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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In a recently published article by Villareal et al. (1), it is concluded that the *TCF7L2* variant rs7903146 confers reduced incretin effect as a consequence of a reduced insulinotropic effect of the two incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), although this was actually not tested. However, mechanisms other than the variant might explain or at least contribute to the reduced incretin effect observed in the subjects with the *TCF7L2* variant studied by Villareal et al. The *TCF7L2* group ($n = 8$) was characterized by a mean 2.3 kg/m^2 larger (nonsignificant) BMI compared with the control group ($n = 10$). Furthermore, 2-h plasma glucose values after the 75-g oral glucose tolerance test (OGTT) tended to be higher among the *TCF7L2* group (7.7 vs. 8.6 mmol/l, $P = 0.09$) and, hence, on average this group exhibited impaired glucose tolerance (IGT). Looking at Fig. 1, the *TCF7L2* group seems to be—in line with their "average" IGT status—characterized by a larger area under the curve (AUC) for plasma glucose during OGTT as compared to the control group (it is not clear whether total, incremental, or positive incremental AUCs were used in either this case or for the AUCs relating to β-cell secretion and incretin effect); a difference reported to be borderline significant in Table 2 (1.9 vs. 2.1 nmol/l · min, $P = 0.08$). Generally, it is accepted that reduced incretin effect (most often accompanied by normal OGTT-induced incretin hormone responses as in the study by Villareal et al.) and attenuated insulinotropic effect of the incretin hormones occur as consequences of a blunted glucose homeostasis (2–4). This also seems to be the case for diabetic hyperglucagonemia (3) (results from the glucagon analyses mentioned in the RESEARCH DESIGN AND METHODS paragraph of the article by Villareal et al. are missing). Interestingly, recent data suggest that the incretin effect is reduced in obese subjects who, despite their insulin-resistant state and subtle β-cell deficiencies, maintain normal glucose tolerance (5). Similarly, Muscelli et al. (6) showed that high BMI alone predicts attenuation of the incretin effect, and, importantly, the same group has shown that the incretin effect is affected in IGT subjects (7). Therefore, the results found by Villareal et al. could be interpreted as follows: the *TCF7L2* group was characterized by insulin resistance and a blunted glucose tolerance, and consequently their incretin effect was diminished. Thus, subjects without the *TCF7L2* variant exhibiting an identically affected glucose homeostasis as the *TCF7L2* group in the study by Villareal et al. would most likely be characterized by the same degree of incretin effect reduction. Therefore, the conclusion reached by Villareal et al. that the *TCF7L2* variant affects risk for diabetes by modification of the insulinotropic effect of the incretin hormones may be true, but, actually, the impaired incretin effect might simply be secondary to IGT.

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