COMMENTARY

Pharmaceutical chemistry of sodium glucose co-transporter 2 inhibitors (SGLT2-I)

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ABSTRACT

According to the World Health Organization, Diabetes Mellitus (DM) is one of the top causes of mortality in 2019. It is also regarded as a key contributor to other illnesses such as heart attack, stroke, kidney failure, blindness, and lower limb amputation. A protein called Sodium Glucose Co-Transporter 2 (SGLT2) reabsorbs about 90% of the glucose present in plasma glucose. For the treatment and management of diabetes, SGLT2 is a known target. SGLT2 inhibitors (SGLT2-I) are now available on the market to control blood glucose levels in people with diabetes. The human body contains six SGLT proteins, each of which has a different predilection for binding sugar. The SGLT2 enzyme, which is mostly found in the gut and early proximal tubule of the nephron and promotes glucose absorption by around 90%, is the target of the therapeutic strategy. As SGLT2 expression and tubular glucose load rise in the diabetic state, glucose reabsorption results in hyperglycemia. SGLT2-I works by preventing the reabsorption of glucose into the renal tubule and increasing the excretion of glucose through the urine. The identification and creation of selective SGLT2-I hold considerable promise for the management and treatment of diabetes mellitus.

INTRODUCTION

Diabetes Mellitus (DM), a metabolic disease that causes long-term harm to the heart, blood vessels, nerves, kidneys, and eyes, is characterized by high or abnormal blood sugar levels. People all around the world, particularly those in rural areas of low- and middle-income nations, are affected by diabetes. The frequency and incidence of diabetes have gradually risen during the last few decades. The International Diabetes Federation (IDF) has been releasing reports on the prevalence of diabetes globally, regionally, and nationally since 2000. Diabetes was estimated to affect 285 million people in 2009, 366 million in 2011, 382 million in 2013, 415 million in 2015, and 425 million in 2017. The IDF estimates that 463 million adults worldwide had diabetes in 2019, and that number will increase to 643 million by 2030 and 700 million by 2045. One in ten individuals, or 537 million people, have diabetes at this time. One in five fatalities, or 6.7 million, were caused by diabetes in 2021. People with diabetes make up more than 75% of the population in low- and middle-income nations. High-income countries (10.4%) have a higher prevalence than low-income countries (4.0%), while urban areas (10.8%) have a higher incidence than rural areas (7.2%). 50.1% of diabetic individuals are fully unaware of their condition. Pancreatic beta-cell dysfunction or destruction is what causes diabetes. Numerous elements, such as a genetic predisposition, insulin resistance, and autoimmune disease, can result in the malfunction or total devastation of cells. In maintaining or improving glucose tolerance, identifying diabetes subtypes, and determining the best course of treatment, it may be helpful to distinguish between -cell dysfunction and reduced cell bulk. The three primary kinds of diabetes are type 1 diabetes, type 2 diabetes, and gestational diabetes mellitus. Type 1 diabetes is often referred to as insulin-dependent

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diabetes. The damaged pancreatic cell does not produce insulin in this chronic disease. Because the pancreatic beta cells that make insulin are attacked by the body's defense system, the body either produces no insulin at all or very little insulin. The body needs the hormone insulin to make it easier for glucose to enter cells where it may be used as a source of energy. While several infections can potentially influence the onset of type 1 diabetes, it has a high hereditary propensity. Although it can occur in adults as well, the prevalence of this illness is most common in childhood or adolescence. Insulin injections can largely control the rise in blood glucose levels in type 1 diabetic patients. Insulin independent diabetes or insulin resistance are terms used to describe type 2 diabetes. In type 2 diabetes, the pancreatic beta-cells produce, store, and release insulin with efficiency, but the cells are unable to use the insulin to help the cells use glucose as an energy source. the blood sugar steadily increases as a result. Diabetes of type 2 affects about 90% of cases. Obesity is a significant predictor of the chance of developing type 2 diabetes because the increase in fatty tissues in obese people causes their cells to become insulin resistant. Even those with thin builds can get type 2 diabetes, even if obesity is a major risk factor. The risk of type 2 diabetes rises when the body starts to store fat in the abdomen rather than the thighs or hips. Diabetes can be prevented or delayed by following a healthy diet, exercising regularly, and getting regular screenings. Traditional diabetes treatments have side effects such as bone fractures, hypoglycemia, weight gain, and an increased risk of heart failure. There are many therapeutic and targeted strategies available for the management and treatment of diabetes. Using SGLTs to stop the kidneys from reabsorbing glucose is one of the most current ways to lower blood sugar in persons with type 2 diabetes. It is generally known that Diabetes Mellitus (DM) increases the chance of developing heart conditions like coronary artery disease, heart failure, atherosclerosis, ischemia, and myocardial infarction, which may be the main causes of cardiovascular morbidity. In the end, there are several etiologic factors that contribute to the vicious cycle of diabetic vascular disease. These factors can be divided into conventional ones like hypertension, dyslipidemia, or obesity, as well as unconventional ones like insulin resistance, postprandial hyperglycemia, inflammation, genetics, microalbuminuria, and a host of others. Metabolic syndrome, however, succeeds variables including inflammation, insulin resistance, or microalbuminuria.

Additionally, it has been demonstrated that inflammation is closely related to endothelial dysfunction, which is a major contributor to insulin resistance and the metabolic syndrome. Additionally, it was discovered that inflammation functions as a separate component in the development of nephropathy with high CRP. Significant correlations exist between elevated CRP and serum lipids, fasting blood sugar, or obesity. Furthermore, over the past ten years, extensive research on the mechanistic effects of inflammation has demonstrated that it increases the risk of cardiovascular diseases by increasing a number of biomarkers, including nitrotyrosine, CRP, interleukins, apolipoprotein E, microRNA, adiponectin, TNF-, and many others. Despite the significant influence of inflammatory response on the development of cardiovascular diseases, the precise mechanism and role is still unknown because inflammation has many different biological effects. However, SGLT2 overexpression is also brought on by inflammation. Therefore, by decreasing SGLT2, management of the inflammatory responses in a T2DM patient mayslow the progression of cardiovascular disease in addition to glycemic control. However, higher concentrations of SGLT2 and leptin generate inflammation, which increases the risk of cardiac events. It has been clearly demonstrated in studies that SGLT2-I affects the expression of leptin, which inhibits the activity of visceral fats leading to reduction in inflammatory burden. Human SGLTs are composed of six different isoforms, and glucose and sodium are transported into cells through a gradient of sodium concentration. Glucose and salt are transported through intestinal and renal cell membranes with the help of SGLT1 and SGLT2. Through the use of expression and cloning techniques, SGLT1 was found in 1987. The kidney, gut, and heart all contain SGLT1 to control cardiac glucose transport. About 10% of plasma glucose is reabsorption by SGLT1, which is found in the small intestine and the lateral S3 section of the proximal renal tubule. Incretin-secreting cells express SGLT1, which is involved in incretin secretion. Upon eating a meal, the intestinal hormone incretin is released.