Impact of impaired insulin secretion and insulin resistance on the incidence of diabetes in a Japanese cohort

Keishi Yamauchi · Toru Aizawa

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Abbreviation

IIS Impaired insulin secretion
IR Insulin resistance
PAF Population-attributable fraction

To the Editor: On the basis of the data obtained in a longitudinal study of 3,059 Japanese participants without diabetes at baseline, Morimoto et al [1] concluded that impaired insulin secretion (IIS) had a greater impact than insulin resistance (IR) on the incidence of type 2 diabetes in a Japanese population. We think that it would have been better to pay slightly more attention to the method of analysis and interpretation of the data, and that this might have significantly raised the impact of the article.

First, as Morimoto and colleagues point out, IIS and IR or attenuated insulin sensitivity are pathophysiological components of diabetes. The two have been identified as risk factors for incidence of diabetes in many cross-sectional and longitudinal studies [2, 3]. On the other hand, there had been no previous study in which the population-attributable fraction (PAF), an estimate of population-based risk, of IIS and IR for incidence of diabetes had been calculated in any ethnic groups, including Japanese. In this regard, the data presented in this manuscript [1] are highly novel and the authors may have revealed an important feature of the Japanese population. However, at the same time, it is unknown whether the finding that, on the basis of PAF, isolated IIS (i-IIS) had a greater

impact than isolated IR (i-IR) on the incidence of diabetes, is a unique characteristic of Japanese or Asian populations; this hypothesis has not been tested in other populations.

Of note, the pathophysiological risk of developing diabetes associated with attenuated insulinogenic index might not be significantly greater than that associated with increased HOMA-IR in this cohort because the 95% CIs of the AUCs for receiver operating characteristic (ROC) curves for diabetes were clearly overlapping (Table 1 in Morimoto et al [1]). In addition, i-IIS might not be a significantly greater risk than i-IR because the 95% CIs of the HRs were also overlapping, albeit slightly (Table 3 in Morimoto et al [1]). The relevance of these differences was not specifically examined. Nevertheless, the authors stated in the Discussion that ‘...the development of type 2 diabetes in many Asians may be due to IIS’ [1], which could be misleading. The authors would have done better to explain the difference between HR and PAF, that is, the estimates of pathophysiological risk and population-based risk; in this way, they would have better distinguished pathophysiological and public health impacts.

Second, IR was estimated exclusively using HOMA-IR, which primarily reflects hepatic IR [4]. Because it is known that whole body IR, but not hepatic IR, is a significant pathophysiological risk factor for type 2 diabetes [5], the claim that IIS had a greater impact than IR on the incidence of diabetes, without measuring whole body IR, may not be well balanced.

Third, in the multivariate Cox model, no adjustment was made for numerous variables that were significantly different between the four groups (Table 2 in Morimoto et al [1]), such as anthropometry (BMI, waist measurement, per cent fat, blood pressure), lipids, liver function and all glucose values. Accordingly, it is uncertain whether i-IIS and i-IR were independent pathophysiological risk factors for diabetes. Even if they are confirmed to be independent risk factors after a full adjustment for all confounders, HR values are expected to be different from the values shown in Table 3. The issue is important because HR

K. Yamauchi · T. Aizawa (✉)
Diabetes Center, Aizawa Hospital, 2-5-1, Honjo,
Matsumoto 390-8510, Japan
e-mail: taizawax@ai-hosp.or.jp

obtained in the multivariate Cox model formed the basis of the PAF calculation and the authors' conclusion was heavily dependent on the PAF values [1].

Fourth, insulinogenic index cannot be calculated in a certain fraction of the general population owing to negative values for ΔIRI_{0-30} and/or ΔPG_{0-30} [6], where IRI and PG denote immunoreactive insulin and plasma glucose, respectively. It would therefore have been helpful if the authors had provided details of the numbers of such individuals and explained how they handled the data. The simple omission of these individuals in a longitudinal analysis of this kind is problematic because negative values for ΔIRI_{0-30} occur predominantly in those with excellent glucose tolerance.

We have two additional comments. The failure to find high PAF values for the 'IIS plus IR' group, which had the highest HR for incidence of diabetes, may well be due to the fact that the number of participants in this category was small. Furthermore, if beta cell function, as measured by oral disposition index [7], had been used instead of glucose-stimulated insulin secretion, this would have been a stronger predictor of the incidence of diabetes.

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