Dear Editor,

Impaired insulin secretion and insulin resistance are the two main mechanisms that lead to type 2 diabetes mellitus (T2DM). Insulin resistance associated with innate immune system is known to be triggered by the activation of pattern-recognition receptors (PRRs) (Olefsky and Glass, 2010). Recently, our research group showed that serum ficolin-3, a kind of soluble PRR within the lectin pathway varied significantly between individuals with normal glucose tolerance (NGT) and those with T2DM (Li et al., 2008).

Here we performed a human cross-sectional study and a prospective study to investigate whether serum ficolin-3 levels associate with insulin resistance and predict the incidence of T2DM.

In the cross-sectional study, in which 170 had NGT and 95 had T2DM without any diabetic complications, we found that serum ficolin-3 in the T2DM group was significantly lower than that in the NGT group and multiple linear stepwise regression analyses revealed that serum ficolin-3 was independently correlated with high-density lipoprotein-cholesterol (HDL-c), homeostasis model assessment index of insulin resistance (HOMA-IR), hemoglobin A1c (HbA1c), and age (Supplementary Tables S1 and S2). The glucose disposal rate (GDR) used as a measurement of insulin sensitivity by euglycemic–hyperinsulinemic clamp technique was positively correlated with serum ficolin-3 in 51 NGT subjects (Figure 1A). Further logistic regression analyses showed that there was a significant correlation between serum ficolin-3 and T2DM, after adjustment for age and sex (model I), age, sex, HDL-c, HOMA-IR and HbA1c (model II), age, sex, HDL-c, HOMA-IR, HbA1c, triglycerides (TG), systolic blood pressure (SBP), C-reactive protein, creatinine and uric acid (model III) (Supplementary Table S3).

To explore the role of serum ficolin-3 in the prediction of future risk of T2DM, we performed a prospective study in which 1951 subjects recruited from China communities for the Shanghai Diabetes Study (conducted in 1998–2001) and had returned for the follow-up assessment (an average of 3 years). Among them, 1742 had NGT and 209 had impaired glucose regulation at baseline. Serum ficolin-3 was significantly lower in subjects with impaired glucose regulation than in those with NGT (Supplementary Table S4). After the follow-up, 130 subjects had developed T2DM. The baseline level of serum ficolin-3 was significantly lower in subjects who developed T2DM than those who did not (Supplementary Table S5). Participants in the highest quartile of serum ficolin-3 had a significantly decreased risk of diabetes compared with those belonging to the lowest quartile even after the adjustment of age, sex, body mass index, and waist circumference (Figure 1B). The relative risk (RR) of T2DM for serum ficolin-3 was affected by further adjustment for HDL-c, TG, fasting plasma glucose, SBP, diastolic blood pressure (DBP), and HOMA-IR separately (Figure 1C). In subgroup analysis, a significant association was found between serum ficolin-3 and risk of diabetes among participants who were females, and those who had hyperglycemia, non-abdominal obesity, dyslipidemia, and hypertension (Figure 1D).

Ficolin-3, a secreted PRR, was first identified as a serum glycoprotein that reacted with autoantibodies from patients with systemic lupus erythematosus (Epstein and Tan, 1973) and considered to have a primary role in the activation of the lectin pathway in the complement system and in the clearance of late apoptotic cells (Honore et al., 2007). Besides these specific effects on the immune response, a new phenomenon of ficolin-3 was detected in this study. Serum ficolin-3 was significantly lower in T2DM patients and was independently related to insulin resistance which was further confirmed by euglycemic–hyperinsulinemic clamp technique. The mechanism linking ficolin-3 with insulin resistance is not yet fully understood. Ficolin-3, containing the C-type carbohydrate recognition domain and the fibrinogen h/g (homology) domain, has evolved to recognize the surface sugar codes of microbes. Toll-like receptors, which are membrane-bound PRRs, have a similar function, in that they can bind to cell surface carbohydrate molecules in the same way as ficolin-3 does (Smith et al., 2011). Toll-like receptors have been shown to be associated with insulin resistance in T2DM (Raetzsch et al., 2009) through the activation of the innate immune response and subsequent inflammatory pathways in combination with free fatty acids. In addition, mannan-binding lectin, which shares many structural and functional similarities with ficolin-3, has previously been reported to be associated with the development of insulin resistance by increasing fatty acid oxidation in the rat soleus muscle (Fernandez-Real et al., 2006). However, it is unclear whether ficolin-3 affects the development of insulin resistance by similar mechanisms.

The most important finding in the prospective study was that low serum ficolin-3 levels at baseline predicted the incidence of T2DM. Interestingly, an inverse association was observed among participants with elevated levels (within the non-diabetic range) of plasma glucose,
hypothesis and diabetes-related dyslipidemia. Our findings therefore suggest that the measurement of serum ficolin-3 levels may be particularly important for the evaluation of the individual risk of T2DM in people who already have risk factors for the disease. Additionally, an inverse association was observed between serum ficolin-3 and the risk of T2DM in females and individuals with non-abdominal obesity. The exact reason for this association is not understood owing to the limited data currently available.

As stated above, serum ficolin-3 decreased significantly in patients with T2DM in the present study in contrast to our previous study. The discrepancy between the two studies is not clear. Recently, it is reported that ficolin-3 levels were elevated in the vitreous fluid and serum of patients with proliferative diabetic retinopathy (Zheng et al., 2011). Therefore, we speculated that diabetic microvascular complications might be an important factor that influences the level of serum ficolin-3. Different splicing isoforms and mutants of ficolin-3 and its related acetylation-induced complement activation (Munthe-Fog et al., 2009), might be involved in the development and progression of diabetes and complications.

In summary, we have demonstrated that decreased serum ficolin-3 was independently correlated with insulin resistance and low serum ficolin-3 predicted the development of T2DM.

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References


