Heterogeneity of Altered Cytokine Levels Across the Clinical Spectrum of Diabetes in China

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OBJECTIVE—To determine the relationship between selected cytokines and diabetes in Chinese subjects.

RESEARCH DESIGN AND METHODS—Adult patients with recent-onset type 1 diabetes (n = 53), latent autoimmune diabetes in adults (LADA) (n = 250), and type 2 diabetes (n = 285) from multiple centers were compared with normal subjects (n = 196). We centrally tested serum GAD antibodies (GADAs), interleukin-6 (IL-6), lipocanl 2 (LCN2), high-sensitivity C-reactive protein (hs-CRP), and adiponectin.

RESULTS—After adjustment for age, sex, and BMI, all diabetes types had increased IL-6 and LCN2 (P < 0.01), and all four cytokines were increased in LADA (P < 0.01). In type 1 diabetes, adiponectin but not hs-CRP was increased (P < 0.01), whereas in type 2 diabetes, hs-CRP but not adiponectin was increased (P < 0.01). Adiponectin was correlated positively with GADA titer and negatively with hs-CRP (P < 0.01 for both).

CONCLUSIONS—In China, inflammatory markers are increased in all three major types of diabetes—even in autoimmune diabetes—but probably for different reasons.

Statistical analysis
We used SPSS (version 13; SPSS, Chicago, IL) for statistical analysis. Data are expressed when normally distributed as means ± SD and when skewed as median (25th–75th percentiles). Logarithmic transformations were applied on non-normally distributed parameters before comparison. Frequency differences were compared using χ² test. Variance analysis compared means by one-way ANOVA as
RESULTS—Results are shown in Supplementary Table 1. Of 784 subjects, patients with both LADA and type 2 diabetes were significantly older than subjects with normal glucose tolerance or type 1 diabetic patients. As expected, LADA patients had lower insulin secretion than type 2 diabetic patients, while in type 1 diabetic patients, insulin secretion was lower than in both LADA and type 2 diabetic patients. Metabolic syndrome in type 1 diabetic and control subjects was less frequent than in type 1 diabetic patients, while in type 1 diabetic patients, insulin secretion was lower than in control subjects and highest in type 2 diabetes (5). However, hs-CRP was increased in both LADA and type 2 diabetes, but not type 1 diabetes, while adiponectin was only increased in LADA and type 1 diabetes. Despite adiponectin being positively correlated with GADA titer, it has no established role in autoimmune diabetes and certainly cannot predict it (12). However, low-grade inflammation could be important in autoimmunity, potentially explaining any benefit of rosiglitazone (13). Indeed, each cytokine (IL-6, LCN2, hs-CRP, and adiponectin) was increased in Chinese LADA, though probably for different reasons (14). Given the relative lack of obesity in China, comparative Chinese and European studies could delineate the relative roles of obesity, diabetes, and autoimmunity on cytokines. Surprisingly, therefore, metabolic syndrome was prevalent in this large LADA cohort, in contrast to European studies (5,6). These results point toward a complex relationship between diabetes types and altered cytokine levels.

CONCLUSIONS—Some inflammatory markers were increased in diabetes (i.e., IL-6 and LCN2) irrespective of diabetes type, implying that cytokine changes are secondary features of the disease independent of obesity, and consistent with a proinflammatory effect in diabetes in general. Nevertheless, obesity (waist-to-hip ratio) was associated with all four cytokines assayed, and the pattern of cytokine changes differed according to diabetes type.

Cytokines (IL-6, TNFα, and IL-1 receptor antagonist) in Europeans with these same major diabetes types were also positively associated with BMI, which was higher in diabetic patients than in control subjects and highest in type 2 diabetes but similar in LADA and type 1 diabetes; after correction, only TNFα in LADA and type 1 diabetes was no longer different from that in control subjects (5). In both the European study and this Chinese study, IL-6 showed remarkably similar increases in major diabetes types; IL-6, as well as LCN2, levels were higher than in control subjects and highest in type 2 diabetes (5). However, hs-CRP was increased in both LADA and type 2 diabetes, but not type 1 diabetes, while adiponectin was only increased in LADA and type 1 diabetes. Despite adiponectin being positively correlated with GADA titer, it has no established role in autoimmune diabetes and certainly cannot predict it (12). However, low-grade inflammation could be important in autoimmunity, potentially explaining any benefit of rosiglitazone (13). Indeed, each cytokine (IL-6, LCN2, hs-CRP, and adiponectin) was increased in Chinese LADA, though probably for different reasons (14). Given the relative lack of obesity in China, comparative Chinese and European studies could delineate the relative roles of obesity, diabetes, and autoimmunity on cytokines. Surprisingly, therefore, metabolic syndrome was prevalent in this large LADA cohort, in contrast to European studies (5,6). These results point toward a complex relationship between diabetes types and altered cytokine levels.
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References