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An insight to the diabetic ketoacidosis and lactic acidosis among the SARS-COV2 infected individuals

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Abstract

A huge number of studies have demonstrated the significance correlation between diabetic ketoacidosis as well as other type of ketosis/hyperosmolar metabolic state deterioration conditions and the SARS-COV2 infection. It is investigated in various infected age group, geneders, and countries. It is reported to be correlated to the two types of diabetes (type I DM and type II DM) available as pre-existing co-morbidity, infection related new-onset developed diabetes of both types or even due to hyperinflammation related acute pancreatitis. In fact, although most of the studies have reported greater survival, however, small single center retrospective studies have reported the association of diabetic ketoacidosis with elevated mortality rate that approaches 50%. Mechanistically, the DKA caused metabolic state deterioration due to the glucose metabolism fluctuation is attributed to the bidirectional sophisticated SARS-COV2 infection and different reasons hyperglycemia disease-disease interaction. Nevertheless, exaggerated inflammatory/immune response may also worsen the glycemic state that brings about ketosis. Remarakably, DKA can be developed even in cases of approximately normoglycemic conditions of the SARS-COV2 infection which is fewly reported, yet, it is attributed to SGLT2 inhibitors therapy. The SARS-COV2 infection related DKA complication among diabetic individuals have been treated with the same therapeutic protocol of non-infectious conditions including insulin and IV replenishment therapy however, with significantly greater dosing regimen. It is worthy to note that the infused replenishment fluids should be carefully calculated along with monitoring the lung function besides careful monitoring the potassium and some other electrolytes level particularly while insulin is intravenously infused. Thus, in order to explore the significance of correlation of this metabolic complication with the virus infection poor prognosis as well as higher mortality rate this survey reports the development of DKA as well as the ketosis related metabolic abnormailities while the course of SARS-COV2 infection among individuals with pre-exisitng and new onset diabetes.

Keywords: Diabetes; DKA; SARS-COV2 Infection; Acidosis; Prevalence; Mechanism

1. Introduction

In general, diabetes when accompanied with poor glycemic state control is thoroughly reported to be associated with high potential of microbial infection vulnerability as well as their poor prognosis [1-8].In addition, hyperglycemia within the coarse of viral infection particularly of corona viruses, elicits a deleterious burden on the pulmonary/their immune surveillance functions leading to extensive inflammatory destructive immune response or even the development of cytokines storm [9-12]. Therefore, since the emergence of SARS-COV2 infection, individuals with either types of diabetes have exploited a much significantly observed hospitalization, intensive unit admission, poorer prognosis and mortality rates particularly if diabetes is accompanied with other co-morbidity such lung disease, hypertension,

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cardiovascular anomalies and nephropathic conditions [13, 14, 15, 16]. However, the incident prevalence of SARS-COV2 infection among diabetic individuals varies from 2-20% according to the state of glycemic control [17, 18] while associated with 7.7% and 22.2% ICU admission according to (Huang, et al., 2020) and (Wang, et al., 2020) [19, 20].Interestingly, (Abid, et al.,2020), have suggested that the overall prevalence of SARS-COV2 is 14.5% greater among the diabetic than the non-diabetes infected individuals [21].

An extra-ordinary abnormal immune response induced by either the viral infection and/or diabetes complications, thus, tightly close continuous glucose level monitoring to the blood glucose, properly safe antihypertensive therapy particularly insulin, optimal metabolic controlas well as earlier viral infection detection/diagnosis, are significantly required [13, 14, 19, 20]. Glycemic control is a highly delicate issue while such conditions; yet, blood glucose above the 12 mmol/L indicates hyperglycemia while bellow 4 mmol/L indicates hypoglycemia during such infection conditions [13, 14].However, reports from Wuhan multiple SARS-COV2 management centers have reported that the other recommended oral hypoglycemic agent have failed to control blood glucose level in the diabetic SARS-COV2 infected patients who have developed uncontrolled hyperglycemia that have brought about other (secondary) microbial infection associated with ICU fatalities [8, 22, 23-26].

Probably, a considerable percentage of poor prognosis SARS-COV2 infection cases exhibiting hyperglycemia symptoms are among obese individuals, since obesity inclines the diabetes and cardiovascular co-morbidities risks characterized with coagulopathy enhancement related viral infection disease severity and mortality rate [27-29].Consequently, an Indian, a meta-analysis study has exploited that diabetic SARS-COV2 infected people are more liable to hospitalization and especially to intensive care unit (ICU) admission [28]. Respiratory functions impairment, metabolic syndrome complications or incline in the adipose tissue pro-inflammatory cytokines are potentially the mechanisms to which the severity of SARS-COV2 in obese individuals is attributed [30]. In fact, there are accumulating reports that have revealed diabetes fundamental involvement in the complications of SARS-COV2 infection as well as with its mortality rate elevation [31]. However, it is reported that even food restriction along with blood glucose control irregularity in diabetic individuals with SARS-COV2 infection, never alleviate disease severity outcomes particularly the cytokines storm due to diabetes associated insulin resistance. In addition, a potential invasion of SARS-COV2 to the pancreatic β-cells may also be involved in the development of such irregularities that deteriorates the disease condition [32]. Autopsies have revealed that the highest higher mortality rate is associated with SARS-COV2 infection related lungs, spleen, pancreas, the lymph nodes and other multiple organs damage in severe infection cases [33].However, diabetes (particularly type II DM) associated hyperglycemia synergistically amplifies such deleterious virus infection consequences probably due to both immune (characterized by lymphocytopenia), hyper-inflammatory response, coagulatory (venous/arterial) and respiratory systems related mechanisms which are potentiated by diabetes [27, 34-37] as well as diabetes related insulin-resistance that brought about higher insulin doses/doses disproportionalities in the critically ill patients [38, 39]. Both of diabetes as well as cardiovascular (even in no-diabetic individuals) have contributed to the elevated mortalities among SARS-COV2 victims especially those with type II DM [40] due to the enhancement of the inflammation mediated vascular permeability which in turn participate in the development of albumin urea kidney complications of micro- as well as macro-vascular type, metabolic syndrome besides, other cardiovascular diseases [41] which is exacerbated by the vasodilator cytokines released while SARS-COV2 infection promoted cytokines storm [42].Thus, some has correspondently reported that this diabetes related albumin urea, elevated liver enzyme blood levels (Alt) as well as dyslipidaemia are closely related to deterioration of the SARS-COV2 infected diabetic individuals disease state as well as poor prognosis development [43].

In this context, a Chinese meta-analysis study in agreement with other multicenter, retrospective longitudinal study of over ten folds associated higher mortality rate, have demonstrated that 4.4 folds higher mortality rate, compared to the non-diabetics, among diabetes infected individuals is co-related to type II DM [43, 44], of which 20-40% are in Wuhan city, china as exploited by (Novel, 2020) and (Yang, et al, 2020)studies [15, 45], although it is aggravated by other co-morbidities like age and cardiovascular diseases [46].Besides, been associated with severe disease complications including acute respiratory distress syndrome (ARDS), acute kidney injury, and septic shock contributing to the reported greater fatalities in cases of poor blood glucose control (>7.6 mmol/L) [44].However, very large meta-analysis Chinese study involved 782314 SARS-COV2 infection cases, have revealed that the mortality rate among diabetic individuals is around 7.3% [47]. A third study from New York city, USA, have also shown that diabetes is associated with greater mechanical ventilation, ICU care admission and mortality rate among diabetic individuals rather than with non-diabetic infected individuals [48]. Nevertheless, a fourth cohort study form the England has revealed that, compared to non-diabetic infected individuals, twice higher mortality rate of SARS-COV2 infection victims is among type II DM individuals while 3.5 times among type I DM diabetic ones particularly among geriatrics although a high risk is also present for young patients [49]. Diabetic individuals of particularly those over 70 years old are much liable to, infection vulnerability, disease severity, poor prognosis as this age is associated to formerly mentioned co-morbidities and immune system functions decline/anomalies [2, 13, 36, 50-53]. Remarkably, (Moss et al., 2020) has reported less

incidence of acute respiratory distress is encountered among diabetic SARS-COV2 infected individuals than the non-diabetic ones [54]. Thus, the level of hyperglycemia at the time of admission/pre-admission glycemic state of SARS-COV2 patient are determinant factors for the disease prognosis, glycemic state control however is also determined by the glycosylate hemoglobin level [55].

From an opposite perspective, acute viral infections to the pulmonary tissues may lead to a temporary insulin-resistance state development even within an euglycemic state in both obese and non-obese infected individuals [56] while some viral infections such as SARS-COV2 have a direct impact on the treatment of metabolic disorders including type II DM explained by the closely related pathophysiological mechanism. The corona viruses entry receptorsACE2 as well as DPP4 besides other contributing factors such as transmembrane Protease Serine 2 (TMPRRSS2) are also reported to be involved in regulating many metabolic signaling such as glucose homeostasis, physiological functions such as renal and cardiovascular physiology in addition to immune response control [52, 57]. Hyper/hypo-glycemia and dyslipidemia are involved in SARS-COV2 management, thus, careful treatment protocol as well as drugs selection is a critical issue in case SARS-COV2 infected diabetic individuals which is further complicated if other diabetes related co-morbidity is also existed as in case of corticosteroids forbidden use as anti-inflammatory/immune depressing drug for SARS-COV2 developed acute respiratory distress in the hospitalized infected individuals [6, 58, 59].Furthermore, co-administration of the antiviral drug ritonavir with corticosteroids may exacerbate the hyperglycemic influence of corticosteroids since it reduces corticosteroids metabolism as it acts as an enzyme inhibitor [60].

Moreover, the reported gut tropism by SARS-COV2 virus probably due to the considerable expression of DPP4, ACE2 and TMPRRSS2may also explains the virus glycemic state altering influence characterized by blood glucose level characteristic fluctuation. This influence can be explain by the fundamental role of gut in glucose and other metabolic hemeostasis via its released hormones and involvement of in gluconeogenesis [61] beside, the virus infection caused reduction of oral anti-hyperglycemic drugs particularly metformin by the enterocytes [6]. Nevertheless, despite the less rate of incidence of GIT SARS-COV2 invasion reported in china at the beginning of the pandemic outbreak [62], yet, an increasing incidence profile of GIT infection has been globally reported and is associated with hyperglycemia as well as liver injury particularly in severe cases of infections [63]. Antihypertensive drugs such as ACE inhibitors and renin-angiotensin aldosterone system inhibitors also interfere with these signaling and regulatory pathways, hence, probably contributing SARS-COV2 infection poor prognosis on one hand. On the other hand, other drugs such as corticosteroids, redemsivir, lopinavir/ritonavir, themselves may cause direct pancreatic β-cells injury, insulin-resistance (via their lipodystrophic effect) and hypokalemia that deteriorates the SARS-COV2 encountered glycemic irregularities making rational election of the proper drug for better glycemic control is a hardly approachable task[58, 60].In addition, extensive corticosteroids use causes hypercortisolism and glucose elevation due to metabolic deterioration. While, Darunavir/Cobicistat and interferon-b1also causes insulin-resistance by a lesser extent due to a similar lipodystrophic effect [60]. Thus some have speculated that corticosteroids accompanied with catecholamines takes part in the deleterious effect of SARS-COV2 induced hyperglycemia as well as the hyper-inflammatory stress [58, 64]. Interferons particularly type I interferon such as (interferon-b1) also not useful to be used for counteracting SARS-COV2 virus infection since they may contribute to further pancreatic β-cells damage via innate immunity mediated autoimmune reaction as well as that both lead to more deleterious case of hyperglycemia [65, 66].Finally, unfortunately in case of either of the use of azithromycin/other macrolide type antibacterial agents, co-administered with hydroxychroquine, or the use floroquinolones antibiotics a lone, glycemic control irregularities are also reported [67, 68].

Furthermore, during SARS-COV2 viral infection as well as its complicating secondary microbial infections besides the extremely elevated blood glucose level due to the uncontrolled glycemic state, it is unwise to switch insulin therapy suddenly to other hypoglycemic agents [69-72] since it may lead to further blood glucose irregularities including hypoglycemia [73]. Nevertheless, although hypoglycemia has a beneficial influence of enhancing innate immune response to the endotoxins of secondary microbial infections via promoting pro-inflammatory monocytes recruitment, it negatively affects the co-existing cardiovascular co-morbidities leading to higher mortality rate [74].Moreover, although the virus infection is generally of milder course, some have reported that merely type I DM in pediatrics are not enough to propose incline in the risk of SARS-COV2 infection in case of good glycemic control [75]. However, frequent records have related cardiovascular conditions to type II DM which are mostly associated with diabetic ketoacidosis development in patients with poor glycemic control [76, 77]. In this context it is reported that the rate of hospitalization of children with new-onset type II DM has inclined during the era of SARS-COV2 infection emergence [78] thus it has been emphasized that this infection may give rise to the development of new cases of DM due the damage of the pancreatic cells that provoke a novel diabetes pathophysiological mechanisms [79]. Consequently, in the united kingdom (Unsworth, et al,2020) study that involve many medical centers, have reported an inclined post SARS-COV2 infection development of new-onset type I DM [80] leading to an inclined mortality rate in these new onset and other of pre-existing diabetes due to a diabetic ketoacidosis [81]. Therefore, SARS-COV2 infection contribute to two potential hazards, the first is due to insulin resistance triggered by acute hyperglycemia and cytokine storm that gives rise to

diabetes complication such as ketoacidosis episodes on one hand or even due to the development of loss of appetite related hypoglycemia encountered in case of severe to moderate cases of infection [82, 83]. The second hazard, involve the macrovascular as well as microvascular complications of diabetes as well as hyperglycemia related abnormal immune response.

2. Diabetes related ketoacidosis (DKA) complication and SARS-COV2 infection

In general, ketone bodies are metabolically produced by the liver from the fatty acid accompanying hyperglycemia which is when accumulated in the blood due to the declined ketone consumption [84, 85].This severe metabolic life-threatening disorder mostly triggered by diabetes while seldom provoked by other diseases yet, it is developed by stress provoking conditions such as infections and cardiovascular infarction [86, 87, 88] or even inadequate insulin therapy during diabetes condition [89, 90]. In fact it is one of the complications of both types of complications mostly type I DM indicated by the hyperglycemia as well as the elevated HbA1C level [91] that brought about counteracting fatty acid breakdown to ketones [88] due to the accompanied prolonged insulin insufficiency that contribute to the declined glucose consumption by the peripheral tissues as in case of type I DM particularly when lately diagnosed giving rise to neurological disorder [89, 90, 92, 93], while, less common in case of type II DM [37]. In addition, type II DM upon traumas, surgery or infection have an elevated liability to DKA [93]particularly in cases of association with severe illnesses that may cause fatality [91], alcohol abuse as well as using sodium-glucose co-transporter-2 inhibitor drugs [94-96]. However, some reporters have been reported to exhibit an elevated prevalence of DKA among type II DM patients [96, 97]. The declined insulin secretion in case of DKA contributes to the inclined blood level of counter regulatory hormone, liver gluconeogesis, and fatty acid oxidation [98, 99]. This case of ketoacidosis causes acid-base condition disorder occur during respiratory conditions [98] characterized by hyperglycemia, lipolysis, ketosis, glycosuria with progressive dehydration, alteration of electrolytes, vomiting, and metabolic acidosis caused by infections and insulin use insufficiency [100-105].In children DKA is one of serious emergent metabolic complications affecting 20-40% of those with type I DM that may precipitated by even non-specific conditions such as SARS-COV2 [106] while it is reported that 16-55.3% of diabetic pediatric patients may develop DKA [107-111].However, early diagnosis leads to a successfully management [109-113] since it become the most deleteriously fatal diabetic conditions complication if not controlled [99, 114] particularly in case of type I DM besides, being contributed to longer hospitalization with negative impact on the disease state that can be avoided with good glycemic control using insulin [115]. It is the most common cause of poor prognosis as well as mortality in most of type I DM fatalities of pediatrics and adolescents mostly upon missing the use of insulin treatment especially several doses [91, 101]. In dead, acute infections such as viral infections that infect the lower respiratory airways and other pulmonary tissues may cause insulin resistance/deficiency among diabetic individuals, hence, precipitating DKA especially those causing multi-organ failure [48]. Frankly, there are two types of DKA, the first is known as ketosis prone diabetes while the second type is identified by the American diabetes association known as Euglycemic DKA that constitutes 10% of the DKA patients [91].

Diabetic ketoacidosis is diagnosed to be associated with blood glucose level greater than 250 mg/dL [116]or 200mg/dL (greater 11 mmol/L) as reported for pediatrics under 5 years old [117], yet, not always diabetic ketoacidosis may occur even within the normoglycemic conditions as in case of euglycemic diabetes [118, 119] where the blood glucose level may be less than 11 mmol/L, blood pH below 7.3,ketemia where the blood level of the ketone bodies exceeds 3 mmol/L and high anion gap [120]. While, the urine analysis demonstrate glycosuria/ketonuria and elevated two pluses ketones level[107, 108], and serum bicarbonate less than 18 mmol/L [116] or less than 15 mmol/L for children [117]. However, 50-75% of the DKA patients have exploited the symptoms of nausea, vomiting, abdominal pain with poor oral intake, fasting, extensive thirst and tapering insulin doses [91, 121] developed by hyperglycemia triggered elevated glycogen as well as catecholamine blood level that induce gastrointestinal motility [121] which is also encountered in many reported studies of SARS-COV2 infection. remarkably the physiological hormonal and anatomical fluctuation in case of pregnancy give rise to respiratory alkalosis along with enhanced bicarbonate renal excretion compensatory mechanism thus declining the physiological acid-base balance buffering capacity as well as predisposing these women to metabolic acidosis [122].

In addition, pregnancy enhances insulin resistance that brings about promotion of gluconeogenesis, lipolysis, hyperlipidemia and ketogenesis make them also more liable to DKA to about 8.9% of the diabetic pregnant female as compared to 3.1% in diabetic non-pregnant ones [96, 123-125] which is aggravated by the placental hormones like lactogen, prolactin and cortisole that counteract the insulin activity which is aggravated by co-existing stress condition [125, 126]. The level of ketone bodies is elevated 2-4 times greater with 12 hrs of fasting in pregnant women as compared with non-pregnant women [127] since long time fasting or even starvation [128, 129] since pregnancy is a hypermetabolic state that fasten the starvation state [125, 130].

Therefore, from the contributing factors to DKA is young age (childhood and adolescence) [131] which is inclined due to enhanced severity and frequency during quarantine of SARS-COV2 infection among type I DM due to a delayed diagnosis and management [132, 133]. Thus, metabolic hazardous conditions such as Hyperglycaemic Hyperosmolar State (HHS), Euglycaemic DKA (EDKA)and DKA recommend emergent hospitalization but, fortunately they share a similar therapeutic protocols [134]. Interestingly, HHS is developed even in normal insulin level [135] like what happens in euglycemic ketoacidosis. Nevertheless, despite HHS is associated with an elevated blood glucose levels 33.3 mmol/L accompanied with elevated osmolality of the serum above 320 m.osmol/Kg, yet, both of EDKA and DKA have acidic blood pH below 7.3 along with low serum bicarbonate level below 15 mmol/L [120].Furthermore, it is reported that before hospitalization diabetic patients with uncontrolled hyperglycemia symptoms should be tested for ketone body levels if they are on SGLT2 inhibitors hypoglycemic drugs since it may gives rise to EDKA [136, 137]. Hence, DKA is primarily diagnosed by the inclined ketone levels in the blood and urine [91].

The potential pathophysiological mechanism of DKA is owed to the declined tissue utilization of glucose and body fluids volume decline. The mild cases of DKA can be overcome by the fluids oral intake with instructions of self-management on one hand. On the other hand, the management of severe DKA due to a hyperglycemic crisis requires ICU admission, IV insulin therapy with frequent glucose level monitoring every 1-2 hours besides potassium and electrolytes levels monitoring [91].

2.1. The Mode of DKA Development in SARS-COV2 Patients

The potential mechanism of SARS-COV2 induction of DKA particularly via interaction with the ACE2 receptors within the pancreatic tissues is still not fully uncovered particularly in the infected diabetic individuals with type II DM [83, 138]. However, in case of SARS-COV2 infection among diabetic individuals, ketone bodies levels should be evaluated just before hospital admission [91]. Moreover, some has reported that SARS-COV2 infection prevalence is inclined among diabetic individuals due to the DKA attributed low cytosolic pH as well as ACE2 inclined expression [139-141]. In addition, this virus infection participate in the deterioration of DKA via the up-regulation of the level of serum lactate dehydration dehydrogenase enzyme (LDH) besides, the encountered hypoxic/anaerobic acute respiratory distress condition causes overproduction of lactate in both blood and extracellular fluids [142-144] that leads to acidic conditions [139, 143] that also contribute to cytokine storm related pro-inflammatory cytokines release [139]. It is important to note that the viral infection frequently activate Lactate dehydrogenase (LDH) and creatine kinase enzymes which causes modification of the metabolic pathway including the insulin signaling pathways thus the anaerobic glycolysis, lactate level incline and hypoxia besides the established hyperglycolysis are established under the developed anerobic conditions in this case of infection hence, precipitating DKA [145].

However, form other prospective, the cell membrane, body pH controlling symporter, lactate/H^+ causes the introduction of lactate and its counter ion, the proton intracellularly that gives rise to a rapid decline of the cytosolic pH thus enhances the viral entry and replication. However, the other cell membrane counteracting antiporter Na^+/H^+ pump causes ejection of the proton outside of the cell with the influx of calcium and sodium ions contributing to the increased of cellular osmolarity that leads to cell destruction [139, 146, 147]. However, this antiporter as involved in the development of insulin resistance and diabetes mellitus [148]. Some have reported that SARS-COV2 can infect RBCs as well as attack the hemoglobin that brings about hypoxia due to the loss of hemoglobin oxygen transportation which in turn also promotes the production of lactate that establish lactic acidosis in the SARS-COV2 infected diabetic patients [139, 149]. However, (Chee, et al., 2020)have reported that the SARS-COV2 virus interaction with the renin angiotensin-aldosterone system (RAAS) represent an additional pathophysiological mechanism of development of DKA via down regulation of the ACE2 leading to the incline of angiotensin II and aldosterone that also complicate DKA in addition, this RAAS enhances the pulmonary vasculature permeability as well as fluid accumulation even during its treatment that may deteriorate the patient's condition including hyperglycemia [150]. It is necessary to note that the SARS-COV2 infection is associated with several stresses including the respiratory distress, hypoxia and sepsis that require IV insulin with fluid therapy for the infected diabetic individuals to control hyperglycemia and its metabolic complications [151]. However, IV insulin treatment of DKA contributing hyperglycemia may lead to hypokalemia [151, 152].Remarkably, ACE2 is enormously expressed in many body tissues including the pancreatic tissues including the beta-cells leading to hyperglycemia besides, multiple organs damage/failure [83, 152, 153-156], thus, SARS-COV2 infection to these cells causing a decline of insulin secretion as well as due to the damage of these cells to precipitate DKA [83, 157, 158], in addition to the development of new onset diabetes mellitus due to the tropism of this tissue [38, 159-162]. Moreover, the SARS-COV2 infection also induces NHE activation involved in insulin secretion that aggravate the insulin secreting tissue leading to a permanent damage [158] via activation of disintegrin and metalloprotease 17(ADAM17) that is associated with ACE2 expression decline along with increasing NHE activation [148, 163] which is also with shedding of ACE2 from the endothelial cells of blood vessels to the blood circulation. Interestingly, AT1R causing (ADAM17) up regulation, thus this receptor inhibitors can retard the virus cell entry [156, 164, 165]. Remarkably, animal studies have

reported that the use of insulin causes normalization of ADAM17 and ACE2 expression as well as inclines the ACE2/ACE ratio in mice [115, 166].Therefore, any SARS-COV2 infected individuals must be monitored for diagnosis of new-onset diabetes in order to avoid its metabolic disturbance risk [150].Furthermore, the severe illness like SARS-COV2 causes the enhancement of the release of insulin counteracting hormones that promote the liver and kidneys gluconeogenesis along with impairment of tissue glucose metabolism that worsen the pre-existing hyperglycemia [167].

From other prospective hypokalemia is attributed to SARS-COV2 interaction with angiotensin II possibly induce aldosterone secretion thus retard the uptake of insulin by the cells thus the virus induction of RAAS will complicate the DKA condition as well as its management [168]. In addition, the SARS-COV2 caused ACE2 down regulation provokes the pro-inflammatory response as well as angiotensin 1 and angiotensin 2 beta-cells damaging effects that hinders insulin secretion [83, 169, 170].Thus, this infection decrease the cleavage of Ang II that precipitate the β-cells, insulin resistance and NHE stimulation that develop lactic acidosis on one hand. On other hand, the decline of the Ang 1-7 potentiates influence [139]. In fact, the activated NHE that is activated by SARS-COV2 interaction contribute to the establishment of acidic/hypoxic conditions to which reactive oxygen species that in turn also participate in the development of insulin-resistance and pancreatic damage [139, 158] on one hand. On other hand, the moncarboxylate transporter (MCT)system is induced to further activation of NHE through cellular internalization of the proton and lactate ions thus reduce extracellular lactic acidosis [147, 149, 171] which is with the co-existing diabetes deteriorate the SARS-COV2 infection conditions. Therefore, virus negative impact on NHE and lactate metabolism pathway [139]. Furthermore, diabetes besides other stress inducing conditions like infections provokes the hyperglycemia mediators, catecholemaine and glucocorticoids, release to the circulation that promote diabetes/diabetes related complications such as DKA or hyperosmolar hyperglycemic state (HHS) in the infected diabetic individuals [172, 173].

However, it is noteworthy that ACE2 cleaves angiotensin I into angiotensin 1-9 while, angiotensin II into angiotensin 1-7 the later one interact with the renal tissues to cause water and sodium excretion while induce the nitric oxide production to reduce the inflammatory response [174] thus ACE2 decrease the Ang II level [79, 150, 151,172, 173,175-177]. The other isomer of the enzyme, ACE1 cleaves Ang I to Ang II which enhances sodium and water retention through interaction with the angiotensin receptor 1 (ATR1) that induce their reabsorption by the kidneys while, inducing the inflammatory response along with giving rise to fibrosis via inclining the oxidative stress [178].

2.2. ACE2/Diabetes and Ketoacidosis in the Co-existing SARS-COV2 Infection

Both of the DKA and HHS are life-hazardous acute diabetes complications that occur individually or together, since HHS and hyperosmolar ketoacidosis are also developed in case of hyperglycemia [179], particularly in geriatrics type II diabetic patients [94, 180]. However, both of glucose indices as well as triglycerides are considered as standing markers of insulin resistance associated with hyperglycemic complications which are reported to be a SARS-COV2 infection illness severity as well as mortality predictors [79].Besides, the SARS-COV2 infection itself have been reported to exploit a diabetogenic influence that contributes to the overlapping deterioration of the glycemic control as well as triggered immune irregularity (cytokine storm) overwhelm the body metabolic defenses. Hence, contributing to further hyperglycemia as well as DKA complication induction that requires hospitalization of the co-existing diabetes, even induction of autoimmune insulin-deficiency dependent new-onset diabetes or even in the non-diabetic infected individuals [153, 177, 181, 182]. This happensprobably via development of the pancreatic tissue expressed viral antigen directed auto-immune antibodies [183] in agreement with the SARS-COV2 infection tropism necrotic acute pancreatitis reported by (Kumaran, et al., 2020) [184]that in turn contribute to DKA via inclining lipolysis/ketosis and new-onset diabetes [172, 185], particularly when exhibiting GIT symptoms [186], due to β-cells apoptosis [187]on one hand.On the other hand, DKA itself is considered as an inflammatory condition that is probably provoked by any existing acute illnesses including infections [188] as it elevates the level IL-6 inflammatory marker associated with abnormal, cytokines storm characterized, immune response associated with poor prognosis and elevation of the mortality rate. However, DKA is related to the elevated IL-6 level within the coarse of SARS-COV2 infection [91, 189] particularly among infected individuals with type I DM in Egypt [190, 191] due to the IL-6 as well as other inflammatory mediators elevation related insulinopenia, yet, this mechanism is still within emphasization [192]. While, from other prospective triggers the cytokine storm [193]. However, as previously mentioned DKA is a significant glycemic state uncontrolled predictors of poor prognosis and fatality particularly in type I DM, while, uncommon in type II DM [194, 195] which is further aggravated to by the viral infection or even its glucocorticoids therapy that is seldom reported [196, 197]. Interestingly, in England it is reported that type I DM causes 3.5 folds greater mortality rate while type II DM causes 2 folds greater mortality rate [198] and 1.4 folds in other study [44] among the hospitalized SARS-COV2 infected diabetic individuals [197] attributed to the HHS or DKA complications [199]. However, it seems that age plays a significant role in DKA caused mortality as reported by (Alkundi, et al., 2020) who exploited that older diabetic patient even without the development of DKA have greater mortality rate than young diabetic patients even when they develop DKA [176] which comes in agreement with the reported lower mortality rates/disease severity of this infections among pediatric diabetic

individuals [200-202].Although it is believed that DKA is also developed in cases of SARS-COV2 infections even among non-diabetic infected individuals [152, 173], thus, glycemic control state as well as anion gap monitoring is required [203]. Ultimately, SARS-COV2 infection is bounded to ACE2 receptor expressed in the pancreatic tissue beta-cells causing the receptor deficiency [204, 205, 206] that inclines the level of Ang II [83, 207]that impede the insulin secretion leading to insulin resistance related hyperglycemia [58, 161] as well as developing a new–onset type I DM, that deteriorate disease condition besides triggering ketoacidosis [38, 152, 153, 157, 175, 177, 208] via enhancement of lipolysis [173, 209] due to the decline of the insulin dependent antilipolytic effect developing DKA and HHS [210, 211, 212] as encountered with SARS-COV1 infection [213].Thus, during SARS-COV2 infection the insulin deficiency related decline of antilipolytic influence besides the steroids anti-inflammatory therapy related adverse metabolic behavior enhanced the insulin resistance related DKA among both diabetic and non-diabetic individuals as well as new-onset diabetes development [210]. In this context, in a multicenter study from United States 64 SARS-COV2 infected patients have exhibited hyperglycemia DKA complication [214].

In addition, the incidence of DKA with potassium level disturbance is closely linked to this virus infection [83, 204].In addition, the developed DKA associated hypokalemia is established by the hyperaldosteronism induced by the SARS-COV2 infection [202] which is aggravated by insulin therapy used to correct DKA metabolic disturbances [152]. Moreover, the thrombo-embolic SARS-COV2 severe condition complications is also provoked by the DKA induced hypercogagulation in those infected individuals [215] aggravated by the Ang II vasoconstriction/hypertension [83, 150, 155]. In addition, besides IL-6 level induce insulin resistance via SOSC pathway, it promotes the pancreatic tissues damage through tissue macrophages-mediated inflammation leading to β-cells apoptosis, amyloidosis as well as fibrosis [64, 215]. Hence, the elevation of IL-6 level along with HbA1c, within the coarse of infections can be considered as predictive factor to the DKA development potential [186, 187, 216, 217]. Consequently, it is potential to correct DKA through the correction of IL-6 level as a part of these severe illnesses therapy [218, 219]. Nevertheless, it is necessary to note that it is reported that the elevation of HbA1clevel in type II DM individuals is a predictive for the increased incidence of DKA as reported by (Hoffman, et al., 2003) who have demonstrated that ketosis incidence more than 10.1% among new-onset type II DM and more than 8.6% in patient with pre-existing diabetes [191].In this prospective, DKA is repeatedly reported in cases of SARS-COV viral infections particularly in those with pre-existing type II DM and infection established newly developed one [83, 220]. Although, both of viral infection and extensive immune response promoted insulin counter-regulatory hormones induction that brought about liver gluconeogenesis, insulinopenia, insulin resistance, lipolysis and ketogensis, they are common factors for DKA development in any disease conditions with both co-existing infection and abnormal immune response rather than being specific to SARS-COV2 infection [221-223]. It necessary to note that the SARS-COV2 infection related cytokine storm also enhances these peripheral hormonal (inclines glycogen/insulin ratio) as well as metabolic disturbances to bring about DKA [185]. Finally (Palermo, et al., 2020) have reported that the elevation of the pro-inflammatory cytokines including in first degree the IL-6 level as well as TNFα + IL-1ß in the second degree causes the elevation of the insulin counter-acting hormones including glucagon, catecholamines, cortisol and growth Hormone hence, provoking the hormones triglycerides catabolism sensitive pathways into fatty acids as well as fatty acids catabolism to ketone bodies, β-Hydroxybutyrate, Acetoacetate ketone bodies leading to metabolic ketoacidosis on one hand. On other hand, the same insulin-counteracting hormones stimulate the glycogenolysis as well as gluconeogenesis promotion that may lead to dehydration and electrolyte loss established by the hyperglycemia caused insulin-resistance due to the decline of the insulin release [91]. In addition the virus interaction with the RAAS is also indicated by reported the renal tissues tropism sufficiently expressing the ACE2 as well as the virus detection in urine [224, 225].

However, it is necessary to note that (Chee, et al., 2020) have reported one case of diabetic patient of SARS-COV2 infection that exhibits hyperglycemia of 39.7 mmol/L blood glucose level while seriously decreased bicarbonate level of 12 mmol/L along with marked acidosis with blood pH of 7.28 and ten folds incline of ketones level of 6.4 mmol/L that is resolved within one day IV insulin therapy [152, 226]. Consequently, in Asia [173] and Germany DKA is demonstrated to be increasingly incident among the hospitalized SARS-COV2 infected patient, however, the later shows elevation in the incidence among children and adolescence [225] beside the precipitation of new-onset type I DM [228].Thus, the reported SARS-COV2 infection association with DKA precipitation happens with a considerable ratio of patients whether they are of pre-existing diabetes, new-onset or with no diagnosed diabetes [228, 229]. In this perspective (Li, et al., 2020) have reported in their study that 37.5% of the SARS-COV2 infection who developed DKA are with pre-existing diabetes while the remaining 63.3% are of no previous diagnosis of diabetes [183] emphasizing that this viral infection precipitating DKA due to fats catabolism enhancement even without pre-existing diabetes [173] as it causes insulinopenia [91].However, high HbA1c% value along with low body mass index is a type I DM associated DKA development risk factors in young adults [230, 231], which in accordance with other SARS-COV2 studies that demonstrate that young patients with elevated rate of acute respiratory distress which requires mechanical ventilation and those with acute liver injury exhibit DKA complication hence, exacerbating the disease severity[173].It is noteworthy to know that lactate is one of the hepatic gluconeogenesis pathway substrates that exaggerates diabetes as

well as SARS-COV2 related hyperglycemia along with activation of NHE that brings about lactic acidosis. However, SARS-COV2 infection also contributes to additional mechanisms to lactic acidosis via β-cell damage/lysis, hypoxia which are all leads to the infection poor prognosis, deterioration of clinical outcomes [157, 232, 233].Authors and specialist hopes that the genetic investigation may explains the participation of insulin-resistance, cardiovascular and DKA co-morbidities in addition to, severe immune system/inflammatory response and hyper-coagulability as predictors for the SARS-COV2 infection incidence as well as severity [234].

2.3. Drugs Participation in the Development of DKA

The use of anti-inflammatory glucocorticoids therapy enhances the risk of DKA development in various acute rather than chronic hyperinflammatory conditions, as encountered in SARS-COV2 infection, particularly in case of pre-existing diabetes mostly in type II DM [195, 196, 235] since they potentiate the insulin resistance through multiply diverse pathways including the declining of GLUT4 transporters in the muscles, inclining lipolysis as well as proteolysis besides, promoting the release of glucagon and epinephrine, insulin counter-regulatory hormones [236, 237]. However, sodium-glucose cotransporter 2 (SGLT2) inhibitors are frequently associated with euglycemic diabetic ketoacidosis (eu-DKA) whether in cases of infections like SARS-COV2 infection or not such as in cases of surgery [238-240] which is sometimes unnoticed during pandemic infections because of the volume depletion along with the lack of diabetes associated hyperglycemia since SGLT2 inhibitors induces glycosuria [241-246].Thus, patients on SLGT2 inhibitors treatment due to insulin deficiency hyperglycemia, in cases of type II DM particularly in the co-existence of cardiovascular risk, requires mandatory continuous monitoring to urine ketone bodies [94, 95]. SLGT2 inhibitors including glifozins and empagliflozin are frequently recommended to be discontinued in case of SARS-COV2 infection and other flu-like severe infections due to the potentiality of development of eu-DKA and other ketoacidosis [241, 243, 245, 247]. In this context, (Koufakis, et al., 2020), has reported a case of eu-DKA development in a SARS-COV2 infection in an individual with type I DM on 25 mg empagliflozin four time daily [247].

In general SGLT inhibitors develop ketoacidosis via enhancement of carbohydrate urinary excretion, fatty acids liver delivery and elevation of glycogen blood level [248] leading to eu-DKA even in cases of no pronounced hyperglycemia although their eu-DKA is rarely reported [249] during clinical trials particularly empagliflozin used for type II DM with cardiovascular co-morbidity [250]. In agreement in Australia, a retrospective cohort analysis study has demonstrated that the use of SGLT2 inhibitors exploit development of DKA in 14.8% of diabetic users as compared to the non-users, 41% of them are of peak glucose level of less than 13.8 mmol/L (less than 250 mg/dL) [251]. However, (Mandal, et al., 2021) have reported that no remarkable pre-admission variation in DKA development among SARS-COV2 infected diabetic individuals who are on insulin, SGLT2 or other oral hypoglycemic agents, yet in the co-existence of body mass index less than 25.56 Kg/m^2,HbA1c more than 8.35% or IL-6 level greater than 50.95 pg/ml the DKA development due to the use of SGLT-2 inhibitors enhances [209]. In addition, this class of hypoglycemic agents may produce ketoacidosis at elevate, near-normal or normal glucose levels particularly in cases fasting, co-existing illnesses like infections, pancreatitis, cardiovascular illnesses, surgical stress insulin deficiency [252].Furthermore, SGLT2 inhibitors as well as insulin may induce lactic acidosis even accompanying euglycemia condition therefore, they are reported to be avoided in diabetic individuals with moderate-severe cases of SARS-COV2 infection [38, 46, 91,253-256] particularly Omicron (B. 1.1. 529) mutation strain, thus, requires high precaution of their use due to dehydration [257], although cardiovascular as well as cardio-renal protection advantages are lost [258].However, they are reported to enhance ACE2 receptor expression in different tissues [163].Dapagliflozin, a gliflozin chemical class of SGLT2 inhibitors has an exclusive lactate level declining influence from circulations and tissues [139, 259]via inhibition of NHE activity [260] while lactate/H^+ symporter activity still introduce the lactate intracellulary [146, 147], increase renal excretion of lactate [143], activated aerobic glucose metabolism via declining oxygen tissue consuming that further reduces lactate level to restore the normal intracellular pH [139, 143], which are all maintain cellular integrity [139]. Hence, due to former mechanism dapagliflozin exhibits cardiovascular protective influence as it prevent epicardiac tissue lactate release [261]. Nevertheless, some have emphasized that dapagliflozinmay prevent SARS-COV2 infection as well as disease severity specially in diabetic mechanism one of which reducing the intracellular pH via inducing lactate dehydrogenase LDH enzyme activation although it elevate ACE2 expression while counteract the viral infection related cytokine storm in diabetic individuals [139, 261, 262].It is worthy to note that insulin also enhances NHE thus reduces intracellular pH along with reduction of the ACE2 expression [261] thus can be used to replace SGLT2 inhibitors [263]. Therefore, insulin anddapagliflozin along with good patient hydration is an elegant combination for the treatment of diabetic individual infected with SARS-COV2 to reduce mortality rate as dapagliflozin has the lowest potential among its class to develop the eu-DKA [261]. Interestingly, some have recommended extensive rehydration along with potassium blood level monitoring during the use of insulin therapy of DKA [264]. In contrast, using metformin as well asdapagliflozin should be avoided as they may precipitate lactic acidosis as well as eu-DKA [257, 261, 263, 265, 266],although, several authors have reported that metformin pre- and post-hospitalization therapy has associated with lower mortality risk/benefit among type II DM infected diabetic individuals[267-273], besides, SARS-COV2 infection

counteracting ACE2 receptor expression enhancement as well as anti-inflammatory influence [274]. Metformin has immunomodulatory/anti-inflammatory influence via declining TNFα and IL-6 levels that is also elevated in case of DKA besides the SARS-COV2 infection [186] while elevating IL-10 level [266, 275-277], antioxidant activity, and antiviral potentiality. Hence, explaining its cardiovascular-pulmonary protection in SARS-COV2 infected patients as well as its superiority over insulin in reducing the viral infection disease severity and mortality rate [278]. Besides, declining neutrophils extracellular traps as well as neutrophil to lymphocyte count [279], in addition to prohibiting the viral replication/protein production blocking effect via blocking the mTOR pathway which is crucial for apoptosis as well as senescence [265].

Other have reported that advantage of usingDPP-4 inhibitors alone or in combination with insulin therapy particularly for obese infected diabetic individuals [280]. Moreover, paracetamol extensive use toxicity for SARS-COV2 infection fever potentially induces metabolic acidosis due to the accumulation of the acidic substance, 5-oxoproline [261, 281] causing high anion gap [282]. In case of pregnancy, the eu-DKA is frequently encountered as the glucose level tends to be lowered under the burden of pregnancy awing to the feto-placental uptake along with the decline of glycogenolysis as well as liver gluconeogenesis [283] although, in the third trimester of pregnancy, starvation ketoacidosis is also rarely reported due fasting [126, 284, 285]. Finally, eu-DKA is associated with high anion gap, ketosis along with normoglycemic condition. Furthermore, insulin therapy itself may participate in DKA precipitation due to therapy disturbance as well as poor blood glucose monitoring particularly those newly diagnosed with type I DM [119, 286], however, DKA is developed while shifting from IV insulin infusion to the subcutaneous one [91].

3. Diagnosis and Treatment of DKA Complication of SARS-COV2 Infection

Diabetic ketoacidosis characterized by urine glucose level of greater than 3 mmol/L with characteristic (++) level in the urine, acidosis with blood hyperglycemia of blood glucose level less than 800 mg/dL (greater than 10 mmol/L) pH less than 7.3 along with low bicarbonate level below 10 mmol/L and anion gap greater than 12 mEq/L [126] elevated HbA1c level [225]. However, some have reported that the serum bicarbonate level may eual or less than 15 mmol/L [287]. It is necessary to measure the blood ketone bodies in type I DM infected patients at blood glucose level greater than 15 mmol/L every 1-2 hrs with necessity of increasing the insulin dose to avoid the development of DKA [13]. In Europe a case of DKA has been reported in a hospitalized type I DM 31 years old male SARS-COV2 infected individuals who has expressed elevated glucose level (23.7 mmol/L) and ketone bodies (5.2 mmol/L) along with low blood pH of 7.2[288].Another SARS-COV2 associated DKA hospitalized case from USA however with no diabetesis pre-existance has expressed hyperglycemia of 463 mg/dL blood glucose level, blood glucose level of greater than 160 mg/dL while normal LDH as well as coagulopathy predictor d-dimer [174].A third hospitalized SARS-COV2 infection case of 23 years old male form Iran with no previously diagnosed type I DM who develops DKA has expressed hyperglycemia of 449 mg/dL blood glucose level, HbAlc of 12.2%, while, declined blood bicarbonate level of 22.6 mmol/L, blood pH (7.3) and anion gap of 13 mEq/L, however, it is diagnosed as SARS-COV2 associated autoimmune stage 2 type I DM [289]. Thus blood glucose, bicarbonate, ketone bodies level as well as pH must be monitored at admission and while therapy [288].

Unfortunately, DKA complication is a severe metabolic imbalance SARS-COV2 complication which is reported to be un-related to the severity of lung injury [116] that makes the therapeutic strategy particularly those admitted to the ICU is an uneasy task [290, 291], for instance (Li, et al., 2020) have reported three adult patients SARS-COV2 infection with DKA [172].Thus, any infected patient whether diabetic or non-diabetic presenting symptoms of DKA [172, 209, 292] including eu-DKA [220] due to endocrinal dysfunction [293] must be investigated for SARS-COV2 infection[160, 172,294, 295] particularly in children with type I DM even of virus induced new-onset [79, 296-300]estimated to be in certain reports as 5.7% [79, 180, 301] and as reported in UK in other reports [80] as well as in adult as globally reported [302],while, (Chao, et al., 2021) has reported its development of SARS-COV2 infection established type II DM in pediatrics [303].In addition to its investigation in patients with pre-existing diabetes as there is a bidirectional disease-disease interaction between diabetes and SARS-COV2 infection since both have tendency of potential developing DKA as well as HHS complications [21, 151, 172, 251, 304, 305, 306] since both cause insulin release impairment [151, 172]. Despite, the existence of SARS-COV2 infection DKA causes patient hospitalization in USA although the rate of hospitalization as well as mortality [79], the infection has been reported to incline the prevalence as well as severity of DKA that requires hospitalization [307].

However, in general, DKA is treated with insulin, intensive fluid rehydration therapy [91, 138, 193, 288, 308] as reported by the American diabetes association [309], which is similarly used for SARS-COV2 associated DKA. Besides, electrolytes disturbance correction is also required involving correction of hypokalemia, hypokalemia and hypomagnesemia [91, 289] according to the patient condition [310]. Route of insulin administration and type used is dependent of DKA severity. In general the insulin dose used for DKA complication during the course of SARS-COV2 infection requires higher dose than ordinarily used dose particularly in critically SARS-COV2 infection ill patients [39].It is reported that

subcutaneous rapid/short-acting insulin therapy (a dose every 4-6 hr other reported every 3-4 hrs) with diabetic diet is just enough for the mild to moderate uncomplicated cases of SARS-COV2 infection accompanying DKA condition [39, 91, 174, 207, 311] in a dosing frequency every 1-2 hrs along with increasing of insulin dose, particularly in case of glucose level above 15 mmol/L [13], without co-existence of kidney impairment or cardiovascular co-morbidity [99, 193]. Nevertheless, some have reported the inferiority of IV insulin infusion over the subcutaneous one [308, 312] particularly in critically ill SARS-COV2 patient [91, 309]while no difference between them in mild case [91] on one hand. On the other hand, insulin dose varies from one SARS-COV2 infected patient with DKA complication to another according to the condition severity and blood glucose level, besides, requires less continuous glucose level monitoring but it may reduce the intensive care unit admission [91]. However, in severe cases of DKA continuous IV insulin is required in a dose of 4 units/Kg/day along with potassium ion and glucose blood levels continuous monitoring [91, 207] particularly in case of co-existence of other morbidity like renal impairments [39] for at least 4 days before starting subcutaneous insulin. In a case of Irena SARS-COV2 infection DKA complication in an un-diagnosed type I DM is treated with IV insulin infusion in a dose of 0.1 unit/Kg/hr in a half saline solution [310] which is an inclined dose over the ordinarily recommended dose of DKA in the absence of infection [195]. In severe case of DKA, HHS or DKA-HHS co-existing conditions requires continuous IV infusion at a dose of 0.1 unit/Kg/hr with glycemic state monitoring 1-2 hr [32].However, long acting insulin should be used beside IV insulin infusion in order to avoid IV insulin associated rebound hyperglycemia [192, 313] since the targeted treatment blood glucose level is within the range of 140-180 mg/dL [32].Therefore, high insulin doses are required for treatment of DKA and HHS [151]. However, one of the drawbacks of IV insulin therapy is the overdose hypoglycemia and reflex hypokalemia [255, 314]. Some institutions have recommended the monitoring of blood glucose [39] every 4 to 6 hrs or every 2 to 4 hrs as others reported in case of continuous stable rate IV insulin infusion in addition, hourly IV insulin flow rate adjustment along with continuous glucose fluid infusion [91, 310, 315-317]. Nevertheless, despite that insulin has beneficial anti-inflammatory potential [288], it is also associated with enhancing airway reactivity as well as resistance [314]. However, co-administration of vasopressors as well as corticosteroids to the severely ill patients may reduce insulin sensitivity which requires dose adjustment [39, 91, 318].It is necessary to note that insulin therapy may actually cause hypokalemia causing respiratory muscles functions weakness since it promotes uptake of potassium ion intracellularly thus requires potassium ion monitoring or even replacement therapy [91, 319, 320]. In addition, bicarbonate administration is required to treat severe, life-threatening metabolic acidosis at blood pH less than 6.9 [91]. Furthermore, molecular heparin is used to manage DKA related coagulopathy in cases of SARS-COV2 infections [321, 322].

Moreover, SARS-COV2 developed DKA induced fluids as well as electrolytes modifications triggered via the RAAS provoking, bringing about inclined mortality rate, hence, enhances the infected individuals that is considered additional management challenge that requires painstaking replenishment [64, 91, 227].Therefore, fluid replenishment is the second approach to manage DKA [323], however, the challenge of extravasation of these fluid to the pulmonary tissues leading to acute respiratory distress and hypoxia with quick respiratory functions deterioration [207, 309, 324]. DKA patients with hyperglycemic crisis requires fluid replacement as it causes marked dehydration due to dieresis using conservative isotonic 0.9% sodium chloride solution although it causes prolongation and deterioration of ketonemia condition, despite the lung protection objective [91, 96, 325]. According to UK guidelines established by the national inpatients diabetes COVID-19 response group using 250 ml of fluids each 15 minutes according to patient's body weight and his blood pH [91], yet, much intensive fluid replenishment rate is required for much severe cases than mild one with blood pH less than 7.1 [96, 325].In addition, the selection of sodium or glucose solution as well as this their concentration depends on patient biochemical measurements [91].The treatment of eu-DKA is basically resembles that DKA, hence, similarly, the treatment of eu-DKAdue to SGLT2 inhibitors therapy is basically dependent on fluid replacement therapy that may extend to a long time besides, it may requires to correct the glycosuria induced hypoglycemia [304, 326] using dextrose solution as the primary step of treatment which probably takes several days [325]. Thus, SGLT2 inhibitors should be discontinued during SARS-COV2 infection coarse regardless of insulin use/regimen [38, 91, 237, 238, 239,314] as it causes ketonemia in type II DM that requires 35 hrs in diabetic patients [213] while 12 hrs in non-diabetic ones to be resolved with therapy [99] which may extend to 24 hrs in case of SARS-COV infection co-existence [210]. In addition, the reduction of blood glucose as well as ketones has a beneficial influence on both prothrombin time [151].

4. Prevalence of DKA complication in SARS-COV2 infection:

A reterospective study in USA including 1122 SARS-COV2 infected hospitalized patient from 88 hospitals with admission uncontrolled hyperglycemia or diabetes co-morbidity is associated with greater fatalities [327, 328, 329] besides, being contributor to the deterioration of the radiological findings [330]. Nevertheless, as earlier stated, the SARS-COV2 infection has a sophisticated multidirectional interaction with diabetes [78] especially if the infection is exploited with the GI symptom [331]. Interestingly, (Parasa, et al, 2020) have reported that 30-50% of the infected patients have SARS-COV2 infection positive rectal swabs [332].The incidence of SARS-COV2 infection DKA complication

is highly prevalent among hospitalized patients [64, 172]. In this context, (Cavalcanti, et al., 2020) have reported a SARS-COV2 infection related DKA complication with subcortical hemorrhage in a 23 years old [333] on one hand. On the other hand, (Heaney, et al., 2020) have reported a case of DKA complication of SARS-COV2 infection induced new-onset diabetes complication in a 57 years old male [174]. A third case study have reported 37 years old male exhibiting SARS-COV2 infection with GIT symptoms with DKA complication of 30 mmol/L anion gap, low bicarbonate level of 12 mmol/L, low pH of 7.28 while high level of ketone bodies of 6.4 mmol/L and HbA1c of 14.2% [151].In fact, DKA complication of SARS-COV2 may be developed even without diabetes comorbidity. In agreement, (Li, et al., 2020) have reported that 6.4% of 658 hospitalized SARS-COV2 patients admitted with ketosis, however, 64.3% of the DKA suffering patients are non-diabetic while 35.7% of them are with diabetes co-morbidity, yet, DKA has associated with 21.4% of the mortalities [172]. Furthermore, (Pal, et al., 2020) have reported a meta-analysis from 19 case studies that have involved 110 cases which demonstrated that SARS-COV2 infection among diabetic individuals brings about DKA or HHS, actually 77% of them for the first time [64]. In addition, a Chinese retrospective study have demonstrated that 6.4% of the infected SARS-COV2 have developed ketosis although only 35.7% with diabetes comorbidity as well as 39% mortality rate [334].In USA it is reported that the prevelance of DKA complication of SARS-COV2 infection is 45.5% among the infected type I DM from multicenters [241, 288].

Furthermore, case studies have also reported association of DKA complication of SARS-COV2 infection with pre-existing undiagnosed type II DM diabetes [166, 305, 335] and diagnosed one [171, 172, 336]. It is reported that the primary cause of SARS-COV2 infection complication is DKA in India [337]. It is reported that DKA complication is the primary cause of type I DM SARS-COV2 infected individuals hospitalization [300, 338].SARS-COV2 infection associated DKA in elderlies, as it is associated with poor therapy responsiveness [227, 339] with unusual symptoms presentation [151].In this context, (Pasquel, et al., 2020) have reported that 74% of SARS-COV2 infection are above 45 years, yet, in non infected DKA patient has low mortality rate of 3-8% [64].While, in a small number small size SARS-COV2 associated DKA mortality rate approaches ranges from 7.5% to 12.9 to 50%mortality rate [175, 210, 227, 340] which is characteristically higher rate [287] although (Beliard, et al,2021) have reported no difference in the prevalence of DKA among diabetic and non-diabetic infected individuals [300]. Outside China (Croft, et al., 2020) have reported five novel cases of DKA complication due SARS-COV2 infection among type II DM infected individuals with an extraordinary severity [335].

Moreover, it is reported that SARS-COV2 infection can trigger acute DKA/HHS in diabetic individuals of poor glycemic control [91, 305]. However, (Armeni et al, 2020) has reported 2 cases of HHS while 13 cases of mixed DKA/HHS [210]. Consequently in (Gou, et al, 2020) study 8% of the SARS-COV2 infected dianetic individuals have developed DKA while, 50% of them died [37] which is reported to be potentially DKA or mixed DKA/HHS [64, 120]. Remarkably, (Pal, et al., 2020) have also reported 110 DKA developing SARS-COV2 infected diabetic patients (77% with type II DM), of them DKA alone expressing cases constitute 83% while DKA and HHS expressing cases constitute 17%. In addition, 50% mortality rate among the SARS-COV2 infected individuals and postulated that the mortality rate among DKA/HHS combination (69%) is greater than DKA individual complication (29%) as the combined DKA/HHS constitute 20% of the DKA attributed SARS-COV2 fatalities [64] which agrees with (Pasquel, et al., 2020) speculation [341].

In a Chinese study of 658 hospitalized individual spacemen, 6.4% of them have exhibited ketosis on admission, yet, only 15 of them are diabetic while 3 of them diagnosed as DKA (2 of them with type I DM and 1 of type I DM), while, 7 of them (3%) are based on the urine and blood diagnosed ketosis [172]. In a case study (Chekhlabi, et al., 2021) have reported a child with SARS-COV2 infection who has hospitalized with DKA and treated with IV insulin with IV fluids replenishment then followed by Sc insulin [302] on one hand. On other hand, (Meza, et al., 2020) have reported four cases of SARS-COV2 infections of acute DKA with secondary viral and bacterial infections of poor clinical prognosis [116].Interestingly, (Eskandarani and Sawan, 2020) have reported while the flera of SARS-COV2 infection in Riyadh city, Saudi Arabia a surge of DKA have been encountered in even non-diabetic infected individuals [182]. In contrast, (Alkundi et al, 2020) have emphasized that DKA exploiting SARS-COV2 infected patients are of better survival than non-DKA exploiting ones in UK [175]. However, in USA case studies have reported 50% mortality rate of SARS-COV2 infection DKA complication [227]. Interestingly, in Germany within the first two month of SARS-COV2 infection outbreak 44.74% of 532 infected individuals are pediatrics and those in the age of adolescence with new-onset type I DM exploiting DKA complication which is greater than that prior infection outbreak, yet, 19.4% of the DKA cases are of high severity [225]. In addition, a multicenter study in UK has demonstrated that 70% of the type I DM infected pediatric patients have DKA complications of which 50% are of severe symptoms [80]. However, in UK the infected SARS-COV2 children exhibited DKA complication in 51% of the cases reported by the UK Association of Children's Diabetes Clinicians [342]. Moreover,(Unsworth, et al., 2020), have reported that SARS-COV2 infection have inclined the development new-onset type I DM as well as DKA among 80% of those newly diagnosed diabetic children [80]. In Italy, a study from multiple centers to evaluate the prevalence as well as severity from 68 children diabetic centers has demonstrated higher prevalence frequency and severity in 2020 as compared to 2019 despite 23% reduction in the

prevalence of type I DM among children [343]. Nevertheless, it is reported that during the flera of SARS-COV2 in 2020 there has been 12% greater prevalence of DKA among children in Poland with greater severity [297].

From other perspective, DKA complication is also reported to be developed in case of SARS-COV2 infection with neither insulin-resistance existence, nor, auto antibodies even 5-7 weeks prior the viral infection [151, 226] although their blood glucose greater than 11.1 mmol/L while HbA1c less than 6.5% [344], since the prevalence of new-onset diabetes is reported to be from 5.5% to 27.5% [344, 345]. Consequently, (Armeni, et al., 2020) have reported that two cases of new-onset diabetes in SARS-COV2 infected individuals in UK among 35 cases while nine cases [210], while, (Li, et al., 2020) have reported cases of new-onset SARS-COV2 infection caused diabetes from China [345]. A third study from UK have reported that 1.8% of the hospitalized infected diabetic individuals exhibited DKA complication, 75% of them are of pre-existing diabetes, 25% are newly diagnosed ones, while, 2% of the total cases are due to glucocorticodes [339].

However, SARS-COV2 infection in type II DM individual has exhibited DKA [151, 171, 174] in 25% of them in cohort studies [346, 347] on one hand. On other hand, fatal case have reported to be associated with 6.4% of the SARS-COV2 infection with DKA complication in type II DM patients (20%) in a Korean study besides association with HHS cases of delayed curing [171]. While, in three hospitals in UK, the SARS-COV2 hospitalized patients have demonstrated that 31.4% of admitted with DKA, 7.5% admitted with HHS, 37.1% admitted with DKA/HHS accompanied complication two of them have died and 25.7% with hyperglycemic ketosis, yet, 80% of them are with co-existent type II DM while, 5.7% with type I DM [210].In fact in USA the prevalence of DKA among the infected type I diabetic children as well as adults from 52 clinical sites is reported to be more prevalent among non-hispanic block patients [348].Remarkably, SARS-COV2 vaccination have also gives rise to the development of DKA as well as HHS particularly among diabetic individuals, consequently one case has been reported in this regard [349, 350]. However, some have reported that the prevalence of DKA development by the SARS-COV2 infected type II DM diabetic individuals is 75-90% while few cases are of new-onset diabetes [64, 172]. Other USA retrospective study has reported that 6 cases of the hospitalized ICU admitted SARS-COV2 infection have exploited DKA and HHS complication mainly rather than the classical infection manifestations with 67% mortality rate, yet, one of them of no previously diagnosed diabetes and 5 cases with type II DM co-morbidity [137].

Table 1 Retrospective and cohort reporting DKA complication in SARS-COV2 infected patients

Type of the study	Size of the study	Age group	Co-existing of diabetes	Number of patients with DKA	% of DKA	No. of DKA mortality	Ref.
Retrospective cross-sectional	87	Geriatrics	Yes	8	9.2%	-----	[175]
Retrospective cross cohort	129	Geriatrics	Yes	15 DKA 3 DKA/lactic acidosis	11.63%	1 died	[172]
Retrospective	218	Adults and geriatrics	Yes	4	1.83%	----	[339]
Retrospective	5	Adult and geriatrics	Yes (one of them newly-diagnosed)	5	100%	1 Died	[166]
Retrospective	12	Adult and geriatrics	Yes (3 type II DM and 9 type I DM) 486 mg/dL	11	100%	1 died	[210]
Retrospective	50	Adult and geriatrics	Yes (6 type I DM, 44 type II DM of then 8 new-onset) 506 mg/dL	50	100% 2 of them Eu-DKA due to SLGT2 inhibitor	50% died	[227]

Retrospective	6	Adult	Yes (5 type II DM and 1 new-onset) 1041 mg/dL	6	100%	4 died	[137]
Retrospective	4	Adult and geriatrics	Yes (type II DM) 399 mg/dL HbA1c = 11.3%	4	100%	1 died (25%)	[335]
Two case reports	2	Geriatrics	Yes (type II DM) 1084 mg/dL HbA1c = 9.8	2	100%	---	[375]
Retrospective cohort	56	Adult	Yes (44 type I DM, 11 new-onset)	56	100%	4 died	[348]
Retrospective	4	Adult and geriatrics	Yes (3 type I DM and 1 new-onset) 378 mg/dL HbA1c = 10.8%	4 (1 use SLGT2 inhibitors)	100%	2 died (50%)	[339]
Retrospective	5	Geriatrics	Yes (3 type I DM and type II DM) 587 mg/dL HbA1c = 8.9%	5 (1 use SLG2 inhibitors)	100%	1 died (20%)	[331]
Retrospective	2	pediatrics	Yes (new-onset)	2	100%	----	[356]
Retrospective	2	Young adults	Yes (new-onset) 518 mg/dL HbA1c = 10.9%	2	100%	---	[358]
Retrospective	2	Geriatrics	Yes (type II DM) 672 mg/dL HbA1c = 12	2	100%	1 died (50%)	[171]
Retrospective	3	adults	Yes (new-onset) 582 mg/dL HbA1c = 12%	3	100%	---	[362]
Retrospective	3	adults	Yes (type II DM) 382 mg/dL	3	100%	2 died	[172]
Retrospective	26	Geriatrics	Yes (type II DM)	26	100%	3 died	[208]

Retrospective	2	Adult	Yes (type II DM, new-onset) 395 mg/dL HbA1c = 10%	2 one of them eu-DKA and used SGLT2	100%	---	[91]
Retrospective	212	Geriatrics	523 mg/dL HbA1c = 11.3	---	100%	64 died	[387]
Retrospective	2	Adult	Yes (type II DM, new-onset) 77.4 mg/dL	---	100%	---	[122]
Retrospective	4	Adult and geriatrics	New-onset 740 mg/dL	---	100%	---	[388]
Retrospective	3	Adult	New-onset 679 mg/dL HbA1c = 4.5%	---	100%	---	[389]
Retrospective	5	Geriatrics	Yes (new-onset) 538 mg/dL HbA1c = 5.9%	---	100%	---	[389]
Retrospective	7	Adult	Yes (6 type II DM, new-onset)	---	100%	1 died	[391]
Retrospective	2	Adult	Yes (type II DM, new-onset) 568 mg/dL HbA1c = 11.1%	---	100%	---	[305]
Retrospective	5	Young adult	Yes (2 type I DM, 3 new onset) 425 mg/dL HbA1c = 13.1%	---	100%	---	[368]
Retrospective	8	Adult	Yes (type I DM, 5 type II DM, new-onset) 454 mg/dL HbA1c = 11.4%	---	100%	3 died	[393]
Retrospective, cohort	157	Geriatric	Yes (156 type II DM, type I DM) >250 mg/dL HbA1c = 10.7%	---	100%	58 died	[396]

Retrospective	3	Adult	Yes (new-onset) 496 mg/dL HbA1c = 11.4%	---	100%	---	[180]
Retrospective	11	Adult and geriatrics	Yes (8 type II DM, Type I DM, 2 new-onset)	One case of eu-DKA One use SGLT2	100%	7 died	[392]
Retrospective	4	Adult	Yes (new-onset)	---	100%	---	[397]
Retrospective	20	---	Yes (5 type I DM, 15 type II DM)	465 mg/dL	100%	---	[399]
Retrospective	4	Mostly geriatrics	Yes (1 new-onset, 3 unknown type)	740 mg/dL HbA1c = 14.3%	100%	2 died	[401]

Table 2 Case studies and reports reporting DKA complication in SARS-COV2 infected patients

Number of case subjects	Gender of the subject	Age group (years)	Co-existing of diabetes	Blood glucose and HbA1c	Blood pH	Blood/urine ketones	HCO_3 level	Fate	Ref.
1	Male	23	Yes	1,384 mg/dL	7	----	----	----	[333]
1	Male	37	Yes (new-onset)	HbA1c = 14.2%	7.28	6.4 mmol/L	----	----	[151]
1	Male	57	Yes (new-onset)	436 mg/dL	7.193	>160 mg/dL (urine)	---	---	[174]
1	Male	59	Yes	655 mg/dL HbA1c = 11.4%	----	4.9 mmol/L	---	---	[171]
1	Male	52	Yes (type I DM)	250-270 mg/Dl HbA1c = 6.5%	7.48	A case of eu-DKA	----	----	[306]
2	Male	45	Yes (new-onset)	599 mg/dL HbA1c = 12.6%	7.18	----	----	----	[91]
	Female	53	Yes	151 mg/dL HbA1c = 7.5%	7.41	----	----	----	
2	Male	30	Yes (new-onset)	555 mg/dL HbA1c = 9.6%	7.07	+ urine ketones	-----	-----	[305]

	Male	60	Yes (new-onset)	582 mg/dL HbA1c = 12.6%	7.3	+ urine ketones	----	----	
2	Male	7	Yes (new-onset) type I DM	423 mg/dL HbA1c = 10.3%	---	+ urine ketones	----	----	[302]
	Female	4	Yes (new-onset) type I DM	390 mg/dL HbA1c = 11.8%	---	+ urine ketones	----	----	
1	Female	7	Yes (new-onset)	555 mg/dL HbA1c = 10.3%	7.1	---	10 mmol/L	----	[363]
1	Male	17	Yes (new-onset)	566 mg/dL HbA1c = 14.7%	6.8	---	---	---	[371]
1	Male	53	Yes (new-onset)	295.2 mg/dL HbA1c = 6.9%	6.83	---	5 mmol/L	Died	[372]
1	Male	1.3	Yes (new-onset)	805 mg/dL HbA1c = 9.5%	7.0	---	4 mmol/L	---	[364]
1	Male	46	Yes (new-onset)	657 mg/dL HbA1c = 13.5%	7.4	---	29 mmol/L	Died	[373]
1	Female	41	Yes (type II DM)	500 mg/dL	7.29	---	20 mmol/L	died	[373]
1	Female	21	----	84.6 mg/dL	7.34	----	8.7 mmol/L	---	[398]
1	Male	56	Yes (type II DM)	118 mg/dL	7.2	A case of eu-DKA due to SLGT2	7.8 mmol/L	---	[236]
1	Male	23	Yes (new-onset)	1384 mg/dL	7.0	----	----	died	[333]
1	Male	37	Yes (new-onset)	715 mg/dL HbA1c = 14.2%	7.28	----	12 mmol/L	---	[151]
1	Female	15	Yes (new-onset)	414 mg/dL HbA1c = 13.5%	6.9	---	2 mmol/L	---	[292]
1	Male	51	Yes (type II DM)	592 mg/dL HbA1c = 7.8%	7.0	---	---	---	[376]
1	Male	60	Yes (new onset)	540 mg /dL HbA1c = 5.1%	7.2	---	13 mmol/L	---	[377]

1	Female	46	Yes (type I DM)	590 mg/dL	---	---	---	---	[378]
1	Male	19	Yes (new-onset)	552 mg/dL HbA1c = 16.8%	7.1	---	---	---	[226]
1	Male	36	Yes (new-onset)	500 mg/dL	7.0	---	11 mmol/L	---	[379]
1	Male	54	Yes (new-onset)	463 mg/dL	7.19	---	9.9 mmol/L	---	[174]
1	Female	33	Yes (new-onset)	638 mg/dL HbA1c = 15.7	6.74	---	4.8 mmol/L	---	[191]
1	Male	54	Yes (type I DM)	1100 mg/dL	6.79	---	4 mmol/L	---	[380]
1	male	43	Yes (type II DM)	948 mg/dL	6.96	---	---	Died	[381]
1	Female	52	Yes (new-onset)	1114 mg/dL HbA1c = 17.4%	7.25	---	---	---	[382]
1	Female	28	Yes (type I DM)	401mg/dL 12.9%	7.0	---	3.2 mmol/L	----	[383]
1	Female	8	Yes (now-onset)	429 mg/dL HbAc1 = 12.0%	7.3	----	14 mmol/L	----	[365]
1	Male	7	Yes (new-onset)	470 mg/dL HbA1c = 14.8%	7.01	---	3.5 mmol/L	---	[366]
1	Female	45	Yes (type I DM)	344 mg/dL HbA1c = 13.7%	7.22	---	13 mmol/L	---	[384]
1	Male	52	Yes (type I DM)	270 mg/dL HbA1c = 7.4%	7.25	Eu-DKA Use SLGT2 inhibitor	19 mmol/L	----	[306]
1	Female	42	Yes (type II DM)	196 mg/dL	7.08	Eu-DKA Use SGLT2 inhibitor	----	----	[246]
1	Male	59	Yes (type II DM)	387 mg/dL HbA1c= 11.3	7.25	---	19 mmol/L	---	[385]
1	Male	51	Yes (type II DM)	369 mg/dL	7.22	---	9.3 mmol/L	1 died	[386]
1	Male	31	Yes (new-onset)	427 mg/dL	7.25	---	8 mmol/L	---	[288]
1	Male	16	Yes (new-onset)	512 mg/dL HbA1c = 12.9%	6.95	---	8 mmol/L	---	[367]

1	Male	24	Yes (new-onset)	507 mg/dL HbA1c = 15.8%	7.16	---	2 mmol/L	1 died	[394]
1	Female	36	Yes (gestational diabetes)	111 mg/dL HbA1c = 6.1%	7.22	---	5.8 mmol/L	---	[359]
1	----	0.7	Yes (New-onset)	571 mg/dL HbA1c = 8.5%	7.08	---	7 mmolo/L	---	[369]
1	Male	40	Yes (type I DM)	328 mg/dL HbA1c = 11.5%	---	---	18 mmol/L	---	[395]
1	Male	16	Yes (type I DM)	687 mg/dL HbA1c = 13.5%	6.77	---	3 mmole/L	---	[370]
1	Male	55	Yes (type II DM)	525 mg/dL	7.11	---	8 mmol/L	---	[400]

Furthermore, remarkably the mortality rate SARS-COV2 infection HHS complication is 5-16% which approximately 10 folds greater than that of the associated DKA [351-353] as well as enhance the infection susceptibility [354]. In addition, the gender has influence on the prevalence rate of DKA among SARS-COV2 infected individuals, (Alhumaid, et al., 2021), have reported that SARS-COV2 have greater tendency of developing DKA among infected males [81]. In agreement, (Ehrmann, et al., 2020) who have reported higher prevalence of DKA complication in 67% of the infected males [355] as well as deteriorating the SARS-COV2 outcomes [356]. In fact, it is earlierly reported as a risk factor before the outbreak of SARS-COV epidemics [357]. However, several other reports have postulated equivalent tendency between the two genders [91, 171, 354, 358]. Remarkably, two cases of pregnancy associated eu-DKA complication accompanying SARS-COV2 infection in a normoglycemic condition [359, 360] as pregnancy is a well know diabetogenic condition associated with insulin-resistance and related to 8.9% of DKA complication as compared to the non-pregnant ones (3.1%) [123]. However, some type II DM treatment hypoglycemic agents such as SGLT2 inhibitors are associated with 0.016-0.076% of the patients [38, 244, 361] thus they should be withdrawn as the initial symptoms of SARS-COV2 infection started and switched to insulin [255]. However, DKA complication development in SARS-COV2 infected diabetic patients of new-onset type II DM diabetes who are of good glycemic control upon using DPP-4 inhibitor and metformin combination [362].

In general huge number of studies, retrospective, cohort and case studies are reported from different countries; USA, UK, Saudi Arabia, Qatar, Egypt, France, Netherland, Belgium, Germany, India, China, Korea, Japan, Singapore, Indonesia, Turkey, Brazil, Peru, Maldives. However, some have reported DKA complication among SARS-COV2 infected children [292, 356, 358, 363-370], adults, pediatrics and adults [91, 122, 137, 151, 166, 171, 172, 174, 180, 191, 208, 210, 226, 227, 236, 246, 288, 305, 306, 331, 333, 335, 339, 359, 362, 371-401]. Some are reported case studies [166, 208, 210, 331, 390, 391-393, 397, 399,] of which are from Arabian countries [166, 363, 369, 371-373, 376], and multi-center studies [210, 348, 387, 396]. The reported retrospective, cohort and multicentered studies are listed in table (1) however, the case studies and series in table (2).

As has been formerly listed in the table (2) there are seven case studies of development of DKA complications in the SARS-COV2 infected pediatrics [302, 363-366, 369] and four retrospective studies [356] in both types of diabetes in table (1), all of them accompanied with new-onset diabetes mostly type I DM [227, 302, 331, 339]. In addition, to listing two case studies of eu-DKA associated with SGLT-2 inhibitors hypoglycemic agent therapy utilization in males with type I DM [306] and type II DM [236] in table (2) while one male case of eu-DKA complication in SARS-COV2 infected adults accompanied with type II DM on SGLT-2 inhibitors treatment [91]. In general, in most reported cases, the eu-DKA complications of the SARS-COV2 infection are associated with gastrointestinal symptoms of the infection [359].

5. Conclusion

Diabetic ketoacidosis as well as other type of ketosis type complications such as eu-DKA and HHS are thoroughly investigated and reported in SARS-COV2 infection cases in different age group, gender and from different countries. In most of the studies DKA is reported to happens in diabetic individuals, of both types (I and II DM), whether the diabetic state is diagnosed before acquiring the viral infection or developed while the course of infection (new-onset diabetes). However, despite the greater number of survival in the majority of the reported cases however, in some other cases the DKA related mortality is very significant that approaches 50% of some small single center retrospective studies. Indeed, DKA in these cases is a metabolic state deterioration due to the bidirectional sophisticated disease-disease interaction between SARS-COV2 and hyperglycemia due to diabetes or acute pancreatitis related conditions. However, excessive inflammation/immune response irregularities may also deteriorate the glucose metabolic state/control that potentially brings about ketosis on one hand. On the other hand, ketoacidosis state are also reported however among infected individuals of good glycemic control although the cases are the few and mostly associated with SGLT2 inhibitors type hypoglycemic agents. Finally, similar non infection associated DKA treatment protocol is used to control ketosis as well as other metabolic abnormalities, yet, significantly higher dose is used particularly insulin. It is worthy to note fluid replishment therapy requires administration volume careful calculation besides monitoring lung function owing to the outstanding SARS-COV2 caused acute respiratory distress. In addition, potassium, magnesium and phosphate levels should be carefully monitored and replaced especially potassium ion while IV insulin therapy. Finally, DKA is significantly correlated to the deterioration of diabetic condition as one of SAR-COV2 serous cormorbidity besides being associated with infection poor prognosis and enhancing its mortality rate.

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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