A review on type 2 diabetes mellitus in patients with polycystic ovary syndrome: Study on the risk factor, pathogenesis, lifestyle modification and pharmacological treatment

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Abstract- **Polycystic ovary syndrome is recognized as a common endocrine disorder in women of reproductive age, associated with clinical and biochemical hyperandrogenism, chronic ovulatory dysfunction, and polycystic ovaries. In addition to reproductive and psychological consequences of PCOS, there are several other established long-term risks and consequences. PCOS is also associated with an array of metabolic abnormalities- obesity, impaired glucose tolerance which can exacerbate the occurrence of T2DM. Insulin resistance and its compensatory hyperinsulinemia is the underlying cause for many of the endocrine, metabolic and reproductive features in PCOS women. The aim of this review is to give a better understanding of the correlation between the metabolic and reproductive dysfunction in PCOS, to summarize the factors related to the pathogenesis of T2DM in PCOS women, other possible risk factors and its management. Non-pharmacological management- diet plan and exercise training are taken as a major consideration for prevention as well as for maintaining a healthy physique during the course of the disease which can ameliorate certain aggravating risk factors.**

Keywords: **Hyperandrogenism, insulin resistance, hyperinsulinemia, polycystic, obese**

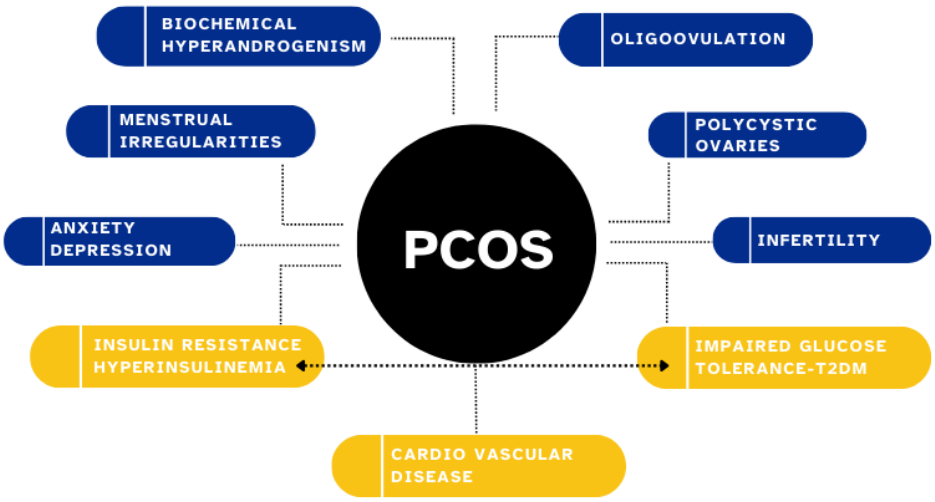
1. INTRODUCTION

In fertile women, the prevalence of polycystic ovarian syndrome is estimated to be 8–13%, Up to 70% of affected women remain undiagnosed worldwide[1]. The hallmarks of polycystic ovarian syndrome [PCOS] include increased risk factors for impaired glucose tolerance [IGT], type 2 diabetes mellitus [DM2], and cardiovascular disease [CVD], while the major symptoms include increased ovulatory dysfunction [anovulation], hyperandrogenism, and psychological manifestations that significantly impair a patient's quality of life [anxiety and depression] [2,3]. Hyperandrogenism manifests as both hirsutism and acne and the other common characteristics are menstrual irregularity and infertility[2,4]. PCOS is associated with metabolic anomaly such as insulin resistance [IR] and β-cell dysfunction. An important part of the pathophysiology of androgen excess in PCOS is played by hyperinsulinemia [HI], a result of insulin resistance[5,6].Insulin resistance affecting between 10-25% of general population becomes an essential part of PCOS and T2DM pathology. In PCOS, the term "resistance" to insulin action frequently refers to the hormone's diminished effects on anti-lipolysis in adipocytes and glucose transport in adipocytes, skeletal and cardiac muscles. As a result, in PCOS, the IR causes compensatory hyperinsulinemia, in which excess insulin magnifies the effects in other tissues which includes increased endothelial and vascular hyperreactivity and abnormal peripheral lipid metabolism[7]. Type 2 diabetes mellitus is a heterogeneous metabolic disorder that eventually results in serious damage to the heart, blood vessels, eyes, kidneys, and nerves. It is characterized by elevated blood glucose levels due to a combination of resistance to insulin action and an insufficient compensatory insulin secretory response. Diabetes affects 422 million people worldwide, the bulk of whom live in low- and middle-income countries. An estimated 1.5 million deaths each year are directly related to the condition[8]. Over half of women with PCOS often develop type 2 diabetes by the time they are 40 years old [9]. The circulating hyperinsulinemia in women with PCOS, which amplifies androgen production, plays a role in the development of type 2 diabetes by maintaining a higher level of insulin resistance[5,10,11]. This further exacerbates dysglycemia [impaired glucose tolerance] in PCOS women, and it's thought to hasten the shift from IGT to T2DM[12]. Therefore, it may be inferred that women who have PCOS may have a 5- to 10-fold higher risk of developing type 2 diabetes mellitus. This review will focus on the complex pathophysiology of PCOS, additional mechanisms that accelerate the development of T2DM in PCOS patients, risk factors linking T2DM to PCOS, and a thorough description of the prevention and treatment of T2DM in PCOS-affected women.

2. PATHOGENESIS OF PCOS AND TYPE 2 DIABETES IN PCOS:

The underlying hypothesis for the pathogenesis of T2DM in PCOS patients is that complex conditions surrounding one ailment exacerbate the other. The pathophysiology of PCOS is influenced by several complex factors that intervene at different phases of the hypothalamic-pituitary-ovarian axis.

Figure 1. Complications associated with Polycystic ovary syndrome



2.1. Hyperandrogenism in PCOS

PCOS is characterized by hyperandrogenaemia, a metabolic condition that manifests clinically as hirsutism, acne, and baldness. Both the adrenal glands and the ovaries produce excessive amounts of androgen, which leads to hyperandrogenism. As free testosterone plays a key role in the pathogenesis of PCOS, higher free testosterone levels are indicative of hyperandrogenism.[13,14] A neuroendocrine system dysregulation leading to an imbalance in the HPO axis causes the hypothalamus to release more gonadotropin-releasing hormone [GnRH] on a regular basis, which in turn causes the release of selective gonadotropic hormone-luteinizing hormone over FSH. LH stimulates several steroidogenic enzymes [3β-hydroxysteroid dehydrogenase, cytochrome P450s, and CYPs] in the ovarian theca cells, leading to hyperproliferation of the cells. The overproduction of androgens is caused by this increase in follicles and the expression of essential enzymes involved in the synthesis of androgens which feeds back to the hypothalamus to decrease the ability of progesterone and oestrogen[15–17].

2.2. Insulin resistance and hyperinsulinemia in PCOS

The relation between hyperandrogenism and insulin resistance in women with PCOS is a vicious circle. One way that androgens may assist in suppressing hepatic and peripheral insulin activity is by lowering the amount and efficiency of GLUT4, especially in adipose tissue and muscles. Furthermore, androgens in relation to the increased free fatty acid [FFA] levels [One common characteristic of women with PCOS] suppress insulin-dependent glucose uptake in skeletal muscles and hepatic excretion of insulin, which exacerbates insulin resistance and compensatory hyperinsulinemia[5,18,19]. This hyperinsulinemia condition caused by the circulating high androgen levels potentiates excess androgen secretion by the ovarian theca cells [LH-stimulated androgen production] contributing to the pathogenesis of PCOS. Hence, it is obvious that women with hyperandrogenism have a higher level of IR compared with those without hyperandrogenism[7,10,20].On the contrary, insulin plays a direct role in ovarian steroidogenesis and in ovulation control [hyperinsulinemia due to various other factors-obesity, sedentary lifestyle, genetic predisposition][21,22]. In fact, insulin directly stimulates the ovaries to produce more androgens, which in turn enhances the activity of CYP17α and other steroidogenic enzymes with higher androgen production. Reduced blood concentrations of sex hormone binding globulin [SHBG] are associated with a 10% decline in insulin sensitivity because insulin inhibits the hepatic production of SHBG and it also inhibits the release of [insulin-like growth factor binding protein] IGFBP-1, an enzyme that increases androgen and free IGF levels. Furthermore, insulin stimulates pituitary LH production. This combination increases androgen biosynthesis in theca cells by acting synergistically with insulin[4,23,24]. Hence insulin resistance can be the key pathophysiological feature of PCOS contributing to both reproductive and metabolic disturbances.

2.3. Type 2 diabetes in PCOS

Insulin resistance [IR] is considered a key component in the pathogenesis of PCOS, despite the fact that it is not a consistent trait in patients with the disease. It is the main component connected to the development of T2D in those women. It has been found that between 45% and 72% of women with PCOS also have IR which then leads to impaired glucose tolerance which in turn leads to the development of type 2 diabetes mellitus[11]. Women with T2D and PCOS

share similar impaired glucose patterns, which are defined by a disturbance in fasting blood glucose levels. High insulin resistance [IR] puts stress on pancreatic beta cell function, which increases the risk of prediabetes and type 2 diabetes by early functional depletion of insulin secretory capacity[25].

2.3.1. Mechanism of serine phosphorylation

In women with PCOS, excessive serine phosphorylation appears to be a genetic anomaly and is likely the cause of a mutation that results in insulin resistance[26]. The insulin signalling pathway in which Phosphatidylinositol-3-kinase [PI3K] activates the phosphorylation of phosphatidylinositol to produce 3,4,5 phosphotidylinositol-3,4,5-triphosphate [PIP3] is disrupted by excessive serine phosphorylation by inhibiting the binding of insulin receptor substrate with PI3K. This prevents the signal downstream, causing downstream defects in insulin receptor signalling in PCOS women. Because of this central role in which inhibition of insulin receptor substrate-mediated multiple organ effects of insulin is developed, IR is developed, and compensatory hyperinsulinemia can be the pathogenesis of the disease.

2.3.2. Mechanism of muscle mitochondrial dysfunction

According to recent findings, women with PCOS may also be more susceptible to type 2 diabetes as a result of their illness due to muscle mitochondrial malfunction[27,28]. Damage to the mitochondria is a known cause of many chronic noncommunicable diseases, such as obesity, insulin resistance/type 2 diabetes, cancer, and cardiovascular ailments. Insulin, in addition to increasing glucose absorption, also stimulates mitochondrial activity in adipocytes, skeletal muscle, and cardiac muscle[29,30]. Impaired insulin signalling can arise from mitochondrial dysfunction through interference with the conventional insulin signalling route, which promotes glucose absorption by sequentially activating a phosphorylation cascade. Abnormalities in this pathway, which is controlled by the proximal elements of insulin signalling [PI3K, Akt, and IRS1], can serve as molecular markers of insulin resistance[31].
Hence, the elevated risk of type 2 diabetes in individuals with PCOS is closely linked to insulin resistance [IR], which is present in 45-75% of PCOS patients and 95% of obese patients with this syndrome. Moreover, IR deteriorates in PCOS individuals as they age. The aetiology of type 2 diabetes in female PCOS patients is complex.

Figure 2. Impact of IR in the pathogenesis of PCOS and T2DM

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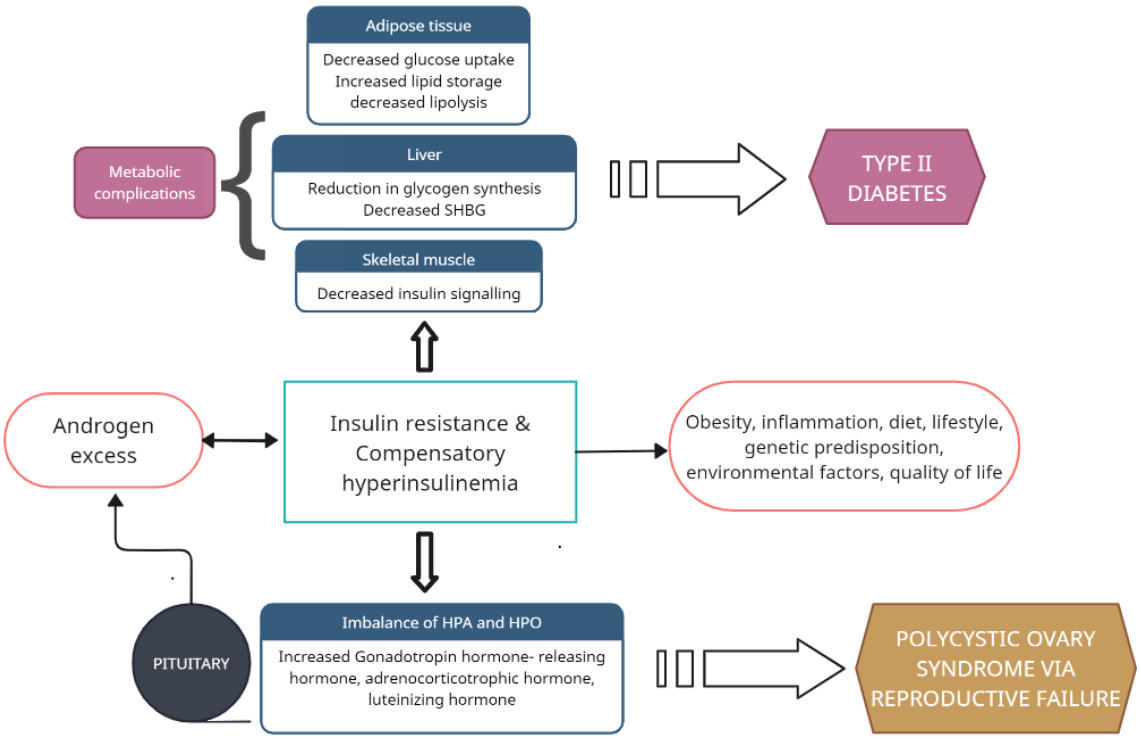

RISK FACTORS FOR THE DEVELOPMENT OF T2DM IN PCOS

The following conditions enhance the likelihood of developing DM2 and other metabolic issues in PCOS: insulin resistance, obesity, abdominal obesity, dyslipidaemia, inflammation, and elevated levels of circulating proteins thought to induce vascular damage[2].

4.1. Obesity

Several meta-analyses showed that throughout a 24-year follow-up period from their reproductive years into the peri- and postmenopausal age, women with PCOS who acquired T2DM to a significant degree [19%] had obesity, especially

in the distribution of abdominal fat. Between 40 and 80% of women with PCOS have a BMI that is higher than normal; individuals having a BMI greater than 30kg/mg^2 have increased risk of metabolic abnormalities[32]. This emphasizes the unique effects of visceral obesity. Despite the possibility of beta-cell malfunction and insulin resistance in non-obese PCOS women when compared to their BMI-matched, unaffected counterparts, visceral fat buildup is required for the onset of type 2 diabetes[33]. Diet consisting of high glycaemic index foods can also negatively impact BMI in PCOS women[34]. Therefore, non-medical management—focusing on dietary changes and physical activity to facilitate weight loss—becomes the standard of care for individuals who suffer from obesity and PCOS.

4.2. Environmental factors

Environmental factors have a significant impact on the development of T2D in PCOS patients. An interesting topic that has garnered increasing attention over time is the role of advanced glycation end-products [AGEs] in the pathophysiology of T2D development in PCOS. Thermally processed foods, which are primarily high in fat and protein and a staple of Western diets, are accountable for the incredibly high intake of exogenous AGEs, which persist in the body and are covalently absorbed into various tissues. These dietary AGEs have been linked to endothelial dysfunction and subclinical inflammation in both T2D patients and healthy individuals. When women with PCOS consumed a diet high in AGEs, their IR and hyperandrogenaemia deteriorated[35,36].

4.3. Pregnancy

The term "gestational diabetes mellitus" [GDM] refers to glucose intolerance that develops or is identified during pregnancy. In comparison to women without PCOS, pregnant women with PCOS had a 2.8–4.3 times higher chance of getting GDM. This is due to the fact that pregnant condition is defined by a sequence of metabolic changes that stimulate the formation of adipose tissue during the early phase[5,37], followed by tissue resistance to insulin mediated by placental hormones, resulting in an IR state that peaks in the third trimester or later[38].

4.4. Insulin secretion

In PCOS, defects in insulin secretion and action are due to the high prevalence of dysglycemia. Dysglcemia develops when the β-cell is no longer able to secrete adequate amounts of insulin to meet the increased requirements [Pancreatic β-cell dysfunction is required for the development of T2DM]. This is regarded by examining the insulin secretion with context to the peripheral insulin sensitivity[39]. Persistent hyperglycaemia can rapidly covert IGT to T2DM in PCOS women.

5. MANAGEMENT OF T2DM IN PATIENTS WITH PCOS

5.1. Lifestyle modification and adaptation

Women with PCOS often complain that even with low-calorie diets, they are not losing weight or are losing it slowly because of their lower basal metabolic rates. As mentioned earlier obesity being the major risk factor for T2DM in PCOS patients [through hyperandrogenism, IR, alteration in lipid profile], it also has a significant impact on psychosocial status, quality of life and cardiovascular disease onset[40]. This makes non-medical management—which prioritizes dietary changes and exercise to encourage weight loss, the primary line of treatment for people with PCOS and obesity.

5.1.1. Diet

The control of appetite is influenced by both the central nervous system and the endocrine system. Low levels of cholecystokinin and ghrelin disturb this balance in PCOS patients. As a result, women with PCOS have greater difficulty upholding proper lifestyle practices, such as managing their eating[41]. On the other hand, it has been shown that in overweight women with PCOS, a 5% reduction in body mass by a proper diet can lower testosterone and serum insulin levels[42]. A low-carb ketogenic diet [LCKD] can be adopted, which restores the normal appetite through endocrine re-normalization and promotes increased weight loss and it is beneficial in improving insulin sensitivity. LCKD should be devised in such a way [no more than 50g of carbohydrate, moderate protein, and low-fat content] that it aids a negative energy balance of 35% to achieve an calorie deficit of 700 kcal/day for effective weight loss; hence, a minimized carbohydrate diet becomes an added advantage over a standard weight loss diet[43,44]. A smooth adaptation to a low glycaemic index diet hastens the fat burning and initiates new muscle fibre growth which will have a positive metabolic effect consisting of reduced free fatty acid and TGs, inhibition of gluconeogenesis and increasing the insulin sensitivity[34].

Table 1. Foods shown to have glycaemic index that can help stabilize the satiety and highly preferred in patients with PCOS

FOOD	GI	SERVING SIZE	Net CARBS	GL
Apple	38	140g	16	6

Grapefruit	25	165g	11	3
Peanuts	14	115g	15	2
Green-leafy vegetables	15	-	-	1
Low fat yogurt	33	245g	47	16
Oranges	48	130g	12	6
Foods high on glycaemic index- refined carbohydrates, white bread, potatoes, sugary beverages, fried foods possess increased risk of worsening the existing metabolic comorbidities and should be avoided.				

5.1.2. Physical training

A healthy lifestyle that includes at least two hours of physical activity per week, together with appropriate diet management, will help PCOS patients lose weight and reduce their chance of acquiring type 2 diabetes[45]. High-intensity aerobic exercise and resistance strength training can enhance insulin resistance-induced impaired glucose tolerance [IGT] by changing the body composition and maintaining lean tissue during energy-restricted weight reduction[46]. Performing this aerobic exercise and strength training in combination can be highly beneficial in reducing abdominal fat and overall weight and can be more effective in improving insulin sensitivity and glycaemic level.

5.2. Pharmacological management

In addition to addressing symptoms, PCOS treatment should be recommended to stop long-term issues from developing. There are no particular guidelines for selecting anti-diabetic medication for PCOS patients with T2DM diagnoses. Therefore, the best course of treatment is metformin plus lifestyle modifications; if metformin is not enough to reach glycaemic objectives, patients can add any antidiabetic medication[27,47].

I. Sulfonylureas
II. DPP-4 inhibitors
III. Pioglitazone
IV. GLP-1 agonists
V. SGLT2 inhibitors
VI. Inositol

5.2.1. Metformin

Metformin is commonly prescribed as an insulin sensitizer for patients with PCOS. In PCOS, metformin improves ovulatory function and insulin sensitivity while only marginally lowering testosterone levels and hirsutism scores[48]. The primary sites of action for metformin's hypoglycaemic effects are the liver, gut, skeletal muscle, endothelium, adipose tissue, and ovaries. Metformin acts at the mitochondrial level in the liver by inhibiting the complex-1 of the respiratory chain which subdues ATP production and alters the redox state of the hepatocyte by inhibiting the mitochondrial glycerophosphate dehydrogenase [mGPD], thus continuously reducing the gluconeogenesis process[49]. Also, cellular energy equilibrium is restored by metformin by the mechanism of maintaining an energy imbalance state that could activate 5' adenosine monophosphate-activated protein kinase [AMPK], which enhances the catabolic pathway. Recent studies have proposed an action of metformin in the gut. Metformin has been shown to increase glucose uptake and increase the secretion of glucose-like peptide-1, which is secreted in response to food consumption[50,51]. This makes metformin a first-line drug treatment for T2DM in women with PCOS, supported by its insulin-sensitizing effect and direct effect on androgen production.

5.2.2. GLP-1 receptor agonists

Glucagon-like peptide-1 secretion is significantly declined in obese patients with PCOS. GLP-1 agonists are new drug molecules used for treating T2DM, this treatment decreases the BMI and androgen level in obese PCOS patients and improves the ovulation capacity and increases the insulin secretion and prolongs the endogenous hormone half-life[5,52]. A GLP-agonist medication [liraglutide, 1.2 mcg/day] and metformin [1000 mg twice a day] work better together to regulate insulin. When metformin was used in conjunction with GLP-1 agonists, weight reduction was more moderate[53]. The typical gastrointestinal adverse effects of metformin include anorexia, diarrhoea, and flatulence. GLP-1 agonist therapy was more successful than metformin in terms of weight loss and insulin sensitivity since the combined treatment had fewer GI side effects[54]. Hence, the combined treatment of a biguanide and a GLP-1 agonist can be a better therapy plan in obese patients with PCOS who is highly susceptible to develop T2DM, the only drawback of this treatment is the high economic costs of GLP-1 agonist medications.

5.2.3. Other anti-diabetic medications

Sodium-glucose cotransporter-2 inhibitors drugs are postulated to have a prominent role in management of PCOS due to their effect on weight loss, fat mass reduction and IR by increasing the urinary glucose secretion. But these drugs are

not generally preferred either in alone or in combination with metformin as a study involving empagliflozin [25mg/per] and metformin [1500mg/day] for 3 months showed no change in metabolic parameters and hormonal profile on both drugs[55].Thiazolidinediones [pioglitazone] is now a highly preferred medication for the management of T2DM in PCOS women that metformin because of its less GI toxicities than biguanide. Pioglitazone through their action on peroxisome proliferator-activated receptor gamma, produces decline in circulating fatty acids and enhances the synthesis of adiponectin which favours insulin sensitizing effect, lipogenesis and glucose uptake in adipocytes[5].

CONCLUSION

Insulin resistance which impacts about 10 to 25% of the overall population, is frequently linked to T2DM and PCOS. Women with PCOS are more inclined to rapidly progress from impaired glucose tolerance to type 2 diabetes because of aggravating factors like abdominal fat deposits, obesity, and hormonal changes during pregnancy that exacerbate insulin resistance [IR] and worsen glucose tolerance. It can be inferred that patients who have this one condition are more likely to develop the other. The metabolic irregularities of PCOS can be accelerated by having a sedentary lifestyle and consuming more calories. Regular screening is crucial for early diagnosis of impaired glucose metabolism in women with PCOS, particularly in obese individuals, as prediabetes is a common condition in this population. Non-medical treatment, which includes certain lifestyle adaptations, is the first line of prevention and management of T2DM in PCOS patients. Regular physical training with proper nutritious, healthy, and low-calorie diets can improve the body's metabolism, which can be beneficial for subsiding IR and other reproductive abnormalities. Long-term adaptation to these modest lifestyle changes can lessen the severity of IGT and prevent the conversion to T2DM.In terms of pharmacological approach, biguanide [metformin] and thiazolidinediones [pioglitazone] are the two major insulin sensitizers which are in current use for glucose control and for the improvement of reproductive aberrations associated with PCOS. We conclude that the early screening which helps the quick detection of PCOS and recognises the features that predispose to T2DM will give a better understanding to the population and push them to undergo more effective treatment which will result in reproductive and metabolic wellbeing. We reach the conclusion that early screening, which aids in the prompt detection of PCOS and identifies the characteristics that predispose to T2DM, will improve public awareness and encourage them to undergo more efficacious treatment, ultimately leading to improved metabolic and reproductive health.

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