared with whites or Ashkenazi Jews. An extensive listing of different populations with their allele and haplotypes frequencies has already been produced by Rady *et al.* [120] and can be observed in the study by Hoffman *et al.* [108]. It is however, clear from these studies that whilst the frequency of the -1082 allele tends to be low in white populations it is still variable [107, 115, 120] and it is higher in Asian, African, Mexican and Arabian populations. The exact significance of differences in genotype frequency on circulating levels of the gene product and the relationship to the prevalence and progression of many diseases remains to be determined.

(ii) Other Factors that Could Explain the Observed Ethnic Difference in Interleukin Levels

Adjustments for age, sex and smoking need to be performed before ethnic differences in cytokine levels can be examined. In addition, it has been shown in rats that IL-1 levels are associated with feeding status [121] and body-mass index, blood pressure, serum lipids and insulin sensitivity [122] may also be important. Whilst in man, pre-exercise carbohydrate status affects IL-1Ra levels [123] and exercise training in CAD patients lowers IL-1 and IL-6 levels [124]. A further new emerging field suggests that sleep may affect inflammatory processes [125] and as such may have an effect on circulating levels of inflammatory cytokines [98].

5) TNF-α

TNF-α is a pluripotent cytokine that seems to play a key pro-inflammatory role in the process of atherosclerosis and CVD. It is produced by macrophages associated with atherosclerotic plaques [126] and it appears to be important in determining plaque stability and rupture [126]. Moreover, it may play an important role in the pathophysiology underlying CVD by its action on the modulation of lipid metabolism [127,128], obesity susceptibility, insulin resistance [129] and production of other inflammatory cytokines (e.g. IL-6) as well as its effect on myocardial contractility [130]. However, it is unclear whether this inflammatory cytokine is a prognostic indicator of CHD and CVD.

Elkind *et al.* [93] compared levels in American black and whites individuals but did not find any difference whereas Kalra *et al.* found that the level of TNF-α was significantly higher in individuals of UK African origin compared to whites [99]. These individuals also had higher fasting insulin levels compared to whites (p=0.03). Petersen *et al.* [100] failed to find any difference in levels between Asian Indian individuals and whites (P=0.32) even after adjustment for Insulin-Sensitivity (p=0.35); (Table **3**).

Factors That May Lead to Ethnic Differences in TNF-α Levels

(i) Genetic Factors

In Italian individuals, the frequency of allele TNFA*1 at position -380 was 87.7% and that of TNFA*2 was 12.4% was

Table 3. Ethnic Differences in Inflammatory Markers

Study (Author and Ref)	Subjects	Molecule (assay details)	Key Outcomes
Petersen [100]	15 Asian Indian and 82 Whites.	TNF-α	Whites: 1.13 (1.02 to1.25) pg/mL v Asian-Indian: 1.29 (1.02 to 1.62) pg/mL; p=0.32.
Kalra [99]	78 Afro-Caribbeans and 82 matched Whitess with no vascular disease or medication.	TNF-α	Whites 4.3+/-3.6mg/m/L v Afro-Caribbean 6.7 +/-6.1pg/mL; p=0.001.
Elkind [93]	Whites n= 48; blacks n=47.	TNF-α	Whites 2.71 +/-4.25pg/mLv blacks 1.04 +/- 1.63pg/mL; ns.

significantly different to that in UK and Japanese populations but not significantly different to that of a population in Gambia [107]. In healthy volunteers, a relationship between the TNF-d3 polymorphism and the *in vitro* production of TNF-α has been observed [111]. Likewise, Abdallah *et al.* [131] and Pociot *et al.* [132] have demonstrated that genetic variation in the TNF-α gene plays a role in regulating TNF-α production and circulating TNF-α levels. The role of these polymorphisms in determining any ethnic difference in TNF- α levels remains to be determined.

(ii) Other Factors that Could Affect TNF-α Levels

TNF-α levels do not appear, at least in women, to be associated with many anthropometric variables [122] although the levels are affected by food intake both in animal studies [121] and in man [133].

6) CRP

C- reactive protein (CRP), which is an acute phase protein, belongs to an ancient family of proteins called the pentraxins. It is calcium-dependent and can bind a number of ligands. It was thought to be produced by the liver although a recent study suggests that it may be produced by vascular smooth muscle cells and macrophages too [134]. CRP levels increase dramatically in a wide range of infections and immune related disorders and has been shown to be associated with long-term CVD risk [135]. However, it is the raised levels of CRP present in non-symptomatic individuals which are particularly relevant to CHD. These levels can be determined by the high sensitivity methods (hs-CRP) [136]. CRP is associated with atherosclerotic plaques, the elevation in CRP levels precedes clinically symptomatic atherosclerosis [137] and increased levels increase the vulnerability of a plaque to rupture.

A dramatic increase in CRP gene transcription and subsequent protein production requires the presence of IL-6 and interleukin-1-β (IL-1β) [138]. Observational studies have shown that elevated CRP is associated with an increased risk of developing future cardiovascular events [17, 28, 29]. High-sensitivity CRP (hs-CRP) may represent one of the strongest independent predictors of vascular death [27,29, 55,139-142].

It is known that several pro-atherogenic factors identified in childhood 'track' into adulthood causing disease. Indeed childhood obesity is associated with high levels of CRP. A recent review has examined CRP and it associations in children, adolescents and young adults of different ethnicities [143]. It was concluded that further prospective studies are required to investigate the precise significance of high CRP levels in young individuals but that in the meantime attempts to reduce CRP levels in children should be addressed including those aimed at reducing adiposity.

In addition to being a biomarker CRP may also have direct effects, including down regulation of NO synthase, stimulation of ET-1 and IL-6 release, up-regulation of adhesion molecules and stimulation of MCP-1 [55]. CRP also facilitates the uptake of LDL by macrophages and may also increase NF-κB and by doing so facilitate the transcription of numerous pro-atherosclerotic genes [55]. Furthermore, CRP is synthesized within atherosclerotic lesions by vascular smooth muscle cells and macrophages.

Numerous studies have now shown a link between CRP and CVD [144] and evidence now suggests that CRP surpasses all other biomarkers including LDL-cholesterol in predicting cardiovascular events [15,27]. This may in part be due to the fact that CRP is very stable on storage, it has a long half-life and it does not show diurnal variation. Furthermore, the levels can be determined in a reliable and non-expensive way and similar results can be obtained from fresh, stored or frozen plasma. Calls have been made to include a CRP –modified coronary risk score for global risk prediction in both men and women [16]. However, one recent study has suggested that it may have a lower predictive value than classical risk factors such as cholesterol and smoking [142] and another has indicated that whilst hs-CRP is a significant predictor of cardiovascular events in subjects with a moderate risk as determined by Framingham Risk Scores (FRS) this is not the case for those individuals with low or high risk scores [145]. Furthermore, it is not possible to apply Framingham risk scores indiscriminately to different ethnic groups [24]. There are often marked differences in the populations studied and in their associated risk factors. Additional studies, and in particular prospective studies, need to be carried out in various age, sex and ethnic groups to be able to properly evaluate the value of CRP as a risk factor for CVD and to ensure that proposed new guidelines can be consistently applied.

With regards to ethnic differences in circulating CRP levels, although the number of studies reporting CRP levels has increased dramatically the number of studies specifically addressing ethnic differences is still few. Let us first consider the differences between white and South Asian individuals: Forourhi *et al.* [146], demonstrated that South Asian women living in London had nearly double the level of CRP as compared to European women. Furthermore, they demonstrated that the level of CRP was correlated with visceral adiposity and insulin resistance. Likewise, Chambers *et al.* [147], in a much larger study, demonstrated that CRP concentrations were 17% higher in Indian Asians compared with European whites. However, they found that this difference was mainly accounted for by the difference in central obesity and insulin resistance between the two groups. Chatha *et al.* [148] however, were unable to demonstrate any differences in serum CRP concentrations between Indo-Asians and whites living in the UK.

In contrast, to the previous study in UK Asians [147], Chandalia *et al.* [149] also found that CRP levels were associated with measures of central obesity however; the Asian Indians living in the United States still had higher levels of CRP than whites even after adjustment for total fat or waist circumference. Furthermore, Albert *et al.* [150] found that Asian women living in the United States had significantly lower CRP levels than their white counterparts. The reason for these discrepancies is unclear but may reflect the number and different selection of the individuals in the studies and the level of adjustment for confounding factors. It is of interest to note that whilst significantly different levels between Pakistani European and African Caribbean individuals were also demonstrated by Heald *et al.* [151], in that study multiple linear regression indicated that ethnicity was not independently associated with CRP (see Table **4**).

Considering studies which have examined differences in CRP between black and white individuals is apparent that the majority of studies have looked at differences in African American and white individuals. Two studies have reported levels in the UK. The first indicated that the level of CRP was significantly lower in African-Caribbean individuals compared with whites [151]. In multiple regression analysis however, ethnicity was not independently associated with CRP. Moreover, a subsequent smaller study reported no difference, despite an increase in insulin levels in the individuals of African and Caribbean origin [99].

African Americans have a higher CHD risk than their UK counterparts and the majority of studies of African American individuals have reported higher CRP values than for the white population [150,152-156]. This is also true for the comparison between African and white women from South Africa [153]. These studies are in contrast to the data from the National

Table 4. Ethnic Differences in CRP Levels

Study (Author and Ref)	Subjects	Molecule (assay details)	Key Outcomes
Studies containing individuals of Asian origin.			
Albert [150]	24,455 white, 475 black, 357 Asian, and 254 Hispanic women, all of whom are participants in the Women's Health Study in the United States.	CRP	Median CRP levels were significantly higher among black women (2.96 mg/L, interquartile range [IQR] 1.19 to 5.86) than among their white (2.02 mg/L, IQR 0.81 to 4.37), Hispanic (2.06 mg/L, IQR 0.88 to 4.88), and Asian (1.12 mg/L, IQR 0.48 to 2.25) counterparts.
Chandalia [149]	82 Asian Indian men and 55 Whites men of similar age living in the United States.	CRP (high-sensitivity)	Asian Indians also manifested a significant elevation of plasma hs-CRP (Asian Indians 0.99 mg/dL v Caucasians 0.58mg/dL; p=0.002 (adjusted for total fat).
Chatha [148]	102 men (63 Whites and 39 Indo-Asians) and 89 women (58 Whites and 31 Indo-Asians). UK resident Indo-Asians compared with Whites.	CRP	Serum CRP concentrations were similar in Indo-Asians (women 2.29 (1.52) mg/l [mean (SD)]; men 1.77 (1.46) mg/l) and Whites (women 2.23 (1.54) mg/l; men 1.94 (1.45) mg/l).
Chambers [147]	1025 healthy male subjects (518 Indian Asians and 507 European whites) aged 35 to 60 years. UK Indian Asian and European white men.	CRP	The geometric mean CRP concentration was 17% higher (95% confidence interval, 3% to 33%) in Indian Asians compared with European whites and are accounted for by greater central obesity and insulin resistance in Indian Asians.
Forouhi [146]	Cross-sectional study: Total of 113 healthy South Asian and European men and women in West London (age 40-55 y, body mass index (BMI) 17-34 kg/m).	CRP	Median CRP level in South Asian women was nearly double that in European women (1.35 vs 0.70 mg/L; P=0.05).
Studies containing individuals of African origin. a) In the UK			
Kalra [99]	78 Afro-Caribbeans and 82 matched Whites with no vascular disease or medication. Subjects were recruited from general practices in South London.	CRP (high sensitivity turbidi-metric assay).	Afro-Caribbean 2.5mg/L v Whites 2.1mg/L; p=0.82.
Heald [151]	European (n=155), Pakistani (n=108) and African-Caribbean (African Caribbean) (n=177). Recruited from a population-based community survey in Manchester UK.	CRP (high sensitivity ELISA)	CRP was significantly lower in African Caribbean men and women than in other ethnic groups. Men: African-Caribbean (82) 1.0 (0.3-1.3) v European (72) 2.2(1.9-2.9) v Pakistani (68)1.7(1.4-2.2) mg/L; p<0.05. Women: African-Caribbean (111) 1.3 (1.0-1.6) v European (70) 2.1(1.7-2.7) v Pakistani (62) 2.8(2.1-3.6) mg/L; p=0.05.
Studies containing individuals of African origin. b) In the the US			
McDade [152]	Representative sample of 188 52- to 70-year-olds from a larger population abased sampleof Cook County residents in America.	CRP (high sensitivity)	Log-transformed CRP concentrations were examined in a series of nested multivariate regression models. African American and female participants were found to have higher CRP concentrations, as did individuals with lower levels of education. However, ethnic differences disappeared after the addition of behavioral and psychosocial variables.
Schutte [153]	102 apparently healthy African women and 115 Whites women matched for age and body mass index, from South Africa: the POWIRS study.	CRP (high sensitivity kit)	The level of hsCRP was significantly higher (p<0.05) in the African women.
Patel [154]	1083 black and white Americans (mean age 36.1 years) from the Bogalusa Heart Study.	CRP	The Level of CRP was greater in black compared to white individuals; p<0.01. Male: White (n=358)1.8+/-1.9mg/L v black (n=129)2.3+/-2.3mg/L). Female:White (n=412)2.5/-2.3mg/L v black (n=184)2.7+/-2.4mg/L.
Khera [155]	CRP measured in 2,749 white and black subjects (ages 30 to 65) participating in the Dallas Heart Study, a multiethnic, population-based, probability sample.	CRP	Black subjects had higher CRP levels than white subjects (median, 3.0 vs. 2.3 mg/L; p<0.001) and women had higher CRP levels than men (median, 3.3 vs. 1.8 mg/L; p<0.001).
Ford [157]	2205 women >or=20 years of age from the National Health and Nutrition Examination Survey 1999-2000 in America.	CRP was measured with a high-sensitivity turbidi-metric assay	CRP concentration ranged from 0.1 to 296.0 mg/L (median, 2.7 mg/L). After exclusion of women with a CRP concentration >10 mg/L, the median was 2.2 mg/L. CRP concentration varied by race or ethnicity (Mexican American > white).
Ford [158]	3348 US children and young adults 3-19 years of age who participated in the National Health and Nutrition Examination Survey, 1999-2000. Individuals were of white, African American and Mexican-American origin.	CRP was measured with a high-sensitivity turbidi-metric assay	The range of CRP concentrations was 0.1-90.8 mg/L (mean, 1.6 mg/L; geometric mean, 0.5 mg/L; median, 0.4 mg/L). CRP concentrations increased with age. Females 16-19 years of age had higher concentrations than males in this age range (P = 0.003). White and African American US children and young adults had similar values but the levels in Mexican Americans tended to be higher (p <0.001).

(Table 4). contd.....

Study (Author and Ref)	Subjects	Molecule (assay details)	Key Outcomes
Ford [159]	This analysis used data from NHANES obtained during 1999–2000. A representative sample of the noninstitutionalized civilian US population was selected by use of a stratified multistage sampling design.	CRP (high sensitivity, nephelo-metric assay)	The medianC-reactive protein concentrations were 1.6 mg/L for all men, 1.6 mg/L for white men, 1.7 mg/L for African-American men, 1.5 mg/L for Mexican-American men, and 1.8 mg/L for other men. The authors conclude that there did not appear to be any effect of ethnicity.
LaMonte [156]	Tri-ethnic group of women (Native American, Whites and African American) from the American Cross-Cultural Activity Participation Study (CAPS).	CRP	Serum CRP levels were lower in Native American (0.25+/-0.03 mg/dL (n=45) and Whites women (0.23+/-0.13 mg/dL (n=46) compared with African American women 0.43+/-0.03 mg/dL (n=44): p=0.002.
Elkind [93]	279 subjects was (49% were men; 63% were Hispanic, 17% black, and 17% white). Recruited from the Northern Manhattern Stroke Study.	CRP	Whites (n=48) 1.88+/-2.75 v blacks (n=47) 2.64+/-4.62 v Hispanics (n=175) 2.11 +/- 3.50 mg/dL ns.
Wener [160]	Blood taken on > 22,000 individuals age > or = 4 yrs representative of the noninstitutionalized population of the United States, as part of the Third National Health and Nutrition Evaluation Survey (NHANES III).	CRP (Nephelo-metric immuno-assay)	The 95th percentile value of CRP on the overall population was 0.95mg/dL for males and 1.39mg/dL for females. Values varied with age and race. For ages 25-70 yrs, the age adjusted approximate upper reference limit (mg/dl) was CRP = age/50 for males, and CRP = age/50 + 0.6 for females. The upper limits for Mexican-Americans and non-Hispanic whites were similar, whereas for non-Hispanic black adults the approximate upper limit was CRP = age/30 for males and CRP = age/50 + 1.0 for females.

Health and Nutritional Examination Survey (1999-2000) in which no difference in CRP between African American (adults and children) and whites was observed [157-159] although they did report that the upper boundary of the 4th quintile was higher amongst African American men [159]). Although Elkind *et al.* [93] reported that the unadjusted level of CRP was higher in blacks than in whites (2.64+/-4.62 v 1.88 +/-2.75ng/mL, this was not significant.

It is important to note that whilst McDade *et al.* [152] reported that African American females have higher CRP levels than white females, these differences disappeared after the adjustment of behavioural and psychosocial variables. Furthermore, in a multivariate model Patel *et al.* [154] observed that sex but not ethnicity was retained as an independent correlate of CRP. However, Albert *et al.* [150] demonstrated that even though multiple adjustments attenuated the difference between blacks and whites, it was still significant (p=0.01; Following adjustment for; age, BMI, history of hypertension, smoking status, alcohol use, exercise, history of myocardial infarction, estrogen use, education & LDL). Likewise, Khera *et al.* [155] in a multiple analyses adjusting for traditional risk factors, BMI, oestrogen and statin use found that both gender and ethnicity were independently associated with CRP.

From many of the studies it has become apparent that gender is an important determinant of CRP levels, in that the level in women is higher than in men [154,155,160]. Results from our own study of UK black, South Asian and white individuals suggest that the basal circulating levels of CRP vary with gender and that they have a different distribution in these different populations but analysis using fully adjusted models is yet to be completed (manuscript in preparation). In many of the reported studies to date the number of individuals is small and thus the normal levels of CRP in different ethnic groups have yet to be established [144]. Furthermore, it remains to be seen whether these differences in circulating levels are associated to differences in CVD outcomes.

Factors Responsible for Ethnic Differences in CRP Levels

(i) Genetic Factors

Russell *et al.* [161] showed that basal levels of CRP are influenced independently by two polymorphisms at the CRP locus, CRP 2 and CRP 4. In a separate study [162] a polymorphic GT-repeat in the intron of the CRP gene contributed to variation in baseline CRP in both normal individuals and in patients with the inflammatory disease systemic lupus erythematosus. Furthermore, there was a difference in the frequency of this polymorphism in whites and African-American individuals. However, it is not yet known how this genetic polymorphism mediates its effects on CRP expression. The +1444C>T promoter polymorphism is associated with CRP levels in male army recruits before and after exercise and peak CRP levels are higher in 1444TT homozygotes compared with +1444C-allele carriers following surgery in coronary artery bypass graft patients [163]. These findings clearly demonstrate that the CRP gene +1444C>T variant influences basal and stimulated CRP levels and has implications both for the prediction and pathogenesis of CHD.

Zee *et al.* [164] examined CRP levels and the 1059G/C polymorphism of the CRP gene in a large prospective cohort of apparently healthy men. They found that plasma CRP concentrations were significantly reduced among carriers of the C allele (G/C and CC) as compared with non-carriers (GG). However, this polymorphism was not significantly associated with the risk of arterial thrombosis. In other studies, Ferrari *et al.* [165] have demonstrated an association between IL-6 -572 and -174 genotypes and serum C-reactive protein (CRP) levels. There was a significant increase in the level of CRP (up to +79%; P = 0.007) with a decreasing number (from four to one) of IL-6 protective alleles -572G and -174C [155]. Likewise Berger *et al.* [166] in patients undergoing coronary angiography have demonstrated that CRP levels are influenced by common variants in the IL-1 gene.

(ii) Other Factors that May be Responsible for Ethnic Differences in CRP Levels

CRP levels are related to BMI, waist circumference, blood pressure, serum lipids levels, plasma glucose and insulin sensitivity [122]. HRT increases CRP levels [61,150] and La Monte *et al.* [156] have demonstrated that CRP levels are related to estrogens but, that only in whites and not Native Americans or African Americans. Likewise Ridker *et al.* [167] demonstrated that both oral contraceptives and hormone replacement therapy influence CRP levels. La Monte *et al.* [156] also found that CRP levels decreased with increasing fitness levels in Native American and white women but not in African American women and analysis of the NHANES (1999-2000) data indicated that educational status may be important [152,157] confirmed that

not only was CRP independently associated with waist circumference and smoking but also to latency of sleep and perceived stress.

It is possible that ethnic differences in CRP may be related to differences in adiposity but that gender differences are related to estrogen levels. It is therefore important that the levels in both pre and post menopausal women are established. Furthermore, these levels need to be examined in each ethnic group separately.

7) Fibrinogen

Several cross-sectional angiographic studies have shown correlations between the fibrinogen level and the extent of CAD [168]. It has been suggested that this relationship is mainly due to luminal occlusion. Moreover, there is evidence to suggest that there is a significant relationship between fibrinogen levels and subsequent IHD. The fibrinogen level is also associated with the recurrence of IHD in those who have survived a myocardial infarction and with the onset and recurrence or progression of cerebrovascular disease and lower extremity arterial disease.

Differences in fibrinogen levels have been demonstrated between African (n=479), South Asian Indians (n=459) and white individuals (n=453) from the Wandsworth Heart and Stroke Study (WHSS) [169]. The fibrinogen levels of South Asians were not consistently different from those of whites. However, plasma fibrinogen levels were lower in blacks than in whites by 0.22 g/liter (95% confidence interval (CI): 0.08, 0.36) in men and 0.11 g/liter (95% CI: -0.01, 0.23) in women. These differences were not explained by measured environmental variables, including smoking, or by genotypes [169]. This study is in contrast to an earlier study by Meade *et al.* [168], which did not find any difference between UK black and white individuals. A number of studies have reported that fibrinogen levels are higher among African Americans than among white Americans. A review of such studies has been recently included in the study by Lutsey *et al.* [66] and is therefore not duplicated here. A recent study has also demonstrated that African women from South Africa have higher fibrinogen than whites women 3.89(3.67 to 4.10) g/L v 3.05(2.95 to 3.15) $p \leq 0.001$ and that this difference was maintained following adjustment for waist circumference [153].

Duncan *et al.* [170] have found that whereas in white individuals inflammatory markers, including white cell count and fibrinogen levels, are associated with the development of diabetes in whites, this is not the case for African Americans. Moreover, evidence from several trials has suggested that whilst African Americans may have higher fibrinogen levels they also have enhanced fibrinolytic characteristics and better response to fibrinolytic therapy compared to whites [171]. It would appear therefore that both levels and function of such inflammatory mediators may vary with ethnicity.

Factors Responsible for Ethnic Differences in Fibrinogen Levels

(i) Genetic Factors

The fibrinogen genotype has been determined at two sites in the promoter of the beta-fibrinogen gene (G-455-->A and C-148-->T) in individuals from the WHSS [169]. The A-455 and T-148 alleles were less common in blacks than whites or South Asians: In whites and South Asians, but not in blacks, there was complete allelic association between the two variants. The T allele was associated with higher fibrinogen levels with the average fibrinogen-raising effect of the T-148 allele across all ethnic groups being 0.14 g/liter in women and 0.15 g/liter in men.

(ii) Other Factors that Could be Responsible for Ethnic Differences in Fibrinogen Levels

In women, fibrinogen levels are associated with BMI, waist circumference, diastolic blood pressure and insulin sensitivity [122], all of which vary by ethnic group.

8) Matrix Metalloproteinases (MMPs)

More than 16 MMPs have been described to date. This family of enzymes plays a role both in normal as well as in pathological tissue remodeling. MMPs also have a regulatory function through their action in enzyme cascades and by the processing of other molecules such as matrix proteins, cytokines, growth factors and adhesion molecules which results in molecules with either enhanced or reduced biological effects. It is known that endothelial dysfunction and inflammatory responses stimulate the production of matrix metalloproteins which in turn may lead to increased plaque instability. Moreover, many membrane-bound cytokines adhesion molecules and receptors can be removed from the surface of cells by the action of MMPs. This may in turn lead to down regulation of cell-surface signalling. Alternatively, it may extend the range of influence of a given molecule by releasing a soluble form into the circulation. Oxidized LDL, *via* LOX-1 activation, modulates the expression and activity of MMPs in human coronary artery endothelial cells [172] and hence ethnic differences in oxidized LDL could affect MMP activity. Little research has been carried out on ethnic differences in MMP levels. Tayebjee [173] failed to find any ethnic difference in MMP-2 levels between whites, Afro-Caribbean, Asian and Far Eastern individuals from the UK but they did find that the levels of MMP-9 were significantly lower in the Far Eastern individuals compared with the other three groups (Table **5**). Further research in this area is needed but it may be of interest to note that we have found that there are ethnic differences in the levels of circulating antibodies to oxLDL (Miller unpublished observation). Furthermore, Mason *et al.* [174] performed an *in vitro* comparison of MMP expression in breast cell lines and found that of the 26 MMPs examined the expression of 12 (3,7,8,9,11-15,23B,26 and 28) were elevated in breast cancer cell lines from African American women compared

Table 5. Ethnic Differences in Inflammatory Markers

Study (Author and Ref)	Subjects	Molecule (assay details)	Key Outcomes
Tayebjee [173]	93 healthly volunteers from 4 ethnic groups recruited in the UK. Afro-Caribbean (n=21); Asian (n=26); Whites (n=21) and Far Eastern (n=16).	MMP-2	No ethnic differences
Tayebjee [173]	93 healthly volunteers from 4 ethnic groups recruited in the UK. Afro-Caribbean (n=21); Asian (n=26); Whites (n=21) and Far Eastern (n=16).	MMP-9	Levels in the Far Eastern group were significantly lower than the other three groups: P=0.012. Afro-Caribbean 376 (292-560) ng/mL; Asian 384(288-504) ng/mL; Whites 400(328-560)ng/mL; 323 (194-427)ng/mL.

to whites. It remains to be seen if any ethnic differences in circulating levels may be found and whether these have any implication for CVD risk.

Possible Factors that Could Contribute to Ethnic Variation

(i) Genetic Factors

In a recent study the frequency of a MMP-3 polymorphisms was shown to be different in populations with different CHD risk. The study [175] examined the prevalence of three genes, which have been shown to be associated with myocardial infarction in African Americans (AA) and European Americans (EA). The genotypes examined were connexin-37 (GJA-4), plasminogen activator inhibitor-1 (PAI-1), and stromelysin-1 (MMP-3). They found that the frequencies of two of the three "risk-associated" genotypes (MMP-3 and PAI-1) were significantly higher in the AA population compared to the EA (MMP3 -1171delA A/A: AA, 78%, EA, 24% ($p < 0.001$); PAI-1 -668delG G/G: AA, 55%, EA, 16% ($p < 0.001$)). However future studies are required to assess whether such genetic profiles predict adverse outcomes in the different U.S. populations.

Therapeutic Implications

Ethnic differences in CHD do exist. In this review we have examined the importance of inflammatory pathways in the processes leading to vascular damage and disease, and assessed the possibility that ethnic differences in new inflammatory markers might contribute to ethnic differences in CHD risk. Understanding these mechanisms may enable new therapeutic interventions to be developed. Given that oxidation leads to activation of the inflammatory pathway, the use of antioxidants may become important in slowing down the progression of vascular damage especially in T2DM. Indeed, studies have demonstrated that administration of alpha-tocopherol supplements can lead to a decrease in soluble cell adhesion molecules in normotriglyceridemic diabetic subjects [176]. More recently, however, the benefit of anti-oxidant vitamin supplements for the prevention of CVD has not been confirmed in large prospective randomised clinical trials, predominantly in white individuals [177]. Nevertheless, before the usefulness of these approaches can be ascertained and tested in other ethnic groups, the level of oxidation in these different ethnic groups needs to be determined as well as the development of prospective studies to determine their ability to predict disease development, progression and prognosis. Moreover, a greater understanding of these processes and the factors which can directly influence them is required so as to determine whether these inflammatory markers are merely 'by-standers' or whether they are casually related. Indeed, the development of new tools, for example the application of the Mendelian randomisation approach may help to determine causality. Yet its use in these complex disease processes has to be viewed with caution.

Standard Reference Ranges for Different Ethnic Groups

Results from our own and others groups have shown that the basal level of inflammatory markers differ between West African, Caribbean, South Asian and white individuals. Data on the levels of inflammatory markers among specific ethnic groups in the United States is sparse and particularly so for African Americans due to their under representation in clinical cohorts [178]. It is necessary that reference ranges are established within these groups before inflammatory markers can be added to global risk assessments. Moreover, the response to therapeutic or lifestyle interventions cannot be fully assessed until baseline and prospective data is obtained in these groups.

Our understanding of inflammatory process in the development and progression of CHD is only just beginning. Moreover, most of the outcome studies to date have been performed on white populations. Hence our understanding of possible ethnic differences in these processes is even more limited. Furthermore, even within homogenous populations like West Africans the role of environmental influences in determining the role of inflammatory markers in CVD remains to be determined. The study of such populations in their own original environment and in the host environment would be extremely valuable. These limitations must be recognised and addressed when therapeutic strategies are devised so that the best available treatment for each individual can be developed. For CRP and other inflammatory markers the levels increase dramatically in a wide range of infections and immune related disorders but for CRP, it is the moderately elevated levels, which are determined with the high sensitivity methods that are associated with long-term CVD risk [136]. It remains to be seen if a similar effect is seen with other inflammatory markers and studies are required to determine whether these associations are present in populations where chronic low-grade infections are endemic. Notwithstanding this, a number of drugs used to prevent cardiovascular disease have been shown to be effective in reducing the level of inflammatory mediators such as CRP levels [139]. These include lipid lowering drugs such as statins [179], fibrates [180] and aspirin [181]. However, the relative efficacy of these drugs in individuals from different ethnic groups remains to be established.

In this review we have described how activation of the innate immune system, which forms the first line of defence against invading foreign bodies, may be associated with cardiovascular disease development and atherosclerotic processes. Furthermore, we have discussed how an individuals' ethnic origin or environment may modulate these factors. Studies have demonstrated that monocytes, monocyte-derived macrophages and T lymphocytes accumulate in atherosclerotic plaques. The latter are responsible for the described in situ production of enzymes, growth factors, cytokines, and chemokines that further expand the process. Therapeutic strategies may be developed to prevent each part of these processes and described pathways however, there is a large body of evidence which suggests that there is a very delicate balance that is maintained between the T-cell populations (T1 and T2 helper cells), which modulate the bodies immune response and the balance between infection and allergy. Sleep has recently been considered to play a role in the development of obesity [125] modulates the balance between types 1 and 2 cytokine activity toward increased type 1 activity, thereby supporting adaptive cellular immune responses [182]. The recent withdrawal of rofecoxib and other Cox-2 inhibitors, which had been prescribed for arthritic conditions but were associated with an increase in cardiovascular risk has highlighted that it is imperative that these pathways and the balance between prevention of infection and development of autoimmune, cardiovascular or allergic conditions is fully investigated before any potential new therapeutic strategies are devised.

Treatment and Therapeutic Effects

1) Modification of Toll-Like Receptors

The Toll-like receptor (TLR) 9 is capable of recognising synthetic oligodeoxynucleotides (ODN) containing unmethylated deoxycytidyl-deoxyguanosine (CpG) motifs. Studies are currently ongoing to investigate the modification of the TLR9 signalling pathway for the treatment of various diseases including asthma and systemic lupus erythematosus (see review[183]) and it is possible that these may have some implication for cardiovascular disease prevention.

2) Lipid Lowering Treatments

Statins which are lipid lowering drugs have been shown to improve CVD end points. However, their lipid lowering effect is believed not to be the only mechanism underlying the clinical benefits. Indeed, more recent studies have suggested that they exert many actions on the cellular adhesion pathway [184]. They are able to inhibit the production of pro-inflammatory cytokines, prevent the activation of monocytes into macrophages and decrease cellular adhesion molecules. Consequently, the adhesion of monocytes to the endothelium is decreased. A recent analysis of the ASCOT study reported an interaction between anti-hypertensive therapy and statin therapy on CVD outcomes in line with such a hypothesis [185].

3) Aspirin

The protective effects of aspirin on coronary events may in part be mediated by its anti-inflammatory actions. IL-6 and other inflammatory cytokines have been shown to be reduced by aspirin [181]. Data from the Physician's Health Study have suggested that the beneficial effects of aspirin in reducing CVD risk are directly proportional to the degree of elevation of CRP [28].

4) Angiotensin Modulators: Angiotensin Converting Enzyme (ACE) / Angiotensin II Type I Receptor blockade

In a study to determine the anti-inflammatory effects of statins, aspirin, and Angiotensin II modulators on CRP levels in patients, with and without ischemic heart disease, it was shown that statins and Angiotensin II modulators, but not aspirin, in commonly used doses brought about a reduction in CRP levels [186].

5) Ppar- Gamma Agonists: Thiazolidinediones

Thiazolidinediones (TZDs) are peroxisome proliferators-activated receptor-gamma (PPAR-gamma) agonists. They are effective in the treatment of type-2 diabetes but not only do they increase insulin sensitivity they also exhibit anti-inflammatory effects which can benefit endothelial function as well. They have been shown to reduce CRP and IL-6 levels and thus may be useful for the prevention of CVD, especially in type-2 diabetic patients. Moreover, given the increased prevalence of diabetes and increased circulating levels of CRP in South Asians, it is plausible that they may be of particular importance in the treatment regime for this group of individuals.

The mobilization and differentiation of endothelial progenitor cells (EPCs) is important in the development of myocardial ischemia and angiogenesis and appears to be nitrogen oxide dependent. However, a recent study has shown that the ability of CRP to inhibit EPC differentiation and survival can be attenuated by pretreatment with rosiglitazone, a PPARgamma agonist [187]. The ability of CRP to inhibit EPC differentiation and survival may represent an important mechanism that further links inflammation to CVD and provides further treatment options.

6) Effect of Estrogens: HRT

The results from observational studies have claimed that HRT may reduce CVD risk by 35-50%. This view has been recently refuted following the Women's Health Initiative findings [188]. HRT can also reduce the expression of adhesion molecules [189] and results from our own study have demonstrated that blood pressure is significantly and directly associated with circulating sE-selectin but only in women younger than 50 years [89]. However, hormone replacement therapy (HRT) has been also been shown to elevate CRP levels [168]. Padham *et al.* [190] investigated postmenopausal women from the Women's Health Initiative, a large nationwide American study. They found that whilst CRP and IL-6 independently predict vascular events among apparently healthy postmenopausal women and that HRT increases CRP, the use or nonuse of HRT had less importance as a predictor of CVD risk than did baseline levels of either CRP or IL-6.

7) Antibiotics

A link between infection and atherogenesis has been suggested. In particular, attention has focussed on Cytomegalovirus (CMV), *Chlamydia pneumoniae* and *Hylicobacter pylori* [191]. As such it has been suggested that antibiotics may provide a useful treatment for CVD [192]. Short term intervention trials with antibiotics effective against *Chlamydia pneumoniae* in patients with ischemic heart disease do not currently support this view [193].

8) AGI-1067

AGI-1067 is an antioxidant with a similar structure to that of probucol. It has been shown to inhibit inducible VCAM-1 expression in vascular endothelial cells and to inhibit atherosclerosis development in various animal models [194].

9) Dietary Modifications- Fish oil Supplements

Indian Asians living in the UK have an increased prevalence of CVD and in particular metabolic syndrome which is characterized by raised plasma triglycerides, reduced HDL-cholesterol (HDL-C), insulin resistance and central obesity [195]. Brady *et al.* [196] examined the evidence to support the hypothesis that this increase in metabolic syndrome may in part be due to a dietary imbalance of poly unsaturated fatty acids (PUFA). The results from their investigation demonstrated that dietary supplementation with long chain n-3 PUFA had no impact on insulin action in those subjects consuming either the moderate- or high-n-6 PUFA diet. They concluded that contrary to the prevailing hypothesis the prevalence of metabolic abnormalities in Indian Asians compared with whites may not be attributable to differences in intakes of n-6 and n-3 PUFA.

Low rates CHD have been found in Greenland Eskimos and Japanese who are exposed to a diet rich in fish oil. It has been suggested that this cardio protection may arise in-part from the ability of n-3 fatty acids to suppress TNF-α and the synthesis of interleukins and may explain the beneficial effect of dietary n-3 fatty acids in the management of essential hypertension and atherosclerosis and other conditions [197].

10) Dietary Modifications- Anti-Oxidant Vitamin Supplements

Anti-oxidants inhibit the binding of monocytes to the endothelium as well as preventing platelet activation and providing protection against the effects of oxLDL. However, trial evidence to date including that from: the Heart Protection Study (HPS), the Heart Outcomes Prevention Evaluation (HOPE) trial, the Cardiovascular Disease, Hypertension and Hyperlipidemia, Adult-Onset Diabetes, Obesity, and Stroke (CHAOS) study, or the Secondary Prevention with Antioxidants of Cardiovascular Disease in End Stage Renal Disease (SPACE) trial have failed to show any clear beneficial effect of, for example, Vitamin E supplementation on atherosclerosis and heart disease.

11) C1-inhibitor

Inhibition of cell recruitment and inflammatory processes using C1-inhibitors protect against brain-ischemia-reperfusion injury [198]. Storini *et al.* [198] demonstrated that this drug decreased the expression of the adhesion molecules ICAM-1 and P-selectin. Moreover, the levels of pro-inflammatory cytokines (TNF-α, IL-18) were reduced and the levels of protective cytokines (e.g. IL-10) increased. Activation and or recruitment of macrophages were also inhibited and a marker for cellular apoptosis decreased.

12) Other Approaches

Atherosclerosis results from the development of inflammation, smooth muscle cell proliferation and the formation of thrombi. Any of the parts of these pathways are potential targets for therapeutic intervention. Perlecan is a heparin sulphate proteoglycan that is present in the extracellular matrix of blood vessels. These molecules are important in maintaining endothelial function and perlecan also plays a role in preventing thrombosis after injury to the vessel wall, it is susceptible to down regulation by cytokines and to increased degradation by matrix metalloproteinases (MMP) and as such it is an ideal candidate for therapeutic intervention [194].

SUMMARY

It is clear that inflammatory processes are important in the development and progression of CVD. Historically ethnic minority groups have been markedly underrepresented in published studies to date and it is evident that more data is required. Despite these limitations, it is clear from this review that ethnic differences in some adhesion molecules and cytokines levels exist. Possible reasons for these ethnic differences have been discussed. Genetic, environmental and dietary factors are important determinants. There have been suggestions that some inflammatory markers show sufficient predictability of CVD to warrant their inclusion in the risk factor analysis. However, it is equally clear that as yet the variation in these markers due to ethnicity has not been fully determined and the 'normal' ranges for each group would need to be evaluated. Furthermore, as the existing Framingham risk estimates have been shown not to be equally applicable to each ethnic group it is important that separate risk estimates are determined and validated for each major ethnic group [25]. As our understanding of these processes develops and as data from large prospective studies becomes available it may be possible to develop new therapeutic regimes to further improve the prevention and treatment of CVD. We are seeing an increase in CVD rates in developing third world countries, thus it will become increasingly important to develop therapeutic regimes that are equally effective in each ethnic group. The importance of environmental interactions should not be forgotten and reference ranges for these inflammatory markers for African individuals living in Africa as opposed to the US or UK should also be determined. In the absence of other 'western' risk factors it may be possible that these inflammatory markers may be of more importance in third world countries. The concept of the 'relative importance due to competing risks', known to epidemiologists and population scientists, has not been applied widely to try and explain apparent discrepancies of results between different populations. It is possible that the 'inflammation and CVD hypothesis' may benefit from such studies of populations of African descent living in different parts of the world and in white populations living in different Western countries investigated with common protocols and methodologies. This approach may unveil important differences in the way inflammatory pathways lead to vascular damage.

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