ISSN 2475-5451

Review Article

International Journal of Diabetes & Metabolic Disorders

SGLT2 Inhibitors: The "Metabolic Molecule" Or "Disease Modifying Anti Metabolic Drugs- DMAMDs"?

Vishwa Unadkat*

Sr Consultant Diabetologist, Tricolour Hospital & Yashvee Diabetes Care, Vadodara, Gujarat, India

***Corresponding author:**
Vishwa Unadkat, Yashvee Diabetes Care, 1st Floor, Shagun Synergy, 2- Navneet Park, Near SNDT College, Akota, Vadodara, Gujarat, India.

Submitted: 08 June 2021; **Accepted**: 15 June 2021; **Published**: 23 June 2021

Citation: *Vishwa Unadkat (2021) SGLT2 Inhibitors: The "Metabolic Molecule" Or "Disease Modifying Anti Metabolic Drugs- DMAMDs"? Int J Diabetes Metab Disord 6(1): 147-151.*

Abstract

The major health hazard of the modern world, "Metabolic Syndrome" or "Syndrome X", defined by WHO, as pathologic condition characterised by abdominal obesity, insulin resistance, hypertension and dyslipidemia [1]. The criteria for diagnosis are listed in Figure 1 [2]. It is being accepted almost a decade ago that we are in the phase of epidemic for this Non Communicable Condition. Though it was started in western world, spread of western lifestyle across the globe, truly it has now become the major global issue. Until recently the condition was far more prevalent in urban population than rural but in today's time, especially in Country like India, the incidence showed trends towards becoming almost equal [3]. Though recognised all over the world, the condition is rather dealt as managing different component(s) of the syndrome rather than taking the syndrome per say as diagnosis. We rather tend to care much of those patients who actually show prominently one or more components of metabolic syndrome, and this approach is leading us to neglect rather major bulk of patients who, in spite qualifying for criteria of diagnosis of metabolic syndrome, where not only patients are in early asymptomatic phase, but also the physicians caring for them do not reinforce the importance of the needed care at this very moment to prevent or delay the progression of the condition.

Healthcare all over world, particularly in India has shown enormous growth, in terms of not only infrastructure but also skill development [4]. Today we do have much better level of expertise in all the subspecialty with regards to high end care of all such conditions arise from one or more components of metabolic syndrome like Heart Failure, Chronic liver disease, chronic kidney disease and Diabetes (related complication). In developing country like India, somewhere 3 to 4 decades ago to subject a patient for liver or kidney transplant used to be mere dream of treating consultants but today we are not only doing the transplants smoothly but also survival rate is getting better and better [5]. But its quiet unfortunate that in spite of all these progresses, the actual numbers of such patients needing high end care is steadily on rise, thanks to increase in life expectancy in general and relatively better exposure to needed healthcare [5]. But author do strongly believe that still whatever we are seeing is more at treatment cum cure level but nothing much at prevention level is going on. In decades to come, we have large population at risk, at this very moment, for all such advanced staged chronic metabolic conditions. We are in genuine need of a molecule which can be offered to all such early or intermediate metabolic syndrome patient, expecting the improvement in almost all the aspect on the syndrome. Author do believe, the group of drugs known as "SGLT2 Inhibitors", an originally used for Hyperglycemia management, has now expanded its preventive effects on various metabolic conditions, showing promising results in all the trials and early real world evidences, is the real nomination for the "Metabolic Molecule" or "Disease modifying anti metabolic drugs- DMAMDs" of today.

Keywords: Metabolic syndrome, SGLT2I, Diabetes, Hypertension, Heart Failure, Chronic Kidney Disease, Dyslipidemia, Primary prevention, Metabolic molecule, DMAMDs.

	WHO (1999)	NCEP-ATP III (2001)	NCEP-R (2004)	IDF (2005)	AACE
Obesity	WHR >0.90(male) >0.85(female) or BMI>30 kg/m2	WC ≥ 102 cm (male) ≥ 88 cm (female)	WC ≥ 102 cm (male) ≥ 88 cm (female)	[REQIREMENT] WC ≥ 94 cm (male) ≥ 80 cm (female)	Overweight/ Obesity BMI ≥ 25 kg/m^2
Serum triglycerides	≥ 150mg/dl	≥ 150 mg/ dl	≥ 150 mg/ dl or medication	≥ 150 mg/ dl or medication	≥ 150 mg/ dl
Serum HDL Cholesterol	< 35 mg/ dl (male) < 39 mg/ dl (female)	< 40 mg/ dl (male) < 50 mg/ dl (female)	< 40 mg/ dl (male) < 50 mg/ dl (female) or medication	<40 mg/ dl (male) <50 mg/ dl (female) or medication	<40 mg/ dl (male) <50 mg/ dl (female)
Blood pressure	≥ 140/ 90 mmHg	≥ 130/85 mmHg or medication	≥ 130/85 mmHg or medication	≥ 130/85 mmHg or medication	≥130/ 85 mmHg or medication
Fasting plasma glucose	[REQUIREMENT] FPG≥110 mg/ dl	≥ 100mg/ dl	≥ 100mg/ dl	≥ 100mg/ dl or previously diagnosed T2DM	110-126 mg/ dl
Other risk factors	Urinary albumin excretion rate ≥ 20µg/ min or albumin / creatinine ratio ≥ 30 mg/g				Family history of T2DM, HTN, or CVD. Polycystie ovary syndrome, sedentary life stly, Advancing age and ethnic groups having high risk for DM
Diagnosis	Impaired FPG+any 2 criteria	Any 3 criteria	Any 3 criteria	WC+any 2 citeria	or CVD Physician's judgement

T2DM: Type 2 diabetes mellitus, HTN: Hypertension, CVD: Cerebrovascular accident, DM: Diabete mellitus, WC: Waist circumference. NCEP ATP III : National cholesterol education program adult tretment panel III, NCEP-R: NCEP-R: revised NCEP, IDF: International diabetes federation, ACE: American association of clinical endocrinologists, WHO: World Health Organization, WHR: Waist-to-hip ratio, BMI: Body mass index, HDL: high density lipoprotein

Figure 1: Metabolic Syndrome Criteria

Introduction

Approximately one fourth of the adult European population is estimated to have metabolic syndrome, with a similar prevalence in Latin America. The prevalence of metabolic syndrome in East Asia may range from 8-13% in men and from 2-18% in women, depending on the population and definitions used [6]. According to global survey of obesity in 195 countries, done in 2015, 604 million adults and 108 million children were obese [7]. According to IDF diabetes atlas, global prevalence of diabetes is 8.8% (415 m) as of 2015 and is expected to increase to 10.4% (642 m) by 2040 [8]. We do not have similar global data on metabolic syndrome—which is harder to measure, but since metabolic syndrome is about three times more common than diabetes, the global prevalence can be estimated to be about one quarter of the world population. In other words, over a billion people in the world are now affected with metabolic syndrome [1].

In India, the overall prevalence of metabolic syndrome, in population aged 15-49, was 1.5% among women and 1.1% among men [9]. As per current Govt registry, nearly 51% of total population is in between 15 to 49 age group, which makes total number of metabolic syndrome patients, In India, to more than 120 million [10]. So, for brains caring for future of mankind, its gives nothing but shock to realise the amount of future impact of all those patients progressing to full blown disease and one can only pray and concentrate to act at this moment to hold at least some percentage of patients progressing to further disease state and to reverse some if we can.

Before discussing the advantages of SGLT2I in details, "can SGLT2I, is the group of drugs, which we must imply to every patient diagnosed to have metabolic syndrome, regardless of presence or absence of Diabetes", is the question, of which author is trying to find the answer.

Current Evidences on SGLT2 Inhibitors

Since its inception in initial part of last decade globally and couple of years later in Indian markets, SGLT2 inhibitors has attracted much attention for both its effects and side effects. In spite of very impressive CVOT data of large trials namely CANVAS, EMPAREG, which actually demonstrated substantial positive impact on progression and events of ASCVD patients with diabetes, major concerns remained for consultants for its use were the fear of side effects, mainly genital mycotic infections, ketosis and probability of rise in some non-fatal stokes/ amputations [11, 12]. With experience we came to know that all such side effects are largely preventable by proper patient selection and counselling regarding maintenance of hygiene and hydration [13]. It's interesting to note unique insulin sparing MOA of SGLT2i, also by producing glycosuria along with natriuresis, it gives favourable overall metabolic and hemodynamic effects, Figure 2 [14].

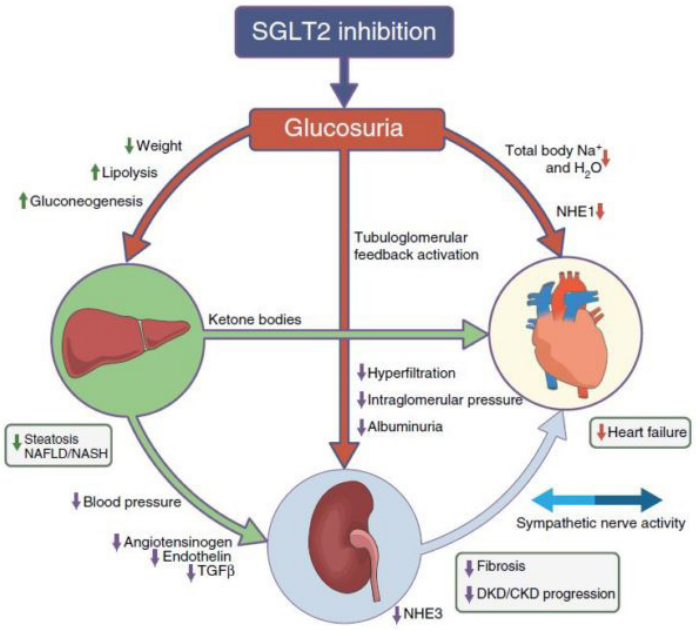

Figure 2: SGLT2I MOA.

In recently published trials like CREDENCE, DAPA- HF, DAPA-CKD, EMPEROR REDUCED shown us that the group of drugs, gives cardiovascular/kidney event protection and retard the progression of CKD as well in not only diabetics but also non diabetic patients, whether all those complications were there at baseline or not [15-18]. Its worth to note the promise these molecules impart for primary prevention for ASCVD/CKD in high risk patients as well.

SGLT2 (sodium-glucose cotransporter 2) inhibition in humans leads to increased levels of LDL (low-density lipoprotein) cholesterol and decreased levels of plasma triglyceride, because of reduced clearance of LDL from the circulation and greater lipolysis of triglyceride-rich lipoproteins [19]. But regardless of its effects on lipids, all SGLT2i have shown reduction in cardiovascular death beyond reasonable doubts.

While not approved as antihypertensive agents, SGLT2i may potentially aid in lowering blood pressure in patients with diabetes. A review of studies in both hypertensive and normotensive patients with type 2 diabetes demonstrates a 4–10 mmHg reduction of systolic blood pressure. SACRA study showed us that in Asian population, empagliflozin significantly reduced nocturnal hypertension as compared to placebo, in diabetic patients [20]. Even studies like SWIFT- J (Cana Vs Placebo) and Y-AIDA (Dapa Vs Placebo), also supported favourable reduction in home SBP with SGLT2i [21, 22]. Though we are still lacking data for BP reduction by SGLT2i in non- diabetic population, but all experts in various academic forums are in favour to reduce the dose of ongoing antihypertensive and diuretic medicines for a week or two while initiating SGLT2is.

However, the magnitude of weight loss with SGLT2i is modest both in T2D and in obesity without diabetes. For approved SGLT2 inhibitors (Canagliflozin, Dapagliflozin and Empagliflozin) there is on average some 1.5–2 kg weight loss (placebo-adjusted). Though weight loss, largely accounted to loss of body fat, is sustained for years on therapy, we are in need of more effective weight loss therapy [23].

Another condition worth mentioning over here, though not a part of metabolic syndrome, but has significant overlapping with it, is NAFLD- increased fat content of liver with insulin resistance. This major etiological factor of cirrhosis of liver, after alcohol and chronic hepatitis, has been affected positively with the use of SGLT2i. Recent findings from both randomized controlled trials and open-label studies have also shown that SGLT2 inhibitors are able to reduce fatty liver content, as assessed by different imaging techniques, and improve biological markers of NAFLD, especially serum liver enzymes, in patients with T2DM [24]. There are early reports of Dapa in non-diabetic NAFLD patients, giving as promising results as in diabetics [25].

Early real-world data from various experts all over world, shows that not only the positive impact we are getting, mimics those in trials but also, they are relatively very safe to be used. Data of more than 3 lac patients of US veteran affairs, on SGLT2 inhibitors and Scandinavian RW study on more than 29k new users, early results of EMPRISE study of more than 78k new users, removed all the doubts and exactly duplicated the trial results as far as safety, efficacy and CV/kidney protection are concerned [26, 27, 28].

Current Issue and Conclusion

Let us assume a scenario, where a middle-aged corporate employee, BMI of 27, in his health check-up gets blood pressure of 136/86, FBS of 106 and LDL of 136. In the current system, it's difficult to see that this person gets an ideal discussion of his metabolic syndrome status and possible future consequences. At max he gets either a medical officer or junior consultant visit of hardly 5 min, where very casually he is been advised some diet modification and exercise, which is barely durable and effective in an otherwise asymptomatic person. Probably before getting diagnosis of diabetes or have some end organ damage in upcoming years, he may encounter such health check up 3 to 4 times in a decade. Though system is advancing gradually, the person getting health check-up and person giving advice, largely failing at the moment to get the advantage of very good rise in health check-up numbers.

In all such early cases, we must search an option, which, along with lifestyle modification, should be able to provide good durable effects on nearly all metabolic aspect. We wish to get not only prevention of further progress but also reversal of the condition. We wish to see more research with SGLT2i as 1st line therapy for the patient who got diagnosed as early metabolic syndrome, and to see whether the group of drugs is actually having disease modifying effect on metabolic syndrome or not?

Author has published his own real-world study regarding screen-

ing tool for selection of patients for SGLT2i, which clearly showed that the side effects with SGLT2i are largely avoidable [13]. One real world study of SGLT2 effect on blood pressure of T2D patient is ongoing. Author clearly wishes to do some more research work with this group of drugs to get some more details which would help for managing these metabolic syndrome patients well in daily clinical practice.

References

1. Saklayen MG (2018) The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep 20: 12.
2. Ritthikrai Thaweecharoen, Warut Chaiwong, Chulathip Boonma, Kitsuchart Pasupa, Piyawan Massa Ard, et al. (2019) Diagnosis of metabolic syndrome using radar chart. BKK Med J 15: 11-18.
3. Prabhakaran D, Chaturvedi V, Shah P, Manhapra A, Jeemon P, et al. (2007) Differences in the prevalence of metabolic syndrome in urban and rural India: a problem of urbanization. Chronic Illn 3: 8-19.
4. https://knowledge.wharton.upenn.edu/article/technology-changing-health-care-india.
5. Soin A S, Thiagarajan S (2016) Liver transplant scene in india. MAMC J Med Sci 2: 6-11.
6. https://www.medscape.com/answers/165124-176381/what-is-the-global-prevalence-of etabolicsyndrome#:~:text=Metabolic%20syndrome%20is%20a%20burgeoning,similar%20prevalence%20in%20Latin%20America.
7. The GBD 2015 Obesity Collaborators (2017) Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med 377: 13-27.
8. K Ogurtsova, J D da Rocha Fernandes, Y Huang, U Linnenkamp, L Guariguata, et al. (2017) IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 128: 40-50.
9. Trupti Meher, Harihar Sahoo (2020) The epidemiological profile of metabolic syndrome in Indian population: A comparative study between men and women. Clinical Epidemiology and Global Health 8: 1047-1052.
10. https://censusindia.gov.in/census_and_you/age_structure_and_marital_status.aspx
11. Bernard Zinman, Christoph Wanner, John M Lachin, David Fitchett, Erich Bluhmki, et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 373: 2117-2128.
12. Bruce Neal, Vlado Perkovic, Kenneth W Mahaffey, Dick de Zeeuw, Greg Fulcher, et al. (2017) Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 377: 644-657.
13. Unadkat V, B, Sharma S, Omar R (2020) Real-World Clinical Experience with SGLT2 Inhibitors: Use of Special Screening Tool for Type 2 Diabetes Patients to Avoid Serious Adverse Events: A Single-Centre Prospective Study. Dubai Diabetes Endocrinol J 26: 38-43.
14. Christoph Wanner, Nikolaus Marx (2018) SGLT2 inhibitors: the future for treatment of type 2 diabetes mellitus and other chronic diseases. Diabetologia 61: 2134-2139.
15. Vlado Perkovic, Meg J Jardine, Bruce Neal, Severine Bompoint, Hiddo J L Heerspink, et al. (2019) Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 380: 2295-2306.
16. John J V McMurray, Scott D Solomon, Silvio E Inzucchi, Lars Køber, Mikhail N Kosiborod, et al. (2019) Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 381: 1995-2008.
17. Hiddo J L Heerspink, Bergur V Stefánsson, Ricardo Correa Rotter, Glenn M Chertow, Tom Greene, et al. (2020) Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 383: 1436-1446.
18. Milton Packer, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Stuart J Pocock, et al. (2020) Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 383: 1413-1424.
19. Debapriya Basu, Lesley Ann Huggins, Diego Scerbo, Joseph Obunike, Adam E Mullick, et al. (2018) Mechanism of Increased LDL (Low-Density Lipoprotein) and Decreased Triglycerides with SGLT2 (Sodium-Glucose Cotransporter 2) Inhibition. Arteriosclerosis, Thrombosis and Vascular Biology 38: 2207-2216.
20. Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, et al. (2018) 24-Hour Blood Pressure-Lowering Effect of an SGLT-2 Inhibitor in Patients with Diabetes and Uncontrolled Nocturnal Hypertension: Results from the Randomized, Placebo-Controlled SACRA Study. Circulation 139: 2089–2097.
21. Kario K, Hoshide S, Okawara Y, Tomitani N, Yamauchi K, et al. (2018) Effect of canagliflozin on nocturnal home blood pressure in Japanese patients with type 2 diabetes mellitus: The SHIFT-J study. J Clin Hypertens (Greenwich) 20: 1527-1535.
22. Kinguchi S, Wakui H, Ito Y, Kondo Y, Azushima K, et al. (2019) Improved home BP profile with dapagliflozin is associated with amelioration of albuminuria in Japanese patients with diabetic nephropathy: the Yokohama add-on inhibitory efficacy of dapagliflozin on albuminuria in Japanese patients with type 2 diabetes study (Y-AIDA study). Cardiovasc Diabetol 18: 110.
23. Maria J Pereira, Jan W Eriksson (2019) Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity. Drugs 79:219-230.
24. Scheen AJ (2019) Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: A common comorbidity associated with severe complications. Diabetes Metab 45: 213-223.
25. Lucas Ribeiro dos Santos, Ricardo Baer Filho (2020) Treatment of nonalcoholic fatty liver disease with dapagliflozin in non-diabetic patients. Metabolism Open 5: 1-3.
26. Yan Xie, Benjamin Bowe, Andrew K Gibson, Janet B McGill, Yan Yan, et al. (2020) Comparative Effectiveness of the Sodium-Glucose Cotransporter 2 Inhibitor Empagliflozin Versus Other Antihyperglycemics on Risk of Major Adverse Kidney Events. Diabetes Care 43: 2785-2795.
27. Pasternak B, Wintzell V, Melbye M, Eliasson B, Svensson

AM, et al. (2020) Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: Scandinavian cohort study. BMJ 369: 1186.

28. Joban Vaishnav, Kavita Sharma (2019) A Promising EMPRISE: Empagliflozin and Heart Failure Outcomes in Type 2 Diabetes Patients. American College of Cardiology 2019.https://www.acc.org/latest-in-cardiology/articles/2019/09/17/15/02/a-promising-emprise.