The latter half of the 20th century has witnessed rapid advances in medicine. Concurrently, secular trends in lifestyle practices in our increasingly sedentary society have led to burgeoning rates of obesity, metabolic syndrome, and type 2 diabetes. The number of Americans with type 2 diabetes more than doubled between 1980 and 2004 and the prevalence increases with age. Potential causes of this growing epidemic include changes in dietary patterns, physical inactivity, and obesity but may also include as yet unidentified genetic and environmental determinants. In this regard, experimental data provide evidence for a direct link between obesity and subclinical inflammation and support the concept that the metabolic syndrome and type 2 diabetes are, at least in part, inflammatory conditions. Furthermore, elevated levels of inflammatory biomarkers are not only associated with the development of future diabetes but cardiovascular disease as well. These findings suggest that subclinical inflammation may be a contributing factor not only to the etiology of these metabolic disorders but also their cardiovascular complications.

Key words: inflammation, cytokines, type 2 diabetes, obesity, metabolic syndrome, glucose metabolic disorders, insulin resistance, C-reactive protein, coronary heart disease

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INTRODUCTION

The emerging epidemic of diabetes in the United States and around the world cannot be ignored. According to the World Health Organization, over 180 billion people now have diabetes worldwide, and this number is expected to double by the year 2030.1 In the United States, diabetes affects 19.3 million people (9.3% of the population)2 and is the sixth leading cause of death.3 Similarly alarming is the high prevalence of two factors closely linked with increased risk for diabetes: metabolic syndrome (MetS) and obesity. In the United States today, over 27% of people have MetS, and obesity is estimated to affect approximately one-third of the adult population.4,5 While a number of common factors including genetic predisposition, poor dietary patterns, increased physical inactivity and longer life expectancy6,7 contribute to the rising prevalence of these disorders, subclinical inflammation may represent an additional novel risk factor. In this regard, epidemiologic data suggest that inflammatory biomarkers may serve as important risk indicators for the future development of diabetes.8

INFLAMMATION IS ASSOCIATED WITH INSULIN RESISTANCE

Compelling evidence linking inflammation to insulin resistance derives from both epidemiological studies and experimental data in humans and animal models. It is well known that the prevalence of diabetes, obesity, and MetS all increase with age.2,5 In a cross-sectional study of 70 healthy individuals aged 21–94 years, advancing age was negatively correlated (r=-0.38, P<0.001) with whole-body glucose disposal (WBGD) and positively correlated (r=0.64, P<0.001) with plasma concentrations of tumor necrosis factor-alpha (TNF-α).9 Furthermore, a significant negative association was noted between WBGD and plasma TNF-α, independent of age, sex, body fat, and waist-to-hip ratio.9 In 439 non-diabetic women followed in the Women’s Health Study, fasting insulin was strongly associated with plasma concentrations of tumor necrosis factor-alpha (TNF-α).9 Furthermore, a significant negative association was noted between WBGD and plasma TNF-α, independent of age, sex, body fat, and waist-to-hip ratio.9 In 439 non-diabetic women followed in the Women’s Health Study, fasting insulin was strongly associated with plasma concentrations of the acute-phase reactant C-reactive protein (CRP), with a smaller, non-significant trend for the pro-inflammatory cytokine, interleukin-6 (IL-6).10 Similar findings were noted in the Insulin Resistance Atherosclerosis Study. In an analysis of 1,008 non-diabetic men and women, a strong association was identified between plasma CRP concentration and insulin sensitivity. Furthermore, a linear rise in CRP levels was noted with

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increasing numbers of MetS components (dyslipidemia, abdominal obesity, insulin resistance, hypertension). Using the ATP-III definition of MetS (Table 1), similar results were reported among 14,719 non-diabetic women enrolled in the Women’s Health Study; median CRP concentrations increased from 0.68 mg/L in women with no characteristics of MetS, to 5.75 mg/L in those with five characteristics.

Inflammation is also a corollary of obesity. In recent years, it has rapidly become apparent that obesity is marked by a broad inflammatory response. The first molecular link between obesity and inflammation was elucidated just over a decade ago by Hotamisligil et al. in seminal work demonstrating that the inflammatory cytokine TNF-α is constitutively expressed in adipose tissue and over-expressed in rodent models of obesity. In humans, TNF-α mRNA expression is 2.5-fold higher in adipose tissue extracted from obese individuals relative to lean controls, with a strong correlation between TNF-α mRNA expression and hyperinsulinemia. Body weight reduction in obese individuals is also associated with a reduction in both TNF-α mRNA expression and in improved insulin sensitivity. Interestingly, TNF-α expression in obese adipose tissue may originate from macrophage infiltration rather than adipocytes themselves.

Macrophages comprise a significant fraction of the stromovascular compartment in adipose tissue and macrophage accumulation in obesity appears to contribute substantially to gene expression. Whether this inflammatory infiltrate is central to the development of obesity-mediated insulin resistance remains uncertain. In this regard, Xu et al. found that upregulation of murine macrophage-specific inflammatory genes within adipose tissue precedes the dramatic rise in plasma insulin levels in high-fat-diet-induced obesity. These investigators also demonstrated downregulation of macrophage-derived genes upon treatment with rosiglitazone, an insulin-sensitizing peroxisome proliferators-activated receptor (PPAR) agonist. Finally, in support of a direct role for inflammation in the development of insulin resistance, in vivo inhibition of TNF-α in obese rats significantly improved insulin sensitivity (although insulin resistance was not completely reversed). At the cellular level, the JNK (Jun N-terminal kinase) and IKKβ/NF-κB (Ikappa B kinase beta/nuclear factor kappaB) pathways are implicated in the development of insulin resistance, and can be activated by a number of trans-cellular pro-inflammatory receptors, including those for TNF-α, interleukin-1 (IL-1), and Toll and advanced glycation end-product (AGE) receptors (Figure 1), providing further evidence for the role of inflammation in insulin resistance.

**Table 1. Clinical identification of the metabolic syndrome, according the ATP III definition.** At least three risk factors must be present for a diagnosis to be made.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>≥40 inches (102 cm) in men</td>
</tr>
<tr>
<td></td>
<td>≥35 inches (88 cm) in women</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;40 mg/dL in men</td>
</tr>
<tr>
<td></td>
<td>&lt;50 mg/dL in women</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol

Subclinical inflammation, detectable by measurement of plasma-based inflammatory biomarkers has also been implicated in the development of diabetes. In a prospective nested case-control study involving participants in the Women’s Health Study who were non-diabetic on entry, baseline concentrations of CRP and IL-6 were significantly higher in the 188 women who developed diabetes over the four-year study than in the 362 matched controls. The multivariable-adjusted relative risk of developing diabetes in the highest versus lowest quartiles of these inflammatory markers was 2.3 for IL-6 (95% CI, 0.9 –5.6; P for trend, 0.07) and 4.2 for CRP (95% CI, 1.5–12.0; P for trend, 0.001). Analyses were adjusted for body mass index (BMI), family history of diabetes, smoking, exercise, use of alcohol, and hormone replacement therapy (HRT).

In the Insulin Resistance Atherosclerosis Study of 1,047 non-diabetic individuals, elevated levels of fibrinogen, CRP, and plasminogen activator inhibitor-1 (PAI-1) were shown to predict the development of diabetes over the five-year study period. Plasminogen activator inhibitor-1 was the strongest predictor in adjusted models. A subsequent analysis from this study revealed that in addition to high baseline levels of PAI-1, progressive PAI-1 elevation over time is also significantly related to incident diabetes, with change in PAI-1 levels correlating with rising glucose concentrations.

Given the significance of macrophage migration and accumulation in adipose tissue for the development of insulin resistance, markers of cellular adhesion and endothelial function have been studied as risk markers for diabetes. In a recent prospective nested case-control study involving 737 participants in the Nurses’ Health Study who were non-diabetic at baseline but who developed diabetes over 10 years of follow-up, and 785 age-matched controls, those who developed diabetes had higher baseline concentrations of E-selectin, intercellular
adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). In models adjusting for BMI, family history of diabetes, smoking, alcohol, diet score, physical activity, postmenopausal HRT, and CRP, as well as each adhesion molecule, the relative risks of developing diabetes for the top versus the bottom quintiles were 5.4 for E-selectin (95% CI, 3.5–8.5) and 3.5 for ICAM-1 (95% CI, 2.28–5.58). VCAM-1 was not a significant predictor associated with incident diabetes.21

In addition to these studies, a number of others have confirmed that indicators of subclinical inflammation can be used to predict incident diabetes.18,19,22–26 Most of these have assessed CRP as the indicator of inflammation,18,23–26 but IL-6,25 white blood cell count,22 and PAI-119 have also demonstrated a positive relationship with risk of diabetes. Together, these epidemiologic data along with experimental findings noted above support a role for subclinical inflammation in diabeticogenesis.

SUBCLINICAL INFLAMMATION IS ASSOCIATED WITH INCREASED CARDIOVASCULAR RISK IN IMPAIRED INSULIN SENSITIVITY

A major concern in the current epidemic of diabetes is its impact on cardiovascular disease (CVD). According to the American Heart Association, heart disease and stroke account for over 65% of deaths in people with diabetes,27 and adults with diabetes have a two- to four-fold higher risk of CVD compared with the non-diabetic population.28 The public health impact of these statistics was highlighted in an analysis of New York death certificate data between 1990 and 2000. The intervening decade was marked by decreases in age-adjusted all-cause and CVD mortality, stroke, and acute myocardial infarction (MI). Over the same period, however, diabetes-related mortality increased from 30.5 to 49.1 per 100,000 population.29 Hospitalization rates for acute MI remained constant over this period, but this masked a significant increase (from 186 to 286 per 100,000 population) among people with diabetes, which was offset by a reduction in incidence among the non-diabetic population.29

Subclinical inflammation increases the risk of CVD in both the MetS and overt diabetes. In an analysis of 3,097 participants in the Women’s Health Study who met the ATP-III criteria for MetS,12 those with plasma CRP concentrations >3 mg/L were at significantly greater risk for CVD than those with CRP concentrations <1 mg/L (odds ratio [OR], 2.1; 95% CI, 1.3–3.3; P = 0.001).13 Using a slightly different definition of MetS, similar results were reported in 5,974 men in the West of Scotland Coronary Prevention Study, including a cohort of 1,691 men with MetS at baseline.30 Over a six-year follow-up period, the probability of a coronary heart disease (CHD) event was greatest in individuals with MetS and elevated CRP levels (>3 mg/L), followed by those with either MetS or elevated CRP levels, and lowest in individuals without MetS and normal CRP levels (<3 mg/L).30 This study also confirmed elevated CRP as a significant predictor of incident diabetes in subjects with MetS.30

A cross-sectional study of 3,873 participants in the 1999–2000 National Health and Nutrition Examination Survey also confirmed that CRP concentration increases with CVD rates in people with MetS, and these findings extended to those with diabetes (Figure 2).31 Cardiovascular disease prevalence increased according to risk group from no diabetes or MetS, to MetS and diagnosed diabetes. Within groups, increasing CRP concentrations were also associated with prevalent CVD, so individuals with both diabetes and high levels of CRP (>3 mg/L) had a nearly eight-fold higher prevalence of CVD (OR, 7.73; 95% CI, 3.99–14.95) than those with low CRP.
concentrations and no diabetes. Interestingly, the presence of diabetes and low CRP concentration (<1 mg/L) conferred similar odds for CVD prevalence (OR, 3.21; 95% CI, 1.27–8.09) to MetS and high CRP levels (OR, 3.33; 95% CI, 1.80–6.16). These findings have been confirmed in longitudinal studies. In a cohort of 1,045 Finnish men with diabetes, the CHD mortality rate was about 1.6-fold higher in patients with elevated CRP concentrations (>3 mg/L) at baseline over a seven-year follow-up period. Results were similar if those subjects who had a prior MI at baseline were excluded. Elevated levels of another inflammatory marker, soluble TNF-α receptor II (sTNF-RII), were also found to predict CHD events in a study of 929 women with diabetes from the Nurses’ Health Study. Over a 10-year follow-up period, multivariate analyses demonstrated a two-fold increased risk of CHD in individuals in the highest quartile of sTNF-RII concentrations compared to those in the lowest quartile (P=0.011). Taken as a whole, these data provide strong associative evidence supporting subclinical inflammation as a unifying factor accelerating the progression of both insulin resistance and CVD.

CONCLUSIONS

Inflammation sits at the convergence of two major public health issues: the triumvirate of diabetes, obesity, and the metabolic syndrome, and the development of CVD. Inflammatory biomarker concentrations are increased along with raised fasting glucose levels, diminished insulin action, obesity, and the metabolic syndrome. Experimental data provides compelling support for inflammation as a contributor to insulin resistance, and provides insights into the underlying molecular pathways. Emerging clinical data suggest that inflammation precedes development of clinically overt diabetes, and is also an important predictor of the subsequent cardiovascular events. While further research is required, the role of inflammation as an etiologic determinant of glucose metabolic disorders may offer additional methods both for risk assessment and diagnosis and may prove a novel target for therapeutic intervention.

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