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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Stability of Body Weight in Type 2 Diabetes

Response to Chaudhry et al.

In a recent volume in this journal, Chaudhry et al. (1) reported their findings of weight change in 205 men with diabetes. They conclude that over the course of at least 5 years, modest weight gain is the norm in men with diabetes. In contrast, we have previously published data (2) on 816 adult Pima Indians with diabetes, which showed that the general pattern of weight change after a diagnosis of diabetes was weight loss. These apparently discrepant findings may reflect ethnic differences, but there are a number of other potential reasons for the differences.

The Chaudhry et al. study was limited to men, while our study included men and women. We found no difference in patterns of weight change between the sexes; therefore, that does not seem to explain the divergent results. We also found that the pattern of weight change varied at different durations of diabetes, with weight gain being predominant in the first 2 years after diagnosis, followed by continuing weight loss. Diabetes duration was not a factor that was analyzed in the Chaudhry et al. study, but all subjects had a minimum duration of diabetes of 5 years; thus, it seems an unlikely reason for the differing results. A more likely explanation is the difference in treatments reported. In our study, the majority of subjects were receiving no pharmacological agents for diabetes, and there was a greater degree of weight stability among those receiving insulin or oral agents; in fact, among those taking insulin, there was a tendency toward weight gain in some of the duration groups. The Chaudhry et al. study only includes subjects receiving either oral agents or insulin. They reported weight loss among subjects taking metformin. If the majority of our subjects had been receiving metformin, that might explain the weight loss we reported among the subjects taking oral agents. However, at the time of our study, metformin was not as widely used as it is today, and not enough patients received metformin to allow for a subanalysis of this group, which primarily consisted of people taking sulfonylureas. Finally, the criteria for enrollment in the two studies were very different. In the Chaudhry et al. study, only men who had attended annual examinations over the study period were included, with data taken only from the baseline and final examination. In our study, we only required that a subject had attended two or more research examinations (after being diagnosed with diabetes) with no regard to how regularly they attended hospital appointments. It would be interesting to know whether the Chaudhry et al. findings would differ if they had included all possible subjects, regardless of clinic attendance or pharmacologic therapy.

In summary, the pattern of weight change in type 2 diabetes is not well understood and may be quite variable according to patient characteristics.

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Stability of Body Weight in Type 2 Diabetes

Response to Looker et al.

We thank Looker et al. (1) for their comments regarding our study (2). We also appreciate the authors calling attention to their study (3) regarding weight change in Pima Indians before and after the diagnosis of diabetes. As Looker et al. point out, the two study populations are very different in regard to age, sex, and genetic background. The study design, the study inclusion criteria, and the treatment categories were all different, and the number of times the subjects were observed during the study period was different. Therefore, it is difficult for us to compare our results with those published previously by Looker et al. Nevertheless, our own data, as well as the data obtained in Pima Indians, indicate that rapid weight gain is not a characteristic of most people with type 2 diabetes.

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