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HYPOGLYCAEMIA, CARDIOVASCULAR RISK, AND WEIGHT: WHAT ARE THE GOLD STANDARDS FOR TREATMENT OF TYPE 2 DIABETES?

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ABSTRACT

Hypoglycaemia is a side effect of diabetes treatment. It is commonly associated with symptoms that alert the individual to take corrective actions to prevent further reduction in blood glucose level. Impaired awareness of hypoglycaemia (IAH) refers to the diminished ability to pick up symptoms of hypoglycaemia. Patients with IAH may fail to take corrective actions to prevent worsening hypoglycaemia. Such individuals may potentially lose consciousness or fall into coma as blood glucose level continues to decrease. Hence, it is important to address hypoglycaemia during clinic consultations.

Sodium-glucose-co-transporter 2 (SGLT2) inhibitors and Glucagon-like-peptide-1 (GLP-1) receptors agonists are two classes of diabetes treatment that target cardiovascular risk of type 2 diabetes treatments. These two agents should be used early in the course of treatment of diabetes.

The gold standard for type 2 diabetes treatment should be aimed at lowering glycated haemoglobin, addressing cardiovascular risk, and minimising hypoglycaemia. Type 2 diabetes treatment should be patient-centred and individualised especially for elderly patients with significant comorbidities.

Keywords: Hypoglycaemia, Type 2 diabetes

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WHAT IS HYPOGLYCAEMIA?

Hypoglycaemia refers to low blood sugar levels, which is typically referring to a blood glucose level of <4 mmol/l. Cells in the body, particularly the brain, need glucose as a form of fuel. Four mmol/l is generally used as the threshold for treatment of hypoglycaemia. Severe hypoglycaemia refers to an episode of hypoglycaemia whereby third-party assistance is required as the patient has been incapacitated by the hypoglycaemic event. Brain functions are severely compromised when blood glucose level falls to a very low level, which is when loss of consciousness, seizures, and coma may set in.

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Hypoglycaemia rate for type 1 diabetes is about two episodes per week, with severe hypoglycaemia rate of 1-2 episodes per patient year.[1,2] Data on hypoglycaemia rate among type 2 diabetes vary widely, depending on the methodologies being used. Severe hypoglycaemia rate among type 2 diabetes is believed to be approximately 0.2 episodes per 100 patient years for non-insulin-treated or sulphonylurea-treated, and around two episodes per 100 patient years for insulin-treated or sulphonylurea-treated.[3] More worrying is untreated severe hypoglycaemia leading to seizure, coma, or even death as the blood glucose level is no longer able to support normal brain functions.

Hypoglycaemia is associated with counterregulatory responses that collectively aim to bring the blood glucose level back up to the normal level. The counterregulatory responses consist of increased glucagon, catecholamines, cortisol, and growth hormone levels. Hypoglycaemia is also associated with symptomatic responses that are collectively termed either autonomic, neuroglycopenia, or non- specific symptoms. Examples of such symptoms are palpitations, tremors, and sweating, which alert the affected individuals about the falling blood glucose levels so that appropriate corrective actions can be taken to restore the blood glucose levels.

However, recurrent episodes of hypoglycaemia is associated with progressive blunting of the counterregulatory hormonal responses and hypoglycaemic symptoms. Hence, individuals with recurrent hypoglycaemia experience very few or no symptoms of hypoglycaemia. This can be problematic for the individual concerned as the blood glucose can fall quickly into a range that insufficient to support brain function. This diminished ability to perceive the onset of hypoglycaemia is termed as impaired awareness of hypoglycaemia (IAH).[4]

IAH is reported to affect between 10 to 33 percent of insulin-treated type 2 diabetes in Singapore, with a severe hypoglycaemia rate of seven percent per year depending on the type of questionnaire used.[5] Many of these patients are older adults who are more likely to be adversely affected by severe hypoglycaemia. IAH can be picked up by careful clinical history-taking. Simple questionnaires such as the Gold questionnaire have been developed to quantify the extent of IAH.[6] The Gold questionnaire uses a single question of asking the respondents to assess their abilities to pick up hypoglycaemia from a score of 1 (always aware) to 7 (never aware). It is important to appreciate that complete absence of hypoglycaemia symptoms is rare in clinical practice but what is more commonly reported is a diminished or vague set of hypoglycaemia symptoms associated with very low blood glucose level. It is important to pick this up in the routine clinical assessment of diabetes patients, particularly those with seemingly good Hba1c.

Education is the key towards reversal of IAH. Capillary blood glucose monitoring forms a significant part of the education programme to reverse IAH. Affected individuals should be able to appreciate the potential detrimental effects of IAH. Relaxation of capillary glucose targets is key towards reversal of IAH. The affected individuals and the clinicians involved should appreciate that severe hypoglycaemia brings about immediate risk to the affected individual with IAH whereas reducing diabetes complications through tight glycaemic control occurs over years. Hence, the relaxation of glycaemic targets in an attempt to reverse IAH is of paramount importance for diabetic patients with IAH. However, the glycaemic targets can be tightened appropriately once hypoglycaemia awareness status has been restored.

IS HYPOGLYCAEMIA A CARDIOVASCULAR RISK FACTOR?

The UK Prospective Diabetes Study showed reduction in macro- and microvascular events.[7] However, three recent landmark trials failed to show a reduction in cardiovascular mortality with intensive diabetes treatment. The Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) showed an increase in cardiovascular mortality with intensive treatment of diabetes. This led to an early termination of ACCORD, which divided the diabetes patients into two groups: the intensively controlled arm which showed an increased mortality and the less intensively controlled arm.[8]

It is difficult to attribute causality. Hypoglycaemia may be a contributory factor. Hypoglycaemia has been shown to be associated with adverse haemodynamic sequelae through actions of the catecholamines on the cardiovascular system. But it is conceivable that hypoglycaemia may behave as a cardiovascular risk factor. Hence, all effort should be focused on minimising the occurrence of hypoglycaemia amongst diabetic patients.

CARDIOVASCULAR RISK AND WEIGHT IN TYPE 2 DIABETES

Type 2 diabetes patients are at higher risk of developing cardiovascular complications such as myocardial infarction. Targeting risk factors such as smoking, lipid, blood pressure, weight, and glycaemic control is crucial in addressing cardiovascular risk.

Two classes of medications of interests have emerged in the past 10 to 20 years to address cardiovascular risk and weight issues.

SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

Sodium-glucose co-transporter 2 (SGLT2) inhibitors act through inhibition of renal glucose reabsorption, which result in excretion of up to 100 g of glucose at therapeutic doses. The removal of glucose from the circulation lowers the blood glucose levels and improves glycaemic control.

Besides lowering of glycated haemoglobin level of 0.5 to 0.9 percent within one year of commencement of SGLT2 inhibitors, there are associated weight and blood pressure reduction of 2 kg and 2.5-5 mmHg respectively.[9] Cardiovascular outcomes trials of SGLT2 inhibitors showed a 30 percent reduction in hospital admissions with heart failure and reduction in death associated with heart failure or arrhythmias.

Canagliflozin and renal outcomes trial have shown a 30 percent reduction in composite end stage renal disease associated with Canagliflozin as compared to placebo. There were also significant reductions in cardiovascular death and heart failure admissions among those on Canagliflozin.[10] Similarly impressive results were also highlighted by the use of Dapagliflozin as compared to placebo among patients with chronic kidney disease with or without diabetes in DAPA-CKD trial.[11]

Glucagon-Like-Peptide-1 (GLP-1)

Glucagon-like-peptide-1 (GLP-1) is released by intestinal L cells in response to glucose and fat. It is an incretin hormone that increases insulin released by pancreatic beta cells and decreases glucagon released by pancreatic alpha cells.[12] Moreover, it promotes satiety through its action on the hypothalamus. Hence, GLP-1 receptors agonists have been identified as a therapeutic standard for treatments of diabetes. Most of the GLP-1 receptors agonists are administered subcutaneously.

Liraglutide is the one of the most extensively studied GLP-1 receptors agonists. Liraglutide is associated with mean reduction in glycated haemoglobin of 0.9 to 2.2 percent and weight reduction of 1.3 to 8.65 kg.[13]

GLP-1 receptor agonists have shown a consistent effect of lowering glycated haemoglobin, weight, and blood pressure in clinical trials. Of note, the longer-acting GLP-1 receptors agonists lower the blood glucose level and cause less gastrointestinal side effects as compared with shorter-acting GLP-1 receptor agonists.[14]

Meta-analysis of seven clinical trials of GLP-1 receptor agonists involving 56,004 participants have shown significant reduction in all-cause mortality by 12 percent, hospital admissions for heart failure by nine percent, and composite renal outcomes by 17 percent.[15]

OPTIMISATION OF MODERN TYPE 2 DIABETES TREATMENTS AND OUTCOMES

A combination of SGLT2 inhibitors and GLP-1 receptor agonist with other diabetes treatment help to improve glycaemic control. One exception to this is the combination of GLP-1 receptor agonists with dipeptidyl-peptidase 4 inhibitors, which do not bring about additional benefits compared with just GLP-1 agonists on their own due to mechanisms of actions of these two medications. The combination of SGLT2 inhibitors and GLP-1 receptor agonists may have additive benefits due to different mechanisms of actions but this is yet to be proven. In current clinical practice, it is acceptable to combine these two agents whilst waiting for conclusive data to come out.

It is important to be aware of risk of retinopathy progression with rapid improvement in glycated haemoglobin level with the use of semaglutide. Frequent retinal screening should be considered for these patients.

A slow pace of titration is recommended for GLP-1 receptor agonists. This is to minimise the gastrointestinal side effects, which are often mild and transient.

It is important to consider the use of SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes patients with established atherosclerotic cardiovascular disease or high risk of cardiovascular diseases independent of glycated haemoglobin levels. SGLT2 inhibitors are preferred if there is a history of heart failure or chronic kidney disease, if the GFR is above 45 mL/min.

Metformin is still being recommended as first-line therapy for type 2 diabetes by most societies. There is some debate as to whether metformin confers cardiovascular benefits. This may not be easily resolved as most cardiovascular trials have not been conducted with SGLT2 inhibitors or GLP-1 receptor agonist as the first-line therapy. There are metabolic benefits associated with metformin use and early use of the SGLT2 inhibitors or GLP-1 receptors agonists for appropriate patients with established cardiovascular disease or who are at risk of cardiovascular disease is key to improving patient's outcomes.

Data from the US showed that less than three percent of type 2 diabetes patients in a study involving 150,000 type 2 diabetes patients were treated with statins, ACE inhibitors, or A2 receptors blocker and SGLT2 inhibitors or GLP-1 receptors agonists.[16] This shows that there is still some way to go in bridging the gap between clinical practice and treatment guidelines. We should aim to bridge the gap through early use of SGLT2 or GLP-1 receptor agonists in appropriate type 2 diabetes patients.

WHAT SHOULD WE AIM FOR IN TREATMENT OF TYPE 2 DIABETES? WHAT IS THE GOLD STANDARD?

The ideal agent for treatment of type 2 diabetes is one that lowers Hba1c, weight, hypoglycaemic, and cardiovascular risk.

Traditionally, doctors tend to focus on lowering Hba1c when treating type 2 diabetes. This may sometimes happen at the expense of increasing hypoglycaemic risk, which is unacceptable. The shift towards addressing cardiovascular disease, heart failure, and chronic kidney disease rather than just focusing on hyperglycaemia is welcomed. Many diabetes patients suffer from cardiovascular disease, which is a known complication of diabetes. There is also evidence to suggest that hypoglycaemia may be associated with increased cardiovascular mortality among diabetes patients.

SGLT2 inhibitors and GLP-1 receptor agonists are type 2 diabetes treatments that address cardiovascular risk. Current treatment guidelines advocate the early use of SGLT2 and GLP-1 receptors agonists in type 2 diabetes treatment to address cardiovascular risk independent of glycaemic control. Of note, these treatments do not cause hypoglycaemia in general, which is another advantage in deploying these treatments.

It is still reasonable to continue with metformin as the first-line agent. What is more important is early escalation of diabetes therapy in those patients with high cardiovascular risk or suboptimum diabetes control. All these should happen in conjunction with a well-structured education programme for type 2 diabetes patients, especially early in the course of the disease. Well-structured education is the cornerstone of good diabetes treatment. If patients do not have a proper understanding of diabetes control or institute appropriate changes in lifestyles, both patients and treating clinicians will not be in the driver's seat in treating diabetes. Progressively more diabetic medications are likely to be added to treatment therapy as the years go by due to deterioration in glycaemic control.

Finally, ideal treatment strategies need to be patient-centred and individualised especially for the very elderly type 2 diabetes patients with significant comorbidities.

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LEARNING POINTS

- **IAH predisposes the individual to severe hypoglycaemia due to diminished or absence of symptomatic responses to hypoglycaemia.**
- **Early use of SGLT2 inhibitors and GLP-1 receptors agonists is crucial to address the cardiovascular risk of type 2 diabetes patients.**
- **An ideal type 2 diabetes treatment strategy should lower glycated haemoglobin level, minimise weight gain, and reduce the likelihood of hypoglycaemia.**