Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications

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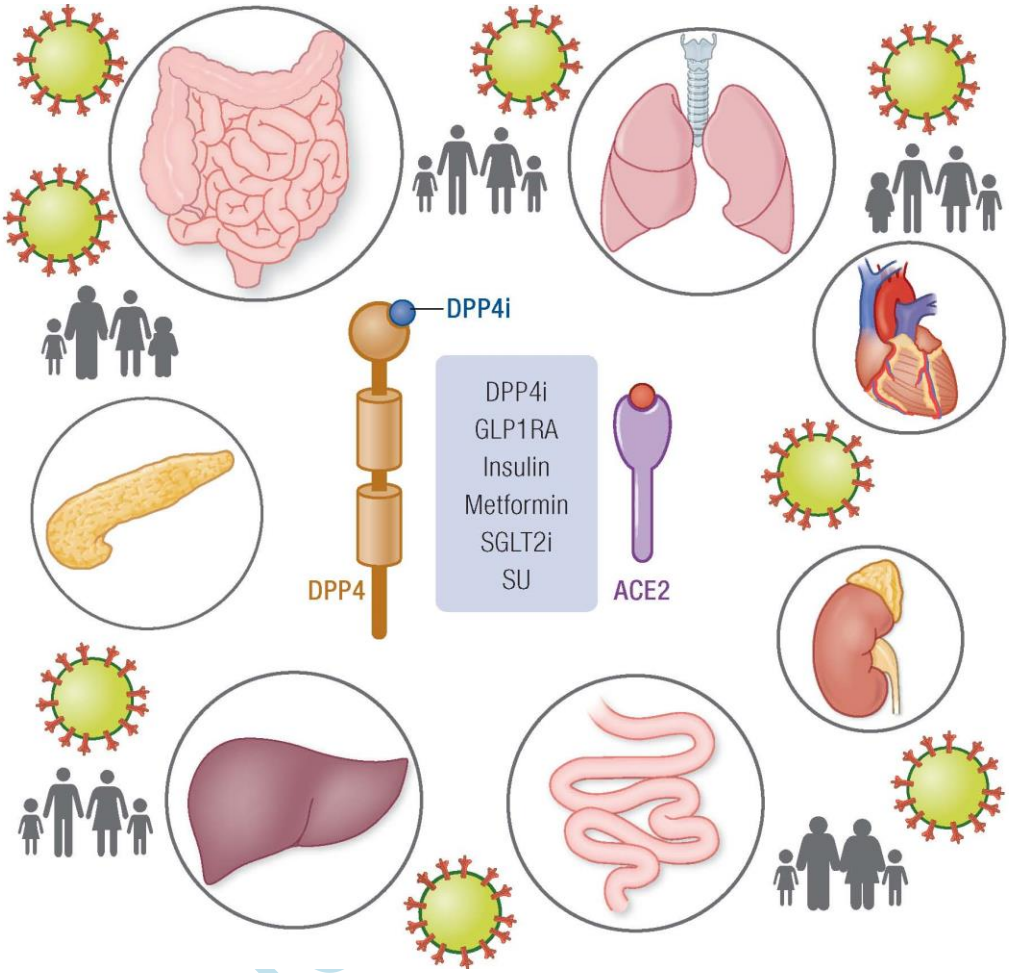
Abstract

Individuals with diabetes are at increased risk for bacterial, mycotic, parasitic and viral infections. The severe acute respiratory syndrome (SARS)-CoV2 (also referred to as COVID-19) coronavirus pandemic highlights the importance of understanding shared disease pathophysiology potentially informing therapeutic choices in individuals with Type 2 diabetes (T2D). Two coronavirus receptor proteins, Angiotensin Converting Enzyme 2 (ACE2) and Dipeptidyl Peptidase-4 (DPP4) are also established transducers of metabolic signals and pathways regulating inflammation, renal and cardiovascular physiology, and glucose homeostasis. Moreover, glucose-lowering agents such as the DPP4 inhibitors, widely used in subjects with T2D, are known to modify the biological activities of multiple immunomodulatory substrates. Here we review the basic and clinical science spanning the intersections of diabetes, coronavirus infections, ACE2, and DPP4 biology, highlighting clinical relevance and evolving areas of uncertainty underlying the pathophysiology and treatment of T2D in the context of coronavirus infection

Keywords: Diabetes, Obesity, Virus, Dipeptidyl Peptidase-4, Angiotensin Converting Enzyme 2, Receptor

Graphical Abstract



Abbreviations

ACE=Angiotensin Converting Enzyme

Ang=Angiotensin

CD=Cluster of Differentiation

CoV=Coronavirus

CRISPR= Clustered regularly interspaced short palindromic repeats

CRP=C-Reactive Protein

DPP4=Dipeptidyl Peptidase-4

GLP-1=Glucagon-like Peptide-1

HIV=Human Immunodeficiency Virus

IL-6= Interleukin-6

MERS=Middle East Respiratory Syndrome

REGN=Regeneron

SARS= severe acute respiratory syndrome

sDPP4= Soluble DPP4

TMPRRSS2= Transmembrane Serine Protease 2

TNF=Tumor Necrosis Factor

T1D=Type 1 Diabetes

T2D=Type 2 Diabetes

The global epidemic of SARS-CoV-2 has immediate implications for the therapy of common metabolic disorders such as type 2 diabetes (T2D). Moreover, individuals with obesity are known to be at increased for complications arising from influenza, and obesity is emerging as an important comorbidity for disease severity in the context of SARS-CoV-2 (1). Cells within the lung, including pneumocytes, represent major cellular sites for coronavirus entry and inflammation (2). Some of these pulmonary cells may also express key proteins facilitating coronavirus entry into cells, such as Angiotensin-converting enzyme 2 (ACE2), Transmembrane Protease Serine 2 (TMPRRSS2), and for some viral strains, Dipeptidyl Peptidase-4 (DPP4). ACE2 and DPP4 also have established pleiotropic metabolic activities directly contributing to the physiological and pharmacological control of cardiovascular and glucose homeostasis, and DPP4 inhibitors are widely used for the treatment of T2D. Here we discuss current and evolving concepts relevant to the metabolic impact of coronavirus infections with attention to key pathways and mechanisms simultaneously linked to the pathophysiology and treatment of T2D.

Rates of diabetes and obesity in subjects with coronavirus infections

Diabetes is associated with an increased risk of severe bacterial (3) and viral respiratory tract infections, including H1N1 influenza (4). Analysis of over 500 subjects hospitalized with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in China revealed that elevations in fasting glucose were associated with increased rates of death; however, hyperglycemia was often transient, and generally resolved after discharge from hospital in the majority of subjects (5). A diagnosis of diabetes was associated with a 3-fold increased risk of mortality in a retrospective analysis of 114 adults hospitalized with SARS-CoV in Toronto in 2003 (6). A meta-analysis comparing patients presenting with H1N1 influenza vs. MERS-CoV reported that subjects with MERS-CoV were older (average age 54. vs. 36.2 yrs), with a 3-fold higher prevalence of diabetes (54.4 vs. 14.6%) in subjects with MERS-CoV vs. H1N1, respectively (7). Diabetes was the co-morbidity most strongly associated with adverse outcomes in several smaller studies of MERS-CoV+ hospitalized subjects in Saudi Arabia (8, 9) and both hypertension and diabetes were strongly associated with mortality in larger retrospective analysis of 281 MERS-CoV+ Saudi subjects (10).

The rates of T2D in subjects with SARS-CoV-2 vary, depending on the age and location of the study population, the severity of illness, and the method of testing. In one report, diabetes was present in ~15% of 1,099 patients, including children and adults, hospitalized in China with laboratory confirmation of the diagnosis (11). In contrast, diabetes was reported in 8.2% of 1,590 Chinese subjects (mean age 48.9 yrs) hospitalized with SARS-CoV-2, and rates of diabetes were higher (34.6% vs. 14.3%) in subjects with a composite endpoint (intensive care unit admission, requirement for ventilation, death) reflecting disease severity (12). Consistent with these observations, a retrospective analysis of 174 hospitalized persons in one hospital in Wuhan China in February 2020 revealed a greater severity of illness, as assessed by laboratory evaluation of blood counts, parameters of coagulation and biomarkers of inflammation in subjects with T2D (24/174) presenting without other co-morbidities (13). Similarly, diabetes is among co-morbidities associated with adverse outcomes in hospitalized patients with SARS-CoV-2 in both China and Italy (14). In a series of 168 lethal cases of SARS-CoV-2 pneumonia collected from 21 hospitals between January 21-January 30 2020 in Wuhan China, 75% were men, with a median age of 70, and diabetes was reported in 25% of the cases (15).

Analysis of a randomly selected subset of fatal SARS-CoV-2 cases in Italy (mean age of 79.5 years) revealed a prevalence of diabetes of 35% (16). A larger retrospective analysis of 1,591 patients with SARS-CoV-2 hospitalized in intensive care units of Lombardy Italy over a 4 week period reported a

prevalence of T2D of 17% (17). Data reported for laboratory-confirmed SARS-CoV-2 infections in the United States from February 12-March 28 2020 and tabulated by the Centers for Disease Control for 7,162 subjects with completed case information revealed a prevalence rates for diabetes of 6%, 24% and 32%, for non-hospitalized, hospitalized but not requiring intensive care unit (ICU) admission vs. hospitalized in the ICU, respectively (18). Among hospitalized SARS-CoV-2 positive patients assessed at a single health care centre in New York from March 1-April 2 2020, the prevalence of diabetes was 15% in the SARS-CoV-2+ population (19). However, prevalence rates for diabetes (31.8% vs 5.4%) and obesity (39.8% vs. 14.5%) were greater in the hospitalized vs. non-hospitalized subgroups, respectively. Furthermore, a BMI>40 was among risk factors most predictive of the need for hospitalization (19).

Pancreatic injury, determined by assessment of plasma levels of amylase and lipase, was reported in 9/52 patients hospitalized with SARS-CoV-2-associated pneumonia in China, and 6/9 subjects also exhibited moderate increases in plasma glucose (20). This emerging putative association of pancreatic injury and SARS-CoV-2 is consistent with expression of ACE2 in the exocrine and endocrine pancreas (2).

Obesity is also a risk factor for increasing severity of SARS-CoV-2-related illness. Analysis of 124 consecutive ICU admissions in a single center in Lille France from February 27-April 5 2020 revealed greater rates of obesity and severe obesity among SARS-CoV-2 patients, relative to historical non-SARS-CoV-2 controls (21). The frequency of obesity was 47.5% in this observational study, compared to 25.8% in a historical control group of ICU subjects with non-SARS-CoV-2 illness, and the requirement for intubation and mechanical ventilation was higher in subjects with obesity. Related observations were reported in a retrospective analysis of 3,615 SARS-CoV-2+ subjected presenting to the emergency room at a single medical center in New York from March 4-April 4 2020. Individuals with obesity or severe obesity <60 years old were more likely to require acute medical care and admission to the intensive care unit (22). Consistent with these findings, a great proportion of 3,883 critically ill patients with SARS-CoV-2 admitted to ICUs from March 1-April 5 2020 in England, Wales and Northern Ireland were reported to have a BMI >30, relative to critically ill historical controls hospitalized in the ICU from 2017-2019 with viral pneumonia (23). Moreover, a progressive increase in BMI was associated with greater mortality in subjects with SARS-CoV-2 infection, relative to BMI-matched hospitalized ICU controls with viral pneumonia.

Diabetes, infection and immune responses

Acute viral respiratory infection has been linked to the rapid development of transient insulin resistance, both in otherwise healthy euglycemic normal weight or overweight individuals (24). Moreover, infection, severe illness, and medications such as glucocorticoids impair insulin sensitivity and often necessitates adjustment of glucose-lowering medications and insulin dosage in the hospital. Worldwide, infectious diseases contribute to excess mortality in individuals with diabetes (25). Mortality was increased in older patients with diabetes in a retrospective analysis of people in French intensive care units hospitalized with pulmonary and invasive pneumococcal infection (26). Nevertheless, some studies show no differences, when corrected for age and co-morbidities, in plasma biomarker responses or hospitalization outcomes in people with diabetes hospitalized in the intensive care unit with sepsis (27). The diagnosis of diabetes has been linked to increased susceptibility to and adverse outcomes associated with bacterial, mycotic, parasitic and viral infections (28), attributed to a combination of dysregulated innate immunity and maladaptive inflammatory responses (3). Pulmonary and systemic coronavirus infection, including SARS-CoV-2 may be complicated by secondary bacterial infection,

reflecting compromise of epithelial barrier function in the lungs and in the gastrointestinal tract. A substantial number of subjects with diabetes are at increased risk for infection due to concomitant immunosuppression associated with a history of solid organ transplantation (29).

Coronavirus infections and the gastrointestinal tract

As the primary site of energy absorption, the gut plays an important role in metabolic homeostasis, through production of metabolically active gut hormones, interaction with microbiota, and via its potential capacity to contribute to gluconeogenesis (30). Moreover, a healthy gut is essential for the absorption and action of several glucose-lowering medications, including widely used metformin (31), delivered orally for the treatment of T2D. Of potential clinical relevance, DPP4, ACE2 and TMPRRSS2 are substantially expressed beyond the lung within epithelial tissues including small and large bowel enterocytes (2, 32, 33). Experimental inoculation of MERS-CoV into the murine gut of human DPP4+ transgenic mice produces a lethal infection, associated with progressive systemic viral dissemination (34). Initial reports describing clinical symptoms in 1,099 hospitalized SARS-CoV-2 patients in China reported a low rate (<5%) of gastrointestinal complaints. Consistent with the potential importance of enterocyte viral entry, symptoms of gut inflammation, including nausea, vomiting and diarrhea, are reported in some severely ill individuals with MERS (8). Notably, subjects with SARS-Cov-2 may present with gastrointestinal distress without symptoms of pulmonary infection (33). A subset of these individuals also exhibit clinical evidence of liver injury, and glucose levels were higher in more severely ill patients (35). Whether oral absorption of medications for T2D, or the actions of some of these drugs on the liver, might be impaired in a proportion of infected subjects with T2D and gastrointestinal dysfunction has not been determined.

ACE2 biology relevant to diabetes

ACE2, a 805 amino acid transmembrane carboxypeptidase enzyme, and functional coronavirus S1 subunit receptor, cleaves the last amino acid of Angiotensin II (Figure 1), and generates vasodilatory Ang(1-7), collectively modulating often opposing actions of Angiotensin II and Angiotensin Converting Enzyme (ACE) through Angiotensin and MAS receptors. For example, reduction of ACE2 activity in the context of unopposed ACE1 action may lead to augmented signaling through angiotensin receptors (Figure 1), increased aldosterone, and possibly, increased blood pressure and hypokalemia.

The physiological actions of ACE2 relevant to metabolism are mediated in part through its expression in blood vessels, pancreas and renal tubular epithelium and via its enzymatic generation of angiotensin(1-7), which may antagonize the actions of angiotensin II (Figure 1) (36). Within the pancreas, ACE2 expression has been described in acinar cells and within subsets of islet cells (37). Gain and loss of ACE2 function in preclinical studies reveals physiological and pharmacological roles for ACE2, both dependent and independent of Ang(1-7), in glucose control and β-cell function, renal physiology, blood pressure, atherosclerosis and amelioration of experimental diabetes (38-42). Nevertheless, the importance of ACE2 for glucose control, independent of the angiotensin pathway in humans, has not been conclusively established.

ACE2 expression in the lung has been detected at low levels in some studies, and may be upregulated in the context of SARS-CoV-2 infection, with type 2 pneumocytes potentially serving as a key cell type

facilitating pulmonary inflammation (43). However, ACE2 is highly expressed in several extra-pulmonary tissues, including the gut (2), and has multiple, often beneficial roles in cardiometabolic physiology, including potential therapeutic activities in the heart, pancreas, and kidney. The potential biological importance, clinical relevance and use of drugs such HMG CoA-reductase inhibitors, or medications blocking components of the renin–angiotensin–aldosterone system (RAAS), such as ACE inhibitors and angiotensin receptor blockers, in the context of hypertension, cardiovascular and renal disease, diabetes and active SARS-CoV-2 infection has been reviewed (44-47).

Levels of urinary ACE2 protein and enzymatic activity are increased in subjects with both T1D (48) and T2D (49), and values for urinary ACE2/Creatinine ratios correlate positively with fasting blood glucose and hemoglobin A1C (50). However whether ACE2 is mechanistically linked to the development of dysglycemia or complications in people with diabetes is uncertain. ACE2 is also highly expressed in the human small and large intestine (51) and *ACE2* mRNA transcripts are upregulated in duodenal biopsies taken from individuals treated with ACE inhibitors (52). Expression of ACE2 RNA and protein, as well as Ang(1-7) is upregulated in jejunal enterocytes isolated from rats with streptozotocin-induced diabetes (53). Whether hyperglycemia and/or insulin deficiency similarly regulates ACE2 expression in human tissues has not been studied.

ACE2 can also cleave other metabolically active substrates in addition to angiotensin, including apelin-13, des-Arg9-bradykinin, neurotensin(1-13) β-casomorphin, dynorphin A 1–13, and ghrelin (36). The cell-associated proteases MPRSS2 and a disintegrin and metalloproteinase (ADAM)17 both cleave ACE2 however TMPRSS2 predominantly facilitates SARS spike protein-driven cellular entry (54). As described for DPP4, the membrane-tethered ACE2 enzyme can be cleaved to yield a soluble circulating form ACE2(1-740), however the biological importance of sACE2 remains uncertain. The extracellular domain of both ACE2 and sACE2 bind SARS-CoV (55), and SARS-CoV-2 (56), raising the possibility of exploring pharmacological administration of recombinant sACE2 as a therapeutic approach to sequester and block coronavirus cellular entry (57).

Rats with streptozotocin-induced diabetes exhibit reduced pulmonary expression of ACE2 mRNA. Treatment of diabetic rats with the GLP-1R agonist liraglutide twice daily for 7 days increased pulmonary ACE and ACE2 mRNA expression, associated with increased surfactant protein expression in the lung, and up-regulated circulating levels of Angiotensin(1-7) (58) . Notably, liraglutide had no effect on glucose control or insulin levels in this model, consistent with the possibility that direct augmentation of pulmonary GLP-1R signaling, rather than indirect GLP-1 actions on islet hormones, contributes to the restoration of the pulmonary renin-angiotensin system. Similarly, administration of the DPP-4 inhibitor linagliptin once daily, or liraglutide twice daily for 4 weeks, attenuated cardiac fibrosis and prevented the Ang II-mediated reduction in cardiac ACE2 activity in rats with AngII-induced hypertension (59). However, the putative pathophysiological significance of these findings in the context of experimental coronavirus infection has not been explored.

Transmembrane serine protease TMPRSS2

TMPRSS2 is a serine protease highly expressed within the lung and gastrointestinal tissues, including stomach, small and large bowel, pancreas and liver. TMPRSS2 cleaves and activates some influenza A and influenza B virus hemagglutinin envelope glycoproteins, thereby enabling viral membrane infusion and infectivity in human airway cells and type 2 pneumocytes (60). TMPRSS2 also cleaves and activates the spike protein of SARS-CoV and MERS-CoV, enabling virus-membrane fusion. Indeed, genetic

inactivation of TMPRSS2 in mice attenuates the extent of lung damage and inflammation induced by experimental infection with MERS-CoV and SARS-CoV (61). The importance of TMPRSS2 for viral pathogenicity is also revealed through studies employing TMPRSS2 inhibitors, such as camostat mesylate, which attenuates SARS-CoV-2 infection of human lung cells cultured ex vivo (62). Camostat mesylate has been improved in Japan for the treatment of pancreatitis and short term use for 28 days reduced urinary protein excretion, evident by 7 days, in 3 subjects with nephrotic syndrome secondary to diabetic kidney disease, without co-existent pancreatitis (63). There is little information informing whether the regulation of TMPRSS2 expression or activity is regulated by glucose, or dysregulated in the context of experimental or clinical diabetes.

Dipeptidyl Peptidase-4

DPP4, originally identified as the T-cell activation antigen cluster of differentiation CD26, is a widely expressed 766 amino acid cell surface endopeptidase that interacts with cellular proteins such as adenosine deaminase (ADA) and caveolin-1 to generate intracellular signals governing immune responses (64). DPP4 also cleaves a wide range of peptide hormones, chemokines and bioactive immunomodulatory proteins (Figure 2) (65), most commonly at the position 2 alanine or proline, resulting in inactivation of peptide action, or switching of peptide receptor affinity (64). DPP4, like ACE2, is also shed from the cell membrane, and circulates as a 727 amino acid soluble moiety (sDPP4) containing amino acid residues 39-766 that retains catalytic activity. sDPP4 exerts pro-inflammatory activity alone, or through association with factor Xa, independent of its catalytic actions by interacting with cell-associated caveolin-1 or Proteinase Activated Receptor 2 on macrophages or lymphocytes (66). Circulating DPP4 activity and levels of sDPP4 are increased in humans with hepatitis C and miscellaneous viral infections (67). However, sDPP4 levels were lower when measured in 14 subjects with MERS-CoV infection (68). Similarly, circulating sDPP4 levels were also reduced in humans with primary HIV infection (69). Within the human respiratory tract, immunoreactive DPP4 has been localized to immune and endothelial cells, pleural mesothelium, lymphatics and both type 1 and type 2 pneumocytes (70). Increased DPP4 RNA and protein expression was detected in pneumocytes from subjects with a history of smoking, or lung disease, including chronic obstructive pulmonary disease (70, 71).

Human DPP4 is a coronavirus receptor

Membrane-associated human DPP4 is also a functional coronavirus receptor (72), interacting with MERS-CoV through the spike glycoprotein $S1^b$ domain. After binding DPP4, MERS-CoV S protein is cleaved and activated by TMPRSS2 or cathepsin L, facilitating viral entry (73). Human neutralizing antibodies directed against the receptor-binding domain (RBD) of the MERS-CoV Spike protein block viral binding to human DPP4 thereby inhibiting MERS-CoV infection (74). Similarly, recombinant human ADA blocks spike protein S1 binding to DPP4 and inhibits MERS-CoV infection of cells transfected with human DPP4 (75). Studies examining 10 different bat cell lines ex vivo demonstrate that the susceptibility or resistance to MERS-CoV infection correlates with the presence or absence of cell surface-expressed DPP4, while anti-DPP4 antibodies blocked acute viral infection in susceptible bat cells in a dose-dependent manner (76).

A few naturally occurring *DPP4* polymorphisms have been described which alter the amino acid sequence of DPP4 so as to diminish binding of MERS-CoV subunit 1 protein with specific DPP4 isoforms, and these variants are associated with reduced viral cell entry (77). Mouse DPP4 does not bind coronavirus spike protein subunits due to differential glycosylation of the mouse vs. the human DPP4

protein. The key amino acid differences mediating differential glycosylation have been localized to positions 288 and 330 (78, 79). Substitutions of the amino acids at A288L and T330R from human to mouse DPP4 using CRISPR-Cas9 gene editing is sufficient to confer murine susceptibility to MERS-CoV viral infection and replication (80), resulting in infected mice exhibiting severe lung injury and features of respiratory distress syndrome.

Similarly, transgenic mice engineered to express human DPP4 become susceptible to lethal coronavirus infection with MERS-CoV (81). High fat diet-fed transgenic mice expressing human DPP4 infected with MERS-CoV exhibit more severe prolonged disease with unresolved pulmonary inflammation and delayed recovery, associated with dysregulated cellular immune and cytokine responses, despite apparently similar levels of viral replication and clearance (82). Humanized (hDPP4) mice may represent useful preclinical models for assessment of anti-viral therapeutics. Studies administering two human antibodies (REGN3051 and REGN3048), demonstrate interruption of the interaction of the MERS-CoV spike protein with hDPP4, and attenuated lung pathology in mice with experimental MERS-CoV infection (83).

Surprisingly, transgenic mice over-expressing hDPP4 exhibited relative resistance to MERS-CoV infection, exemplified by less lung inflammation and reduced rates of mortality. Intriguingly, these hDPP4 transgenic with higher levels of hDPP4 expression mice also exhibited increased circulating levels of sDPP4 and administration of recombinant sDPP4 attenuated lung histopathology and reduced the titers of virus recovered from lung tissue (84). In a small study of 14 subjects hospitalized in Korea, circulating levels of sDPP4 were lower in human subjects with MERS-CoV, relative to healthy controls (68). Levels of sDPP4 found effective for partial suppression of viral MERS-CoV entry into cells ex vivo were much higher than circulating levels of sDPP4 in human subjects. Hence, whether sDPP4 exhibits therapeutic potential for use as a soluble decoy receptor (Figure 2), binding to and partially sequestering circulating MERS-CoV requires further investigation. Intriguingly, MERS-CoV strains with point mutations in the RBD of the viral spike (S) protein have been isolated from an outbreak in South Korean subjects and these strains exhibit reduced binding to human DPP4 and decreased viral entry into cells ex vivo (85). However, the pathophysiological significance and implications of these findings requires further analysis.

DPP4, inflammation and the human immune system

Early studies examining the immunological properties of DPP4 often used non-selective DPP4 inhibitors, however highly selective DPP4 inhibitors have been developed for the treatment of T2D (64). Administration of the DPP4 inhibitor sitagliptin for 28 days to healthy human subjects had no effect on circulating leukocytes, including lymphocyte and T cell subsets. Levels of 27 different plasma cytokines, and levels of more than a dozen cytokines released by stimulation of peripheral blood mononuclear cells with lipopolysaccharide or anti-CD3 antibody were not different in sitagliptin-treated subjects (86). Similarly, sitagliptin administration for 24 weeks to HIV+ men and women, without an AIDS-defining illness or diabetes, had no effect on viral RNA load, CD4+ T cell count, RANTES or levels of soluble TNF receptor II concentrations, however levels of total stromal cell-derived factor-1, also known as CXCL12, declined in sitagliptin-treated subjects (87).

The immunological consequences of sitagliptin therapy for 8 weeks was also studied in 36 HIV+ men and women with impaired glucose tolerance, simultaneously treated with chimeric antigen receptor T cell therapy. Sitagliptin treatment was associated with reduced circulating levels of both C-reactive protein and the C-X-C motif chemokine 10 (88). A larger study randomized 90 HIV+ subjects on stable anti-

retroviral therapy without diabetes with ≥100/μL CD4 cells to either sitagliptin or placebo for 16 weeks. No differences were observed in the primary study endpoint, the levels of soluble CD14, a circulating marker of monocyte activation (89). Levels of CXCL10 decreased, however levels of other inflammatory biomarkers such as sCD163, IL-6, high sensitivity C-reactive protein (CRP), sDPP4, sTNF-RI, sTNF-RII and levels of total CD4 and CD8 counts were not different in sitagliptin-treated subjects (89). Similarly, in a small open label non-randomized observational study of 34 subjects with T2D initiated on sitagliptin, levels of CD4(+)/CD8(+) cells, NK and Th2 cells and plasma cytokine levels were not different after 1 year of therapy (90).

Consistent with the lack of a major effect of DPP4 inhibitors on immune function, administration of either the DPP4 inhibitor vildagliptin or the glucosidase inhibitor acarbose was compared in a cross over design for several weeks in 16 individuals with T2D. No differential effect of either drug was detected on plasma levels of IL-6 or CRP, nor was there any difference in the relative production of inflammatory cytokines from human mononuclear cells isolated from the study subjects and stimulated ex vivo (91). Hence the available evidence does not support clinically meaningful alterations in markers of immune function after administration of DPP4 inhibitors in human subjects with or without T2D.

Clinical safety of DPP4 inhibitors

DPP4 inhibitors are widely used clinically for the therapy of T2D, and act selectively to inhibit the catalytic activity of cell-associated and circulating sDPP4. When used in people with T2D, DPP4 inhibitors produce ~50-95% inhibition of DPP4 activity over a 24h period (92). Hence, some residual DPP4 enzyme activity is always present within tissues and in the circulation of subjects treated with DPP4 inhibitors. Extensive preclinical studies using highly selective DPP4 inhibitors have not demonstrated evidence of impaired T cell-dependent immune responses (93). Despite initial concerns surrounding the potential safety of DPP4 inhibitors (64), there have been no major safety concerns related to infections or compromised immune function after more than 13 years of clinical experience. A population-based cohort study of subjects with T2D assessed data from the UK Clinical Practice Research Datalink, and found no increased risk of pneumonia in 22,435 subjects treated with DPP4 inhibitors, compared to 188,614 individuals treated with other non-insulin glucose lowering agents (94). These findings are consistent with a meta-analysis of multiple DPP4 inhibitor trials encompassing 23,456 study participants with T2D treated with a DPP4 inhibitor compared to 15,300 controls in studies ranging from 18 to 104 weeks (95). No increased risk of infection was detected in subjects treated with DPP4 inhibitors. Consistent with these findings, results of large trials examining the safety of saxagliptin, alogliptin, sitagliptin, and linagliptin in humans with T2D at risk for cardiovascular or renal disease did not reveal clinically relevant safety concerns related to infections, immune or inflammatory disorders (96-100).

Use of glucose-lowering therapies in subjects with coronavirus infections

Metformin exerts anti-inflammatory actions in preclinical studies and reduces circulating biomarkers of inflammation in people with T2D (101). Metformin has also been used successfully in non-hospitalized subjects with stable hepatitis or HIV infections, however there is scant information about the immunomodulatory actions of metformin in the context of coronavirus infection. Several reports studying antibody titres in a small number of individuals have suggested that immune responses to influenza vaccination are modestly impaired in metformin-treated subjects, however the clinical significance, if any, of these observations is uncertain (102, 103). Metformin should be used with caution

in unstable hospitalized patients and should be discontinued in people with concomitant sepsis or severe impairment of hepatic and renal function.

Although DPP4 serves as a co-receptor for a subset of coronaviruses, there is little data informing whether any of the structurally distinct small molecule DPP4 enzyme inhibitors might sterically interfere with and modify the binding of MERS-CoV subunits to DPP4. DPP4 activity also potentially modulates the levels and bioactivity of multiple immunomodulatory chemokines and cytokines (Figure 2) (64). However, preclinical studies of mice with genetic or chemical reduction of DPP4 activity in the setting of diet-induced inflammation did not reveal dysregulation of tissue or systemic inflammatory markers, despite complete absence or marked reduction of DPP4 activity (104). The available evidence is insufficient to determine the impact, if any, of sustained partial reduction of DPP4 activity, as achieved clinically in subjects with T2D treated with DPP4 inhibitors, on clinical outcomes in humans with active coronavirus infection. In individuals with active SARS-CoV-2 infection and clinically significant volume depletion or systemic sepsis, a reduction in renal function may necessitate adjustment of the dose of some DPP4 inhibitors.

GLP-1R agonists exert broad anti-inflammatory actions in animals with experimental inflammation, and reduce biomarkers of systemic inflammation in human subjects with T2D and in people with obesity (105). Circulating GLP-1 levels are induced by lipopolysaccharide in animals and humans (106), are increased in human subjects with sepsis and critical illness and correlate with illness severity and mortality (107, 108). Multiple preclinical studies demonstrate that GLP-1R agonists attenuate pulmonary inflammation, reduce cytokine production and preserve lung function in mice and rats with experimental lung injury (109-111). Notably, GLP-1R agonism reduces pulmonary type 2 immune cytokine responses and the extent of lung injury in mice following infection with a respiratory syncytial virus isolated from a child with severe lower respiratory tract infection (112).

The results of several large studies examining the cardiovascular safety of GLP-1R agonists did not reveal imbalances in rates of inflammatory disorders or severe infections (113-116). Liraglutide has been shown to be safe and effective when used for acute perioperative control of blood glucose in adult human subjects undergoing elective cardiovascular surgery (117). Similarly, twice daily exenatide appears safe and effective when used alone or in combination with basal insulin for blood glucose management in non-critically ill hospitalized patients with T2D treated on general medicine or surgery wards (118) . GLP-1R agonists have been explored as glucose-lowering agents in the perioperative period and in the intensive care unit, and have generally been proven safe and effective for blood glucose management (119). However, the total number of subjects studied is small and duration of therapy is limited. Although GLP-1 safely lowers blood glucose in short term studies of ventilated patients with critical illness (120), there is insufficient experience with the safety and use of GLP-1R agonists in critically ill subjects to make therapeutic recommendations for use of these agents in the context of coronavirus infection (121) and exenatide-based formulations should be stopped in subjects with deteriorating kidney function.

Insulin has been extensively used for decades to control glucose in critically ill hospitalized subjects with diabetes and the emerging use of continuous glucose monitoring may lower the rates of hypoglycemia associated with insulin use in the hospital, including in some subjects with critical illness (122). Intriguingly, selective loss of insulin action in murine immune cells has been shown to attenuate the anti-inflammatory T cell response to experimental influenza infection (123). Moreover insulin exerts

anti-inflammatory actions in humans, and reduces biomarkers of inflammations in hospitalized individuals with critical illness (124). Amongst available agents for the treatment of acute illness complicated by diabetes, insulin has been the most extensively used agent in human subjects with bacterial or viral infections and in hospitalized critically ill patients. However there is little information surrounding potential benefits or risks of insulin in the context of acute coronavirus infection.

Sulfonylureas increase the risk of hypoglycemia and are best avoided in hospitalized subjects with severe medical illness. Although SGLT2 inhibitors are generally well tolerated in the outpatient setting, and cardioprotective most notably in the context of heart failure, SARS-CoV-2 infection may be associated with anorexia, dehydration, and rapid deterioration in clinical status. Hence, symptomatic individuals with T2D and active SARS-CoV-2 infection may be at heightened risk for volume depletion and euglycemic ketoacidosis. Accordingly, the available evidence suggests re-evaluation of or discontinuation of these agents in very unwell ambulatory individuals, and the SGLT2 inhibitors should be routinely discontinued in unstable patients with severe SARS-CoV-2 infection upon admission to hospital (125).

Type 1 Diabetes and SARS-CoV-2

The available information does not indicate increased susceptibility to coronavirus infections in children or adults with type 1 diabetes (T1D). People with T1D may find that interruption of normal daily activities, changes in type and frequency of exercise, and alteration of diet routines, may alter glucose control necessitating re-examination of insulin requirements. In many instances, interactions with health care providers may be facilitated through telephone, email as well as telemedicine interactions, including uploading of glucose data facilitating adjustment of insulin regimens. A rise in blood glucose or marked change in 24h glucose patterns may be an early harbinger of impending clinical infection in some individuals, prompting more frequent blood glucose and ketone monitoring. In some areas, disruption to medication supply chains may require additional vigilance and more regular communication between pharmacies, insurance companies, health care providers and individual patients. The use of medications such as acetaminophen may introduce error into some technologies used for glucometer readings or continuous glucose monitoring systems (126). Despite limitations of access to health care providers, individuals with unstable kidney function or active retinopathy may need to be seen in the diabetes clinic for assessment and appropriate therapy.

Conclusions, limitations and areas of uncertainty

The available evidence implicates diabetes and obesity as important risk factors impacting the clinical severity of coronavirus infections, including SARS-CoV-2. While ACE2 and DPP4 are important physiological regulators of glucose homeostasis, there is little compelling clinical evidence that drugs targeting ACE2-or DPP4-related pathways produce differential harm or benefit in the context of human coronavirus infections. Soluble decoy receptors for ACE2 or antisera directed against ACE2 may be promising investigational interventions to block cellular coronavirus entry, however the metabolic consequences, if any, of these investigational agents have not been carefully studied and requires ongoing scrutiny.

DPP4 inhibitors and GLP-1R agonists may exert anti-inflammatory actions in human subjects and have been successfully used to control glucose in hospitalized patients. However, there is insufficient experience with these agents to suggest they might safely replace insulin in critically ill subjects with

coronavirus infection. Hence, the extensive historical experience with the use of insulin, bolstered by increasing adoption of continuous glucose monitoring, supports the ongoing use of insulin as the agent of choice in the management of severely ill subjects with diabetes and coronavirus infections. There is insufficient experience with diabetes and pregnancy in subjects with SARS-CoV-2 to make tailored therapeutic recommendations, however modified screening guidelines for gestational diabetes have been proposed in the context of SARS-CoV-2 for individuals with limited access to regular clinics (127). The expression of ACE2 within the exocrine and endocrine pancreas highlights the need for vigilance in consideration of whether pancreatic inflammation reported in some individuals with SARS-CoV-2 infection may contribute to the exacerbation or development of diabetes in a subset of acutely ill patients. In hospitalized individuals with deteriorating renal function, the use of SGLT2 inhibitors and exenatide should be re-considered or discontinued, and metformin and sulfonylurea dosing may also need to be reduced or stopped.

The rapid flow of new clinical information stemming from the SARS-CoV-2 epidemic requires ongoing scrutiny to understand the prudent use, risks and benefits of individual glucose-lowering agents and related medications commonly used in subjects with diabetes at risk of, or hospitalized with coronavirus-related infections. Moreover, the current pandemic highlights the importance of opportunities for continuing and expanding innovative delivery of diabetes care, through use of wearable and portable monitoring devices, and regular communication between people with diabetes, and their health care providers.

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Figure Legends

Figure 1

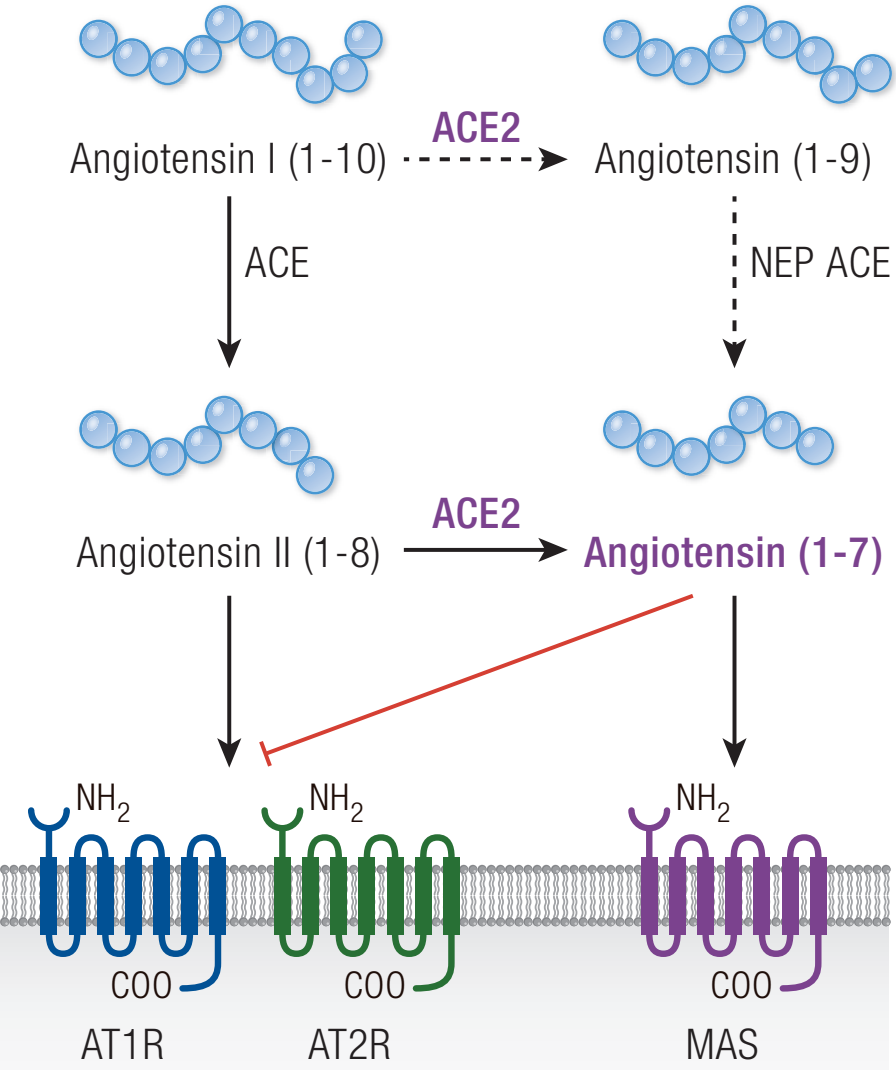
Metabolism of Angiotensin I by ACE and ACE 2 (left panel) to yield different bioactive Angiotensin peptides that exert their actions through distinct G protein coupled receptors. Selective cardiometabolic actions of Ang(1-7) are shown AT1R=Angiotensin II receptor Type 1; AT2R= Angiotensin II receptor Type 2; MAS=Angiotensin(1-7) receptor

The ACE2 receptor consists of 2 forms (right panel), a 805 amino acid membrane-spanning molecule, and a smaller 740 amino acid soluble (sACE2) circulating form, depicted below, which can theoretically serve as a decoy receptor for the MERS-CoV-2 protein. Both molecular isoforms of ACE2 are capable of binding a subset of coronavirus spike proteins, including the SARS-CoV-2 spike protein. TMPRSS2, the membrane-anchored protease important for activation of the SARS-CoV-2 spike protein, and one of its inhibitors, camostat mesylate, is depicted

Figure 2

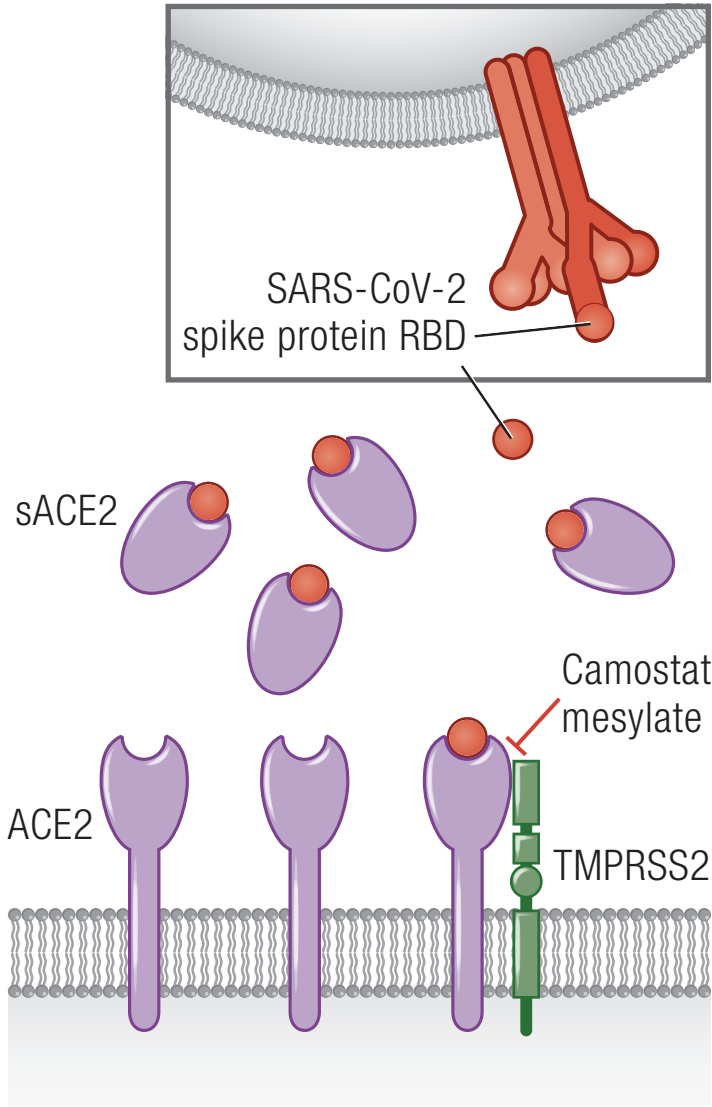
Dipeptidyl Peptidase-4 exists as a membrane anchored and smaller circulating smaller form (left panel), with both molecules retaining enzymatic activity. Right panel depicts peptide substrates of DPP4, as modified from (64). BNP=Brain Natriuretic Peptide; CCL=CC Motif Chemokine Ligand; CCXL= C-X-C Motif Chemokine Ligand; GALP= Galanin-like Peptide; GHRH=Growth hormone release hormone; GIP=Glucose-dependent Insulinotropic Polypeptide; G-CSF= Granulocyte colony stimulating factor; GLP-1=Glucagon-like Peptide-1; GLP2=Glucagon-like Peptide-2; GM-CSF=Granulocyte Macrophage Colony Stimulating Factor; GRP=Gastrin Releasing Peptide; HMGB1=High Mobility Group Box 1; IGF-1=Insulin-like Growth Factor-1; IL-3=Interleukin-3; NPY=Neuropeptide Y; PACAP=Pituitary Adenylate Cyclase activating Peptide; PHM=Peptide Histidine Methionine; PYY= Peptide YY; VIP=Vasoactive Intestinal Polypeptide; XCL-1= X-C Motif Chemokine Ligand 1.

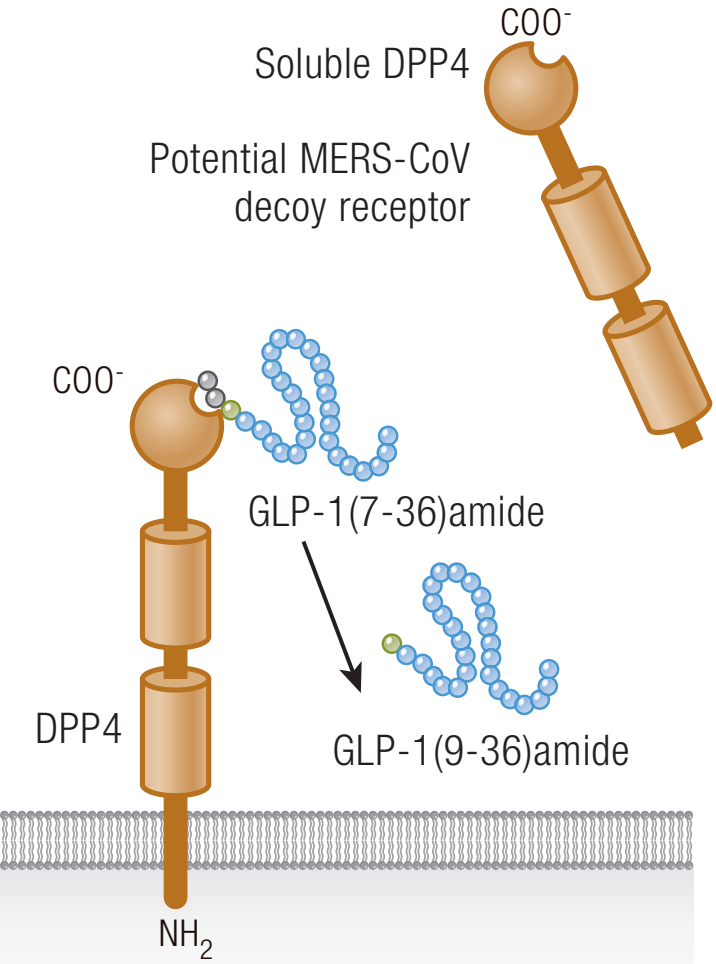
- ACE2 and DPP4 are coronavirus receptors
- ACE2 and DPP4 control inflammation, and cardiometabolic physiology
- DPP4 is a MERS-CoV but not a SARS-Cov-2 receptor
- DPP4 inhibitors do not meaningfully modify immune response in human subjects
- SARS-CoV-2 hospitalizations are more common in people with diabetes and obesity
- Acute SARS-Co-V-2 illness requires re-evaluation of medications used for type 2 diabetes
- Insulin is the glucose-lowering therapy of choice for acute coronavirus-related illness in hospital



Ang (1-7)

- ↑Blood Flow
- ↑Cardioprotection
- ↓Cell proliferation
- ↑Endothelial function
- ↓Fibrosis
- ↓Inflammation
- ↑Insulin
- ↓Insulin resistance
- ↑Vasodilation
- ↑Vasopressin





Dipeptidyl Peptidase-4 Substrates

β-casomorphin	Eotaxin	NPY
BNP	Erythropoietin	Orexin-B
CCL2	GALP	Oxyntomodulin
CCL3	Glucagon	PACAP
CCL4	GIP	Promellitin
CCL5	GLP1	Procalcitonin
CCL22	GLP2	PHM
CXCL4	Galanin-like peptide	Pro-Colipase
CXCL5	G-CSF	Prolactin
CXCL6	GHRH	PYY
CXCL8	GM-CSF	Secretin
CXCL9	GRP	Substance P
CXCL10	Hemomorphin-7	Trypsinogen propeptide
CXCL12	HMGB1	Tyr-MIF-1
Chorionic Gonadatrophin	IGF-1	Vasostatin-1
Endomorphin-1	IL-3	VIP
Endomorphin-2	Kentsin	XCL1
Enterostatin	Morphiceptin	