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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

An "Urgent" Call for Action to Reclassify Diabetes With a Focus on β-Cells

In the perspective published in this issue of *Diabetes Care* (**p. 179**), Schwartz et al. issue an urgent call to reclassify diabetes on the basis of the β-cell being "the final common denominator" for all hyperglycemia and diabetes. They argue that the current system of categorizing patients as having type 1 or type 2 diabetes is insufficient, since even classic "textbook" cases may show signs of both categories of the disease. Consequently, they suggest, patient treatment might not be optimal with risks of hypoglycemia and weight gain being needlessly high. Equally, they argue that the definition and cause of latent autoimmune diabetes in adults (LADA) is not clear, does not fit well in current classifications, and thus imposes limitations on individualized treatments. For these reasons, they propose a new β-cell–centric classification system for diabetes based on the known biological pathways damaging or affecting the function of β-cells. The model focuses on 11 interlocking pathways that contribute to β-cell dysfunction and the associated downstream effects. These currently include the so-called ominous octet plus pathways involving systematic low-grade inflammation, the gut microbiota, and changes in gastric emptying. The key, the authors go on to report, is that treatments should target pathways with the most relevance to each individual patient and to treat the most number of pathways with the least number of interventions, and because the pathways are not unique to one particular type of diabetes or prediabetes, they suggest that treatments can have broader applicability than currently possible. Finally, they urge all the major diabetes organizations to reevaluate diabetes classifications with the aim of informing research programs and ultimately improving patient care. Commenting more widely on their call to action, Dr. Schwartz stated: "The current, older, valid-at-the-time, classification system has just outlived its usefulness in the face of new knowledge. Our new construct seems intuitively obvious and provides a structure to give direction for research, education, public health policy, and, most importantly, better therapy for all patients with diabetes."

Schwartz et al. The time is right for a new classification system for diabetes: rationale and implications of the β-cell–centric classification schema. Diabetes Care 2016;39:179–186

Semaglutide Dose Escalation Established in Trial for Type 2 Diabetes Glucose Control

Efforts to optimize semaglutide for glucose control in type 2 diabetes treatment continue with the results of a randomized trial (**p. 231**) suggesting that weekly doses are sufficient for reducing both HbA_{1c} and weight in a clinically meaningful manner. On top of this, it is likely that dose escalation could be key for reducing side effects that have consistently posed an issue for the drug in the past. The phase 2 study by Nauck et al. investigated the dose-response relationship of semaglutide versus placebo and positive control liraglutide. They established that weekly injections over 12 weeks could reduce HbA_{1c} by up to 1.7% and weight by up to 4.8 kg. There was also a dose-dependent increase in gastrointestinal side effects. The attraction of using semaglutide is that it has a long duration of action, meaning it can be given weekly. In comparison with other GLP-1 agonists that are given as much as daily, this is seen as a considerable advantage. However, gastrointestinal side effects have been a consistent issue to the extent that the drug was not taken to phase 3 before this trial. Significantly then, the establishment of efficacy and acceptable side effects following dose escalation over 4 weeks means that semaglutide has since been taken into phase 3 studies. The SUSTAIN trial program, which is a series of phase 3 trials looking into clinical use of semaglutide in type 2 diabetes, is due to start reporting in 2016. Commenting more widely on the study, Dr. Nauck stated: "Whereas most once-weekly GLP-1 receptor agonists provide weaker effects with regard to glucose control and body weight reduction, semaglutide seems to be unique in being more effective even than daily liraglutide, the reference compound. Thus, there seems to be a chance to develop the class of GLP-1 receptor agonists to have greater effectiveness and the convenience of once-weekly administration in one compound. It is hoped that a slower uptitration schedule will mitigate the gastrointestinal adverse events with semaglutide."

Nauck et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. Diabetes Care 2016;39:231–241

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Metformin Lowers Glucose in Diabetes via Mechanisms in the Gut

A set of clinical studies (**p. 198**) suggests that metformin reduces blood glucose levels primarily via mechanisms in the gut rather than blood circulation and that metformin delivered directly to the lower bowel may be as effective in type 2 diabetes at lower doses in comparison with the standard version. The studies by Buse et al. focus on an encapsulated form of metformin that ensures that the drug becomes available only in the distal small intestine and beyond. This meant they could study the suspected gastrointestinal mechanisms while largely excluding any plasma-related effects. The first study focused on bioavailability of metformin in a crossover design in 20 volunteers and demonstrated that plasma concentrations were ~50% lower than standard and extended-release versions of metformin. There was also a significant delay in peak plasma concentrations. Meanwhile in the second study, which used a larger placebo-controlled, multicenter, dose-finding design, they found that the encapsulated delayed-release metformin produced sustained reductions in fasting plasma glucose over the 12 weeks of the study. This was in comparison with placebo. In comparison with an extended-release version of metformin, the encapsulated version may be ~40% more potent, as the authors report. The outcomes, according to the authors, suggest that the approach could have significant consequences for patients with diabetes with impaired renal function, since metformin is contraindicated in their case due to risks of lactic acidosis. This is because the encapsulated type reduces plasma exposure and thus potential lactic acid buildup. Perhaps more importantly, this discovery will enrich the debate around metformin and its mechanisms, which have never been fully established. The authors suggest that secretion of gut peptides including GLP-1 into the circulation, bile acid metabolism, and indeed metabolism by the gut microbiome may all contribute to the glucose-lowering effects of metformin. Commenting on the significance of the results, Dr. Fineman stated: "Discovery of this novel mechanism of action allows for development of a product that may meet the large unserved population with type 2 diabetes with renal impairment."

Buse et al. The primary glucose-lowering effect of metformin resides in the gut, not the circulation: results from short-term pharmacokinetic and 12-week dose-ranging studies. Diabetes Care 2016;39:198–205

CNS Responses to Food Cues Are Decreased in the Short Term Following Treatment With Liraglutide, a GLP-1 Agonist

Liraglutide, a GLP-1 receptor agonist, is associated with reduced appetite and weight loss in diabetes, and, according to a clinical study by ten Kulve et al. (**p. 214**), the drug might achieve this through decreased central nervous system (CNS) activation. Using a randomized crossover design, the authors compared liraglutide with insulin glargine (a long-acting insulin analog) and then determined effects of the treatments on CNS responses to food pictures via fMRI. Sampling was performed at baseline, after 10 days, and after 12 weeks. Exposure to the food pictures did not differ in terms of CNS responses between the two treatments at baseline or after 12 weeks. However, there were reduced effects in patients treated with liraglutide after 10 days. In particular, effects were noted in insula, putamen, and amygdala areas of the brain, which, the authors note, all are involved in regulation of feeding and particularly reward processing. Accordingly, this suggests that the effects of liraglutide on CNS may contribute to the induction of weight loss but not necessarily to its maintenance. Commenting more widely on the study, Dr. ten Kulve stated: "The role of CNS in the regulation of food intake and appetite is well known. Research investigating which signals or hormones may influence CNS responses to food and food intake is important, as this may help to understand pathophysiological mechanisms contributing to overfeeding and obesity and may aid the development of treatment strategies for obesity. We now show that treatment with GLP-1 analog affects CNS responses to food stimuli and may alter food intake by this mechanism. However, since this effect ceased to be significant after longer-term therapy, we believe that it is important to investigate why this effect decreases during treatment and whether combining therapy with other hormones may improve the effect on CNS and consequently on weight reduction."

ten Kulve et al. Liraglutide reduces CNS activation in response to visual food cues only after short-term treatment in patients with type 2 diabetes. Diabetes Care 2016;39:214–221

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