Hypoglycaemia and the heart – cause and effect

KEY MESSAGES

- Hypoglycaemia is a contributor to cardiovascular disease (CVD) and all-cause mortality in diabetes
- There are multiple mechanisms by which hypoglycaemia increases risk of CVD
- Important risk factors for hypoglycaemia are duration of diabetes and insulin therapy
- Symptoms of hypoglycaemia in older patients are often attributed to CVD
- Prolonged effects of hypoglycaemia on cardiac autonomic neuropathy, inflammatory cytokines and coagulation may explain why a direct link between hypoglycaemia and mortality is difficult to make.

“The use of this level is problematic as it is frequently reached without any particular consequences in early type 2 diabetes.” Dr Zane Stevens, specialist endocrinologist in private practice from Cape Town, noted at the outset of his presentation on hypoglycaemia and the heart at the Diabetes Update Symposium held in Cape Town in January.

“With regard to interpreting clinical trials, it is probably more useful to focus on just two categories – severe hypoglycaemia, where the help of another person/healthcare provider is required to deal with the situation or mild hypoglycaemia, which the diabetic patient can address himself.”

“We tend to associate hypoglycaemia with type 1 diabetes, and where our type 2 diabetic patients are concerned, we focus on getting HbA1c levels down, rather than thinking about hypoglycaemic consequences,” Dr Stevens pointed out.

The incidence of hypoglycaemia is, however, related to the duration of type 2 diabetes and duration of insulin therapy. After five years of insulin treatment type 2 diabetic subjects experience more hypoglycaemic events than type 1 diabetics in the first five years of their insulin treatment (Figure 1). It is important to realise in interpreting the lower prevalence of mild hypoglycaemia and severe hypoglycaemia in type 2 diabetes as compared to type 1 diabetic patients that the overall burden for the healthcare system nonetheless lies with type 2 diabetic-related hypoglycaemia because of the numbers. There are many more type 2 diabetics than type 1 diabetic patients.

Hypoglycaemia is of particular concern in the elderly as compensatory mechanisms for hypoglycaemia are down-regulated with age. In addition, 74% of asymptomatic hypoglycaemic...
Hypoglycaemia and glucose variability

events occur at night when adrenergic responses are blunted allowing a vagal response, which has been associated with the ‘death-in-bed’ phenomenon.3

The physiological response to hypoglycaemia is also important to our understanding of its consequences; the initiating response is a down-regulation of endogenous insulin secretion, increased glucagon and an increased sympathoadrenal response leading to elevated plasma adrenaline/noradrenaline, which signals the need to address the hypoglycaemia. Indirectly, hypoglycaemia also results in an inflammatory cytokine response, endothelial dysfunction, reduced vasodilation and pro-coagulation effects which last for 2-3 days after a hypoglycaemic event, thereby complicating the interpretation of the consequences of hypoglycaemia on the cardiovascular system.

Table 1. Response to hypoglycaemia

- Decreased insulin
- Increased glucagon
- Increased sympathoadrenal response
- Elevated plasma adrenaline/noradrenaline
- Elevated adrenocorticotropic hormone (ACTH) and glucocorticoids
- Indirectly: Inflammatory cytokine response, endothelial dysfunction, effects on coagulation

It is possible that hypoglycaemia-induced rhythm abnormalities combined with autonomic neuropathy contribute to the risk of death in diabetes. However, there is a paradox here as individuals with cardiac autonomic neuropathy, and an existing longer QT interval, experience lesser increases in the QT interval as a result of hypoglycaemia.4 “Perhaps this is a protective effect, similar to ischaemic preconditioning, although this is currently uncertain,” Dr Stevens pointed out. In addition, there is evidence that hypoglycaemia begets hypoglycaemia in diabetic patients, because recurrence reduces the glucose level that precipitates the counter-regulatory response to restore euglycaemia. This phenomenon is referred to as hypoglycaemia-associated autonomic failure (HAAF). This condition can be partially reversed by carefully avoiding hypoglycaemic events.

Dr Stevens concluded that hypoglycaemia contributes to cardiovascular morbidity and mortality via a number of mechanisms and deserves much more attention in type 2 diabetes management.
Blood glucose variability

“Not everything that counts can be counted and not everything that can be counted, counts” Albert Einstein

KEY MESSAGES

• It has been suggested that in addition to fasting glucose, ‘glucose variability’ might be a factor in vascular endpoints in diabetes
• However, there is no clear opinion on its exact role, if any
• Whether it’s important and how it should be measured and treated has been the subject of much debate
• Current thinking is that it may be less important with regard to long-term outcomes such as cardiovascular events than was previously thought, given more recent findings from studies such as the HEART2D study
• HbA1c remains the primary element of focus when it comes to cardiovascular endpoints and needs to be optimised via a combination of lifestyle measures and treatment compliance
• Glucose variability does matter to patients as it affects quality of life. Patient behaviours such as taking their insulin, diet and exercise can help to reduce variability.

“It is well known that dysglycaemia is associated with atherosclerosis progression and there is a clear link between higher blood glucose levels and increased cardiovascular risk,” said Dr David Segal.

The DECODE study \(^5\) in 1999 suggested that both elevated fasting and post-prandial blood glucose levels contribute individually and additively to cardiovascular risk.

Equally, hypoglycaemia and its contribution to cardiovascular risk are receiving more attention today and there is some evidence that increased glucose variability increases the risk of hypoglycaemia.

“The term ‘glucose variability’ was born in 1995 after further analysis of type 1 diabetes patients in the intensive and conventional arms of the DCCT trial who had the same HbA1c but a different calculated risk of complications.” \(^6\) The lower rate of complications in the intensive arm was ascribed to reduced glucose variability as compared to the conventional therapy.

But what is the evidence for this? “Does glucose variability matter, and should we be measuring and treating it?” asked Dr Segal. “And how do you measure it? How much amplitude is acceptable? Does the frequency of the swings or duration of the variable period play a role?”

There are many mathematical models for calculating variability, but mean amplitude of glycaemic excursion (MAGE) and SD are the most commonly used (Figure 2). \(^7\)

Experimental evidence in rats has shown that intermittent high glucose levels are associated with increased apoptosis and endothelial dysfunction. However, the role of glycaemic variability in humans is less clear cut. A 2006 study by Monnier \(\text{et al.}^8\) suggested that glucose fluctuations during postprandial periods and, more generally, during glucose swings exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycaemia and that interventional trials in type 2 diabetes should target not only HbA1c and mean glucose concentrations but also acute glucose swings.

However, when reviewing the evidence for putting glucose variability into or out of the heart of glycaemic disorders in type 2 diabetes five years later, Monnier and Colette \(\text{et al.}^9\) concluded that while there is ‘consensus’ that total glucose exposure as reflected by HbA1c levels represents a major risk factor for the development or progression of diabetes complications, there is continuing dissent (‘dissensus’) on glycaemic variability. “At present, there is no evidence-based data that permit … a clear opinion on its exact role. Further studies are warranted for confirming or refuting the role of glycaemic variability.
For the moment, we are certainly not at the end of the glucose variability story, but it is difficult to know whether we are at the beginning of the end or at the end of the beginning.”

The most important aspect for the clinician is whether glucose variability matters to patients in terms of adverse outcome.

“A 2008 re-analysis of the DCCT findings showed them to be flawed,” continued Dr Segal. “Glucose variability explains only a small part of the differences seen with either conventional or intensive treatment and HbA1c remains the primary element.” Efforts have been made to see if glucose variability matters in the HEART2D study, which evaluated insulin treatment strategies targeting either post-prandial hyperglycaemia (in order to reduce intraday-variability) versus insulin therapy targeting fasting/interprandial hyperglycaemia in type 2 patients who had experienced an MI. Despite an 18% lower MAGE in the post-prandial focus, there was no difference in glycaemic control or in cardiovascular events between the two therapies (Figure 3). “So now we know glucose variability exists, but not how important it is or whether it should be addressed. However it must be acknowledged that glycaemic variability affects patients’ quality of life.”

What can be done about glucose variability by the clinician? The use of long-acting analogues and GLP-1s can help to reduce glucose variability. “It also comes down to patient behaviour, including whether they take their medication regularly,” said Dr Segal. “Behaviours matter and can be used to moderate glucose variability. Patients need to teach themselves how much to eat and how much to inject.
“Current thinking is that glucose variability may be less important with regard to long-term outcomes such as cardiovascular events than was previously thought”

Dr David Segal

At least 50% of patients don’t take their insulin every day. Taking all their insulin, taking it on time and following a meal plan proven to reduce blood glucose fluctuations will give patients the best chance of achieving HbA1c targets.

When it comes to diet, Dr Segal feels that a diet low in refined carbohydrates is advisable as high carbohydrate loads lead to an exponential increase in post-prandial blood glucose. Where exercise is concerned, a combination of aerobic and anaerobic is good for long-term HbA1c control. A surprising recent finding is that an alcoholic drink before a meal can also help with post-prandial glucose control and in this regard wine, beer and gin all offer advantages over water.12

Concluding, Dr Segal underscored that while glucose variability does play a role, it is probably not as important as was once thought and has only a small effect on vascular endpoints. “HbA1c is still the key factor when it comes to overall complications and we need to focus on lifestyle measures to optimise it,” he concluded.
Bone and diabetes – the intersection

**KEY MESSAGES**

- In type 1 diabetes mellitus poor glucose control and episodes of diabetic ketoacidosis affect bone quality at a time when bone formation should be optimal. This then predisposes to osteoporosis in later years.

- Osteoporosis should be excluded in both male and female patients who suffer from diabetes.

- Improved glycaemic control affects bone quality positively; at HbA1c >10% there is evidence of increased bone resorption.

- Diabetic medication has an effect on bone quality; insulin counters bone loss and improves osteosteat activity, while thiazolidinediones may have an adverse effect on bone formation. Metformin has a direct protective effect on bone as it reduces advanced glycated end-products (AGEs), while incretin mimetics are reported to reduce bone fractures.

- Favoured treatment options are the bisphosphonates (inhibitors of bone resorption that increase bone mineral density (BMD) by altering osteosteat activation and function) and strontium ranelate (effective on bone formation and resorption, thereby improving bone architecture and strength of both cortical and trabecular bone).

- Ensure an adequate vitamin D and calcium intake.

**References**


