Anti-Diabetic Agents in Covid-19, Their Possible Role Beyond Diabetes

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ABSTRACT: Recent reports from various observational investigations revealed and published the outcomes of Non-insulin Anti-diabetic agents. Patients additionally with Type-II Diabetes Mellitus and coronavirus disease, caused by severe acute respiratory syndrome [SARS] has become widespread disease in the world since last 3 years. Age, sex, ethnicity, obesity and co-morbidities all apparently enhance the risk of worst consequences. Glucose lowering drugs and anti-viral drug treatment could limit the risk but impose restrictions on their usage which needs to be carefully assessed. This severe acute respiratory syndrome [coronavirus] might be a potentially triggering and worsen the aspect for the diabetic patients that can bring about severe metabolic complications effecting β-cell function leading to hyperglycaemia and diabetic ketoacidosis.

KEYWORDS: Coronavirus, Co-morbidities, Diabetes Mellitus, Diabetic ketoacidosis, Hyperglycemia, Severe acute respiratory syndrome.

INTRODUCTION

Diabetes Mellitus is a very widely known risk factor in patients with coronavirus disease which appear to be in mutual ways [1]. One of the direct effects result is tied to a viral illness, while the other indirect is related to how managing blood sugar is affected by a pandemic. The patient's metabolism underwent drastic modifications as a result of the direct influence of COVID-19 and higher blood glucose levels [2, 3]. It is thought to cause an increase in cytokine and inflammatory mediator release. The indirect effects of COVID-19 studies on various populations indicate an improvement in glycemic control as a result of lockdown. While other research claim there has been no substantial impact or that the management of blood glucose in this population has got worse.

Glycemic control has been demonstrated to be essential for COVID-19 patients, and carefully controlled glucose management had reduced mortality rates compared to poor outcome which may have an impact on the outlook and severe consequences of the viral infection. Several therapies have been altered to combat COVID-19. Early research has linked that a biguanide category of oral hypoglycemic drug, Metformin might have resulted with a reduction in mortality [4]. But few recommendations from endocrinologist experts indicates the choice of glucose lowering agents mainly Metformin to be avoided in diabetic patients with COVID-19 due to lactic acidosis leading to multi-organ dysfunction [5]. However, experimental studies in research have shown that Metformin possessing anti-inflammatory and anti-viral properties beyond its glucose lowering action [6].

EPIDEMIOLOGY

Diabetes is considered to be the increased risk factor for infections in common and also the infections of the respiratory tract. Diabetes patients had more severe pneumonia, higher levels of lactate dehydrogenase, α-hydroxy butyrate dehydrogenase, alanine aminotransferase and γ-glutamyl transferase along with lymphocytes having higher neutrophil count [7]. Several studies in USA, UK and other parts of Europe revealed that patients with COVID-19 and diabetes led to an greater possibility of ICU admission [8, 9, 10]. COVID patients with diabetes will have worse prognosis because of conquering multiple factors. In an American survey, they have identified that young men with high glucose concentrations, obesity, hypertension and cardiovascular diseases are the conventional co-morbidities [11]. Older age is an important epidemiological feature related to high prevalence of COVID-19 [12, 13]. The high prevalence and worst consequences of COVID-19 are due to lifestyle, socio-economic factors and prevalence of cardiovascular risk factors and obesity.

PATHOPHYSIOLOGY

Infection with SARS-COVID and Diabetes Mellitus results in increased mortality with resulting cascade of events that predisposes individuals with hyperglycemia leading to increased viral proliferation [14].

Deteriorating Hyperglycemia influence inflammation, endothelial dysfunction and thrombosis by promoting oxidative stress causing dysfunction of glucose metabolism [2].

Impaired immunity may draw attention to thrombotic and ischemic complications that may connect multiple organ failure and increased risk of mortalities.

Abnormal signaling pathways like Advanced Glycation End Products (AGEs) and oxidative damage accelerating macro-vascular and micro-vascular damage that may also contribute in worsening Hyperglycemia associated with Covid-19[15].

In addition metabolic abnormalities causes endothelial cells of small and large vessels to change as per the superoxide expression in mitochondrial. Overtime, elevated production of superoxide causes persistent expression of pro-inflammatory pathways irrespective of regulating blood glucose levels [16].

Since active immune responses can worsen hyperglycemia and enhance systemic insulin resistance during acute viral infections, the consequences of chronic hyperglycemia are exacerbated [17]. Increased blood glucose levels are significantly linked to severe COVID-19 development [18].

It is yet unclear how diabetes and COVID-19 are related, although abnormal immune responses may impede the development of the illness by hastening the development of thrombotic and ischemic consequences that lead to multiple organ failure and higher mortality [14].
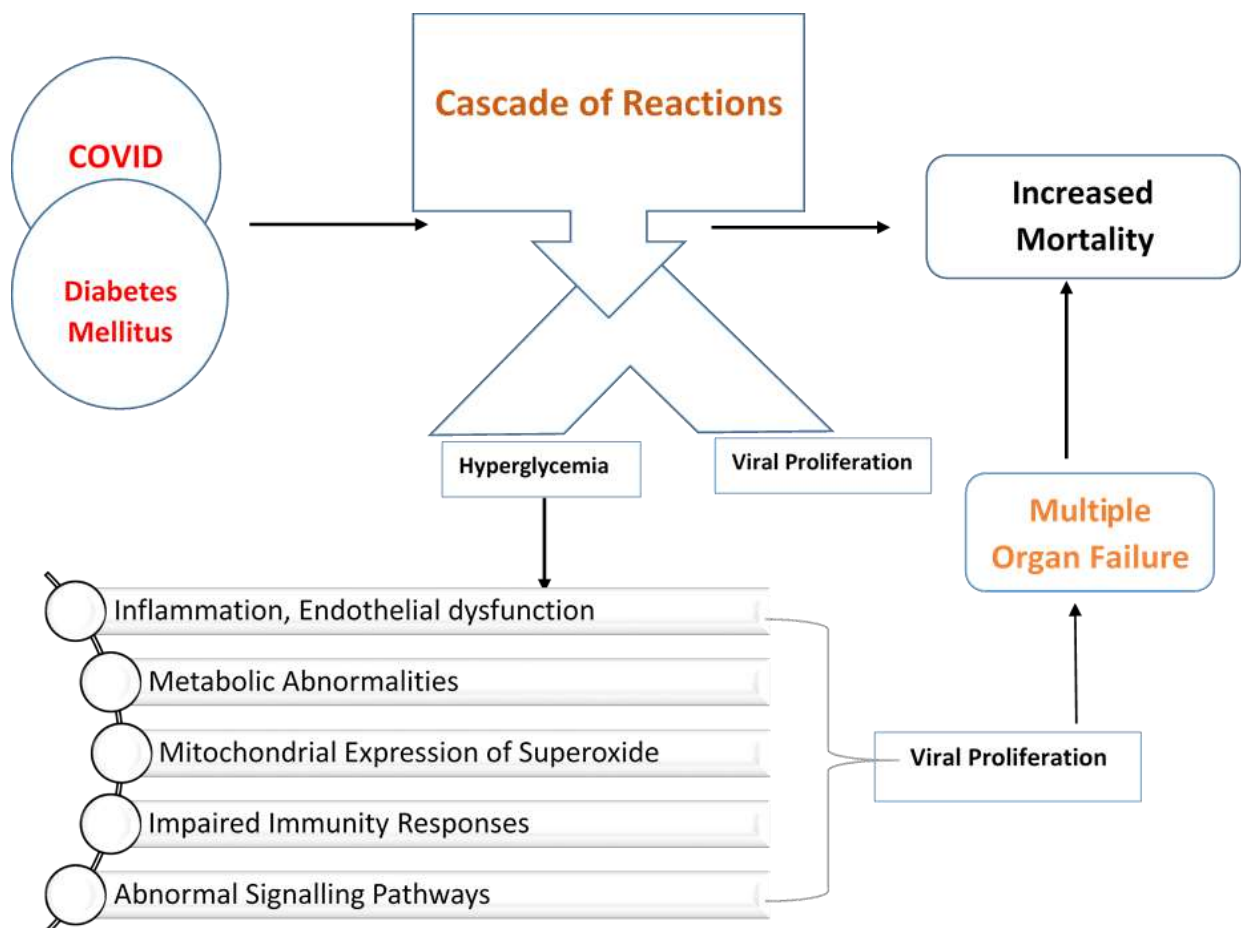

Figure I: Pathophysiology of COVID and Diabetes.

A study also demonstrated that there is a direct metabolic relationship between SARS-COVID and diabetes which theorized that the virus infects pancreatic islets that express ACE-2, causing acute-cell devastation and short-term Type-2 diabetes mellitus [19].

DRUG THERAPY OF DIABETES MELLITUS FOR COVID-19 PATIENTS

Chloroquine and Hydrochloroquine are the known drugs for curing or controlling COVID-19 but it shows effects on insulin secretion, breakdown, and action that might result in hypoglycemia, especially in individuals taking insulin or sulfonylureas [20]. Therefore, medical teams have to ensure that patients with diabetes and COVID-19 have proper glycemic management, which necessitates considering all possible implications.

Originally created as an anti-malarial agent, metformin—more commonly known as anti-diabetic medication—was marketed as an anti-influenza treatment with the side effect of decreasing blood glucose levels. Since receiving approval by the Food and Drug Administration in 1995 for use as an oral hypoglycemic, Metformin has grown in popularity as one of the most often prescribed anti-diabetic drugs globally [21].

The majority of Type-II Diabetes Mellitus receive Metformin either alone or with other drugs. Metformin is the best preferred initial drug of choice to treat Type-II Diabetes Mellitus. This can be used in patients with mild symptoms or in COVID-19 patients who are asymptomatic [22]. But due to greater chances of lactic acidosis, Metformin should be ceased in hospitalized patients or patients with severe COVID-19 infection [23]. This is prominent in mentioning that very good health benefits have been updatted in COVID-19 patients receiving Metformin and it is hypothesized that Metformin may block the viral entry into cells as it is shown to have anti-inflammatory and anti-viral effect beyond its glucose lowering effect [24].

It has been speculated that these collective effects of metformin might potentially be beneficial which is related through adenosine monophosphate [AMP]-activated protein kinase activation which possibly ameliorate ACE2 expression [25, 26] and inhibiting Mammalian target of rapamycin [m TOR] signaling pathway leading to downstreaming influence on SARS-COVID [27].

Insulin therapy is very much preferred for hospitalized patients with moderate to severe COVID-19 disease [28]. Intensive insulin therapy was found to exert an anti-inflammatory effect in critical ill patients and reduce the level of inflammatory markers like C-reactive protein [CRP] and Mannose binding lectin [MBL] [29]

CORTICOSTEROIDS IN COVID-19

Steroids show negative effects on diabetes, though they are used for short-term and long-term as anti-inflammatory agents. Various factors like duration of treatment, dosage, potency and associated infection contribute to the degree of hyperglycemia stating that if the dosage of steroid therapy is higher, higher could be the chances of developing steroid- induced diabetes. Hence the steroid usage in diabetic patients may increase the risk of hospitalization due to uncontrolled blood sugar levels [30, 31]. Despite steroids have beneficial effects in the hyper inflammatory condition which may be hallmark of COVID-19, but at the risk of worsening hyperglycemia and other complications [32].

ANTI-COAGULANTS

Coagulation has been associated with COVID-19 and several studies revealed that changes in lung vessels, massive pulmonary interstitial fibrosis, hemorrhagic pulmonary infarction, endothelial injury, spread vascular thrombosis, occlusion of alveolar capillaries, structurally deformed capillaries and growth of new vessels through a mechanism of intussuseptive angiogenesis [33, 34, 35]. Anti-coagulant therapy seems to improve prognosis.

DIABETES PATIENTS WITH CO-INFECTIONS IN COVID-19

Studies have shown that people with diabetes mellitus have a 10-fold higher chance of mortality, making the illness an important prognostic factor [36]. By lowering the T-lymphocyte count, Covid decreases the immunological response. Additionally, it has an effect on glucolipid metabolism, which lowers the innate immune response and results in immunosuppression [37].

These patients are therefore more prone to bacterial, viral, and fungal infections. One of the co-infections seen in COVID-19 individuals that can also result in fungal pneumonia is the Candida species. Invasive pulmonary Aspergillosis is another serious fungal super-infection that is linked to a high fatality rate [38]. In COVID-19 patients, *Pneumocystis jirovecii* and cryptococcal illness have also been identified with poorly controlled type 2 diabetes in the ones treated with immunosuppressants [37].

It was found that people with diabetes mellitus who had poor blood glucose control and COVID-19 had a higher risk of developing coccidiomycosis. Diabetes enhanced the likelihood of spreading coccidioidomycosis and respiratory illness [39]. Perhaps the most commonly isolated pathogens *Mycoplasma pneumoniae* and *Legionella pneumophila* gives rise to respiratory disease in COVID-

19 patients are. Mucormycosis is an emerging fungus that has a wide range of clinical presentations causing severe, frequently lethal illness symptoms.

This could be attributed by the fact that there is second highest prevalence of adult diabetes and greatest incidence of mycormycosis in the entire world. In patients with poorly controlled diabetes and a compromised immune system this can turn to be aggressive and destructive [40].

DISCUSSION

Large population with COVID-19 and Diabetes are more likely to have more worse adverse outcome of prognosis and mortality. Individuals with diabetes have less favourable outlook as a consequence of syndromic character of diseases like hyperglycemia, advanced age, co-morbidities, whereas hypertension and obesity raise the risk in individuals in different ways. Diabetic therapy in COVID-19 patients pose a greater clinical challenge. The choice of drug therapy and a coordinated team effort to reduce the risk of medical complications, careful assessment of different parameters would help to treat the patients in a prompt and effective manner.

CONCLUSION

Diabetes Mellitus leads to substantially raise the risk of complications, prolonged hospital stays and death rates in COVID-19 infected patients. Hence, insulin and other oral hypoglycemic medications are recommended in the management of diabetic patients who are hospitalized with COVID-19 infections. Metformin and other oral-hypoglycemic agents may help reduce mortality and negative composite outcomes like intubation, ventilation, ICU admission, disease progression and other adverse outcomes. In individuals with diabetes long term usage of oral anti-diabetics would not rise the risk of death or poor composite outcomes particularly in COVID-19 patients.

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