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Diabetes Care®

In This Issue of *Diabetes Care*

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Joint Position Statement on Reporting Blood Glucose Levels in Relevant Clinical Trials of Glucose-Lowering Drugs

A joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes in this issue of *Diabetes Care* details the recommendations of the International Hypoglycaemia Study Group (IHSG) (**p. 155**) for the inclusion of the frequency of detection of blood glucose concentrations <3.0 mmol/L (<54 mg/dL) in reports of clinical trials of glucose-lowering drugs for diabetes. According to the IHSG, this level of blood glucose is important as it unequivocally represents a level that is "clinically significant biochemical hypoglycemia." The definition of such a threshold should allow comparison of the effectiveness of interventions in reducing hypoglycemia and additionally permit meta-analysis as a tool to compare interventions. Based on this, the IHSG calls for all relevant publications on clinical trials of relevant drugs to include the number. The IHSG suggests that blood glucose concentrations <3.0 mmol/L do not occur in individuals without diabetes and so, therefore, unequivocally represent hypoglycemia. Additionally, the IHSG suggests that such levels cause defective glucose counterregulation as well as impaired awareness of hypoglycemia and that the level is associated with increased mortality in a number of major studies. Ultimately the study group agreed that a level of <3.0 mmol/L is sufficiently low to indicate serious clinically important hypoglycemia. The ADA previously has not quantitatively defined a blood glucose level that represents hypoglycemia because the threshold likely varies between individuals. It has previously only loosely defined hypoglycemia as episodes of abnormally low glucose levels that expose an individual to harm and severe hypoglycemia as an episode additionally requiring another person's help to recover. Commenting more widely on the statement and recommendations, the chair of the IHSG, Simon Heller said: "It is increasingly clear that hypoglycemic episodes that are not classified as severe are associated with clinically important consequences including mortality. If the diabetes community can agree on an additional glucose level that captures this information, we can both calculate the clinical risk to patients and more effectively compare treatments and approaches that aim to reduce rates of hypoglycemia. This would be an important advance."

International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155–157

ADA Statement on Prevention and Treatment of Diabetic Neuropathy

A position statement from the American Diabetes Association (ADA) summarizes various forms of diabetic neuropathy for practicing clinicians and provides new evidence-based recommendations for its diagnosis and management. In particular, the statement provides updates on distal symmetric polyneuropathy (DSPN) and cardiovascular autonomic neuropathy (CAN), two of the most common forms of neuropathy encountered in practice. According to the statement, authored by Pop-Busui et al. (**p. 136**), prevention of both DSPN and CAN should be of primary concern since no treatments exist that can reverse the underlying nerve damage that is characteristic of diabetic neuropathy. In short, prevention should be focused on optimal glucose control in both type 1 and type 2 diabetes and also on lifestyle modifications. The statement discusses in more detail DSPN screening and diagnosis and provides evidence-based recommendations for the available drug interventions for pain management. It includes a specific warning against the use of opioids due to the very high risk of addiction and other serious complications. Additional considerations are also given on the treatment of foot complications, fall prevention, and psychosocial issues. A series of recommendations are also provided for CAN with a focus on clinical manifestations, key diagnostic steps for clinical practice, and the evidence relating to its prevention. Again, glucose control and lifestyle modifications are the primary strategies for prevention. As with DSPN, therapies for CAN once it is established reportedly focus on alleviating symptoms. Further consideration is also given to less common or atypical neuropathies such as gastrointestinal, urogenital, and mononeuropathies. Finally, a series of recommendations are made on the ideal end points to be used in research and future clinical studies. According to the co-chairs of the position statement Rodica Pop-Busui and Andrew J.M. Boulton: "This new ADA statement, the work product of an international panel of recognized experts in diabetic neuropathy, summarizes the most up-to-date data in this field with the goal to provide all clinicians with straightforward, practical, and evidence-based approaches for the diagnosis and management of diabetic neuropathy."

Pop-Busui et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40:136–154

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Cardiovascular Autonomic Neuropathy Modifies Later Cardiovascular Risk in Type 1 Diabetes: The DCCT/EDIC Study

The outcomes of another analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study suggest that cardiovascular autonomic neuropathy (CAN) in type 1 diabetes may predict higher long-term risk of cardiovascular disease (CVD) events. According to Pop-Busui et al. (**p. 94**), while the diagnosis of CAN is likely to be useful for identifying individuals at higher risk of CVD events, it is not independent of historic glycemic exposure (HbA_{1c}), underlining its utility to predict risk and the use of intensive glucose control in the disease. The analysis is based on the DCCT cohort and subsequent EDIC long-term follow-up and includes detailed assessments of medical history and status and a protocol to monitor the development of CAN. Following the DCCT closeout assessment (the baseline), more participants with CAN (25%) had a CVD event during the EDIC follow-up than those who did not have CAN at baseline (10%). The cumulative incidence of first occurrence of CVD events was also reportedly significantly higher in the participants with CAN at baseline. However, after adjusting for numerous factors relating to CVD risk, including HbA_{1c}, the independent association between CAN and CVD became attenuated. In particular, nearly all differences between the prior treatment groups could be explained by differences in HbA_{1c}. Commenting on the study, author Rodica Pop-Busui told *Diabetes Care*: "In this large study we showed that an earlier diagnosis of CAN was associated with an increased risk for subsequent CVD events in patients with type 1 diabetes after controlling for multiple traditional risk factors. Although CAN was not an independent predictor with respect to the glucose control over time as documented by the HbA_{1c}, it is to be noted that the HbA_{1c} is one of the major determinants of CAN in these patients. Thus, a diagnosis of CAN identifies individuals with type 1 diabetes at high risk for developing major CVD events over time."

Pop-Busui et al. Cardiovascular autonomic neuropathy and cardiovascular outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes Care 2017;40:94–100

Metformin Action Mediated By Specific Gut Microbes Involved in Intestinal Barrier Function

More evidence of the role of the gut microbiota in the mode of action of metformin is reported this month by de la Cuesta-Zuluaga et al. (**p. 54**) with the suggestion that metformin may specifically promote a number of species involved in either mucin degradation, short-chain fatty acid production, or both, hinting at improved intestinal barrier function and that these effects might drive the glucose-lowering effect of the drug. The study focused on a large Colombian cohort in which 28 individuals with type 2 diabetes were identified, and specifically 14 were taking metformin and 14 were not. They were then matched 1:3 with 84 participants without diabetes on the basis of sex, age, and BMI. After collecting information on demographics, anthropometrics, and blood chemistry, the researchers then collected fecal samples and subjected those to 16S rRNA gene sequencing to deeply examine the composition and structure of the microbiota at the molecular level. Confirming previous reports, the authors write that they found significant associations between diabetes status and microbiota community structure and that metformin did significantly modify composition. Author Juan S. Escobar said: "On one hand, we hope this work will foster others to disentangle the effect of [metformin] treatment from disease-associated dysbiosis. Our study demonstrates that the mechanism of action of metformin medication might partly be mediated by the gut microbiota and that its effects are different from those directly produced by diabetes. On the other hand, metformin is a beautiful example of a molecule that may be able to modulate the gut microbiota in a positive way." And according to author Noel T. Mueller: "What is needed now are randomized controlled trials to determine whether the associations observed in our study may be causal. This line of inquiry could help inform novel ways in which metformin could potentially be used to prevent and treat an assortment of gut microbiota–associated diseases, beyond just type 2 diabetes."

de la Cuesta-Zuluaga et al. Metformin is associated with higher relative abundance of mucin-degrading *Akkermansia muciniphila* and several short-chain fatty acid–producing microbiota in the gut. Diabetes Care 2017;40:54–62

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