

### Treatment of Type 2 Diabetes Mellitus – What is the Direction?

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The growing global type 2 diabetes mellitus (T2DM) epidemic has shown no signs of slowing down. The parallel increase in obesity implicates unhealthy diet and sedentary lifestyle as main factors, which are fast becoming a way of life. Environmental and genetic factors have offered alternative perspectives to the diabetes front, although the aging population could be a much simpler explanation. Little has remained constant and a great deal more is being discovered.

A particular concern of the T2DM epidemic currently is the preponderance towards the developing countries and the younger age groups. Asia has been identified to be at the epicentre of the diabetes turmoil, significantly affected, whereby patients are diagnosed younger and thinner in comparison to their Caucasian counterparts [1]. Malaysia has observed an alarming rise in the prevalence of T2DM over the past and recent decades. The latest Malaysian National Health and Morbidity Survey (NHMS) in 2015 reported the prevalence of T2DM among adults above 18 years to be 17.5% [2]. This has been a steady rise from 15.2% in 2011 and 14.9% in 2006 [3,4]. More alarmingly, the same national survey in 2015 showed the prevalence of obesity among adult Malaysians to be 30.6%, which is more than double the 2014 world prevalence of 13% [5]. Differences within the ethnic groups have been observed but not fully understood. Based on that latest survey, the highest prevalence was detected among the Indians of 22.1% (95% CI: 19.2, 25.3), whilst the Malays had a prevalence of 14.6% (95% CI: 13.8, 15.5), the Chinese had 12.0% (95% CI: 10.7, 13.5), and finally the Bumiputras had 10.7% (95% CI: 8.8, 13.0) [2].

Diabetes is a major health concern whereby many are killed but more are debilitated. Cure remains impossible and progression of the disease over time is

certain. The International Diabetes Federation (IDF) has estimated that twice as many people have died because of diabetes through premature cardiovascular deaths in comparison to HIV–AID [6]. The National Cardiovascular Disease- Acute Coronary Syndrome (NCVD-ACS) registry reported a mean age of between 55.9 to 59.1 years among Malaysians experiencing ACS in comparison to most of the developed countries, which had mean ages of between 63.4 to 68 years [7]. In addition, microvascular complications has placed Malaysia among the top 5 countries with the highest prevalence of end stage renal disease (ESRD) in the world secondary to diabetic nephropathy, attributed to in 61% of patients initiating renal replacement therapy, according to national data [8].

After decades of discovering the disease, new data surrounding diabetes continue to emerge, underscoring its complexity. What was previously known as the triad of insulin resistance,  $\beta$ -cell dysfunction, and impaired hepatic glucose production has evolved to the more elegant concept of the ominous octet. The complexity of the pathophysiology of the disease is enhanced with the additional theories on renal glucose reabsorption, abnormal glucagon secretion, the incretin effects, increased lipolysis and neurotransmitter dysfunction [9]. This theory affects many aspects of diabetes as it opened up a field of potential therapeutic targets aimed to normalize glycaemia and achieve a target, which has been debatable over time.

Billions of dollars have been invested in the development of the various aspects of management of this complex disease. As the financial burden surrounding diabetes continues to rise, the questions remain- Have we actually got it right? Could the growing figures above indicate that our understanding

of the disease is flawed as are our theories on the management? What is the direction of T2DM?

### Treatment options in diabetes

Diabetes is a lifelong progressive illness, associated with complications that could only worsen despite current treatments. Management of diabetes has received immense amount of attention in recent years due to many factors. The worsening global figure, the recognized complications, increased public awareness and intensified health campaigns are among some contributing factors. It has also been mostly driven by the pharmaceutical industry with the growing armamentarium of anti-diabetic medications, particularly over the past two decades. The aim of T2DM treatment has fortunately not evolved to anything other than to reduce the risk of development of diabetic complications. Fortunately, recent guidelines have placed a lot of emphasis on the need to minimise side effects, improve quality of life and ultimately prolong life.

The ominous octet theory paved the way to multiple new therapeutic options, which could target various pathways and thus may prove to be more potent. Furthermore, it suggested that treatment of T2DM should utilize combination therapies to address many abnormalities simultaneously, synergistically or otherwise. It also suggested that therapeutic agents are created not merely to reduce HbA1C but more so to treat identified pathophysiological anomalies. Finally, treatment must be initiated early to prevent progressive  $\beta$ -cell failure [9].

Among the more recent buzz in anti-diabetic treatments is the discovery of the new sodium-glucose co-transporter 2 (SGLT-2) inhibitors. This group of drugs has challenged the conventional understanding of glycosuria being harmful and instead lowers glucose level by promoting renal glucose excretion via inhibition of glucose reabsorption at the proximal tubules. Clinical studies have demonstrated improvements in HbA1c by between 0.32% and 1.17% with the SGLT2 inhibitors, efficacies of which are dose-dependent and determined by baseline glycaemic levels [10]. Added benefits include weight reduction due to glucose loss and blood pressure reductions

possibly due to fluid loss and effects on the juxta-glomerular apparatus.

The injectable Glucagon-like Peptide 1 (GLP-1) agonist is another anti-diabetic medication approved for the treatment of T2DM. It is an incretin mimetic, acting through a glucose-dependent mechanism to reduce glucagon secretion, increase satiety and delay gastric emptying. The mean HbA1c reduction ranged between 0.7% and 1.7%, dependent on the administered dose [10]. Liraglutide has demonstrated lower rate of cardiovascular endpoints among patients with T2DM compared to placebo, accompanied by minimal difference in glycaemic control (mean difference of  $-0.40\%$  (95% CI,  $-0.45$  to  $-0.34$ ) [11]. Another GLP-1 agonist, Semaglutide also showed improvement in kidney end points, despite increased risk of retinopathy [12]. The added benefit of significant weight loss has led to added indication as a weight losing therapy, albeit at a higher dose.

However, each therapeutic group has particular adverse effects. The SGLT-2 inhibitors have evidently high risk for genital mycotic infections with reported hypoglycaemia only in combination with sulfonylurea and insulin. Other side effects include diabetic ketoacidosis and bone fractures, controversial to whether they are of class effect or drug-specific [13].

### Treatment plan - Reduction of HbA1c or cardiovascular risk reduction?

Previous landmark clinical trials have provided evidence that glycated haemoglobin (HbA1c) is a reliable tool for the measurement of glycaemic control. Lower HbA1c is pivotal in reducing macrovascular complications, albeit less evident with microvascular complications [14]. Evidence-based medicine has aggressively driven the glycaemic target down to near normal levels of HbA1c less than 6%, which has subsequently shown deleterious effects rather than benefit [15], prompting caution in overzealous tightening of glycaemia. Instead, the use of other drugs including statins and renin-angiotensin system inhibitors had provided more impactful data on lowering of cardiovascular risks in this group of high-risk patients. Emergence of more robust clinical trials in recent years is indeed consequential of this

development. Trials are designed to assess cardiovascular safety of the anti-diabetic medications rather than the glycaemic effects, leading to further understanding and debate on the role of HbA1c in determining macrovascular and microvascular outcomes. The trials have to date, suggested that the means of how the reduction in HbA1c is achieved, could play a more important role in determining the final clinical outcome.

The year 2016 had provided us with a lot of exciting new data in diabetes. The widely discussed EMPA-REG study has shown significant reductions in cardiovascular deaths (38% relative risk reduction) and kidney outcome (relative risk reduction of 39%) with empagliflozin despite minimal changes in glycaemic control throughout a median follow up of 3.1 years [16]. Similarly, the LEADER clinical trial concluded that Liraglutide compared to placebo, lowered major cardiac outcome risks by 13%. It also reduced 15% risk for all-cause death and 22% of CV death, over a, relatively, short study duration of 3.8 years.

Combination therapies have gained momentum towards the forefront of T2DM management, with the aim to increase efficacy whilst minimizing side effects. The combination of GLP-1 agonists and SGLT-2 inhibitors is an ideal match for multiple reasons. Both agents have dependable efficacies in glucose and weight-lowering effects, which are achieved through contrasting pathways. DURATION-8 trial studied the combination therapy of exenatide and dapagliflozin in T2DM patients who were inadequately controlled by metformin monotherapy [17]. The data from the study showed that the regime was well tolerated with minimal hypoglycaemic events. There was significant improvements in glycaemic measurements with HbA1c reduction of 1.95% from baseline compared to 1.58% and 1.37% with exenatide or dapagliflozin alone, respectively,  $p < 0.01$ . Similarly, there was greater weight loss with the combination therapy versus monotherapy (-3.4 kg versus -1.5 kg and -2.2 kg, respectively;  $p < 0.01$ ) accompanied by significant reductions of systolic blood pressure [17]. Thus, the combination therapy of GLP-1 agonist and SGLT2 inhibitor hold immense potential for the treatment of

T2DM, specifically in obese patients and those with concomitant cardiovascular diseases.

The standard treatment for T2DM in almost all guidelines includes dietary changes, physical activities, and metformin followed by other anti-diabetic medications. Individualisation of patient care has been at the centre of T2DM management strategy. The American Diabetes Association/European Association for the Study of Diabetes and NICE treatment guidelines have emphasized that the choice of anti-diabetic therapy must revolve around an appropriate glycaemic target, with ability of patients to adhere to the treatment plan while experiencing minimal to no side effects, at an affordable cost [13, 18]. Based on recent evidence-based data and updated guidelines, healthcare providers should consider the cardiovascular effects besides the specific side effects and hypoglycaemia risks of a particular medication to provide maximum benefit of the prescribed treatment plan to the patient.

However, other challenges are yet to be overcome. Durations of these clinical trials are relatively short and long-term adverse effects are currently unknown, especially on the risks of malignancy. Current global economic uncertainty is another major concern and cost effectiveness studies are needed to provide scientific rationale for this expensive combination option. The developments of newer agents continue to threaten the relevance of current and older medications. Finally, will HbA1c again manage to emerge champion and remain vital in the management process of diabetes?

In conclusion, anti-diabetic therapies have evolved over time. Many post-marketing, safety surveillance clinical trials have provided robust data beyond the initial aims of the studies. A lot of emphasis has been placed on the importance of reductions in cardiovascular and renal outcomes, which consequently diminish the reference towards glycaemic control. This has underscored more recent medications, mainly the SGLT2 inhibitors and GLP-1 agonists as the ideal choice of therapy. Despite the added cost, this might prove to be a more appropriate direction as selection of medications will be made based on a patient's underlying comorbidities and cardiovascular risk factors, true individualization for a common illness.

## REFERENCES

1. Corkey B. Diabetes: Have we got it all wrong? Insulin hypersecretion and food additives: cause of obesity and diabetes? *Diab Care*. 2012; 35: 2432-7.
2. National Health & Morbidity Survey 2015. Non communicable diseases, risk factors & other health problems. <http://www.iku.gov.my/images/IKU/Document/REPORT/NHMS2015-VolumeIII.pdf>. Accessed on 2 Feb 2017.
3. Feisul M. Current burden of diabetes in Malaysia. Proceedings of the 1st National Institutes of Health (NIH) Scientific Meeting 2012. Selangor, Malaysia: National Institute of Health.
4. Letchuman GR, Wan Nazaimoon WM, Wan Mohamad WB, Chandran LR, Tee GH, Jamaiyah H, Isa MR, Zanariah H, Fatanah I, Ahmad Faudzi Y. Prevalence of diabetes in the Malaysian National Health Morbidity Survey III 2006. *Med J Malaysia*. 2010; 65: 180-6.
5. World Health Organisation (WHO) Updates. ([www.who.int](http://www.who.int)). Accessed on 2 Feb 2017.
6. International Diabetes Federation (IDF) Atlas 2015. [http://www.oedg.at/pdf/1606\\_IDF\\_Atlas\\_2015\\_UK.pdf](http://www.oedg.at/pdf/1606_IDF_Atlas_2015_UK.pdf). Accessed on 2 Feb 2017.
7. Lu HT, Nordin R Bin. Ethnic differences in the occurrence of acute coronary syndrome: results of the Malaysian National Cardiovascular Disease (NCVD) Database Registry (March 2006 - February 2010). *BMC Cardiovasc Disord*. 2013; 13:97. doi: 10.1186/1471-2261-13-97.
8. Goh BL, Ong LM, Lim YN, (Eds). 21st Report of the Malaysian Dialysis & Transplant Registry 2013. Kuala Lumpur, Malaysia: National Renal Registry; 2014.
9. DeFronzo. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009; 58(4): 773-95.
10. Qaseem A, Barry MJ, Humphrey LL, Forciea MA, for the Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: A clinical practice guideline update from the American College of Physicians. *Ann Intern Med*. 2017. doi:10.7326/M16-1860.
11. Marso SP, Daniels GH, Brown-Frandsen K, LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016; 375(4):311-22.
12. Marso SP, Bain SC, Consoli A, SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016; 375(19):1834-44.
13. American Diabetes Association. Standards of medical care in diabetes-2016: Summary of revisions. *Diabetes Care*. 2016; 39(Suppl 1): S4-S5.
14. Abaira C, Duckworth W. The need for glycemic trials in type 2 diabetes. *Clin Diabetes*. 2003; 21 (3):107-111. doi:10.2337/diaclin.21.3.107.
15. The action to control cardiovascular risk in diabetes study group. *N Engl J Med*. 2008; 358:2545-59.
16. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, for the EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015; 373(22):2117-28.
17. Frías JP, Guja C, Hardy E, Ahmed A, Dong F, Öhman P, Jabbour SA. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4(12):1004-16.
18. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, DeFronzo RA, Einhorn D, Fonseca VA, Garber JR, Garvey WT, Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez GE. American Association of Clinical Endocrinologists and American College of Endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract*. 2015; 21(Suppl 1):1-87.