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SGLT2-Inhibitors in the Management of Type 2 Diabetes Mellitus among East Asians-A Comprehensive Review

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Review Article

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Abstract

The burden of type 2 diabetes in East Asia is frightening. There have been dreadful changes in environmental, lifestyle, and dietary factors in East Asia during the past few decades which resulted in major lifestyle changes and an astounding increase in the prevalence of obesity, metabolic syndrome, and diabetes mellitus. Although well-established treatment modalities exist for type 2 diabetes mellitus management, they are limited by their side effect profile. Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new class of glucose lowering agents developed for the treatment of type 2 diabetes mellitus. These drugs prevent the kidneys from reabsorbing sugar into the blood. Instead, the sugar is excreted in urine. Subsequent reduction of glucotoxicity improves beta-cell sensitivity to glucose and tissue insulin sensitivity.

Keywords: Diabetes Mellitus; East Asia; Effect; Sodium Glucose Co-Transporter 2; Insulin.

Introduction

Type 2 diabetes was once considered a disease of the west, but now is a global health priority [1]. The prevalence of diabetes is increasing globally, but the situation is particularly disturbing in Asia as it remains the world's most populous region. The International Diabetes Federation has predicted that the number of individuals with diabetes will increase from 240 million in 2007 to 380 million in 2025, with 80% of the disease burden in low and middle-income countries [2]. Asia has undergone marked economic and epidemiologic transition in recent decades. Increasing globalization and East-West exchanges have been accompanied by increasing population movements, changes in food supply and dietary patterns, technology transfer, and cultural admixtures [3]. Sodium-glucose co-transport-2 (SGLT2) inhibition is a rational and is a new way to treat type 2 diabetes mellitus. SGLT2 inhibitors are a group of oral glucose-lowering agents that prevent renal glucose reuptake, with an additional weight-loss benefit. SGLT2 inhibitors reduce renal glucose reabsorption, leading to favourable effects on glycemic, blood pressure, and weight control. The insulin-independent mechanism enables their use as monotherapy or combination therapy with insulin and other oral antidiabetic agents [4]. Hence, this review summarizes and discusses the key factors influencing the high prevalence diabetes in East Asians,

efficacy and safety of SGLT2 inhibitors in East Asians, and how SGLT2 inhibitors can be beneficial in this group of population.

Factors Influencing the High Prevalence Diabetes in East Asians

The frightening rise in the prevalence of diabetes in Asia can be explained in terms of several key causes which are narrated as under-

- The typical ethnic background of the Asian population which involves a lower body mass index (BMI) with more visceral fat.
- A young age of diabetes onset.
- Insufficient beta-cell response to counter insulin resistance.
- Beta-Cell Dysfunction.

Another important contributor to the high prevalence of diabetes in Asia is the presence of the most populated countries, China and India. These two nations have the highest numbers of patients with diabetes in the world, they thus make a major contribution to the worldwide prevalence of diabetes [2].

Increasing Prevalence of Obesity

The occurrence of type 2 diabetes mellitus at a lower mean BMI in East Asians is one of the most striking observations [4]. Data from the Diabetes Fact Sheet released by the Korean Diabetes Association in 2013 indicated the proportion of individuals with obesity, defined as BMI >25 kg/m2, reached 44.4%, indicating that almost half of the Korean individuals with diabetes are overweight [5]. A report based on the KNHANES from 2001 to 2013 found that the age-standardized prevalence of adult obesity increased from 29.2% to 31.8% [6]. Although not all obese subjects develop diabetes, it is evident that obese individuals have a higher risk for the development of diabetes.

Young Age of Onset of Diabetes

The onset of type 2 diabetes mellitus in younger age groups is likely to result in a major economic burden for countries in Asia due to premature ill health and the phenomenon of living long with chronic illness. In developed countries, diabetes affects mainly those older than 65 years [7]. Based on the National Health and Nutrition Examination Survey (NHANES) data the prevalence of diabetes among adults aged 18- 44 years in the United States was 13.0% [8]. In contrast, one in five adults was diagnosed with type 2 diabetes mellitus before the age of 40 years in East Asia [9]. In addition, the behavioural patterns of younger children have been rapidly altering worsening the situation [10]. A recent increase in the prevalence of gestational diabetes mellitus in Asian countries may also contribute to the increase in diabetes in young Asians, as the offspring of mothers with gestational diabetes mellitus have increased adiposity at birth and increased risk of diabetes and obesity later in life [11].

Insufficient Beta-Cell Response to Counter Insulin Resistance

Asians are known for dysfunctional pancreatic insulin secretory function. Many studies assessing glucose tolerance in healthy subjects have found slight insulin secretory defects in Asian individuals [12]. Although East Asians have lower insulin resistance; they have greater amounts of visceral fat. A minor increase in insulin resistance as sequelae of visceral adiposity can lead to decreased insulin-secretory capacity in East Asians [13].

Beta-Cell Dysfunction

Type 2 diabetes mellitus in East Asians is characterized primarily by beta-cell dysfunction. Decreased beta-cell function and impaired beta-cell compensation for progressive decline in insulin sensitivity play a vital role in the deterioration of glucose tolerance [14].

SGLT2 Inhibitors in Type 2 Diabetes Mellitus Management in East Asians

Most of the plasma glucose (99%) filtered through the glomerulus is reabsorbed through SGLT in the luminal membrane of proximal renal tubules. Two distinct isoforms of SGLT have been identified. The low capacity, high-affinity SGLT1 transporters are found in various tissues, including the small intestine, heart, skeletal muscle and kidney. The high-capacity, low-affinity SGLT2 transporters are located almost exclusively in the kidney and are responsible for 90% of the glucose reabsorption from the S1 and S2 segments of the proximal convoluted tubule. SGLT2 inhibitors reduce blood glucose through selective and reversible inhibition of the SGLT2, thereby preventing the renal reabsorption of glucose and increasing its urinary excretion, a mechanism

independent of β-cell function and insulin resistance [15,16] .

Efficacy and Safety of SGLT2 Inhibitors

Effect on Hyperglycaemia: Kaku K, et al. [17] stated that in placebo-controlled trials SGLT2 inhibitor monotherapy reduced the HbA1c level by up to 1.11% from baseline, with a greater reduction observed in patients with high baseline HbA1c levels [17]. The risk of hypoglycaemia is low with SGLT2 inhibitors when used as monotherapy or in combination with other oral GLDs. The risk of hypoglycaemia should be monitored when SGLT2 inhibitors are used in combination with insulin. SGLT-2 inhibitors have insulin-sparing effects; adjustment of the insulin dose may be required.

Effect on Glycaemic Variables: Concluded that in Asian patients with type 2 diabetes mellitus, SGLT2 inhibitors alone or in combination with oral GLDs improved insulin sensitivity and β-cell function, reduced insulin and proinsulin levels, and decreased postprandial glucose levels [18].

Effect on BP, Pulse Pressure and Arterial Stiffness: Treatment with SGLT2 inhibitors is associated with clinically relevant reductions in BP and arterial stiffness. Stated that SGLT2 inhibitors reduce systolic BP by 3 to 5 mmHg and diastolic BP by 2 to 3 mmHg, with similar findings for 24-hour systolic and diastolic BP and pulse pressure [19,20].

Effect on Body Weight and Fat Mass: SGLT2 inhibitors are associated with a reduction in body weight and visceral adiposity stated that by inducing glycosuria, SGLT2 inhibitors produce a calorie deficit with a net weight loss of 2 to 3 kg over 52 weeks of therapy, with a similar effect in Asian populations range 1.29 to 3.9 kg [21].

Effect on Lipids: SGLT2 inhibitors are associated with a reduction in atherogenic small dense LDL-C, an increase in HDL-C, and less atherogenic large buoyant LDL-C. Concluded that in an open-label 12-week study of Japanese patients with type 2 diabetes mellitus comparing the effects of dapagliflozin and sitagliptin on lipid subfractions, treatment with dapagliflozin reduced the atherogenic small dense LDL by 20% from the baseline levels ($P<0.01$) and increased the less atherogenic large buoyant LDL by 18% ($P<0.05$), while no changes were observed with sitagliptin [22].

Effect on Haematocrit: Treatment with SGLT2 inhibitors is associated with an increase in haematocrit. Concluded that in a meta-analysis of 25 randomized controlled trials, treatment with SGLT2 inhibitors was associated with an increase in haematocrit by 1.4% [23].

Effect on Cardio Vascular Outcomes: Stated that the cardiovascular benefits of SGLT2 inhibitors have been shown in multiple randomized controlled trials and real-world evidence studies, suggesting a class effect of SGLT2 inhibitors on cardiovascular outcomes. SGLT2 inhibitors are recommended for use in patients with type 2 diabetes mellitus with multiple risk factors to prevent and reduce hospitalization for heart failure. SGLT2 inhibitors are recommended for use in patients with type 2 diabetes mellitus with established cardiovascular disease to reduce the risk of cardiovascular death [24].

Conclusion

Type 2 diabetes mellitus has become an epidemic in Asia. To curb this epidemic, an integrated strategy combining population-wide preventive policies, early detection, and multidisciplinary care programs may reduce the risk of diabetes and associated complications in the general population. With the increasing prevalence of type 2 diabetes mellitus in Asia, SGLT2 inhibitors represent a novel, key therapeutic agent for clinicians. The only drawback associated with SGLT2 is that it may increase the risk of mycotic genital infections, bacterial urinary tract infections. As a result of diuretic and mild natriuretic effects, SGLT2 inhibitors may cause intravascular volume contraction in patients with impaired renal function, elderly patients, and those receiving diuretics. Although significant positive results are in favour of SGLT2, further research in this area is expected with larger sample size and multiple observers where the minimum risks are also covered in order to consider SGLT2 a better and safer substitute.

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