Endothelial inflammation in insulin resistance

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Context **Type 2 diabetes and attendant cardiovascular morbidity are becoming major health concerns globally. Obesity-related type 2 diabetes is rapidly rising in prevalence, probably largely because of increased longevity and sedentary lifestyles. Insulin resistance and type 2 diabetes are associated with increased coronary heart disease, but the severity of glycaemia during the diabetic phase can only to a minor extent explain the increased risk. Increased levels of the acute-phase inflammatory marker, C-reactive protein (CRP), are related to insulin resistance and the metabolic syndrome, suggesting a role for chronic low-grade inflammation. CRP levels might predict the development of type 2 diabetes.**

Starting point **Subodh Verma and associates (*Circulation* 2004; 109: 2058-67) recently showed that CRP attenuates the survival, differentiation, and function of endothelial progenitor cells, partly by CRP reducing expression of endothelial nitric-oxide synthase. Rosiglitazone, a peroxisome-proliferator-activator receptor γ agonist, inhibits the negative effects of CRP on endothelial progenitor cells. The results are consistent with the suggestion that CRP directly promotes atherosclerotic processes and endothelial cell inflammation. CRP might thus directly trigger the development of a proinflammatory and proatherosclerotic state, leading to atherothrombosis.**

Where next **Cell-surface CRP receptors and signalling pathways need to be characterised. From such study might come novel drugs that will defer proinflammatory reactions leading to insulin resistance and atherothrombosis.**

Type 2 diabetes is a leading cause of morbidity and mortality in western societies, and is quickly approaching pandemic proportions: the number of cases is expected to rise to 300 million globally by 2025.[1] With recent trends in obesity, we can expect a momentous increase in the prevalence of the metabolic syndrome in westernised populations. About 80% of all type 2 diabetes coexists with insulin resistance.[1] Endothelial dysfunction is an early abnormality in insulin-resistant states that might contribute to premature atherosclerosis.[2,3] Subclinical chronic low-grade inflammation might be an important player in the pathogenesis of insulin resistance and type 2 diabetes,[4-6] and C-reactive protein (CRP) promotes atherosclerotic processes and endothelial cell inflammation.[7-9]

Epidemiological studies

Population studies show strong correlation between proinflammatory biomarkers (such as CRP, interleukin 6, and tumour necrosis factor α) and perturbations in glucose homoeostasis, obesity, and atherosclerosis.[10-13] CRP levels might be independently related to the degree of insulin resistance, independently of obesity.[14,15] Plasma levels of high-sensitive CRP predict future cardiovascular risk, even in apparently healthy individuals.[12] In a post-hoc analysis of the predictive value of CRP for the risk of developing diabetes in the WOSCOPS cohort of middle-aged men, a dose-dependent correlation, independent of established risk factors, was indeed found.[16]

Type 2 diabetes might be partly precipitated or accelerated by an acute phase reaction as part of the innate immune response, in which large amounts of cytokines are released from adipose tissue.[17] This process, driven by caloric excess, might be regulated by genetic factors. In this hypothesis (figure), cytokines exert toxic effects on endothelial cells and cause increased capillary permeability. Cytokines produced locally in inflamed plaques, which are common in poorly controlled diabetes, could induce oxidative stress and endothelial dysfunction that might further aggravate the atherosclerotic process.[17] Mechanisms involving other adipocytokines that counter the proinflammatory actions also exist, such as the anti-inflammatory action of adiponectin which is inversely related to body-mass index and probably associated with reduced insulin resistance and atherosclerosis.[18] If true, this hypothesis might have important clinical implications in that drugs that inhibit the acute phase response and inflammation might increase insulin sensitivity and possibly also halt the progressive nature of type 2 diabetes.

Figure: **Induction of reactive oxygen species (ROS) and inflammation (NF-κB activation) by macronutrient intake, obesity, free fatty acids, leptin, infection, smoking, mental stress, and genetic factors**

Interference with insulin signalling (insulin resistance) leads to hyperglycaemia and proinflammatory changes. Proinflammatory changes (increased tumour necrosis factor α [TNFα] and interleukin 6 [IL-6]) also lead to inhibition of insulin signalling and insulin resistance. Inflammation in ß cells leads to ß-cell dysfunction which, with insulin resistance, leads to type 2 diabetes. T1D=type 1 diabetes, T2D=type 2 diabetes. From reference 2 with permission.

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Interventions and mechanisms

CAPPP was the first controlled study to show that captopril, an angiotensin-converting-enzyme inhibitor, decreased the risk of developing type 2 diabetes in hypertensive patients.[19] The study was designed to compare the effect of captopril with conventional antihypertensive treatment on cardiovascular morbidity and mortality. There were 11% fewer patients with new-onset type 2 diabetes in the captopril group than in those on conventional treatment.

These results were confirmed in HOPE, in which 10 mg ramipril daily was given as monotherapy or add-on to conventional treatment.[20] Over 4 years, ramipril caused a 33% relative-risk reduction of developing diabetes.[20] In LIFE, the angiotensin-receptor blocker losartan

reduced the relative risk of getting diabetes by 25% compared with the ß-blocker atenolol.[21] However, since this trial was not placebo-controlled, the lowered diabetes incidence probably reflects the net effect of increased insulin sensitivity by losartan and increased insulin resistance by atenolol.

Similar findings were reported with candesartan in ALPINE and CHARM.[22-24] CHARM was placebo-controlled and therefore very informative: candesartan evoked a 22% relative-risk reduction of developing diabetes in 7601 patients,[22] and a 39% decrease in the relative risk of getting diabetes in patients with congestive heart failure class II-IV with ejection fraction of 40% or higher.[23]

The renin-angiotensin system might be activated in insulin-resistant states, resulting in increased oxidative stress in vascular endothelial cells.[25] The mean arterial pressure is also higher during hyperglycaemic than euglycaemic conditions, and responds well to losartan, whereas the response to losartan during euglycaemia is minimal.[26] Moreover, the renal vasodilator response to captopril and eprosartan is enhanced during hyperglycaemia, suggesting that hyperglycaemia leads to increased renal vascular tone mediated by angiotensin II.[27]

Many of the above studies did not have diabetes incidence as a primary endpoint,[28] although such studies are in progress. Alternative explanations to the metabolic effects of angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers should be considered. One trivial explanation for the improvement in insulin sensitivity could be that blood flow through the microvasculature to insulin-sensitive tissues increases after treatment with certain vasoactive substances, thus allowing more insulin to reach metabolically active tissue. Alternatively, blockade of the renin-angiotensin system might reduce the risk of diabetogenesis by stimulating proliferation and differentiation of adipocytes.[29] Thus, ectopic fat storage (eg, in liver, skeletal muscle, and pancreas), which is associated with insulin resistance, would be prevented. This mechanism, if it can be confirmed, is in good agreement with the manner in which glitazones reduce insulin resistance in patients with type 2 diabetes.[3,6,17] Nonetheless, whatever the mechanism, the net effect would still be a reduced risk of diabetes.

In WOSCOPS, post hoc, pravastatin lowered by 30% the relative risk of developing diabetes compared with placebo over 4·9 years, and this effect was paralleled by a decrease in CRP.[30] Rapid CRP-lowering effects of pravastatin were also reported in the prospective PRINCE trial,[31] and occurred independently of decreases in LDL-cholesterol levels. There appear to be important differences between the statins in this regard, as pravastatin is in a class of its own in terms of preventing diabetes. For instance, no such effect was reported in the Heart Protection Study, in which simvastatin was used.[32] Suggestively, pravastatin differs in several respects from other statins, with the possible exception of rosuvastatin, for which there are as yet no data on mortality.

The glitazone class of insulin-sensitising agents--which have been introduced for type 2 diabetes and insulin resistance--activate peroxisome-proliferator-activator receptor ϒ (PPAR-ϒ) in the cell nucleus, where it influences a range of transcription factors.[33] Glitazones ameliorate endothelial dysfunction in patients with diabetes, and lower inflammatory markers and reactive oxygen species in serum.[6,17,33] Within a week, glitazones can reduce CRP by 30%; the corresponding effect of statins is only 14%.[2,17] Data on other antidiabetic agents are scarce, but metformin, but not sulphonylurea, might have similar anti-inflammatory activity.[3,4,12,17]

It has long been debated whether insulin causes atherogenesis, which has contributed to reluctance to prescribe insulin to patients with early type 2 diabetes. Insulin's role in inflammation and atherogenesis remains controversial, not least because of our inability to distinguish between insulin resistance and insulin as possible proinflammatory cardiovascular risk factors. The evidence implicating

insulin as an atherogenic hormone includes data from animal studies, in-vitro studies, and prospective epidemiological studies.[34] Insulin also causes in-vitro proliferation of smooth muscle cells in animal models and in human beings.[34] Thus insulin could promote atherogenesis by direct action on the arterial wall. Several prospective epidemiological studies have tested the hypothesis that the circulating insulin concentration is a cardiovascular risk factor.[35] None of these studies, however, distinguished between insulin and insulin resistance as the possible atherogenic factor, and proinsulin was not separated from insulin. It might be the other way around--that the insulin resistance itself, by production of proinflammatory cytokines, induces atherogenesis and that the hyperinsulinaemia could be the body's compensatory attempts to suppress the inflammation and overcome insulin resistance.[2,3,12,17,36] Eventually, however, the total amount of insulin secreted by the pancreas is also depressed after several years of insulin resistance--ie, ßcells become exhausted, implying that, eventually, prevailing insulin concentrations will not be sufficient to counter the overwhelmingly strong insulin resistance.

In obese human beings, infusion of low doses of insulin reduces the production of reactive oxygen species in leucocytes (which increases the bioavailability of the anti-inflammatory nitric oxide), and lowers CRP and other inflammatory markers in serum.[2,3,6,17] The effect corresponded quantitatively to that of an intravenous dose of 100 mg hydrocortisone. It appeared rapidly, within 2 h of infusion, and receded quickly. In addition, in-vivo studies show that insulin acts via nitric-oxide-mediated mechanisms to suppress synthesis of proinflammatory substances in endothelial cells from human aorta.[2,3,6,17,36] A vicious circle can also develop: decreased insulin sensitivity in organs such as skeletal muscle, adipose tissue, and liver leads to increased inflammatory activity, which in turn leads to further reductions of insulin sensitivity. Moreover, glucose has proinflammatory effects: it increases synthesis of reactive oxygen species and accentuates several inflammatory markers in vitro.[6,12,17] Similarly, under hyperglycaemic clamp conditions, if endogenous insulin secretion is suppressed with somatostatin, the synthesis of interleukin 6 and tumour necrosis factor α increases.[6,12,17]

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Clinical perspectives

That subclinical chronic inflammation might be an important pathogenetic factor in the development of insulin resistance and type 2 diabetes opens new perspectives for diagnosis and treatment of early insulin resistance and incipient glucose intolerance. More specific and sensitive biomarkers should be identified, to predict early disturbances in insulin sensitivity and cardiovascular risk. Inflammatory signalling pathways need to be explored in greater detail, as possible drug targets.

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