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Review Article

Licogliflozin as a Novel Therapeutic Target in Polycystic Ovary Syndrome and Metabolic Disorders

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Abstract

Background: PCOS is a complex endocrine-metabolic disorder characterized by hyperandrogenism, oligo-anovulation, insulin resistance, obesity, and chronic inflammation. Because current treatments primarily target insulin resistance and ovulatory dysfunction, they do not enhance weight, metabolic risk, or postprandial glucose management. Licogliflozin, a dual SGLT1/2 inhibitor, has attracted interest as a potential drug because of its combined effects on renal glucose excretion and intestinal glucose absorption.

Objective: This study describes the pharmacological profile, molecular basis, and expanding body of evidence for licogliflozin to evaluate its potential as a novel therapeutic option for managing metabolic and endocrine dysfunction in PCOS.

Methods: Using published preclinical research, phase II clinical trials in type 2 diabetes and obesity, mechanistic reports, and comparisons with current PCOS treatments, a narrative synthesis was carried out. We looked closely at the data about the impact on inflammation, hormones, metabolism, and safety.

Results: By reducing fasting and postprandial glucose, boosting insulin sensitivity, and generating dose-dependent weight loss through glycosuria, decreased intestinal glucose absorption, and incretin activation, licogliflozin dramatically improves glycaemic control. Anti-inflammatory qualities also reduce uric acid levels. These strategies directly address several of the primary metabolic causes of PCOS, such as visceral obesity, hyperinsulinemia, and low-grade inflammation. Genital infections and GI distress, particularly diarrhoea from SGLT1 inhibition, are class-associated hazards that remain unexplained and severe. Crucially, licogliflozin has not yet been particularly examined in any clinical trials, including PCOS populations, as of this writing.

Conclusion: Thus, by treating insulin resistance, obesity, postprandial dysglycemia, and inflammation, licogliflozin offers a strong biological justification for the therapy of PCOS. There are no PCOS-specific studies to determine licogliflozin's potential to improve ovulation, androgen excess, and reproductive outcomes, despite its promising metabolic benefits for PCOS patients. For women with PCOS, safety and treatment potential must be established through randomized controlled trials and trustworthy preclinical models.

Keywords: *Polycystic Ovary Syndrome; Licogliflozin; SGLT1/2 Inhibitor; Insulin Resistance; Hyperinsulinemia; Obesity; Metabolic Dysfunction; Incretins*

Introduction

Depending on the diagnostic criteria employed and the ethnic group under study, the prevalence of polycystic ovarian syndrome (PCOS), also known as hyperandrogenic anovulation or Stein-Leventhal syndrome, a common ring gynaecological condition affecting women in their reproductive years between the ages of 15 and 49, can range from 5 to 10% [1]. Further study indicates that this complex endocrine

disorder affects between 6 to 20% of premenopausal women globally, or about 1 in 15. A recent study found that between 8.2 and 22.5% of Indian women are diagnosed with PCOS [2]. Stein and Leventhal published the first account of it in 1935. Anovulation, irregular menstruation, metabolic dysfunctions like insulin resistance or dyslipidaemia, and clinical signs of excess androgen (acne, hirsutism, and alopecia) are the hallmarks of this illness [3]. The 2003 ESHRE/ASRM (Rotterdam) criteria state that a person may be diagnosed with PCOS if they exhibit two of the following three traits: polycystic ovaries, hyperandrogenism, and oligo-ovulation/anovulation. The Rotterdam 2003 criteria are one of the main diagnostic criteria now used in PCOS clinical and biochemical diagnoses [4].

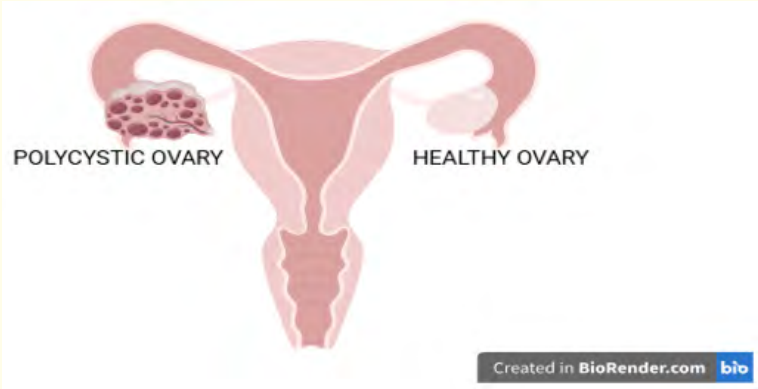

Figure 1: *Comparison of polycystic ovary and healthy ovary (The structural differences between a polycystic ovary and a healthy ovary are depicted in this image. The healthy ovary exhibits normal follicular development, but the polycystic ovary contains several small peripheral cysts, increased ovarian volume, and disrupted folliculogenesis, all of which are features of polycystic ovary syndrome (PCOS)).*

PCOM is defined by the most recent 2023 guidelines as having at least one of the following characteristics: Ovarian volume ≥10 mL, follicle count ≥20 in at least one ovary, or ≥10 follicles per section [5]. These criteria only apply to adult patients because there is no established consensus for assessing PCOM in minors. Interestingly, whereas PCOS patients usually have greater levels of anti-Müllerian hormone (AMH), the 2023 guidelines recommend utilizing AMH rather than ultrasonography to identify PCOM [6].

Four PCOS phenotypes, designated A through D in alphabetical order, have been defined based on the combination of the diagnostic criteria [7]. Since all diagnostic criteria are met, phenotypic A is sometimes referred to as the "complete" form of the condition, whereas phenotype B lacks PCOM but is also marked by hyperandrogenism and irregular menses [8]. Sometimes referred to as "classic" PCOS, phenotypes A and B are associated with a higher risk of metabolic disorders such insulin resistance and dyslipidaemia. While phenotypic D, or "non-hyperandrogenic" PCOS, has milder symptoms with only PCOM and irregular menstrual cycles, phenotype C, or "ovulatory" PCOS, is marked by hyperandrogenism and PCOM without ovulatory dysfunction [9,10].

Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH), obesity, metabolic syndrome, infertility, poor glucose tolerance, type 2 diabetes mellitus, heart risk, depression, and endometrial cancer are only a few of the numerous morbidities associated with PCOS [11,12]. Numerous factors, such as age, family history, genetic vulnerability, PCOS phenotype, comorbidities, and treatment taken, affect the prevalence and severity of these issues [13].

Insulin resistance and hyperinsulinemia are crucial markers of hyperandrogenism because they lead the ovaries' theca cells to overproduce androgen and LH. Up to 90% of women with PCOS have increased body mass indices (BMIs), which worsen insulin

resistance and hasten the onset of diabetes [14]. Consequently, it suggests that obesity is a fundamental factor in poor insulin metabolism, which accelerates the onset of diabetes in PCOS. Abdominal obesity also promotes androgen secretion, hyperadiponectinemia, cytokine production, oxidative stress, and hyperinsulinemia. We might therefore conclude that PCOS is associated with numerous morbidities [15].

Common treatment approaches include pharmacological medications and lifestyle modifications. For those who do not wish to get pregnant right away, hormonal contraceptives are the first line of treatment. They address both excess androgen and irregular menstruation [16]. Anti-androgens like flutamide and spironolactone, insulin-sensitizing medications like metformin, and ovulation-inducing medications like letrozole and clomiphene citrate are examples of further pharmacologic therapies [17-20].

Despite this arsenal, there is a significant therapeutic gap with regard to the concomitant treatment of the underlying metabolic dysfunction that supports the endocrine and reproductive aspects of PCOS, such as considerable obesity, postprandial dysglycemia, and hyperinsulinemia. This unfulfilled need has sparked the search for novel pharmacologic classes with complementary processes. Among these are the insulin-independent metabolic benefits of SGLT2 inhibitors. Licogliflozin, a new dual SGLT1 and SGLT2 inhibitor, further advances this paradigm. By simultaneously inhibiting renal glucose reabsorption (SGLT2) and intestinal glucose absorption (SGLT1), licogliflozin is a novel way to significantly lower plasma glucose, encourage weight reduction, minimize hyperinsulinemia, and regulate gut-derived incretin hormones [21]. This enables the use of a single medication to target multiple significant PCOS pathologic axes. Treatment strategies should be tailored to each patient's needs based on the metabolic hazards and hyperandrogenism symptoms associated with PCOS [22,23].

Pathophysiology of PCOS

The phenotype of PCOS at diagnosis reflects a vicious loop of neuroendocrine, metabolic, and ovarian abnormalities. Over the years, many theories have been proposed on the proximal physiologic origins of PCOS. This condition was first believed to be caused by an excess of intrauterine androgens. Thus, insulin resistance may have an impact on PCOS and hyperandrogenism. PCOS is a complex disorder caused by a variety of environmental and genetic variables, including excessive oxidative stress, abnormal insulin signalling, and unchecked ovarian steroidogenesis. Neuroendocrine involvement in the etiology of PCOS is suggested by recent clinical, experimental, and genetic findings.

Hyperandrogenism

Hyperandrogenism is one of the primary pathologic features of polycystic ovarian syndrome (PCOS), contributing significantly to the metabolic and reproductive symptoms of the illness [24]. Dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis, where a higher gonadotropin-releasing hormone (GnRH) pulse frequency favours luteinizing hormone (LH) hypersecretion with relatively low or normal follicle-stimulating hormone (FSH) levels, results in an elevated LH:FSH ratio, a characteristic of PCOS [25]. In ovarian theca cells, excess LH stimulates key steroidogenic enzymes such CYP11A1 and CYP17A1, which leads to an excess of androgens like testosterone, androstenedione, and dehydroepiandrosterone (DHEA) [26]. Reduced FSH also lessens the activity of granulosa cells' aromatase, which interferes with proper folliculogenesis and lessens the conversion of these androgens to oestrogens. Follicle stoppage, anovulation, and the distinctive polycystic ovarian morphology are the overall results [27]. Granulosa cells (GCs) with high testosterone levels trigger the endoplasmic reticulum (ER) stress response, which in turn triggers cellular apoptosis mediated by death receptor 5 (DR5). DR5, a transcriptional target of C/EBP homologous protein (CHOP), is essential for ER stress-mediated cell apoptosis because it amplifies the signalling cascade of released death ligands [28]. Insulin resistance and compensatory hyperinsulinemia worsen hyperandrogenism in PCOS by decreasing the hepatic production of sex hormone-binding globulin (SHBG) and boosting LH-stimulated androgen synthesis, which raises levels of free, physiologically active testosterone [29]. Anovulatory infertility is made worse by early granulosa cell luteinization and follicular atresia, both of which are encouraged by elevated insulin. Some PCOS women also have elevated DHEA and DHEAS levels due to adrenal hyperandrogenism, which is brought on by elevated CYP17A1 activity in the zona reticularis and adrenocorticotropic hormone

(ACTH). Additionally, it has been demonstrated that recently discovered 11-oxygenated androgens, including 11-ketotestosterone, have strong androgenic effects in PCOS [30]. By causing endoplasmic reticulum (ER) stress, oxidative damage, and granulosa cell death through DR5-mediated pathways, hyperandrogenaemia directly harms the ovarian microenvironment. This results in poor oocyte maturation, disturbed angiogenesis, and abnormal follicular development. Additionally, a vicious cycle that maintains follicular arrest and anovulation is created when tiny antral follicles release high levels of anti-Müllerian hormone (AMH), which inhibits FSH sensitivity and primordial follicle recruitment. Seborrhoea, acne, hirsutism, and androgenic alopecia are some of the clinical signs of hyperandrogenism. Biochemical markers that verify it include elevated levels of total or free testosterone, androstenedione, or DHEAS, with free testosterone being the most sensitive [31]. The reproductive, metabolic, and dermatological aspects of PCOS are thus caused by hyperandrogenism, which is the result of complex interactions between neuroendocrine dysfunction, intrinsic theca cell steroidogenic hyperactivity, insulin resistance, and adrenal contributions.

Hypothalamic-pituitary-ovarian (HPO) axis dysregulation

HPO axis regulates female reproductive activity by secreting GnRH, LH, FSH, and ovarian steroid hormones [32]. The anterior pituitary produces FSH and LH in response to pulsatile GnRH from the hypothalamus. While increasing oestradiol sets off a positive feedback loop on LH that causes the mid-cycle LH surge and ovulation, FSH encourages follicle maturation and oestradiol production. Progesterone is secreted by the corpus luteum following ovulation; inhibin B and oestradiol give GnRH and FSH negative feedback, preserving cyclicity.

The disturbance of the HPO axis caused by PCOS results in hyperandrogenism, increased LH, a high LH/FSH ratio, and aberrant GnRH pulsatility. Low FSH inhibits granulosa cells' aromatase activity, which stops the development of dominant follicles, whereas increased LH causes ovarian theca and stromal cells to overproduce androgens. LH secretion is further increased by persistent estradiol and estrone feedback, which maintains hyperandrogenism and anovulation. The expression of hypothalamic progesterone receptors is suppressed by high testosterone, as evidenced by the restoration of normal LH regulation by anti-androgen therapy. These anomalies result from progesterone and estradiol's ineffective negative feedback [33,34]. Furthermore, anti-Müllerian hormone (AMH) stimulates GnRH-dependent LH release, suggesting that increased AMH levels in the brain and ovaries worsen follicular and neuroendocrine dysfunction in PCOS [35]. The lack of uniform cut-off values and measurement variability limit the diagnostic use of an elevated LH/FSH ratio, despite its clinical association with hyperandrogenism and anovulation.

Insulin resistance and hyperinsulinemia

50 - 75% of PCOS patients have insulin resistance (IR), a serious metabolic condition that frequently coexists with compensatory hyperinsulinemia. Although weight exacerbates the illness, even thin women can have it [36]. IR is an indication of decreased insulin sensitivity in the liver, muscle, and adipose tissue. Chronic hyperglycaemia, poor glucose absorption, and reduced hepatic glucose production regulation are the outcomes of this. The hyperinsulinemia state brought on by pancreatic beta cells adapting by secreting more insulin may eventually result in beta-cell malfunction and an elevated risk of type II diabetes [37]. IR is impacted by genetic, epigenetic, prenatal, and environmental factors in addition to caloric excess and inflammation linked to obesity [38].

Hyperinsulinemia aggravates hyperandrogenism in PCOS by disrupting the HPO axis. Insulin increases the expression of the LH receptor on ovarian theca cells, increases the activity of the CYP17A1 enzyme, and stimulates the production of androgens, especially testosterone [34]. Additionally, by preventing the liver from producing SHBG and IGF-binding protein-1 (IGFBP-1), insulin increases the availability of free testosterone and IGF-1 [39]. Hyperinsulinemia further promotes an androgenic environment by inhibiting granulosa cells' aromatase, which reduces the conversion of androgens to oestrogens [40]. Here, dysregulation of nuclear receptors like as PPAR-γ, which regulate steroidogenesis and insulin sensitivity, leads to aberrant follicular growth and ovulatory failure [41].

The loop of hyperinsulinemia and hyperandrogenism is complicated by the paradox of insulin action in PCOS-resistance in metabolic tissues but continuous sensitivity in steroidogenic tissues. Anovulation, hyperandrogenism, and metabolic syndrome-all common

symptoms of PCOS-are the clinical outcomes of this combo. Evidence that treatments that target insulin sensitivity, such as weight loss or insulin-sensitizing medications, enhance metabolic and reproductive outcomes highlights the critical role of insulin in the etiology of PCOS.

Obesity and dyslipidaemia

Because obesity increases insulin resistance (IR), hyperandrogenism, and dyslipidaemia, it greatly exacerbates the pathophysiology of PCOS. Long-term nutritional excess results in adipocyte hypertrophy and reduces adipose storage capacity, according to the adipose tissue expandability theory. The hypoxia, macrophage infiltration, and proinflammatory cytokine release of hypertrophic adipocytes provide a lipotoxic environment that causes IR and metabolic stress. enhanced circulating free fatty acids (FFAs) and triglycerides (TGs), enhanced hepatic *de novo* lipogenesis, and ectopic fat deposition in the pancreas, skeletal muscle, and liver (hepatic steatosis) are all consequences of impaired insulin action.

Atherosclerotic plaque and endothelial dysfunction are encouraged by IR-driven disturbance of lipid metabolism, which results in TG build-up and increased LDL-C. Low HDL-C prevents reverse cholesterol transfer, which lowers cholesterol clearance from arterial walls and raises cardiovascular risk [42,43]. Preliminary research indicates a connection between altered lipid profiles and carotid intima-media thickness, suggesting early vascular injury in PCOS.

The prevalence of PCOS increases by around 9% for each BMI unit above normal, indicating that obesity significantly exacerbates hyperandrogenism and metabolic issues. Nonetheless, it appears that lean and obese phenotypes have different pathogenic pathways because 30 - 50% of women with normal weight develop PCOS. Imaging studies reveal preferential visceral fat growth and subcutaneous adipose IR even in PCOS women of normal weight, while visceral fat ablation improves metabolic parameters and menstrual cyclicity [44,45]. Developmental studies reveal that low birth weight, early adiposity rebound, and childhood adipocyte malfunction promote IR, β-cell impairment, and metabolic inflexibility, forming a continuum from early life until the onset of PCOS.

At the molecular level, adipose tissue androgen metabolism contributes to the vicious cycle of hyperandrogenism and metabolic dysfunction. While decreased SRD5A1 alters androgen metabolism, promoting insulin resistance, hyperinsulinemia, and fat accumulation [46], overexpression of AKR1C3 in adipose tissue increases local androgen activation [47]. Additionally, because obese PCOS individuals have poor fat oxidation and reduced metabolic flexibility, lipid dysregulation gets worse. The metabolic and reproductive problems associated with PCOS are exacerbated by adipose dysfunction caused by obesity, insulin resistance, dyslipidemia, and hyperandrogenism.

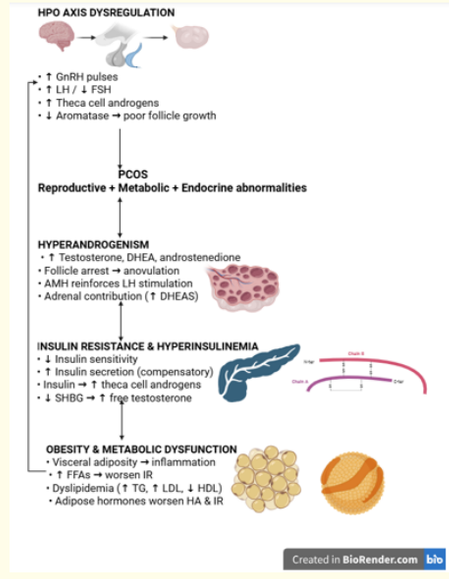

Figure 2: *Pathophysiology of PCOS (The interrelated ovarian, metabolic, and neuroendocrine pathways causing PCOS are depicted in this picture. Hyperandrogenism, insulin resistance, inflammation associated with obesity, altered GnRH pulsatility, elevated LH/FSH ratio, decreased folliculogenesis, and consequent anovulation are important factors. The PCOS phenotype is sustained by these processes, which create a vicious cycle).*

SGLT inhibition: A novel mechanistic approach

The sodium gradient created by the Na^+/K^+-ATPase pump is used by membrane proteins known as sodium-glucose co-transporters (SGLTs) to enable active glucose transport across epithelial cells [48,49]. The roles of the two primary isoforms, SGLT1 and SGLT2, in glucose regulation and energy balance have been extensively researched. SGLT1 is extensively expressed in the brush border of the small intestine mucosa, where it facilitates the absorption of dietary glucose and galactose, to a lesser degree in the renal DCT. SGLT2 reabsorbs around 90% of the filtered glucose from the glomerular filtrate back into the circulation [50], This is primarily located in the renal proximal tubule's S1 section. Through their complementary roles, SGLT1 and SGLT2 cooperate under physiological conditions to preserve normoglycemia and prevent glucose loss in the urine.

Pharmacological reduction of SGLTs is one innovative therapy strategy for metabolic illnesses, particularly type 2 diabetes mellitus (T2DM) [51]. SGLT medications decrease renal glucose reabsorption by specifically inhibiting these transporters. This leads to glycosuria and a subsequent decrease in plasma glucose levels that is unrelated to the synthesis of insulin by the pancreas. For those with insulin resistance or β-cell loss, this insulin-independent pathway offers a special benefit [52]. Additionally, while osmotic diuresis can lower blood pressure, glycosuria's subsequent calorie loss results in a little but long-lasting drop in body weight. SGLT inhibition not only lowers blood sugar but also enhances lipid metabolism, systemic inflammation, and vascular health [53]. This therapy paradigm is extended by dual inhibitors, like licogliflozin, which target both SGLT1 and SGLT2 to reduce intestinal glucose uptake and renal glucose reabsorption. In addition to improving insulin sensitivity and reducing postprandial glucose excursions, this dual impact also modifies gut-derived incretin responses like glucagon-like peptide-1 (GLP-1), which improves glucose homeostasis [54].

The substantial metabolic overlap between T2DM and PCOS provides the biological justification for investigating SGLT inhibition in PCOS. The primary pathophysiological characteristics of PCOS are insulin resistance and compensatory hyperinsulinemia, which lead to increased ovarian androgen production, reduced folliculogenesis, and anovulation [55]. Additionally, hyperinsulinemia increases inflammation in adipose tissue and encourages weight gain, resulting in a vicious circle of reproductive and metabolic problems. By increasing insulin sensitivity and lowering circulating insulin levels, SGLT inhibitors' insulin-independent glucose-lowering action may aid in breaking this cycle. The consequent decrease of hyperinsulinemia, which indirectly inhibits the production of testosterone by ovarian thecal cells, can enhance ovulatory function.

Additionally, the ability of SGLT inhibition to reduce weight is especially helpful for overweight and obese women with PCOS since visceral adiposity exacerbates endocrine and metabolic issues in these individuals. By altering gut hormone production and microbiota composition-both of which are widely acknowledged as significant factors in PCOS pathophysiology-licogliflozin's simultaneous inhibition of SGLT1 and SGLT2 may provide further advantages. Metabolic and reproductive homeostasis may be influenced by increased GLP-1 secretion, improved hepatic insulin sensitivity, and decreased systemic inflammatory mediators.

Therefore, SGLT inhibition offers a comprehensive and innovative treatment approach that tackles important aspects of PCOS pathogenesis, such as insulin resistance, inflammation, and obesity [56]. A new paradigm for the combined treatment of endocrine and metabolic illnesses may be established by the growing body of evidence from cardiovascular and metabolic research, which offers a solid basis for assessing dual SGLT1/2 inhibitors, such licogliflozin, in the context of PCOS.

Licogliflozin: Pharmacological profile and mechanism of action

Licogliflozin, also known as LIK066 in clinical trials, is a small-molecule dual inhibitor of the sodium-glucose co-transporters SGLT1 and SGLT2 that was developed to combine reduced racikgliflozin family, it was engineered for considerable action at both renal SGLT2 and enteric SGLT1. This led to the development of a once-daily oral drug intended to produce additive metabolic benefits as opposed to targeted SGLT2 inhibition [57]. This dual target profile-increased urine glucose excretion (by SGLT2 blocking) and decreased postprandial glucose uptake from the gut (via SGLT1 inhibition) is the source of licogliflozin's potential advantages. These actions should improve calorie loss, decrease postprandial excursions, and trigger gut hormone-mediated satiety signals.

Licogliflozin pharmacodynamically promotes glycosuria in an insulin-independent manner, but intestinal SGLT1 blockage decreases the absorption of carbs and enhances incretin responses (GLP-1 and PYY), which may help suppress hunger and improve post-prandial glycaemic management [58]. Phase II clinical pharmacology reports show dose-dependent metabolic effects: over a 12-week period, increasing daily doses (studied at 2.5, 10, 25, and 50 mg) resulted in progressively larger reductions in body weight, fasting plasma glucose, and HbA1c, as well as significant reductions in serum uric acid [59]. As a result, the dual mechanism produces a composite of decreased caloric absorption, renal glucose loss, and beneficial control of hormones originating from the gut-mechanistic components that contribute to the explanation of the significant glycaemic and weight advantages shown in trials.

Licogliflozin was administered once daily with particular dose-response relationships for efficacy targets based on available pharmacokinetic and tolerability data from the published phase II program. Higher doses (25 - 50 mg daily) produced the greatest metabolic benefits, according to clinical data, but they were also linked to a dose-dependent increase in gastrointestinal side effects, especially diarrhoea, which is consistent with SGLT1 inhibition and decreased intestinal monosaccharide absorption [60]. The GI adverse-event profile and the requirement for longer-term safety data were noted as significant limitations of the early development experience, even though renal safety signals common to SGLT modulation (such as changes in urine albumin/creatinine or eGFR monitoring) were evaluated in trials without the discovery of new, unexpected renal toxicities in the comparatively short treatment windows reported. These safety and PK/PD findings highlight the therapeutic trade-offs associated with concurrent SGLT1/2 inhibition: enhanced metabolic efficiency at the cost of gastrointestinal adverse effects that could limit tolerability at higher dosages [61].

Licogliflozin has advanced through phase II development in metabolic indications. Adults with overweight/obesity (as well as subgroups with dysglycemia or type 2 diabetes) showed statistically significant, dose-dependent reductions in body weight and clinically significant reductions in HbA1c and fasting glucose. Concurrent SGLT1/2 inhibition can significantly reduce uric acid and have weight benefits that are more noticeable than those frequently seen with SGLT2 monotherapy, according to these studies, which were funded by the developer. Although the majority of published trials to far have been fairly small and short (12 weeks), confirming signal and tolerability, longer-term safety, cardiovascular or renal consequences, and long-term efficacy have not yet been defined. In addition to encouraging continued development, the clinical program makes it abundantly evident that longer and larger trials are required to properly evaluate benefit-risk.

The primary distinction between licogliflozin and the selective SGLT2 inhibitors now available on the market is their intestinal SGLT1 activity. Large outcome trials have demonstrated that the SGLT2 class (dapagliflozin, empagliflozin, canagliflozin, and others) improves cardiovascular and renal health and consistently lowers blood pressure. Class-typical adverse events include genital mycotic infections and, less frequently, volume-depletion events and euglycaemic ketoacidosis in predisposed individuals. On the other hand, licogliflozin's dual inhibition aims to improve weight loss and reduce postprandial glucose peak through intestinal SGLT1 blockage and incretin effects [62]. Preliminary research indicates a greater uric acid-lowering effect than targeted SGLT2 drugs. A increased incidence of gastrointestinal side effects, primarily diarrhoea, linked to intestinal carbohydrate malabsorption is the trade-off shown in phase II trials; this adverse-event profile differs significantly from that of selective SGLT2 inhibitors. Licogliflozin may therefore benefit some individuals more metabolically (weight, postprandial glycaemia), but at the expense of tolerability problems that will dictate the ideal dosage and patient selection.

In summary, licogliflozin is a well-known dual SGLT1/2 inhibitor whose combined intestinal and renal effects result in additive metabolic benefits in early human testing, such as improved glycaemic control, dose-dependent weight loss, and a significant decrease in uric acid. While the phase II experience confirms the mechanism, it also emphasizes the lack of long-term outcome data and raises questions regarding the tolerance of intestinal SGLT1 inhibition. To determine the clinical niche where the dual-inhibition strategy provides a net advantage, more dose optimization, longer safety follow-up, and head-to-head comparisons with selective SGLT2 inhibitors will be necessary for translational applications, such as PCOS trials or specialized cardiovascular/renal outcome programs.

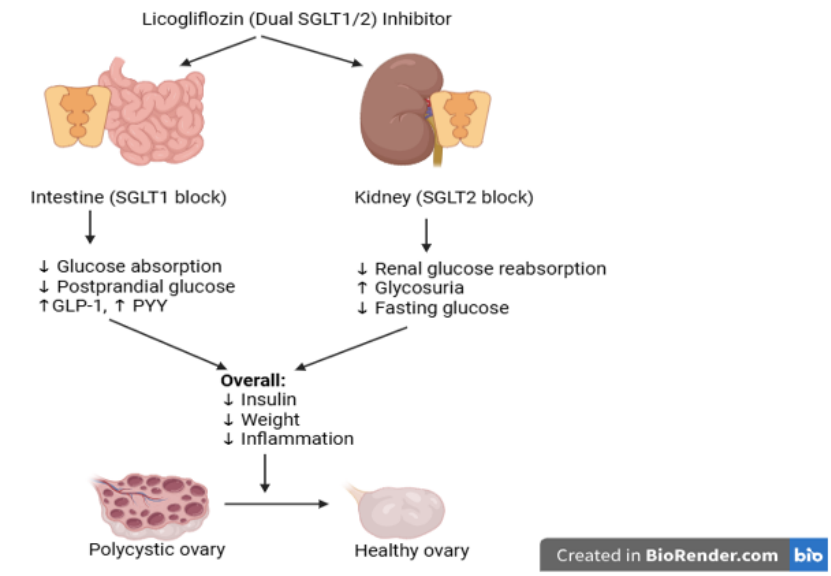

Figure 3: *Mechanistic action of licogliflozin (Dual SGLT1/2 inhibitor) (Licogliflozin inhibits intestinal SGLT1, which lowers carbohydrate absorption and increases incretin (GLP-1, PYY) signaling, and blocks renal SGLT2, which increases glycosuria. Improved glycemic control, lowered insulin levels, appetite suppression, decreased uric acid, and weight loss are all combined outcomes).*

Parameter	Licogliflozin (Dual SGLT1/2 Inhibitor)	Dapagliflozin	Empagliflozin	Cana-gliflozin	Ertugliflozin
Inhibition type	Dual SGLT1 (intestinal) and SGLT2 (renal) inhibition	Selective SGLT2 inhibition	Selective SGLT2 inhibition	Predomi-nantly SGLT2, mild SGLT1 inhibition	Selective SGLT2 inhibition
MOA	Increases GLP-1 secretion while decreasing intestine and renal glucose absorption.	causes glucosuria by reducing renal glucose reabsorp-tion.	Comparable renal glucose excretion that is insulin-inde-pendent	Has a minor impact on intestinal absorption and inhibits renal glucose reabsorption.	Prevents the reab-sorption of glucose by the kidneys
Effect on Fasting Glucose	Significant reduction	Moderate reduction	Moderate reduction	Moderate to high reduction	Moderate reduction
Effect on Postprandial Glucose	Strong reduction due to intes-tinal SGLT1 inhibition	Mild reduction	Mild reduction	Moderate reduction	Mild reduction
Effect on Body Weight	Higher loss	Average loss	Average loss	Average loss	Average loss
Effect on GLP-1 and PYY Hormones	Increases secretion due to intestinal glucose delay	No effect	No effect	Slight increase (at high doses)	No effect

Uric Acid Reduction	Marked	Mild to moderate	Moderate	Moderate	Moderate
BP Effect	Moderate reduction due to diuresis	Moderate reduction	Moderate reduction	Moderate reduction	Moderate reduction
Renal Outcome Evidence	Early stage evidence only	Proven renal protection	Proven renal protection	Proven renal protection	Limited renal data
Adverse Effects	GI disorders (bloating, diarrhea, SGLT1 inhibition); genital infections	Mild dehydration and genital infections	Depletion of volume and genital infections	Mild fractures, infrequent DKA, and genital infections	Genital infections
Limitations	Higher dosages may cause intestinal intolerance; long-term safety information is scarce	Mild volume depletion	Rare hypotension	Volume loss	Limited data
Development Stage	Phase II (in obesity, T2DM)	Approved (global)	Approved (global)	Approved (global)	Approved (global)

Table 1: *Comparison of licogliflozin with other SGLT inhibitors (The mechanism of action, metabolic effects, hormonal impact, cardiometabolic benefits, adverse-effect profiles, and special therapeutic advantages or limitations of licogliflozin (a dual SGLT1/2 inhibitor) and authorized SGLT2 inhibitors are summarized in this table) [63].*

Preclinical and clinical evidence of licogliflozin in metabolic disorders

Early-phase clinical trials and preclinical programs for licogliflozin indicate that dual SGLT1/2 inhibition offers significant metabolic effects that go beyond those of selective SGLT2 inhibitors. Compared to controls, licogliflozin decreased body weight, increased urine glucose loss, and decreased fasting and postprandial glucose excursions. In animal models, intestinal SGLT1 inhibition improved incretin (GLP-1, PYY) responses by reducing carbohydrate absorption and increasing distal-gut glucose transport. These molecular cues aided dose-ranging clinical studies and anticipated the metabolic endpoints later seen in humans [64].

Licogliflozin showed dose-dependent improvements in insulin sensitivity and glycaemic control in clinical trials, mostly phase II dose-finding trials. Higher daily doses considerably reduced fasting plasma glucose and HbA1c in patients with dysglycemia or type 2 diabetes when compared to placebo; typical phase-II estimates showed placebo-subtracted HbA1c reductions in the moderate range (~0.5-1.0%, dose-dependent) over 12 weeks in treated populations. Because of the drug's insulin-independent glycosuric action and reduced postprandial glycaemic burden from intestinal SGLT1 blockade, improvements in measures of insulin resistance (surrogate indices like HOMA-IR in exploratory analyses) were found to be consistent with lower circulating insulin concentrations following treatment.

Licogliflozin improves lipid markers and body weight. Dose-dependent weight loss was often documented in clinical trials, with higher dosages leading to larger reductions (average mean placebo-subtracted weight loss in short 12-week studies ≈2-4% of body weight). Reduced intestinal glucose absorption, decreased hunger due to incretin, and caloric loss via glycosuria are all possible reasons of weight reduction. Early studies showed modest improvements in the lipid profile, including mild decreases in triglycerides and neutral or slight changes in HDL-C and LDL-C. Since these gains were not significant, larger and longer trials are required to draw definitive conclusions [65].

In preclinical and early clinical trials, licogliflozin demonstrated anti-inflammatory and gut-metabolic benefits in addition to traditional metabolic endpoints. In exploratory analyses, the dual SGLT1/2 action was linked to lower levels of biomarkers of low-grade inflammation. It also raised circulating GLP-1 and PYY after meals, which are hormonal changes that promote improved insulin sensitivity, satiety, and

possibly advantageous changes in adipose and hepatic metabolism. Additionally, licogliflozin significantly decreased serum uric acid, a potentially beneficial pleiotropic effect associated with gout risk and metabolic syndrome.

Safety and tolerability results indicate a common trade-off for simultaneous SGLT1/2 blockage. Due to partial intestinal glucose malabsorption from SGLT1 inhibition, the most frequent treatment-emergent side events were gastrointestinal, including dose-dependent diarrhea and associated GI symptoms. Two class effects of SGLT2 inhibition, genital mycotic infections and volume-depletion events, were mostly under control and were seen at rates comparable to those of other SGLT inhibitors. No further renal toxicities appeared during the brief studies that were presented, despite the need for a longer follow-up. To determine the therapeutic niche for licogliflozin, longer safety/outcome trials, focused patient selection, and dose optimization are needed to balance increased GI intolerance against higher metabolic efficacy at higher doses.

Domain	Preclinical Evidence	Clinical Evidence (Phase II, short-term)
Glucose metabolism	In animal models, fasting and postprandial glucose lead to increased glycosuria.	HbA1c and fasting glucose versus placebo (dose-dependent)
Insulin sensitivity	Reduced insulin responses and enhanced insulin action in animals	Lower insulin AUC and improvements in HOMA-IR were noted in exploratory analysis.
Postprandial glucose and incretins	Animals with elevated distal glucose → increased GLP-1, PYY	Reduced glucose excursions and increased postprandial GLP-1/PYY
Body weight	Loss of weight in diet-induced obesity models	Placebo versus dose-dependent weight loss
Lipid profile	Animal hepatic lipid handling is affected in several ways.	Triglycerides are moderate, neutral, and variable. HDL-C and LDL-C
Uric acid	N/A	Serum uric acid levels were found to have significantly decreased.
Inflammation / markers	Reduced	Exploratory reductions in inflammatory biomarkers
Gut microbiome / metabolism	Animal microbiota changes and altered luminal carbohydrate delivery	Mechanistic plausibility and lack of extensive clinical microbiome data
Adverse events - GI	Animal diarrhea due to an increase in unabsorbed carbohydrates	GI distress and dose-dependent diarrhea (most common)
Adverse events - SGLT2 class effects	N/A	Osmotic diuresis, genital mycotic infections, and infrequent volume depletion
Renal / CV outcomes	Renal metabolic advantages in models	Only brief phase II trials with no long-term outcome data

Table 2: *Summary of preclinical and clinical evidence for licogliflozin (The main conclusions from research on licogliflozin's effects on glucose metabolism, insulin sensitivity, lipid profile, body weight, inflammatory markers, gut-hormone responses, and safety results are shown in this table) [66,67].*

Licogliflozin in polycystic ovary syndrome: Emerging insights

Because polycystic ovary syndrome (PCOS) is characterized by insulin resistance, hyperinsulinemia, obesity, and persistent low-grade inflammation, licogliflozin is warranted in its treatment. Licogliflozin reduces the body's reliance on insulin for glycaemic regulation

since it lowers glucose levels through both intestinal glucose absorption (by SGLT1 inhibition) and renal glucose elimination (via SGLT2 inhibition) [68]. In PCOS, where hyperinsulinemia directly causes ovarian thecal cells to overproduce androgens, this insulin-independent method can help lower circulating insulin levels. Licogliflozin offers a solid scientific foundation for treating a variety of metabolic disorders that cause reproductive dysfunction in PCOS by enhancing insulin sensitivity, lowering postprandial glucose spikes, and encouraging weight loss [69].

Currently, there aren't many direct experimental or clinical trials assessing licogliflozin in PCOS populations. Phase II trials involving people with type 2 diabetes, obesity, or overweight provide the majority of the drug's published data. Along with increases in incretin hormones like GLP-1 and PYY, these trials regularly show improvements in fasting glucose, HbA1c, insulin sensitivity, body weight, and uric acid levels. These results are promising, but they have not yet been investigated in relation to PCOS-specific effects on metabolism and reproduction. No major clinical trials have yet assessed the effects of licogliflozin on ovulatory function, ovarian morphology, androgen levels, or menstrual regularity in women with PCOS [70]. Therefore, rather than direct clinical proof, current understanding of its potential advantages in PCOS is dependent on translational reasoning.

However, more research is necessary due to several possible effects of licogliflozin on hormonal and ovulatory function. By lessening insulin-mediated stimulation of androgen synthesis in the ovary, lowering insulin levels may enhance the follicular microenvironment and reduce total testosterone. Weight loss, which is often observed with licogliflozin, may further improve hormonal balance by improving adipose function and reducing inflammatory mediators associated with androgen excess. greater synthesis of GLP-1 and PYY, which may also improve metabolic flexibility and reduce hunger, may indirectly encourage greater menstrual cyclicity. All of these mechanisms suggest that licogliflozin may improve metabolic parameters that are closely linked to PCOS reproductive failure, decrease androgen excess, and increase ovulation frequency.

Safety and tolerability considerations are critical when considering the use of licogliflozin for PCOS. At larger dosages, intestinal SGLT1 inhibition and partial carbohydrate malabsorption increase the chance of gastrointestinal side effects, especially diarrhea and stomach pain, even if the medication is typically used as directed. Monitoring is also necessary for class-related adverse effects such minor volume depletion and vaginal mycotic infections [71]. Licogliflozin's effects on pregnancy and fetal development are unknown, hence its usage in women trying to conceive should only be investigated in carefully monitored clinical trials.

In conclusion, because of its combined effects on insulin resistance, body weight, inflammation, and incretin biology, licogliflozin represents a viable theoretical therapy alternative for PCOS. However, because no specific clinical studies have assessed its hormonal or reproductive effects in PCOS, there is a substantial data gap. To ascertain whether licogliflozin can be a major therapeutic advancement in PCOS management, future priority research should include preclinical PCOS models, pilot randomized trials in overweight or obese women with PCOS, and longer-term studies evaluating ovulation, androgen levels, menstrual regularity, and metabolic outcomes.

Comparative analysis with current therapies

For PCOS, licogliflozin provides a mechanistically unique substitute for traditional metabolic treatments including metformin, thiazolidinediones (TZDs), and GLP-1 receptor agonists. Metformin has no effect on weight but increases insulin sensitivity, somewhat promotes ovulation, and decreases androgen levels [72]. Although weight gain and fluid retention restrict their use, TZDs have potent insulin-sensitizing effects. GLP-1 agonists cause the greatest improvements in metabolism and weight loss, and there is growing evidence that they also improve the androgen profile and ovulation. However, they can cause nausea, are costly, and are injectable. Licogliflozin, on the other hand, promotes mild weight loss by glycosuria and reduced intestinal glucose absorption and lowers both fasting and postprandial glucose through dual SGLT1/2 inhibition. The absence of direct PCOS clinical trials and gastrointestinal irritation at larger dosages are its primary drawbacks. However, because of its insulin-independent glucose-lowering and additional effects on weight and incretin hormones, licogliflozin may complement existing medications, especially metformin or GLP-1 agonists, making combination techniques an attractive route for future PCOS therapy research.

Feature	Licogliflozin (dual SGLT1/2)	Metformin	Thiazolidinediones (e.g. pioglitazone)	GLP-1 RAs (e.g. liraglutide, semaglutide)
Primary mechanism	decreased Intestinal glucose absorption (SGLT1) + renal glucosuria (SGLT2)	Decreased Hepatic gluconeogenesis, increased peripheral insulin sensitivity	PPARγ agonist leads to enhanced adipocyte insulin sensitivity	GLP-1 receptor agonism → enhanced insulin secretion (glucose-dependent), reduced appetite
Effect on fasting glucose / HbA1c	Insulin-independent, moderate glycemic reduction	Moderate; lowers HbA1c and fasting glucose	Glycemia and insulin sensitivity have improved moderately to significantly.	Strong reduction of blood sugar (particularly after meals)
Effect on postprandial glucose	Strong	Mild	Mild	Strong
Weight effect	Modest to moderate weight loss	Neutral	Weight gain	Substantial weight loss
Effects on ovulation / androgens (PCOS)	There is no direct PCOS RCT evidence, however there is a plausible indirect benefit through weight and insulin.	Modest increases in androgens and ovulation (supported by PCOS research)	increases menstrual regularity and ovulation, but weight gain restricts use	In modest PCOS trials, positive signals for ovulation and androgen reduction
Impact on lipids	Modest TG reduction; neutral/variable LDL/HDL	Mild beneficial	May have favorable TG/HDL changes	neutral to favorable
Key adverse effects	Volume depletion, vaginal infections, diarrhea/GI (SGLT1), and insufficient long-term data	B12 insufficiency, GI distress (nausea, diarrhea), and infrequent lactic acidosis	Edema, weight increase, fracture risk, and heart failure exacerbation risk	Injection site reactions, nausea, vomiting, and a potential risk of pancreatitis
Evidence base in PCOS	Translational rationale	Strongest clinical evidence	Limited PCOS RCT data	Emerging PCOS data (small trials) showing benefit on weight/ovulation
Practical advantages	Oral; uric acid reduction; postprandial control; supplemental to other medications	Low cost, extensive experience, and enhanced ovulation	Potent insulin sensitiser	Strong weight loss that enhances reproductive and metabolic indicators
Practical limitations	GI intolerance at higher dosages; hazards of infection and volume; lack of data on reproductive outcomes	Modest weight effect; GI side effects	Gaining weight, holding onto fluids, and safety issues	Pregnancy limitations, GI adverse effects, injectable method, and cost

Table 3: *Comparative analysis: licogliflozin vs. metformin, TZDs, GLP-1 Ras (In terms of mechanisms, metabolic and reproductive effects, safety concerns, benefits, drawbacks, and possible usage in combination therapy, this table contrasts licogliflozin with metformin, thiazolidinediones, and GLP-1 receptor agonists) [73-75].*

Challenges and limitations

Licogliflozin has a decent metabolic profile, but before it can be used to treat PCOS, a number of issues and restrictions need to be resolved. The biggest drawback is the absence of direct clinical evidence assessing its hormonal or reproductive effects in PCOS, as the majority of the data currently available comes from studies on type 2 diabetes and obesity. Long-term compliance and dose escalation may be hampered by gastrointestinal distress, especially diarrhea brought on by SGLT1 inhibition. Additionally, especially in women of reproductive age, monitoring is required for class-related adverse effects like vaginal mycotic infections and mild volume depletion. Ignorance of safety during conception, pregnancy, and nursing is a significant barrier for women thinking about reproductive treatment. The absence of long-term cardiovascular, renal, or endocrine outcome data further restricts its present therapeutic use. These limitations indicate that the potential benefits of licogliflozin in PCOS should be regarded cautiously until further research is completed.

Future Perspectives and Conclusion

Future studies should concentrate on carefully designed clinical trials to ascertain how licogliflozin affects hormones, metabolism, and reproduction, especially in women with PCOS. Studies should evaluate ovulation rates, androgen profiles, menstrual regularity, ovarian morphology, and reproductive outcomes in addition to long-term safety, which includes cardiovascular and renal endpoints. Combination treatments, such as licogliflozin with metformin or GLP-1 receptor agonists, present a strong alternative since their complementary mechanisms may enhance metabolic benefits and promote weight loss. Preclinical PCOS models may also provide important insights into how licogliflozin impacts ovarian steroidogenesis and inflammation prior to more comprehensive trials. In conclusion, licogliflozin's combined effects on glucose regulation and weight loss provide a strong biological justification for treating PCOS; nevertheless, its actual usefulness is still up for debate. Licogliflozin is an intriguing but unproven possibility in the developing field of PCOS therapy; before it can be suggested as a therapeutic substitution, strong data from PCOS-focused trials are needed.

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Volume 14 Issue 5 May 2026