COMMENTS AND RESPONSES

Circulating Retinol-Binding Protein-4, Insulin Sensitivity, Insulin Secretion, and Insulin Disposition Index in Obese and Nonobese Subjects

Response to Stefan et al.

We acknowledge the interest of Stefan et al. (1) in our findings in which they tried to replicate in their study of 75 men and women (mean BMI 29 kg/m^2). Circulating retinol-binding protein (RBP)-4 did not correlate with insulin secretion even after adjustment for age, sex, and insulin sensitivity. We studied only men (n = 107). Marked sex differences in glucose-stimulated insulin secretion have been described in humans (2) and experimental models (3). Sex has been described to impact insulin secretion, insulin action, and hepatic insulin extraction, which results in substantial differences in the regulation of postprandial glucose metabolism in men and women (2).

Stefan et al. did not adjust for BMI. In multiple regression analyses to predict insulin secretion (AIR_g), RBP4 emerged as an independent factor that contributed independently to AIR_g variance (23%) after controlling for BMI, age, and insulin sensitivity in obese subjects (4). Insulin sensitivity was the only factor that contributed to 17% of AIR_g variance in nonobese subjects (4). The association between circulating RBP4 and insulin secretion should be evaluated separately in men and women and, among men, separately in obese and nonobese subjects.

Stefan et al. also stated that retinoids in blood are not exclusively transported by RBP4 but also by albumin and lipoprotein particles. However, in fasting circulation, retinol RBP is the preponderant retinoid form, accounting for >95% of retinoids. Circulating levels of retinoic acid are always low relative to retinol RBP (<1%). Most retinoid is acquired by tissues from retinol RBP (5). Importantly, vitamin A deficiency impairs fetal islet development and causes subsequent glucose intolerance in adult rats (6).

Additionally, Stefan et al. reported that STRA6 has been recently identified as one of the main membrane receptor for the RBP and retinoid RBP in the cellular surface of several tissues, mainly in the retinal pigment epithelium (7). Stefan et al. affirm that "STRA6 was not reported to be expressed in the pancreas and/or in β-cells." In fact, STRA6 was not investigated in these tissues in both the recent article in *Science* (7) or in a previous article (8). Furthermore, RBP circulates in serum forming a complex with transthyretin (TTR), a transport protein for thyroxine. TTR constitutes a functional component in pancreatic β-cell stimulus-secretion coupling because the affinity from the binding of RBP4 to TTR is very strong and the relative stoichiometry and affinity of the two proteins in serum could conceivably influence kinetics of RBP4 antibody binding (4).

Stefan et al. hypothesized that fatty liver may be a source of increased RBP4. This is an interesting hypothesis. We have also found that circulating RBP4 correlated positively with serum AST activity (r = 0.40, P = 0.02) in obese subjects, whereas this association was not significant among nonobese subjects (r = −0.03, P = 0.7).

Finally, the measurement of circulating RBP4 levels by different methods (Western blot, immunoassays, or nephelometry) may give considerable discrepancies in its absolute values (4). The new data about the potential participation of RBP4 in insulin secretion and fatty liver raise new issues that certainly deserve more study before clear conclusions can be reached.

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References

1. Stefan N, Hennige AM, Staiger H, Schleicher E, Fritsche A, Häring H-U: Circulating retinol-binding protein-4, insulin sensitivity, insulin secretion, and insulin disposition index in obese and nonobese subjects (Letter). *Diabetes Care* 30:e92, 2007. DOI: 10.2337/dc07-0767
2. Basu R, Dalla Man C, Campioni M, Basu A, Klee G, Toffolo G, Cobelli C, Rizza RA: Effects of age and sex on postprandial glucose metabolism: differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction. *Diabetes* 55:2001–2014, 2006
3. Sugden MC, Holness MJ: Gender-specific programming of insulin secretion and action. *J Endocrinol* 175:757–767, 2002
4. Broch M, Vendrell J, Ricart W, Richart C, Fernández-Real JM: Circulating retinol-binding protein-4, insulin sensitivity, insulin secretion, and insulin disposition index in obese and nonobese subjects. *Diabetes Care* 30:1802–1806, 2007
5. Blaner WS: STRA6, a cell-surface receptor for retinol-binding protein: the plot thickens. *Cell Metab* 5:164–166, 2007
6. Matthews KA, Rhoten WB, Drscoll HK, Chertow BS: Vitamin A deficiency impairs fetal islet development and causes subsequent glucose intolerance in adult rats. *J Nutr* 134:1958–1963, 2004
7. Kawaguchi R, Yu J, Honda J, Hu J, Whitelegge J, Ping P, Wiita P, Bok D, Sun H: A membrane receptor for retinol binding protein mediates cellular uptake of vitamin A. *Science* 315:820–825, 2007
8. Bouillet P, Sapin V, Chazaud C, Messaddeq N, Decimo D, Dolle P, Chambon P: Developmental expression pattern of Stra6, a retinoic acid-responsive gene encoding a new type of membrane protein. *Mech Dev* 63:173–186, 1997