COMMENTS AND RESPONSES

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

Response to Broch et al.

In the recent article by Broch et al. (1), circulating retinol-binding protein-4 (RBP4) (measured by nephelometry) was not correlated with adiposity or insulin sensitivity; however, negative correlations with indexes of insulin secretion were detected. The authors concluded that RBP4 may impair β-cell function in human subjects.

This is an interesting hypothesis, particularly because retinol seems to be required for adequate glucose-stimulated insulin secretion (2). However, retinoids in blood are not exclusively transported by RBP4 but also by albumin and lipoprotein particles (3). This suggests that the availability of retinoids in tissues also depends on the availability and function of the latter two transport proteins. Most recently, STRA6 was identified as a cell-surface receptor for RBP4 (3). Whereas STRA6 is expressed in sites of insulin action like muscle and liver, STRA6 was not reported to be expressed in the pancreas and/or in β-cells (3). Thus, further research is necessary to investigate the effects of RBP4 on β-cell function. In contrast, RBP4 was found to induce insulin resistance in mice (4). Moreover, a strong negative correlation of circulating RBP4 with insulin sensitivity was found in human subjects (5). We confirmed the relationship between plasma RBP4 levels and insulin sensitivity, and we additionally found plasma RBP4 levels to positively correlate with liver fat (6). We hypothesize that fatty liver may be a source of increased RBP4 production and/or that RBP4 may be directly involved in the generation of fatty liver and hepatic insulin resistance, thereby playing a role in the pathophysiology of type 2 diabetes. Based on the data by Broch et al. (1), we further investigated whether circulating RBP4 was associated with insulin secretion in our population.

A total of 75 subjects with mean BMI 29 kg/m^2 who were included in our previous report (6) had measurements of glucose-stimulated insulin secretion by an intravenous glucose tolerance test (IVGTT). Insulin secretory function was also estimated from an oral glucose tolerance test (OGTT) (7). Circulating RBP4 was measured using two enzyme-linked immunoassay tests (AdipoGen and ALPCO Diagnostics) and a radioimmunoassay test (Phoenix Pharmaceuticals). Insulin secretion measured by the IVGTT (mean insulin levels at 2–10 min) and OGTT correlated with insulin sensitivity determined by the euglycemic hyperinsulinemic clamp ($r = -0.53$, $P < 0.0001$, and $r = -0.60$, $P < 0.0001$, respectively). In contrast, cirulating RBP4 measured by each of the three kits did not correlate with insulin secretion before (IVGTT, all $P > 0.20$; OGTT, all $P > 0.23$) or after (IVGTT, all $P > 0.25$; OGTT, all $P > 0.13$) adjustment for age, sex, and insulin sensitivity.

In conclusion, our data do not provide evidence for a key role of circulating RBP4 in the regulation of insulin secretion in human subjects.

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References

1. Broch M, Vendrell J, Ricart W, Richart C, Fernandez-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
2. Chertow BS, Blaner WS, Baranetsky NG, Sivitz WI, Cordle MB, Thompson D, Meda P: Effects of vitamin A deficiency and repletion on rat insulin secretion in vivo and in vitro from isolated islets. *J Clin Invest* 79:163–169, 1987
3. Blaner WS: STRA6, a cell-surface receptor for retinol-binding protein: the plot thickens. *Cell Metab* 5:164–166, 2007
4. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, Kahn BB: Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* 436:356–362, 2005
5. Graham TE, Yang Q, Bluher M, Hammarstedt A, Ciaraldi TP, Henry RR, Wason CJ, Oberbach A, Jansson PA, Smith U, Kahn BB: Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. *N Engl J Med* 354:2552–2563, 2006
6. Stefan N, Hennige AM, Staiger H, Machann J, Schick F, Schleicher E, Fritsche A, Haring HU: High circulating retinol-binding protein 4 is associated with elevated liver fat but not with total, subcutaneous, visceral, or intramyocellular fat in humans. *Diabetes Care* 30:1173–1178, 2007
7. Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Jarvinen H, Van Haeften T, Renn W, Gerich J: Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. *Diabetes Care* 23:295–301, 2000