where IR is an index of whole-body insulin resistance and I is the circulating insulin concentration.

But I is an increasing function of G which we represent here simply as:

$$I = G * \beta$$

where β is the insulin secretory sensitivity to glucose.

Under steady-state conditions such as fasting, or quasi-steady-state conditions such as 2 hours after an oral glucose load, dG/dt is small and the above three equations can be combined to yield:

$$G = \frac{R_{in}}{\beta} * IR$$

where R_{in} is hepatic glucose output + any rate of glucose absorption by the gut.

If the model is valid across the conditions used to measure the Index, this is equivalent to:

$$G = \frac{R_{in}}{Index}$$

Correlations between the Index and G provide tests of the validity of this model. And in fact, the close relationships between the Index and G_0 and G_{120} ($r^2=83\%$) reported by Gastaldelli et al. support this strongly. The unexplained variance in these relationships (17%) is consistent with the likely measurement errors in the Index (10–15%) and G (~3%).

Other factors which could contribute to error variance include: (i) variations within subjects in insulin secretory sensitivity to glucose and index of whole-body insulin resistance across the different conditions (fasting, OGTT, glucose clamp); (ii) independent (of β and IR) variations in R_{in} between subjects during fasting or OGTT; and (iii) the many physiological complexities excluded from the model. The very good fits obtained by Gastaldelli's team suggest that all of these factors have little influence on the responses observed. The model appears equally valid across the ranges of glucose tolerance, measurement conditions and adiposity in the sample.

In this model, the Index or other Disposition Indices provide no information on the causes of variations in glucose tol-

erance apart from apparently negligible effects of variations in R_{in} . Measures of any two of G , IR and β are sufficient to calculate the third.

In summary, the strong fits to this model obtained by Gastaldelli et al. do not address any effects that obesity may have on underlying β or IR . We suggest that any attempt to relate between subject variations in indices of the type used in the study in question (Disposition Indices) and glycaemia with the aim of investigating the pathogenesis of glucose intolerance will be similarly invalid.

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Author's Reply

Reply to Comment on: Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA (2004) Beta cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia* 43:31–39

To the Editor: Dr Jenkins and colleagues raise two issues. The first relates to the validity of the strong inverse relationship between disposition indices and plasma glucose concentrations.

The second relates to the effects of obesity on indices of beta cell function. They state that our conclusion appears inconsistent with their finding that “baseline adiposity predicts reduced beta cell function at 6-year follow up, and does so independently of diabetes risk status.” They also state that our findings “are based on spurious correlations.” We offer the following comments.

Firstly, the disposition indices we used are: $(\Delta I_{30}/\Delta G_{30} \cdot 1/IR)$ and $(\Delta I_{0-120}/\Delta G_{0-120} \cdot 1/IR)$ respectively for the 30-min values of plasma insulin and glucose increments and the average 0 to 120-min values of plasma insulin and glucose increments (see Fig. 3 of original article). The insulin resistance index IR is the inverse of the ratio of total glucose disposal (TGD) to the steady-state plasma insulin concentration (I) achieved during the euglycaemic insulin clamp.

In general, Dr Jenkins develops equations to argue that any disposition index e.g. $(\Delta I_{0-120}/\Delta G_{0-120} \cdot 1/IR)$ must be inversely related to plasma glucose (G) through R_{in} (rate of glucose input into the pool). In principle, we do not disagree with Dr Jenkins' model. We do, however, feel it is grossly oversimplified. TGD is not simply proportional to circulating insulin concentration (I) and is not fully independent of G . Likewise, I is not simply proportional to G , and it is not

true even by approximation that quasi-steady-state conditions obtain 2 hours after glucose ingestion. More importantly, insulin sensitivity and, even more importantly, beta cell function cannot be reduced to a single universal index that is the same whatever in vivo test and formula are used to compute it and that applies to all conditions (like IR and β in Dr Jenkins' model). It cannot therefore be taken for granted that for a given pair of indices of beta cell function and insulin resistance the resulting disposition index should be inversely related to glucose concentrations, with no differences between groups.

A strong correlation would be obvious only by presupposing the existence of universal indices of beta cell function and insulin resistance. In fact, if from our data we were to calculate a disposition index in which the secretion index is the ratio of fasting plasma insulin to fasting plasma glucose (a HOMA- β equivalent), the plot of this disposition index against 2-hour plasma glucose levels would look quite different from those in Figure 3 of our paper [1]. It therefore makes sense to show, as we did, that the relationship between specific disposition indices and glucose tolerance is similar in lean and obese subjects, and to discuss the physiological meaning of the finding. The potential for differences is not only in R_{in} (rate of glucose input into the pool), as Dr Jenkins suggests, but also in factors that differentiate the various aspects of beta cell function, since beta cell function cannot be reduced to a single universal index [2]. For this reason, we maintain that our indices of beta cell function and insulin resistance are indeed close surrogates of the determinants of glucose tolerance according to Dr Jenkins' model. This, however, is a conclusion and not a premise. On the other hand, we also agree that caution must be exercised when using indices that may exhibit self-correlation.

Our second comment is to point out that in our paper we concluded the following: "Irrespective of the degree of glucose tolerance, when one relates the insulin secretory response to the concomitant severity of insulin resistance, it can be seen that for any given glucose stimulus the beta cell response in obese individuals is superimposable on that of lean subjects." The cross-sectional data upon which our analyses were based preclude any inference as to whether initially normal beta cell secretory responses may with time deteriorate faster in obese than in non-obese subjects. The paper cited by Jenkins and co-

workers [3] was based on data from 35 women, in whom beta cell function was estimated by HOMA- β , a simple measure of baseline insulin secretion and a rather distant surrogate of beta cell function. While this is an important issue, we believe it remains to be conclusively settled by detailed analysis of beta cell function in large groups of subjects in prospective evaluation.

Sincerely,

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