Fig. 1. Light microscopy of MHC class II expression by pancreatic cells using immunohistochemical staining of a paraffin-embedded section of the pancreas of a 15-week-old female NOD mouse. MHC class II is expressed by beta cells (arrow a) but not by exocrine cells (arrow b)

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Comment

re: 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* 47:31–39

Keywords Diabetes · Disposition index · Glucose tolerance · Insulin resistance · Insulin secretion.

To the Editor: Gastaldelli and co-workers [1] report an analysis of cross-sectional OGTT and euglycaemic clamp data from a sample with varying glucose tolerance (NGT, IGT, Type 2 diabetes) and conclude that “...beta cells in obese individuals function in an identical fashion to those of lean individuals.”

This conclusion is supported by a lack of effect of obesity on the strong correlations between the insulin secretion/insulin resistance Index ($\frac{\Delta I_{30}}{\Delta G_{30}} * \frac{1}{IR} \equiv$ Disposition Index [2]) and the fasting or 2-h glucose concentrations of the subjects studied.

This conclusion appears inconsistent with our recent finding that baseline adiposity predicts reduced beta cell function at 6-year follow up, and does so independently of diabetes risk status [3]. However, we would suggest that there is no real inconsistency between the two studies, as the conclusions of Gastaldelli and colleagues are based on spurious correlations. Fasting and 2-hour glucose levels are themselves determined by beta cell function and insulin sensitivity, so that the relationships obtained in the study in question are predominantly the result of plotting the Index against an inverse function of itself.

To illustrate this point, consider the simple one-pool model of glucose dynamics which is implicit in the calculation of the Index:

$$\frac{dG}{dt} = R_{in} - TGD \quad (1)$$

where R_{in} is the rate of input of glucose into the pool and TGD is the whole-body disposal rate of glucose. TGD is an increasing function of insulin, which Gastaldelli et al. represent as:

$$TGD = \frac{I}{IR}$$

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