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A Comparison of Lipid and Glycemic Effects of Pioglitazone and Rosiglitazone in Patients With Type 2 Diabetes and Dyslipidemia

Response to Bell and Brunzell

In his commentary, Bell (1) presents specific criticisms of the head-to-head trial comparing the effects of rosiglitazone with pioglitazone on lipids and lipoproteins. Bell raises a concern over study recruitment (in particular the high rate of screen failures), the exclusion of patients on statin therapy, and the limited data supporting the role of hypertriglyceridemia in cardiovascular risk. By excluding patients on other glucose- and lipid-lowering medication, we were able to demonstrate that the two agents have different effects on each of the components of the lipid profile. In doing so, the differences observed could only be attributed to the active thiazolidinedione (TZD) therapy. Targets for LDL cholesterol were lowered during the active phase of this trial. Given that, recruitment of appropriate subjects was challenging. Although this population does not currently represent the standard of practice, the study as performed allowed careful assessment of the isolated drug effect of each TZD on lipids.

Unfortunately, Bell and others have misrepresented the two prior studies of the add-on effect of statin (2) or statin + ezetemibe (3) therapy to TZD. First, this subanalysis of LDL cholesterol (not lipid profiles as stated by Bell) was over a wide range of doses of the nonrandomized TZD treatments and, unlike our study, was substantially underpowered to compare differences in lipid parameters between agents. Furthermore, only change from baseline (without baseline and end point) LDL cholesterol results were presented in the studies. Therefore, contrary to Bell's assertion, baseline differences (as anticipated from our data and others [4]) would be expected to be preserved at end point since changes from baseline were similar for the two TZDs. To conclude that there are no differences between the TZD effects on lipids in statin-treated patients without any data is therefore questionable. More recently, the results of the COMPLEMENT study were reported (5) confirming that the difference in the effect of the two TZDs persisted in over 305 subjects on statin therapy.

The role of triglycerides in determining cardiovascular disease risk remains controversial, and we did not evaluate postprandial lipemia in our study. No head-to-head comparative study has been performed assessing the differential impact of the two TZDs on postprandial lipids. In response to Bell's and Brunzell's (6) request for data on HDL subclasses, we have reported that both HDL size and large HDL cholesterol increased with pioglitazone and decreased with rosiglitazone (7), and a detailed analysis of the results of lipoprotein particle analysis on LDL, VLDL, and HDL is currently underway.

Lastly, we used a standard definition of "completers" in our patient flow diagram: all patients who completed the full 24 weeks of active therapy. The numbers of patients exposed to the full dose of each active therapy were very similar (323 for pioglitazone and 314 for rosiglitazone). The data presented in Fig. 2 of the report along with the last-observation-carried-forward analysis *P* value (Table 2) clearly refutes Brunzell's speculations and underscores the absolute robustness of our data and conclusions (8).

In summary, currently available data clearly demonstrate more favorable effects of pioglitazone on plasma lipids and lipoproteins compared with rosiglitazone (lowering triglycerides, raising HDL to a greater extent, and not increasing non-HDL cholesterol and apolipoprotein B levels or LDL particle concentration). These differences may be associated with long-term vasculoprotective advantages.

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Dietary Glycemic Index, Glycemic Load, Fiber, Simple Sugars, and Insulin Resistance: The Inter99 Study

Response to Lau et al.

In their important analysis of data from the Inter99 Study on the relationship among glycemic index, glycemic load, and insulin resistance as estimated by the homeostasis model, Lau et al. (1) unfortunately do not provide adequate descriptive information on the distribution and variation in levels of glycemic index and glycemic load in their population. Additionally, the reader is left wondering about the associations of glycemic index and glycemic load with other (dietary) variables.

These types of information are critical for comparison and interpretation of the Inter99 Study to other studies. To date, the strongest association between dietary glycemic index and risk of type 2 diabetes was reported from the study with the largest variation in dietary glycemic index (2). In the absence of the respective data for the Inter99 Study, it is difficult to evaluate whether small variations in the levels of glycemic index and glycemic load could be responsible for the lack of an association with insulin resistance. A small variability can in turn be either inherent to the population or result from the dietary assessment method.

First, some indirect evidence for the latter comes from the fact that the authors used a total of only 57 glycemic index values to estimate the dietary glycemic index of all participants. Second, intakes of soft drinks and selected sweet products were not assessed; however, most of these foods have a high glycemic index and are highly predictive of the overall dietary glycemic index and glycemic load (3,4). In addition, the consumption of socially undesirable sucrose-containing foods may have been selectively underreported by the Inter99 participants, who were invited to partake in a health survey. Although most sucrose-containing foods have only intermediate glycemic index levels, they are often consumed in large amounts. A selective underassessment may thus affect the estimates of glycemic index, glycemic load, and sucrose without affecting estimates of dietary fiber intake. In this context, the discussion of reasons for the lack of an association between sucrose and the homeostasis model may need reconsideration given that sucrose has a glycemic index of 97 (white bread standard), which is very similar to the glycemic index of white bread, which is 100. Finally, alcohol intake was not considered in glycemic index and glycemic load estimation but has been shown to be highly predictive of glycemic index (3).

Thus, in conclusion, this discussion of the article by Lau et al. points out some of the challenges and complexities faced by applying the concept of glycemic index estimation to dietary data collected with a food frequency questionnaire.

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Dietary Glycemic Index, Glycemic Load, Fiber, Simple Sugars, and Insulin Resistance: The Inter99 Study

Response to Buyken and Liese

Buyken and Liese (1) raised the relevant question of whether low variability in glycemic index and glycemic load could explain the lack of association with insulin resistance (2). The complete ranges (medians) of glycemic index and glycemic load in our study are 16–105 (79) and 0–1,208 (197), respectively. This is in accordance with previous studies (3), and thus, it is unlikely that this explains the lack of association.

We disagree that our article should have provided data on associations of glycemic index and glycemic load with other (dietary) variables because this would have expanded the extent of the article considerably and furthermore blurred the focus of the article.

We are aware of the methodological problems related to dietary assessment methods including estimation of glycemic index (2). Unfortunately, we cannot change the fact that information on intake of soft drinks and selected sweet products were not available in our study. Soft drinks may not, however, contribute substantially to the daily intake of glycemic index–inducing carbohydrates (4), despite the high–glycemic index value of sucrose. Additionally, the intake of sucrose from sucrose-containing foods and soft drinks is not consumed in large amounts in the general Danish population (25–65 years) (5). Thus, the lack of data on soft drinks and selected sweet products may not be a major concern.

Bias introduced in all dietary studies with underreporting cannot be excluded (2). It is, however, impossible to estimate the exact degree of underreporting. Therefore, we do not have a rational basis for a sensitivity analysis. Hence, we would have to make up a set of assumptions re-