Review Article

Glucuretics: A New Class of Drug for the Treatment of Type 2 Diabetes

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Abstract

Type 2 diabetes is a common, chronic disease with a prevalence that is increasing at epidemic proportions. Management involves advice on lifestyle changes, oral anti-hyperglycaemic agents and/or insulin. The kidney plays an important role in glucose homeostasis via its production, utilization, and, most importantly, reabsorption of glucose from glomerular filtrate which is largely mediated via the sodium glucose co-transporter 2 (SGLT2). Competitive inhibition of SGLT2 induces glucosuria in a dose dependent manner and appears to have beneficial effects on glucose regulation in individuals with type 2 diabetes. Agents that inhibit SGLT2 represent a novel class of drugs, which has recently become available for treatment of type 2 diabetes. This article summarizes the rationale for use of these agents and reviews available clinical data on their efficacy, safety, and risks/benefits.

Introduction

Type 2 diabetes is a common, chronic disease and the global prevalence of type 2 diabetes mellitus (T2DM) is increasing at epidemic proportions[1]. It is a progressive disease of the endocrine system with a significant economic burden, is estimated to affect more than 371 million people worldwide and close to one-fifth of all adults with diabetes in the world live in the South-East Asia region. Current estimates-indicate that 8.3% of the adult population, or 71.4 million people, have diabetes in 2011[2]. The number of people with diabetes in the region will increase to 120.9 million by 2030, or 10.2% of the adult population[2]. The immediate purpose of lowering blood glucose is to provide relief from osmotic symptoms (thirst, polyuria, nocturia and blurred vision). There after, the aim is to prevent microvascular complications: retinopathy, nephropathy and neuropathy[3]. Modifications of diet habit and lifestyle are seldom sufficient to produce good, long-term, metabolic control in patients with type 2 diabetes, so pharmacological adjuncts are often required early in the management in the majority of patients. The choice of drug depends on clinical and biochemical factors; as with all pharmacological agents, anti-hyperglycaemic therapy should only be initiated following careful consideration of the possible benefits and risks of treatment for the individual patient. Antihyperglycaemic agents include metformin, sulphonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, DPP-IV inhibitors and GLP-1 analogues[4]. All of the oral anti-hyperglycemic drugs currently available are accompanied by some undesirable side effects or problems with long term efficacy[4]. These agents are effective initially, glucose-lowering effects are not typically sustained long term as beta cell dysfunction progresses. Historically, orally-active agents are usually employed first line while insulin is reserved for patients in whom tablets prove insufficient[5]. The majority of T2DM patients are overweight or obese, which increases insulin resistance and complicates treatment[6].

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Hyperglycaemia along with hypertension and dyslipidaemia are associated with macrovascular complications (myocardial infarction, stroke and peripheral arterial disease). The effects of glucose-lowering therapies along with treatment of hypertension and dyslipidaemias have a major impact on cardiovascular morbidity and mortality[7]. Therefore, newer agents that are able to lower glucose long term without causing hypoglycemia, delay decline in beta cell dysfunction, assist with weight loss, and have beneficial effects on cardiovascular disease need to be developed. Several new classes of medications are currently in development. Anti-hyperglycaemic agents that act through inhibition of renal sodium glucose co-transporters are one of them and showing considerable potential[8,9]. The kidney plays an important role in glucose homeostasis and has recently become a target for treatment of diabetes. The majority of glucose reabsorption from glomerular filtrate is mediated via a transporter protein called sodium glucose co-transporter[2] (SGLT2). Pharmacological inhibition of SGLT2 increases urinary glucose excretion (UGE) and decreases plasma glucose levels in insulin-independent manner[11]. SGLT2 inhibitors represent a novel class of drugs that has recently become available for treatment of T2DM. Glucose Homeostasis: Role of Kidney During the fasting state, the plasma glucose level is predominantly maintained by endogenous glucose production by the liver specially through glycogenolysis and gluconeogenesis[10]. The kidney contributes to glucose homeostasis by the consumption of glucose to meet its own metabolic requirements, gluconeogenesis, plus filtration and reabsorption of filtered glucose[11].

In the 1930s, Bergman and Drury first demonstrated that interfering with kidney function in hepatectomized rabbits, either by ligation of the vascular pedicles or the ureters, resulted in an increase in glucose utilization rates[12]. Glucose remains unbound within the circulation and is filtered freely at the glomerulus. Under physiological circumstances, approximately 180 gm of glucose is filtered in a 24hr period[11]. To prevent such large losses in glucose, the kidney reabsorbs all filtered glucose. With increases in the filtered load either by a rise in plasma glucose concentration or an increase in glomerular filtration rate, the rate of reabsorption increases to prevent increased excretion of glucose. Glucosuria results when the filtered load overwhelms the reabsorptive capacity of the kidney. Given that the kidney typically consumes 25–35 gm per day and produces between 15 and 55 gm of glucose per day, it is

clear that the reabsorption of glucose is the most important role that the kidneys play in glucose homeostasis[13].
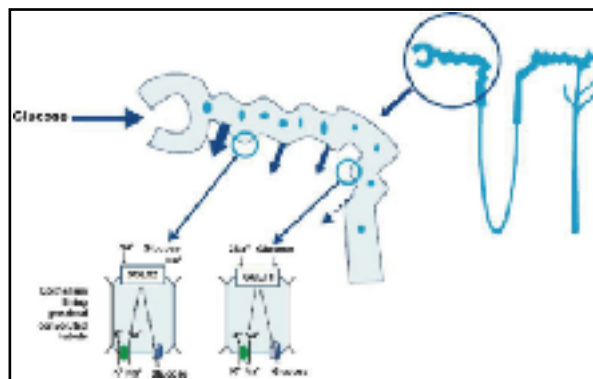
The transport of glucose across the proximal tubular epithelium along with the main molecular participants is now well described. Glucose enters eukaryotic cells via two different types of membrane associated carrier proteins, the faciliative glucose transporters (GLUTs) and the Na+-coupled glucose co-transporters (SGLTs)[14,15]. SGLTs couple the transport of glucose against a concentration gradient with the simultaneous transport of Na+ down a concentration gradient[16]. Two important SGLT isoforms (SGLT1 and SGLT2) have been cloned and identified. SGLT1 is located primarily in small intestinal cells but is also present in the kidney and the heart[17]. SGLT1 is a high-affinity, low-capacity transporter and therefore accounts for only a small fraction of renal glucose reabsorption; it serves predominantly as a sodium-glucose co-tranporter[18]. In contrast, SGLT2 is a lowaffinity, high capacity SGLT located exclusively at the apical domain of the epithelial cells in the early proximal convoluted tubule (S1 segment) (Figure-1). 90% of filtered glucose is reabsorbed by SGLT2; rest 10% is reabsorbed by SGLT1 in the late proximal straight tubule[14,15].

Therapeutic implications of SGLTs inhibition

Phlorizin, a non-specific SGLT1 and SGLT2 inhibitor first isolated from the root bark of the apple tree in 1835,[19] was found to increase glucosuria, reduce hyperglycemia, and normalize insulin sensitivity in a partial pancreatectomized animal model of T2DM[20]. However, it was not developed as a treatment for diabetes because of a number of practical shortcomings. It is non-selective and inhibits SGLT1 at the intestinal brush border, which is responsible for absorption of dietary glucose[21]. Inhibition of SGLT1, therefore,

has the potential to result in glucose–galactose malabsorption and thus diarrhea, as occurs in naturally occurring SGLT1 deficiency[23]. Furthermore, phlorizin is poorly absorbed in the intestine and is readily hydrolyzed to phloretin, a compound that blocks the facilitative glucose transporter, GLUT1. This might lead to interference with glucose uptake in a number of tissues[23]. To overcome phlorizin short-comings, highly specific inhibitors of SGLT2 were developed[24]. Early SGLT2 inhibitor candidates, remogliflozin[25] and sergliflozin[26], were selective for SGLT2 versus SGLT1 (296- and 395-fold, respectively) but remained susceptible to glucosidase cleavage in the gut[27] and had relatively short half-lives[28]. The discovery of C-arylglucoside SGLT2 inhibitors, which are resistant to gastrointestinal tract bglucosidases, followed. Initial Carylglucoside compounds had lower affinities for SGLT2, but further modifications produced the more potent dapagliflozin[27]. In preclinical studies dapagliflozin had a longer half-life (13.8h following a single oral 50-mg dose) than the earlier SGLT2 inhibitors[29]. The longer halflife allowed for once daily administration to achieve continuous controlled glucosuria. In addition, dapagliflozin is highly selective toward SGLT2, compared with SGLT1. Early in vitro studies with dapagliflozin determined that it was 3000-fold more selective for human SGLT2 versus SGLT1[30]. In addition, dapagliflozin is 32- fold more potent than phlorizin in SGLT2 inhibition[31]. Dapagliflozin produces a dosedependent increase in renal glucose excretion in humans though SGLT2 inhibition[31]. Fasting and postprandial glucose values decreased with treatment as well, and longer-term studies documented reduction in HbA1C. Dapagliflozin became recently available for clinical use. Canagliflozin, a similar stable, competitive, reversible, and highly selective SGLT2 inhibitor shortly followed. Currently, multiple agents in this class are being developed for the treatment of T2DM[24]. This approach to lowering hyperglycemia in T2DM is appealing for a number of reasons. Unlike the insulin secretagogues and insulin sensitizers, the action of SGLT2 inhibitors is independent of pancreatic beta cell function, which deteriorates over time. The insulin independence of their action plus the fact that they only lower the threshold without completely blocking renal glucose reabsorption means that hypoglycemic episodes are less likely. In fact, no major increase in hypoglycemic events was noted in clinical trials of SGLT2 inhibitors as well. Furthermore, the glucosuric effects of these drugs translate into caloric loss and decrease in bodyweight. For example, the glucosuria

induced by dapagliflozin monotherapy in patients with T2DM has been reported in one study to be associated with weight reduction of 2.5–3.4 kg in 12 weeks and a net loss of 200– 300 kcal/day[33]. Modest blood pressure reduction is consistently noted in clinical trials of SGLT2 inhibitors[34]. The mechanism of that is not entirely clear. The natriuretic effect of SGLT2 inhibitors, due to sodium-dependent co-transport mechanism of SGLT2, in addition to glucose-induced osmotic diuresis may be contributing. There is also a suggestion that some inhibition of the renin– angiotensin–aldosterone system, secondary to increased sodium delivery to the juxtaglomerular apparatus, may be present with SGLT2 inhibitors use[35]. As mentioned earlier, SGLT2 reabsorbs approximately 90% of the filtered glucose load in healthy individuals. Unexpectedly, available SGLT inhibitors are incapable of completely blocking this in humans. The maximum effect noted is 80 gm/day of urinary glucose excretion (UGE), which is less than 50% of the filtered glucose load. Increasing SGLT2 inhibitor dose after the 50% inhibition is achieved does not result in higher inhibition rate[36]. Dapagliflozin for example induced approximately 60 gm/day of UGE when used at 20 mg/day or at the much higher dose of 500 mg/day in one study[37]. The reason for this incomplete inhibition is not known. Liu et al. has explored and proposed several potential explanations such as an inability of SGLT2 inhibitor to reach and interact with some SGLT2 transporters, or that SGLT2 could be in fact responsible for less than the previously reported 90% glucose reabsorption fraction[36].

Sodium Glucose Co-transporter^2 Inhibitors (SGLT-2) decreased HbA1C anywhere from 0.5 to 1.5%, promoted weight loss, and demonstrated low incidences of hypoglycemia. Incidence of adverse effects with these agents has been low with no severe episodes of hypoglycemia documented. The most common adverse effects reported with these agents were urinary tract infections (UTIs) and/or genital tract infections[38]. Dapagliflozin, a first-in-class SGLT-2 inhibitor, has been studied the most extensively. In a small study that evaluated 5 doses of dapagliflozin (2.5, 5, 10, 20, or 50 mg), extended-release metformin (titrated to1500 mg), and placebo in drug-naïvepatients with T2DM, dapagliflozin demonstrated statistically significant reductions in A1C of 0.55% to 0.9% over 12 weeks when compared with a decrease of 0.18% with placebo. A reduction of 0.73% was noted with patients taking metformin. Additionally, weight loss of 1.3 kg to 2 kg was observed in study participants[33]. Patients with T2DM who were inadequately controlled on metformin

were evaluated in a phase 3, double-blind, placebo-controlled randomized controlled trial (RCT). Patients received metformin plus once-daily dapagliflozin 2.5, 5, or 10 mg, or matching placebo. Statistically significant decreases in mean A1C from baseline at 24 weeks were observed when dapagliflozin was compared with placebo (2.5 mg: 0.67%, 5 mg: 0.7%, 10 mg: 0.84%, placebo:–0.3%). Weight loss was also seen in the dapagliflozin groups. Dapagliflozin was well tolerated; however, more genital infections were seen in patients receiving dapagliflozin[39]. Recently published study shared results of the effects of dapagliflozin in patients not controlled with the TZD pioglitazone. Patients were randomized to receive open label pioglitazone plus either 5 mg or 10 mg of dapagliflozin for 48 weeks after a 10- week dose optimization phase with pioglitazone. Statistically significant reductions in A1C were seen after 24 weeks with both 5- and 10-mg strengths (5 mg: 0.82%, 10 mg: 0.97%, pioglitazone monotherapy: 0.48%), and these reductions were maintained through week[48]. The decrease in A1C at 48 weeks was greater with each group: 0.95%, 1.21%, and 0.54%, respectively. Dapagliflozin also decreased the effect of pioglitazone-associated weight gain and edema. Overall, dapagliflozin was well tolerated; however, the incidence of genital infections was increased compared with placebo[40]. A total of 800 patients with T2DM who were inadequately controlled on 30 units or more of insulin were evaluated in a double-blind, placebo-controlled RCT that investigated the effects of 24 weeks of dapagliflozin or placebo on A1C. Patients may have been also taking up to 2 oral antidiabetic agents. Patients were randomized to receive 2.5, 5, or 10 mg of dapagliflozin or placebo in addition to their usual insulin dose and oral agents. At 24 weeks, patients receiving dapagliflozin experienced statistically significant decreases in A1C (2.5mg: 0.79%, 5 mg: 0.89%, 10 mg: 0.96%) compared with placebo (0.39%). A secondary outcome was to evaluate the change in A1C at week 48. Statistically significant decreases in A1C were maintained (2.5 mg: 0.79%, 5 mg: 0.96%, 10 mg: 1.01%). Over 48 weeks, increases in mean insulin doses increased with time in patients of the placebo group (10.54 units) but not with dapagliflozin therapy. Decreases in body weight were observed in patients taking dapagliflozin, but increased with the placebo. Rates of hypoglycemic episodes, genital infection, and UTIs were higher in patients taking dapagliflozin[41]. Despite the positive effects on A1C, dapagliflozin has not been approved by the US Food and Drug Administration (FDA) till mid 2013 due to concerns of a potential link to breast and bladder cancers[42]. SGLT-2 is not thought to be expressed in either bladder or breast tissue, and therefore the mechanism of SGLT-2 inhibitors should not have a link to breast and bladder cancer risk; however, long-term surveillance is needed to exclude the association[42]. The U.S. Food and Drug Administration today approved dapaglifozin (Farxiga) tablets on 8 May of 2014. Canagliflozin is another SGLT-2 inhibitor currently in phase III development. A doseranging, double-blind RCT of canagliflozin added to metformin therapy demonstrated A1C reduction over a 12-week period. Canagliflozin therapy (50, 100, 200, or 300 mg once daily or 300 mg twice daily) was compared with the DPP-4 inhibitor, sitagliptin, which was used as an active reference treatment group, or placebo. A1C reduction with canagliflozin was noted with all doses investigated; however, the largest reductions were seen with 300 mg daily (0.92%) and 300 mg twice daily (0.95%) versus with placebo (0.22%). A weight loss of 2 kg to 2.9 kg was noted with canagliflozin compared with 0.8 kg with placebo and 0.4 kg with sitagliptin. Canagliflozin was well tolerated; however, females experienced an increased frequency of genital infections, including vulvovaginal mycotic infections and candidiasis. A third SGLT-2 inhibitor is in phase III development named empagliflozin. Empagliflozin demonstrated A1C lowering and improvements in glucose tolerance in animal studies, and had the highest selectivity of the SGLT-2 receptors compared with dapagliflozin, canagliflozin, and other SGLT-2 inhibitors[43].

Conclusion

There is an unmet need for more medications in the management of type 2 diabetes. The kidneys play a very important role in glucose homeostasis. Significant interest has emerged in the use of SGLT2 inhibitors. Since inhibition of SGLT2 provides an insulin-independent approach to the treatment of diabtes, its efficacy is not limited by the extent of either insulin resistance or degree of beta cell dysfunction and hence could be useful at all stages in the natural history of diabetes. The reduction in HbA1c is modest (at < 1%), however it has the additional advantage of weight loss and possible reduction in blood pressure. Current research has concentrated on type 2 diabetes, but theoretically SGLT2 inhibitors could also benefit patients with type 1 diabetes for reasons stated above. The research on SGLT2 inhibitors has mainly focused on dapagliflozin: a number of other SGLT2 inhibitors are undergoing phase II and III clinical trials.

Dapagliflozin is the only recently approved drug which can be implemented. Longer-term studies need to be undertaken to assess a number of issues including newer agent, the possible benefit of the negative caloric effect of glucosuria, the risk of renal and genital infections, and possible further renal damage in the presence of micro and macro albuminuria along with cardiac outcome data.

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