Since the proposal of insulin resistance by Professor Reaven about 30 years ago, it has been well known that individuals with insulin resistance are at greatly increased risk of having a combination of atherosclerosis risk factors, including glucose intolerance or diabetes, dyslipidemia characterized by elevated triglyceride, low high-density lipoprotein (HDL) cholesterol concentrations, and hypertension.\(^1,2\) In addition, it has been demonstrated that insulin resistance can also predispose an individual to the development of several other chronic diseases such as coronary artery disease, nonalcoholic fatty liver disease, polycystic ovary syndrome, hypothyroidism, and possibly several forms of cancer.\(^3,4\) In view of the great impact of the described disorders on human health, an understanding of the pathogenesis of insulin resistance is of prime importance.

**Inflammatory Hypothesis**

It is believed that ancient human beings developed several mechanisms to promote the accumulation of fat tissue during periods of feasting to enable their survival during periods of famine. As a consequence, if this human gene pool, adapted to a pre-agricultural hunter–gatherer lifestyle, still persists, then the current environment of readily available high-energy foods and little physical activity would result in an epidemic of obesity, which is an important contributor of insulin resistance, thus promoting the development of type 2 diabetes.\(^5\) In 1993, Hotamisligil reported a landmark study in which tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) was shown to be hyperexpressed in adipose tissue in obese animals, and to mediate their insulin resistance.\(^6\) Subsequently, several other proinflammatory cytokines were also found to be produced in adipose tissue, including interleukin (IL)-1, IL-6, IL-10, IL-18, etc., and all these cytokines can exert potential negative or positive effects on insulin sensitivity.\(^7\) It has been shown in \textit{in vitro} studies that the inflammatory cytokines can lead to activation of some transcription factors, such as nuclear factor (NF)-\(\kappa\)B and activation protein-1 (AP-1), and their key enzymes I\(\kappa\)B kinase (IKK) and c-Jun NH\(_2\)-terminal kinase (JNK), respectively, and ultimately result in suppression of insulin signal transduction by serine/threonine (Ser/Thr) phosphorylation (inactivation) of the insulin receptor substrate (IRS).\(^5,6\) On the contrary, animals with a genetic knockout of the IKK and JNK genes are protected from insulin resistance in spite of high-fat feeding.\(^5,6\) Notably, these adipose-derived pro-inflammatory cytokines, in addition to exerting an effect on insulin sensitivity through a paracrine fashion, can also have peripheral effects in an endocrine manner on the immune and hemostatic system, such as elevation of \(\gamma\)-globulin concentration, white blood cell (WBC) count, C-reactive protein (CRP), ferritin, and fibrinogen levels.\(^5\) Clinically, several cross-sectional studies in nondiabetic subjects, or in individuals with impaired fasting glucose or impaired glucose tolerance, have shown that acute-phase reactants (e.g. high sensitive CRP), serum TNF-\(\alpha\), and IL-6 levels are positively correlated with insulin resistance, body mass index/waist circumference, and circulating triglyceride and negatively with HDL cholesterol concentration.\(^8\) In diabetic patients, circulating CRP and IL-6 levels are also elevated compared with those in nondiabetic controls, and have a positive relationship with the homeostasis model-measured insulin resistance.\(^8\) Moreover, many prospective studies have confirmed the roles of proinflammatory cytokines, acute-phase proteins, and several indirect markers of inflammation.
including WBC count, CRP, IL-6, fibrinogen, etc., as predictors of type 2 diabetes independent of their adiposity or upper fat distribution.\(^8\)

**The Inflammatory Response: Cause or Consequence of Insulin Resistance?**

Insulin has been shown to suppress several proinflammatory transcription factors, such as NF-κB, Egr-1 and AP-1, and the corresponding genes regulated by them, which mediate inflammation in mononuclear cells.\(^9\) Therefore, an impairment of the action of insulin (insulin resistance) may also possibly lead to activation of these proinflammatory transcription factors and an increase in the expression of the corresponding genes. In this issue of the *Journal of the Chinese Medical Association*, Chen et al\(^10\) report an association between insulin resistance index (measured by the homeostasis model assessment) and WBC count in a Taiwan community-based population. Their findings are consistent with those of several previous studies carried out in the US, Europe and other Asian countries.\(^11\) After an adjustment of body mass index, subjects with WBC count > 7,190/mm\(^3\) still had a 3-fold odds ratio of having an increased insulin resistance index compared with those with WBC count < 4,960/mm\(^3\), providing a further hypothetical link between inflammation and insulin resistance. Yet, their report is subject to criticism. Although the homeostasis model assessment of insulin resistance (HOMA) is currently widely used in large-scale studies, its accuracy and the cutoff values chosen remain controversial.\(^12\) In addition, all the diabetic individuals enrolled in their analysis had insulin resistance, thus making it very difficult to isolate the effects of insulin resistance in those subjects, let alone oral hypoglycemic agents used, which might also interfere with values of HOMA insulin resistance. Furthermore, a definite causality between insulin resistance and WBC count could not be drawn from this cross-sectional study. It was possible that the hormonal change associated with insulin resistance (i.e. cortisol, sex hormone, insulin) might be another possible link, because these hormonal alterations, usually observed in the insulin-resistant state, can stimulate proliferation of the myeloid cells in the bone marrow.\(^13\) Also, the study by Chen et al\(^10\) was performed in a cross-section of individuals with normal and impaired fasting glucose and diabetes mellitus, who showed a broad range of blood glucose levels. Whether or not the association between WBC count and insulin resistance index was secondary to hyperglycemia itself was not determined, because high blood glucose levels can stimulate inflammation, or even cause cardiovascular disease, which, in consequence, increases the circulating WBC.\(^9\) In addition, Chen et al’s study\(^10\) did not show any association between 2 other hematologic parameters, red blood cell (RBC) and platelet counts, and insulin resistance, although a previous study had reported a positive association.\(^14\) Probably, body iron store (i.e. by measuring ferritin level) and coagulation status (i.e. by measuring fibrinogen or plasminogen activator inhibitor levels) rather than total RBC and platelet numbers are more reliable surrogates to link inflammation and insulin resistance.\(^11,15\)

**Origin of Inflammation**

It has been thought that adipocytes are the main focus to generate inflammatory mediators.\(^7\) However, adipose tissue is not only composed of adipocytes but also contains the so-called stromal–vascular fraction consisting of endothelial cells, cells characteristic of progenitor cells, and leukocytes.\(^8\) Several experiments in fat reported that the majority of the adipose tissue-derived cytokines originated from the nonfat cells (with the notable exception of leptin and adiponectin).\(^6\) In this regard, recent attention has been focused on the potential role of macrophages in the process. It has been shown that in obese subjects, adipose tissue contains an increased number of resident macrophages (even greater than 40% of the total cell population in some circumstances).\(^6,16\) It is obvious that the infiltrating macrophages in the adipose tissue are a potential source of secreted proinflammatory factors, and a correlation was observed between the number of macrophages and body mass index, adipocyte size, body fat, and systemic insulin resistance. Moreover, the circulating mononuclear cells, a precursor of tissue macrophages, in obese individuals, have also been shown to be in an inflammatory state, expressing increased amounts of proinflammatory cytokines and related factors.\(^6,9\) If, indeed, inflammation interferes with insulin signal transduction, then what is the origin of firing peripheral mononuclear cell activation or macrophage recruitment adipose tissue? It has been proposed that several factors, including genetic factors, environmental factors, nutrition, age, and stress, may all be responsible for this process.\(^5,6\) For example, specific polymorphism of TNF-α gene promoter, TNF-α receptor gene, and IL-6 gene are variously associated with insulin insensitivity. Regarding nutrition, many dietary factors may contribute to the inflammatory response, including the effect of fat, and
the n3:n6 fatty acid ratio in cytokine production. In addition, the production of cytokines from monocytes and macrophages can also increase with aging and life stress.\textsuperscript{5,6,8,9}

\textbf{Clinical Implication}

To date, several clinical studies utilizing agents with potential anti-inflammatory effects, including aspirin, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and statins, have demonstrated that these drugs can improve insulin resistance to some degree and, thus, decrease the risk of type 2 diabetes. In addition, the two available insulin sensitizers, thiazolidinediones and metformin, have been shown to have anti-inflammatory effects in addition to their glucose-lowering effect in diabetic patients. Finally, it should also not be forgotten that lifestyle change by weight reduction, diet modification, and exercise can improve inflammation.\textsuperscript{9,17}

\textbf{Conclusion}

In recent years, several studies have clearly demonstrated that subclinical inflammation is an important pathogenetic factor in the development of insulin resistance. This may hold new promise for early diagnosis or treatment of insulin resistance. With an increased understanding of the chain of molecular events linking inflammation to impairment of insulin signaling, novel targets can be made available for drug development that may form a basis against the epidemic of insulin resistance and its related disorders.

\textbf{References}