



THE CEYLON MEDICAL JOURNAL

Established 1887

The Official Publication of the
Sri Lanka Medical Association

Volume 67, No. 3, September 2022

Quarterly ISSN 0009-0875

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Changing paradigm in the management of type 2 diabetes

DOI: <http://doi.org/10.4038/cmj.v67i3.9706>

Ceylon Medical Journal 2022; **67**: 71-74

Introduction

The global and local epidemic of diabetes

Diabetes is becoming a serious public health issue both globally and in the Sri Lankan context [1-3]. Most of this increase in diabetes is contributed by the rapid rise in type 2 diabetes (T2DM) compared to type 1 diabetes (T1DM). According to the latest estimates of the International Diabetes Federation (IDF) over 500 million people are affected with diabetes worldwide [1]. Diabetes prevalence in Sri Lanka among adults was reported as 10% in 2008 [2] and the urban prevalence was reported as 27.6% in 2018 [3]. Although data from recent studies are yet to be published the numbers may have further increased by now. Given the previous estimates of 26.1%, 62.6% and 50.8% on retinopathy, neuropathy, and nephropathy respectively, diabetes is going to contribute to increasing mortality and morbidity in the Sri Lankan population [4].

Main causes of mortality and morbidity in T2DM

Cardiovascular disease which includes ischemic heart disease and stroke are the main causes of mortality in patients with T2DM [5]. In addition, chronic kidney disease (CKD) and heart failure also have been identified as important causes of mortality and morbidity [5,6]. Diabetes foot disease is the other category of complications that increase hospitalization and morbidity as well as increased health care costs in patients with T2DM [7]. Any interventions aimed at reducing the mortality and morbidity in patients with T2DM should specifically address the above causes which mostly contributes to mortality and morbidity.

Glucose centric diabetes management in the past

Over several decades metformin and sulfonylureas coupled with lifestyle modification remained main strategies in the management of T2DM [8]. The subsequent additions, glitazones and alpha-glucosidase inhibitors remained third or fourth line and were less commonly used in the management of T2DM [9]. Insulin was considered when control was not achieved with oral therapies [10]. Whatever the initial treatment most patients with T2DM failed in achieving good glycaemic control with time [11]. None of the initial major randomized controlled trials using traditional therapies did show major benefits in the



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reduction of cardiovascular disease which is the main cause of mortality in patients with T2DM as well as all-cause mortality [12]. The long-term follow-up study of the United Kingdom Prospective Diabetes Study (UKPDS) [13] showed significant mortality and CVD risk reduction benefit suggesting a legacy effect when T2DM is managed intensively at early stage of disease rather than at later stage which may even be harmful as indicated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [12] study.

Ominous octet and pathophysiology based novel therapies

Research on basic and applied physiology has revealed several pathophysiological mechanisms in the causation of T2DM which include eight main mechanisms popularly labelled as the ominous octet [14]. Over the last one or two decades several newer therapies have been added to the diabetes pharmacological armamentarium predominantly based on the pathophysiology of T2DM. Incretin based therapies and sodium-glucose cotransporter-2 inhibitors (SGLT2i) stand out among these drugs due to many reasons [15, 16]. Incretin based therapies include Glucan Like Peptide Receptor Agonists (GLP1-RA) and Dipeptidyl-peptidase 4 inhibitors (DPP-4i) [15]. The main advantage of these agents is the lower risk of hypoglycaemia and being either weight neutral or ability to cause weight loss. In addition, the cardiovascular outcome studies (CVOTs) on mainly liraglutide, semaglutide and dulaglutide have shown marked benefits on weight loss, favourable CVD outcomes and overall mortality reduction in addition to some benefit on renal and heart failure outcomes [17]. The sodium-glucose cotransporter-2 (SGLT2) inhibitors are a novel class of pharmacological agents that act by inhibiting the reabsorption of glucose at proximal convoluted tubules [16]. In addition to sustainable glycemic control the other beneficial effects of SGLT2 inhibitors include significant weight loss, reducing insulin resistance, lowering of blood pressure and lower risk of hypoglycaemia [16]. The subsequent CVOTs on several key SGLT2i agents which included empagliflozin, dapagliflozin and kanagliflozin have shown marked reduction of CVD outcomes, CVD mortality, overall mortality, slowing the progression of DKD and reducing mortality and morbidity due to heart failure [18].

Remission strategies in T2DM

T2DM was considered a progressive incurable condition due to progressive beta cell failure. The common understanding was that beta cells that would initially fail would have an inevitable cell death. However, the increased use of bariatric surgery for weight control of severely obese individuals showed that a significant percentage of patients with T2DM who underwent bariatric surgery had their diabetes disappeared [19]. This knowledge led to a change of perception that T2DM is an irreversible condition. Recent studies like the Diabetes

Remission Clinical Trial (DiRECT) [20] and the Look AHEAD study [21] which aimed to achieve significant weight loss by very low calorie-based diets (VLCD) have shown that non-surgical remission is possible in patients with T2DM who achieves a loss of about 10kg body weight.

Paradigm shift in the management of patients with T2DM

Control versus remission

The knowledge on the possibility of reversing T2DM with (VLCD) approaches have led to efforts in the introduction of diabetes remission as a strategy in managing patients with T2DM especially those who were diagnosed within less than 5 years [22]. This needs to be further explored in low-income settings and if proven effective should be introduced to national management guidelines as it would have major benefits on health care systems in terms of cost reduction in addition to multiple benefits to patients.

Glucose centric treatment management versus outcome-based management

With the availability of pharmacological therapies that would reduce CVD, heart failure outcomes, reduces progression of diabetes kidney disease (DKD), overall mortality along with other benefits such as lower risk of hypoglycaemia and weight gain, consensus has emerged on the preferential use of these drugs to reduce outcomes rather than mere control of blood glucose in patients with T2DM (23). Accordingly in patients who had already had or having high risk of CVD or heart failure SGLT2 inhibitors with proven efficacy to reduce CVD and heart failure such as empagliflozin, kanagliflozin or dapagliflozin should be preferentially used unless contraindicated. GLP1Ras may be also considered in patients with high CVD risk. Patients who had early stages of DKD may benefit from the use of SGLT2is unless they have eGFR less than 20. Patients who would need weight loss or would have high risk from weight gain may benefit from SGLT2is or GLP1Ras based on other co-morbidities. Those who have higher risk of hypoglycaemia would be preferentially commenced on SGLT2is, DPP4is or GLP1Ras after metformin.

However, the cost of novel agents would be a major challenge in the current global and local economic recession. Medical fraternity along with policy makers should work with the industry in looking at cost reduction of these agents by adopting strategies like the use of low-cost good quality generics and local manufacturing in low-income countries. In the meantime, when the cost, availability and affordability make it prohibitive to use novel therapies, judicious use of sulfonylureas and insulin will help achieving glycaemic control [24]. The choice of sulfonylurea drug is important especially in elderly, those with CKD or has high risk of hypoglycaemia. In such patients long-acting renally excreted drugs like gliben-

clamide should be replaced with newer generation sulfonylureas such as gliclazide and glimepiride or agents with lower risk of hypoglycaemia such as tolbutamide.

Novel methods of monitoring and targets for control

Glycosylated haemoglobin (HbA1c) became the main target of glycaemic control after it was shown to be associated with diabetes outcomes in major studies like the UKPDS. However, HbA1c gives only the average blood glucose, and it does not detect or indicate major fluctuations both hypoglycaemia and episodic hyperglycaemia. Therefore, a patient who has episodes of serious hypoglycaemic episodes as well as hyperglycaemic episodes can have a very good HbA1c like a patient who has very consistent and good glycaemic control. The introduction of continuous glucose monitoring systems (CGMS) as well as flash glucose monitoring systems have enabled detection of numerous blood glucose readings with a course of a specified periods without the need for needle pricks [25]. These technologies have introduced a new set of targets and parameters that can be used in monitoring blood glucose. Time in range is a similar parameter which can be used to evaluate a person's overall glycaemic status and also been linked to outcomes [26]. Use of novel methods of glucose monitoring would help more people to detect and avoid major fluctuations of blood glucose and to be in acceptable range in their glucose profile [27].

Summary

As type 2 diabetes is affecting a large percentage of people in the society, innovative strategies need to be adopted to minimize the impact of the disease on the individuals as well as the society. Primary prevention strategies should be considered targeting high risk groups to reduce the overall burden of people with T2DM. Evaluation of remission strategies in lower- and middle-income countries and if successful widespread introduction in national guidelines would help reduce the number of patients needing pharmacological treatment. In addition, constant attention to lifestyle of patients would help achieve better glycemic control as well as in minimizing the pharmacological burden and cost of care. Selection of pharmacological therapies should be based on specific characteristics and prognostic benefit of the therapy on patients based on co-morbidities and risk factors like CVD, CKD, hypoglycaemia, obesity and heart failure instead of mere glucose control. However, the cost, availability and affordability should always be kept in mind in low resourced settings.

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