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Incidence of Type 2 Diabetes in Individuals With Central Obesity in a Rural Japanese Population: The Tanno and Sobetssu Study

Response to Oda

We are grateful for Dr. Oda's comments (1) on our recent report (2) regarding the usefulness of central obesity assessed by waist circumference in clinical risk assessment for type 2 diabetes in Japanese people. We agree with his opinion that the current Japanese cutoff points for central obesity (85 cm for men and 90 cm for women) are problematic and that there is ground for controversy.

We recalculated the risk of central obesity assessed by waist circumference for type 2 diabetes, applying the cutoff points proposed by Hara et al. (3) (85 or 83 cm for men and 78 or 73 cm for women) and Asian criteria of central obesity (90 for men and 80 cm for women). When applying Hara et al.'s cutoff points, the relative risks of central obesity for type 2 diabetes were 5.26 (95% CI 2.06–13.44) in men with an 83-cm waist circumference, 1.12 (0.51–2.48) in women with a 78-cm waist circumference, and 1.63 (0.68–3.91) in women with a 73-cm waist circumference. When applying the Asian criteria, the relative risks were 1.35 (0.59–3.06) in men and 1.53 (0.69–3.40) in women. We also plotted the receiver-operator characteristic curves for waist circumference to predict the presence of type 2 diabetes after 10 years, separately in men and women. According to the receiver-operator characteristic curves, waist circumference is a good predictor for occurrence of type 2 diabetes in men (84.5 cm: sensitivity 71.4% and specificity 59.6%) but is not a good predictor in women. There seem to be sex differences in the effect of central obesity assessed by waist circumference for occurrence of type 2 diabetes.

We are now analyzing the risk of metabolic syndrome for type 2 diabetes in Japanese patients using the same study population (in progress), and the results we have so far give us the impression that central obesity plus the accumulation of two or more risk factors (i.e., metabolic syndrome according to the International Diabetes Federation definition) is a stronger predictor for type 2 diabetes in both men and women than only central obesity without considering the presence of risk factors. The results also give us the impression that the current Japanese criteria of waist circumference is appropriate for men but that the appropriate cutoff point for women may be smaller than the current criteria.

Since there seem to be different impacts on the risk of central obesity for type 2 diabetes and the risk for cardiovascular events, further studies are needed to establish appropriate cutoff points of waist circumference in the Japanese population.

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Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin

Response to Bowker et al.

We read with interest the article by Bowker et al. (1), which suggests that sulfonylurea or insulin therapy may increase cancer-related mortality. The premise that insulin is mitogenic for neoplastic cells is not proven. An expanding body of epidemiologic literature has linked insulin resistance and IGF-I, rather than absolute levels of insulin, with cancer incidence and prognosis.

There are several inherent limitations to this retrospective analysis. A total of 82.4% of the metformin group was also treated with sulfonylureas over the observation period. Also, patients requiring insulin likely had relatively poor glycemic control, longer duration of disease, and more subclinical or overt diabetes complications, perhaps not accounted for by the chronic disease score. These factors might increase mortality.

An area of pathophysiologic common ground between insulin resistance/diabetes and neoplastic diseases is the in-

flammatory milieu, which likely contributes to both of these disease states. The hyperglycemic, hyperinsulinemic, insulin-resistant state is proinflammatory and is very different than the euglycemic, hyperinsulinemic state achieved with intensive insulin therapy. Insulin itself possesses anti-inflammatory properties (2). Intranuclear levels of nuclear factor κβ, important in cancer progression, as well as plasma levels of several inflammatory cytokines (including vascular endothelial cell growth factor, i.e., vascular endothelial growth factor) are reduced through intravenous insulin infusion in obese nondiabetic subjects (3,4). Reduction in plasma vascular endothelial growth factor levels has also been shown during insulinization of poorly controlled or newly diagnosed diabetic adults and children (5,6). These data suggest that insulin possesses antiangiogenic as well as anti-inflammatory properties, which could benefit oncologic patients. As the authors point out, establishing a cause-and-effect relationship by a retrospective study in such a complex population is not possible. The positive or negative effects of aggressive insulinization in cancer patients remains an opened question that urgently requires randomized controlled clinical trials.

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Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin

Response to Farooki and Schneider

We thank Farooki and Schneider (1) for their comments on our recently published article (2) on diabetes treatments and cancer-related mortality. As we had indicated (2), we agree with Drs. Farooki and Schneider that additional clinical data would aid our understanding of pathophysiologic mechanisms. Clinical intervention studies may be optimal in obtaining such pathophysiologic data. However, such studies may be impractical given the large numbers of patients required and long follow-up time needed to demonstrate statistically significant differences. It is for this reason that we used administrative databases that, in addition to the benefits of quick and inexpensive answers, also have the benefits of population-based estimates and no selection bias.

Drs. Farooki and Schneider point out that 82.4% of the metformin group was also treated with sulfonylureas during the observation period in our retrospective analysis. We did explore the cancer-related mortality in the metformin monotherapy group; however, there was a very small number of events (i.e., cancer-related mortalities) in the metformin monotherapy group (n = 40, 3.3%) compared with the combination therapy group (n = 205, 3.6%) and the sulfonylurea monotherapy group (n = 162, 4.9%). Thus, while it seems that the mortality rate in the metformin monotherapy group had lowest cancer-related mortality, the numbers are too small to allow for meaningful statistical analyses. As such, we combined the metformin monotherapy group and combination therapy group into the metformin users group as presented in the article.

Drs. Farooki and Schneider also states that the premise that insulin is mitogenic for neoplastic cells is not proven. We do agree that insulin resistance and IGF-1 may play a role in cancer incidence and prognosis. Other authors (3,4) have found evidence in the literature that insulin is a growth-promoting hormone that does in fact have mitogenic properties. It may be that hypersinulinemia in the face of insulin resistance, such as may be seen in insulin-treated type 2 diabetic patients, is increasing the risk, and, therefore, we do not want to exclude the potential link between insulin and cancer mortality.

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