

COMMENTS AND RESPONSES

Comment on: Tam et al. Defining Insulin Resistance From Hyperinsulinemic-Euglycemic Clamps. *Diabetes Care* 2012;35:1605-1610

We have read with interest the article in the July issue of *Diabetes Care* by Tam et al. (1) in which they define a cutoff point for having insulin resistance and provide classification trees for predicting insulin resistance from clinical and biochemical markers. We appreciate the authors' effort to translate detailed phenotypic data into clinical usefulness; however, defining a cutoff point is always challenging, and the study raises a number of questions.

Whether the overall aim of setting a cutoff point for insulin resistance is to guide treatment in patients with type 2 diabetes or to prevent or delay the development of diabetes in the general population, the rationale for determining insulin resistance should be clearly defined in order for the cutoff point to be useful. In the study by Tam et al. (1), the rationale is not clear to us. The presence of self-reported type 2 diabetes was used to validate "true" insulin resistance, which seems inappropriate if the aim is to provide "clinically meaningful messages for patients" (1), since all diabetic patients then per definition will be insulin resistant. Conversely, all nondiabetic individuals will be regarded as insulin sensitive, which is inconsistent with the fact that some obese and glucose intolerant

individuals have the same degree of insulin resistance as diabetic patients (2).

Clamp-derived glucose disposal rate (GDR), as measured by Tam et al. (1), is the gold standard for measuring insulin sensitivity. Therefore, rather than using diabetes status per se, we suggest using the distribution of GDR values to define the presence of insulin resistance. For instance, the cutoff point could be defined by the lowest quartile of insulin resistance in the background population (3). Alternatively, if a true bimodal distribution of GDR exists, the crossing point of the two underlying normal distributions could be relevant (4). Tam et al. (1) claim that the GDR distribution was bimodal in their population, but this is not substantiated in the article. If present, it is likely to be driven by the oversampling of diabetes cases in the studied population and may not apply to the background population (5). Therefore, the most pertinent method for defining a cutoff point for insulin resistance may be to use an appropriate quantile of the GDR distribution in either the diabetic or the general population depending on the overall aim.

With a meaningful cutoff point for GDR, we certainly agree on the potential value of deriving a decision tree for predicting insulin resistance as suggested by Tam et al. (1). However, the population for which the classification tree is intended needs to be considered when developing the model. What is routinely measured in diabetic patients (e.g., homeostasis model assessment of insulin resistance and LDL cholesterol) may not be available in a general population. Also, the classification of "high-risk" terminal nodes in the tree model should ultimately depend on the clinical implications of being a false negative compared with a false positive, which may also differ between populations. Therefore, the context in which the models should be used needs to be carefully considered in order for the results to be useful in practice.

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