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An insight to the treatment of diabetes within the era of SARS-COV2 in the existence of cardiovascular co-morbidity

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Abstract

Viral infections deteriorates the infected diabetic individuals' glycemic state, hence developing hyperglycemia as frequently reported for SARS-COV2 viral infection. However, higher prevalence, poorer prognosis as well as higher mortality rates associated with SARS-COV2 infection among diabetic individuals. Consequently, it is strictly recommended good glycemic control for ensuring reducing disease severity as well as better survival rate. Uptodate, insulin seems to be the hypoglycemic agent of choice for treating hyperglycemia condition encountered during acute/severe microbial infection that requires hospitalization. Nevertheless, paradoxical spectulations are issued regarding the feasibility of considering oral hypoglycemic agents such as metformin,(GLP-1) Receptor Agonists, Sodium-Glucose-Transporter-2 (SGLT-2) Inhibitors, pioglitazone administration to SARS-COV2 infected diabetic patients' therapy. Although, several reports about various side effects associated with these drugs including dehydration, hypovolemia, gastrointestinal and perecipitating lactic acidosis side effects. Thus, this report surveys the paradoxical spectulations and recommendation are reported for these classes of hypoglycemic drugs beside some other drugs related to other comorbidities such as those acting on renine- angiotensine system and hydroxychloroquine.

Keywords: Hyperglycemia; Diabetes; SARS-COV2; Treatment; Oral Hypoglycemic

1. Introduction

Co-morbidities like diabetes mellitus, obesity, chronic renal impairment as well as cardiovascular diseases are thoroughly reported to be associated with disease severity, poor prognosis and high mortality rate of SARS-COV2 infection however, best glycemic control gives rise to better infection curing outcomes besides determining the therapeutic protocol intensiveness [1-8]. In fact, diabetes mellitus is associated with severe illness that requires intensive care unit ICU admission [9-11], yet, in this context, some authors as well as meta-analysis studies have postulated that diabetes mellitus comes in the second level of significance after hypertension as SARS-COV2 infection co-morbidity [3, 12, 13]. Diabetes mellitus co-related to the elevated mortality rates risk among the diabetes infected individuals besides causing prolongation of recovery interval [2, 14-21].There is a mutli-array of diabetes-SARS-COV2 diseases interactions that affects the infected individuals survival [22].The poorly controlled blood glucose is well known to compromise patients' immunity thus modulatory monitoring of SARS-COV2 infected individuals in addition to other endocrinal parameters are strictly required [22, 23, 24]. Nevertheless, it is worthy to note SARS-COV2 related stress has developed hyperglycemia regardless the co-existence of diabetes in the infected patients [25]. Furthermore, diabetic individuals are also reported to have high risk of SARS-COV2 infection susceptibility [5, 11, 14, 23, 26] like the liability to other corona virus infections as well as high risk of developing poor prognosis [27, 28, 29].In this context,

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According to an American cohort study, 15% of the hospitalized SARS-COV2 infected patients in USA have been diabetic individuals, while, the highest diabetes prevalence among the American patients have been reported in New York city to be around 32% [30]. Certain authors has speculated that type II rather than type I diabetes mellitus is more related to the higher liability to SARS-COV2 infection, much extensive infection severity as well as ICU admission as it is related to DPP4 receptors involvement [31]. However, in china SARS-COV2 with have exhibited greater respiratory distress, hospitalization as well as higher mortality rates as compared to the non-diabetic infected individuals [7, 32, 33].

Like what happens in other human infectious corona virus infections [5, 34] hyperglycemia inclines the pulmonary tissues secretions glucose level [35] that compromise the local immune surveillance/response causing higher viral replication as well as deterioration of the patient's condition which may enhance the mortality rate [36-38]. The locally affected immune system components include monocytes as well as lymphocytes tissue infiltration in addition to the pattern of the released cytokines. Corona virus infection causes ACE2 tissue repairing system down regulation besides induced tissues overt inflammatory cytokine response [33, 39].Moreover, pulmonary tissue structural modification involving fibrosis of the alveo-cappilary membrane with the collapse of the alveolar membrane, have been reported to diabetes during viral infections making blood glucose level control a critical issue during corona viruses infection particularly SAS-COV2 [40]. Furthermore, hyperglycemia whether due to SARS-COV2 or pre-existing diabetes is also associated with IL-6 related D-dimmer level elevation coagulopathy [41].Thus, the earlier insulin based blood glucose level control is considered as a lifesaving priority treatment particularly for hospitalized patients [21, 42, 43].

From other point of view, like the impact of diabetes on the SARS-COV2 virus infection condition, others have reported that SARS-COV2 infection in turn may deteriorate the vasculopathy, coagulopathy as well as psychological stress [21, 43]. SARS-COV2 is reported to trigger an extra-ordinary inflammatory response that causes imbalance in the pancreatic ACE2 physiological influence [43] leading to impairment of β-cells function. In general diabetes or stress related hyperglycemia contributes to the susceptibility of community acquired microbial/viral infections [44-46]. Three potential mechanisms lies behind the poor co-morbidity/disease severity contribution of diabetes particularly type II diabetes mellitus on SARS-COV2 infection, first, tropism of SARS-COV2 to many ACE2 expressing tissues including the pancreatic tissues [47, 48]. Nevertheless, ACE2 is also expressed in other body tissues such as intestine, kidneys, and blood vessels which are up-regulated in diabetic patients on thiazolidinones type hypoglycemic agents, Ibuprofen NSAID, or o hypotensive agents such as ACE inhibitor and angiotensin receptor-I inhibitors [4].Second; diabetic patients have been reported to express an elevated level of the SARS-COV2 spike protein pre-activator furins that cleaves a viral activation/entry site localated between S1 and S2 spike protein units of the spike proteins [49] that facilitate the virus infection even to the low activation factors TMPRSS2 and/or lysosomal cathepsins expressing tissues [50]. Third, diabetes prohibits the immune response including suppressing neutrophils chemotaxis, phagocytosis, and microbial neutralization mechanism [51] which is reflected by the reported decline counts of CD4+ and CD8+ T cells leading to abnormal immune cytokines response (cytokine storm) indicated by the reported elevated levels of cytokines as well as pro-inflammatory Th17 CD4+ T cells counts [6, 7, 14, 33, 52-54].Besides, diabetes induced micro-vascular abnormalities [51]. Both of microvascular, thrombotic as well as immune irregularities consequences of diabetes are also contributing risk factor to cardiovascular diseases; the first priority co-morbidity of SARS-COV2 infection via pro-inflammatory response triggering [12, 33, 55, 56]. The cytokine storm triggered acute respiratory distress as well as the intravascular disseminated coagulopathy always evident in the second week of the SARS-COV2 infection is reported to be intensified, hence, deteriorating the patients' conditions in case of DM co-morbidity existence [57]. Diabetes mellitus induced pro-inflammatory response as well as platelets functions anomalies accompanied with inclined fibrin and other coagulation factors levels, hence, contributing to coagulopathy. In addition, modification of Willebr and factors besides, inducing oxidative stress are also associated with such coagulopathy [58].

Both of SARS-COV1 and SARS-COV2 can invade the pancreatic tissues expressing their primary receptor ACE2 including beta-cells [59-62] that ends with insulin deficiency acute pancreatitis. As encountered with SARS-COV1 the burden of long term complications of SARS-COV2 is expected even long after curing the infection. Remarkably, SARS-COV1 reported complications including that related to glucose/lipid metabolism such as insulin resistance, hyper-insulinemia or even hyperglycemia, that have resulted in the development of type I and type II diabetes mellitus as well as cardiovascular conditions 12 years post SARS-COV1 infection [63, 64]. It is worthy to postulate, that acute as well as chronic viral infections that compromise/disturb both the immune and metabolic intracellular insulin secretion related pathways are risk factors for the inclined incidence of type II DM post SARS-COV1 infections [65], thus similar future outcomes are expected to SARS-COV2 infections due its reported tropism to the pancreatic beta-cells [60].Therefore, theoretically individuals with diabetes are greatly vulnerable to SARS-COV2 infection, enhanced disease severity as well as long term complications due various factors such as much elevated ACE2 expression within the pancreatic as well as pulmonary tissues, compromised immune surveillance/response especially that related to T-cells activity accompanied by the extensive incline of the pro-inflammatory cytokines levels particularly interleukins [66, 67]. However, geriatrics with poor glycemic control are the most vulnerable to SARS-COV2 which is owed to the hyperglycemia attributed

immune response irregularities, obesity, chronic renal impairments on dialysis, hepatic illnesses in addition to its contribution to cardiovascular co-morbidities such as hypertension and dyslipidemia co-morbidities. Besides, higher infection illness severity, poorer prognosis as well as greater mortality rate are encountered in this group of population [68-70].Therefore, tight monitoring of glycemic control in out- and in-hospital diabetic individuals is strictly required during the SARS-COV2 pandemic [71, 72].

Chinese studies have revealed that cross country estimations that the prevalence diabetes among SARS-COV2 infected individuals including the hospitalized patients is around 5% [13, 33] while other studies have demonstrated 8-16% prevalence [73] which escalate to 34.6% among the ICU admitted patients [70] in which the WBCs count as well as biochemical variables including coagulation and inflammatory parameters [74]. However, a higher estimation is reported in a study from china that has demonstrated 25% prevalence of diabetes among SARS-COV2 infected geriatric males [75]. While, a collection of Chinese retrospective studies have demonstrated that the prevalence of diabetes among infected individuals occurs within the range of 1-14%, some of them have included more than 1000 patients[1, 2, 7, 10, 11, 14, 16, 33, 76-80].A second collection of Chinese studies have found that the prevalence of diabetes among the infected individuals is within the range of 10-20% [1, 6, 81-85], while a third small group of studies have reported more than 20% prevalence of diabetes among the infected individuals [86-88]. Nevertheless, one Chinese study has found that no significant association between diabetes and SARS-COV2 infection vulnerability [89]. In Italy, a study has demonstrated that the prevalence of diabetes among the ICU admitted SARS-COV2 infected individuals [90]. The prevalence of diabetes among SARS-COV2 infected individuals in USA has been reported to be 6, 24 and 32% in out-patients, in-patients and ICU admitted patients respectively [91].Yet, another study from one medical center in New York has demonstrated that 15% of the SARS-COV2 hospitalized patients are diabetic while the cross city are 5.45 and 31.8% among the non-hospitalized and hospitalized ones respectively [92]. Thus, diabetes is co-related with the hospitalization, ICU admission, poor prognosis and high fatality in the 3 countries USA, china and Italy besides Latin America [1, 2, 29, 68, 93-101]. While, in Belgium, the prevalence of diabetes among SARS-COV2 infected individuals is 9.4% [102].Nevertheless, the variation in the prevalence of diabetes among SARS-COV2 infected individuals in different studies are probably due variation in age, gender, disease severity as well as country/locality [103]. Indeed, there are at least more than 18 meta-analysis studies from different countries that speculated 14.5% prevalence of diabetes among the SARS-COV2 infected individuals, which is associated with the reported greater mortality rate as reported by (Abdi, A., et al.,) [104].

Interestingly, diabetes developed micro vascular damages involving pulmonary vasculatures is gender dependent and is resulted in declining the carbon monoxide diffusion capacity besides retarding gases exchanging even in non-smokers. In addition, an angiopathy complications are encountered in the pulmonary and other tissues microvasculature due to diabetes contribution to endothelial malfunctions which also influences vasodilatation, fibrinolysis in addition to platelets aggregation counteracting activity [105-108].The hyperglycemia associated endothelitis/endothelial function impairment is encountered frequently in SARS-COV2 severely infected Asian and African populations. However, endothelitis as well as hemoglobin glycosylation are developed either via viral endothelial cells tropism or through infection induced cytokine storm exaggerated inflammatory response [110]. In a Chinese analysis study, it has been demonstrated that SARS-COV2 infected individuals are of mean glycosylated blood level of 8.1%, however, good glycemic control is reflected in term of HbA1c at blood level of 7.3%. consequently, patients with poor glycemic control reflected by elevate HbA1c blood level have exhibited low oxygen saturation (below 95%), increased neutrophils count while decreased lymphocytes count, besides, elevated levels of C-reactive protein, D-dimer, procalcitonin and aspartate transaminase leading to the development other hyperglycemia developed co-morbidities in the SARS-COV2 infected individuals [97].The hyperglycemia caused immune suppression/abnormal immune response, disturbance of the normal endothelial function, decline of the antimicrobial surveillance occurs at uncontrolled fasting blood glucose exceeding 11 mmole/L (more than 180 mg/dL) [111-113] that complicate the patients' condition through giving rise to acute respiratory distress, septic shock, and acute kidney/heart injuries [97] as in case of SARS-COV2 infection induced cytokine storm [113]. However, good blood glucose control is considered at blood level less than 180 mg/dL (less than 11 mmol/L) which should be maintained in diabetic individuals while SARS-COV2 pandemic outbreak [97, 114-116]. Furthermore, in USA an analysis study has demonstrated that poor glycemic control individuals who have experienced greater SARS-COV2 infection symptoms severity, poorer prognosis as well as fatalities are those with HbA1c levels exceeding 6.5 mmol/L [116]. Interestingly, other meta-analysis studies have co-related such various infectious diseases severity, poor prognosis and higher mortality rates are due to acute stress caused hyperglycemia rather than solely the pre-existing chronic diabetes outcomes [117, 118]. Remarkably, in Iran, one study has revealed that a half of the SARS-COV2 infected individuals are diabetic with hypertension co-morbidity and are on ACE inhibitors/angiotensin receptor blockers hypotensive agents, beside, being of low survival pattern [119].

Moreover, it is reported that poorly controlled glycemic state is associated with 87% greater mortality rate than infected SARS-COV2 individuals as compared to that of good blood glucose control since hyperglycemia is associated with acute respiratory distress, acute renal as well as acute heart complications of this infection [97]. Studies from globally different locations including the very large (Wu & McGoogan, 2020) Chinese over 73 thousand case study, have reported 7.3% to 20.3% diabetes associated mortality rates among the SARS-COV2 fatalities [2, 74, 120] indicating the hidden correlation between the fatal mild cases of SARS-COV2 and the silent symptoms of diabetes [74]. In this context in Italy more than 70% of SARS-COV2 infection fatalities are related to chronic co-morbidities including diabetes [26] that has contributed to 35% of the infection mortalities [120]. Currently, diabetes is considered as an independent co-morbidity to which poorer morbidity as well as greater fatality rates of SARS-COV2 are attributed [21, 69, 121]. Nevertheless, the diabetes associated facilities, if not owed to hyperglycemia itself, it can be attributed to diabetes related other co-morbidities like hypertension, cardiovascular and cerebrovascular complications. These complications deteriorate the infected patients' conditions to require hospitalization, ICU admission or even lead to death [1, 12, 26, 29, 116, 122-125] particularly among elderly [7, 126, 127], although only one study has emphasized that there is no significant differences the infected diabetic and non-diabetic individuals [124]. Remarkably, from other prospective, due to the complex disease-disease interactions between SARS-COV2 infection and diabetes has led some authors to emphasize that SARS-COV2 itself deteriorates the infected individual diabetic pre-existed condition or even establish diabetes in the non-diabetic ones [128]. In this context, one CT-scanning based study has demonstrated a significant modifications in the CT-scan images as well as scores between diabetic and non-diabetic infected individuals however, no significant difference between diabetic infected individuals regarding glycemic control state. Much deteriorated CT-scan scores are observed in the images of diabetic individuals, in addition, greater frequency of linear image opacity is encountered in CT-scan images of infected individuals of elevated disease severity and poor blood glucose control [74, 127]. Therefore, diabetic individuals self-care as well as tight blood glucose monitoring/control while the onset of SARS-COV2 pandemic [5, 129, 130].Good blood glucose control may declines the risk, yet, not entirely abolishes the virus infection liability, severity or prognosis [72] due to the involvement of other un-related co-morbidities and genetic factors involvement.

2. SARS-COV2 Infection: Pancreatic Tissue ACE2 Targeting and Triggering Exaggerated Immune Response with coagulopathy complications

Molecular studies have reported the distribution of ACE2; the SARS-COV1 and SARSC-COV2 tissue tropism receptor, in most of body tissues including the respiratory system airways/pulmonary tissues, pancreas, adipose tissue, bones, testes pituitary gland, adrenal gland ..etc. indifferent abundances. This scattered expression of ACE2 along the body organs makes them targets for corona virus infection particularly the respiratory system [2, 72, 114, 131, 132].In fact, animal studies has Longley prior the emergence of human infectious corona virus epidemic outbreaks, demonstrated the involvement of ACE2 in the development of acute pulmonary tissues damages [133] via the involvement of AMP-activated protein kinase (AMPPK)-rapamycin (mTOR) signaling pathway that gives rise to autophagy [134]. Nevertheless, the infection associated inflammation induces the ACE2 expression as well as stability via phosphorylation of the ACE2 active site serine-680 residue [135]. This active site phosphorylation alters ACE2 binding site hence hindering RBD binding of SARS-COV2 spike protein as it causes conformational alterations in the receptor site [136, 137].Yet, its harmful influence causes imbalance in the renin- angiotensin- aldosterone system due to the SARS-COV2 cells infection caused ACE2 down regulation which starts a deleterious pro-inflammatory and pro-fibrotic effects to both respiratory and cardiovascular systems [138]. While, a compensatory ACE2 up-regulation response to the renin- angiotensin- aldosterone system imbalance presents additional cell-entry paths to the virus [137].

Tropism of SARS-COV2 may lead to the pancreatic islets β-cells explaining the reported SARS-COV2 infections associated hyperglycemia even in non-diabetic infected individuals [131] binging about acute pancreatitis. It has been hypothesized that SARS-COV2 viral infection brings about pancreatitis via one of two potential mechanisms, the first, involves direct invasion to the ACE2 expressing pancreatic acinar cells leading to insulin secreting cells β-cells injury [139] as previously reported to SARS-COV1 infection [60]. The second involve systemic extraordinary extensive cytokine storm inflammation associated mal-immune response giving rise to multi-organs damage, one of them is the pancreas [140-142]. The last one explains the pancreatic damage evident autopsy findings in SARS-COV2 infection fatality victims despite the absence of SARS-COV2 microscopic findings [143], which potentiates some authors suggestions that relates SARS-COV2 associated pancreatitis to hypo-perfusion due to ARD hypoxia and shock as previously encountered with SARS-COV1 patients [140, 142-145].Furthermore, Invasion of ACE2 expressing pancreatic tissues causes angiotensin II cleavage into angiotensin (1-7) decline, hence, contributing to the development of beta-cells injury, insulin-resistance and NHE activation related lactic acidosis [146]. It is worthy to note that, the physiological activity of ACE2 within the β-cells as well as other subsets of cells of the pancreas acinars is to cleave the angiotensin II to the angiotensin (1-7) that are partly contributing to the glucose metabolism as well as insulin secretion [147-149] that explains diabetes related micro- and macro-vascular complications [150-153]. However, ACE2 is also involved in apelin-13, des-Arg9-bradykinin, neurotensin (1-13) β-casomorphin, dynorphin A 1–13, and ghrelin cleavage [147]

which may co-relate to a non-angiotensin II cleavage dependent glycemic control molecular pathways [103]. Remarkably, SARS-COV2 infection associated acute pancreatitis has been reported for the first time by (Wang, et al., 2020) with prevalence of 17.35 of the infected individuals [141].

Moreover, many biochemical studies have speculated that SARS-COV2 infection brings about mild [141, 148] to severe acute pancreatitis [144] indicated by the evident inclined serum lipase/amylase, pancreatic enzymes levels despite the lack of any previous predisposing factors [141]. The elevation of these pancreatic enzymes in acute pancreatitis symptoms exploiting SARS-COV2 infected individuals ranges from 16.41%in one study to 18.75% in other study or may be escalated to 48% in a third one[142, 148, 154] some of which have presented altered pancreatic tissues CT-san images, 7.46% according to (Liu, F., et al., 2020) study [142]. It is reported that SARS-COV2 developed diabetes mellitus is established 5-7 weeks post SARS-COV2 infection, yet, typical auto antibodies against pancreatic β-cells and other molecular targets including glutamic acid decarboxylase, tyrosine phosphatase, insulin and zinc-transporter-8 thus, type 1B diabetes mellitus is proposed to be developed by mean of this viral infection in one case that exhibited extremely elevated blood glucose of 30.6 mmol/L and HbA1c of 16.8%[155]. This speculation is encouraged by the results of mechanistic to the infection of alpha and beta pancreatic cells by both SARS-COV2 and pseudo-entry virus. Other potential reasons for insulin-dependent diabetes is due to the viral infection induced chemokine and cellular death factors release as other virus do [156, 157].[156, 157]. Nevertheless, some medical experts have suggested that merely the encountered surgical complications besides the SARS-COV2 infection a typical manifestations are enough to potentiate the virus infection developed acute pancreatitis [158].Interestingly, those SARS-COV2 infected individuals exhibiting acute pancreatitis symptoms the lipase level extremely inclined to three folds greater than the normal upper limit, yet, some authors attribute this elevation to the virus infection related/history of non-related diarrhea, gastritis enteritis as well as colitis [154, 159]. In this context, animal model studies have exploited the high expression of ACE2 in both small as well as large intestines [160], in addition to inclined duodenal and jejunal enterocytes ACE2 expressions in cases of ACE inhibitor use and diabetes respectively [161, 162].

Frankly speaking, there is controversy regarding the pancreatic tissues ACE2 existence/expression density between authors to attribute acute pancreatitis to which [148, 163], however, some who have admitted ACE2 expression related the issue to the genetic inter-individuals variations [148]. Interestingly, both (Schepis, et al, 2020) and (Liu, et al, 2020) have reported densior ACE2 expression within both exocrine and endocrine tissues than within the respiratory system tissues that may become the SARS-COV2 provoker of acute pancreatitis [148, 163] which is further up regulated by the virus tissue invasion [164].

The damaging cytokine storm based inflammatory response provoked by diabetes in SARS-COV2 infected patients is suggested to influence the insulin sensitive tissues causing poor blood sugar control [167], besides, elevation of D-dimer level that brings about coagulopathy [167, 168] and related thrombotic poor prognosis like stroke [32]. Postmortem microscopical examinations have revealed the establishment of both macro-vascular as well as micro-vascular thrombosis in SARS-COV2 infection victims [169] which are also reported to diabetes as one of its complications [170].In fact, ACE2 is extensively expressed within the endothelial layer of lungs blood vessels hence, facilitating SARS-COV2 invasion to these cells that leads to their injury/dysfunction, enhancing endothelial permeability, triggering cytokine storm, down regulation of the ACE2 caused angiotensin II level elevation that causes both vasoconstriction as well as building up of thrombotic clots via inducing platelets aggregation [48, 171-173]. Coagulopathy may worsen to develop disseminated blood coagulation, one of the critically significant mostly fatal poor prognosis of SARS-COV2 infection [174,175] particularly in the co-existence of metabolic co-morbidity like diabetes [176] evident by the reported inclined D-dimer (higher in diabetic individuals), fibrin as well as hypofibrinolysis [74, 173, 177-180]. SARS-COV2 infection caused endothelial dysfunction also elevates the blood levels of complement system and plasminogen activator inhibitor-1 (PAI-1), besides, inclines Hypofibrinolysis probably encouraging the formation of microthrombi [181, 182].In addition, the ACE2 cleavage product into angiotensin 1–7 that inhibits the renin-angiotensin system via binding to the protein coupled receptor Mas which mediates vasodilatory, antithrombotic, antiproliferative and antioxidative activities [183, 184]. Consequently, in a Chinese study that almost exclusively (98%) considered SARS-COV2 with type II DM of which 47% with inclined platelet count, 62.47% of inclined D-dimer level while 41.7% are of inclined fibrinogen level [16], however, of these coagulation parameter D-dimer is the most significantly related to the elevation of the virus infection fatalities [1, 16, 185, 186]. Furthermore, the virus infection itself increases the viscosity of blood due to the infection symptoms such as the encountered severe pneumonia as well as respiratory distress thus, maximizes the risk of coagulopathy co-morbidity [187], besides, diabetes pre-existed complications such as atherosclerosis vascular injury, oxidative stress and inflammation [16, 188]In addition, SARS-COV2 infection causes ACE2 expression down regulation evident by the inclined blood pressure of the infected individuals which is aggravated by diabetes co-existence particularly type II DM [169].

3. SARS-COV2 infection and human dipeptidyl peptidase (DPP4) receptor

The human type II trans-membrane enzyme; dipeptidyl peptidase (DPP4) is broadly dispersed along several body tissues particularly the immune system (known as CD26) through regulation if T-lymphocytes activation, chemokines/bioactive peptides secretion as well as adipocytes, yet, it also plays a crucial part in insulin dependent glucose metabolism. It reduces the insulin secretion via its catabolic activity against peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide as well as other immune-modulatory proteins [189], causing by the way abnormal viscera accumulated white adipose tissue lipid metabolism, hence, develops adipose tissues insulin resistance and inflammation[31, 190-192]. DPP4 also contributes to the immune system response including the expression of CD86 and NF-jB pathway [31] s it is expressed in the $CD4^+$ and $CD8^+$ T-cells, natural killer cells, dendritic cells as well as macrophages [193, 194] particularly in the pulmonary tissues [195, 196]. In addition, DPP4 stimulates the CD26 type T-cells differentiation via binding to adenosine deaminase (ADA) as well as caveolin-1 that triggers the release of the immune response mediated intracellular response [197]. Furthermore, in type II DM this enzyme mediates inflammation particularly in adipose tissue via direct enzymatic and indirect non-enzymatic modes of action that targets multiple cytokines, chemokines, and growth factors inflammatory mediators [31, 194]. In addition, DPP4 has a primary role in modulation of inflammatory as well as immune response via up regulation of one the immune system components Kabba-b nuclear factor and T-cells reserve recruitments [198]. Thus, since DPP4 is co-related to the diabetes known complications, individuals with obesity and/or type II DM are currently treated with DPP4 inhibitors, like sitagliptin, vildagliptin, and saxagliptin in order to elevate insulin secretion via blocking GLP-1 and/or GLP-1 receptor analogs activities [31].

However, despite the controversy between author points of view regarding full understanding of the DPP4 inhibition consequences on the immune system integrity, some reports have exploited a non-significant effect of the DPP4 inhibitors on the expansion of the upper respiratory tract viral infection [199]. Interestingly, DPP4 resembles ACE2 in being shed from the cell membrane forming body fluids soluble enzyme with a catabolism unrelated pro-inflammatory on macrophages or lymphocytes alone or in cooperation with factor Xa via interaction with the (ADA) and caveolin-1 pathways [200, 201] particularly in the viral infections like MERS-COV infection [195, 202].Both transgenic type II DM diabetic mice infected MERS-COV and DDP4 directed antibody against epithelial cells of the human bronchi and Huh-7 cells studies [203, 204] indicates that DPP4 is the mutual tissue tropism and cell entry receptor for MERS-COV virus infection [203, 205, 206]. While, the MERS-COV infection abnormal inflammatory response is triggered due to the binding of the virus spike protein to the T-cells DPP4 binding domain and NF-jB [203].However, in transgenic mice with type II DM MERS-COV infection slow inflammatory response due to declining the $CD4^+$ T-cells in addition to TNFα, IL-6 and Arg1expressionparticularly the pulmonary tissue with weight loss. This have contributed to the disease severity, prolonged onset, inclined disease complications, delayed curing, besides inclined poor prognosis as well as mortality rate of the disease mediated by binding to DDP4 receptor. In general, as have been reported in some animal studies, the binding of the MERS-COV to the DPP4 will trigger the inflammatory response through DPP4 interaction with polypeptides and nuclear factors of specific T-cells bringing about disease severity and high lethality [207, 208]. Consequently,DPP4 inhibitors and GLP-1 receptor analogs are reported to elicit an anti-inflammatory via declining the recruitment of macrophage and M1/M2 macrophage polarization regulation through blocking the GLP-1 pathway signaling activation while DPP4 inhibition [209]. Furthermore, it is reported that there is amino acid type/location modifications, as well as glycosylation brings about the polymorphism of the DPP4 receptor, hence, declining the MERS-COV entry as well as infection liability [210-212] due to the conformation modification in this corona virus spike protein altering the affinity of its RBD which also changes the shaded receptor blood level, receptor activity, the receptor immune-modulatory chemokines and cytokines [189].Yet, no significant dysregulations of the inflammatory mediators [213].

Moreover, human infectious corona virus spike proteins have affinity to bind a wide range of the cellular membrane receptors as a cell binding and entry factor that have a critical role in the pathogenesis mechanism of cellular invasion [214-216] and mostly used as by more than strain even when they are genetically different [217]. Nevertheless, although the severity of the SARS-COV2 virus infection is of moderate severity located between that of MRS-CoV and SARS-CoV infections [218], its immunological response is un-related to its sub-optimal binding to ACE2 as well as the ACE2 expression [219] explaining the involvement of another receptor involved in SARS-COV2 pathogenesis [217]. In addition, unlike SARS-COV1, the S1 unit of SARS-COV2 spike protein has conserved some glycosylation sites that probably explains its immune shielding as well as abnormal distinguished immune response [220, 221].Interestingly, (Vankadari and Wilce, 2020), have reported that protein-protein virtual docking evaluations between certain amino acid sequence in the SARS-COV2, spike protein S1 unit may have the capability of tight interactions with the human DPP4 receptor through a large interaction surface that is identical to that of S1 unit of MERS-COV spike protein [220] particularly at the amino acid residues K267, T288, A289, A291, L294, I295, R317 ,Y322 and D542 [222]. Thus, through such interaction may evade the immune surveillance, and cause cytokines inflammatory storm as DPP4 is the principle

response mediating immune as well as inflammatory responses receptor [220]. Furthermore, the S1 unite of SARS-COV2 spike proteins have been found to possess two virus strains unique additional interaction surfaces with DPP4, the first provides vander Waals interaction and H-bonding site of the following amino acids (Q286, I287, N338, V341, R336). The second sequence that can interact with both ACE2 and DPP4 [223] involve the following amino acids (R408, Q409, T445, V417, L461, D467,S469, L491, N492, D493, Y 494, T497, T150, Y504) facilitating ACE2 poorly expressing tissues tropism particularly the immune tissues. In this context, the expressed immune system T-cells CD26 enzyme can also cleave the virus active L-proline or L-alanine N-terminus peptides to a polypeptides that activate these cells, hence, provoking the exaggerate immune response against the virus invasion [220].

Moreover, crystal structure based SARS-COV2 spike protein RBD and DPP4 protein-protein docking has shown that there is elevated binding affinity but lower than that with the primary receptor ACE2making DPP4 a candidate binding receptor. Therefore, as in case of MERS-COV, SARS-COV2 can interact with both ACE2 and DPP4 particularly CD26 expressed on the immune cells making DPP4 part of virus tissue tropism and cell entry [217].(Li, 2020) study has also demonstrated that the spike protein RBD has a binding interface of the sequence residue of Q498, D405, E484, Y489/N487, N501 and Y505 with the DPP4 interface residues of K267, R336, R317, Q344, Q286 and T288.Besides,other receptor binding residues L294 and I295 to which vander Waals interaction with the virus spike protein RBD [217] instead of H-bonding interaction encountered with MERS-COV spike protein RBD[224]. Interestingly, the E484 residue of the SARS-COV2 spike protein RBD is the most critically DPP4 (to the R317 binding pocket residue) binding affinity determining residue in addition to the D405A residue. A third spike protein RBD binding interface residue to the DPP4 receptor (through the DPP4 residue K267) is the Q498Y [217]. From the opposite site of interaction interface at the DPP4, the virtually explored four potential interaction residues (K267, R336, R317 and Q344) are shared between MERS-COV and SARS-COV2 spike protein RBDs via critically significant H-bonding for the virus spike proteins interactions regardless the structurally resembled SARS-COV2 and MERS-COV spike protein RBDs. These formerly mentioned residues are potentially modified by mutations via evaluation process of the corona viruses, however, any sequence or amino acid residues modifications (insertion or substitution) are potentially enhances the DPP4 potential [217] while, fortunately in animals the DPP4 binding interface residues are still reserved without any mutation yet [224, 225].Thus, the unique N-terminal domain of the RBD S1 unit in the SARS-COV2 spike protein justifies both the multiple human biomolecules unusually ACE2 interaction just like SARS-COV1 and the unexpected DPP4 receptor interaction just like MERS-COV which both can invested for drug therapy due to the shared amino acid residues at the docking interface with the two other strains [217, 220, 225, 226] and targeting DPP4 as a therapeutic approach seems to be an therapeutic option [217].Furthermore, (Qi, et al., 2020) have also reported such virtually potential interface interaction between DPP4 receptor and the SARS-COV2 spike protein [227]. From other prospective, (Singh, et al., 2020) have reported that DPP4 has a potential interaction with the RAS pathway [21]. Oppositely, other in vitro studies has argued the previous two virtual studies revealing that DPP4 receptor can not be an independent SARS-COV2 entry factor in cell lines like HeLa and BHK2 that not express ACE2 primary entry receptor [62, 131, 228]. It is worthy to note that, that SARS-COV2 infection co-morbidities such as obesity and type II DM are contributing factors to the inclined circulating blood level of DPP4 that is aggravated by aging [229, 230], presumably explaining the virus various tissues tropism, disease severity, multiple organs damage and higher mortality rates [231]. Thus, it is presumed that monitoring the plasma levels of this circulating DPP4 enzyme may be a fruitful tool for prediction of virus infection liability, disease severity/prognosis and treatment responsiveness in these individuals as proposed by (Iacobellis, 2019) [31].

Remarkably, as in case of MERS-COV virus infection, it is proposed that DPP4 lies behind the diabetes co-morbidity related SARS-COV2 infection complications leading to disease severity, poor prognosis, and higher mortality rate due to the macrophages recruitment within the pulmonary tissues [204]. Nevertheless, (Barchetta, et al., 2020) study has revealed that the DPP4 inhibitors, sitagliptin, vildagliptin and saxagliptin has failed to prevent hCoV-EMC coronavirus cell entry as the virus may interact with a receptor other than DPP4 [231].

4. Treatment Of Diabetes/Hyperglycemia In SARS-COV2 Infected Individuals

The tightly strict blood glucose/diabetes control is a matter of optimum priority for both out- and inpatient particularly the ICU admitted hospitalized SARS-COV2 infected individuals in order to ensure high recovery/survival rate as it contributes to evading the disease complications [12, 13, 41, 48, 74, 97]. Good blood glycemic state within the infected individuals have been exploited to reduce the development of ARD, septic shock, diffused intravascular coagulation, acute cardiac distress and kidney function deterioration[5, 232, 233] as it can counteract the reversible glycosylation of the ACE2, hence, reducing the virus spike protein-ACE2 binding affinity and virus infection induced cytokines storm [234]. In addition, hyperglycemia symptoms management in both diabetic and non-diabetic infected individuals, beside, rational election of the proper hypoglycemia agents with minimum drug-drug as well as drug-disease interactions particularly those with immune-modulation influence, with long term case monitoring [68] are the only options available within the fact that no global diabetes specific hypoglycemic agent(s) therapy is conveniently recommended

by medical experts including the currently approved hypoglycemic agents classes regardless the so many individual opinions, for SARS-COV2 infected individuals with such co-morbidity. Thus, any hypoglycemic agent has an interaction/contraindications with any other condition co-morbidity of SARS-COV2 infection used to control the patient's glycemic state has been suggested to be cautionaly considered [68]

In this context, hypoglycemic agent are not always included in SARS-COV2 infected individuals with or without pre-existed diabetes exploiting hyperglycemia.(Han, et al., 2020) study has demonstrated that only antimicrobial agents (antibacterial and antiviral drugs) have been used besides management hyperglycemia symptoms without the administration of hypoglycemic drugs [235]. However, (Singh, et al., 2020) study has recommended the co-administration of hydroxychloroquine to the WHO approved treatment protocol in order to control diabetes related complications in case of diabetes infected patients [236]. A paradoxical group of studies have strictly recommended necessity of optimum glycemic controlling hypoglycemic agent of minimum possible adverse effects and interactions is a critical issue for SARS-COV2 /diabetes co-morbidity associated hyperglycemia management. However, the studies have also recommended best hydration state as well as dose tapering particularly that of oral hypoglycemic drugs in order to minimize the potential side effect [5, 40, 237, 238]. Therefore, despite the reported insulin efficiency in establishing good glycemic control state in the diabetic infected individuals at approximately all disease severity states, oral hypoglycemic drugs use is also recommended, yet, for mild to moderate infection [239]. Moreover, the influence of oral hypoglycemic drugs such as metformin, pioglitazone, liraglutide, sodium-glucose cotransporter-2 inhibitor (SGLT2) inhibitor, and insulin, on the expression of SARS-COV2 cell-entry receptor, ACE2 in various body tissues including the lung and pancreas is also discussed as it is related to enhancing the tissue repairing, as previously reported in animal studies, versus viral entry [240-245]. Moreover, some have recommended that neither metformin nor sodium glucose co-transporter-2 inhibitors should be used for cases of moderate to severe SARS-COV2 infection conditions among diabetic individuals, since, they may contribute to lactic acidosis even in good glycemic control state [5, 21, 71, 130, 247, 248] beside, the reported ACE2 virus tropism receptor expression promotion in various tissues [240]. Nevertheless, their avoidance may contribute to deteriorations of both cardiovascular and cardio-renal functions [249]. While, others have recommended the avoidance of sulfonylureas hypoglycemic agents use in severe cases of infections as they are expected to develop hypoglycemia [103]. Remarkably, the IL-6 counteracting monoclonal antibody drug, Toclizumab, has been reported to elicit promising results in both clinical trials to overcome the cytokine storm consequences in SARS-COV2 infected diabetic individuals with an elevated serum IL-6 level [128, 250] as well as in practice.

Physical/athletic activities are also advised for maintaining an acceptable state of euglycemia as it is previously recommended for other clinical issues associated with hyperglycemia [251-256] since it is at least reported to promote both of the basal as well as the bolus insulin influence by 20-40 prior 2-4 days of these activities [257, 258]. (Assaloni, et al., 2020)study has exploited that the quarantine related reduction of diabetic individuals physical activity is associated with poor glycemic control in 42% of type I DM while, so that about 62% of the diabetic subjects have required to alter their insulin dosing/delivery regimens [259]. Furthermore, tight glycemic state control is also required in both diabetic geriatrics and pediatric individuals with type I DM as the blood glucose level rather than the diabetic condition co-existence accompanying SARS-COV2 infection is the matter of concern, thus, reports data neither have exploited any inclined vulnerability to the virus infection nor to bad complications associated with this state in case of euglycemia [103]. Nevertheless, it is worthy to note that, the antipyretic drug of choice often used in the fibril SARS-COV2 patients, acetaminophen is also reported to interfere with blood glucose reading giving rise to errors [260]. However, No undoubted cause have been identified regarding the co-relation between the inclined SARS-COV2 infection survival rate and the tight good control of the patient's glycemic state in diabetic individual, yet, the degree of hyperglycemia as well as the used hypoglycemic agents used may have unrevealed contribution [68]. In addition, designing of universal rational hyperglycemia treatment protocol for diabetic SARS-COV2 infected individuals suffering symptoms of hyperglycemia not yet been achieved, thus a case/patient condition specific tailored treatment protocol based on type of DM and any other risk factor/co-morbidity [130, 261-263]. Thus, the selection, continuation and discontinuation of the antidiabetic drugs is a critically important issue that requires precise evaluation to the pathophysiological condition as well as the patient's condition involving the existence of co-morbidities [233]. Accordingly, some authors and medical experts have reported the necessity of oral hypoglycemic drug discontinuation and starting parenteral insulin upon hospitalization [5, 48, 232, 233, 264].

4.1. Hyperglycemia Insulin Therapy During SARS-COV2 Infection

A long time ago, it is well established that insulin therapy is used to re-establish normal blood glucose in any emergency hospital admitted cases whatever its renal or hepatic function conditions, however, it can be given subcutaneously to oral food tolerant patients. Thus, as a case of emergency, insulin can be used to correct hyperglycemia to euglycemia in cases of SARS-COV2 conditions in both diabetic and non-diabetic infected individuals even at mild to moderate infection

severities while; intravenous insulin administration is used for oral food intolerant patients as well as those admitted to the ICU/on mechanical ventilation [21, 130, 239, 265].Although an elevated degree of disease severity has been reported to the SARS-COV2 infected diabetic geriatrics whom on insulin therapy due to the existence of co-morbidities other than diabetes that is also being in an advanced state to expect better prognosis [266]. Therefore, in cases of diabetes co-existence/ infection developed hyperglycemia insulin therapy must be started [5, 71, 267].While, in cases of severe SARS-COV2 infections the oral hypoglycemic agents particularly metformin, sulfonylureas, and sodium glucose cotransporter-2 inhibitors is discontinued and shifted to insulin therapy [48, 130, 268, 269]. Nevertheless, a close blood glucose monitoring every 2 hours to those on continuous IV insulin therapy particularly in case of severely ill infected patients due to the expected insulin resistance [130, 270], is mutually required because of either potential hypoglycemia or hyperglycemia related ketoacidosis. The potentially expected hypoglycemia developed in the infected patients who are on insulin therapy is probably established by the declined patient appetites [48, 130] on one hand. On the other hand, in case the potential insulin-un responsiveness development of ketoacidosis can be avoided using subcutaneous rapid acting soluble insulin injections in cases of mild to moderate cases of ketoacidosis in adults as reported previously for other emergencies in pediatrics [21, 271, 272].However,(Singh & Khunti, 2020) has reported that using either of single dose long acting subcutaneous insulin or continuous short acting insulin infusion have bring about similar clinical outcomes in cases of critically ill diabetic patients with hyperglycemia associated with other emergencies [273].Furthermore, diabetic outpatients should also undergo very close self blood glucose and urinary ketones monitoring every four hours in case of SARS-COV2 infection while, the insulin therapy continuation [48, 130, 274]. Insulin also have other useful benefits other than hypoglycemic influence which include, first, in animal studies it is found to prevent diabetic nephropathy via decreasing the expression of A disintegrin and metalloproteinase-17 (ADAM-17) [275]. Second, it may hinder ACE2 via ADAM-17 activity thus, declining the SARS-COV2 cell entry [240]. Third, insulin is related to T-cell mediated inflammation modulation [276] as it has been reported to has an anti-inflammatory influence in the critically ill microbial infection hospitalized patients [277]. In fact, insulin counteracts the immune system response abnormalities via renormalization of chemotaxis and phagocytosis, neutrophils bactericidal activities in case of SARS-COV2 infection related hyperglycemia treatment [278, 279]. It is not worthy to postulate that dose tapering is required for both oral hypoglycemic agents (sulfonylureas and thiazolidinones) as well as insulin according to the underlying glycemic state while the episode of SARS-COV2 onset [21], although there is no reported co-relation between sulfonylureas and the enhancement if the expression of ACE2 in case of community acquired pneumonia [280, 281].

4.2. Hyperglycemia Metformin Therapy During SARS-COV2 Infection

Several reports have been issued regarding broadly diverse protective influences of metformin against SARS-COV2 infections among diabetic patients conformed by the lower metformin therapy receiving virus infection mortality rates [137, 282] as also reported by a Chinese study that demonstrated that metformin reduces the mortality rate in the hospitalized infected diabetic users by 9.4% but with slightly higher blood glucose[283]. Although there is no treatment protocol difference between metformin receiving and non-metformin taking drugs except 9% of the metformin taking drugs are on traditional Chinese antiviral therapy to which synergism most of the mortality rate reduction ratio potentially attributed according to multi-variant analysis while no significant influence on the hospital residence time. The metformin attributed reduction in the mortality rate is owed to several reasons, first, the multiple hypoglycemic effect modes of action including promoting insulin activity along with reducing tissues insulin tolerance, reducing hepatic gluconeogenesis. Second, its immune modulation influence via exhaustion of the inflammatory mediators despite its minimum negative impact on SARS-COV2 viral load as well as insignificant viral clearance effect. Besides, its low lactic acidosis inducing side effect particularly in patients with hepatic or renal impairment [284]. Third, its antioxidant influence via modulation of the activities of catalase and superoxide dismutase antioxidant enzymes [285].Fourth, it possesses anti-inflammatory influence via reducing the circulating inflammatory mediators blood levels especially in type II DM patients [103, 286-288].

Furthermore, the metformin immune response alteration effect is also performed through enhancement of the immune response versus reduction of the innate immune inflammatory response via targeting various molecular pathways including, first, enhancing typeM2 macrophages, T-regulatory cells as well as CD8 memory T-cells production [289]. Yet, (Luo, et al., 2020) have reported that metformin receiving diabetic SARS-COV2 infection patients have exploited no significant alteration in lymphocytes, monocyte, neutrophils and basophiles counts as compared to the non-receiving ones, besides close platelets counts [284]. Second, through declining cytokines and chemokines gene expression hence, counteracting SARS-COV2 developed cytokine storm probably via prohibiting the pro-inflammatory responses through targeting nuclear factor-κB[289-291]. Third, ameliorating the autophagic activity included in immune/inflammatory response control and microbs eradication [291]. Fourth, it enhances oxidative stress microbs killing activity of the natural killer cells via modulating catalase and superoxide dismutase enzymes [285, 292].

Moreover, the SARS-COV2 better prognosis of the metformin anti-proliferative, antioxidant, as well as immune-modulatory activities is brought about via AMP activated protein kinase stimulation [293-297] thus can enhance the innate and adaptive immune responses while opposing the accompanying cytokines storm [294, 298]. In addition, metformin via influencing AMPK-signaling pathway, can counteract SARS-COV2 developed ACE2 down regulation [137, 274] beside, the presumed hindering SARS-COV2 virus spike protein interaction with ACE2 receptor via AMP-activated protein kinase phosphorylation of its serine residues [136]. Thus, although this pathway induction activates ACE2 receptor, but, it blocks the virus cell entry as well as its infection related immunological/inflammatory destructive effect [137]. Metformin also can attenuate the rapamycin (mTOR) signaling pathway via AMPK activation that causes ACE2 serine-680 residue phosphorylation [299]. In addition, via phosphorylation of the insulin receptor substrate 1 (IRS-1) phosphorylation, it declines the Protein kinase B (PKB, or Akt) pathway activity [300]. Nevertheless, the involvement of the PI3K/AKT/mTOR pathway signaling in the pathogenesis mechanism of MERS-COV and probably with that of SARS-COV2 provides a clue for a potential metformin SARS-COV2 pathogenesis counteraction role [301].

Remarkably, metformin has lung protective effects against microbial infections, sepsis and chronic obstructive pulmonary disease [291, 293-296, 298, 302].In this context, via multi-array modes of action, including declining insulin resistance, metformin possesses an antiviral activity against different viruses such as hepatitis C virus (HCV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV) [303] as well as co-relating, like other biguanides, to a better influenza virus infection survival fate [304]. Moreover, metformin AMPK pathway activation also may induce various virus counteracting modulators expression genes such as that of IFNs, OAS2, ISG15, and MX, hence adding further involvement to metformin in blocking some SARS-COV2 pathogenesis mechanism in addition to prohibiting inflammatory mediators like TNF-α and CCL5. Therefore, via mTOR signaling prohibition, metformin has probably has SARS-COV2 pathogenesis/replication potentially critical protein counteraction [137].In this context, studies have demonstrated that metformin use has reduced the hospitalization, enhancing better disease prognosis as well as mortality rates even by four folds in metformin receiving, SARS-COV2 infected diabetic patients as compared to the non-receiving group [298]. An acceptable safety, better prognosis, better glucose level control at 70-180 mg/dL, as well as lower mortality rate have been reported by (Zhu et al, 2020) for the use of metformin to control blood glucose in both diabetic and non-diabetic infected individuals [97, 302]. Interestingly, (Chen, et al. 2020) have reported that metformin can reduce the blood IL-6 level significantly in case of higher albumin level concentration [305]. A third mega study (of >1300 subjects) has reported similar results of (Luo et al., 2020) retrospective analysis study of the significant role of metformin of reducing hospital resistance, good blood glucose level control as well as up to four folds reduction of the mortality rate among metformin receiving infected patient as compared to the non-receiving ones [282, 284]. In their retrospective analysis study (Luo et al., 2020) have carefully elect their study subjects (metformin receivers and non-receivers) to be of almost equivalent age, sex, clinical severity of covid-19, oxygen requirement and other associated comorbidities such as hypertension, coronary heart disease, COPD, chronic kidney disease and malignancy. In addition to a close resembling biochemical results regarding WBCs count, liver enzymes level and kidney function test parameters besides similar treatment [284]. However, despite the recommended use of metformin by some authors for its obvious undoubted usefulness [137], others have recommended its use with caution for the clinically unstable state hospitalized patients, although recommending its discontinuation in cases of sepsis and severe hepatic/ renal impairments [103]due to its contraindication in these situations [68]. Besides, its reported lactic acidosis [306] promoting and/or acute renal impairment developing effects particularly in the severely ill patients [302]. Thus, some medical experts have earlier recommended deserting its use for the SARS-COV2 infected diabetic or non-diabetic individuals with hyperglycemia particularly in case of developing symptoms like vomiting and loss of appetite [21], due to such reported side effects that may exaggerate the disease severity as well as bringing about multiple organs dysfunction including hepatic as well as renal impairments [5, 21, 71, 130, 247, 248].However, experts have reported that practically despite these reported contraindications of metformin use in case of septic shock, its use for the in-hospital patients with severe septic shock has remarkably reduced the mortality rate among the receivers as compared to non-receivers [307].

Ultimately, within the lack of SARS-COV2 specific therapy strict care and control to the infected diabetic patients euglycemic state in order to ensure normal boasted patients' innate immune response [5, 121, 308, 309], therefore, neither un questionable data available for the use of a particular hypoglycemic agents nor avoiding the use of oral hypoglycemic drugs [31] despite, the fact that the animal studies have demonstrated their ACE up-regulation effect [240].Some have advised the use of ACEi, ARBs, thiazolidinediones, and liraglutide for their reported potential benefits [121].In addition, it is not worthy to postulate that initial objective of motorman design as antiviral agent may explain some of its viruses infection opposing effect as it is designed to counteract influenza virus infection before discovering its marked hypoglycemic effect as a permanent adverse effect [310, 311].

4.3. Hyperglycemia DPP-4 Inhibitors Therapy During SARS-COV2 Infection

Attention have been focused on the DPP4-inhibitors, at beginning of SARS-COV2 pandemic emergence, as a promising glucose level controlling hypoglycemic agent useful for the SAS-COV2 infection hyperglycemia flares besides being antiviral drug of use. Besides, counteracting effect to MERS-COV infection through blocking its DDP4 mutual receptor [210] although DPP4 inhibitors such as sitagliptin, vildagliptin and saxagliptinare reported to be ineffective to block the hCoV-EMC human corona virus invasion to the human bronchial epithelial cells [203]. Various reasons have been reported to explain the feasibility of using DPP4 inhibitors as a hypoglycemic agent against hyperglycemia in case of SARS-COV2 infections. First, its reported anti-inflammatory and antifibrotic influences that reduces the extensiveness of cytokines storm, which in turn provides pulmonary tissues protective effect while the episode of severe disease status [72]. Second, blocking the DPP4 receptor recently reported to be a potential sub-optimal tissue tropism entry receptor to SARS-COV2[72, 220] although this postulation is argued by the fact that gliptin type inhibitors such as like sitagliptin, vildagliptin and linagliptin are proven to bind to a receptor pocket at least other than the MERS-COV [312] and SARS-COV2 spike protein interaction interface. Third, gilptin type inhibitors can modulate the immune components to a more controlled immune response [204, 313] as DPP4 is structurally resembles CD26 of T-lymphocytes, besides, enhancing insulin secretion. However, this receptor blockage by the use of its inhibitors for glycemic control in the infected diabetic individuals causes reduction of macrophages activity [51], hence, promoting the presumed SARS-COV2 infection severity. In addition, previous reports have demonstrated that there is no infection acquiring risk incline of their use in the immune compromised individuals [103, 314]. Fourth, the cardioprotective effect of some gliptin type DDP4 inhibitors like sitgliptin is preformed via ACE inhibition however, its counteraction by ACE inhibitors inclines the risk of angioedema development by 4-5 folds [315] potentially via bradikinine abolishment as well as substance P catabolism [316]. Thus, in case of existence of SARS-COV2 infection co-morbidity such as hypertension and cardiovascular disease some have recommended taken DPP4 inhibitors into consideration [103, 317] as they also have immune response interfering influence [31].

The immune response inhibitory/modulatory activity and SARS-COV2 infection liability promotion effects of the DDP4 inhibitors is still a paradoxical issue [318] since some meta analysis studies have emphasized their contribution to the elevation of various infections risks like promoting upper respiratory tract infections vulnerability although not inclining the risk of acquiring pneumonia [31, 220], while, other meta analysis studies have proposed the opposite [319-321]. In addition, DPP4 inhibitors also elevates the nasophayringitis as well as urinary tract infections due to its potential declining to the local inflammatory response because DPP4 is expressed in various immune cells including T-cells facilitating their activation as well as both CD86 and NFjb pathway expressions which mediate the inflammatory response [240]. Yet, other have reported no DPP4 inhibitors interference with the T-cells based immune response [322], hence, their use is not associated with any elevation in pneumonia acquiring risk [323, 324]. Furthermore, like other oral antidiabetic drugs, DPP4 inhibitors have been reported to interfere with various immune-modulatory biomolecules [103]. In this context, the thiazolidinone class of DPP4 can counteract the insulin resistance via targeting incretin system as a part of its hypoglycemic as well as anti-inflammatory effects which is presumed to decline SARS-COV2 infection disease severity as concluded from the preclinical investigations data [31, 325]. Pioglitazone, for example, have been reported to exhibit prohibiting influence on the proinflammatory cytokines including IL-6 release via its both anti-inflammatory and insulin resistance opposing influences besides its other opposing effect against diabetic ketoacidosis, cardiovascular conditions as well as other metabolic syndrome [326, 327]. Thus, some have recommended including it, as a hypoglycemic agent co-therapy in case of SARS-COV2 infection in diabetic individuals [327].

Remarkably, the highly selective DPP4 inhibitor, Sitagliptin when has been used for viral infections in cases of existence or lacking diabetes co-morbidity, it has exhibited a C-reactive protein, total stromal cell-derived factor-1 (CXCL12) and C-X-C motif chemokine 10reducing effect while, no alteration in the levels of other different twenty seven cytokines as well as several of the circulating activation factors of the monocytes induced by lipopolysaccharide or anti-CD3 antibody including CD14 sCD163, IL-6, sDPP4, sTNF-RIV and sTNF-RII. In addition no alterations have been reported in count of leukocytes (lymphocytes and T-cells) or TNF receptor II [328-331]even one year post starting treatment in type II diabetic individuals [332].Nevertheless, the DPP4 inhibitors anti-inflammatory as well as immune-modulatory influences dependent, SARS-COV2infection related cytokine storm counteraction still requires further investigations [31, 103].

Although the majority of the molecular biology studies have considered ACE2 as the virus solely receptors, however, a significant number of other studies have considered DPP4 as another sub-optimal receptor for unusual tissue tropism, thus its inhibitor can act as cell entry blocking antiviral as well as hypoglycemic drugs to treat SARS-COV2 infected diabetic individuals [31, 333, 334]. However, a fundamentally outstanding wanderings is the limit to which one can rely on oral anti-diabetic drugs particularly the DPP4 inhibitors to affect SARS-COV2 infection severity, prognosis and outcomes in the diabetic patients, since DPP4 inhibitors can block 50-95% of the membrane bounded as well as

circulating soluble DPP4 receptors [335] in addition to the reported 21.6% prognosis improvement of SARS-COV2 in diabetes infected individuals [31, 103, 240, 282].In this context, no significant safety issues was reported for saxagliptin, alogliptin, sitagliptin, and linagliptin concerning immune/inflammation abnormalities while infections when they are used for type II DM with the existence of cardiovascular/renal comorbidities according to clinical trial data [336-339]. Some DPP4 inhibitors such as vildagliptin have no influence on the immune response including the level of immune modulators such as IL-6 or CRP and other inflammatory cytokines [340].In addition, none of the use of DPP4 inhibitors in either of diabetetic and non-diabetic infected individuals have safety issues even in case of immune compramsiation [189]. SARS-COV2 infected diabetic individuals treated with DPP4 inhibitors have exploited lower disease severity and mortality rate [97]. Consequently, ongoing clinical trial for the use of DPP4 inhibitors for diabetic SARS-COV2 infected individuals, sitagliptin and linagliptin are in the third and fourth phases of clinical trials respectively [48, 130] although rosiglitazone is reported to elevate ACE in hypertension animal models [341]. However, unsufficient evidences are available for the long use of DPP4 inhibitors in type II DM on the SARS-COV2 infection due to this virus infection related sepsis, hypovolemia and renal impairment that requires dose adjustment for some agents while discontinuation of the others [146].

Moreover, pioglitazone have been demonstrated to elevate ACE2 expression in both insulin sensitive tissues of liver and muscle tissues hence promoting these tissues tropism while down regulation of disintegrin and metalloproteinase-17 (ADAM-17) in muscles [4, 240, 242] thus, both clinical practice and pharmacologist have recommended deserting their use [240, 342, 343] because the mentioned reason besides, elevated correlation to the vulornablity to community acquired pneumonia [21, 342, 344, 345]. However, its immune prohibiting influence may explain various reports regarding its lung protective influence against SARS-COV2 infection provoked cytokines storm as well as controlling blood sugars in the infected diabetes individuals [327]. Consequently, these human studies have reported pioglitazone related proinflammation cytokines declining effect againstIL-1b, IL-6, IL-8 and TNF-α in addition to its insulin-resistance counteraction and fibrosis inhibition effects [346, 347] although its use is contraindicated in cases of heart failure co-morbidity existence [68].

4.4. Hyperglycemia Sodium-Glucose-Transporter-2 (SGLT-2) Inhibitors Therapy During SARS-COV2 Infection

In general, SGLT-2 inhibitors are reported to enhance the SARS-COV2 kidneys tissue tropism as they inclines ACE2 expression/activity in the renal tissues [240], for their renal tissue protective influence in diabetic individuals is attributed [244, 348] as well as inclining the vasodialtory mediators, Ang 1-7levels although may enhance SARS-COV2 cell entry extent [349, 350].This class of hypoglycemic agents particularly gliflozins are also useful to manage nephron- and retino-pathies. They exert their hypoglycemic effect via inhibition of renal reabsorption of glucose from kidney tubules leading an elevated water and electrolytes excretion that may precipitate hypovolemia and dehydrate in male nourished diabetic individuals. In addition, this class of antidiabetic drugs has a reported immune modulatory influence via prohibition of pro-inflammatory amatoryes release especially IL-6 [351], highly elevated in most of poor prognosis cases of SARS-COV2 infection. Nevertheless, a state of euglycemic ketoacidosis is a potential issue presumed to occur in acute illnesses including SARS-COV2 among diabetic individuals on SGLT-2 inhibitors therapy [352, 353] which one of the common diabetes as well as SARS-COV2 infection co-morbidites [354]. Similarly SARS-COV2 infection itself also develops a state of diabetic ketoacidosis through pancreatic beta-cells tropism caused damage that mediates much worsened hyperglycemia [355].

Some authors have postulated that, in case of type II DM individuals with mild SARS-COV2 infection oral antidiabetic drugs probable can be continued in the usual dose, nevertheless, instant and continue modifications should be considered according the patient's situation including blood glucose level, fever, dehydration etc. Dehydration, loss of appetites and hypovolemia necessitate the immediate discontinuation of metformin andSGLT-2 inhibitors, particularly empagliflozin, dapagliflozin, ertugliflozin, in patients with type II DM when the disease condition becomes more seriousin moderate to severe states of infection [48, 68,86, 130] because at least SGLT-2 inhibitors are associated with development of dehydration and euglycemia ketoacidosis [21, 146, 356] on one had. Thus, drugs of this class particularly dapaglifozin approval for its use in moderate cases of SARS-COV2 infection is still a paradoxical issue between authors [72] since some of them have reported its feasibility to decline lactic acidosis during hypoxia in some infected diabetic individuals. On the other hand, An encouraging opposing effect to the cytokines storm, inflammatory blocking, as well as cardio/renal protective effects reported to this class of hypoglycemic agents in addition to its blocking influence to the tissue hypoxia, oxidative stress, autophagy and energy metabolism [146].However, clinical trial for its assessment regarding declining disease progress and death is continued [72, 146]. Thus, some authors have recommended their resume of administration after resolving the illness severity for their good outpatient tolerability, cardio/renal protective and metabolic advantages [86, 356]. Although (Bornstein, et al., 2020) have reported that severe diabetic ketoacidosis has been encountered in type I DM SARS-COV2 infected patients on SGLT2 inhibitors therapy [130].

Regarding dapagliflozin, some authors have reported that it inclines the blood pH through reducing circulating lactates via various mechanisms involving lactate/proton symporter activation while Na/hydrogen antiport inhibition. Thus, its cytosolic pH decline reducing activity is believed to lie behind viral load counteracting effect and reducing SARS-COV2 disease severity in the infected diabetic individuals on its therapy [68, 146, 240, 357]. However, according to theoretical perspective, dapagliflozin, through NHE inhibition, higher risk of dehydration contribution and acute kidney injury may cause intracellular acidosis [358] that is exaggerated by the SARS-COV2 developed fever and tachypnea that contribute to water loss [130].Consequently, some authors have reported their speculations regarding the potential deleterious influences of using SGLT2 inhibitors in the SARS-COV2infected diabetic individuals [240, 359]. Although only 1% reported euglycemia diabetic ketoacidosis are encountered with SGLT2 inhibitors, it is postulated that dapagliflozin dose reduction and its lactate declining effect may lie behind its diabetic ketoacidosis side effect [353].Thus, reconsidering the use of SGLT2 inhibitors eventide for diabetic individuals who encountered renal functions impairments due to acquiring SARS-COV2 infection is required after discontinuation while metformin and suflonylureas requires dose tapering or even discontinuation during such conditions [103].

4.5. Hyperglycemia Glucagon-Like-Peptide-1 (GLP-1) Receptor Agonists Therapy During SARS-COV2 Infection

Few short period studies have been performed regarding the use of the GLP-1 receptor agonists antidiabetic drugs for cases of preoperative as well as ICU treatment of diabetes [360, 361], yet, short inadequate experiences are available for its use for critically ill diabetic patients in the ICU units [362], currently the outstanding SARS-COV2 pandemic. However, a beneficial wide spectrum anti-inflammatory activity including reducing the level of circulating inflammatory mediators such as cytokines have been reported to these drugs while using by type II DM obese diabetic individuals during pulmonary inflammations leading to decline lungs injury whether induced by lipopolysaccharide or allergens[103, 363-366]. Similarly, it is reported that this class of the antidiabetic drugs can also decline the innate type 2 pulmonary cytokines responses next to viral infections [367]. In addition, this class of drugs particularly liraglutide when used alone or in combination with insulin also has exhibited a good safety profile in patients with cardiovascular diseases even in cases of co-existence of inflammatory disorders as well as severe infections [368-373] although some have recommended eventide discontinuation [146].

Interestingly, some authors has proposed that GLP1 receptor agonists elicit their hypoglycemic activity via influencing ACE2 and Mas receptors axis pathway related to both inflammation as well as fibrosis processes thus through using this class of antidiabetic drugs for diabetic SARS-COV2 individuals two advantages are gained, the hypoglycemic effect as well as counteracting SARS-COV2 virus entry through ACE2 binding compaction [374] beside, their cytokines storm and insulin resistance counteracting influence through declining the circulating inflammatory mediators [103, 375] despite their reported nausea and dehydration side effects. Nevertheless, tightly close monitoring is still necessary [130].The renal and cardiovascular protective influence of both GLP-1 receptor agonists and SGLT-2 inhibitors makes these two classes of the antidiabetic drugs are rational choices to be used for SARS-COV2 diabetic individuals with both renal cardiovascular as well as renal co-morbidities [1]. However, ACE2 over-expression inducing effects of the two classes is the only obstacle facing their prescribe [240] beside the reported gastrointestinal reported adverse effect, thus, medical experts have recommended avoiding their use [239]. In addition, eventide group of the GLP1 should be immediately while SAR-COV2 infection onset particularly in presence of renal impairment co-morbidity [68].

Liraglutide, is unfortunately have been reported to elevated ACE2 expression in both lung and heart tissues [240, 243] making them much susceptible to SARS-COV2 tropism despite this enhanced ACE2 expression as well as its mutual anti-inflammatory influence are beneficial for acute lung and cardiovascular tissues damage mitigation [376]. Besides, in type I DM animal models, it can also enhance lung tissues ACE2 expression while inclining the circulating Angiotensin(1-7) levels without affecting glycemic control or insulin level [243]. This probably happens via direct lungs GLP-1R signaling pathway- liraglutide without influencing the pancreatic hormones release [103]. Interestingly, both liraglutide and linagliptin (DPP4 inhibitor) have been reported to exhibit cardio-protective as well as antihypertensive influences [377] which as useful for such SARS-COV2 infected diabetic patients with hypertension and other related cardiovascular illnesses.

In fact, there are very limited clinically approved evidences reported regarding the benefit/disadvantages of ACE2 or DPP4 targeting drugs to be included as corona viruses infections particularly in the existence of diabetes/metabolic burden of the virus infection. The clinical experience evidences for their use as an oral replacement to parenteral insulin for the critically ill hospitalized diabetic patients with SARS-COV2 infection are still inadequate. However, both of the orally administered DPP4 inhibitors and GLP-1 receptor agonists have been reported to be successfully used to control the glycemic state in hospitalized patients with making use of their anti-inflammatroy advantages. Therefore, it is obvious that both theoretical perspectives as well clinical evidences/back grounds support the use of parenteral insulin

as a hypoglycemic agent of choice for non-diabetic individuals hyperglycemia flares/diabetic individuals with SARS-COV2 infection [103] although tightly close and continues blood glucose monitoring is required.

5. The use of other drugs

Identifying the existent co-morbidity as accompanying risk factor that determines the prognosis of SARS-COV2 infection in diabetic individual is the cornerstone for both medical intervention and preventing the deleterious fate of the infection [357]. The benefit of using angiotensine converting enzyme (ACE) inhibitors or angiotensine II (Ang II) receptor blockers is a matter of controversy between authors. Some have proposed that using of ACE inhibitors or Ang II blockers, prescribed for patients with cardiovascular and nephropathy condition, is correlated to a lower mortality rate [103, 378-381], thus, recommending their use [382] for their renal/cardiovascular protective, anti-inflammatory insulin sensitivity maintenance influences besides the (Ang II) receptor blockers normal coagulation functions maintenance [383, 384].While, the others not agree with that speculation [379, 380] as the utilization of these two classes of the antihypertension drugs for diabetic individuals are co-related to the up regulation of ACE2 receptor compensation to the inclined levels of angiotensines, thus enhancing viral tissues tropism [4, 121, 385] particularly the lungs, heart, intestine, kidney and vascular endothelium leading to poor prognosis and elevated mortality rate [4].Losartan for example inhibits the internalization/cytosolic catabolism of ACE2 receptors via inhibiting angiotensin II interaction with the AT1 receptor [4, 386].It is reported that ACE inhibitor use in diabetic individuals infected with SARS-COV2 inclines the disease severity [14, 33].However, a third group of author have reported a neutral impact on SARS-COV2 infection severity, prognosis or mortality rate [282].It is believed that this paradoxical influences to the ACE2 receptor polymorphism caused by diabetes and SARS-COV2 infection. However, some reported that no valuable evidences have been presented for the involvement of these two classes of drugs in the up regulation of ACE2 receptor [183, 387]. Thus, in the co-existence of cardiovascular as well as hypertension co-morbidities it is proposed that renin–angiotensin–aldosterone system (RAAS) blockers as well as dipeptidyl peptidase (DPP)-4 inhibitors should be avoided as they may enhance SARS-COV2 virus cell entry, although DPP4 inhibitors has immune system interference [31, 103, 317, 379]. Others have reported that its reduce tracheal intubation in the virus infection [388, 389]. In addition, DPP4 inhibitors, angiotensin II receptor blockers, ACE inhibitors advantages for use in diabetic infected individuals are not exclusively confirmed [390].

Hydroxychloroquine is hypothesized to inhibit the SARS-COV2 virus spike protein-ACE2 receptor interaction via pH dependent receptor stereochemistry changes induced by its cytosolic pH inclining effect [349, 391]. Hydroxychloroquine alone or in combination with zinc supplement is safe to be used for the treatment of SARS-COV2 in diabetic individual [392]. However, it is reported that hydroxychloroquine induces non-insulin hypoglycemia associated with QT wave interval abnormality that may precipitate many complications such as cardio-vascular, cerebrovascular, as well as neurologic complications [67]. In fact, hydroxychloroquine use for SARS-COV2 infection is primarily considered for its immune modulatory influence, yet, the existence of diabetes retino- as well as cardio-pathies should be considered prior administration [240, 393]. Interestingly, in India, hydroxychloroquine is recommended as a third line added drug to treat type II DM at a dose of 400 mg as it reduce the blood sugar via two potential modes of action. The first; involve inhibition of insulin degradation via its intracellular pH inclining effect, thus, insulin in its active form elicits additional activity. The second, involve reducing insulin resistance via its immune modulatory effect that reduces cytokines release particularly IL-6 as well as TNF α [240, 394]. Furthermore, hydroxychloroquine also exhibits its SARS-COV2 induced cytokine strom via inhibition of virus antigen release through inclining the intracellular/endosomal pH, cytosolic Toll-like receptor (TLR)-signaling, pro-inflammatory cytokines transcription as well as T-cells activation [392, 236]. Diabetic individuals with asymptomatic SARS-COV2 infection who are on hydroxychloroquine have been recommended to monitor their blood glucose for hypoglycemia. In addition, other oral hypoglycemic drugs must be taken in consideration to avoid the potential hypoglycemia, metformine dose should be reduced while and SGLT2 inhibitors, GLP1 analogues should be discontinued [395].

6. Conclusion

Hyperglycemia is an outstanding issue associated with several microbial infection particularly in case of diabetes co-existence however, some viral infections deteriorates the infected diabetic individuals glycemic state as frequently reported for SARS-COV2 viral infection. Reports have established the higher prevalence, poorer prognosis as well as higher mortality rates associated with SARS-COV2 infection among diabetic individuals. Consequently, all authors and medical practitioners have globally recommended good glycemic control for ensuring reducing disease severity as well as better survival rate. Up to date, insulin is the hypoglycemic agent of choice for treating hyperglycemia condition encountered during the onset of SARS-COV2 infection although a tightly close monitoring to blood glucose is required in order to avoid hypoglycemia especially in critically ill or ICU admitted patients who are intolerant of food intake.

Nevertheless, paradoxical speculations and reports are issued regarding oral hypoglycemic agents, although good reports about additional advantages of immune modulation, anti-inflammatory, cardiovascular and renal protective beside their hypoglycemic effects are reported to (GLP-1) Receptor Agonists, Sodium-Glucose-Transporter-2 (SGLT-2) Inhibitors, pioglitazone. Although, several reports about various side effects associated with these drugs including dehydration hypovolemia, gastrointestinal and precipitating lactic acidosis side effects. Thus, paradoxical speculations and recommendation are reported for this class of drugs. Some authors and clinical experts recommended their discontinuation in cases of GI symptoms and severe illness, while, the others recommended their use at least for the mild cases of infection in diabetic patients. However, few data analysis reports are issued regarding oral hypoglycemic drugs use in practice, while the current SARS-COV2 in order to conclude an exclusive judgment for their clinical feasibility.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors confirm that there is no conflict of interest.

References

[1] Zhou F, Yu T, Du R, Fan G, Liu Y, Guan L, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet. 2020; 395(10299):1054-1062.

[2] Wu Z, McGoogan J M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13): 1239-1242.

[3] Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. Journal of Clinical Virology. 2020;(127): 104354.

[4] Fang L, Karakiulakis G, Roth M. (2020). Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?. The Lancet. Respiratory Medicine. 2020; 8(4):e21.

[5] Gupta R, Ghosh A, Singh A K, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diabetes & metabolic syndrome. 2020; 14(3): 211-212.

[6] Wu C, Chen X, Cai Y, Zhou X, Xu S, Song J, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine.2020; 180(7):934-943.

[7] Yang X, Yu Y, Xu J, Shu H, Liu H, Wang Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020; 8(5): 475–481.

[8] Yuan M, Yin W, Tao Z, Tan W, Hu Y. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. PloS one. 2020;15(3): e0230548.

[9] Cao J, Hu X, Cheng W, Yu L, Tu W J, Liu Q. Clinical features and short-term outcomes of 18 patients with corona virus disease 2019 in intensive care unit. Intensive care medicine. 2020; 46(5):851-853.

[10] Huang C, Wang Y, Li X, Ren L, Zhao J, Cheng Z, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506.

[11] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhao Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020; 323(11):1061-1069.

[12] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Zhou Y. et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020; (94):91–95.

[13] Al-Sa'idy HAH, Alyousif BT, Al-Snafi AE. An insight to the incidence of acute pancreatitis, and co-morbidity of diabetes in SARS-COV2 infection. GSC Biological and Pharmaceutical Sciences, 2022;19(1):113–137.

[14] Zhang J J, Dong X, Cao Y Y, Yuan Y D, Yang Y B, Gao Y D, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-1741.

[15] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine. 2020;46(5):846-848.

[16] Chen N, Zhou M, Dong X, Qu J, Gong F, Yu T, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020; 395(10223):507-513.

[17] Sun P, Lu X, Xu C, Sun W, Pan B. Understanding of COVID-19 based on current evidence. Journal of Medical Virology. 2020; 92(6): 548-551.

[18] Frier B M. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. Nature Reviews Endocrinology. 2014;10(12):711.

[19] Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. Journal of Infection. 2020;81(1):e13-e20.

[20] Chen X, Hu W, Ling J, Mo P, Zhang Y, Zheng R, et al., (2020). Hypertension and diabetes delay the viral clearance in COVID-19 patients. Med Rxiv. 2020;https://doi:10.1101/2020.03.22.20040774.

[21] Singh A K, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(4):303-310.

[22] Kalra S, Mittal S. COVID-19 and diabetes: Covidiabetology. J Pak Med Assoc. 2020; 70(6):954-955.

[23] Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian Journal of Endocrinology and Metabolism. 2012; 16(Suppl1): S27-S36.

[24] Kalra S, Khandelwal D. Thyrovigilance in diabetes; glucovigilance in thyroidology. Primary Care Diabetes. 2018; 68(6): 966-67.

[25] Vanhorebeek I, Gunst J, Van den Berghe G. Critical care management of stress-induced hyperglycemia. Current Diabetes Reports. 2018; 18(4) :17.

[26] Remuzzi A, Remuzzi G. COVID-19 and Italy: what next?. The Lancet. 2020; 395(10231): 1225-1228.

[27] Yang J K, Feng Y, Yuan M Y, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med. 2006;23(6):623–628.

[28] Song Z, Xu Y, Bao L, Zhang L, Yu P, Qin C, et al. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses. 2019;11(1):59.

[29] Fadini G P, Morieri M L, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. Journal of Endocrinological Investigation. 2020; 43:867–869.

[30] Petrilli C M, Jones S A, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. Bmj. 2020;(369):1966.

[31] Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role?. diabetes research and clinical practice. 2020;(162):108125.

[32] Cuschieri S, Grech S. COVID-19 and diabetes: The why, the what and the how. Journal of Diabetes and its Complications. 2020;34(9):107637.

[33] Guan W J, Ni Z Y, Hu Y, Liang W H, Ou C Q, Du B, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18):1708-1720.

[34] Hill, M. A., Mantzoros, C., & Sowers, J. R. Commentary: COVID-19 in patients with diabetes. Metabolism. 2020; (107):154217.

[35] Morra M E, Van Thanh L, Kamel M G, Ghazy A A, Altibi A M, Elabd S S, et al. Clinical outcomes of current medical approaches for Middle East respiratory syndrome: a systematic review and meta-analysis. Reviews in Medical Virology. 2018; 28(3): e1977.

[36] López-Cano C, Lecube A, García-Ramírez M, Muñoz X, Sánchez E, Simó R, et al. Serum surfactant protein D as a biomarker for measuring lung involvement in obese patients with type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2017; 102(11): 4109-4116.

[37] Lecube A, Simó R, Pallayova M, Punjabi N M, López-Cano C, Barbé, F, et al. Pulmonary function and sleep breathing: two new targets for type 2 diabetes care. Endocrine reviews. 2017; 38(6): 550-573.

[38] Philips B J, Meguer J X, Redman J, Baker E H. Factors determining the appearance of glucose in upper and lower respiratory tract secretions. Intensive Care Medicine. 2003; 29(12): 2204-2210.

[39] Tay M Z, Poh C M, Re´nia L, MacAry P A, Ng L F P. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6): 363-374.

[40] Zhou J, Tan J, Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. Metabolism. 2020; (107), 154216.

[41] Sardu C, D'Onofrio N, Balestrieri M L, Barbieri M, Rizzo M R, Marfella R, et al. Outcomes in Patients With Hyperglycemia Affected by Covid-19: Can We Do More on Glycemic Control?. Diabetes Care. 2020; 43(7): 1408-1415.

[42] Lucas Martín A M, Guanyabens E, Zavala-AraucoR, Chamorro J, Granada M L, Mauricio D, Puig-Domingo M. Breaking therapeutic inertia in type 2 diabetes: active detection of in-patient cases allows improvement of metabolic control at midterm. International Journal of Endocrinology. 2015;(2015):1–5.

[43] Rayman G E R R Y, Lumb A, Kennon B, Cottrell C, Nagi D, Higgins K, et al. New Guidance on Managing Inpatient Hyperglycaemia during the COVID-19 Pandemic. Diabetic Medicine. 2020;37(7):1210-1213.

[44] Kornum J B, Thomsen R W, Riis A, Lervang H H, Schønheyder H C, Sørensen H T. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. Diabetes Care. 2008;31(8):1541-1545.

[45] Kornum J B, Thomsen R W, Riis A, Lervang H H, Schønheyder H C, Sørensen H T. (2007). Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care. 2007;30(9):2251-2257.

[46] Martins M, Boavida J M, Raposo J F, Froes F, Nunes B, Penha-Gonçalves C, et al. Diabetes hinders community-acquired pneumonia outcomes in hospitalized patients. BMJ Open Diabetes Research and Care. 2016; 4(1):e000181.

[47] Asselta R, Paraboschi E M, Mantovani A, Duga S. ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging (Albany NY). 2020;12(11):10087-10098.

[48] Bansal R, Gubbi S, Muniyappa R. Metabolic syndrome and COVID 19: endocrine-immune-vascular interactions shapes clinical course. Endocrinology. 2020;161(10):1-15.

[49] Fernandez C, Rysä J, Almgren P, Nilsson J, Engström G, Melander O, et al. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. Journal of internal medicine. 2018;284(4): 377-387.

[50] Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach, A, Li F. Cell entry mechanisms of SARS-CoV-2. Proceedings of the National Academy of Sciences. 2020;117(21):11727-11734.

[51] Hodgson K, Morris J, Bridson T, Govan B, Rush C, Ketheesan N. Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. Immunology. 2015;144(2):171-185.

[52] Hadjadj, J., Yatim, N., Barnabei, L., Corneau, A., Boussier, J., Carlier, N., et al. Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients. Science. 2020; 369(6504):718-724.

[53] Blanco-Melo D, Nilsson-Payant B E, Liu W C, Uhl S, Hoagland D, Wang T T, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020; 181(5):1036-1045.

[54] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Tai Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine. 2020; 8(4):420-422.

[55] Grundy S M, Metabolic syndrome. In: Bonora E, DeFronzo R A, eds. Diabetes Complications, Comorbidities and Related Disorders. Cham: Springer International Publishing. 2020:71–107.

[56] Wu J, Li W, Shi X, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). J Intern Med. 2020; 288(1):128-138.

[57] Soares A L, Sousa M D O, Fernandes A P S M, Carvalho M D G. Hemostatic changes in patients with type 2 diabetes mellitus. Rev. bras. hematol. Hemoter. 2010;32(6):482-488.

[58] Oggianu L, Lancellotti S, Pitocco D, Zaccardi F, Rizzo P, De Cristofaro R, et al. The oxidative modification of von Willebrand factor is associated with thrombotic angiopathies in diabetes mellitus. PLoS One. 2013;8(1):e55396.

[59] Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerging Microbes & Infections. 2020; 9(1):687-690.

[60] Yang J K, Lin S S, Ji X J, Guo L M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta diabetologica. 2010;47(3):193-199.

[61] Mukherjee S, Banerjee O, Singh S, Maji B K. COVID 19 could trigger global diabetes burden–A hypothesis. Diabetes & Metabolic Syndrome. 2020;14(5):963.

[62] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler Müller, M A, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;(181):1-10.

[63] Ding Y, He L I, Zhang Q, Huang Z, Che X, Geng J, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. The Journal of Pathology. 2004;203(2):622-630.

[64] Wu Q, Zhou L, Sun X, Yan Z, Hu C, Li K, et al. Altered lipid metabolism in recovered SARS patients twelve years after infection. Scientific Reports. 2017;7(1):1-12.

[65] Wensveen F M, Šestan M, Turk Wensveen T, Polić B.'Beauty and the beast'in infection: How immune–endocrine interactions regulate systemic metabolism in the context of infection. European Journal of Immunology. 2019; 49(7):982-995.

[66] Ghosal S, Arora B, Dutta K, Ghosh A, Sinha B, Misra A.Increase in the risk of type 2 diabetes during lockdown for the COVID19 pandemic in India: A cohort analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020; 14(5):949-952.

[67] Lamptey R, Ahomagnon S, Acheampong F, Kalra S. Glucovigilance in COVID-19. J Pak Med Assoc. 2020; 70(Suppl 3)(5):S80-S82.

[68] Jeong I K, Yoon K H, Lee M K. Diabetes and COVID-19: Global and regional perspectives. Diabetes Research and Clinical Practice. 2020;(166):108303.

[69] Huang I, Lim M A, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia–a systematic review, meta-analysis, and meta-regression. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020; (14):395–403.

[70] Guan W J, Liang W H, Zhao Y, Liang H R, Chen Z S, Ou C Q, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. European Respiratory Journal. 2020; 55(5):2000547.

[71] Puig-Domingo M, Marazuela M, Giustina A. COVID-19 and endocrine diseases. A statement from the European Society of Endocrinology. Endocrine. 2020;68(1):2-5.

[72] Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Reviews in Endocrine and Metabolic Disorders.2020; 21(4):495-507.

[73] Leung C. Risk factors for predicting mortality in elderly patients with COVID-19: a review of clinical data in China. Mechanisms of Ageing and Development. 2020;(188):111255

[74] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Zhao L, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes/Metabolism Research and Reviews. 2020;36(7):e3319.

[75] Xie J, Tong Z, Guan X, Du B, Qiu H. Clinical characteristics of patients who died of coronavirus disease 2019 in China. JAMA. 2020;3(4):e205619-e205619.

[76] Liu K, Fang Y Y, Deng Y, Liu W, Wang M F, Li G C, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020;133(9):1025-1031.

[77] Xu X W, Wu X X, Jiang X G, Xu K J, Ying L J, Sheng J F, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;(368):606.

[78] Wang G, Wu C, Zhang Q, Wu F, Yu B, Zhong Y, et al. Epidemiological and clinical features of corona virus disease 2019 (COVID-19) in Changsha, China. Medicine (Baltimore). 2020; 99(34):e21824.

[79] Wan S, Xiang Y, Fang W, Zheng Y, Li B, Huang X, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. Journal of Medical Virology. 2020; 92(7):797-806.

[80] Hui H, Zhang Y, Yang X, Wang X, He B, Chen Y, et al. Clinical and radiographic features of cardiac injury in patients with 2019 novel coronavirus pneumonia. Med Rxiv. 2020; https://doi.org/10.1101/2020.02.24.20027052.

[81] Shi H, Han X, Jiang N, Cao Y, Alwalid O, Zheng C, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases. 2020; 20(4) :425-434.

[82] Zhao S, Ling K, Yan H, Zhong L, Peng X, Yao S, et al. Anesthetic management of patients with COVID 19 infections during emergency procedures. J Cardiothorac Vasc Anesth. 2020; 34(5):1125–1131.

[83] Hu L, Chen S, Fu Y, Gao Z, Long H, Xu Q B, et al. Risk factors associated with clinical outcomes in 323 COVID-19 hospitalized patients in Wuhan, China. Clinical Infectious Diseases. 2020;71(16):2089-2098.

[84] Wang L, He W, Yu X, Hu D, Bao M, Jiang H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. Journal of Infection. 2020;80(6): 639-645.

[85] Liu Y, Sun W, Chen L, Wang Y, Zhang L, Yu L. Clinical Characteristics and Progression of 2019 Novel Coronavirus-Infected Patients Concurrent Acute Respiratory Distress Syndrome. Med Rxiv. 2020; https://doi.org/10.1101/2020.02.17.20024166.

[86] Sacks L J, Pham C T, Fleming N, Neoh S L, Ekinci E I. Considerations for people with diabetes during the Coronavirus Disease (COVID-19) pandemic. Diabetes Research and Clinical Practice. 2020; (166):108296.

[87] Xu S, Fu L, Fei J, Xiang H X, Xiang Y, Tan X Y, et al. Acute kidney injury at early stage as a negative prognostic indicator of patients with COVID-19: a hospital-based retrospective analysis. Med Rxiv. 2020; https://doi.org/10.1101/2020.03.24.20042408.

[88] Bhatraju P K, Ghassemieh B J, Nichols M, Kim R, Jerome K R, Kritek P A, et al. Covid-19 in critically ill patients in the Seattle region—case series. New England Journal of Medicine. 2020;382(21):2012-2022.

[89] Li X, Wang L, Yan S, Yang F, Xiang L, Gong Z. (2020). Clinical characteristics of 25 death cases with COVID-19: a retrospective review of medical records in a single medical center, Wuhan, China. International Journal of Infectious Diseases. 2020;(94):128-132.

[90] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Iotti G, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020; 323(16):1574-1581.

[91] Covid C D C, COVID, C, COVID, C, Chow N, Fleming-Dutra K, Roguski K, et al. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States. Morbidity and Mortality Weekly Report. 2020; 69(13):382.

[92] Petrilli C M, Jones S A, Yang J, Rajagopalan H, O'Donnell L F, Horwitz L I, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. BMJ. 2020;(369) :1966.

[93] Ferrari R, Maggioni A P, Tavazzi L, Rapezzi C. (2020). The battle against COVID-19: mortality in Italy. European Heart Journal Eur Heart J. 2020; 41(22):2050-2052.

[94] Gentile S, Strollo F, Ceriello A. COVID-19 infection in Italian people with diabetes: Lessons learned for our future (an experience to be used). Diabetes Res Clin Pract. 2020; (162):108137.

[95] Wang W, Lu J, Gu W, Zhang Y, Liu J, Ning G. Care for diabetes with COVID-19: Advice from China. Journal of Diabetes. 2020; 12(5):417-419.

[96] Kluge H H P, Wickramasinghe K, Rippin H L, Mendes R, Peters D H, Kontsevaya A, Breda J. Prevention and control of non-communicable diseases in the COVID-19 response. The Lancet. 2020; 395(10238):1678-1680.

[97] Zhu L, She Z G, Cheng X, Qin J J, Zhang X J, Li H, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020; 31(6):1068-1077.

[98] Kirby T. South America prepares for the impact of COVID-19. Lancet Respir Med. 2020;8(6):551-552.

[99] Rodriguez-Morales A J, Gallego V, Escalera-Antezana J P, Méndez C A, Zambrano L I, Risquez A, et al. COVID-19 in Latin America: The implications of the first confirmed case in Brazil. Travel Med Infect Dis. 2020;(35):101613.

[100] Cimerman S, Chebabo A, da Cunha C A, Rodríguez-Morales A J. Deep impact of COVID-19 in the healthcare of Latin America: the case of Brazil. Braz J Infect Dis. 2020;24(2):93-95.

[101] Hussain A, Bhowmik B, do Vale Moreira N C. COVID-19 and diabetes: Knowledge in progress. Diabetes research and clinical practice, Diabetes Res Clin Pract. 2020; (162):108142.

[102] Han Cho, N. International Diabetes Federation (IDF). IDF Diabetes Atlas, 6th ed. International Diabetes Federation, Brussels, Belgium, 2014.

[103] Drucker D J. Coronavirus infections and type 2 diabetes—shared pathways with therapeutic implications. Endocrine Reviews. 2020;41(3):11.

[104] Abdi A, Jalilian M, Sarbarzeh P A, Vlaisavljevic Z. Diabetes and COVID-19: A systematic review on the current evidences. Diabetes Research and Clinical Practice. 2020;(166):108347.

[105] Avogaro A, Albiero M, Menegazzo L, de Kreutzenberg S, Fadini G P. Endothelial dysfunction in diabetes: the role of reparatory mechanisms. Diabetes Care. 2011; 34(Suppl 2):S285–290.

[106] Palladino R, Tabak A G, Khunti K, Valabhji J, Majeed A, Millett C, Vamos E P. Association between pre-diabetes and microvascular and macrovascular disease in newly diagnosed type 2 diabetes. BMJ Open Diabetes Research and Care. 2020; 8(1):e001061.

[107] Chance W W, Rhee C, Yilmaz C, Dane D M, Pruneda M L, Raskin P, et al. Diminished alveolar microvascular reserves in type 2 diabetes reflect systemic microangiopathy. Diabetes Care. 2008;31(8):1596-601.

[108] Sandler M, Bunn A E, Stewart R I. Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. Am Rev Respir Dis. 1987;135(1):223-229.

[109] Mori H, Okubo M, Okamura M, Yamane K, Kado S, Egusa G, et al. (1992), Abnormalities of pulmonary function in patients with non-insulin-dependent diabetes mellitus. Intern Med. 1992;31(2):189-193.

[110] Whyte M B, Vas P, Heiss C, Feher M D. The contribution of diabetic micro-angiopathy to adverse outcomes in COVID-19. Diabetes Research and Clinical Practice. 2020; (164):108217.

[111] Vague P, Raccah D, Juhan-Vague I. Hemobiology, vascular disease, and diabetes with special reference to impaired fibrinolysis. Metabolism. 1992; 41(5):2-6.

[112] Williams S B, Goldfine A B, Timimi F K, Ting H H, Roddy M A, Simonson D C, Creager M A. Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. Circulation. 1998; 97(17), 1695-1701.

[113] MacRury S M, Gemmell C G, Paterson K R, MacCuish A C. Changes in phagocytic function with glycaemic control in diabetic patients. Journal of clinical pathology. 1989; 42(11):1143-1147.

[114] Wan Y, Shang J, Graham R, Baric R S, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. Journal of Virology. 2020; 94(7): 127.

[115] Singh A K, Singh R. Does poor glucose control increase the severity and mortality in patients with diabetes and COVID-19?. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, Diabetes Metab Syndr. 2020; 14(5):725-727.

[116] Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, Klonoff D C. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. Journal of Diabetes Science and Technology. 2020; 14(4):813-821.

[117] Olariu E, Pooley N, Danel A, Miret M, Preiser J C. A systematic scoping review on the consequences of stress-related hyperglycaemia. PloS one. 2018; 13(4):e0194952.

[118] Umpierrez G E, Isaacs S D, Bazargan N, You X, Thaler L M, Kitabchi A E. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. The Journal of Clinical Endocrinology & Metabolism. 2002; 87(3): 978-982.

[119] Raoufi M, Khalili S, Mansouri M, Mahdavi A, Khalili N, Well-controlled vs poorly-controlled diabetes in patients with COVID-19: Are there any differences in outcomes and imaging findings?. Diabetes Research and Clinical Practice. 2020;(166):1018286.

[120] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323(18):1775-1776.

[121] Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. diabetes research and clinical practice. 2020;(162):108132.

[122] Wang Z, Du Z, Zhu F. Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients. Diabetes Research and Clinical Practice. 2020; (164):108214.

[123] Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol-Endocrinol Metabol. 2020; 318(5):E736–741.

[124] Alkundi A, Mahmoud I, Musa A, Naveed S, Alshawaf M. Clinical characteristics and outcomes of COVID-19 hospitalized patients with diabetes in UK: A retrospective single centre study. Diabetes Research and Clinical Practice. 2020;(165):108263.

[125] Covid C, Team R, Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States. MMWR Morb Mortal Wkly Rep. 2020; 69(12):343–346.

[126] Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Radiology. 2020; 295(1):210–217.

[127] Li K,Wu J,Wu F, Guo D, Chen L, Fang Z, et al. The Clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol. 2020; 55(6):327–331.

[128] Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes/Metabolism Research and Reviews. 2020;36(7):3321.

[129] Katulanda P, Dissanayake H A, Ranathunga I, Ratnasamy V, Wijewickrama P S, Matthews D R, et al. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. Diabetologia. 2020; 63(8):1440-1452.

[130] Bornstein S R, Rubino F, Khunti K, Mingrone G, Hopkins D, DeVries J H, et al. Practical recommendations for the management of diabetes in patients with COVID-19. The lancet Diabetes & endocrinology. 2020;8(6):546-550.

[131] Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020;5(4):562–569.

[132] Pal R, Banerjee, M. COVID-19 and the endocrine system: exploring the unexplored. Journal of Endocrinological Investigation.2020; 43(7):1027-1031.

[133] Gheblawi M, Wang K, Viveiros A, Nguyen Q, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circulation Research. 2020;126(10):1456-1474.

[134] Zhang X, Zheng J, Yan Y, Ruan Z, Su Y, et al. Angiotensin-converting enzyme 2 regulates autophagy in acute lung injury through AMPK/mTOR signaling. Archives of Biochemistry and Biophysics. 2019; (672):108061.

[135] Liu ., Li X, Lu Q, Ren D, Sun X, et al. AMPK: a balancer of the renin–angiotensin system. Bioscience Reports. 2019;39(9):BSR20181994.

[136] Plattner F, Bibb J A.Serine and threonine phosphorylation. In Basic Neurochemistry. Academic Press. Elsevier. 2012; https://doi.org/10.1016/B978-0-12-374947-5.00025-0.

[137] Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: A possible role beyond diabetes. Diabetes Research and Clinical Practice. 2020;(164):108183

[138] Wang K, Gheblawi M, Oudit G Y. Angiotensin converting enzyme 2: a double-edged sword. Circulation. 2020; 142(5) :426-428.

[139] Thaweerat W. Current evidence on pancreatic involvement in SARS-CoV-2 infection. Pancreatology. 2020; 20(5):1013-1014.

[140] Muniraj T, Dang S, Pitchumoni C S. PANCREATITIS OR NOT?–Elevated lipase and amylase in ICU patients. Journal of Critical Care. 2015;30(6) :1370-1375.

[141] Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic injury patterns in patients with COVID-19 pneumonia. Gastroenterology. 2020; 159(1):367-370.

[142] Liu F, Long X, Zou W, Fang M, Wu W, Zhang Z, et al. Highly ACE2 expression in pancreas may cause pancreas damage after SARS-CoV-2 infection. Med Rxiv. 2020, https://doi.org/10.1101/2020.02.28.20029181.

[143] Yao X H, Li T Y, He Z C, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. Zhonghua Bing Li Xue Za Zhi. 2020; 49(5) :411-417.

[144] Hadi A, Werge M P, Kristiansen K T, Pedersen U G, Karstensen J G, Novovic S, Gluud L L. Coronavirus Disease-19 (COVID-19) associated with severe acute pancreatitis: Case report on three family members. Pancreatology. 2020;20(4): 665-667.

[145] Aloysius M M, Thatti A, Gupta A, Sharma N, Bansal P, Goyal H. COVID-19 presenting as acute pancreatitis. Pancreatology. 2020; 20(5):1026–1027.

[146] Cure E, Cure M C. Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes & Metabolic Syndrome. 2020;14(4):405-406.

[147] Jiang F, Yang J, Zhang Y, Dong M, Wang S, Zhang C, et al. Angiotensin-converting enzyme 2 and angiotensin 1–7: novel therapeutic targets. Nature Reviews Cardiology. 2014;11(7):413.

[148] Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clinical Gastroenterology and Hepatology. 2020;18(9):2128-2130.

[149] Bindom S M, Hans C P, Xia H, Boulares A H, Lazartigues E. (2010). Angiotensin I–converting enzyme type 2 (ACE2) gene therapy improves glycemic control in diabetic mice. Diabetes. 2010;59(10):2540-2548.

[150] Shoemaker R, Yiannikouris F, Thatcher S, Cassis L. ACE2 deficiency reduces β-cell mass and impairs β-cell proliferation in obese C57BL/6 mice. American Journal of Physiology-Endocrinology and Metabolism. 2015;309(7):E621-E631.

[151] Oudit G Y, Liu G C, Zhong J, Basu R, Chow F L, Herzenberg A M, et al. Human recombinant ACE2 reduces the progression of diabetic nephropathy. Diabetes. 2010;59(2):529-538.

[152] Thomas M C, Pickering R J, Tsorotes D, Koitka A, Sheehy K, Chin-Dusting J, et al. Genetic Ace2 deficiency accentuates vascular inflammation and atherosclerosis in the ApoE knockout mouse. Circulation Research. 2010; 107(7):888-897.

[153] Takeda M, Yamamoto K, Takemura Y, Takeshita H, Hongyo K, Takeya Y, et al. Loss of ACE2 exaggerates high-calorie diet–induced insulin resistance by reduction of GLUT4 in mice. Diabetes. 2013;62(1):223-233.

[154] Jin D X, Yang A L, Suleiman S L, McNabb-Baltar J, Banks P A. Tu1424–Marked Serum Lipase Elevations are Associated with Longer Hospitalizations in Patients with Non-Pancreatic Hyperlipasemia. Gastroenterology. 2019; 156(6): S-1033.

[155] Hollstein T, Schulte D M, Schulz J, Glück A, Ziegler A G, Laudes M, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. Nature Metabolism. 2020;(2):1021–1024.

[156] Yang L, Han Y, Nilsson-Payant B E, Gupta V, Wang P, Zhang T, et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. Cell stem cell. 2020;27(1):125-136.

[157] Rodriguez-Calvo T, Sabouri S, Anquetil F, von Herrath M G. The viral paradigm in type 1 diabetes: Who are the main suspects?. Autoimmunity Reviews. 2016;15(10):964-969.

[158] Saberzadeh-Ardestani B, Karamzadeh R, Basiri M, Hajizadeh-Saffar E, Farhadi A, Baharvand H, et al. Type 1 diabetes mellitus: cellular and molecular pathophysiology at a glance. Cell Journal (Yakhteh), 2018;20(3):294.

[159] Knip M, Simell O. Environmental triggers of type 1 diabetes. Cold Spring Harbor Perspectives in Medicine. 2012;2(7):a007690.

[160] Mukherjee, R., Smith, A., & Sutton, R. Covid-19-related pancreatic injury. British Journal of Surgery.2020; 107(7): e190.

[161] Zhang H, Kang Z, Gong H, Xu D, Meng T, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell co-expression pattern of key proteins in viral entry process. Gut. 2020; 69(6):1010-1018.

[162] Tipnis S R, Hooper N M, Hyde R, Karran E, Christie G, Turner A J. A human homolog of angiotensin-converting enzyme cloning and functional expression as a captopril-insensitive carboxypeptidase. Journal of Biological Chemistry. 2000;275(43):33238-33243.

[163] Vuille-dit-Bille R N, Camargo S M, Emmenegger L, Sasse T, Kummer E, Kuyumcu S, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. Amino acids. 2015;47(4):693-705.

[164] Wong T P, Ho K Y, Ng E K, Debnam E S, Leung P S. Upregulation of ACE2-ANG-(1–7)-Mas axis in jejunal enterocytes of type 1 diabetic rats: implications for glucose transport. American Journal of Physiology-Endocrinology and Metabolism. 2012;303(5):E669-E681.

[165] Schepis T, Larghi A, Papa A, Miele L, Panzuto F, Rapaccini G L, et al. SARS-CoV2 RNA detection in a pancreatic pseudocyst sample. Pancreatology. 2020;20(5):1011-1012.

[166] Li Y, Zhou W, Yang L, You R. Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. Pharmacological Research. 2020; (157):104833.

[167] Kassir R. Risk of COVID-19 for patients with obesity. Obesity Reviews. 2020;21(6) :e13034.

[168] Kaye S M, Pietiläinen K H, Kotronen A, Joutsi-Korhonen L, Kaprio J, Rissanen A, et al. Obesity-related derangements of coagulation and fibrinolysis: a study of obesity-discordant monozygotic twin pairs. Obesity. 2012;20(1):88-94.

[169] Kernan K F, Canna S W. Should COVID-19 take advice from rheumatologists?. The Lancet Rheumatology. 2020; 2(6): e310-e311.

[170] Rahman S, Rahman T, Ismail A A S, Rashid A R A. (2007). Diabetes-associated macrovasculopathy: pathophysiology and pathogenesis. Diabetes, Obesity and Metabolism. 2007;9(6):767-780.

[171] Ciceri F, Beretta L, Scandroglio A M, Colombo S, Landoni G, Ruggeri A, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc. 2020; 22(2):95-97.

[172] Leisman D E, Deutschman C S, Legrand M. (2020). Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Medicine. 2020; 46(6):1105-1108.

[173] Varga Z, Flammer A J, Steiger P, Haberecker M, Andermatt R, Zinkernagel A S, et al. *Endothelial cell infection and endotheliitis in COVID-19*. Lancet. 2020; 395(10234):1417-1418.

[174] Piarulli F, Lapolla A. COVID 19 and low-glucose levels: Is there a link?. Diabetes Research and Clinical Practice. 2020; (166):108283.

[175] Klok F A, Kruip M J H A, Van der Meer N J M, Arbous M S, Gommers D A M P J, Endeman H, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis Research. 2020; (191):145-147.

[176] Serné, E. H., De Jongh, R. T., Eringa, E. C., IJzerman, R. G., & Stehouwer, C. D. (2007). *Microvascular dysfunction: a potential pathophysiological role in the metabolic syndrome*. Hypertension, 50(1):204-211.

[177] Siordia Jr, J A. (2020). Epidemiology and clinical features of COVID-19: A review of current literature. Journal of Clinical Virology. 2020;(127):104357.

[178] Barton L M, Duval E J, Stroberg E, Ghosh S, Mukhopadhyay S. Covid-19 autopsies, oklahoma, usa. American Journal of Clinical Pathology. 2020;153(6):725-733.

[179] Wichmann D, Sperhake J P, Lütgehetmann M, Steurer S, Edler C, Burdelski C, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Annals of Internal Medicine. 2020; 173(4):268-277.

[180] Dunn E J, Grant P J. Type 2 diabetes: an atherothrombotic syndrome. Current Molecular Medicine. 2005; 5(3):323-332.

[181] Suruchi Singh, Pankaj Bhatt, Narjes Alfuraiji, Mahdi M. Thuwaini, Ali Esmail Al-Snafi. Cardiovascular comorbidity of COVID-19 disease: A review. WJPMR 2022; 8(4): 216-225.

[182] Jenny L, Melmer A, Laimer M, Hardy E T, Lam W A, Schroeder V. Diabetes affects endothelial cell function and alters fibrin clot formation in a microvascular flow model: A pilot study. Diabetes and Vascular Disease Research. 2020; 17(1):1-11..

[183] Ramchand J, Patel S K, Srivastava P M, Farouque O, Burrell L M. Elevated plasma angiotensin converting enzyme 2 activity is an independent predictor of major adverse cardiac events in patients with obstructive coronary artery disease. PLoS One. 2018; 13(6):e0198144.

[184] Bader M. ACE2, angiotensin-(1–7), and Mas: the other side of the coin. Pflügers Archiv-European Journal of Physiology. 2013; 465(1):79-85.

[185] Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. Journal of Thrombosis and Thrombolysis. 2021; 51(4):1107–1110.

[186] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020;18(4):844-847.

[187] Gupta N, Zhao Y Y, Evans C E. The stimulation of thrombosis by hypoxia. Thrombosis Research. 2019;(181):77-83.

[188] Domingueti C P, Dusse L M S A, das Graças Carvalho M, de Sousa L P, Gomes K B, Fernandes A P. Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. Journal of Diabetes and its Complications. 2016;30(4):738-745.

[189] Mulvihill E E, Drucker D J. Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. Endocrine Reviews. 2014; 35(6):992-1019.

[190] Conarello S L, Li Z, Ronan J, Roy R S, Zhu L, Jiang G, et al. Mice lacking dipeptidyl peptidase IV are protected against obesity and insulin resistance. Proc Natl Acad Sci USA. 2003; 27(100):6825–6830.

[191] Mentlein R. Dipeptidyl-peptidase IV (CD26)-role in the inactivation of regulatory peptides. Regulatory Peptides. 1999; 85(1):9-24.

[192] Serej Z A, Kalan A E, Mehdipour A, Charoudeh H N. Regulation and roles of CD26/DPPIV in hematopoiesis and diseases. Biomedicine & Pharmacotherapy. 2017; (91):88-94.

[193] Song Z, Xu Y, Bao L, Zhang L, Yu P, Qin C, et al. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses. 2019;11(1):59.

[194] Shao S, Xu Q, Yu X, Pan R, Chen Y. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. Pharmacology & Therapeutics. 2020;(209):107503.

[195] Meyerholz D K, Lambertz A M, McCray Jr P B. Dipeptidyl peptidase 4 distribution in the human respiratory tract: implications for the Middle East respiratory syndrome. The American Journal of Pathology. 2016;186(1):78-86.

[196] Seys L J, Widagdo W, Verhamme F M, Kleinjan A, Janssens W, Brusselle G G, et al. DPP4, the Middle East respiratory syndrome coronavirus receptor, is upregulated in lungs of smokers and chronic obstructive pulmonary disease patients. Clinical Infectious Diseases. 2018;66(1):45-53.

[197] Broxmeyer H E, Capitano M, Campbell T B, Hangoc G, Cooper S. Modulation of hematopoietic chemokine effects in vitro and in vivo by DPP-4/CD26. Stem Cells and Development. 2016;25(8):575-585.

[198] Julián M T, Alonso N, Colobran R, Sánchez A, Miñarro A, Puig-Domingo M, et al. CD26/DPPIV inhibition alters the expression of immune response-related genes in the thymi of NOD mice. Molecular and Cellular Endocrinology. 2016;(426):101-112.

[199] Yang W, Cai X, Han X, Ji L. DPP-4 inhibitors and risk of infections: a meta-analysis of randomized controlled trials. Diabetes Metab Res Rev. 2016;(32):391–404.

[200] Andrieu T, Thibault V, Malet I, Laporte J, Bauvois B, Agut H, Cahour A. Similar increased serum dipeptidyl peptidase IV activity in chronic hepatitis C and other viral infections. Journal of Clinical Virology. 2003;27(1):59-68.

[201] Ploquin M J, Casrouge A, Madec Y, Noël N, Jacquelin B, Boufassa F, et al. Systemic DPP4 activity is reduced during primary HIV-1 infection and is associated with intestinal $RORC^{+}$ $CD4^{+}$ cell levels: a surrogate marker candidate of HIV-induced intestinal damage. Journal of the International AIDS Society. 2018;21(7):e25144.

[202] Inn K S, Kim Y, Aigerim A, Park U, Hwang E S, Cho N H, et al. Reduction of soluble dipeptidyl peptidase 4 levels in plasma of patients infected with Middle East respiratory syndrome coronavirus. Virology. 2018;(518):324-327.

[203] Raj V S, Mou H, Smits S L, Dekkers D H, Mu¨ ller M A, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013;(495):251-254.

[204] Kulcsar K A, Coleman C M, Beck S E, Frieman M B, Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight. 2019;4(20):131774.

[205] Gierer S, Bertram S, Kaup F, Wrensch F, Heurich A, Dittmer U, et al. The spike protein of the emerging betacoronavirus EMC uses a novel coronavirus receptor for entry, can be activated by TMPRSS2, and is targeted by neutralizing antibodies. Journal of Virology. 2013;87(10):5502-5511.

[206] Qian Z, Dominguez S R, Holmes K V. Role of the spike glycoprotein of human Middle East respiratory syndrome coronavirus (MERS-CoV) in virus entry and syncytia formation. PloS one. 2013;8(10):76469.

[207] Li K, Wohlford-Lenane C L, Channappanavar R, Park J E,Earnest J T, Bair T B, et al. Mouse-adapted MERS coronavirus causes lethal lung disease in human DPP4 knockin mice. Proc Natl Acad Sci USA. 2017;114(15):E3119-E3128.

[208] Fan C, Wu X, Liu Q, Li Q, Liu S, Lu J, et al. A human DPP4-knockin mouse's susceptibility to infection by authentic and pseudotyped MERS-CoV. Viruses. 2018;10(9) :448.

[209] Iacobellis G, Local and systemic effects of the multifaceted epicardial adipose tissue depot. Nat Rev Endocrinol. 2015;11(6):363-71.

[210] Kleine-Weber H, Schroeder S, Krüger N, Prokscha A, Naim H Y, Hoffmann M, et al. Polymorphisms in dipeptidyl peptidase 4 reduce host cell entry of Middle East respiratory syndrome coronavirus. Emerging microbes & infections. 2020;9(1):155-168.

[211] Peck K M, Cockrell A S, Yount B L, Scobey T, Baric R S, Heise M T. Glycosylation of mouse DPP4 plays a role in inhibiting Middle East respiratory syndrome coronavirus infection. Journal of virology. 2015;89(8):4696-4699.

[212] Cockrell A S, Peck K M, Yount B L, Agnihothram S S, Scobey T, Heise M T, et al. Mouse dipeptidyl peptidase 4 is not a functional receptor for Middle East respiratory syndrome coronavirus infection. Journal of Virology. 2014;88(9):5195-5199.

[213] Varin E M, Mulvihill E E, Beaudry J L, Pujadas G, Fuchs S, Matthews D, et al. Circulating levels of soluble dipeptidyl peptidase-4 are dissociated from inflammation and induced by enzymatic DPP4 inhibition. Cell metabolism. 2019;29(2): 320-334.

[214] Chan C M, Chu H, Wang Y, Wong B H Y, Zhao X, Yan J, et al. Carcinoembryonic antigen-related cell adhesion molecule 5 is an important surface attachment factor that facilitates entry of Middle East respiratory syndrome coronavirus. Journal of Virology. 2016;90(20):9114-9127.

[215] Chu H, Chan C M, Zhang X, Wang Y, Yuan S, Hou Y, et al. Middle East respiratory syndrome coronavirus and bat coronavirus HKU9 both can utilize GRP78 for attachment onto host cells. Journal of Biological Chemistry. 2018;293(30): 11709-11726.

[216] Cui J, Li F, Shi Z L. Origin and evolution of pathogenic coronaviruses. Nature Reviews Microbiology. 2019;17(3): 181-192.

[217] Li Y, Zhang Z, Yang L, Lian X, Xie Y, Lu J, et al. The MERS-CoV receptor DPP4 as a candidate binding target of the SARS-CoV-2 spike. Science. 2020;23(6):101160.

[218] Rockx B, Kuiken T, Herfst S, Bestebroer T, Lamers M M, Schipper D, et al. Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model. Science. 2020;368(6494):1012-1015.

[219] Wei L, Ming S, Zou B, Wu Y, Hong Z, Wen X, et al. Viral invasion and type I interferon response characterize the immunophenotypes during COVID-19 infection. Cell. 2020; https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3564998

[220] Vankadari N, Wilce J A. Emerging COVID-19 coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerging Microbes & Infections. 2020;9(1):601-604.

[221] Xiong X, Tortorici M A, Snijder J, Yoshioka C, Walls A C, Veesler D, et al. Glycan shield and fusion activation of a deltacoronavirus spike glycoprotein fine-tuned for enteric infections. Journal of Virology. 2018;92(4):e01628–17.

[222] Wang Q, Qi J, Yuan Y, Xuan Y, Han P, Iwamoto A, et al. Bat origins of MERS-CoV supported by bat coronavirus HKU4 usage of human receptor CD26. Cell Host & Microbe. 2014;16(3):328-337.

[223] Xu X, Chen P, Wang J, Feng J, Zhou H, Hao P, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Science China Life Sciences. 2020; 63(3):457-460.

[224] Song W, Wang Y, Wang N, Wang D, Guo J, Fu L, Shi X. Identification of residues on human receptor DPP4 critical for MERS-CoV binding and entry. Virology. 2014;(471-473):49-53.

[225] Millet J K, Kien F, Cheung C Y, Siu Y L, Chan W L, Altmeyer R M, et al. Ezrin interacts with the SARS coronavirus spike protein and restrains infection at the entry stage. PLoS One. 2012;7(11):e49566.

[226] Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathogens. 2018;14(8):e1007236.

[227] Qi, F., Qian, S., Zhang, S., & Zhang, Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochemical and biophysical research communications. 2020;526(1):135-140.

[228] Zhou P, Yang X L, Wang X G, Hu B, Zhang L, Chen H D, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.

[229] Barchetta I, Ciccarelli G, Barone E, Cimini F A, Ceccarelli V, Baroni M G, et al. Greater circulating DPP4 activity is associated with impaired flow-mediated dilatation in adults with type 2 diabetes mellitus. Nutrition, Metabolism and Cardiovascular Diseases. 2019;29(10):1087-1094.

[230] Zheng T, Gao Y, Baskota A, Chen T, Ran X, Tian H. Increased plasma DPP4 activity is predictive of prediabetes and type 2 diabetes onset in Chinese over a four-year period: result from the China National Diabetes and Metabolic Disorders Study. The Journal of Clinical Endocrinology & Metabolism. 2014;99(11):E2330-E2334.

[231] Barchetta I, Cavallo M G, Baroni M G. COVID-19 and diabetes: Is this association driven by the DPP4 receptor? Potential clinical and therapeutic implications. Diabetes Research and Clinical Practice. 2020;163:108165.

[232] Korytkowski M, Antinori-Lent K, Drincic A, Hirsch I B, McDonnell M E, Rushakoff R, Muniyappa R. A Pragmatic Approach to Inpatient Diabetes Management during the COVID-19 Pandemic. The Journal of Clinical Endocrinology & Metabolism. 2020;105(9):342.

[233] Ceriello A, Standl E, Catrinoiu D, Itzhak B, Lalic N M, Valensi P, et al. Issues of Cardiovascular Risk Management in People With Diabetes in the COVID-19 Era. Diabetes Care. 2020; 43(7):1427-1432.

[234] Ceriello A. Hyperglycemia and the worse prognosis of COVID-19. Why a fast blood glucose control should be mandatory. Diabetes Research and Clinical Practice. 2020;(163):108186.

[235] Han X, Fan Y, Wan Y L, Shi H. A diabetic patient with 2019-nCoV (COVID-19) infection who recovered and was discharged from hospital. Journal of Thoracic Imaging. 2020; 35(3):W94-W95.

[236] Singh A K, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(3):241–246.

[237] Rogers L C, Lavery L A, Joseph W S, Armstrong D G. All feet On deck—The role of podiatry during the COVID-19 pandemic: Preventing hospitalizations in an overburdened healthcare system, reducing amputation and death in people with diabetes. Journal of the American Podiatric Medical Association. 2020;https://doi:10.7547/20-051.

[238] Iacobucci G. Covid-19: diabetes clinicians set up social media account to help alleviate patients' fears. BMJ. 2020; (368): 1262.

[239] Singh A K, Khunti K. Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: A Narrative Review. Diabetes Research and Clinical Practice. 2020;165:108266.

[240] Pal R, Bhadada S K. Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?. Diabetes Res Clin Pract; 2020;(163):108146.

[241] Zhang J, Dong J, Martin M, He M, Gongol B, Wu Y, et al. AMP-activated protein kinase phosphorylation of angiotensin-converting enzyme 2 in endothelium mitigates pulmonary hypertension. American Journal of Respiratory and Critical Care Medicine. 2018;198(4):509-520.

[242] Tripathy D, Daniele G, Fiorentino T V, Perez-Cadena Z, Chavez-Velasquez A, Gastaldelli A, et al. Pioglitazone improves glucose metabolism and modulates skeletal muscle TIMP-3–TACE dyad in type 2 diabetes mellitus: a randomised, double-blind, placebo-controlled, mechanistic study. Diabetologia. 2013;56(10):2153-2163.

[243] Romaní-Pérez M, Outeiriño-Iglesias V, Moya C M, Santisteban P, González-Matías L C, Vigo E, Mallo F. Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. Endocrinology. 2015;156(10):3559-3569.

[244] Kawanami D, Matoba K, Takeda Y, Nagai Y, Akamine T, Utsunomiya K, et al. SGLT2 inhibitors as a therapeutic option for diabetic nephropathy. International Journal of Molecular Sciences. 2017;18(5):1083.

[245] Salem E S, Grobe N, Elased K M. Insulin treatment attenuates renal ADAM17 and ACE2 shedding in diabetic Akita mice. American Journal of Renal Physiology. 2014; 306(6):F629-F639.

[246] Díaz B B, González D A, Gannar F, Pérez M C R, de León A C. Myokines, physical activity, insulin resistance and autoimmune diseases. Immunology Letters. 2018;(203):1-5.

[247] Sinclair A, Dhatariya K, Burr O, Nagi D, Higgins K, Hopkins D, et al. Guidelines for the management of diabetes in care homes during the Covid-19 pandemic. Diabet Med. 2020;37(7):1090-1093.

[248] Kaiser U B, Mirmira R G, Stewart P M. Our response to COVID-19 as endocrinologists and diabetologists. J Clin Endocrinol Metabol. 2020; 105(5):148.

[249] Hayes C, Kriska A. Role of physical activity in diabetes management and prevention. Journal of the American Dietetic Association. 2008;108(4):S19-S23.

[250] Wang D, Fu B, Peng Z, Yang D, Han M, Li M, et al. (2021). Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. Frontiers of Medicine; 2021;15(3):486-494.

[251] Hill N E, Campbell C, Buchanan P, Knight M, Godsland I F, Oliver N S. Biochemical, physiological and psychological changes during endurance exercise in people with type 1 diabetes. Journal of Diabetes Science and Technology. 2017;11(3):529-536.

[252] Farinha J B, Krause M, Rodrigues-Krause J, Reischak-Oliveira A. Exercise for type 1 diabetes mellitus management: general considerations and new directions. Medical Hypotheses. 2017;104:147-153.

[253] van Dijk J W, Eijsvogels T M, Nyakayiru J, Schreuder T H, Hopman M T, Thijssen D H, van Loon L J. Glycemic control during consecutive days with prolonged walking exercise in individuals with type 1 diabetes mellitus. Diabetes research and Clinical Practice. 2016;(117):74-81.

[254] Riddell M C, Gallen I W, Smart C E, Taplin C E, Adolfsson P, Annan F, et al. Exercise management in type 1 diabetes: a consensus statement. The Lancet Diabetes & Endocrinology. 2017; 5(5):377-390.

[255] Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Holl R W, et .al Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: a cross-sectional multicenter study of 18,028 patients. Diabetes Care. 2015;38(8):1536-1543.

[256] Leal L G, Lopes M A, Batista Jr, M L. Physical exercise-induced myokines and muscle-adipose tissue crosstalk: a review of current knowledge and the implications for health and metabolic diseases. Frontiers in Physiology. 2018;(9):1307.

[257] Duarte C K, de Almeida J C, Merker A J S, de Oliveira Brauer F, da Costa Rodrigues T. Physical activity level and exercise in patients with diabetes mellitus. Revista da Associação Médica Brasileira. 2012;58(2):215-221.

[258] Moser O, Tschakert G, Mueller A, Groeschl W, Pieber T R, Hofmann P, et al. Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin. PLoS One. 2015;10(8):e0136489.

[259] Assaloni R, Pellino V C, Puci M V, Ferraro O E, Lovecchio N, Girelli A, Vandoni M. Coronavirus disease (Covid-19): How does the exercise practice in active people with type 1 diabetes change? A preliminary survey. Diabetes Research and Clinical Practice. 2020;166:108297.

[260] Basu A, Veettil S, Dyer R, Peyser T, Basu R. Direct evidence of acetaminophen interference with subcutaneous glucose sensing in humans: a pilot study. Diabetes Technology & Therapeutics. 2016;18(S2):S2-43.

[261] American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2019. Diabetes Care 2019; 42(Supplement 1):S61-S70.

[262] American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019; 42(Suppl 1):S34.

[263] American Diabetes Association. Diabetes care in the hospital: Standards of medical care in diabetes—2020. Diabetes Care. 2020; 43(Supplement 1):S193-S202.

[264] Umpierrez G E, Hellman R, Korytkowski M T, Kosiborod M, Maynard G A, Van den Berghe G, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2012;97(1):16-38.

[265] Lu M, Zuo Y, Guo J, Wen X, Kang Y. Continuous glucose monitoring system can improve the quality of glucose control and glucose variability compared with point-of-care measurement in critically ill patients: A randomized controlled trial. Medicine (Baltimore). 2018;97(36):e12138

[266] Sinclair A J, Abdelhafiz A H. (2020) Age, frailty and diabetes–triple jeopardy for vulnerability to COVID-19 infection. E Clinical Medicine. 2020;(22):100343.

[267] Garg S K, Rodbard D, Hirsch I B, Forlenza G P. Managing new-onset tye 1 diabetes during the COVID-19 pandemic: challenges and opportunities. Diabetes Technology & Therapeutics. 2020;22(6):431-439.

[268] Gupta R, Ghosh A, Singh A K, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diabetes & Metabolic Syndrome. 2020;14(3):211-212.

[269] Wang A, Zhao W, Xu Z, Gu J. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. Diabetes Research and Clinical Practice. 2020;162:108118.

[270] Rhodes A, Evans L E, Alhazzani W, Levy M M, Antonelli M, Rochwerg B, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: Intensive Care Medicine. 2017;43(3):304-377.

[271] Razavi Z, Maher S, Fredmal J. Comparison of subcutaneous insulin as part and intravenous regular insulin for the treatment of mild and moderate diabetic ketoacidosis in pediatric patients. Endocrine. 2018; 61(2):267-74.

[272] Tran K K, Kibert 2nd J L, Telford E D, Franck A J. Intravenous insulin infusion protocol compared with subcutaneous insulin for the management of hyperglycemia in critically ill adults. Ann Pharmacother. 2019;53(9):894-98.

[273] Bhurayanontachai R, Rattanaprapat T, Kongkamol C. Comparison of glycemic control between continuous regular insulin infusion and single-dose subcutaneous insulin glargine injection in medical critically ill patients. Indian J Crit Care Med. 2018;22(3):174e9.

[274] Hartmann-Boyce J, Morris E, Goyder C, Kinton J, Perring J, Roussel R, et al. Diabetes and COVID-19: risks, management, and learnings from other national disasters. Diabetes Care. 2020;43(8):1695-1703.

[275] Salem E S, Grobe N, Elased K M. Insulin treatment attenuates renal ADAM17 and ACE2 shedding in diabetic Akita mice. American Journal of Renal Physiology. 2014;306(6):F629-F639.

[276] Tsai S, Clemente-Casares X, Zhou A C, Lei H, Ahn J J, Engleman E G, et al. Insulin receptor-mediated stimulation boosts T cell immunity during inflammation and infection. Cell Metabolism. 2018;28(6):922-934.

[277] Hansen T K, Thiel S, Wouters P J, Christiansen J S, Van den Berghe G.Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. The Journal of Clinical Endocrinology and Metabolism. 2003;88:1082-1088.

[278] Xiu F, Stanojcic M, Diao L, Jeschke M G. Stress hyperglycemia, insulin treatment, and innate immune cells. International Journal of Endocrinology. 2014; 2014:486403.

[279] Knapp S. Diabetes and infection: Is there a link? A mini-review. Gerontology. 2013;59(2):99-104.

[280] Gorricho J, Garjo´n J, Alonso A, Celaya M C, Saiz L C, Erviti J, et al. Use of oral antidiabetic agents and risk of community acquired pneumonia: a nested case–control study. Br J Clin Pharmacol. 2017;(83):2034–2044.

[281] Hughes W T, Smith-McCain. Effects of sulfonylurea compounds on pneumocystis carinii. J Infect Dis. 1986; (153) :944–947.

[282] Cariou ., Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Borot S, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia. 2020;63(8):1500-1515.

[283] Zumla A, Hui D S, Azhar E I, Memish Z A, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. The Lancet. 2020; 395(10224):e35-e36.

[284] Luo P, Qiu L, Liu Y, Liu X L, Zheng, J L, Li J. et al. Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. The American Journal of Tropical Medicine and Hygiene. 2020;103(1):69-72.

[285] Diniz Vilela D, Gomes Peixoto L, Teixeira R R, Belele Baptista N, Carvalho Caixeta D, Espindola F S, et al. The role of metformin in controlling oxidative stress in muscle of diabetic rats. Oxidative Medicine and Cellular Longevity. 2016; 2016:6978625.

[286] Cameron A R, Morrison V L, Levin D, Mohan M, Forteath C, Viollet B, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. Circulation Research. 2016;119(5):652-665.

[287] Saenwongsa W, Nithichanon A, Chittaganpitch M, Buayai K, Kewcharoenwong C, Lertmemongkolchai G, et al. Metformin-induced suppression of IFN-α via mTORC1 signalling following seasonal vaccination is associated with impaired antibody responses in type 2 diabetes. Scientific Reports. 2020;10(1):1-12.

[288] Agarwal D, Schmader K E, Kossenkov A V, Doyle S, Kurupati R, Ertl H C. Immune response to influenza vaccination in the elderly is altered by chronic medication use. Immunity & Ageing. 2018;15(1):19.

[289] Schuiveling M, Vazirpanah N, Radstake T R, Zimmermann M, Broen J C. Metformin, a new era for an old drug in the treatment of immune mediated disease? Current Drug Targets. 2018;19(8):945-959.

[290] Ba W, Xu Y, Yin G, Yang J, Wang R, Li C, et al. Metformin inhibits pro-inflammatory responses via targeting nuclear factor-κB in HaCaT cells. Cell Biochemistry and Function. 2019;37(1):4-10.

[291] Yew W W, Chang K C, Chan D P, Zhang Y. Metformin as a host-directed therapeutic in tuberculosis: Is there a promise? Tuberculosis. 2019;(115):76-80.

[292] Martin-Montalvo A, Mercken E M, Mitchell S J, Palacios H H, Mote P L, Scheibye-Schwab M, et al. Metformin improves healthspan and lifespan in mice. Nature Communications. 2013;4(1):1-9.

[293] Kajiwara C, Kusaka Y, Kimura S, Yamaguchi T, Nanjo Y, Tateda K, et al. Metformin mediates protection against Legionella pneumonia through activation of AMPK and mitochondrial reactive oxygen species. The Journal of Immunology. 2018;200(2):623-631.

[294] Zhang M, He J. Impacts of metformin on tuberculosis incidence and clinical outcomes in patients with diabetes: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2020;(76):149–159.

[295] Mendy A, Gopal R, Alcorn J F, Forno E. Reduced mortality from lower respiratory tract disease in adult diabetic patients treated with metformin. Respirology. 2019;24(7):646-651.

[296] Ho T W, Huang C T, Tsai Y J, Lien A S Y, Lai F, Yu C J. Metformin use mitigates the adverse prognostic effect of diabetes mellitus in chronic obstructive pulmonary disease. Respiratory Research. 2019;20(1):69.

[297] Zhou G, Myers R, Li Y, Chen Y, Shen X, Musi N, et al. Role of AMP-activated protein kinase in mechanism of metformin action. The Journal of Clinical Investigation. 2001;108(8):1167-1174.

[298] Singh A K, Singh R. Is Metformin ahead in the race as a repurposed host-directed therapy for patients with diabetes and COVID-19?. Diabetes Research and Clinical Practice. 2020;(165):108268.

[299] Liu J, Li X, Lu Q, Ren D, Sun X, et al. AMPK: a balancer of the renin–angiotensin system. Bioscience Reports. 2019; 39(9):BSR20181994.

[300] Clements A, Gao B, Yeap S H O, Wong M K Y, Ali S S, Gurney H. Metformin in prostate cancer: two for the price of one. Annals of Oncology. 2011;22(12):2556-2560.

[301] Kindrachuk J, Ork B, Hart B J, Mazur S, Holbrook M R, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. Antimicrobial Agents and Chemotherapy. 20115;59(2):1088-1099.

[302] Liang H, Ding X, Li L, Wang T, Kan Q, Wang L, Sun T. Association of preadmission metformin use and mortality in patients with sepsis and diabetes mellitus: a systematic review and meta-analysis of cohort studies. Critical Care. 2019;23(1):50.

[303] Chen Y, Gu F, Guan J L. Metformin might inhibit virus through increasing insulin sensitivity. Chinese Medical Journal. 2018;131(3):376.

[304] Denys A, Bocian J. Effect of Silubin-retard (1-butyl-biguanide hydrochloride) on the course of influenza-virus infection in mice. Polski Tygodnik Lekarski (Warsaw, Poland). 1970;25(9):332-334.

[305] Chen Y, Yang D, Cheng B, Chen J, Peng A, Zheng L, et al.Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care. 2020;43(7):1399-1407.

[306] Misbin R I. The phantom of lactic acidosis due to metformin in patients with diabetes. Diabetes Care. 2004;27(7): 1791-1793.

[307] Doenyas-Barak K, Beberashvili I, Marcus R, Efrati S. Lactic acidosis and severe septic shock in metformin users: a cohort study. Critical Care. 2016;20(1):1-6.

[308] Pal R, Bhadada S K. COVID-19 and non-communicable diseases. Postgraduate Medical Journal. 2020;(162):108132.

[309] Chao W C, Tseng C H, Wu C L, Shih S J, Yi C Y, Chan M C. Higher glycemic variability within the first day of ICU admission is associated with increased 30-day mortality in ICU patients with sepsis. Annals of Intensive Care. 2020;10(1): 17.

[310] Amin S, Lux A, O'Callaghan F. The journey of metformin from glycaemic control to mTOR inhibition and the suppression of tumour growth. British Journal of Clinical Pharmacology. 2019;85(1):37-46.

[311] Romero R, Erez O, Hüttemann M, Maymon E, et al. Metformin, the aspirin of the 21st century: its role in gestational diabetes mellitus, prevention of preeclampsia and cancer, and the promotion of longevity. American Journal of Obstetrics and Gynecology. 2017;217(3):282-302.

[312] Lu G, Hu Y, Wang Q, Qi J, Gao F, Zhang B, et al. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. Nature. 2013; 500(7461):227-231.

[313] Klemann C, Wagner L, Stephan M, von Hörsten S. Cut to the chase: a review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system. Clinical & Experimental Immunology. 2016;185(1):1-21.

[314] Gamble J, Donnan J R, Chibrikov E, et al. Comparative safety of dipeptidyl peptidase-4 inhibitors versus sulfonylureas and other glucose-lowering therapies for three acute outcomes. Sci Rep. 2018; (8):15142.

[315] Brown N J, Byiers S, Carr D, Maldonado M, Warner B A. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. Hypertension. 2009;54(3):516-523.

[316] Abouelkheir M, El-Metwally T H. Dipeptidyl peptidase-4 inhibitors can inhibit angiotensin converting enzyme. European Journal of Pharmacology. 2019;(862):172638.

[317] Khunti S, Khunti N, Seidu S, Khunti K. Therapeutic uncertainties in people with cardiometabolic diseases and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19). Diabetes, Obesity and Metabolism. 2020;22(10): 1942-1945.

[318] Kumar A, Arora A, Sharma P, Anikhindi S A, Bansal N, Srivastava A, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;(14):535-45.

[319] Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008;2008(2):CD006739

[320] Amori R E, Lau J, Pittas A G. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA. 20078;298(2):194-206.

[321] Yang W, Cai X, Han X, Ji L. DPP-4 inhibitors and risk of infections: a meta-analysis of randomized controlled trials. Diabetes/Metabolism Research and Reviews. 2016; 32(4):391-404.

[322] Vora K A, Porter G, Peng R, Cui Y, Pryor K, Eiermann G, Zaller D M, Genetic ablation or pharmacological blockade of dipeptidyl peptidase IV does not impact T cell-dependent immune responses. BMC immunology. 2009;(10):19.

[323] Der Zanden R W, De Vries F, Lalmohamed A, Driessen J H, De Boer A, Den Heijer C, et al. Use of dipeptidyl-peptidase-4 inhibitors and the risk of pneumonia: a population-based cohort study. PloS one. 2015;10(10):e0139367.

[324] Gooßen K, Gräber S. Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2012;14(12):1061-1072.

[325] Lebovitz H E. Thiazolidinediones: the forgotten diabetes medications. Current Diabetes Reports. 2019;19(12):151.

[326] Qiu D, Li X N. Pioglitazone inhibits the secretion of proinflammatory cytokines and chemokines in astrocytes stimulated with lipopolysaccharide. International Journal of Clinical Pharmacology and Therapeutics. 2015;53(9):746.

[327] Carboni E, Carta A R, Carboni E. Can pioglitazone be potentially useful therapeutically in treating patients with covid-19?. Medical Hypotheses. 2020;(140):109776.

[328] Best C, Struthers H, Laciny E, Royal M, Reeds D N, Yarasheski K E. Sitagliptin reduces inflammation and chronic immune cell activation in HIV+ adults with impaired glucose tolerance. The Journal of Clinical Endocrinology & Metabolism. 2015;100(7):2621-2629.

[329] Dubé M P, Chan E S, Lake J E, Williams B, Kinslow J, Yarasheski K E, et al. A randomized, double-blinded, placebo-controlled trial of sitagliptin for reducing inflammation and immune activation in treated and suppressed human immunodeficiency virus infection. Clinical Infectious Diseases. 2019;69(7):1165-1172.

[330] Price J D, Linder G, Li W P, Zimmermann B, Rother K I, Malek R, Alattar M, Tarbell K V. Effects of short-term sitagliptin treatment on immune parameters in healthy individuals, a randomized placebo-controlled study. Clinical and Experimental Immunology. 2013;(174):120-128.

[331] Goodwin S R, Reeds D N, Royal M, Struthers H, Laciny E, Yarasheski K E. Dipeptidyl peptidase IV inhibition does not adversely affect immune or virological status in HIV infected men and women: a pilot safety study. The Journal of Clinical Endocrinology and Metabolism. 2013;(98):743-751.

[332] Sromova L, Busek P, Posova H, Potockova J, Skrha P, Andel M, Sedo A. The effect of dipeptidyl peptidase-IV inhibition on circulating T cell subpopulations in patients with type 2 diabetes mellitus. Diabetes Research and Clinical Practice. 2016;(118):183-192.

[333] Vankadari N, Wilce J A. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microb Infect. 2020;9(1):601e4.

[334] Chen C F, Chien C H, Yang Y P, Chou S J, Wang M L, Huo T I, et al. Role of Dipeptidyl peptidase 4 inhibitors in diabetic patients with coronavirus-19 infection. J Chin Med Assoc. 2020;83(8):710-711.

[335] Bergman A J, Stevens C, Zhou Y, Yi B, Laethem M, De Smet M, Snyder K, Hilliard D, Tanaka W, Zeng W, Tanen M, Herman G A, et al. Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. Clin Ther. 2006; (28):55-72.

[336] Scirica B M, Bhatt D L, Braunwald E, Steg P G, Davidson J, Cavender M A, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. New England Journal of Medicine. 2013;369(14):1317-1326.

[337] White W B, Cannon C P, Heller S R, Nissen S E, Bergenstal R M, Wilson C, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. New England Journal of Medicine. 2013;(369):1327-1335.

[338] Green J B, Bethel M A, Armstrong P W, Buse J B, Engel S S, Lachin J M, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine. 2015;373(3):232-242.

[339] Rosenstock J, Kahn S E, Johansen O E, Zinman B, Espeland M A, Meinicke T, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA. 2019; 322(12):1155-1166.

[340] Van Poppel P C, Gresnigt M S, Smits P, Netea M G, Tack C J. The dipeptidyl peptidase-4 inhibitor vildagliptin does not affect ex vivo cytokine response and lymphocyte function in patients with type 2 diabetes mellitus. Diabetes Research and Clinical Practice. 2014;(103):395-401.

[341] Sánchez-Aguilar M, Ibarra-Lara L, Valle-Mondragón D, Rubio-Ruiz M E, Aguilar-Navarro A G, Sánchez-Mendoza A, et al.Rosiglitazone, a ligand to PPAR, improves blood pressure and vascular function through Renin-Angiotensin System regulation. PPAR Research. 2019; (2019):1371758.

[342] Zhang W, Xu Y Z, Liu B, Wu R, Yang Y Y, Xiao X Q, et al. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. Sci World J. 2014;14:603409.

[343] Gorricho J, Garjón J, Alonso A, Celaya M C, Saiz L C, Erviti J, López A. Use of oral antidiabetic agents and risk of community-acquired pneumonia: a nested case–control study. British Journal of Clinical Pharmacology. 2017;83(9) :2034-2044.

[344] Gorricho J, Garjo´n J, Alonso A, Celaya MC, Saiz LC, Erviti J, et al.Use of oral antidiabetic agents and risk of communityacquired pneumonia: a nested case–control study. Br J Clin Pharmacol. 2017;(83):2034–2044.

[345] Singh S, Loke Y K, Furberg C D., Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systematic review and meta-analysis. Thorax. 2011;66(5):383–388.

[346] Kutsukake M, Matsutani T, Tamura K, et al. Pioglitazone attenuates lung injury by modulating adipose inflammation. J Surg Res. 2014;189(2):295–303.

[347] Zhang W Y, Schwartz E A, Permana P A, Reaven P D. Pioglitazone Inhibits the expression of inflammatory cytokines from both monocytes and lymphocytes in patients with impaired glucose tolerance. Arterioscler Thromb Vasc Biol. 2008; (28):2312–2318.

[348] Cure E, Cumhur Cure M.,Comment on 'Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic?. J Hypertens. 2020;38(6):1189-1198.

[349] Hu S. Comment on "Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19". Journal of Medical Virology. 2020;92(9):1423-1424.

[350] Cure E, Cumhur Cure M. Comment on 'Should COVID-19 concern nephrologists? Why and to what extent? The emerging impasse of angiotensin blockade. Nephron. 2020;144(5):251-252.

[351] Dekkers C C, Petrykiv S, Laverman G D, Cherney D Z, Gansevoort R T, Heerspink H J.Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers. Diabetes, Obesity and Metabolism. 2018;20(8):1988-1993.

[352] Limenta M, Ho C S, Poh J W, Goh S Y, Toh D S. Adverse drug reaction profile of SGLT2 inhibitor-associated diabetic ketosis/ketoacidosis in singapore and their precipitating factors. Clinical Drug Investigation. 2019;39(7):683-690.

[353] Cure E, Cure M C. Comment on:"High released lactate by epicardial fat from coronary artery disease patients is reduced by dapagliflozin treatment". Atherosclerosis. 2020;296:2-3.

[354] Fralick M, Schneeweiss S, Patorno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. New England Journal of Medicine. 2017;376(23):2300-2302.

[355] Chee Y J, Ng S J H, Yeoh E. (2020). Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. Diabetes Research and Clinical Practice. 2020;(164):108166.

[356] Hamblin P S, Wong R, Ekinci E I, Fourlanos S, Shah S, Giri R, et al. SGLT2 inhibitors increase the risk of diabetic ketoacidosis developing in the community and during hospital admission. The Journal of Clinical Endocrinology & Metabolism. 2019;104(8):3077-3087.

[357] Scheen A J, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: Findings from the CORONADO study and other recent reports. Diabetes & Metabolism. 2020;46(4):265-271.

[358] Pal R, Bhadada S K, Reply to comment on ''Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?''. Diabetes Research and Clinical Practice. 2020; (164):108192.

[359] Ceriello A, Stoian A P, Rizzo M. COVID-19 and diabetes management: What should be considered? Diabetes Research and Clinical Practice. 2020;(163):108151.

[360] Hulst A H, Plummer M P, Hollmann M W, DeVries J H, Preckel B, Deane A M, Hermanides J. Systematic review of incretin therapy during peri-operative and intensive care. Critical Care. 2018;22(1):299.

[361] Lee M Y, Fraser J D, Chapman M J, Sundararajan K, Umapathysivam M M, Deane A M, et al.The effect of exogenous glucose-dependent insulinotropic polypeptide in combination with glucagon-like peptide-1 on glycemia in the critically ill. Diabetes Care. 2013;36(10):3333-3336.

[362] Pasquel F J, Fayfman M, Umpierrez GE. Debate on insulin vs non-insulin use in the hospital setting- is it time to revise the guidelines for the management of inpatient diabetes? Current Dabetes Reports. 2019;19(9):65.

[363] Drucker D J. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metabolism. 2018;27(4):740-756.

[364] Viby N E, Isidor M S, Buggeskov K B, Poulsen S S, Hansen J B, Kissow H. Glucagon-like peptide-1 (GLP-1) reduces mortality and improves lung function in a model of experimental obstructive lung disease in female mice. Endocrinology. 2013;154(12):4503-4511.

[365] Zhou F, Zhang Y, Chen J, Hu X, Xu Y, Liraglutide attenuates lipopolysaccharide-induced acute lung injury in mice. European Journal of Pharmacology. 2016;(791):735-740.

[366] Toki S, Goleniewska K, Reiss S, Zhang J, Bloodworth M H, StierM T, Zhou W, Newcomb D C, Peebles R S Jr, et al. Glucagon-like peptide 1 signaling inhibits allergen-induced lung IL-33 release and reduces group 2 innate lymphoid cell cytokine production in vivo., J Allergy Clin Immunol. 2018; (142):1515-1528.

[367] Bloodworth M H, Rusznak M, Pfister C C, Zhang J, Bastarache L, Calvillo S A,Peebles R S Jr, Glucagon-like peptide 1 receptor signaling attenuates respiratory syncytial virus-induced type 2 responses and immunopathology. J Allergy Clin Immunol. 2018;(142):683-687.

[368] Marso S P, Daniels G H, Brown-Frandsen K, Kristensen P, Mann J F E, Nauck M A, Nissen S E, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England Journal of Medicine. 2016;(375):311-322.

[369] Marso S P, Bain S C, Consoli A, Eliaschewitz F G, Jodar E, Leiter L A, Lingvay I, Rosenstock J, Vilsboll T, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine. 2016; (375):1834-1844.

[370] Holman R R, Bethel M A, Mentz R J, Thompson V P, Lokhnygina Y, Buse J B, Chan J C, Choi J, Hernandez A F, Group ES, Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. The New England Journal of Medicine. 2017;(377):1228-1239.

[371] Gerstein H C, Colhoun H M, Dagenais G R, Diaz R, Lakshmanan M, Pais P, Probstfield J, Investigators R. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomized placebo-controlled trial. Lancet. 2019;394(10193):121-130.

[372] Hulst A H, Visscher M J, Godfried M B, Thiel B, Gerritse B M, Scohy T V, Bouwman R A, Hermanides J, Group GS, et al. Liraglutide for perioperative management of hyperglycaemia in cardiac surgery patients: a multicenter randomized superiority trial. Diabetes, Obesity & Metabolism. 2020; (22):557-565.

[373] Fayfman M, Galindo RJ, Rubin D J, Mize D L, Anzola I, Urrutia M A, Ramos C, Pasquel F J, Umpierrez, G E, A Randomized Controlled Trial on the Safety and Efficacy of Exenatide Therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes. Diabetes Care. 2019;(42):450-456.

[374] Simões e Silva A C, Silveira K D, Ferreira A J, Teixeira M M. ACE2, angiotensin-(1-7) and M as receptor axis in inflammation and fibrosis. British Journal of Pharmacology. 2013; 169(3):477-492.

[375] Rizzo M, Nikolic D, Patti A M, Mannina C, Montalto G, Cosentino F, et al. GLP-1 receptor agonists and reduction of cardiometabolic risk: Potential underlying mechanisms. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2018; 1864(9):2814-2821.

[376] Feng Y, Wang L, Ma X, Yang X, et al. Effect of hCMSCs and liraglutide combination in ALI through cAMP/PKAc/β-catenin signaling pathway. Stem Cell Research and Therapy .2020; 11(1) :1-12.

[377] Zhang L H, Pang X F, Bai F, Wang N P, Shah A I, McKallip R J, et al. Preservation of glucagon-like peptide-1 level attenuates angiotensin II-induced tissue fibrosis by altering AT 1/AT 2 receptor expression and angiotensin-converting enzyme 2 activity in rat heart. Cardiovascular Drugs and Therapy. 2015; 29(3):243-255.

[378] Zhang P, Zhu L, Cai J, Lei F, Qin J J, Xia M, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circulation Research. 2020;126(12):1671-1681.

[379] Reynolds H R, Adhikari S, Pulgarin C, Troxel A B, Iturrate E, Katz S D, et al. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. New England Journal of Medicine. 2020;382(25):2441-2448.

[380] Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–angiotensin–aldosterone system blockers and the risk of Covid-19. New England Journal of Medicine. 2020; 382(25):2431-2440.

[381] Vaduganathan M, Vardeny O, Michel T, McMurray J J, Pfeffer M A, Solomon S D. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. New England Journal of Medicine. 2020;382(17):1653-1659.

[382] Kuster G M, Pfister O, Burkard T, Zhou Q, Twerenbold R, Osswald S, et al. SARS-CoV2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19?. European Heart Journal. 2020;41(19):1801-1803.

[383] Jia H. Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease. Shock. 2016;46(3):239-248.

[384] Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug development Research. 2020; 81(5):537-540.

[385] [385] Cure E, Cure M C. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be harmful in patients with diabetes during COVID-19 pandemic. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020; (14):349-50.

[386] Deshotels M R, Xia H, Sriramula S, Lazartigues E, Filipeanu C M. Angiotensin II mediates angiotensin converting enzyme type 2 internalization and degradation through an angiotensin II type I receptor–dependent mechanism. Hypertension. 2014; 64(6):1368-1375.

[387] Walters T E, Kalman J M, Patel S K, Mearns M, Velkoska E, Burrell L M. Angiotensin converting enzyme 2 activity and human atrial fibrillation: increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling. Ep Europace. 2017;19(8):1280-1287.

[388] Zaizafoun M, Henry C, White H D, Akiode O, Stock E, Arroliga A C, Ghamande S.Impact of angiotensin converting enzyme (ACE) inhibitors and statins on outcomes in viral pneumonia. In: Clinical aspects and diagnosis of respiratory tract infections. American Thoracic Society. 2015: A1761.

[389] Gupta R, Misra A. Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infection with reference to use of therapeutic and other drugs used in Co-morbid diseases (Hypertension, diabetes etc). Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(3):251–254.

[390] Rathi S, Ish P, Kalantri K, Kalantri S. Hydroxychroloquine prophylaxis for covid 19 contacts in India. Lancet Infect Dis. 2020;20(10):1118-1119.

[391] Vickers C, Hales P, Kaushik V, Dick L, Gavin J, Acton S, et al. Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. Journal of Biological Chemistry. 2002;277(17):14838-14843.

[392] Baidya A, Shankar A, Ahmed R, Das A K. Relevance and role of hydroxychloroquine in prophylaxis and therapy of COVID-19. J Med Sci Clin Res. 2020; 8, 94-101.

[393] Zhou D, Dai S M, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. Journal of Antimicrobial Chemotherapy. 2020; 75(7) :1667–1670.

[394] Baidya A, Ahmed R. Effect of early addition of hydroxychloroquine in type 2 diabetic patients inadequately controlled on metformin and sulfonylurea combination therapy. International Journal of Research in Medical Sciences. 2018; 6(8):2626-2632.

[395] Bhandari S, Bhargava A, Sharma S, et al. Clinical profile of Covid 19 patients admitted in a tertiary care hospital in north India. J Assoc Physicans India. 2020; (68):13–17.