Review Article

A Comprehensive Review of Anti-Diabetic Drugs in COVID-19 Patients Co-morbidities with Diabetes

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ABSTRACT

Diabetes is a chronic metabolic disorder emerging as a global burden. Diabetes serves as a risk factor for many complications inclusive of COVID-19. The SARS – 2 pathogens have led to Coronavirus disease. Coronaviruses are enveloped viruses with a single-stranded, positive-sense RNA genome recognized to cause respiratory infections in human beings. Diabetes patients being affected by coronavirus become more critical due to worsening hyperglycemia induces aggravation, endothelial dysfunction, and occlusion of blood vessels through the era of oxidative stress riding the down-regulation of glucose metabolism and hyperglycemia. Increased glucose level causes inflammation and tissue damage serves as a supportive factor for higher tissue damage in COVID patients. Sufferers with extreme COVID-19 have an exceptionally impaired interferon type 1 response with low IFN alpha activity in the blood, indicating excessive blood viral load, and an impaired inflammatory response. This can be alleviated by regular screening and appropriate therapy as like as metformin, camostat mesylate, chloroquine, and adjunctive therapy. Metformin is the desired preliminary drug to deal with T2DM. Camostat mesylate drug accelerated glycemia and insulin resistance and reduced fat buildup in mammalian models. Adjunctive treatment can be used to obviate the evolution of COVID-19.

Keywords: Diabetes, COVID, Inflammation, Management, Prevention.

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INTRODUCTION

Diabetes mellitus is a complicated persistent disorder characterized by glucose dysregulation induced via an absolute or relative insulin deficiency. It consists of a variety of distinctive types, with Type 1 and Type 2 diabetes as the most common subtypes[1]. Diabetes has a global fitness threat, the severity of which has multiplied in the remaining 20 years. In 1985, 30 million `humans suffered from diabetes, and through 2010 that parent accelerated to 285 million[2]. According to cutting-edge international estimate from the International Diabetes Federation (IDF), a variety of affected sufferers in 2019 stands at 463 million. It is estimated by the way of 2045, around 700 million human beings will go through diabetes[3, 4].

The SARS-CoV-2 pathogen has resulted into coronavirus ailment 2019 (COVID- 19) pandemic. This virus utilizes multi-organ actions, after a preliminary respiratory infection. Regarding COVID-19, whilst age and male gender are viewed as enormous chance factors, amassing proof suggest a robust affiliation with an impaired cardiometabolic profile in most critically unwell patients[5].

Coronaviruses are enveloped viruses with a single-stranded, positive-sense RNA genome 43 recognized to cause respiratory contaminations in homosapiens[6]. Older people and those with a substantive illness like Cardio Vascular disease, diabetes, chronic respiratory disease, and cancer are more probable to grow intense conditions[7]. SARS-CoV-2 was once mentioned in humans who had been uncovered at a seafood market in Wuhan, China, the place stays animals have been sold. Since then, there has been a fast unfolding of the virus, main to a world pandemic of COVID-19[8]. The outbreak of COVID-19 persists to cause extreme morbidity global and has now contaminated over 6 million humans worldwide, with a loss of life toll of greater than 3,50,000 human beings[9]. World Health Organization declared SarsCOV-19 as a pandemic condition on 11th March 2020. Globally, as of 8:11 PM CEST, 4 April 2022, there have been 489,779,062 confirmed cases of COVID-19, including 6,152,095 deaths, reported to WHO. As of 3 April 2022, a total of 11,183,087,530 vaccine doses have been administered[10].

Patients with diabetes have been in the spotlight since the early levels of the pandemic, as growing epidemiological records have been printed, they are at higher risk of extreme scientific effects of COVID-19. As the global COVID-19 Pandemic continues to evolve, it has additionally come to be clear that the interplay between COVID-19 and Diabetes entails complex pathophysiology. Not solely are COVID-19 results more severe in human beings in relation to diabetes and metabolic dysfunction, though the latest information additionally recommended that COVID-19

could abrubt acute metabolic problems of diabetes, such as diabetic ketoacidosis and hyperglycemia[11].

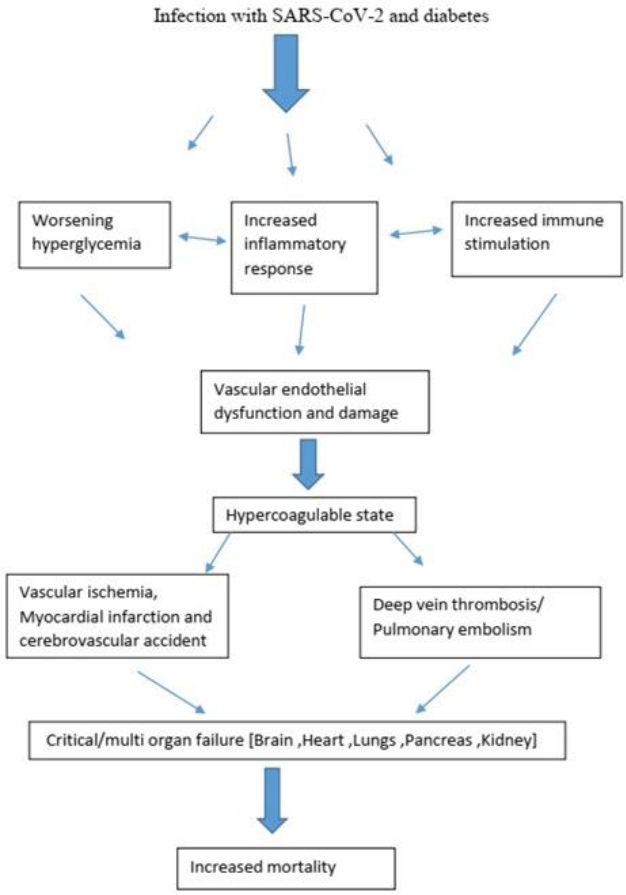
Many remedies have been repurposed for the administration of COVID-19. For instance, glucocorticoids have a great impact on blood glucose. The utilization of glucocorticoids has been related to reduced mortality in significantly unwell sufferers contaminated with COVID-19[12]. It is nicely acknowledged that glucocorticoid use consequences in a widespread trade in glucose homeostasis due to elevated gluconeogenesis and a simultaneous amplification in insulin resistance in more than a few tissues[13]. Several researchers have described the oblique consequences of the COVID-19 pandemic on various populations during the lockdown. Some research indicated that there is an enhancement in glycemic control, whilst in other kingdoms, there is no considerable exchange[14] or that the glycemic manipulation in this population has worsened[15]. Here we will assess the reachable literature associated with COVID-19 and Diabetes Mellitus.

Pathophysiology

Infection with SARS CoV-2 in placing of Diabetes mellitus results in elevated fatality. Infection with COVID-19 predisposes contaminated persons to hyperglycemia causing hyper glycosylation of ACE2 and elevated viral proliferation[16]. Relapsing of hyperglycemia induces inflammation, endothelial dysfunction, and thrombosis through the era of oxidative stress riding the disruption of glucose metabolism and hypercoagulability in addition[17]. Severe contamination in the persons predisposed to vasculopathy and impaired immune response may additionally intensify thrombotic and ischemic issues related to multi-organ failure and accelerated mortality rates. In addition, that built-in evaluation showed that sufferers with extreme COVID-19 have an exceptionally impaired interferon type 1 response with low IFN alpha activity in the blood, indicating excessive blood viral load, and an impaired inflammatory response[18]. Chronic hyperglycemia and insulin resistance culminate in to vasculopathy through quite a several mechanisms. These consist of odd signaling alongside the AGE-RAGE and oxidative damage. Elevated arrangements of superior glycation gives up merchandise [AGEs] and activation of the receptors for superior glycation cease merchandise [RAGE] in the AGE-RAGE axis can speed up vascular harm[19].

Coronavirus–induced pneumonia such as Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome, inflammatory cells pass through the lungs, main to acute lung injury, ARDS, and/or death[20]. This massive burden of inflammatory cells can affect the features of skeletal muscles and liver, the main insulin-responsive organs that are accountable for the bulk of insulin-mediated glucose uptake[21]. In addition, sufferers with extreme COVID-19 show muscle weak spots and elevation of liver enzyme activities which would possibly propose a couple of organ failures, specifically at some point of a cytokine storm[22].

COVID-19 can grow to ARDS, which requires advantageous strain oxygen and intensive care therapy. ARDS is characterized with the aid of extreme edema of the alveolar wall and lung parenchyma, accompanied by a marked rise in inflammatory parameters, such as C-reactive protein degrees and erythrocyte sedimentation rates. Patients with COVID-19 additionally show off the elevation of different inflammatory markers, such as D-dimer, ferritin, and IL-6[23], which would possibly contribute to an accelerated hazard of microvascular and macrovascular issues originating from low-grade vascular infection in sufferers with underlying diabetes mellitus[24].



Diabetes as a Risk of COVID-19

The COVID-19 pandemic is some distance from being entirely a clinical phenomenon. It disrupts private and expert lives severely and impacts human beings and societies on numerous levels. The key techniques promoted for segregation of an outbreak such as isolation, social distancing, and lockdown of cities can have a vast influence on the fitness and lifestyle of an individual. Management of chronic diseases such as Diabetes which require dietary modification, regular exercise, and proper adherence to medications, poses many complicated challenges.

Maintaining a wholesome food plan may additionally be difficult due to the fact of limited access to appropriate food. Careful element resolution and adjusting mealtime insulin by carbohydrate consumption continues to be the

first-rate strategy, in particular for sufferers on multi-dose insulin regimens.

Adopting a regular exercise format would possibly no longer be possible owing to social distancing, restrictions on doors things to do, and issues over the excessive hazard of disorder unfold in gyms and sports activities centers. Activities such as indoor, walking, gardening, and stationary excessive depth things to do may additionally be appropriate picks to keep an active lifestyle[25].

Regular observing of blood glucose is important. Continuous glucose monitoring and flash glucose monitoring structures are beneficial and permit faraway monitoring with the aid of healthcare vendors. For sufferers with T1D monitoring of ketone stages (particularly for human beings who are consistently hyperglycemic) and vigilance for the improvement of signs of DKA are important.

It is additionally necessary that human beings with diabetes have sufficient furnish of their medicinal drugs at home. Improved incidence of DKA amongst youngsters with Type1Diabeteshas been found as a result of a delay in looking for clinical therapy and in providing routine healthcare for newly developed symptoms, as sufferers are scared of contracting COVID-19 in the healthcare setting [26].

Routine clinic visits and overcrowding in hospitals must be minimized to decrease sickness unfolding amongst human beings with diabetes. Measures such as telemedicine discussion or telephone advice, issue of medication to caregivers at lower risk, online coordination of drug delivery, and dispensing medications for prolonged durations need to be considered by healthcare providers. Non-emergency routine evaluations (for foot disease, retinopathy, etc.) must be deferred, as close contact between the healthcare companies and sufferers may also lead to an improved threat of COVID-19 transmission. Patients with limb-threatening or vision-threatening issues must be triaged for immediate attention[27].

During this time of uncertainty, fear, helplessness, and sturdy thoughts may increase stress in some patients. It is vital to ensure psychological wellbeing, as stress may additionally affect glycaemic control. The WHO recommends minimizing reading or listening to information that may want to reason distress and anxiety. Regular sleep routines are essential. Relaxation methods such as meditation can assist human beings with stress and anxiety. Maintaining contact with relatives, buddies, and neighbors via smart phone conversation or the use of online conversation systems can assist to decrease the outcome of social isolation[29].

Employers need to consider WFH strategies or furlough for personnel with poorly managed diabetes or those with cardiac or renal complications, especially for those in excessive chance occupations such as frontline healthcare work or comparable excessive danger jobs and exclusively in areas with excessive COVID-19 prevalence.

Management

1. METFORMIN

The majority of the Type2Diabetes Mellitus sufferers of oral hypoglycemia take Metformin, either alone or with other drugs. Metformin is the desired preliminary drug to deal with T2DM. Metformin therapy might also be related to lactic acidosis. This is uncommon in the absence of different elements predisposing to lactic acidosis however ought to manifest in sufferers struggling with renal impairment, extreme infections, or sepsis[29]. Metformin can be persisted in asymptomatic COVID-19 sufferers or sufferers with moderate symptoms. However, metformin needs to be stopped in sufferers hospitalized with extreme COVID-19 contamination due to the danger of lactic acidosis[30].

It is worth mentioning that better fitness effects have been suggested in COVID-19 sufferers receiving metformin[31]. It is theorized that metformin might also inhibit virus entry into cells via adenosine monophosphate [AMP] activated protein kinase activation and the B- mammalian target of rapamycin [m TOR] signaling pathway[32].

2. SULFONYLUREA

Sulfonylureas need to be investigated for diabetic patients who are not obese or those for whom metformin is contraindicated or is not enough to achieve sufficient glycemic management. Sulfonylurea may additionally set off hypoglycemia, so in the sufferers with extreme COVID-19 with insufficient oral intake, it is safer to preclude their usage. In addition, concurrent use of hydroxychloroquine might also expand the hazard of hypoglycemia[33]. Due to terrible caloric intake in acute infections, the use of sulfonylureas may induce hypoglycemia. It is not perfect in the management of hyperglycemia in COVID-19. This is the case, especially in ICU admissions. Sulfonylureas are no longer for elderly patients and those with kidney or liver impairment. Sufferers with type 2 diabetes can take sulfonylureas in combination with any other oral anti-diabetic medication except meglitinides (nateglinide and repaglinide).

3. DIPEPTIDYL PEPTIDASE 4 [DPP-4] INHIBITORS

DPP-4 inhibitors are well authorized and can be continued safely in COVID-19 sufferers[34]. They are related to a low danger risk of hypoglycemia. DPP-4 may additionally act as a receptor for some coronaviruses, and hence, DPP-4 inhibitors would possibly inhibit such binding and alleviate COVID-19 contamination[35]. However, these anticipated merits have not been proven in clinical trials[36]. Currently, coronavirus's relationship to cellular type-II transmembrane protein DPP4 additionally acknowledged as adenosine deaminase complexing protein 2 or cluster of differentiation 26 (CD26), has generated an exquisite interest. Just as ACE-2 is the receptor for SARS CoV and SARS CoV2, DPP4 acts as the receptor for MERS-CoV Whether the use of DPP4 inhibitors (DPP4i) can decrease MERS-CoV's viral entry has aroused extremely good interest. Briefly, DPP4i appears to increase inflammation in

type 2 diabetes by usingcatalytic and noncatalytic mechanisms. It is imperative to define that the enzymatic activity of DPP4 causes cleavage and might also have an effect on the characteristics of several chemokines, cytokines, and growth factors.

4. GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS [GLP-1 AGONISTS]

GLP-1 agonists might also limit water consumption[37], and they might also additionally cause nausea and vomiting in the patients. Thus, GLP-1 agonist therapy is related to an accelerated chance risk of dehydration and aspiration pneumonia[38]. GLP-1 agonists have to be restrained in sufferers with extreme COVID-19[39]. GLP-1 agonists are administered to COVID-19 patients, they need to be intently closely monitored, and fluid consumption needs to be sufficient[40]. GLP-1R agonists exert wide anti-inflammatory movements in animals with experimental inflammation and decrease biomarkers of systemic infection in human subjects with T2D and people with obesity. It is properly acknowledged that the most severe structure of COVID-19 is the Acute Respiratory Distress Syndrome characterized by the highest levels of inflammatory cytokines recognized as "Cytokine Storm" which hurts alveolar epithelial cells in the lung, inactivates pulmonary surfactant final result appears as the formation of the hyaline membrane and lung parenchyma breakdown.

5. PIOGLITAZONE

Pioglitazone upregulates angiotensin converting-2 enzyme [ACE-2] in rat tissues[41], leading to worries that it can also extend COVID-19 severity. Since ACE-2 acts as a receptor for extremely SARS CoV-2 enter cells[42]. Pioglitazone may be a potent inhibitor of 3 chymotrypsin- protease, which is essential for RNA synthesis and replication of SARS CoV-2[43]. However, this declaration needs both in-vitro and in-vivo confirmation. COVID-19 contaminated diabetic sufferers have a possibility of developing a cytokine storm. Pioglitazone inhibits the secretion of pro-inflammatory cytokines, and it may be mitigated by the cytokine storm[44].

6. SODIUM GLUCOSE Co-TRANSPORTER 2 [SGLT2] INHIBITOR

SGLT2-inhibitor may be a potent antiviral with the aid of increasing lactate concentration and simultaneously reducing the intracellular pH, thereby potentially reducing the viral[45]. Canagliflozin therapy, an SGLT-2 inhibitor, could induce a reduction in interleukin [IL-6] levels, which plays an important vital role in triggering the cytokine release syndrome [CRS] in COVID-19 patients[46]. Besides, SGLT2i extent to a higher in the ACE-2 levels, which leads to higher production of the angiotensin 17, which is a potent vasodilator, anti-oxidant, and anti-fibrotic, which helps in the prevention of acute respiratory distress syndrome (ARDS) and assuaging cytokine storm. This may have a putative role in COVID-19 patients with the aid of myocarditis and adverse cardiac remodeling. SGLT2 inhibitors additionally down regulates the expression of inflammatory genes and decreases oxidative stress, leading to cardio renal dysfunction's amelioration.

7. INSULIN

Insulin therapy is desired for hospitalized patients, inclusive of moderate to severe COVID-19 occurred patients. For non-critical hospitalized patients, a basal plus bolus correction regimen is encouraged with a target blood sugar level range from 140-180 mg/dl[47]. Critically sick COVID-19 diabetic sufferers in ICU are managed with the administration of intravenous insulin infusion. Intensive insulin therapy used to be observed to exert an anti-inflammatory impact in severely unwell sufferers and limit the range of inflammatory markers C-reactive protein [CRP] and mannose-binding lectin [MBL] compared to conventionally insulin therapy[48]. A possible therapeutic regimen in non-critically unwell COVID-19 diabetic sufferers is a combination of basal insulin with GLP-1 agonists, given as a single injection. The rationale beyond this treatment approach is the administration of a single day-by-day injection will result in a drastic reduction in exposure to COVID-19 patients. Also, both insulin and GLP-1 agonists have glucose –a lowering impact and a possible anti-inflammatory effect[49].

8. ANTIVIRAL THERAPY

Camostat mesylate is a serine protease inhibitor being investigated for its potential to inhibit viral entry, as it inhibits transmembrane protease serine 2 [TMPRSS2], which enables viral entry into the host cells[50]. It was reported that comostat mesylate therapy decreased the incidence of new-onset diabetes mellitus in sufferers with persistent pancreatitis[51]. This drug accelerated glycemia and insulin resistance and reduced lipid accumulation in animal models[52].

Antimalarial agents like chloroquine and hydroxychloroquine have been used to deal with SARS-CoV-2 contamination despite their potential unfavorable adverse effects[53]. The two predominant mechanisms of action of hydroxychloroquine are believed to be using its restriction of viral spike protein cleavage at the ACE2 binding site, and its inflammatory andimmunomodulatory properties[54]. Hydroxychloroquine additionally has glucose-lowering efficacy with the aid of increasing insulin sensitivity and enhancing pancreatic beta-cell function[55], which has enabled hydroxychloroquine to be prescribed as an antidiabetic medication in some countries[56]. Therefore, adjustment of pre-existing antidiabetic agents is needed to avoid hypoglycemia in uncommon cases of patients with diabetes mellitus who are taking hydroxychloroquine[57].

Protease inhibitors such as lopinavir and ritonavir have been mentioned to increase the risk of hyperglycemia[58] and new-onset diabetes mellitus[59], exacerbate pre-existing diabetes mellitus, and occasionally prompt the enlargement of diabetic ketoacidosis[60]. In sufferers of HIV infection, these agents decreased insulin sensitivity and β-cell characteristics by way of up to 50%[61]. Another problem

with protease inhibitors is pharmacological interactions with co-administered glucose-lowering drugs. For example, ritonavir acts as an inhibitor of CYP3A4/5[62], increasing plasma concentrations of the DPP4i saxagliptin, and as an inducer of uridine 5′-diphospho-glucuronosyl transferase[63], reducing concentrations of the SGLT2i canagliflozin. Therefore, observing of blood glucose levels has to be done frequently and adjustments in dosings are recommended for patients prescribed the above combinations of drugs. Remdesivir, a nucleotide analog inhibitor of RNA-dependent RNA polymerase, accelerated hyperglycemia, insulin resistance, fatty liver, and endotoxemia in mice fed a high-fat diet[64].

9. ADJUNCTIVE THERAPY

Adjunctive treatment options are used to prevent the advancement of COVID-19 to more extreme forms, such as ARDS and multi-organ failure during the hyperinflammatory phase. However, these agents can additionally impact glucose metabolism. For example, IL-6 receptor inhibitors, a feasible therapeutic alternative option in sufferers severely unwell with COVID-19 who have tremendous lung lesions and high IL-6 levels[65], had beneficial effects on glucose intolerance and insulin resistance in sufferers with rheumatoid arthritis[66]. Furthermore, anakinra, an IL-1β inhibitor that significantly improved respiratory characteristics in patients with extreme COVID-19[67], improved glycemia and β-cell function in patients with T2DM[68]. TNF inhibitors, particularly adalimumab, are promising therapeutic options for mitigating the inflammatory stage in COVID-19[69]. The use of TNF inhibitors improved hyperglycemia, insulin resistance, and β-cell function in patients with active rheumatoid arthritis[70].

Systemic corticosteroids are properly regarded to set of hyperglycemia, specifically by increasing postprandial levels of glucose, insulin resistance, and pancreatic β-cell dysfunction[71], which regularly forces the initiation of insulin therapy. Contrary to this concern, intravenous dexamethasone therapy statistically extensively multiplied the quantity of ventilator-free days among patients with severe ARDS and COVID-19[72]. The patients with diabetes mellitus require further investigation to decode the effect of drug regimens on glucose metabolism used in the COVID-19 treatment.

Prevention

1. Launch far off manage structures and far off learning [telemedicine, social media account]
2. Limit the use of gliptin drugs.
3. Blood glucose ought to be controlled
4. Limit the use of ACE inhibitor drugs.
5. Reduce unnecessary hospital admissions.
6. Vaccination is advisable
7. Take nutrition content foods.
8. About the recommendations of the country's health care system in preventing contamination.
9. Frequently wash your hands with soap and water.
10. Using an alcohol-based hand sanitizer when cleaning, soap and water is no longer available.
11. Avoid frequently disinfecting any probably contaminated surfaces, such as countertops, tabletops, and door handles.
12. Don't touch the eyes, nose, or mouth with unwashed hands.
13. Maintain Physical distancing by staying 6 feet, or 2 meters, away from others in public.
14. Covering coughs and sneezes with a tissue paper or internal elbow – no longer the hands.
15. Avoid all contact with humans who are sick person, specifically if they have a fever, cough, or both
16. Keeping the immune system robust with the aid of getting at least 7 hours of sleep a night time and decreasing stress levels as much as possible
17. Maintaining an adequate intake of food and fluids.
18. Trying to maintain blood sugar level in a healthy range[73].

AFTER INFECTION

1. Monitoring the signs and symptoms and speedy referral.
2. Monitoring the blood glucose level.
3. Monitoring for AKI complication
4. Monitoring for ARDS
5. Use of hydroxychloroquine.
6. Reduction of unfavorable adverse drug reactions.
7. Add vitamins, proteins, and zinc-rich content food on daily basis.
8. Stay hydration
9. Long time follow up
10. Monitoring the SPO2 level[74].

CONCLUSION

Routine clinic visits and overcrowding in hospitals must be minimized to decrease sickness unfolding amongst human beings with diabetes. Measures such as telemedicine consultations or telephone advice, issue of medication to caregivers at lower risk, online coordination of drug delivery, and dispensing medications for prolonged durations need to be considered by healthcare providers. Non-emergency routine evaluations (for foot disease, retinopathy, etc.) must be deferred, as close contact between the healthcare companies and sufferers may also lead to an improved threat of COVID-19 transmission.

Patients with limb-threatening or vision-threatening issues should be triaged for immediate attention. Diabetic patients should be aware and precautions against COVID-19 then only the disease can be preventable. When compared to diabetic patients and non-diabetic patients, diabetic patients are more prone to suffer the health consequences of the virus. Based on the patient's complication and severity, treatment can be given. Diabetic patients should have clear knowledge about the COVID-19, especially while taking diabetes medications strictly followed so that infection can be minimized and controllable, prevention of the infection is the first stage of the solution. The diabetic patient should follow a healthy diet, and lifestyle so that risk factors can be preventable.

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