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Hotline Editorial

Do atherosclerosis and type 2 diabetes share a common inflammatory basis?

The number of adults with diagnosed type 2 diabetes worldwide will grow from 135 million in 1995 to approximately 300 million in 2025[1]. Rapid acculturation to Western lifestyles typified by diets rich in both fat and sugars, physical inactivity, concomitant high rates of both paediatric and adult obesity, and as yet poorly characterized dynamic interactions between environmental and genetic risk factors continue to fuel this global epidemic. As patients with diabetes experience accelerated atherosclerosis, cardiologists will undoubtedly require new strategies for diabetes risk prediction and primary prevention. Indeed, identification of individuals at risk for both type 2 diabetes and atherosclerosis at an early stage when risk factor modification might delay or prevent the clinical onset of these disorders represents a major challenge.

Type 2 diabetes and coronary heart disease — shared antecedents?

Stemming in part from the realization that type 2 diabetes and coronary heart disease are closely linked disease entities, recent efforts have focused on the elucidation of shared aetiological mechanisms. The metabolic syndrome, alternatively called metabolic syndrome X or the insulin resistance syndrome, is a common precursor to overt type 2 diabetes and is characterized by the simultaneous occurrence of several well-recognized cardiovascular risk factors. Features of the metabolic syndrome include abdominal obesity, dyslipidaemia (elevated triglyceride, small dense LDL particles, low HDL cholesterol), hypertension, and insulin resistance in the presence or absence of overt glucose intolerance. Although mechanisms underlying this clustering are complex and remain controversial, their statistical association is remarkably consistent. Furthermore, the strong correlation between glucose metabolic disorders and the incidence of coronary artery disease has raised speculation that atherosclerosis and type 2 diabetes may share common antecedents[2–4]. Indeed, the clinical importance of the metabolic syndrome is highlighted in the recent American National Cholesterol Expert Panel (NCEP) guidelines[5] which identify individuals with this constellation of risk factors as candidates for intensive therapeutic lifestyle changes.

Inflammatory basis of coronary heart disease

Atherosclerosis is now considered in part to be a consequence of chronic low-grade inflammation and inflammation is an important feature of plaque initiation, progression, and thrombosis. Evidence in support of this hypothesis derives from a number of experimental and epidemiological studies which have demonstrated strong, consistent, temporal, graded and biologically plausible relationships between sensitive markers of subclinical inflammation and both subsequent risk of cardiovascular events and severity of underlying atherosclerosis.

Among biomarkers of low-level inflammation which have been pivotal in this regard, C-reactive protein (CRP) has emerged as perhaps the most clinically useful[6]. CRP is an acute phase reactant of hepatic origin synthesized largely under the influence of interleukin-6 (IL-6), a major proinflammatory cytokine. Normally present as a trace plasma constituent, circulating levels of CRP rapidly and dramatically increase in response to a variety of inflammatory stimuli. As a member of the pentraxin family of oligomeric proteins involved in pattern recognition and innate immunity, reported immunoregulatory properties of CRP include opsonization, complement fixation, modulation of platelet activation, enhancement of leukocyte reactivity, induction of cellular adhesion molecule expression and monocyte chemoattractant protein by endothelial cells, and mediation of LDL uptake by macrophages[7–11].

Initial investigations which established the prognostic utility of CRP evaluation in the setting

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of stable and unstable angina[12,13] were followed by several prospective studies describing robust associations between baseline elevations of CRP and future risk of cardiovascular events in otherwise healthy individuals[14–18] and recurrent coronary events after first myocardial infarction[19]. More recent work has demonstrated that (1) CRP evaluation may improve coronary risk prediction beyond assessment of traditional clinical and lipid parameters[20], (2) CRP levels may be modified by HMG-CoA reductase inhibitors (statins) thereby guiding their appropriate use[21,22], and (3) corresponding declines in plasma concentration of CRP may be correlated with a lower incidence of subsequent primary and secondary coronary events, an effect which may be independent of the lipid-lowering properties of these agents[19,22]. Despite abundant epidemiological data, whether CRP is directly involved in atheroma progression, or mainly functions as a sensitive surrogate marker of atherosclerotic burden, or both, remains controversial. However, the practical implications for coronary risk prediction and coronary heart disease prevention are of major clinical significance irrespective of a clearly delineated biological role for CRP in atherothrombosis.

Inflammatory basis of type 2 diabetes

Insulin resistance and progressive pancreatic beta cell failure are key factors in the development of type 2 diabetes. Recently published cross-sectional studies have provided support for the hypothesis that chronic subclinical inflammation may be associated with insulin resistance and precede the development of clinically overt type 2 diabetes. Of the inflammatory biomarkers examined, CRP and IL-6 are particularly informative given the existence of biologically plausible mechanisms and their potential application in coronary heart disease risk prediction.

Among 107 non-diabetic men and women, Yudkin *et al.*[23] showed that CRP, IL-6, and tumour necrosis factor-*α* (TNF-α) are elevated in association with quantitative measures of insulin resistance and features of the insulin resistance syndrome. A subsequent report by Hak *et al.*[24] found similar relationships among healthy middle-aged women. In addition, CRP was strongly correlated with multiple indices of obesity. In the Insulin Resistance and Atherosclerosis Study[25], among 1008 non-diabetic subjects with no prior history of coronary disease, CRP levels were independently associated with insulin sensitivity as measured by a frequently sampled intravenous glucose tolerance test, and higher geometric mean CRP levels were linearly related to an increase in a number of components of the metabolic syndrome. These observations suggest that an enhanced acute phase response is associated with insulin resistance and may presage the development of type 2 diabetes.

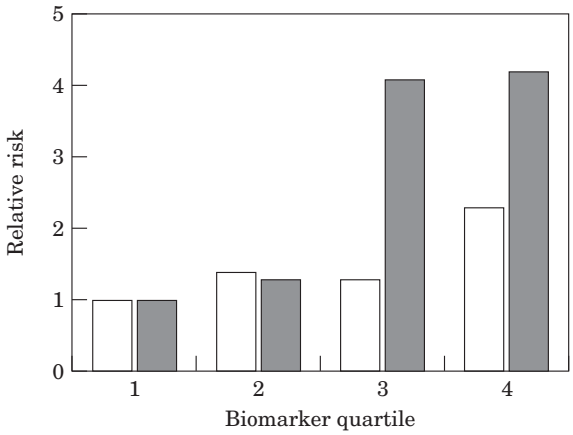

Figure 1 **Risk estimates are age-matched and additionally adjusted for body-mass index, family history of diabetes, smoking, physical activity, alcohol consumption, and hormone replacement therapy. □=interleukin-6; ■=C-reactive protein.**

These epidemiological findings are strengthened by experimental studies which demonstrate the hyperglycaemic effects of several proinflammatory cytokines, including IL-6 and TNF-*α*, both of which derive in part from adipose tissue. In rodent models of glucose homeostasis, IL-6 modifies glucose-stimulated insulin release from isolated pancreatic beta cells[26] and diminishes insulin-stimulated glycogen synthesis by hepatocytes in culture[27]. In humans, the exogenous administration of recombinant IL-6 induces dose-dependent hyperglycaemia and concordant elevations in circulating levels of glucagon[28]. TNF-*α* may induce insulin resistance through a variety of mechanisms, including direct inhibitory effects on the glucose transporter protein GLUT4, the insulin receptor, and insulin receptor substrates[29].

Despite these compelling findings, prospective data evaluating the relationship between chronic subclinical inflammation and the incidence of type 2 diabetes are sparse. In the Atherosclerosis Risk in Communities Study, markers of inflammation such as white blood cell count, fibrinogen, and low serum albumin[30] and inflammation-associated haemostasis variables such as factor VIII and von Willebrand factor[31], were associated with the risk of type 2 diabetes. However, these relationships were largely abolished after adjustment for obesity.

In a recently presented study, we have sought associations between elevated levels of CRP and IL-6 and the risk of type 2 diabetes in otherwise healthy middle-aged women[32]. Among participants of the Women's Heath Study followed for 4 years, in age-matched analyses controlling for obesity, family history of diabetes, and other clinical risk factors we found that elevated CRP levels were associated with a fourfold increase in risk for future diabetes (Fig. 1). Further control for fasting insulin and baseline haemoglobin Alc did not materially alter these results. Elevated IL-6 was similarly associated

with a twofold risk increase, although this relationship was not statistically significant after multivariate adjustments. It is important to note, however, that our ability to adequately assess the impact of IL-6 may be limited by both diurnal variation and a short plasma half-life which thereby render CRP a more consistent marker of low-grade systemic inflammation in large-scale epidemiological settings.

Our prospective findings linking subclinical inflammation to the development of type 2 diabetes raise several intriguing questions regarding novel pathogenic mechanisms for insulin resistance and beta cell secretory failure. Associations between abdominal obesity, inflammation, and abnormal insulin sensitivity have recently become a subject of intense investigation. Mohamed-Ali *et al*.[33], using elegant in vivo techniques, have estimated that approximately 25 to 30% of total circulating concentrations of IL-6 originates from subcutaneous adipose tissue in healthy adults. TNF-α is also appreciably expressed by adipocytes. Other substances implicated in adipocyte activation include leptin, free fatty acids, and resistin. Whether these putative adipocyte signalling molecules act in concert with mediators of inflammation implying an integral role for inflammation in diabetogenesis or whether inflammatory markers are simply co-released in parallel with other truly pathogenic substances remains a matter requiring further study.

It is also possible that microvascular endothelial dysfunction may be involved in the development of insulin resistance, thereby providing an additional link between type 2 diabetes and atherosclerosis[34]. Arteriolar and capillary endothelium play an important role in the regulation of blood flow to insulin-sensitive tissues, such as the liver and skeletal muscle, and also function as barriers to insulin delivery to interstitial compartments. Failure of insulin delivery to metabolically active tissues in the dynamic state during periods of hyperglycaemia may be a rate-limiting step in determining insulin effectiveness. In addition, microalbuminuria, a result of renovascular endothelial dysfunction, is strongly predictive of cardiovascular disease in both diabetic and non-diabetic individuals and is commonly present in insulin resistance and type 2 diabetes. Furthermore, experimental studies have shown that endothelium-dependent vasodilatation in vivo is impaired by exogenous administration of proinflammatory cytokines as demonstrated by profound attenuation of a vasomotor response to both physical and pharmacological vasodilatory agents[35]. To what extent chronic exposure to low levels of inflammation induces or exacerbates insulin resistance via this process or alternatively through impaired vascular permeability is incompletely understood.

Recent reports of reductions in the incidence of type 2 diabetes accompanying pharmacological interventions for coronary heart disease prevention offer further support for an association between inflammation, diabetogenesis, and atherosclerosis. In two large intervention trials of angiotensin-converting enzyme (ACE) inhibitors for the prevention of cardiovascular disease, treatment assignment to captopril in the Captopril Prevention Project (CAPPP)[36] and ramipril in the Heart Outcomes Prevention Evaluation (HOPE) study[37] was associated with a statistically significant reduction in incidence of type 2 diabetes (relative risk 0·86, $P=0·039$ and 0·66, $P<0·001$ for CAPPP and HOPE respectively). In a secondary analysis of the West of Scotland Coronary Prevention Study[38], the use of pravastatin in the primary prevention of coronary heart disease was also associated with a 30% reduction in risk of type 2 diabetes ($P=0·042$). One compelling hypothesis which may account for these effects is modulation of subclinical inflammation. Angiotensin II has been shown to induce IL-6 expression from both macrophages and smooth muscle cells, and is co-localized with IL-6 in human atheroma[39]. Furthermore, preliminary data suggest that long-term ACE inhibition may lower CRP levels among individuals with coronary artery disease[40]. In addition, statin therapy in general appears to lower CRP levels and have beneficial adjunctive effects on restoration of endothelial function[21,22].

Towards a unifying hypothesis

Both type 2 diabetes and atherosclerosis are multifactorial conditions which appear to share a common inflammatory basis[3,4]. Indeed, the interaction between inflammation, diabetes, and atherosclerosis appears to unify previously disparate observations and supports the position that vascular and non-vascular sources of systemic inflammation may be important to variable degrees in the pathogenesis of both disorders. Although several issues remain, the designation of type 2 diabetes as, in part, an inflammatory disease represents a logical framework which considers the weight of recent evidence and offers unique opportunities for both primary prevention and the amelioration of significant diabetes-related cardiovascular complications.

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