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COMMENT ON RICKELS ET AL.

Loss-of-Function Mutations in *ABCA1* and Enhanced β-Cell Secretory Capacity in Young Adults. Diabetes 2015;64:193–199

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We read with great interest the recent article by Rickels et al. (1) on the enhancement of β-cell secretory capacity in young adults with Tangier disease (TD) (MIM 205400). The association of type 1 diabetes and type 2 diabetes (T2D) with reduced levels of circulating HDL cholesterol has been recognized since the early 1980s. In 2007, we identified the critical relationship between the ABCA1-mediated regulation of intracellular cholesterol levels in β-cells and insulin secretory capacity (2). At a mechanistic level, we identified that excessive cholesterol interrupts the depolarization-induced exocytotic fusion of insulin granules in β-cells (3). Work from our laboratory and others confirmed that carriers of loss-of-function mutations in the ABCA1 gene have dysfunctional β-cells (4), a finding that is in contrast with the report by Rickels et al. (1), complicating the interpretation of the relationship between ABCA1 activity and β-cell function in humans.

There are several notable differences between our previous study (3) and that of Rickels et al. (1). The study by Rickels et al. describes a genetically unrelated cohort at a younger age (mean age 27 years) and evaluates β-cell secretory capacity using the arginine-based test, which may mask measurable differences in islet function due to the overly powerful secretagogue effect (1). Our study, on the other hand, described an older cohort (mean age 54 years) that consisted of matched relative control subjects, thereby limiting the confounding effect of differences in genetic background. Our patients also had higher, although nonsignificant, statin use in the carriers (4).

The differences in age may be particularly relevant as TD manifests differently in adult versus pediatric cases. Most pediatric diagnoses for TD are made on the basis of large, yellow-orange tonsils and hepatosplenomegaly, while the most common presenting symptom in adults is peripheral neuropathy. This suggests organ- and age-specific differences in intracellular cholesterol accumulation. The impact of TD on the β-cell may also exhibit age-specific effects.

Unpublished data from our laboratory show that isolated mouse islets loaded with different cholesterol concentrations have a dose-dependent increase in insulin secretion until a critical cholesterol concentration of 12.2 μg/mg islet protein is reached. In these experiments, concentrations of cholesterol exceeding 14.8 μg/mg of islet protein led to a drastic reduction in the insulin secretory capacity without adversely affecting cell survival. This finding lends a mechanistic explanation in support of the different observations obtained by the two studies. The genetic absence of ABCA1 would lead to an age-dependent increment in intracellular cholesterol levels improving β-cell function until threshold concentrations are reached. However, as these individuals age, the cholesterol concentration exceeds the threshold causing a derangement in β-cell secretory capacity.

In addition to cholesterol efflux via ABCA1, cholesterol uptake via the LDL receptor plays a crucial role in regulating β-cell function. Indeed, mice lacking the LDL receptor are protected against hypercholesterolemia-induced islet dysfunction (5). In accordance with this, very recent clinical data have established that patients with inactive LDL receptors are also protected against T2D compared with relatives with normal LDL receptor function (6). This may also explain why statins, which upregulate the expression of LDL receptors, increase the incidence of T2D. Collectively, these findings support the

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concept and importance of the exquisite relationship of intracellular cholesterol and β-cell function. Further studies of glucose homeostasis in patients with TD across a range of ages will be essential to more fully appreciate the natural history of β-cell function in these patients and reconcile the differences between the findings of Rickels et al. (1) with prior data.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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