OBJECTIVE—To examine, for the first time, the association between a novel inflammatory cytokine, angiopoietin-like protein (ANGPTL) 2, and the development of type 2 diabetes (T2DM).

RESEARCH DESIGN AND METHODS—A total of 2,164 community-dwelling Japanese individuals aged 40 to 79 years without diabetes were followed up for 7 years. Serum ANGPTL2 levels were divided into quartile categories at baseline: $< 2.15$, $2.16–2.71$, $2.72–3.40$, and $≥ 3.41$ ng/mL. During follow-up, 221 participants developed T2DM.

RESULTS—In multivariate analyses, after adjusting for comprehensive risk factors and high-sensitivity C-reactive protein (hs-CRP) levels, the risk of developing T2DM was significantly higher in the highest ANGPTL2 quartile than in the lowest quartile (hazard ratio, 1.80; 95% CI, 1.14–2.85; $P = 0.01$).

CONCLUSIONS—Elevated serum ANGPTL2 levels were positively associated with the development of T2DM in a general population, independent of other risk factors including hs-CRP levels.

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Clinical evaluation and laboratory measurements

In the baseline and follow-up examinations, the study participants underwent the oral glucose tolerance test (OGTT) after an overnight fast of at least 12 h. Diabetes was defined by the 2003 American Diabetes Association criteria (7). Serum ANGPTL2 concentrations were measured with the human ANGPTL2 sandwich enzyme-linked immunosorbent assay using two mouse monoclonal antibodies that were confirmed to recognize only ANGPTL2 and not to react with other ANGPTLs or angiopoietins (4).
Table 1—Adjusted incidences and HRs of type 2 diabetes according to ANGPTL2 levels, 2002–2009

| ANGPTL2 levels (ng/mL) | No. of events/person-years (n = 541) | P for trend (across categories) | Continuous log scale* | P for trend (continuous) |
|------------------------|--------------------------------------|---------------------------------|-----------------------|-------------------------|
|                        | 29/3,343                             | 1                               | 9.1                   | 0.001                   |
| ≤2.15                  | 2.16–2.71                            | 1                               | 15.7                  | 0.004                   |
|                        | 2.72–3.40                            | 1                               | 15.5                  | 0.009                   |
| ≥3.41                  | 89/3,108                             | 1                               | 28.7                  |                         |

*HR per 1-SD increase of log-transformed ANGPTL2. †Per 1,000 person-years. ‡Model 1: adjusted for age and sex. §Model 2: adjusted for age, sex, family history of diabetes, fasting insulin, high-molecular-weight adiponectin, BMI, triglycerides, HDL-cholesterol, hypertension, alcohol intake, smoking habits, and regular exercise. ¶Model 3: model 2 plus hs-CRP.

and ≥3.41 ng/mL. The incidence of T2DM was calculated by the person-year method and adjusted for age and sex by the direct method using 10-year age groupings. The adjusted hazard ratios (HRs) and their 95% CIs were calculated using the Cox proportional hazards model.

RESULTS—At baseline, the mean age of participants was 58.6 years, and the proportion of men was 40.9%. The age- and sex-adjusted incidences of T2DM increased significantly with elevating quartiles of ANGPTL2 concentrations, and the risk was significantly higher in the second, third, and fourth quartiles than in the first quartile (Table 1, model 1). In the multivariate analysis, this association remained substantially unchanged even after adjustment for age, sex, family history of diabetes, fasting insulin, high-molecular-weight adiponectin, BMI, triglycerides, HDL-cholesterol, hypertension, alcohol intake, smoking habits, and regular exercise (model 2). As shown in model 3, after further adjustment for high-sensitivity C-reactive protein (hs-CRP) values, the risk of developing T2DM was significantly higher in the highest ANGPTL2 quartile than in the lowest quartile (HR, 1.80; 95% CI, 1.14–2.85; P = 0.01). These findings remained substantially unchanged when waist circumference was used instead of BMI in the adjusted models.

CONCLUSIONS—In a prospective study of a cohort of the general Japanese population, we clearly demonstrated that the risk for the development of T2DM increased with increasing serum ANGPTL2 levels. This association remained robust even after controlling for other confounding factors, including hs-CRP levels. To our knowledge, this is the first report to indicate that serum ANGPTL2 levels are an independent risk factor for developing T2DM in a general population. The concept that heightened inflammation is important in the pathogenesis of T2DM (8) is supported by the evidence that inflammation in islets, adipose tissue, liver, and muscle may provoke insulin resistance and β-cell dysfunction (9,10) and may therefore antedate the diagnosis of T2DM. Prospective observational studies have demonstrated that several nonspecific indicators of inflammation were found to be predictive of incident T2DM (11–14). Among them, C-reactive protein is a nonspecific inflammatory marker and the most commonly measured circulating marker for subclinical inflammation (13,15). The standardized assays for its measurement are widely available (13,15). In this study, the association between serum baseline ANGPTL2 levels and incident T2DM was found to be independent of the hs-CRP levels. Nevertheless, further studies would be required to reveal whether the association is truly independent of other established inflammatory markers.

This analysis clearly showed that elevated serum ANGPTL2 levels were independently associated with incident T2DM. Further studies are needed to reveal the role of ANGPTL2 in inflammation in human adipose tissue and the development of T2DM.

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