Letter to the Editor

Combined Influence of Insulin Resistance and Inflammatory Biomarkers on Type 2 Diabetes: A Population-based Prospective Cohort Study of Inner Mongolians in China*

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This prospective study was designed to examine the combined influence of insulin resistance (IR) and inflammatory biomarker levels on type 2 diabetes mellitus (T2DM) among 1,903 Inner Mongolians. During follow-up, 205 (10.77%) participants developed T2DM, and the incidence of T2DM was higher among subjects with IR, elevated C-reactive protein (CRP), elevated sICAM-1, elevated sE-selectin, or the coexistences of IR with elevated CRP, elevated sICAM-1, elevated sE-selectin, and elevated angiotensin II (all $P < 0.05$) compared with patients without IR or any elevated biomarkers. In multivariate analysis, the odd ratios [*OR*, (95% confidence intervals)] for these conditions were 1.944 (1.405-2.691), 2.003 (1.449-2.767), 1.706 (1.232-2.362), 1.560 (1.123-2.165), 2.708 (1.809-4.054), 1.885 (1.155-3.078), 2.101 (1.340-3.295), and 2.260 (1.426-3.582), respectively. Our findings demonstrated that IR and elevated inflammatory biomarkers were associated with T2DM, and that the coexistence of IR and elevated inflammatory biomarkers increased the risk of T2DM.

Type 2 diabetes mellitus (T2DM) is a major worldwide public health problem. T2DM rates have rapidly risen in China over the last few decades, increasing disease burden. Previous studies have shown that insulin resistance (IR) is a risk factor for T2DM[1]. It is also generally accepted that chronic low-grade inflammation may play an important role in IR pathogenesis; thus, increased levels of inflammatory markers might predict future T2DM development[2]. Endothelial progenitor cells are important for maintaining normal endothelial function and vascular repair in T2DM patients, especially for reducing the peripheral vascular complications of T2DM[3]. In contrast, endothelial dysfunction aggravates glycaemia during the diabetic phase. Additionally, the coexistence of IR and inflammation can predict cardiac disease among T2DM patients[4]; however, few studies have evaluated the combined influence of IR, inflammation biomarkers and endothelial dysfunction on T2DM development. In this study, we examined the combined influence of inflammatory biomarkers [circulating C-reactive protein (CRP), soluble intercellular cell adhesion molecule-1 (sICAM-1), soluble E-selectin (sE-selectin) and angiotensin II], endothelial dysfunction, and IR on T2DM among Inner Mongolians.

This prospective cohort study was conducted from 2002 to 2013 in 32 villages of two adjacent townships, Kezuohou banner (country) and Naiman banner, Inner Mongolia, China. The methods for participant recruitment and baseline data collection have been described elsewhere. Briefly, 2,589 Mongolians ≥ 20-years-old were recruited from Inner Mongolia. All participants signed informed consent and completed a baseline questionnaire. Individuals with cardiovascular diseases, endocrine diseases, infectious diseases within the last 2 weeks and antihypertensive drug users were excluded. Additionally, 94 T2DM patients and 36 individuals without complete key variables were excluded. Finally, 2,459 Mongolians who have lived in this region for many generations and maintained a

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traditional diet and lifestyle, were included at baseline. This study was approved by the Soochow University Ethics Committee (Suzhou, China).

A standard questionnaire was administered by trained staff to obtain demographic information, personal characteristics, lifestyle risk factors and personal medical histories. Cigarette smoking was defined as having at least one cigarette per day for 1 year or more. Alcohol drinking was defined as having consumed at least 50 g alcohol per day for 1 year or more. Each subject's height and weight were measured while wearing light clothing and without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference was measured at a level 1 cm above the umbilicus. Blood pressure was measured using a standard mercury sphygmomanometer according to standard protocols. A fasting condition of at least 10 h was required for all subjects before blood samples were collected for laboratory examinations. Plasma glucose was measured using a modified hexokinase enzymatic assay. Total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) concentrations were analyzed enzymatically on a Beckman Synchrony CX5 Delta Clinical System (Beckman Coulter, Fullerton, CA, USA) using commercial reagents. Low-density lipoprotein cholesterol (LDL-C) concentrations were calculated using the Friedewald equation. Serum insulin was measured using a radioimmunoassay method, and the homeostasis model assessment (HOMA) index was calculated by the following formula: HOMA-IR = fasting insulin (mU/L) × fasting glucose (mmol/L) ÷ 22.5. Subjects with IR were defined as a HOMA-IR ≥ 75th percentile (≥ 3.28). The CRP concentration was measured by immunoturbidimetry on a Beckman Synchrony CX5 Delta Clinical System using commercial reagents. sICAM-1 and sE-selectin were measured with an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA) that employed the quantitative sandwich enzyme immunoassay technique. Angiotensin II was measured with a double antibody radioimmunoassay. Elevated CRP, sICAM-1, sE-selectin and angiotensin II were defined as 10.64 mg/L or greater, 391.14 ng/mL or greater, 24.17 ng/mL or greater, and 68.90 pg/mL or greater (the upper quartile), respectively.

For follow-up, the study population was re-investigated from 2013 to 2014. After an overnight fast of at least 10 h, fasting plasma glucose was measured using the same hexokinase assay within 24 h. Participants without a history of T2DM were instructed to maintain their usual physical activity and diet at least 3 d before the oral glucose-test. All participants were given a standard 75-g glucose solution and required to drink it within 5 min; plasma glucose was measured 2 h after administering the during the oral glucose tolerance test. Incident T2DM was defined based on the 1999 World Health Organization criteria (≥ 7.0 mmol/L fasting or ≥ 11.1 mmol/L 2-h glucose) or validated physician diagnosis or the use of antidiabetic medication at any investigation or diagnosed as T2DM in medical records or death certificates.

Continuous variables that showed a normal distribution were expressed as means ± standard deviations or medians (quartile intervals) for variables with non-normal distribution. Differences between groups were analyzed with independent *t* test (for continuous variables), Wilcoxon rank test (for non-normally distributed variables), or chi-squared test (for proportions). Unconditional logistic regression was used to evaluate the association of T2DM with IR, elevated inflammatory biomarkers, endothelial dysfunction, and for the coexistence of IR and elevated inflammatory biomarkers. Age, gender, systolic blood pressure, diastolic blood pressure, smoking, drinking, waistline, TC, TG and HDL-C were used as adjustments for repeating the analyses. All statistical analyses were performed with SAS 9.2 statistical software (SAS Institute, Cary, NC, USA), all *P* values were two-tailed, and the statistical significance was set at $P < 0.05$.

Among the 2,459 participants, 1,903 participated in the follow-up, 274 were deceased, and 282 were lost to follow-up. The mean follow-up period was 10.48 years, and a total of 19,402 person-years were observed. There were 205 (10.77%) cases of incident T2DM during follow-up.

Table 1 shows the baseline characteristics of subjects stratified into two groups: non-T2DM at follow-up (reference group) and T2DM at follow-up. Compared with the reference group, subjects with T2DM were more likely to be older, and have higher drinking rates, systolic blood pressure, diastolic blood pressure, BMI, waist circumference, fasting plasma glucose, LDL-C, HDL-C, TC, TG, HOMA-IR, CRP, sICAM-1, and sE-selectin. There were no significant differences in gender, smoking or angiotensin II.

Figure 1 presents the incidence of T2DM according to IR, inflammatory biomarkers, and endothelial dysfunction. Compared with patients without IR or