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Review Article

ASSOCIATION BETWEEN TYPE 2 DIABETES MELLITUS AND COVID-19 SEVERITY: A LITERATURE REVIEW

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ABSTRACT

We conducted a review and evaluated the already documents reports for the relationship among diabetes and COVID-19. The review outcome shows that the COVID-19 severity seems to be greater among patients with diabetes as comorbidity. So, strict glycemic control is imperative in patients infected with COVID-19. Thus, world-wide diabetes burden and COVID-19 pandemic must be deliberated as diabetes increases the COVID-19 severity. Established on this, it is precise significant to follow specific treatment protocols and clinical management in COVID-19 patients affected with diabetes to prevent morbidity and mortality.

Keywords: Diabetes, Infection, Coronavirus, COVID-19, SARS-CoV-2.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is primarily a respiratory disorder and the chief causative agent is the novel coronavirus SARS-CoV-2 [1]. The coronavirus be appropriate to the Coronaviridae family which is core relevant agents for acute upper respiratory tract infections. The kind of spread is through droplets, which is analogous to SARS-CoV-2 and cold virus [2]. The present pandemic was declared on March 11, 2020; then, the first case was reported from Wuhan, China. Subsequently January 2020, there has been a global spread with Italy, Spain, and the United States having a maximum number of cases with high mortality figures. Transmission at the R0 phase imposes a greater risk of nosocomial infection and, thus, affects the health-care professionals. The average incubation period is between 1 and 14 days with maximum infectivity between 2 days earlier to the start of symptoms to 7 days after. Over all cases, the individuals develop mild-to-moderate symptoms, and 10–20% of cases are severe enough to require hospital admission. Emergency admission rate is 5% as a consequence of respiratory distress, sepsis, multiple organ dysfunctions, and a mortality rate of 2–4% [3].

REVIEW AIMS

The frequency of diabetes in COVID-19 patients based on numerous studies was 5-36%. As diabetes is most comorbidity in SARS patients, it is essential to elucidate all the characteristics regarding the associations among the two circumstances to offer the scientific and clinical community those elements advantageous to face this illness in the greatest probable approach. This present review was done to assemble the published data interrelated to diabetes and COVID-19 infection. The leading effort is to delineate the association among diabetes and COVID-19 by considering the epidemiology, pathophysiology, and therapeutics.

TYPE 2 DIABETES IS A RISK FACTOR FOR WORSE CONSEQUENCE IN COVID-19 PATIENTS

Recent studies reported COVID-19 found to be more prevalent among individuals having heart disease, hypertension, and diabetes; however, the incidence varies in a wide range of studies and country-wise data.

Type 2 diabetes mellitus patients with COVID-19 were at high risk of exaggerated with amplified hypercoagulable state and uncontrolled inflammation responses which may lead to worse consequence [4]. To be specific, previous history of T2DM and fasting blood glucose levels higher than 7.0 mmol/l, before the initiation of steroid treatments were connected with greater mortality threat (OR [3.0–3.3]) [5].

In a recent study conducted in 132 T2DM patients, there was a negative association between SaO_2 and HbA1c, in the meantime, there was a positive association between HbA1c ≥7.5% and C-reactive protein (CRP), serum ferritin, and fibrinogen levels [6]. Numerous documented reports show that COVID-19 patients with T2DM have 14–32% increase in disease severity when compared to COVID-19 patients without any comorbidity [7,8].

In a study done by Wu *et al.* [9], in 201 diabetic patients with COVID-19, the hazard ratio for the development of acute respiratory syndrome was 2.34 (95% CI: 1.35–4.05) and it was significant (p=0.002).

A meta-analysis study (n=46, 248) conducted by Yang *et al.* [10] states that the OR for severe COVID-19 was not higher in T2DM patients (OR: 2.07; 95% CI: 0.89–4.82), but, in contrast, the COVID-19 patients with hypertension (OR: 2.36; 95% CI: 1.46–3.83) had increased disease severity. A meta-analysis based on nine published studies (n=1936) reported on Chinese COVID-19 patients revealed that there was a significant interrelation between COVID-19 severity and diabetes (OR: 2.67; 95% CI: 1.91–3.74; p<0.01) [11]. A summary reported published by Chinese Disease Control and Prevention showed a case fatality rate (CFR) of 2.3% (1023 out of 44,672 cases) and the CFR was higher in T2DM cases as compared to hypertension (7.3% vs. 6%) [12].

However, Zhou *et al.* [13] reported a dissimilarity data, in univariate analysis on 191 COVID-19, T2DM had OR of 2.85 for in-hospital mortality (p<0.001). Nevertheless in the case of multivariate regression analysis, there was no significant association between diabetes and mortality, and then the other variables such as age, SOFA score, and D-Dimer levels displayed encouraging association with mortality.

In a study conducted on positive cases of COVID-19 (n=174), these findings between diabetics and non-diabetics were evaluated and compared for biochemical and radiological findings. Demographical variables were not significant, but the incidence of nausea and vomiting (83.2% vs. 59.5%) and morality (16.7% vs. 0%) was greater in T2DM patients as related to non-diabetics. The absolute neutrophil

count, markers of inflammation (IL-6 and CRP), erythrocyte sedimentation rate (ESR), ferritin, and D-dimer levels were higher in diabetic cases as related to non-diabetics. In the meantime, parameters namely absolute lymphocyte count, red blood cell count, and hemoglobin levels were found to be significantly decreased in T2DM patients when compared to non-diabetics. The levels of organ injury markers such as lactate dehydrogenase, α-hydroxybutyrate-dehydrogenase, alanine aminotransferase, and G-GT were increased in T2DM patients as compared to non-diabetics. These data conclude that there is a marked biochemical, hematological disturbances, and organ injury in COVID-19 patients with diabetes when compared to non-diabetics [4].

Finally, even when chest computed tomography (CT) imaging of COVID-19 patients with or without diabetes was associated, the latter showed more severe pathological changes than the previous. To confirm this, the diabetes group presented higher CT imaging scores in association with the non-diabetes group [4].

Pooled analysis of ten studies conducted in China (n=2209) on the estimation of COVID-19 comorbidities by Singh *et al.* [14] has shown hypertension incidence in 21%, diabetes in 11%, and CVD in 7% of the patients. Similarly, in a meta-analysis conducted by Yang *et al*. [10] among 46,248 COVID-19 patients, revealed prevalence of hypertension 917%), diabetes (8%), and CVD (5%). Research study conducted by the Chinese Epidemiology Working Group encompassing 20,982 COVID-19 patients reports that 13%, 5%, and 4% had hypertension, diabetes, and CVD as comorbid correspondingly [15]. Conversely, in a study done by Onder *et al.* [16] on Italian 355 COVID-19 patients, 36% had diabetes then CVD was present in 43% of the patients. Similarly, in a study conducted on 24 COVID-19 patients in the USA, 58% were associated with diabetes [17]. The surveillance study conducted on 481 COVID-19 patients, among the non-survivors 34% had diabetes [18], and data from 7162 COVID-19 patients reported by the COVID-19 response team of USA described a comorbid prevalence rate of 11% [19].

EFFECT T2DM AS COMORBIDITY IN COVID-19 PATIENTS: MORBIDITY AND MORTALITY OUTCOMES

Mounting studies reported that COVID-19 patients with T2DM showed increased disease severity with wide range of complications. A study conducted by Wang *et al.* [9] encompassing 138 COVID-19 patients' shows that ICU admission was higher in patients with comorbidities comprising diabetes as associated to patients without comorbidities (72% vs. 37%) correspondingly. A study conducted by Wu *et al.* [20] on 201 COVID-19 patients conceals a hazard ratio of 2.34 for developing acute respiratory syndrome (ARDS) in diabetic patients and was found to be significant (p=0.002). In contrast, a meta-analysis done by Yang *et al.* [10] with the inclusion of 8 studies (n=46, 248) reveals that COVID-19 severity was not higher in diabetic patients with an odds ratio (OR) of 2.07 than that of hypertension (OR, 2.36) and CVD (OR, 3.42). In addition, the prevalence of mortality was higher in diabetic patients having COVID-19 ranging between 22% to 31% [10,20]. In Wu *et al.* [21] study, COVID-19 patients with diabetes showed a hazard ratio (HR) of 1.58 for mortality during bivariate cox regression analysis. In COVID-19, summary report evaluated on 44,672 patients exposed an overall fatality rate of 2.3% (n=1023) with increased mortality patients with CVD (10.5%), diabetes (7.3%), and hypertension (6%) [12]. Findings of Wang *et al.* [22] COVID-19 patients with comorbidities must be stratified for accurate management and to improve the prognosis. In their study, they classified the patients as type A; COVID-19 with pneumonia, devoid of comorbidities, type B indicates pneumonia with severe comorbidities; and type C patients had pneumonia with multiple organ failure.

COVID-19 AND THE NEW ONSET OF TYPE 2 DIABETES

COVID-19 has the aptitude of hamper insulin release, which indicates the progression of new onset of T2DM [23] and similarly an important indicator of COVID-19 mortality with an HR of 3.75 [24]. Study done by Li et al [25] on 453 COVID-19 patients, 94 cases have been detected as new onset of T2DM (FPG ≥7 mmol/L and HbA1c ≥6.5%) during admission. Additional, they also reported that COVID-19 patients with new-onset diabetes have high mortality rate (HR, 9.42), more ICU admissions (11.7%), and great need of ventilator assistance (11.7%) as compared to non-diabetic patients (HR, 1) and patients with existing T2DM (HR, 4.63) [25]. In the same study, they also reported COVID-19 patients with new-onset and pre-existing diabetes had high incidence of severe complications and reported more severe complications such as ARDS (3.1–10.5% vs. 0.8–3.1%), acute kidney injury (15.3–17.0% vs. 1.5–3.1%), shock (11.2–23.4% vs. 2.3–4.7%), hypoalbuminemia (36.7–39.4% vs. 10.8–19.4%), and severe COVID-19 complications (82.7–89.4% vs. 61.4–72.1%) as that of the normal and hyperglycemic COVID-19 patients [25]. Similarly, in another study (n=605), COVID-19 patients with new-onset of diabetes displayed higher in-hospital impediment (29%, OR, 3.99) and overall mortality (HR, 2.30; p=0.002) as compared to non-diabetic patients in a duration of 28 days [26].

Similarly, in a study conducted on COVID-19 (n=413) cases, new-onset of diabetes had substantial association with proliferation in ICU admission and death as compared to diabetic patients with pre-existing diabetes or without diabetes (relative risk 3.06 vs. 1.55) [27]. Etiological mechanism for the progress of new onset of diabetes is not clear, but there may be complex interrelated etiologies for this effect. The proposed mechanism might be due to dysregulation of glucose transport, insulin release, stress-induced hyperglycemia, pre-diabetes, steroid-mediated hyperglycemia, etc. Additional mechanism for new-onset diabetes is that, in some cases, there may be undiagnosed diabetes before admission, which might be as a outcome of recent weight gain caused by unhealthy lifestyle, isolation, social distancing, and decreased physical activity also altered mental health during COVID-19 outbreak. A recent survey study conducted among 155 countries showed that about 53% of people had reduced their service level access to non-communicable diseases either partially or wholly [28]. Hence, these lifestyle modifications may trigger insulin resistance which also activates inflammatory pathways and progresses to develop new-onset diabetes.

During hospital admission, patients with new-onset diabetes reported with earlier in SARS-CoV-1 and associated great mortality [5]. Stress hyperglycemia is due to the absence of insulin release and related with elevated lipolysis and increased level of circulating free fatty acids during myocardial infarction and infectious diseases [29]. Stress hyperglycemia in COVID-19 cases might be more severe as an effect of cytokine storm.

Earlier reports show that in newly diagnosed diabetes, there has been amplified level of pro-inflammatory cytokines, CRP, ESR, and total leukocyte count. Through cytokine storm, there occurs acute inflammation which further aggravates insulin resistance with elevated levels of D-dimers and neutrophils also inflammatory mediators in hyperglycemic cases as compared to non-diabetic subjects [30]. Obese individuals are also susceptible to diabetes risk and increased severity in COVID-19, with increased adiposity is the hallmark noxious factor for alteration in glucose metabolism, immune changes then inflammation [31].

Viral disease imposes detrimental effects on pancreas either directly or indirectly. Earlier meta-analysis conducted using 34 studies showed improved incidence of T2DM in patients having hepatitis C viral infection as compared non-infected subjects with OR of 1.68 in retrospective and OR of 1.67 in eventual manner [32]. An earlier result shows that the pancreatic tissues (ductal epithelium and microvasculature) are highly populated with ACE2 and SARS-CoV-2 infection primarily infects the pancreatic β-cells and it might be one of the cardinal mechanisms for the progression of diabetes [33].

Steroid use during COVID-19 treatment has been associated with the progression of diabetes. The RECOVERY trial which studied the use

of dexamethasone in COVID-19 patients showed elevated risk for the development of diabetes which might be due to the direct effect of steroid and also delay the recovery of β-cell damage [31].

MECHANISM OF COVID-19 SEVERITY AND DIABETES

Amount of virus

The cardinal mechanism by which diabetes increases the infection severity is due to the increased viral load. Angiotensin-converting enzyme-2 (ACE-2) is the hallmark receptor for SARS-CoV-2 entry and it is positioned in a wide range of tissues such as lung, cardiac and renal tubules and too on the small intestine, and blood vessels luminal surfaces [34]. The previous preclinical studies in diabetic mice show the elevated expression of ACE2 in various organs such as lungs, kidneys, and heart [35]. Hypoglycemic agents such as GLP-1 agonists and anti-hypertensive agents such as ACE inhibitors and statins may increase the expression of ACE-2 [36]. Due to the upregulation of ACE2 receptor expression in various organs during diabetes, there might be an increased severity in these patients. In addition, the ACE2 expressions are mainly limited to the exocrine and endocrine pancreas [34]. Furthermore, inflammatory pancreatitis in COVID-19 patients may lead to the progression of diabetes in some cases. The state of hyperglycemia can elevate the glucose level in the airway secretions and in connection with pulmonary epithelial cells it enhances the replication of the influenza virus and thus increases the severity of infection [37,38]. Even though, *in vivo* studies for the association between elevated glucose level and increased SARS-CoV2 replication remain unclear, this might be one of the possible reasons for severe complications and mortality in COVID-19 patients with diabetes comorbidity.

Reduced immune system and activation of the cytokine system

Innate and adaptive immune reactions orchestrate a pivotal role in the clearance of the virus population in the airway. Amplified glucose levels might also reduce the antiviral response [39]. Increased severity of COVID-19 might also be due to a slow antiviral reaction, as a result, there will be a longer hyperinflammatory condition along with decreased count of CD^{4+} and CD^{8+} cells [40]. Diabetic patients usually have a compromised innate immune status, such as the process of phagocytosis and chemotaxis to identify and kill pathogens, which has been impaired in these patients [41]. In the meantime, the functions of natural killer cells are compromised as well as higher numbers of pro-inflammatory M1 macrophages are observed in type 2 diabetic patients [42]. In addition, T-cell activity in diabetic patients is condensed due to the chronic mild proinflammatory state and there is an alteration in Th1/Th2 levels [43]. Apart from the role of endothelial cells, the delayed interferon response along with the increased inflammatory state in COVID-19 patients with diabetes might trigger a "cytokine storm" and thus increase the severity.

LOSS OF ALVEOLAR FUNCTION

A case series done in the USA among 5700 COVID-19 patients reveals that the requirement of invasive mechanical ventilation was higher in patients who died with diabetes as comorbidity as associated to the patients without diabetes [44]. Similar studies have reported that significant association between type 2 diabetes mellitus and the development of ventilator-associated pneumonia in adult patients admitted during trauma conditions [45]. Therefore, this evidence highlights that type 2 diabetes mellitus patients had compromised alveolar functions and which may worsen the COVID-19 severity. Already documented studies show that the indices of pulmonary functions such as total lung volume, forced vital capacity, and alveolar gas exchange were markedly decreased in type 2 diabetes mellitus [46]. Hence, the impaired pulmonary efficiency in type 2 diabetes mellitus patients furthermore leads to SARS-CoV-2 infections force elevates the pulmonary complications in COVID-19 patients.

IMPAIRED ENDOTHELIAL FUNCTION

Virus-mediated pyroptosis triggers vascular inflammation and damage seen in COVID-19 patients [47]. Respiratory viral infections due to MERS, SARS, and COVID-19 and the damages caused by these viruses are not limited to the lung, but also affect the various vital organs and thus implicate that SARS-CoV-2 also causes infection to vascular endothelial cells and spreads to other organs [22]. Blood vessels contain ACE2 receptors besides recent evidence shows that SARS-CoV-2 has a straight result on blood vessel cells in ACE2 in engineered human capillary organoids [34]. Several reports show that, in vascular endothelial cells of COVID-19 patients, there is an accumulation of viral and inflammatory cells, which further leads to inflammatory cell death [48]. Consequently, the evidence shows that SARS-CoV-2 infection might trigger endothelial inflammation in various tissues and pyroptosis orchestrates a cardinal role in endothelial cell damage and inflammatory reactions. Modifications in the glycemic status trigger the release of proinflammatory cytokines and adhesion molecules from endothelial cells indicating to rapid leukocyte extravasation in alveoli during respiratory viral infections, leading to the deterioration of lung functions [49]. Furthermore, endothelial-mediated cytokine release lead to the formation of pulmonary lesions in COVID-19 patients, and diabetes might be one of the cardinal factors for these harmful events.

COAGULOPATHY

Recent data show that ICU-admitted COVID-19 patients display hypercoagulation in various vital organs with increased D-dimer and degraded fibrinogen levels which considerably disturb the overall mortality of COVID-19 patients [50]. In severe COVID-19 patients, there is a high risk for the progression of deep vein thrombosis and pulmonary embolism [51]. Hypercoagulation in various organs due to infections might be due to the activation of numerous inflammatory processes and coagulation pathways [52]. Hypercoagulation in severe COVID-19 patients might be due to the activation of the cytokine storm. In diabetic patients, there will be a hyper-inflammatory state and they are at higher risk to progress coagulation disorders. In the interim, diabetic condition increases coagulation then elevated insulin level mitigates the process of fibrinolysis in the event of systemic inflammation [53].

CLINICAL MANAGEMENT OF T2DM DIABETES MELLITUS IN COVID-19 PATIENTS

Management of T2DM in COVID-19 patients or in diabetic patients those with high risk of infected with COVID-19 is challenging with correct selection of antidiabetic agents. In the meantime, antidiabetic medications act as a double edge sword since some of the medications increases the ACE-2 expression. Along with that, the physician must be cautious when prescribing antidiabetic agents to diabetic patients with COVID-19 or new-onset diabetes since these drugs promotes the level of ACE-2 in lungs and pancreas and poorer the infection more.

Metformin up regulates the ACE-2 expression and orchestrate a vital role in the micro vascular repair mechanism mediated by AMP- activated protein kinase (AMPK) activation in the event of acute lung injury [54]. The recent study, metformin reduced the mortality rate in T2DM, particularly in women COVID-19 patients. Auxiliary, in that study, there was a marked reduction in TNF–α and IL-6 levels and increase in anti-inflammatory cytokine level IL-10, mast cell stabilization, enhancing the endothelial function then modulation of ACE-2 are the prominent mechanism exhibited by metformin in decreasing the COVID-19 severity [55]. The chief contraindication which is recommended for metformin discontinuation is during lactic acidosis in COVID-19 patients with T2DM [56].

COVID-19 infection triggers the expression of NLRP3 inflammasome, which outcomes in the release of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α [57]. Glyburide, a sulfonylurea derivative, blocks the NLRP3 inflammasome activation by inhibiting the ATP-sensitive K+ channels (KATP) [58]. However, the clinical utility of sulfonylureas such as glipizide, glibenclamide, and tolbutamide must not be recommended in COVID-19 patients as a consequence of hypoglycemia.

ACE inhibitors and angiotensin II type I receptor blockers (ARBs) are recommended for both diabetic and hypertension patients and these agents elevate the ACE-2 expression [59]. TNF-α converting enzyme (TACE) converts ACE-2 to sACE2 (soluble form) and moves into the blood circulation and furthermore located in the extracellular spaces. The SARS-CoV-2 entry into the cell is facilitated by ACE-2 and drug mediated enhancement in ACE-2 expression increases the viral load in diabetic cases and triggers many adverse events comprising mortality. However, sACE2 reduces viral load in the transmission since it binds to SARS-CoV-2 and thus inhibits the host cell interaction of the virus [60]. ACE inhibitors, ARBs, and GLP-1 agonists raises sACE2 level in extracellular tissues, and thus, sACE2 serves as a decoy receptor for virus neutralization.

Pioglitazone also increases the ACE-2 expression and consequently enhances the patient susceptibility to SARS-CoV-2 infection. Pioglitazone elicits antifibrotic and anti-inflammatory effect and inhibits the release of inflammatory mediators form immune cells. Hence, pioglitazone is recommended for diabetic patients with moderate COVID-10 for the prevention of cytokine storm [61]. The use of SGLT2 inhibitors class of molecules in diabetic patients with COVID-19 is analyzed since it enhances the ACE-2 expression in the kidney. Auxiliary, the SGLT2 inhibitor, increases the dehydration risk and diabetic ketoacidosis. Dapagliflozin, a SGLT2 inhibitor, decreases the lactic acidosis during hypoxia and reinstates the intracellular acid-base balance and also inhibits the cytokine storm in preclinical models [61]. With severe COVID-19 patients with diabetes comorbidity, insulin is the most suitable agent with minimal adverse effects. Insulin possesses anti-inflammatory action and decrease the inflammatory markers level in ICU-monitored patients [62].

CONCLUSIONS

Type-2 diabetes mellitus must be considered an independent risk factor for COVID-19 severity. Several pathological mechanisms such as viral load, loss of alveolar function, endothelial dysfunction, cytokine storm, and altered coagulation status are involved in the COVID-19 severity in diabetic patients. Hence, it is vital to monitor the glucose level and stringent control of diabetes by following the clinical guidelines to reduce morbidity and mortality.

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