EDITORIAL (SEE SATHANANTHAN ET AL., P. 2074)

Genetic Determinants Predicting Efficacy of Glucose-Lowering Drugs?

A long way to go …

In this issue of *Diabetes Care*, Sathananthan et al. (1) report differences in the insulinotropic response to exogenous glucagon-like peptide-1 (GLP-1) in healthy volunteers, depending on the presence or absence of certain common polymorphisms of the GLP-1 receptor gene. This study suggests that individuals may variably respond to GLP-1, depending on the presence or absence of minor alleles characterized by single nucleotide polymorphisms. The authors suggest that the insulinotropic activity of GLP-1, as studied with the present protocol, may predict a better or worse clinical response to incretin-based medications (GLP-1 receptor agonists or incretin mimetics and inhibitors of dipeptidyl peptidase-4 [DPP-4], so-called incretin enhancers) and thus may help select a glucose-lowering drug tailored to the individual needs of a given patient.

Guidelines usually present a simplified flowchart to suggest a uniform approach to the treatment of type 2 diabetes, starting with lifestyle changes aiming at a healthier diet, calorie restriction in obese patients, and physical activity to improve fitness and reduce the degree of insulin resistance (2,3). Early in the course of type 2 diabetes, metformin is rather uniformly recommended (2,3), although many other glucose-lowering agents have been approved for use as a single agent. When metformin alone fails to secure adequate glycemic control, the choice includes sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, insulin, and the incretin-based medications, GLP-1 receptor agonists, and DPP-4 inhibitors (3). There is no clear uniform recommendation of any of these agents to be preferentially added to metformin treatment. Today, the choice is left to the individual recommendation of a physician practicing the "art of medicine" by being guided by the drugs' profiles and by individual characteristics of a given patient (e.g., his or her desire to lose weight), and patients may utter preferences after having been fully informed about the broad choice of agents. Costs may also be an important determinant of this choice. Only for some circumscribed, rare conditions (diabetes as a result of autosomal dominant traits, e.g., those leading to maturity-onset diabetes of the young type 3 [4], or as a result of mutations in the potassium channel Kir 6.2 [5]), genetic characterization has been shown to suggest therapies (in this case sulfonylureas) that have obvious advantages over alternative treatment choices (6–9).

For average type 2 diabetic patients, two reasons preclude simpler treatment algorithms making use of a more restricted choice of agents to be used at some stage during the disease: *1*) the growing number of medication classes available for the treatment of type 2 diabetes (3) and 2) the lack of proven superiority of any potential agent over other candidates for the general population of type 2 diabetic patients (2). Clinical characteristics (such as BMI, waist circumference, known diabetes duration, and even laboratory values such as C-peptide or homeostasis model assessment of β-cell function indexes) have largely disappointed as predictors of clinical responses to antidiabetic medications of interest. On top of these difficulties, most clinical studies indicate that a great proportion of patients, even if treated with the most potent available agents, will not successfully control their glycemia to the degree recommended by guidelines (e.g., achieving an A1C value ≤7.0%), indicating a substantial proportion of "nonresponders" to almost all available treatments (10–12).

With respect to "nonresponse" to glucose-lowering treatments, an important distinction has to be made: although clinically a responder will achieve a certain reduction in A1C or reach a given A1C target by the end of such clinical trials (usually lasting 6–12 months), too many variables (eating habits, adherence to regular exercise, etc.) will determine the outcome, so that not reaching any of the goals cannot alone and with certainty be related to the effectiveness of the drug in question. Nevertheless, a mechanistic nonresponse may exist rooted in the patients' probability to respond to any drug based on its mechanism of actions, perhaps mediated by variations in the structures used to elicit response. This may, as a simple example, be related to receptor outfits that play a role in generating responses to the drug in question. In this respect, the study by Sathananthan et al. (1) is one of few examples plausibly showing that genetically different GLP-1 receptors determine some heterogeneity in the insulinotropic effectiveness of GLP-1. Previous studies have already suggested that mutations or variations in the nucleotide sequence of the GLP-1 receptor gene determine the magnitude of intracellular postreceptor signaling (13–16). These mutations were rare, but the presently described polymorphisms are common and potentially affect many subjects.

Two mechanisms can be responsible: *1*) the GLP-1 receptor triggers more or less generation of cAMP compared with the major allele, which is found in the larger proportion of a population, so that the acute insulinotropic effect is modified; or 2) the variation in GLP-1 receptor activity has led to an altered β-cell mass or function, since GLP-1 receptor signaling is coupled to the induction of neogenesis or proliferation of β-cells, and reduces apoptosis, at least in some cell lines and in rodents (17,18). In addition, the normal cellular organization of islets appears to depend on GLP-1 receptor signaling (19). This, in turn, may determine islet function in more general terms, such as responses to glucose and other secretagogues, and not specifically the responsiveness to GLP-1 alone. The latter is suggested by the fact that the heterozygotic rs3765467 polymorphism augments the insulin secretory response to a hyperglycemic clamp alone as well as to exogenous GLP-1 in the present study (1). Responses to GLP-1 may have relevance in predicting the clinical effectiveness of GLP-1 receptor agonists and

DPP-4 inhibitors (20) in patients with type 2 diabetes. To demonstrate this, it will be necessary to repeat the current experiments in patients with diabetes and to correlate the in vitro test results with clinical responses and the likelihood of achieving glycemic targets. It may well be that the β-cell deficiency and altered function generally characteristic of type 2 diabetes may preclude the demonstration of subtle differences in the response to exogenous GLP-1 in such a population.

In the long run, multiple genetic traits, such as polymorphisms related to *TCF7L2* (21–24), *FOXO1* (25), and *WFS1* (26); potassium channels associated with sulfonylurea receptors (5); and many more aspects of β-cell mass and function, including parameters related to insulin resistance, may as a whole help predict the individual response to specific glucose-lowering treatments. This could be of great help in recommending the best possible agent for an individual (27), improving the likelihood of treatment success, and justifying higher costs, if cheaper drugs can be predicted to fail in a given patient. But, we have to admit, this will require a substantial effort in terms of systematic research. There will be no short-term success. Studies such as the one by Sathananthan et al. (1) raise some optimism that eventually this vision will come true.

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