Prolonged low-grade inflammation may ultimately lead to the clinical expression of type 2 diabetes. Such a systemic and subclinical inflammatory process can be characterized by elevated circulating levels of inflammatory cytokines including C-reactive protein (CRP) or high-sensitivity CRP (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha). Various mechanisms have been indicated by which these cytokines can contribute to the development of type 2 diabetes. For example, these cytokines can directly inhibit insulin receptor signaling by activating c-Jun amino-terminal kinase and an inhibitor of nuclear factor kappa-beta kinase, leading to serine phosphorylation of insulin receptor substrate-1.2 In addition, these cytokines have been shown to promote hepatic fatty acid syntheses and induce the liver to produce more acute-phase proteins, as well as recruit more inflammatory cells to adipose tissue and pancreatic beta-cells.3 Therefore, inflammatory cytokines not only affect insulin resistance but may also contribute directly to beta-cell apoptosis and beta-cell failure, ultimately leading to type 2 diabetes. These cytokines are a part of a family of adipose-derived cytokines, also called adipokines, and may be the link between obesity and type 2 diabetes.

The role of inflammatory cytokines in coronary artery disease and atherosclerosis is now better established.4 The following discussion focuses on recent findings from prospective studies of diverse populations that support a role of these inflammatory cytokines in the clinical expression of type 2 diabetes. Because current treatments available for type 2 diabetes do not specifically target the inflammatory process, we also discuss how these available treatments may work by mediating this process of systemic inflammation. The flow chart in Figure 1 illustrates human biochemistry.

**TNF-ALPHA**

The link between obesity, inflammation, and diabetes was first demonstrated when TNF-alpha was found to be overexpressed in the adipose tissue of obese rats, and neutralization of TNF-alpha was associated with increased peripheral insulin sensitivity in these animals.5 Subsequently, cross-sectional studies have found that TNF-alpha is associated with obesity and insulin resistance in various clinical populations. Higher serum TNF-alpha levels correlated with increased insulin resistance in an older, nondiabetic population.6 Obese adolescents (mean body mass index [BMI], 29 kg/m²) were found to have higher serum TNF-alpha levels compared with nonobese adolescents.7 Likewise, higher serum TNF-alpha levels were correlated with decreased insulin sensitivity in a healthy, middle-aged, white population.8 The reduction of insulin resistance by treatment with TNF-alpha antagonists in other inflammatory conditions, such as rheumatoid arthritis, further supports a role of TNF-alpha in the development of type 2 dia-

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**Role of Inflammatory Cytokines in Type 2 Diabetes**

Current evidence shows that inflammatory cytokines play a role in the pathogenesis of diabetes and that inflammation measurement may increase diabetes risk prediction.

BY CATHY C. LEE, MD, MS; AND SIMIN LIU, MD ScD

These inflammatory cytokines are a part of a family of adipose-derived cytokines, called adipokines, and may be the link between obesity and type 2 diabetes.
Prospective data directly linking TNF-alpha to diabetes risk, however, are scarce. One previous study found that elevated levels of TNF-alpha were associated with increased diabetes risk but were not independent of obesity as measured by BMI and waist-hip ratio. In a small study of Pima Indians, TNF-alpha was not related to diabetes risk. Liu et al observed a moderately increased diabetes risk associated with elevated levels of soluble TNF-alpha receptor 2, although this association was no longer significant when simultaneously adjusted for high-sensitivity CRP and IL-6.

SERUM IL-6 LEVELS

Serum IL-6 levels have also been found to be associated with insulin resistance and diabetes. In nondiabetic older populations and healthy, middle-aged, white populations, higher serum IL-6 levels correlated with increased insulin resistance. In individuals with impaired glucose tolerance, type 2 diabetes, or the metabolic syndrome, serum IL-6 levels were also found to be higher compared with those with normal glucose tolerance or those who did not meet the criteria for the metabolic syndrome. Liu et al recently reported that elevated IL-6 levels are also associated with an increased risk of clinical diabetes in a large prospective study of postmenopausal women who participated in the WHI (Women’s Health Initiative) in the United States.

HIGH-SENSITIVITY CRP

TNF-alpha and IL-6 are the major regulatory cytokines for human CRP. CRP is perhaps the most common serum marker of inflammation. Recent prospective studies have reported that elevated CRP levels predict the development of type 2 diabetes. This association has been shown to be present but attenuated by measures of obesity in other studies. In addition to these findings in both genders and different age groups, Liu et al recently reported that hs-CRP is significantly associated with increased diabetes risk in different ethnic groups, including white, black, Hispanic, and Asians/Pacific Islander groups. As the principal downstream mediator of the acute-phase response, hs-CRP may account for the integrated effects of both TNF-alpha and IL-6.

INFLAMMATION TREATMENT FOR DIABETES PREVENTION?

If systemic inflammation is causally linked to diabetes development, antinflammatory treatment would seemingly be beneficial. One recent study specifically targeted another proinflammatory cytokine, IL-1b, which has been implicated in beta-cell apoptosis in patients with type 1 diabetes. Treatment with an IL-1 receptor antagonist was found to decrease levels of IL-6 and CRP, however, these reduced levels did not appear to be involved in improved insulin secretion. Otherwise, few pharmaceuticals currently available for the treatment of type 2 diabetes specifically target inflammation, although various interventions aimed at preventing diabetes have been found to have antiinflammatory properties. These include sodium salicylates, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, angiotensin-converting enzyme (ACE) inhibitors, peroxisome proliferators-activated receptor gamma (PPAR-gamma) agonists, and lifestyle interventions aiming for weight loss.

Salicylates have long been known to lower blood glucose concentrations and were recently shown by Yuan et al to specifically inhibit I kappa B kinase-beta, a master controller of the inflammatory process cascade, and to reverse insulin resistance in rodents. Most evidence in human studies of the effect of HMG-CoA reductase inhibitors in type 2 diabetes has implicated their effect on CRP. In the PRINCE (Pravastatin Inflammation/CRP Evaluation) trial, pravastatin (Pravachol; Bristol-Myers Squibb, New York, NY) therapy significantly reduced CRP levels independent of its effect on serum LDL cholesterol. In the WOSCOPS (West of Scotland Coronary Prevention Study), therapy with pravastatin was noted to decrease the risk of diabetes in a middle-aged male cohort. The effect of ACE inhibition and angiotensin II receptor blockade on inflammation was recently reviewed by Dandona et al. There have been multiple studies demonstrating that therapy with different ACE inhibitors can decrease CRP, IL-6, and TNF-alpha. It has been postulated that this antiinflammatory effect of ACE inhibitors, particularly ramipril and captopril, contributes to their effect in reducing the development of new diabetes cases in high-risk vascular patients.
PPAR-gamma agonists have also been noted to have pleiotropic effects, two of which are to decrease the levels of TNF-alpha and CRP. In a recent animal study, the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone (Avandia; GlaxoSmithKline, Philadelphia) also had an effect to increase beta-cell mass. Finally, nonmedication lifestyle interventions, including exercise and weight loss, well known to reduce all-cause mortality, have also been shown to decrease CRP levels. These observations offer insights into the therapeutic potential of targeting systemic inflammation for prevention and/or treatment of insulin resistance and clinical type 2 diabetes.

CONCLUSION

Current evidence strongly supports the idea that inflammatory cytokines play some role in the pathogenesis of diabetes. Further studies are needed to determine if some measurement of inflammation would add to the risk prediction for diabetes to target individuals for early aggressive intervention. In addition, more prospective trials are needed to further evaluate whether a decrease in inflammation as measured by a decrease in inflammatory cytokines leads to a reduction in the incidence of type 2 diabetes consistently in diverse populations.

Cathy C. Lee, MD, MS, is from the Research Service and GRECC, VA Greater Los Angeles Healthcare System, and is in the Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA. Simin Liu, MD, ScD, is from the Program on Genomics and Nutrition, Department of Epidemiology, UCLA School of Public Health, and the Department of Medicine at UCLA, Los Angeles, CA. Dr. Lee may be reached at cathy.c.lee@ucla.edu or phone: 310-268-4110.