For debate

Is Type II diabetes mellitus a disease of the innate immune system?

J.C. Pickup, M. A. Crook
Department of Chemical Pathology, United Medical and Dental Schools, Guy’s Hospital, London, UK

Summary  Type II (non-insulin-dependent) diabetes mellitus is associated with increased blood concentrations of markers of the acute-phase response, including sialic acid, α-1 acid glycoprotein, serum amyloid A, C-reactive protein and cortisol, and the main cytokine mediator of the response, interleukin-6. The dyslipidaemia common in Type II diabetes (hypertriglyceridaemia and low serum levels of HDL cholesterol) is also a feature of natural and experimental acute-phase reactions. We review evidence that a long-term cytokine-mediated acute-phase reaction occurs in Type II diabetes and is part of a wide-ranging innate immune response. Through the action of cytokines on the brain, liver, endothelium, adipose tissue and elsewhere, this process could be a major contributor to the biochemical and clinical features of metabolic syndrome X (glucose intolerance, dyslipidaemia, insulin resistance, hypertension, central obesity, accelerated atherosclerosis) but also provides a mechanism for many other abnormalities seen in Type II diabetes, including those in blood clotting, the reproductive system, metal ion metabolism, psychological behaviour and capillary permeability. In the short-term, the innate immune system restores homeostasis after environmental threats; we suggest that in Type II diabetes and impared glucose tolerance long-term lifestyle and environmental stimulants, probably in those with an innately hypersensitive acute-phase response, produce disease instead of repair. [Diabetologia (1998) 41: 1241–1248]

Keywords Innate immune system, acute-phase response, cytokines, interleukins

The cause of the common type of Type II (non-insulin-dependent) diabetes mellitus, which affects at least 100 million people throughout the world, is not known. One of the foremost challenges we face is to account mechanistically for not only the defining hyperglycaemia but also for the myriad of other biochemical and physiological abnormalities which are characteristic of this disease. For example, it is now clear that Type II diabetes and lesser degrees of glucose intolerance commonly occur together with a collection of clinical and biochemical features which have been called metabolic syndrome X [1, 2].

These features include central obesity, hypertension, accelerated atherosclerosis, hypertriglyceridaemia and low serum concentrations of high-density lipoprotein (HDL) cholesterol. Though insulin resistance seems to be a central abnormality, the origin of the impaired insulin action and how it explains the many other abnormalities of Type II diabetes is not known.

In recent years, we have been gathering evidence that in Type II diabetes there is a cytokine-associated acute-phase reaction, part of the innate immune response. As an alternative direction for research into the aetiology of Type II diabetes, we propose that it may be helpful to consider whether the mechanisms involved in the acute-phase response can be major contributors to the pathophysiology of many of the features of Type II diabetes and syndrome X, including glucose intolerance, insulin resistance, impair-
ed insulin secretion, dyslipidaemia, hypertension, atherosclerosis and central obesity.

There are, though, wider implications of this hypothesis, which suggests that Type II diabetes, impaired glucose tolerance and syndrome X are only selected and commonly recognised manifestations of the body’s complex innate immune response, which also has wide-ranging effects on, for example, psychological behaviour, sleeping patterns, reproductive hormones, haemostasis, metal ion metabolism and capillary permeability, abnormalities of which are often seen in Type II diabetes. In the short-term, the acute-phase response has survival value and is designed to restore homeostasis after environmental threats [3]; we hypothesise that long-term activation produces disease instead of repair in subjects who develop Type II diabetes.

**A note on the acute-phase reaction and the innate immune system**

The innate or natural immune system, which is phylogenetically older than adaptive or acquired immunity, is a rapid first-line defence system based on non-lymphoid tissue (Fig. 1). It uses a number of soluble and cellular sensing mechanisms to recognise potentially harmful substances [4, 5]. These receptors include broad-specificity proteins encoded in the germ line (i.e. non-clonal) which have been called pattern-recognition receptors as they are not specific for a particular antigen, unlike the conventional B and T cells of the adaptive immune system, but sense conserved structures and molecules characteristic of harmful agents. Examples are the lipopolysaccharide receptor on macrophages, which binds to this common constituent of Gram-negative bacteria, scavenger receptors [6] on macrophages and other cells that recognise altered proteins and other molecules not part of the host tissues, and cells which respond to microenvironmental tissue injury (dendritic [7] and probably other cells).

Signals produced by innate receptors cause effector responses designed to neutralise the stressor and restore homeostasis; the ‘acute-phase response’ is probably the best-studied part of the innate immune system. In reaction to a variety of stresses such as infection, inflammation, tissue injury and malignancy there is a pronounced change in the concentration of certain plasma proteins, called acute-phase proteins [3, 8, 9] – usually an increase – but some proteins decrease. These positive acute-phase proteins include fibrinogen, α1-acid glycoprotein, α1-antichymotrypsin, haptoglobin, C-reactive protein and serum amyloid A. The serum or plasma sialic acid concentration is a marker of the acute-phase response [10] since most of the acute-phase proteins are glycoproteins with sialic acid at the terminus of the oligosaccharide chain. Despite the apparent oxymoron, a sustained acute-phase response is seen in many chronic inflammatory and other illnesses.

The acute-phase proteins are synthesised in the liver, stimulated by cytokines, mainly interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF) α, which are produced in macrophages, monocytes, endothelium and many other cells in the body [11] (Fig.1). The acute-phase proteins have many activities that in general contribute to host defence, healing and adaptation to insult. For example, proteinase inhibitors such as α1-antitrypsin control proteinases released by phagocytes, fibrinogen has a major role in haemostasis, and ceruloplasmin, haptoglobin and metallothionene are antioxidants protecting against toxic oxygen metabolites produced at the site of injury and inflammation.

In addition to their effect on the liver, proinflammatory cytokines also have a major action on the central nervous system, controlling the neuroendocrine, behavioural and psychological responses to stress. This will be discussed below in the context of Type II diabetes. The recently postulated role of the innate immune system in controlling the initiation of an appropriate adaptive clonal response [5] will not be discussed here.

**A model for Type II diabetes as an acute-phase disease**

As a cohesive model for Type II diabetes and its associated clinical and biochemical features, we propose that Type II diabetes is an acute-phase disease in which increased concentrations of cytokines are secreted from many cells such as macrophages, adipose tissue and endothelium, under the influence of stimuli such as overnutrition, perhaps in those predisposed to having an upregulated response because of increasing age, or genetic or fetal metabolic preprogramming (Fig. 2). Cytokines, mainly IL-1, IL-6 and TNF-α, act on the liver to produce the characteristic dyslipidaemia of Type II diabetes (increased very low density [VLDL] lipoprotein and decreased HDL). They also promote the release from the liver of acute-phase proteins which are atherosclerotic risk factors, such as fibrinogen, stimulate leptin release from adipose tissue, and act on the brain to release adrenocorticotropic hormone (ACTH) and thus cortisol. The latter may contribute to obesity, hypertension and insulin resistance. TNFα also is a major factor in causing insulin resistance. Long-term hypersecretion of cytokines may impair beta-cell insulin secretion.

The main implications of this model are: (1) many of the clinical and biochemical abnormalities of Type II diabetes might be explicable in terms of maladaptation of a single integrated but complex physiological response, (2) other known characteristics of the
Evidence for an acute-phase response in Type II diabetes

The ‘dyslipidaemia’ of Type II diabetes (high serum total and VLDL triglyceride, low HDL cholesterol, unaltered total and low density cholesterol concentration) is the same pattern of serum lipid alteration which has been reported in conditions likely to be associated with an acute-phase response (e.g. infection [12] and malignancy [13, 14]) and which occurs in animals when the acute-phase response has been experimentally induced [15]. We reasoned, therefore, that Type II diabetes should be associated with an acute-phase response.

A number of studies have reported increased acute-phase proteins in diabetes [16–18] but have not drawn attention to the differences between Type I (insulin-dependent) and Type II diabetes. We showed, however, that concentrations of the acute-phase marker, serum sialic acid, are raised in Type II diabetes, even in those without diabetic tissue complications, but are not altered in uncomplicated Type I diabetic subjects of similar age and glycaemic control to the Type II diabetic group [19, 20].

In a recent study [21], we showed serum concentrations of several acute-phase markers, including sialic acid, α-1 acid glycoprotein, C-reactive protein, serum amyloid A and cortisol, and the cytokine mediator IL-6 to be increased in Type II diabetes. Concentrations were lowest in non-diabetic subjects, intermediate in patients without syndrome X and highest in Type II diabetic patients with syndrome X. Urinary albumin excretion rate also displayed the same graded increase amongst the three groups, suggesting that microalbuminuria also could be a component of the acute-phase response.

The increased of serum amyloid A in Type II diabetes is particularly interesting since this protein displaces apolipoprotein A1 from HDL₃, increasing HDL binding to macrophages and acting as a signal to direct HDL cholesterol from the liver to the macrophage for tissue repair [9, 15]. Increased catalolism could account for low HDL cholesterol concentrations in Type II diabetes, and uptake by macrophages in the atherosclerotic plaque could be part of the reason for an increased risk of arterial disease in Type II diabetes.

Other acute-phase proteins which have a high concentration in Type II diabetes (Table 1) include fibrinogen, which is a strong risk factor for coronary heart disease [22, 23], von Willebrand factor [9], complement components [24] and plasminogen activator inhibitor-1 (PAI-1) [25]. There is also evidence that Lp(a) lipoprotein, which is associated with coronary heart disease in Type II diabetes [26, 27], is an acute-phase protein [9, 28].

innate immune system could emerge as disordered in Type II diabetes, or vice versa, and (3) the model suggests new therapeutic approaches to Type II diabetes and its complications, such as modulation of the acute-phase response.
**Table 1. Acute-phase responses in blood which are also known to be abnormal in Type II diabetes**

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>1, 2</td>
</tr>
<tr>
<td>HDL (lowered)</td>
<td>1, 2</td>
</tr>
<tr>
<td>α1-Acid glycoprotein</td>
<td>21</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>21</td>
</tr>
<tr>
<td>Serum amyloid A</td>
<td>21</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>22, 23</td>
</tr>
<tr>
<td>von Willebrand factor</td>
<td>8</td>
</tr>
<tr>
<td>Complement</td>
<td>24</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1</td>
<td>25</td>
</tr>
<tr>
<td>Lipoprotein Lp(a)</td>
<td>27</td>
</tr>
<tr>
<td>Cortisol</td>
<td>21</td>
</tr>
<tr>
<td>Zinc (lowered)</td>
<td>49</td>
</tr>
<tr>
<td>Testosterone (lowered)</td>
<td>41</td>
</tr>
<tr>
<td>Sialic acid</td>
<td>19–21</td>
</tr>
</tbody>
</table>

**Cytokines and Type II diabetes**

What is the relevance of raised cytokines in Type II diabetes? As well as stimulating hepatic acute-phase protein production, IL-1 and IL-6 act on the brain, stimulating the release from the pituitary gland of the diabetogenic adrenocorticotrophic hormone (ACTH) and growth hormone [29–31] (Fig. 2). The hypercortisolaemia which we found in Type II diabetes, especially in syndrome X subjects, could contribute to the insulin resistance, glucose intolerance, hypertension and perhaps the central obesity of the condition (cf Cushing’s syndrome). Treating animals and humans with cytokine induces hypertriglyceridaemia and insulin resistance [32, 33]. There are many effects of cytokines on endothelial cells, including inducing prothrombotic properties, promoting leukocyte recruitment by synthesis of adhesion molecules and chemoattractants and increasing capillary permeability [34, 35]. The last is an obvious contributor to the microalbunimuria of diabetes. Finally, TNFα is a potent inhibitor of the tyrosine kinase activity of the insulin receptor and has been implicated in the insulin resistance of Type II diabetes and obesity [36].

Islet beta-cell function is inhibited by IL-1 and IL-6 and TNFα, which have been much investigated as an aetiological mechanism for islet cell destruction in Type I diabetes [37, 38]. High long-term proinflammatory cytokine concentrations have not been studied as a contributor to the impaired beta-cell function in Type II diabetes, but our hypothesis suggests that this should be considered. Prolonged exposure (perhaps years) to marginally raised cytokine concentrations may produce different effects on the beta cell from shorter-term exposure to higher concentrations. Repeatedly giving IL-1β in vivo to normal rats over 3 days reduces glucose-stimulated first-phase insulin secretion from subsequently isolated islets from the rats, but without altering the islet insulin content or ultrastructure [39]. Such studies, however, clearly do not simulate the long-term evolution of Type II diabetes.

**Some other manifestations of the innate immune response in Type II diabetes**

Stress inhibits reproductive function, and cytokine-induced hypothalamic corticotrophin releasing hormone (CRH) production, which inhibits gonadotrophin secretion [40], could explain the low plasma testosterone concentrations seen in men with Type II diabetes [41]. Pathophysiological perturbation of the cytokine and glucocorticoid effects on the central nervous system in long-term inflammatory and stress states are thought to cause behavioural syndromes such as depression, for example, through CRH changes [42–44]. There is a large literature on the subject of diabetes and depression, with many methodological and interpretative problems, but it can be noted that there is considerable evidence for an increased prevalence of depression in Type II diabetes [45], depression predicts the onset of diabetes [46] and insulin resistance is common in depressed subjects [47]. Amongst the brain peptides altered in stress are the appetite-regulating substances such as neuropeptide Y [48]. Overactivity of neurons containing this potent appetite stimulant has been reported in animal models of diabetes [48].

Low plasma zinc concentrations, which are seen in Type II diabetes [49], are also a manifestation of the acute-phase reaction [3] and are probably the result of zinc binding to the acute-phase protein, metallothione.

In animals, endotoxin, IL-1 and TNF induce expression of adipose tissue leptin mRNA [50], the appetite-suppressing ob gene product, which is increased in human Type II diabetes and which is the subject of intense investigation concerning its role in human and animal diabetes. There is, indeed, increasing evidence that leptin is a stress-related peptide [51].

**The acute-phase response and diabetic complications**

We found that even Type II diabetic patients without microvascular or macrovascular complications had a high acute-phase response [20] but tissue complications do further increase stress reactants in Type II diabetes [52]. In non-diabetic subjects with atherosclerosis, a ‘haematological stress syndrome’ has been recognised for many years [53], consisting of high acute-phase reactants such as fibrinogen, increased blood viscosity and increased platelet number and activity. Cytokines produced by endothelium, smooth muscle cells and macrophages of the atherosclerotic plaque could contribute to this acute-phase response seen in atherosclerosis (Fig. 2).
In the general population, serum sialic acid and C-reactive protein concentrations are powerful predictors of cardiovascular disease [54–56]. In a cross-sectional study of Type II diabetic subjects from a diabetic clinic (the Guy’s-Lewisham Diabetes Survey), we found that there was a strong univariate association in men between high serum sialic acid concentrations and coronary heart disease [26]. Apart from the acute-phase proteins which are established or putative risk factors for cardiovascular disease such as fibrinogen, serum amyloid A, PAI-1, Lp(a) lipoprotein and VLDL triglyceride, proinflammatory cytokines produced at the sites of diabetic complications or by the diabetic process itself (see below) may also exacerbate atherosclerosis by acting on the endothelium, smooth muscle cells and macrophages [57]. We found that women with Type II diabetes who lose the protection from cardiovascular disease enjoyed by non-diabetic women and who possibly have a higher risk of this disease than men with Type II diabetes, have a higher serum sialic acid concentration than Type II diabetic men [52].

There is thus likely to be a positive feedback involving cytokines and atherosclerosis, perhaps accounting for the acceleration of arterial disease in diabetes. The plaque produces cytokines, which further exacerbate the process of atherosclerosis locally but also cause an increase in circulating acute-phase proteins, many of which are themselves risk factors for atherosclerosis (Fig. 2).

**Why is there an acute-phase response in Type II diabetes?**

We envisage that an increased acute-phase response can occur in Type II diabetes either because of the presence of one or more specific stimuli (e.g. nutritional, tissue complications) or because of sensitisation to a normal level of stimulus by modulators (such as age, race, insulin action, and genetic or fetal metabolic programming), or a combination of the two occurs — a stimulus in the presence of an upregulating modulator.

In addition to diabetic complications, possible stimulants of the acute-phase response in Type II diabetes include overnutrition or altered nutrition. There are a number of ways in which nutrition can affect cytokine responses which are of relevance to Type II diabetes, for example, the effect of dietary fat on cytokine production [58]. Synthesis of proinflammatory cytokines by peripheral blood monocytes is suppressed by n-3 fatty acid supplementation (fish oil) in normal volunteers [59]; this supports the theory that a diet rich in n-6 and deficient in n-3 essential fatty acids is a major risk factor for diabetes and atherosclerosis [60].

As far as sensitisers of the response are concerned, both the production of cytokines from monocyte and macrophages [61], and circulating acute-phase proteins [62] increase with age.

Another mechanism could involve insulin resistance: in animal models of diabetes we found that the acute-phase response was increased by insulin deficiency [63], and others have found that insulin inhibits acute-phase protein synthesis in animal and human hepatoma cell lines [64, 65]. This suggests that insulin resistance can amplify the cytokine effect on the liver. Hyperglycaemia can also stimulate the acute-phase response [66]. The lack of an increased acute-phase response in uncomplicated Type I diabetes indicate that liver insulin resistance is much more prominent in Type II diabetes or that insulin in fact has a relatively minor role in the regulation of the response.

The effect of glucose, however, is less clear. In samples from non-diabetic subjects, glucose stimulates IL-6 production from peripheral blood monocytes [67] and advanced glycosylation end products are also known to have a similar effect on cytokine production from macrophages [68]. A major effect, however, of hyperglycaemia on the acute-phase response in Type II diabetes is made less likely by the lack of correlation between serum sialic acid concentrations and glycaemic control [26] and the normal sialic acid concentrations in uncomplicated Type I subjects with the same degree of glycaemic control as Type II diabetic subjects [20].

As far as race is concerned, we have provided preliminary evidence that serum concentrations of the acute-phase marker, sialic acid, were higher in Asian Type II subjects originating from the Indian subcontinent but living in London, United Kingdom, than in a group of Caucasian Type II diabetic patients of similar age, sex distribution, diabetes duration, body mass index and glucose control [69]. Both groups were without diabetic complications. Asian subjects living overseas have a very high frequency of diabetes [70], which may relate to racial differences in the acute-phase response.

Genetic or innate programming of the acute-phase response or both, due, for example, to intrauterine nutrition are discussed further below (Type II diabetes as a maladaptation of the innate immune response).

**Arguments against the hypothesis**

It is clear that diabetes does not develop in all subjects or conditions with a long-term stress response, such as rheumatoid arthritis and inflammatory bowel disease; but, equally, not all those with insulin resistance develop diabetes. Genetic or acquired individual susceptibility to stress may determine the extent of glucose intolerance and reside in many factors including sensitivity to cytokines or acute-phase reactants and variable beta-cell function. It is likely, however, that many subjects with a long-term stress response
have syndrome X, even if they do not have overt diabetes. A number of chronic infections, for example, are linked with heart disease, including Helicobacter pylori, Chlamydia pneumoniae, periodontal disease and chronic bronchial inflammation [71–75]. The highest concentrations of serum C-reactive protein in a survey of general practice patients were associated with the highest glucose concentrations, as well as other indices of the acute-phase response and coronary heart disease [75]. There is no evidence as yet for C. pneumoniae infection in Type II diabetes [76].

It can be argued that acute infections and chronic illness will be more common in Type II diabetic patients than age-matched non-diabetics, and an acute-phase response is to be expected (though it does not occur in age-matched and glycaemia-matched Type I diabetic patients without complications [20]). Our hypothesis is that the cytokine-induced acute-phase response is a pathophysiological mechanism that explains some of the features of Type II diabetes, whatever the cause of the stress response. A stress response does occur in Type I diabetic patients with nephropathy [77], but here the effects are altered by the superimposed biochemical and clinical manifestations of severe insulin deficiency. It remains possible that the acute-phase response contributes to the hypertension, hyperlipidaemia, insulin resistance and atherosclerosis which is seen in these Type I diabetic patients.

**Testing the hypothesis**

Animal models may be helpful in testing some aspects of the model but we believe caution should be exercised with animal studies for several reasons. Firstly, the acute-phase response is notoriously heterogeneous between species [78] (e.g. α2-macroglobulin is an acute-phase protein in rats but not humans). Secondly, disruption of genes in, for example, knock-out studies is usually targeted at one or a few genes, whereas our proposal is that, although Type II diabetes can be seen as an abnormality of a single physiological process (the innate immune defence system), it is a highly complex mixture of many interacting gene products.

Notwithstanding the above, recent studies on the targeted disruption of the TNFα gene in mice are of note [79]. Not only was plasma insulin and glucose reduced in null (−/−) lean and obese (gold thioglucose-induced) mice but so were plasma triglyceride concentrations, confirming a major role for TNFα in insulin sensitivity and triglyceride metabolism. Uysal et al. [80] studied diet-induced obesity in mice with a targeted null mutation of the TNFα gene. At 12 weeks, they observed fasting insulin to be fourfold higher in obese +/+ mice than in −/− mice, but insulin and glucose tolerance tests showed a lower hypoglycaemic response to insulin and greater hyperglycaemia in +/+ mice after they had been given glucose. There were also higher non-esterified fatty acid concentrations in the +/+ obese mice. In genetically obese (ob/ob) mice with mutations of the TNFα receptor, hyperglycaemia and hyperinsulinaemia were reduced in mice lacking the TNFα receptor and thus functional TNFα signalling. These studies show that although TNF is an important contributor to the insulin resistance of obesity, its absence does not completely protect against hyperinsulinaemia, hyperglycaemia and other metabolic abnormalities and confirms that several factors are involved in these disorders.

Several compounds, such as tenidap [81] and interleukin-10 [82] are being tested for their ability to suppress the cytokine-induced response, and many other novel anti-inflammatory agents are under development. When safety and efficacy are better established, it would be appropriate to test the effect of these substances in Type II diabetes.

**Type II diabetes as a maladaptation of the innate immune system**

Our hypothesis views many of the abnormalities of Type II diabetes and impaired glucose tolerance as maladaptations of the normal innate immune system response to environmental threats. It can be speculated that some people are genetically or innately imbued with an increased stress response. Malnutrition in fetal and early post-natal life could provide the metabolic programming for both later Type II diabetes [83] and for setting the innate immune system in general. The association between low birth weight or disproportionate size at birth and subsequently raised blood concentrations of the acute-phase reactants, plasma cortisol and fibrinogen, in adult life, supports this notion [84, 85].

The survival value of most of the components of the stress response, such as enhanced blood clotting and wound repair, is obvious. It is worth emphasising, though, that even raised triglyceride-containing lipoprotein has teleological relevance as it binds and inactivates endotoxin [86].

**Conclusions**

This model for the role of cytokines and the innate immune system in the pathophysiology of Type II diabetes is shown diagrammatically in Fig. 2. Our hypothesis thus suggests that, in addition to possible genetic defects, the causes of the common type of diabetes and glucose intolerance could also (or instead) reside in the effects of long-term lifestyle and environmental stimulants on normal physiology. Genetic
or metabolic propensities programmed in early life may set the magnitude of the subsequent innate immune response to the environment.

Acknowledgements. We are grateful to the Special Trustees of Guy’s Hospital and the BUPA Foundation for financial support.

References

27. Watts GF, Gwilym RM, Makurkiewicz J, Colart J (1995) Independent correlation between plasma lipoprotein(a) and angiographic coronary artery disease in NIDDM. Diabetes Care 18: 234–236
44. Herbert J (1997) Stress, the brain and mental illness. BMJ 315: 530–535