Response letter to comment on: Villareal et al. (2009) TCF7L2 Variant rs7903146 Affects the Risk of Type 2 Diabetes by Modulating Incretin Action. Diabetes; 59:479–485

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We appreciate Knop's (1) interest in our recent article (2). Although his suggestion that the impaired incretin response observed in subjects with the *TCF7L2* variant rs7903146 may be due to insulin resistance and impaired glucose tolerance (IGT) is interesting, this hypothesis is not supported by our data. Insulin sensitivity was measured in both groups using the oral glucose minimal model, which has been validated against the clamp technique (3), and no differences were found (14.2 vs. 15.3×10^3 min^{-1} per pmol/l; $P = 0.42$). Although there was a tendency toward a higher BMI in the group with the *TCF7L2* variant, the difference did not reach statistical significance. We directly measured percent body fat by using the dual-energy X-ray absorptiometry technique (4), and there were no significant differences between the control group and the *TCF7L2* group (38.9% vs. 38.2%, $P = 0.82$). Thus, based on this accurate measure of body fat, the two groups are virtually identical, i.e., both have the same percentage body fat. In terms of glucose tolerance, there were also no significant group differences across all parameters, including fasting blood glucose, 2-h glucose, hemoglobin A1C, and glucose area under the curve (AUC) (all $P > 0.05$). Moreover, even if there were trends for slightly higher 2-h glucose ($P = 0.09$) and glucose AUC ($P = 0.08$) in the *TCF7L2* group, these subtle differences (if any) are unlikely to account for the significantly and markedly reduced (30% lower) incretin effect in this group compared with the control group (31.6% vs. 45.5%, $P = 0.02$). All of our subjects had normal glucose tolerance (NGT) or only mild IGT. While the incretin effect is indeed impaired in subjects with type 2 diabetes (5,6), it has been reported to be similar between subjects with NGT and IGT, as assessed from ratios of the insulin secretory rates during oral and isoglycemic glucose infusions (7,8). In addition, no differences in incretin effect were found between first-degree relatives regardless of whether they had type 2 diabetes or NGT (9).

Regarding glucagon measurements, we also found no differences in glucagon suppression during the oral and isoglycemic glucose infusions between the two groups (Table 1). Accordingly, there is no evidence of hyperglucagonemia in the *TCFL2* group.

All AUCs are reported as total AUC. We used total AUCs because it provides the best assessment of integrated hormone levels during the 5-h OGTT (10).

In summary, our study clearly shows that subjects with the *TCF7L2* variant at rs7903146 (TT or TC) have a markedly reduced incretin effect (~30% reduction) when compared with control subjects. These effects cannot be explained by differences in factors such as body fatness, insulin sensitivity, and glucose tolerance, or by differences in incretin hormone concentrations of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1, or glucagon responses to oral and intravenous glucose. We thus suggest that it is the effect of the genetic variant per se that reduces the insulin secretory response to incretin hormones.

TABLE 1
Glucagon suppression during the oral and isoglycemic glucose infusions

	Control, CC genotype	*TCF7L2* genotypes TT and TC	*P*
Glucagon AUC (10^4 pg/ml · min)			
OGTT	1.8 ± 0.1	1.9 ± 0.1	0.71
IGI	1.7 ± 0.1	1.6 ± 0.2	0.79
P	0.29	0.19	

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