International Hypoglycaemia Study Group
Diabetic Hypoglycaemia: New Thinking, new Tools
A symposium at the 53rd EASD meeting
14 September, 2017
Lisbon, Portugal

Unanswered questions during the Q&A portion of the symposium

**Q: If we treat patients to target HbA1C, does this not raise the risk of hypoglycaemia?**
As you will have seen from the presentation, HbA1c is not a consistent marker of risk for severe hypoglycaemia. If we treat all patients to the same tight target, some may have an increased risk of hypoglycaemia while others may not, which underscores the importance of individualized targets. One situation where hypoglycaemia risk is increased is when there is a rapid fall in overall glycaemic control to below or target levels. There may also be more silent hypoglycaemia when HbA1C falls below target. Structured education, frequent monitoring and use of appropriate insulin therapies are key to avoiding hypoglycaemia.

**Q: Do we have a mechanistic explanation for why some people with poor glucose control experience hypoglycaemia at higher blood glucose levels?**
One explanation for this phenomenon, at least in theory, is that some people with poor glucose control may have greater glucose variability. Another possible cause is a shift in the glucose threshold for the counterregulatory response: Just as the threshold shifts to lower glucose values when glucose control improves, it shifts to higher glucose levels when glucose control worsens.

It is important to reassure people that although they may develop symptoms, there is no evidence they can lose consciousness at these higher glucose levels. People are not at risk from brain dysfunction until glucose drops below 3 (54mg/dl). Furthermore, if glucose levels are brought closer to target, these symptoms only develop at glucose levels below 4mmol/l (70mg/dl).

**Q: Why does the supine position reduce the sympathetic response?**
It is well recognized that the increase in hypoglycaemia symptom scores is about 50% less when people are supine than when standing erect. According to one hypothesis, moving to an upright position may prime the adenoreceptors. Combined with diminished catecholamine and symptom responses during sleep, this phenomenon may explain why night time is the period of greatest risk for severe hypoglycaemia.
Q: Does recurrent hypoglycaemia, if not severe, damage the neurons?

At present there is no robust evidence that recurrent moderate hypoglycaemia has long-term detrimental effects on brain function. However, because clinical trials have focused on monitoring severe hypoglycaemia and because cognitive changes take many years to develop, we really do not know the answer to this question. Studies in animal models do suggest there may be consequences from recurrent moderate hypoglycaemia in diabetes, but much more work needs to be done before we can confidently answer this question.

Q: Can you elaborate on the role of exercise in hypoglycaemia and the strategies to avoid it?

It is important first of all to recognize that different forms of exercise have very different effects on glucose profiles and on hypoglycaemia risk. In general, low-moderate intensity aerobic exercise (e.g. walking, jogging) where fuel use is largely through fat oxidation will lead to a drop in glucose levels so there is a risk of hypoglycaemia during exercise. With high-intensity exercise that is more anaerobic, glucose levels may actually rise, but this can lead some individuals to take a corrective dose of insulin and subsequently develop hypoglycaemia shortly after the exercise programme. The night after exercising, there is an additional risk of hypoglycaemia that may stem from increased insulin sensitivity combined with suppression of the nocturnal counterregulatory response.

Any individual with type 1 diabetes embarking on an exercise programme needs to consider hypoglycaemia risk and seek help from their care team to adjust insulin, glucose and carbohydrate management strategies accordingly. Strategies need to be individualized based on the type and duration of exercise. Further information is available at: http://www.runsweet.com

Q: What is the counter-regulatory physiology in recurrent hypoglycaemia with IAH?

This is a difficult question to answer, because the counterregulatory response to hypoglycaemia is complex and involves behavioral and psychological as well as physiological responses to low glucose. We know that exposure to recurrent hypoglycemia leads to a gradual decrease in the glucose level that activates the autonomic (sweating, palpitations, tremor) symptomatic and adrenaline responses to hypoglycaemia, to the point that these symptoms may only occur at the threshold for cognitive dysfunction. This reduces patients’ ability to both perceive and respond to the warning of hypoglycaemia.
Q: Is there a role for islet-cell/pancreatic transplantation for patients with IAH? If so, which subset of patients should be offered this treatment?

Transplantation of either whole-pancreas may be worth considering when recurrent severe hypoglycaemia is having a major effect on quality of life and has not responded to other non-surgical approaches such as structured education, insulin pump use and continuous glucose monitoring. It should be noted that this procedure is only available in a few specialist centers and limited by organ availability and adverse effects.

Q: What are the indications for lowering insulin as a strategy to reduce the risk of hypoglycaemia?

This depends on the situation. For example, if an individual is going to exercise within 2 hours of injecting short-acting insulin to cover a meal, the usual recommendation is to reduce the dose by 50%, with further adjustments as needed. If an individual is planning to go hiking for a few hours, a reduction of 25-90% in basal insulin dose, beginning 90 minutes before the start of the hike, is often advised. In individuals experiencing multiple hypoglycaemic episodes, the strategy needs to incorporate a review of basal insulin needs and carb counting and an examination of the factors that may be precipitating the hypoglycaemia.

Q: Might high-intensity exercise (to restore hypoglycaemia awareness) also work for IAH in nondiabetic hypoglycaemia?

The answer to this question is unknown. The use of high-intensity exercise to restore hypoglycaemia awareness is based on the hypothesis that IAH develops through a process referred to as habituation. Introducing a novel, strong stimulus through dishabituation would then be expected to restore, temporarily, the habituated response. A study in non-diabetic animals exposed to recurrent hypoglycaemia showed that a single burst of high-intensity exercise did indeed restore the suppressed counterregulatory response. To validate this hypothesis, we would need to conduct similar studies in humans.

Q: How important is glycaemic variability and how should we measure it in the clinic? Should we use standard deviation, MAGE, CONGA, or something else?

A growing body of evidence suggests that glycemic variability (GV) may be an independent risk factor for macrovascular complications of diabetes. The simplest method to assess GV is standard deviation (SD), which is a measure of glucose dispersion. Other methods include MAGE [mean amplitude of glycemic excursions], mean of daily differences, and the more complex CONGA [continuous overall net glycaemic action]. Low Blood Glucose Index (LBGI), also provides a measure of hypoglycaemia risk. To date, there is no conclusive evidence favouring one method over another and HbA1c remains by far the most powerful risk predictor of diabetic complications.