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An insight to the incidence of acute pancreatitis, and co-morbidity of diabetes in SARS-COV2 infection

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Abstract

Since the emergence of SARS-COV2 infection, accumulating reports as well as evidences have been reported to the complex disease-disease interactions between this viral infection and the pre-existing diabetes co-morbidity. Hyperglycemia accompanied the onset of infection is repeatedly reported to be associated with the disease severity, prognosis and mortality rate elevation. Various mechanism has been speculated to lay behind the reported hyperglycemia including direct pancreatic tissues tropism besides the indirect cytokine storm overwhelming inflammatory immune response. In another perspective, other collection of studies has reported and emphasized the involvement of SARS-COV2 infection in the development of acute pancreatitis as one of this infection complications during the onset of infection, hence increasing the morbidity of such infection including the admission of the patients to the intensive care unit. Some have related the diagnosis of acute pancreatitis to the serum amylase and lipase levels manifested with the experienced GI symptoms, while, others consider CT scan images to confirm diagnosis. Finally, some reporters has hypothesized that SARS-COV2 infection may develop autoantibodies that probably precipitate type I diabetes mellitus long after infection. Therefore, due to significance of hyperglycemia/ diabetes to fate / severity of the infection as well as long term complications of SARS-COV2 this survey have covered aspects related to these issues.

Keywords: SARS-COV2 Infection; Diabetes; Hyperglycemia; Acute Pancreatitis; Co-Morbidity

1. Introduction

Up-to-date, there is neither specific nor safe therapy to SARS-COV2 as well as to this infection developed conditions including diabetes. Thus blood glucose level requires both close daily monitoring beside rational selection of antiviral drugs with no reported diabetes/hypoglycemic drugs interactions for the sake of tight glycemic state controlling as well as diabetic patients long term follow-up in order to minimize complications and comorbidities of diabetes during such infection [1]. For such task fast developing hyperglycemia at least in SARS-COV2 hospitalized patients is a critical issue due to its mutual role to ACE2 receptor glycation, hence, reducing the viral spike protein-entry receptor binding and its related inflammatory cytokines storm [2]. On other hand, SARS-COV2 infection related appetite and oral food intake reduction and sulfonylureas hypoglycemic drugs intake in the infected diabetic patients may inversely cause hypoglycemia [3, 4]. Although no sufficient evidences available, some medical experts speculates that avoiding hypoglycemic agents with SARS-COV2 co-morbidity relationship in addition to considering drugs of immune-modulation action probably be useful [1]. Tight self-control/monitoring of blood glucose in SAR-COV2 outpatients including continuing insulin-therapy for type I diabetes mellitus patients with daily monitoring of urinary ketones are critically required for those with poor blood glucose control during the infection [3-5]. For non-diabetic patients who

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develops diabetes during SARS-COV2 infections as one of its reported complications [6]. Nevertheless, intensive care units admitted SARS-COV2 patients with profound insulin resistance issues reflected by their highly uncontrolled hyperglycemia intravenously infused insulin is still recommended [4, 7]. Meanwhile, close monitoring blood glucose is required in order to avoid food intake related discontinuous in patients on ventilation [3].

As a viral infection, SARS-COV2 morbidity as well as severity intensified by the patients' improper immune/inflammatory response [8, 9]. For example, in stresses like in case of SARS-COV2 infection, patients with hyperglycemia witness inflammatory, coagulation, glycosylated hemoglobin and, neutrophils elevated blood levels [10, 11]. In addition, it was reported that over 50% of the type II diabetic patients infected SARS-COV2 have developed reduced lymphocytes count in one of the chines study as one of the non-specific immune response reflections [12].

During the episode of SARS-COV2 infection induced cytokine storm, cytokines involving the hyper-inflammation mediators such as interleukins, interferons, chemokines, and tumor necrosis as well as colony-stimulating factors, play a significant role in type I diabetes mellitus development [13], besides their involvement in other co-morbidities such as chronic obstructive pulmonary disease, interstitial lung disease as well as asthma [14] which are also encountered with SARS-COV2related lung destruction. remarkably, the specific innate immune response have been found to be compromised in case of uncontrolled acute hyperglycemia in diabetic patient rendering the exaggeration of the viral replication, on one hand. On the other hand, diabetes causes amplification of the release of thepro-inflammatory cytokines including IL-1, IL-6 and TNFα which are further amplified by the SARS-COV2 infection to cause acute respiratory distress [15, 16] causing an auto-immune like condition. In case of diabetes related auto-immune response beta cells deterioration begins post attack however, it still asymptomatic utile the insulin level decline is just enough to elaborate type I diabetes mellitus signs and symptoms beside its complications such as diabetic ketoacidosis [17].

The pancreatic beta-cell targeting auto-immune response is reflected by the elevated glutamic acid decarboxylase (GAD) and zinc transporter 8 (ZnT8) counteracting autoimmune antibodies blood levels while negative results to the insulinoma-associated-2 (IA2) autoantibodies targeting alpha-cells [18]. Hence, one of the reliable assumptions to propose a pathophysiological mechanism explaining the obvious association of type I diabetes mellitus as well as the greater severity and morbidity profile of SARS-COV2 in diabetic patients is the impaired immune response [16, 19]. Chronic inflammation associated with diabetes will intensify the release of the inflammatory mediators like IL-6 and CRP during SARS-COV2 viral infection leading to a much vulnerability to cytokines storm development and patient condition deterioration [19] on one hand. On the other hand, SARS-COV2 infection also causes non-specific exaggerated immune response characterized by overwalming pro-inflammatory cytokines release caused cytokine-storm in severe cases [20, 21] that ends with irreversible complications like lung fibrosis and multi-organ damage which may even ends with death [22]. Thus, immune system directed therapy like immune modulators have been proposed to be critical for SARS-COV2 patients [23].

In cases of diabetes, hypertension and nephropathy, there is an elevation in the circulating ACE2 enzyme level in order to compensate the activity of angiotensine and RAS over-activity [24-27]. ACE2 is described as the major SARS-COV2 cell entry receptor and tropism of body tissues [28]. It is distributed in many body systems including both endocrinal and exocrinal tissues of the pancreas despite its much dominance in the lung tissues making pancreas is one of potentialSARS-COV2 targets of infection[29, 30-32] besides, the higher affinity to its binding domain as compared to other corona virus such as SARS-COV1 [12, 33, 34]. Remarkably, a previous version of human epidemic corona virus, SARS-COV1 have infected the pancreatic tissues causing transient hyperglycemia in the infected non-diabetic patients which remains in some cases to three years interval to correct the viral infection caused beta-cell damage [32].

Diabetes in turn promotes ACE2 expression in the lung, immune cells, renal cortex, testes, blood vessels endothelium, GIT, pancreatic tissues, as well as liver tissues making it one of the profoundly serious SARS-COV2 infection co-morbidities [29, 34-41] thus insulin therapy in diabetes mellitus animal models declines the ACE2 expression in the animal tissues [42]. Furthermore, diabetes also enhanced the expression of the membrane bounded proteolytic enzyme furin that is involved in addition toTMPRSS2 in the viral entry inside the infected cell to begin viral replication stage [43, 44]. Thus, SARS-COV2 infection to the diabetic individuals causes the development of seriously severe hyperglycemia [45]. The ACE2 cleaves angiotensin I in to angiotensine peptides (1-7) that exhibit antioxidant as well as anti-inflammatory activity. While, ACE1 cleaves angiotensin I to angiotensine peptides (1-9) that play roles in diabetes pathophysiology, thus reduction of pancreatic tissues ACE2 expression due to SARS-COV2 infection explains the co-morbidity of the resulted hyperglycemia that brings about acute respiratory distress and other lung injuries [46, 47] due to the imbalance between ACE1 and ACE2 pathways [48]. Since SARS-COV2 causes down regulation of ACE2 expression, the accumulating angiotensin II ameliorates the insulin secretion, inducing vasoconstriction in the pancreatic blood flow causing ischematic damage, local inflammation and beta-cells proliferation [49]hence, establishment of SARS-COV2 associated hyperglycemia which reversed by angiotensin peptides (1-7) [50, 51].

Therefore, SARS-COV2 acute infection of both liver and pancreatic tissues causes poorly controlled hyperglycemia however, chronic infection may cause type I diabetes mellitus due to the induction of an autoimmune defensive reaction against the pancreatic beta-cells [52]. In fact, there is a mutual relationship between SARS-COV2 and diabetes mellitus regarding both their incidences as well as pathophysiology since ACE2 glycosylation due diabetes related hyperglycemia blocks the ACE2-angiotensine peptides (1-7) pathway as well as reduces the ACE2 expression particularly in the lung tissue leading to the exacerbation SARS-COV2 caused lung injury as well as the disease severity [47, 53].

Recently, a higher ACE2 mRNA expression is found in the pancreatic tissues rather than that in the lung indicating higher ACE2 expression in the pancreas [29, 54]. One genetic data study has revealed that 2. 59% of the pancreatic beta-cells express ACE2 while other one indicated that ACE2 is expressed in 0. 22% of the cells. However, a second study have reported that ACE2 expression is in 16. 35% of alpha, beta, delta and PP cells while in a third study was 15. 79-21. 05%. On the other hand, ACE2 is tremendously expressed in the exocrine tissue of the pancreas; 81. 82% of the cells, 52. 63% of the duct cells and 5. 26% in the acinar cells. Therefore, mild cases of pancreatitis and/or pancreatic lesions have occurred in mild (1-2%) to severe (17%) cases of SARS-COV2 infections. It is speculated that mild untreated of pancreatitis may bring about chronic one [54] manifested in both cases with hyperglycemia. During SARS-COV2 virus infection to the ACE2 expressing pancreatic beta-cells it will alter their functions involving the secretion of insulin [55, 56] through disturbing the hemeosasis of the beta-cells, the probable interruption of the pancreatic alph-beta-cells communication as well as inclining the oxidative stress in the beta-cells [57]. Remarkably, it is reported that SARS-COV2 associated pancreatitis is attributed to the inflammatory response exaggeration as well as hypoxia due to infection related respiratory distress and different lungs injuries [58].

However, the debates continues about the paradoxical role of insulin on ACE2 expression through its effect on the cleavage of ADAM-17, some have reported insulin inducing effect to ACE2 expression [59, 60] while others have argued to exhibit the opposite effect [61]. In fact, the reported direct metabolic relationship between SARS-COV viruses and diabetes probably also highlight the direct viral infection to the ACE2 expressing pancreatic islets that brings about either type II diabetes mellitus [34] or even type I diabetes mellitus. Finally, corona virus infection itself promotes excessive expression of ACE2 in the body tissues such as the pancreas, liver, lung and heart [32]. In general a humoral immune response impairment caused by hyperglycemia in poorly blood glucose control diabetic patients that brings about unusual inflammatory immune response characterized by abnormal cytokines secretion especially interferon besides accumulation of TY-helper cells upon SARS-COV2 infection leading to cytokine storm which ends with multi-organ failure [62].

2. Diabetes and SARS-COV2 infection

Diabetes is reported to be a risk factor to about 20% of SARS-COV2 infection cases and one of its serious co-morbidities that leads to high rate of mortality as earlier reports declares from Wuhan, China [8, 4]. In addition, the mortality rate among infected diabetic patients was greater than that in the non-diabetic [19] which may exceeds 49% of the infected diabetic patients [63]. In fact, the mortality rate among diabetic patients of poor glycemic control may reaches three fold relative to that of non-diabetic ones as reported by univariate data analysis study, yet, the mortality hasn't be significantly different between the two groups of patients as reported by a second bivariate regression analysis [53, 64]. In fact, three meta-analysis reports have shown that diabetic SARS-COV2 infected patients have two to three folds higher mortality rate reaching 7. 3% than the non-diabetic patients [65-71]. In china 5-7% of the reported SARS-COV2 infection cases are with diabetes comorbidity in certain statistical analysis studies [9, 72] while it approaches 13% of mortality cases, more than half of them are male [73]. Generally, collection of chines studies have reported 5. 3- to about 20% of SARS-COV2 infections case are diabetic patients however, mega studies reported 5. 3%-7. 4% of the cases are in diabetic patients [8, 9, 12, 21, 74-76], that encourages to conclude it involved most of diabetic patients population ratio reported in china (10. 9%) [77]. Thus some have reported that there is no co-relation between diabetes and the incidence of SASR-COV2 infection [78] which is equal to global prevalence of diabetes [79] despite the obvious reported statistical analysis, Although other mega studies have a conflict of no relationship between diabetes and SARS-COV2 infection. In fact, these studies have reported a higher prevalence of the viral infection among diabetic individuals to about 16. 3% of the infected individuals [67]. While, other smaller studies reported prevalence rate of 13. 8-22. 2% in severe cases of SARS-COV2 infections [9, 76, 80-81] however, it inclines to 15. 6-31% in non-severe cases patients with type II diabetes mellitus [8, 53, 75, 82, 83].

Nevertheless, two third of the mortality cases of SARS-COV2 was with diabetes co-morbidity [84]. Diabetic individuals in USA infected with SARS-COV2 constitutes around 11%, of them 32% required admission to the intensive care unit [79, 85], yet, the mortality rate about 10% in one study [86]. While, other American retrospective study includes 88 hospitals in the mortality rate among the diabetic infected patients in USA was 28. 8% with uncontrolled glycemic state

of blood glucose value and glycosylated hemoglobin value exceeding 180 mg/dL, and 6. 5% respectively [79, 86]. However, the elevated prevalence of (34% of the total mortalities) mostly among the virus infected Asian and African ethnic population have been reported to the united kingdom [87] due to the higher incidence of type II diabetes mellitus [63, 88] in third study the mortality rate have approached 19% of the diabetic SARS-COV2 infected British patient with an uncomplicated diabetes [89].

Furthermore, other over the world mortality rates from different studies have revealed that the mortality rates among SARS-COV2 infected diabetic are 11. 4%, 19% and 18% in Iran, Spain and Mexico respectively [90-93]. Yet, this mortality rate is reported to be 17% among the infected diabetic patient while declines to 8. 9% in another Italian study [94, 95]. Various mega studies have estimated the SARS-COV2 mortality rate among the infected diabetic patients ranges from 8% to 11% approaching thus prevalence rate of type II diabetes mellitus incidence in china [96-98]. Consequently, diabetes have a fundamental role in promoting SARS-COV2 infection liability, poor prognosis as well as enhanced mortality rate [1]. However, some meta-analysis studies found no significant relationship between diabetes and acquiring this viral infection [99, 100].

The prevalence of SASR-COV2 showed that 8. 6% of the infected people are diabetic, most of them (79. 5%) are of poor glycemic control particularly males of age range 55-75 years old. However, the disease severity is revealed to be irrelative to the glycemic control with no variation in the recovery pattern between genders although a remarkable difference in calcium and vitamin D_3 among them [101]. However, diabetics represents 36. 5% of the SARS-COV2 infected people in South Korea with higher mortality rate of 17. 2% [102, 103]. Actually, ACE receptor polymorphism may lies behind the elevated mortality rate among some ethnic groups and generally all populations in south Asia particularly in India, besides higher insulin receptor resistance reported to these populations due to obesity [104-106]. Remarkably, blood glucose fluctuation is reported to about 59. 5% of the SARS-COV2 infected patients particularly among the young type I diabetes ones. However, type II diabetic viral infected patients have high tendency to exploit severe infection and poor prognosis on one hand. On the other hand the infection have bring about diabetes complications [107, 108]. It is reported that 71. 2% of the infected Brazilian diabetic individuals are more liable to develop hyperglycemia hence experiencing poor prognosis of SARS-COV2 elevated risk although 28. 8% of these patients have HbA1c less than 7. 0% [109,110]. Moreover, in one study from Brazil, geriatrics over 50 years old diabetes infected patients particularly type II diabetes patients are of high risk of mortality because of their liability to develop poor prognosis especially in the presence of other comorbidity like cardiovascular disease or obesity [2, 45, 73, 109-112].

Furthermore, a study involves over 1300 SARS-COV2 infected individuals form 53 centers, demonstrated that 88. 5% of the infected patients are diabetic (type II diabetes mellitus), around two thirds of them are geriatric females of means age 70 years old. In addition, around 47% of the diabetic infected individuals are with micro-vascular complications such as chromic kidney diseases while around 41% are with macro-vascular complications all with mean HbA1c level of 8. 1-11. 9% [113]. Nevertheless, it has been reported that about 18% of the SARS-COV2 hospitalized patients are diabetic where diabetes is the reason of their poor prognosis since about 26% of them are admitted to the intensive care unit [114].

It is worthy to note, that the role of diabetes related hyperglycemia association as a comorbidity of poor prognosis of SARS-COV2 infection is first reported by the Chines and Italian reporters besides, its association with infection severity as well as higher mortality rate [2, 73, 75, 108, 112, 115]. In fact, ASRS-COV2 incidence among diabetic population varies from one country to another. SARS-COV2 infection among diabetic individuals ranges from 5-20%, 11-35. 5% and 33-58% in China, Italy and USA respectively while, other have reported 11% prevalence of SARS-COV2 infection among American diabetic individuals [36, 108, 116-118].

A seventeen million SARS-COV2 infection cases mega study has demonstrated that diabetic infected patients with uncontrolled glycemic state and glycosylate hemoglobin value of (HbA1c ≥ 58 mmol/mol) have significantly greater mortality rate than the patients of well controlled glycemic state and glycosylated hemoglobin value of (HbA1c < 58 mmol/mol) [98, 100]. Some authors have considers that SARS-COV2 developes diabetes in the infected patients, however, others have considered asymptomatic as well as symptomatic diabetes is a co-morbidity of SARS-COV2 infection causing death [100]. Therefore, SARS-COV2 infection may develop hyperglycemia in both diabetic and non-diabetic infected patients which is a serious risk factor that inclines the viral infection mortality rate besides complicating the infected hospitalized patient's conditions [2, 63, 71, 115]. A group of large mega studies and meta-analysis reported from china, France, USA and other countries have considered diabetes mellitus as one of most important risk factors of the infectious disease severity and poor prognosis. It is found be responsible for two to three folds greater intensive care unit admission besides, about doubled mortality rate as compared to norm glycemic non-diabetic infected patients [66, 67, 113, 119-122]. However, in single large meta-analysis that involved one study from

Italy, two studies from USA and thirty one studies from china that has included about 16,000 SARS-COV2 infection cases, about 10% of the infected population are diabetic [65]. This prevalence of infection among diabetic individuals is in accordance with other studies [69, 96, 97, 123] that revealed its correspondence with diseases severity [36] and low disease survivors [124]. Others have concluded no correspondence with the disease severity [69, 96]. Retrospective studies have demonstrated that 85. 4% and 58% of the infected patients are diabetic and associated with disease severity [118, 124]. Yet, the authors in the formerly mentioned meta-analysis study still consider that there is no solid evidence for the correlation between diabetes and the incidence of SARS-COV2 infection [65].

Moreover, poor glycemic control reflected by blood glucose of more than 11 mmol/L, of the hospitalized SARS-COV2 infected individuals with type II diabetes mellitus has brought about development of poor disease prognosis causing intensive care unit admission in about 21. 4% of them due to acute respiratory distress in 23. 2% of them acute, cardiac/renal functions deterioration in 12. 5% of them as well as coagulation related complications characterized by elevated D-dimer levels. Ultimately, poor glycemic control related hyperglycemia is associated with elevating the mortality rate to about 19. 6% and 22% in the infected individuals with type II diabetes mellitus in chines studies [12, 73, 125-128] while 29% in American study [84]. It is speculated that aging as well as complications of diabetes like microvascular, renal as well as cardiovascular complications, besides, diabetes related chronic inflammatory status gives rise to immune function dysregulation [77] making diabetic patients are much liable to SARS-COV2 infections as well as poor prognosis [12, 74, 83, 129, 130]. Therefore, despite the age, gender as well as the existed co-morbidity according to the reported studies the global reported diabetic individuals with SARS-COV2 infection constitutes 5. 3%-33. 9% [8, 9, 12, 19, 21,53, 63, 72,74-76, 79-83, 85, 102, 103, 108, 122, 131-135].

3. Diabetes glycaemic control/glycosylation of haemoglobin and SARS-COV2 infection severity / prognosis

Three important biochemical parameters blood levels have been thoroughly discussed by authors as well as statistically analyzed for their significance for acquiring SARS-COV2 infection, developing complications/poor prognosis and mortality rate, these are blood glucose, D-dimer and lymphocytes count [12, 74, 83, 129, 130]. A chines multivariable data analysis study has demonstrated that hyperglycemia co-related to fasting blood glucose more than 11 mmol/L and D-diamer blood level more than 1. 5 µg/ml are associated with SARS-COV2 and MERS infections complications as well as greater mortalities, since hyperglycemia of elevated blood glucose is associated elevated potential incidence of plural effusion that is found to be from 2. 5% to 17. 4% in various studies [12]. Besides, hyperglycemia causes obstruction of the small airways and diffused/ ventilatory dysfunctions [136]. Other multicenter, data analysis study has revealed that infected diabetic individuals with fasting blood glucose greater than 10 mmol/L is associated with SARS-COV2 damage of several body organs giving rise to poor prognosis as well as high mortality rate [137] as compared to those of good glycemic control with blood glucose range from 4 to 10 mmol/L [73] although poor glycemic control in most diabetic SARS-COV2 is still an outstanding phenomena [138]. Nevertheless, it well known that diabetic hyperglycemia of fasting blood glucose more than 11 mmol/L due to poor glycemic control is generally related to community acquired pneumonia patient hospitalization and poor prognosis [136] in addition to, its induced plural effusion is an independent risk factor to the MERS-COV infection caused mortalities [139].

Regarding the diabetes related glycosylate hemoglobin (HbA1c), its elevation is associated with enhancing the risk of acquiring various type of infection, hyperglycemia of blood glucose level more than 180 mg/dL even in no-diabetic patients with HbA1c value of less than 6. 5% as compared to diabetic patients of HbA1c≥6. 5% with good glycemic control [84]. Hyperglycemic patients of poor glycemic control (blood glucose higher than 180 mg/dL or 10 mmol/L) have high prevalence of incidence of septic shock (4. 7%), acute respiratory distress (21. 4%), acute heart damage (9. 9%) as well as kidney damage (3. 8%) reflecting that hyperglycemic stress particularly that of type II diabetes mellitus lies behind SARS-COV2 infection case worsening, bad prognosis and mortality rate as one of serious co-morbidities besides hypertension cardiovascular disease and cerebrovascular disease [73, 99]. While, infected type II diabetes mellitus individuals of good glycemic control are less susceptible to the infection poor prognosis [73, 10].

The degree of glycemic control and related HbA1c determines the diabetes associated endothelial impairment as well as lung microvasculature [140] which are directly related to SARS-COV2 infection severity. A chines study, has demonstrated that more than 60% of the SARS-COV2 infections are with an elevated levels of HbA1c whether they are diabetic or not, however, at least 10% of the infected individuals are not diagnosed as diabetic patients. In addition,HbA1c level has a positive correlation between both HbA1c besides blood glucose level, and the inflammatory parameters including ferritine, CRP and ESR besides, correlation with the coagulation factors like fibrinogen which explains its association with SARS-COV2 infection inflammation severity, hypercoagubility, declined blood oxygen saturation and multi-organ damage explaining higher mortality rate in the presence of diabetic co-morbidity[11]. In another large chines study that included 72,314 cases of SARS-COV2 infection, about 50% of the cases are diabetic

individuals [75], yet, the same study concluded that there is no direct association between HbA1c level and development of respiratory distress and high mortality rate [113] since only hyperglycemia is found to be correlated to SARS-COV2 infection patients' hospitalization even when HbA1c level is less than 7 [141, 142]. Hyperglycemia is reported to promote the release of inflammatory mediators related to cytokines storm [143, 144], glycosylation of ACE2 which enhances SARS-COV2 tissue tropism/cell binding which both are related to SARS-COV2 infection susceptibility, disease severity in 44. 5% in one meta-analysis study [70] and poor prognosis [145]. Thus in USA, uncontrolled hyperglycemic in the infected diabetic individuals is associated with four folds mortality rate due to hyperglycemia stress [84]. Nevertheless, it has been reported that SARS-COV2 severity and mortality rate is also directly correlated with triglyceride and glucose index (TyG), high index value leads to much more poor prognosis and higher mortality due to diabetes related micro and macro-vascular complications [146]. Furthermore, poor glycemic control is probably associated with the SARS-COV2 infection depressive behavior [147, 148]. The risk of acquiring viral infection as well as developing SARS-COV2 complications among infected diabetic individuals is greater with insulin resistance associated with high HbA1c level due to hyperglycemia related immune-suppression [52, 149, 150]. Thus, blood glucose level as well as its variation rather than baseline HbA1c level determines the glycemic control, and consequently, SARS-COV2 disease conditions and prognosis. Good glycemic control during SARS-COV2 interval should exhibit blood glucose level of 3. 9-10 mmol/L while poor glycemic control exhibit blood glucose level above 10 mmol/L [2, 4, 63, 73, 79, 85].

However, one retrospective chines small sample (48 diabetic individual) hospitalized SARS-COV2 infection cases study has concluded that survival rate is independent on the HbA1c determined glycemic control patients' status [151] as well as severity in another study [113]. Other author argues the proposal of the role of diabetes reloated other comorbidities such as obesity, renal disorders, cardiovascular diseases, hypertension besides immune defense influence of type II diabetes mellitus caused hyperglycemia in acquiring/complication of SARS-COV2 infection to make diabetes as one of its risk factors [152, 153]. In fact, Chronic hyperglycemia has a negative impact on the body immune surveillance hence may brings about unexpected immune response [113] besides, its well-known impact on both blood vessels and coagulation factors that is critically affect SARS-COV2 severity, prognosis and mortality rate since it gives rise to the disease complications [121, 152, 154] particularly cardiovascular and renal damage [69, 155-157]. However, a multivariate analysis study has supposed that considering glucose blood level alone is not significantly related to SARS-COV2 infection severity and hospital admission without considering the impact of age and gender effect among infected diabetic individuals which have a critical role besides blood glucose level in hospitalization of the infected patients within the first week of infection [158].

Moreover, higher blood pressure, high LDL cholesterol levels is also the two co-morbidities of SARS-COV2 disease are two diabetes associated complications besides, diabetes association with psychological disorders, depression and anxiety encountered with SARS-COV infections in type II diabetic individuals that deteriorates the disease condition particularly in case of poor control of blood glucose[159-161]. It is noteworthy to implicate that hypo-vitaminosis D is greatly associated with the development of insulin resistance as well as depression of immune surveillance [162]. Structurally, diabetes caused chronic hyperglycemia is reported to precipitate pulmonary tissues modifications including basal lamina thickening, respiratory muscles stability, and alveolar epithelium endurance [163, 164]. In addition, diabetes related hyperglycemia also co-related neuropathies including dysregularities in the autonomic nervous system functions in the bronchial muscular and respiratory muscular endplates that complicates SARS-COV2 respiratory condition, hence precipitating dyspnes and respiratory distress [163].

One of the interesting speculation explaining SARS-COV2 infection susceptibility, severity and co-morbidity in diabetic individuals [108] is based on three facts, the first is the hyperglycemia related neutrophils dysfunction that hinders the pulmonary antimicrobial defenses that enhances these individuals susceptibility to lower respiratory tract infections as encountered with H1N1 and MERS-COV infections [165-167]. The second is based on hyperglycemia caused pulmonary micro-vascular pathological structural modifications that cause oxygen exchange hindrance. The third is hyperglycemia caused disturbing effect on the immune surveillance giving rise to secondary bacterial infections to precipitate pneumonia [77]. In addition, two potential scenarios lies behind cellular injuries during microbial infections to body tissue Including lung tissues, the first is through increasing glycolic pathway resulted several toxins by-products intracellularly [168]. The second is through up-regulating the glucose transporters mounting the infected cells membrane [169-171]

From other perspective, others have reported that the SARS-COV2 infection related decline in the oxygen saturation while the incline of the neutrophils and lymphocytes levels and inflammatory markers erythrocytes sedimentation rate (ESR)/C-reactive protein (CRP), besides HbA1c and glucose level is due to the viral infection, however, HbA1c and glucose levels are much elevated in the infected diabetic individuals [172]. Other study stated that SARS-COV2 virus attacks the β1-chain of hemoglobin leading to the dissociation of prophyrin part rendering hemoglobin to lose its oxygen transporting function which precipitate hypoxia besides speculation of the virus-HbA1c high binding affinity

[173, 174]. In addition, it is reported that SARS-COV2 infection has caused at least one hypoglycemia episode during the encountered blood glucose level irregularities of less than 3. 5 mmol/L [124] which contributes to sympathetic stimulation, enhancing platelets activation or even excessive cytokines release by the pro-inflammatory mononuclear cells recruitment which some or all bring about cardiovascular complications of the disease [175].

4. Diabetes impact on immune response and SARS-COV2 related hyper-inflammation

The accumulating clinical data analysis studies evidently demonstrated the role of diabetes in enhancing the prevalence as well as severity of SARS-COV2 infection due to the negative impact of diabetes on immune surveillance and inflammatory response besides its promoting role in viral entry [36, 176]. Diabetes related hyperglycemia causes both innate as well as effective humeral immune response depression [177]. In addition, type II diabetic individuals suffers mild chronic inflammatory condition and visceral adipose tissue inflammation caused insulin resistance exacerbation that both influence glucose hemostasis making type II diabetes mellitus a co-morbidity to SARS-COV2 complications [19, 178] that include triggering cytokine storm abnormal inflammatory response [149]. Remarkably, diabetes promotes the release of several pro-inflammatory cytokines including IL-1b from monocytes particularly in case of hypoglycemic [179] as well as hyperglycemia episodes which are encountered with SARS-COV2 infection. Hypoglycemia also promotes glucose transporter 3 (GLUT3) up-regulation, amplified by lipopolysaccharides mounting the monocyte-macrophage [180, 181] causing hyperinsulinemia in acute state in cases of type I diabetes mellitus that induces CD40 expression in monocytes [182]. Furthermore, hypoglycemia enhances the adrenergic response leading to much more inflammation which can trigger cytokine storm [183, 184].

Interestingly, ICU admitted patients with severe SARS-COV2 inflammatory and coagulatory reported parameters elevation varies between diabetic and non-diabetic infected individuals. Critical state hospitalized infected diabetic individuals exhibits inclined blood levels of ; IL-6, C-reactive protein, serum ferritin, coagulation index, and D-dimer binging about cytokine storm as well as coagulatory complications correlated to poor prognosis as well as mortality rate [19, 63, 85]. While in non-diabetic patients the reported inclined inflammatory mediator levels include that of IL-2, IL-7, TNF-α, INF-γ inducible protein 10 granulocyte colony-stimulating factor (CSF), macrophage inflammatory protein 1-α and monocyte chemo attractant protein 1 which also brings about cytokine storm [149]. In this context, a chines study has demonstrated that about 98% of the diabetic SARS-COV2 individuals was with type II diabetes mellitus, with an inclined inflammatory mediator blood levels like IL-6 in 54% of the patients, ferritin in 66% of the patients, ESR in 64. 4% of the patients, CPR in 71% of the patients serum amyloid protein A in 64. 4% of the patients [12]. Remarkably, IL-6 is most inclined inflammatory cytokine among infected diabetic patients, which besides other reported elevated level cytokines are inclined in chronic phase in addition the acute phase, particularly in the flare metabolic disorders of diabetes along with over-expression of their receptors to give rise to the damaging influences as what happens during an autoimmune attack [52, 185]. Form the inflammatory/coagulatory mediators inclined during SARS-COV2 infection in diabetic individuals α-hydroxybutyrate dehydrogenase, lactic dehydrogenase, alanine aminotransferase (ALT), Procalcitonin, and fibrinogen while, hemoglobin remarkably declines besides, leukocytosis, neutrophilia and lymphocytopneaas indication of cytokine storm as well as hyper coagulation, hence much severity and poor prognosis of the disease as is reported by two cohort studies [19, 63].

Furthermore, neutrophils chemotactic response as well as phagocytic activity impairment are of the mechanisms lying behind the poor impact of diabetes on immune surveillance and response which makes diabetic individuals liable to various microbial infections including SARS-COV2 infection [9, 36, 52] and remarkably encountered with MERS-COV infection [186].

From other perspective, severe inflammatory response as well as infiltration of T cells happens due to the viral entry into the infected cells. The stimulated T lymphocytes stimulates recruitment of other immune cells with exacerbated cytokines release hence, establishing cytokine storm via releasing interferon-gamma (INFγ). Later on, if the released cytokines leaks out the systemic circulation they causing affected organs damage or even multi-organ failure [187]. A wide spectrum of cytokines and chemokines are reported to be released while cytokine storm such as IL-6, TNF-α, IL-8, CCL-2, CCL- 4, and CCL-14 [3]. In addition, diabetes also cause down-regulation of ACE2 expression on one hand, while, SARS-COV2 is reported to deteriorate the fluctuation of the glycemic control in diabetic infected individual due to stress on other had. Thus there is an interchangeable complex diabetes-SARS-COV2 disease-disease interaction contributing to poor outcomes of each of them that influence their pathophysiology as well as treatment strategy [174] however, the exact mechanism that lies behinds enhancing the viral infection severity, poor prognosis or elevated mortality rate is still unidentified [65]. Nevertheless, the role of diabetes in disturbance/depression of the immune surveillance plays a significant role in easier development of secondary bacterial infection to viral invasion to body tissues due to depression of phagocytic cells, neutrophile chemotaxis, T-cell response functions besides disturbing cytokines production and release [188]. Consequently, secondary haemophagocytic as well as lymphohistiocytosis

besides, characteristics incline in the cytokines blood level such as IL-2, IL-7, IL-6, granulocyte-colony stimulating factor GCSF, INFγ inducible protein 10, monocyte chemo attractant protein 1, macrophage inflammatory protein 1-a, and TNFα while cytokine storm in case of SARS-COV2 infected diabetic individuals [21, 149]. In other point of view, some authors have assumed that diabetes and SARS-COV infections deleterious disease-disease interactions occurs through a shared DPP4 receptor as encountered in case of MERS-COV infection among diabetic individuals or ACE2 as in case of SARS-COV1 and SARS-COV2 infections. These receptors are involved in several physiological events including glucose hemeostasis, inflammatory response as well as organs functions like kidneys and cardiovascular system [65, 111].

In addition, others have speculated that diabetes related hyperglycemia as well as chronic inflammation aggravated obesity promotes immune response disturbance via a complex multifactorial way including reducedpolymorphonuclear leukocytes recruitment, phagocytic activity as well as neutrophils chemotixic response including lowerinterleukin-1 (IL-1) and IL-6 release. Besides, there are Tumor Necrosis Alpha (TNFα)activity depression owed to the effect of T-cells as well as immunoglobulin glycation [25, 189], release of other inflammatory cytokines such as C-reactive protein, plasminogen activator inhibitor and reactive oxygen species (ROS) particularly in the adipose tissues [190, 191].These diabetes induced pro-inflammatory cytokines disturb insulin signaling pathway via two mechanisms. The first, include phosphorylation of the serine residue of the insulin receptor [152] while, the other one involve precipitation of insulin resistance to develop type II insulin resistance complication such asretinopathy, nephropathy, neuropathy and cardiovascular disease in cooperation with chemokines and proteases [192]. Furthermore, other mechanism of disturbing influences of diabetes on the immune system, first, is promoting the expression of adhesion factors on both endothelial cells and blood vesseles such as intracellular cell adhesion molecule-1, vascular cell adhesion molecule-1, Eselectin and CD11b that diminish neutrophil chemotaxis [193, 194]. Secondly, it declines the neutrophils phagocytic, bactericidal and other oxidative stress associated antimicrobial activities [193, 195-199], besides, prohibiting microbs opsonizing, complement system [16, 200], and monocytes as well as peripheral mononuclear white blood cells cytokines release [152]. Thus, the SARS-COV2 prognosis is not fundamentally based on viral load, yet, it depends on the state of glycemic control in the infected diabetic individuals, hence, in order to avoid establishment of cytokine storm and SARS-COV2 severity/intensive care unit admission of diabetic infected patient's good glycemic control in cases of infection accompanied hypoglycemia or hyperglycemia [201]. Furthermore, these humoral as well as innate immune response suppression of diabetes makes diabetic individuals more liable to infections including viral one as the first immune surveillance/defense response is depressed leading to the reported SARS-COV2 exacerbated immune response [16]. It is worthy to note that bothe inflammatory as well as immune response is under the cholinergic autonomic stimuli via the vagal nerve afferent nerves that is induced by the immune tissue cells hence, declining the macrophages activation [202].

Inversely, from other prospective, exaggerated immune response (cytokine storm) have been reported to occur even in no-diabetic SARS-COV2 infected patients [19], that is speculated to be triggered in both diabetic and non-diabetic individuals by mean of viral entry which promoted the T-helper cells infiltration to the site of infection with the release ofINFγ that triggers inflammatory immune cytokine storm [36] that ends with multi-organ injury/ failure [45]. Molecularly, after viral entrance into the infected cell, it will bind to the single stranded RNA molecular pattern recognition receptor (PRRs), endosomal Toll-like receptors ([TLRs] such as TLR3 and TLR7 (particularly TLR7 as well as the cytosolic retinoic acid-inducible gene-I-like receptors [3, 203]. These receptors stimulates the transcription of nuclear factor-κB and interferon regulator factors that triggers the release of type I interferons (IFNs) by the macrophages, pneumocytes, and dendritic and pro-inflammatory cytokines/chemokines [3]. INF-I stimulates theINF-stimulated genes hence, promoting the inhibition of viral entry and replication via a group ofIFN-induced transmembrane protein as well as and lymphocyte antigen 6 complex locus E [204-208], besides, starting viral irradiation process [204-206]. In addition, interferon I induce pro-inflammatory cytokines from the macrophages, monocytes as well as neutrophils including cytokines such as TNF-α, IL-1, IL-6 and IL-8,in addition tochemokines like CXC-chemokine ligands (CXCL10, CXCL2, CXCL8, CXCL9, and CXCL16), and CC-chemokine ligands (CCL-2, CCL-4, CCL8 and CCL-14) leading to establishment of cytokine storm as well as failure of multiple organs [3, 209]. The released chemokines promotes the accumulation of monocytes/ macrophages via CCL8 and CCL2, T or natural killer cells via CXCL9 and CXCL16, neutrophils via CXCL8 actions [209, 210]. However, despite all these complex defensive mechanisms SARS-COV2 virus has success evading the body immune surveillance via conformational alterations in its spike proteins as well as inhibition of PRR pathway signaling that reduce the immune cells response to the released INF-I [211, 212]. Interestingly, in moderate and sever cases of SARS-COV2 infections reported clinical data oflymphopenia of a characteristic $CD4^+$ and $CD8^+$cells declined count [213-220] owed to the reported elevated IL-6 and TNF-α levels that brings about apoptosis of T-cells [218, 221]. Remarkably, the interferon-I immune response against SARS-COV2 infection is time dependent in the presence of absence of inflammation and lies behind the virus infection pathophysiological mechanism [222-224] which inter-individually different [3]. SARS-COV2 infected diabetic individuals have exploited a delayed weak interferon dependent immune response as well as Th1-cells activation contributing to the extensive antiviral inflammatory response [3], besides possessing neutrophils of higher extracellular

traps NETs particularly in type II diabetes mellitus individuals [225, 226]. It is reported in china, that SARS-COV2 infection has a deleterious impact on insulin sensitivity causing enhancement of insulin resistance in both type I and type II diabetes infectedindividuals, hence provoking excessive inflammatory cytokines release particularlyIL-1b, IL-6, TNFα, monocytchemo-attractant protein-1 (MCP-1) and inducible protein-10 [227]. Remarkably insulin resistance in diabetic individuals also aggravated by hypo-vitaminosis D [162, 174].

Type I diabetes mellitus may be intensively triggered viral infections due to the ACE2 expressing pancreatic endocrinal tissue tropism, as this type of diabetes is an autoimmune condition resulting in the destruction of the pancreatic β-cells associated with this type of diabetes. Yet, the insulin deficiency resulted hypoglycemia is of delayed onset which laso reported to other SARS-COV infectious strains [32, 227]. In this context it necessary to emphasize that SARS-COV2 outbreak may contribute the elevation of type I diabetes mellitus in the future [228].

5. SARS-COV2 caused acute pancreatitis

Accumulating evidences and reports have evidencing the involvement of many body tissues other than the respiratory tissue by the invasion of SARS-COV2 infection including the gastrointestinal tract tissues (GIT) and pancreatic tissues. Signs and symptoms of involvement of the GIT tissues of vomiting and/or diarrhea is reported for 11-15% of SARS-COV2 infected population [172] with or without coagulopathy [76, 172, 229], since these tissues are proved to express ACE2 receptor involved in the virus tissue tropism and cell entry [230-232]. Both of the pancreatic exocrine and endocrine glands including the beta-cells pancreatic islets express the [29, 232, 233] thus SARS-COV2 can infect these tissues leading to pancreatic tissues damage [233] besides reported pancreatic tissue injury secondary to the virus infection [232] that is evidently influenced the mortality rate [233]. Nevertheless, despite the heterogenous signs and symptoms of GIT involved infection that overlap with that of acute pancreatitis, evaluation of blood amylase as well as lipase levels besides CT-scan is required in order to diagnose SARS-COV2 related acute pancreatitis [29, 172, 232, 233] although in the reverse context the impact of hepatitis as well as pancreatitis on SARS-COV2 is still unclear [234, 235]. The possible pathophysiological mechanisms involved in the development of acute pancreatitis due to SARS-COV2 infection is one or more of three potential mechanisms. The first, involve direct tropism of the SARS-COV2 to both the exocrine and endocrine pancreatic tissues that ends with pancreatic tissue deterioration [32]. However, the virus tropism of the insulin secreting pancreatic endocinal cells is argued by the authers due to the results of molecular studies of the cell entry receptors and contributing factors. The first have reported the high abundance of ACE2 and TMPRSS2 within the pancreatic ductal and acinar cells while conversely the other conversely reported insignificant availability of these two biomolecules in the pancreatic tissues [236, 237, 238]. The second, is due to the exacerbated immune related systematic inflammatory response (cytokine storm). The third, is due to the SARS-COV2 infected tissues own immune response. The latter two potential mechanisms lead to multi-organs damage [232, 234, 239].

However, there are interesting speculated hypothesis to the development of acute pancreatitis during and post SARS-COV2 infection that is based on autoimmune pancreatitis that involve the β-cells destruction. It is proposed that the leaking viral replication antigens from the site of infection to the systemic circulation triggers an extensive systemic immune response that include all body organs including the pancreas [240, 241]. The molecular homology between the viral epitope and that of the β-cells auto-antigens is the major contribution factor to the expression of cross-reactive autoantibodies. These auto-antigens continues to be expressed even long after the onset of infection that gives rise to a chronic pancreatic inflammation leading to β-cells destruction precipitating the development of type I diabetes mellitus in these infected individuals [241]. Nevertheless, despite accumulating reports of SARS-COV2 associated pancreatitis co-incidence as well as co-exisitance of clinical manifestations, the exact mechanism/molecular pathways of pathogensis is still uncertain [242,243]. A study from china has reported 17. 3% of SARS-COV2 infected individuals have experienced viral infection related acute pancreatitis while, other study has reported that 18. 75% of SARS-COV2 infected patients have demonstrated elevated acute pancreatitis related markers; lipase as well as amylase blood levels [29, 234, 237] in both mild and severe cases of the virus infection [29, 234]. A third chines study have reported that 18% of the hospitalized SARS-COV2 infected individuals have exhibited elevated serum lipase levels [8, 29]. In deed, in Hubei, china alone where the SARS-COV2 virus outbreak has been firstly reported about 50% of the infected individuals have exhibited the GIT symptom due to the virus invasion [172]. Remarkably, a molecular biology study have exploited the presence of SARS-COV2 genetic material (RNA) within the pancreatic pseudocyst samples of the infected individuals which in addition to the viral entry molecular factor expresis encourages the emphasis of the exsistance of strong association between SARS-COV2 infection and development of acute pancreatitis while onset of infection [242, 244] or even development of auto-immine related type I diabetes mellitus long post infection cure. In addition, viral infection associated pancreatitis have been reported to other virus infections [245-247], yet, the mechanism of its development depends on the type of the viral infection [248]. Others have considered that SARS-COV2 gastrointestinal infection contributes to the elevated blood levels of pancreatic lipase as well as amylase enzymes during the onset of the infection [249] due to the increased GIT permeability [250, 251], hence, they have hypothesized that over 20% of SARS-COV2

hospitalized patients with abdominal pain are misdiagnosed as developing acute pancreatitis or even developing multiple organs failure [242, 252]. Some have attributed such cases of acute pancreatitis to the SARS-COV2 experienced cytokines storm, microvascular thrombosis or acute respiratory distress, thus for such reasons 20% of SARS-COV2 infected individuals with GIT symptoms are reported to have acute pancreatitis [242]. In addition, one of the biggest clinical chines studies have reported that only 5% of the infected individuals have expressed the GI symptoms while 10-20% of the patients have demonstrated biochemical data of mild liver injury [9].

The elevated blood levels of lipase as well amyloidase enzyme is reported as a consequence of SARS-COV2 infection to pancreatic/GIT tissues in various contries and are been related to the diseases severity as well as diasease poor prognosis. An elevated serum lipase level has been reported in 18% of the hospitalized patients as stated in a large cohort retrospective study, 16. 3% of them are male while 92. 9% of them have been admitted to the ICU unit. Abdominal pain as well as diarrhea are reported to both mild and extensive elevation of serum lipase levels. Yet, inclined level of lipase is associated with greater leukocytosis and liver enzymes abnormalities. Interstringly, the multivarient analysis of data has postulated that SARS-COV2 infection associated pancreatic damage indicated by the incline lipase level is signifgicantly correlated, as independent factor, to the disease severity. However, the authors have recommended further investigation to correlated the inclined pancreatic enzymes blood levels to the pancreatic tissue damage due to direct viral tissue invasion rather than overwhelming system inflammatory response (cytokine storm) [253]. Moreover, mega studies have exploited that existence of pancreatic tissues targeting autoantibodies long after various upper as well as lower respiratory tract viral infections in a significant ratio of patients even in mild cases. However, remarkably, both H1N1 and coronaviruses infections have been reported to develop such autoimmune antibodies that is also encountered with type I DM [254, 255]. In other meta-analysis study, it has been reported that 17. 6% of SARS-COV2 inhibited patients in Hong Kong have expressed GIT signs and symptoms [256] in agreement with some chines reported studies of the association of this viral infection with acute pancreatitis as one of its compilications particularly with one family infected members [239, 257, 258]. Other cohort study has demonstrated that the inclined amylase as well as lipase blood levels including its clinical signficiance not conform the pancreatic tissue damage due to SARS-COV2 infaction [253, 259]. A large global study that include SARS-COV2 infected individuals from 96 hospitals has repoeted that approximately 0. 16% of them suffers acute pancreatitis complication of the infection, about 70. 6% of them are never been diagnosed with diabetes before the infection [251]. At least in china main land about 11. 3% to 79. 1% of SARS-COV2 infected individuals have been reported to exploite GIT manifestations [76, 172, 229, 232, 260]. Other meta-analysis involved data analysis of thirty-five studies have demonstrated that 15% of the SARS-COV2 infected individuals have exhibited GIT symptoms [261] however,in a third cohort study, the ratio escalates to 40% of the infected individuals [76]. In America, a fourty-eight percent of the SARS-COV2 infected individuals have exhibited a three folds serm lipase level above the upper normal value, however, authors owed it due to reasons other than accompanied acute pancreatitis [262]. In this context, serum lipase level elevation cauld happen due to shock related pancreatic hypoperfusion, mechanical ventilation, renal failure or even pulmonary diseases [263] which are also reported to SARS-COV2 [9]. It is worthy to note that pre-existing hyperparathyroidism and gall stones also causes elevation in the serum lipase level [258]. In an American retrospective study from six centeres, it has been reported that about 12. 1% of the hospitalized SARS-COV2 infected patients have exhibited mild hyperlipasemia, yet, only 2. 85 of them shows severe hyperlipasemia of serum lipase level three folds greater than the normal level besides expressing GI symptoms. Nevertheless, none of these infected individuals has expressed signs of acute pancreatitis except some mild fatty infiltration around the pancreatic tissue is seen in the CT scan images. Thus, the authores have emphasized that there is no co-releation between SARS-COV2 infection and elevated lipase indication to acute pancreatitis although 44% of the infected individuals with hyperlipasemia have admitted to the ICU and 33. 35% have passedout. The authors have also concluded that SARS-COV2 infection is uncommonly develops acute pancreatitis complication [264].

In addition, several studies have reported cases of acute hyperglycemia associated SARS-COV2 infections without any previous medical history of diabetes [12, 115, 265, 266], many of them of inclined serum lipase and amylase levels in SARS-COV2 indiviuals are also reported [234, 237] which are also proposed to pancreartic damage. However, it is worthy to note that viral pancreatitis is a mild inflammatory uncommon condition, although it is reported to be associated with many other viral infections [248]. In a chines study 16% of the severily SARS-COV2 infected individuals have exhibited inclined blood lipase and amylase levels, yet, only 7% of then experienced pancreatic CT-scan images abnormalities [54]. In pakistran a thirty-two years old SARS-COV2 infected male has been reported toexhibite GIT symptoms with signs of acute pancreatitis ultrasound showing swollen pancreas with peri-pancreatic inflammatory alterations and fluid accumulation besides elevated serum lipase level but not within the three folds limit [267]. In america, a fifty nine years old femal of cholecystectomy and thrombophilia history infected with SARS-COV2 of postivie fecal viral RNA testalso has developed GIT symptoms and CT-scan of acute pancreatitis [257]. In UK, a twenty six years old SARS-COV2 infected femal with no personal of familial history of diabetes has experienced acute pancreatitis characterized by highly elevated lipase level with mild elevation of gamma-glutamyl transferase level in addition to pancreatic enlargement in CT scan images [268]. A three ICU admitted case of SARS-COV2 individuals reported by

(Barlass et al. , 2020) hav exhibited signs of acute pancreatitis but with nieghter serum lipase level exceeds three fold the normal limits nor inclined amylase level [253]. In Iran an ICU hospitalized sixty-five years old femal infected with SARS-COV2 exhibiting GI symptoms with mildly elevated lipase and amylase levels (less than 3 fold above the normal limit) has been diagnosed as an acute pancreatitis case due to out-clinic treatment and viral infection [269]. In india, a cae of an obese SARS-COV2 infected femal expected to be a co-related case of acute pancreatitis have been reported by (Aloysius, M. M. , et al. , 2020). This patient has experienced nonspecific pancreatic enzyme elevation as well as GI symptoms however, it is diagnosed as a case of virus infection related pancreatitis due to multi-organ failure [258]. Furthermore, a case of acute pancreatitis in an ICU admitted SARS-COV2 infected fifty-six years old female has been reported by (Alves A. M. , et al. , 2020). However, the patient has not refelected GI symptoms but the Magnetic resonance cholangiopancreatography (MRCP) and CT scan images have revealed pancreas abnormalities including tail parenchymal enlargement and surrounding retroperitoneal fat stranding besides the elevated biochemical parameters of elevated amylase and lipaseserum levels with mild hyperglycemia [233]. Thus, (Anand et al. , 2020) had diagnosed such cases of acute pancreatitis depending on CT scan images rather than association with GI symptoms or with the elevated lipase/amylase levels since the symptoms of acute pancreatitis during viral infections can be extremely heterogenous making its diagnosis an uneasy task [257]. In Denmark, cases of Two of three family members SARS-COV2 infected in dividuals presenting signs and symptoms of viral infection related pancreatitis has been reported by (Hadi A. , et al. , 2020). The two 68 years old mother and 47 years old daughter has never experienced pre-exisiting factors for acute pancreatitis that required hospitalization. The doughter exhibited rapide elevation of the amylase level to 1500 U/L of a severe case of pancreatitis conformed by ultrasound examination while the mother has exhibited slower elevation in the seum amylase to 934 U/L [239].

Recently, oro-fecal route is suggested to be be one of the SARS-COV2 transmission route of infection evdent by the detections of the virus RNA in the feaces and gut epithelium long after negative airway swap [256, 271, 272] indicating that the infection acompanied GI symptoms are manifestation of the virus invasion to the ACE2 expressing GIT tissues and neighbouring organs [270]. Interstingly, such invasion is encountered by other viruses such as human immunodeficiency virus, mumps, Cytomegalovirus, Coxsackievirus B and Influenza A (H1N1) [272]. In addition, since SARS-COV2 is evidently of close genticresembly (around 89%) with SARS-COV1 that targets the GIT as well as pancreatic ACE2 expressing tissues [32, 273], makes the hypothesis of the involvement of pancrease by the SARS-COV2 direct invasion is a logical one to explain co-related acute pancreatitis complication as what is reported to SARS-COV1 infection [274]. However, autopsy evidences, immunohistochemicalanalysus and PCR test provides no sufficient evidences to the existence of any SARS-COV2 RNA or immunoilogical response in the pancreatic islets [275]. It is noteworthy, to postulate that the reported affinity preference of SARS-COV2 to the GIT tussies for viral replications [270] support the former pancreatic tissue invasion although the onset of GIT menfestations is relatively slower than that of respiratory tissue invasion [232] even one month of after onset of signs of symptoms in 83. 3% of mild cases [276]. In addition, 53. 3% fecal SARS-COV2 genetic materials detection occurs in mild infections during the course of infection while detected in 23. 3% of cases after respiratory tract clearance of infection [277] which is remarkably as accurate as respiratory tract sample [278]. In fact, the virus nucleocapsid protein is also detected in the gastric, duodenal, and rectal epithelium [232].

Ultimately, In both cases of type I and type II diabetes mellitus SARS-COV2 infected patients, the viral infection is clearly exacerbate the pre-infection existed diabetic state or even contribute to the development of diabetes in the severe hospitalized cases due to pancreatic tissues inflammation [111]. However, fortunately, SARS-COV2 studies may give rise to better understanding of diabetes especially type II DM and lead the ways to the invention of novel therapeutic approaches [279].

6. Conclusion

According to the accumulating reports related to hyperglycemia, diabetes and acute pancreatitis related to SARS-COV2 infection, there is a sophisticated disease-disease interaction between this viral infection and these three aspects. Hyperglycemia is evidently one of the most critical co-morbidity to this virus infection as it complicate and enhance severity, poor prognosis as well as mortality rate of the disease. Different pathophysiological mechanisms have been proposed for such SARS-COV2 that involve both direct virus ACE2 pancreatic/GIT tissues tropism while the indirect mechanism is related to the overwhelming inflammatory cytokine storm. Conversely, SARS-COV2 may develop acute pancreatitis through various molecular mechanism however, the arguments between authors still pointing to the uncertainty of such interaction. However, the accumulating evidences encourages the emphasis of autoimmune dependent long term viral infection caused development of type I DM as well as short term acute pancreatitis. Thus, such aspects should be taken in consideration in case of management of SARS-COV2 infection with hyperglycemia manifestation.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors confirm that there is no conflict of interest.

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