REVIEW

Hypothesized mechanisms explaining poor prognosis in type 2 diabetes patients with COVID-19: a review

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Abstract

Purpose Epidemiological data suggest that comorbid patients, mostly those with type 2 diabetes (T2D), are predisposed to poor prognosis in Coronavirus disease 2019 (COVID-19), leading to serious healthcare concerns. The aim of the present manuscript is to review the main relevant mechanisms possibly contributing to worsen the clinical course of COVID-19 in T2D.

Results Poor glucose control, high glycaemic variability and diabetes-related comorbidities at baseline, particularly cardiovascular diseases and obesity, contribute in worsening the prognosis in the above-mentioned cluster of patients. Moreover, both a lower efficient innate immune system response and cytokine dysregulation predispose patients with T2D to impaired viral clearance and more serious pulmonary and systemic inflammation once the SARS-CoV-2 infection occurred. Inconclusive data are currently available for specifically indicate or contraindicate concurrent medications for managing T2D and its comorbidities in infected patients.

Conclusions T2D individuals should be considered as more vulnerable to COVID-19 than general population, and thus require adequate advices about hygienic tips to protect themselves during the pandemic. A careful management of glucose levels and diabetes-related comorbidities remains essential for avoiding further complications, and patient monitoring during the pandemic should be performed also at distance by means of telemedicine. Further studies are needed to clarify whether medications normally used for managing T2D and its associated comorbidities could have a protective or detrimental effect on COVID-19 clinical course.

Keywords COVID-19 · Diabetes mellitus · Cardiovascular disease · Obesity · Immune response · GLP-1RAs

Abbreviations

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SARS-CoV	severe acute respiratory syndrome coronavirus
MERS-CoV	middle east respiratory syndrome coronavirus
COVID-19	coronavirus disease 2019
DM	diabetes mellitus
T2D	type 2 diabetes
IL	interleukin
NK	natural killer
ACE2	angiotensin-converting enzyme type 2
DPP-IV	dipeptidyl peptidase IV
GLP-1RA	glucagon-like peptide 1 receptor agonist
MYD88	myeloid differentiation primary response 88

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Background

Firstly identified and characterized as 2019-nCOV [1], human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported as a novel infective agent arisen at the end of the 2019 [2]. SARS-CoV-2 is a positive-sense, single strand, enveloped RNA virus belonging to the family of Coronaviridae, and is the 7th beta-coronavirus recognized to infect humans [3]. First metagenomic RNA sequencing of SARS-CoV-2 showed the single-strand RNA consisted of 29,906 nucleotides, and was closely related to a group of bat SARS-like coronaviruses (89,1%) [4]. Further observations confirmed that SARS-CoV-2 was closely related (88%) with two bat SARS-like coronavirus (bat-SL-CoVZC45 and bat-SL-CoVZXC21), but was distant from other two human coronaviruses responsible for severe infective pneumonia: SARS-CoV (79%) and Middle East respiratory syndrome coronavirus (MERS-CoV) (50%) [5]. A high grade of homology between genomic sequences of SARS-CoV-2 form different patients (99.98%) has also been reported, thus confirming a human-to-human transmission of the novel infective agent [5]. Phylogenetic analysis suggested that SARS-CoV-2 progenitors circulated in animal host including bats [6], snakes, Malayan pangolins, civets, mouse [7, 8], and underwent to a naturally occurred selection before the zoonotic spillover finally adapting to persistently infect the new host [9]. Official epidemiological report declared that the early cases of infections were detected in December 2019, and involved people who worked or visited the Hua Nan South China Seafood Market [10], in Wuhan capital city (Hubei province; People's Republic of China). However, it remains still debated whether the zoonotic spillover might have been occurred in other places [11], particularly in Southeast Asia [12], and consequently SARS-CoV-2 infection might have been imported to Wuhan. Epidemiological analysis showed a marked widespread of the infection within community places due to a large human-to-human transmission [13] and Wuhan rapidly became the hub of a new pneumonia outbreak [14]. Due to a consistent widespread of detected cases among several countries, the World Health Organization declared the state of pandemic on March 11, 2020 when confirmed cases raised up to 118,000, and SARS-CoV-2 spread into 114 countries [15].

COVID-19 and clinical matter

Clinical manifestations of the novel coronavirus disease 2019 (COVID-19) include fever (87%), cough (58%), dyspnoea (38%), muscle soreness (35%), chest distress (31%) in a context of bilateral pneumonia (76%) with ground glass opacification (70%) at CT scan due to lung interstitial involvement [16]. Autoptic studies described macroscopic features of pleuro-pericarditis, lung consolidation, oedema with overall increased pulmonary weight; while microscopic hallmarks are characterized by pneumocyte hyperplasia, lymphocytic and multinucleated giant cells infiltration, hyaline membranes [17–19]. Other signs and symptoms of COVID-19 include acute conjunctivitis [20, 21]; diarrhoea, abdominal pain/discomfort and vomiting [22–24]; convulsion, headache, muscle soreness [25]; diffuse erythematous rush and widespread urticaria [26]; acute kidney injury [27, 28]; pharyngodynia, nasal congestion with rhinorrhoea and smell/taste impairment [29]. SARS-CoV-2 may directly affect myocardial tissue, and significantly complicate the prognosis of underlying cardiovascular diseases [30, 31]. SARS-CoV-2 infection usually occurs asymptomatically or mildly symptomatic form of the disease but in predis posed patients with specific clinical conditions, a serious clinical course could be observed thus leading to worse prognosis or death [12]. Worldwide reported case-fatality rate for COVID-19 differs considerably among geographical areas [32], and could be attributable to several variables, such as testing strategies for screen suspected cases and identification of infectious patients (statistical); accessibility to intensive care according to restricted national healthcare system capacities (organization); baseline patient age and comorbidities (medical) [33, 34]. From the latter point of view, a poor prognosis is usually observed in elderly patients [35] and worldwide age-specific case-fatality rate occurred very high among patients with one or more underlying chronic diseases including cardiocirculatory, renal, pulmonary, central nervous system and mental illness, diabetes mellitus (DM) and malignancies [36, 37]. According to the data shared by the Italian National Institute of Health, patients who died while tested positive for SARS-CoV-2 exhibited an elevated mean age (78.5 years old), mostly men (70%) and with one or more pre-existent chronic diseases (2.7 in mean) [38]. Of these, blood arterial hypertension (78%) and DM (34%) were the most commonly reported clinical comorbidities, followed by ischaemic heart disease (30%) and atrial fibrillation (22%). The leading cause of deaths was attributable to acute respiratory distress (97%) [38].

Epidemiological considerations in patients with type 2 diabetes

The global estimated prevalence of T2D accounts for more than 450 millions affected patients corresponding to 9.3% of the worldwide population [39]. Therefore, the number of patients with T2D who will contract SARS-CoV-2 infection is expected to be considerable, and should increase

over time. T2D per se does not increase the risk of contracting SARS-CoV-2 infection but could exacerbate the clinical course of COVID-19 leading to a detrimental prognosis [40]. Indeed, the frequency of diabetes in patients with COVID-19 has been reported to 9–12% [41–43], raising up to 16–20% in hospitalized patients including those who required intensive care for severe disease [44, 45]. More recently, data collected from nine hospitals from Seattle-area in the United States demonstrated that 58% of patients who required hospitalization for respiratory symptoms attributable to COVID-19 had T2D [46]. In severely ill patients with COVID-19 a pre-existent T2D was observed in about 35% of the cases and, according to the results of an univariate analysis, the presence of T2D resulted a significant risk factor for poor prognosis in this clinical setting (OR 8.14; $p < 0.0001$) [47]. DM has also been reported as the main clinical condition observed in non-survived patients with COVID-19 (22%) [48], thus resulting one of the most frequently associated comorbidity in COVID-19 deceased patients [33]. This concern has been further confirmed by the results of a cohort study among 85 fatal cases of COVID-19 in Wuhan, hence defining DM as a potentially harmful comorbidity predisposing to worse clinical course or death once SARS-CoV-2 infection occurred [49].

Different hypothesis should be considered for explaining this clinical phenomenon, including glucose control at baseline and during the infection course, pathophysiology and immune system response in SARS-CoV-2 infected patients with T2D, diabetes-related comorbidities and concomitant medications. Herein, a point-to-point discussion about these putative mechanisms has been carried out.

Glucose control

Epidemiological data showed that T2D represents a risk factor for infectious diseases, mostly with bacterial aetiology, particularly at the level of skin and soft tissue, genitourinary, gastrointestinal and respiratory systems [50]. Moreover, life expectancy in individuals with T2D may be affected due to infectious diseases and in certain clusters of patients, such as in elderly with T2D, the leading cause of mortality is attributable to severe pulmonary infections rather than other highly prevalent comorbidities, including cardiovascular diseases and malignancies [51]. On the other hand, DM increases the cumulative risk of medical consultation, hospital admission, intensive care requirement and poor prognosis because of pandemic influenza [52]. Further data reported that airways and pulmonary infections with different aetiologies, including SARS and MERS, were more frequently diagnosed in T2D patients, also showing a severe

clinical course [53–56]. In DM, hyperglycaemia is considered one of the most important factor in determining this burden [57]. Indeed, osteomyelitis, soft tissues infections, endocarditis, tuberculosis and sepsis are most commonly observed in diabetic patients with poor glycaemic control compared to those who achieve better glucose management, and a worse glucose control contributes to increase the rate of hospitalization and mortality, too [57]. Both hyperglycaemia and high glucose variability may consistently complicate the clinical course also in case of influenza A [58]. More recently, a retrospective observational study recruiting more than 7000 cases of COVID-19 from Hubei province (China) and including 952 patients with a pre-existent T2D displayed a higher mortality rate (HR 1.49), more prevalence of multiorgan damage and a greater requirement of medications (antibiotics, systemic corticosteroids, vasoactive substances, oxygen inhalation and either non-invasive or invasive mechanical ventilation) in patients with DM than in non-diabetics [59]. Interestingly, authors also found that, among T2D patients, those with better glucose control (glucose levels between 70 and 180 mg/dl) respective to those with worse glucose control (>180 mg/dl) during hospitalization exhibited a significantly lower rate of mortality (HR 0.14; $p < 0.008$), and a fewer risk of progression to acute respiratory distress syndrome (HR 0.47; $p < 0.009$), acute kidney (HR 0.12; $p < 0.046$) and myocardial (HR 0.24; $p < 0.01$) injury [59]. Similar results were found by another observation in which worse glucose control (glucose levels >110 mg/dl) at the admission and during hospitalization was found to be an independent risk factor for progression to critical ill or death among T2D patients with confirmed COVID-19 [60]. Therefore, hyperglycaemia represents a relevant matter in patients with COVID-19 fostering poor prognosis once the infection occurred. In addition, recent evidences suggest that SARS-CoV-2 may induce beta-cells damage thus leading to insulin secretion impairment. This phenomenon, in addition to a pre-existent hyperglycaemia and considering that systemic inflammation due to the infection exacerbates the insulin-resistance, is thought to play a significant role to further worsen glucose control and complicate the clinical course of COVID-19 [61]. In conclusion, epidemiological data suggested that DM, particularly T2D, is a frequently observed comorbidity in patients with SARS-CoV-2 infection who require hospitalization, more intensive treatment and exhibit poor prognosis or death. Poor baseline and ongoing glucose control in hospitalized patients rather than the presence of T2D per se seems to facilitate COVID-19 progression [62]. Hence, an optimal and timely blood glucose management during pandemic should be considered as an effective strategy to reduce the probability of hospitalization requirement of infected patients, and for improving the

clinical course of those hospitalized for receiving either non-intensive or intensive care.

Immune system response

Innate and adaptive immune responses play a crucial role against viral infections [63]. Immune response against coronaviruses has been reviewed elsewhere, highlighting the role of both innate and adaptive systems to promptly contrast virus replication, facilitate virus clearance, stimulate tissue repair and develop persistent defence [64]. Immune response in COVID-19 is not still completely understood making necessary further investigation to better control the pandemic evolution [65]. However, seriously ill COVID-19 patients exhibit an exaggerate response of neutrophils and alveolar macrophages, and a relevant peripheral lymphocytes dysfunction [66], which lead to an uncontrolled viral shedding, consequent viremia and further systemic immune-mediated damage, thus triggering a harmful vicious circle [66]. Glucose levels may significantly influence immune response as observed in patients with DM. Natural killer (NK) cells activity is weakened in case of hyperglycaemia, and is inversely related with fasting plasma glucose, 2-h postprandial glycaemia and HbA1c levels [67]. Macrophage activation and phagocytosis are both decreased in patients with poor glucose control, but should be restored after an adequate optimization of metabolic control [68]. Neutrophil activation and phagocytosis are both impaired by hyperglycaemia as demonstrated in animal models and humans, thus suggesting a relevant impairment of innate immune response in patients with chronic hyperglycaemia [69]. In an animal model, obese and hyperglycaemic mice experienced higher rate of respiratory infection due to influenza and bacterial pneumonia and that was related to a lower efficient alveolar macrophage response against infections. In addition, a defective Toll-like receptor 4 signalling has been recognized in neutrophils exposed to the gram-negative lipopolysaccharide, leading to a blunted release of chemokines and cytokine, and decreased myeloperoxidase activity [69]. Moreover, T-cells function is significantly dysregulated in T2D and CD4$^+$ lymphocytes preferentially differentiate in T-helper 1 and T-helper 17 instead of T-helper 2 with a consequent imbalance between pro-inflammatory and anti-inflammatory activities [70]. On the other hand, the levels of interferon gamma—which normally stimulates CD4$^+$ T cells maturation in sense of T-helper 1 rather than T-helper 2—were found to be lower in T2D patients sera, and can contribute in a blunted T-cell response in T2D [71]. Nevertheless, lower levels of interleukin (IL)-10 have also been described in T2D patients. Considering that IL-10 is capable to suppress the release of pro-inflammatory cytokines, lower levels of IL-10 could be related with higher IL-6-to-IFN

gamma and TNF-alpha-to-IFN gamma ratios hence suggesting an enhanced activation of circulating monocytes [71]. High levels of IL-6 have been detected in diabetic patients respective to those with euglycemia, suggesting that hyperglycaemia play a crucial role in determining this immunological effect [72, 73]. In animal models, hyperglycaemia and insulin-resistance increase the level of circulating proinflammatory cytokines and oxidative stress at baseline [74]. Since this pro-inflammatory background usually results reversible after an effective treatment of hyperglycaemia, a low dose endotoxemia consistently enhances systemic inflammation in a animal model [75]. Therefore, hyperglycaemia may predispose to an exaggerate immune response even in case of a mild-to-moderate viral load. As known, a hyperinflammatory syndrome with cytokine dysregulation has been well recognized in seriously ill patients [76], thus highlighting its crucial role in serious manifestations of COVID-19 [77]. Specific interleukins and chemokines (IL-2, IL-7, IL-6, TNF-alpha, interferon gamma induced protein 10, granulocyte-colony stimulating factor) are upregulated in patients who exhibited a worsen prognosis [78] and particularly high levels of IL-6 have been detected in case of serious pulmonary involvement or in patients requiring intensive care [79]. These findings are also more evident in elderly patients who display less vigorous immune response against viral shedding, greater susceptibility to more serious pulmonary and systemic involvement, and are finally predisposed to COVID-19 progression [80]. Both the number and function of T cells (both CD4$^+$ and CD8$^+$) [81, 82], B cells depletion, and hypercoagulability have also been observed in seriously ill cases and the greater the magnitude of these haematological and biochemical alterations then the greater the severity of the prognosis [83, 84]. In conclusion, diabetic patients especially elderly individuals and those with worse baseline glucose control may exhibit immune system dysregulation that predispose them to a less effective response against SARS-CoV-2 and to a dysfunctional inflammation that requires to be carefully monitored in confirmed cases of COVID-19, for preventing or avoiding a harmful progression of the disease.

Pathophysiological characteristics

Angiotensin-converting enzyme 2 (ACE$_2$) is a carboxypeptidase normally involved in the cleavage of angiotensin I and angiotensin II, and is the main receptor for SARS-CoV-2 playing a determinant role in viral entry into the host, and clearly explaining both the transmissibility and severity of COVID-19 among humans [85]. ACE$_2$ is expressed at the level of several tissues (transmembrane and soluble forms), such as lung [86], oral mucosa [87], intestine [88], brain [89], pancreatic islets [90], testis [91] and kidney [92].

Differentiated type 2 pneumocytes normally express ACE_2, which is essential to regulate pulmonary homoeostasis and protects against pulmonary injury [93]. Indeed, low levels of ACE_2 have been described in severe acute and chronic pulmonary diseases thus predisposing to poor prognosis [94]. However, ACE_2 is overexpressed in chronic diseases, including T2D, and this phenomenon could be also related with chronical exposure to several medications [94, 95]. This biochemical condition is believed to facilitate the internalization of SARS-CoV-2 into pneumocytes, thus contributing to worse prognosis in COVID-19 [94, 95]. However, the role of ACE_2 overexpression in worsening the prognosis is an emergent issue, and remains currently debated [96].

Diabetes-related comorbidities

Cardiovascular diseases, including coronary and cerebrovascular artery disease and heart failure, are frequently observed in T2D patients and it has been estimated that about a third of them displayed these kind of complications over time [97]. Cardiovascular system is the main extrapulmonary compartment extensively involved in COVID-19, as suggested by a frequent myocardial involvement in affected patients especially in those having hypertension, T2D and cardiovascular diseases at baseline [98]. Vascular inflammation and endothelial dysfunction [99], myocardial injury and cardiac arrhythmias are not-infrequently observed in COVID-19 confirmed cases, significantly influencing the risk of poor prognosis or death in this cluster of patients [100–102].

Overweight-obesity syndrome is a multifactorial disease which significantly predispose to cardiometabolic risk, and is strictly associated with insulin-resistance, glucose metabolism impairment and T2D [103–105]. Despite obesity is usually associated with decreased risk of death in patients with severe acute respiratory distress (obesity paradox), currently available data suggest that an elevated body mass index should be considered as an independent risk factor predisposing to poor prognosis [106] and death in COVID-19 [107–110]. Indeed, the prevalence rate of obesity in this cluster of patients has been reported in 42% of the cases [111] and a BMI greater than $35 \, kg/m^2$ has been usually observed in patients requiring hospitalization and invasive mechanical ventilation [112] also in younger patients (<60 years) [113]. Pathophysiological mechanisms possibly related with poor prognosis in obese patients are not completely understood but may be attributable to a greater inflammatory background as similarly found in DM due to hyperglycaemia and insulin resistance [70]. Obesity is usually associated to other severe comorbidities with high impact on cardio-metabolic health, such as fatty liver disease, vascular inflammation, cardiovascular atherosclerotic

diseases and heart failure [114] that might be related with a higher burden of lethal complications, especially in hospitalized patients with COVID-19 [115]. In addition to cardiometabolic risk factors, obese patients are more prone to have a decreased pulmonary ventilation or obstructive sleep apnoea, which predispose them to low levels of blood oxygenation at baseline and consequently to worse respiratory outcomes in case of acute infective respiratory diseases [116, 117]. Nutritional patterns usually exhibited by obese patients are frequently characterized by an elevated dietary consumption of processed food rich in saturated fat, cholesterol, sugar and a low consumption of fibres and micronutrients, such as vitamin D [118]. These dietary patterns may affect physiological microbiome composition, weaken the immune response against microbial agent and foster immune system dysfunction [115]. In addition, vitamin D deficiency/insufficiency and sedentary lifestyle, which are highly prevalent among obese patients, should be considered as predisposing factors for worse prognosis in response to acute infections, including COVID-19 [119]. Abdominal obesity usually leads to a low cardiorespiratory reserve and systemic inflammatory dysfunction which predispose to a worse prognosis in COVID-19 [120]. Conversely, regular physical exercise, which is normally lacking in an obesogenic lifestyle, is associated to higher levels of cardiorespiratory fitness, and is believed to improve the innate immune response and attenuate cytokine dysregulation often experienced by high risk patients with the so called cytokine storm [121]. Visceral obesity is also a risk factor for both the development and progression of cardiovascular diseases [114] considering that it fosters higher level of pro-thrombotic circulating factors and predisposes to thrombotic events [122]. Furthermore, visceral obesity is more prevalent in men than women and this biological phenomenon has been hypothesized to have a putative role in driven poor prognosis of COVID-19 especially in men. From this point of view, male obesity is usually associated with a functional hypogonadism and these clinical conditions are both associated with one other [123], according to a complex and multifactorial pathogenesis [124] that fosters higher baseline levels of inflammation and endothelial dysfunction [125]. Aromatase gene expression is enhanced by prostaglandin E_2, whose levels were found to be higher in visceral adipose tissue of obese men [126]. An enhanced aromatase activity at the level of adipose tissue increases local levels of estradiol that is thought to be a defensive mechanism against local inflammation and insulin resistance [127]. Whether augmented aromatase levels (and activity) at the level of adipose tissue in men may be responsible for a systemic testosterone-to-oestrogen imbalance remains questionable. However, obese men are usually affected by this biochemical condition and body mass index is inversely

correlated to testosterone-to-oestrogen ratio [128]. A low testosterone-to-estradiol ratio contributes to increase the cardiovascular risk particularly in elderly [129] and in those with previous cardiovascular diseases [130–132]. In addition, hormonal pattern associated with visceral obesity may play a relevant role in reducing the efficacy of immune response against infectious agents, predisposing to cytokine dysregulation, endothelial dysfunction, thrombosis, finally driving patients, particularly men, to poor prognosis or death [133].

Moreover, ACE$_2$ is also expressed on adipose cells [134] and a larger extension of adipose tissue in obese patients may significantly increase the number of available receptors for SARS-CoV-2, thus leading to a much greater viral shedding once the infection occurs [135].

In conclusion, multiple diabetes-associated chronic comorbidities, particularly obesity, have been found to worsen the prognosis in COVID-19 affected patients by acting as independent risk factors. Careful management and prompt interventions are thus required for improve clinical outcome predominantly in type 2 diabetic patients.

Concomitant medications

Pathogenetic mechanisms basically involved in SARS-CoV-2 infection may be exacerbated by the use of concomitant medications for the management of T2D. Of note, an exaggerate pulmonary and systemic expression of ACE$_2$ facilitates SARS-CoV-2 replication and may be responsible for worse clinical course and poor prognosis [94, 95]. In animal model, pioglitazone has demonstrated to increase ACE$_2$ expression particularly at the level of hepatic and adipose tissue [136, 137]. On the other hand, the analysis of potential therapeutic targets for SARS-CoV-2 assessed by a computational model found pioglitazone to have a potential for inhibiting 3CLpro, an essential target for viral replication [138]. These findings did not provide conclusive assumption and diabetologists can safely prescribe pioglitazone taking into account general concerns including fluid retention and heart failure [139].

Gliflozins prescription is increasing over time, also considering a long-term beneficial cardiovascular and renal protection [140, 141]. Many mechanisms of cardiovascular and renal protection have been proposed, including an enhanced induction of ACE$_2$ expression at the level of heart and kidney but it is unclear whether this effect may negatively influence clinical course in COVID-19 [142]. Moreover, despite gliflozins reduce inflammatory injury and endothelial dysfunction, none conclusive data are currently available to confirm their potential beneficial effect in diabetics with COVID-19 [143]. Concerns about gliflozins use in COVID-19 are attributable to volume contraction, renal

insufficiency and increased risk of ketoacidosis that may be supposed to occur particularly in hospitalized patients, including those severely ills.

Dipeptidyl peptidase IV (DPP-IV or CD26) is a transmembrane and soluble ectopeptidase largely expressed in human tissues, including airways, lung and leucocytes [144]. Particularly, DPP-IV is specifically involved in MERS pathogenesis given that it mediate MERS-CoV-2 internalization in host cells [145]. No data actually support the role of DPP-IV in the internalization of SARS-CoV-2 and further study are needed to verify this aspect, and for demonstrating clear protective effects [146]. However, DPP-IV inhibitors have shown to potentiate immune response by increasing T-cells survival, consequently enhance immune response [147], and possibly playing a relevant role in reducing the onset or progression of acute pulmonary manifestations in COVID-19 [145].

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) belong to an effective class of medications approved for the treatment of T2D and for preventing diabetes-related cardiovascular and renal complications over time [148–151]. Immune response and systemic inflammation play a crucial role in SARS-CoV-2 infection, particularly in case of severe clinical course of the disease. In this clinical scenario, it is speculated that the use of GLP-1RAs could provide both a better glucose control and anti-inflammatory effects with consequent improvement of outcomes in COVID-19 affected patients [143]. In patients with pulmonary inflammation, mononuclear circulating cells express lower level of GLP-1 receptors than controls and this condition is associated with a blunted production of interferon gamma by T cells and NK cells. In addition, the expression of programmed death cell protein 1, which mediates T-cell apoptosis, is enhanced on T-cell surface and consequently the efficiency of cell-mediated immune response is weaken. Liraglutide, a once-daily administered long-acting GLP-1RA, demonstrated to restore the expression of GLP-1 receptors on macrophage surface, and potentiate immune-mediated response [152]. In addition, both DPP-IV pharmacological inhibition (linagliptin) and GLP-1RA (liraglutide) were found to contrast pulmonary injury, reduce platelet activation, microvascular thrombosis, and oxidative stress in mice model of endotoxemia [153]. Moreover, GLP-1RAs have been found to reduce the expression of pulmonary IL-33, thus playing an interesting role in contrasting a IL-33 mediated damage in immune-allergic diseases and viral infections [154].

Considering that pancreatic islets express ACE$_2$, glucose impairment in COVID-19 diabetic patients could be attributable to a partial insulin deficiency [56]. However, glucose impairment could also be attributable to SARS-CoV-2 infection-induced stress or as the consequence of some medications or treatment protocols, including high-dose

glucocorticoids, particularly used in hospitalized patients [155]. Insulin therapy is recommended in hospitalized patients [156], including those with COVID-19, and a basal-bolus respective to a sliding scale regimen should be preferred in infected patients for avoiding glycaemic excursion and greater glucose variability [157, 158].

Hypertension is frequently observed in T2D patients leading to a consistent increase in the risk of atherosclerotic cardiovascular and renal diseases [159]. ACE inhibitors and angiotensin receptor blockers compared to other anti-hypertensive medications demonstrated to be more effective to prevent or delay the onset of cardiovascular and renal complications in people with T2D, and are currently used as the first-line treatment in these patients [160, 161]. Evidence from animal models suggested that ACE inhibitors are able to increase the expression of ACE_2 at the level of lung, thus leading to initial clinical concerns about the management of arterial hypertension in diabetic patients [162]. First suggestions advised to replace these medications with calcium-channel blockers in order to avoid undesirable detrimental effects of COVID-19 clinical course [95]. Nevertheless, no sufficient data supported the hypothesis that the use of renin-angiotensin system blockers may interfere with the internalization of SARS-CoV-2 in respiratory cells hence increasing its virulence [163]. In addition, ACE inhibitors and angiotensin receptor blockers protect lung, heart and kidney against inflammation, thus playing a potential beneficial role also in T2D patients with COVID-19 [164].

Statins are usually prescribed especially in T2D patients to protect against cardiovascular complications [165]. The role of statins in COVID-19 is not clearly established, however, some observation should be done. First, COVID-19 is associated with higher cardiovascular mortality specifically in patients with more risk factors, including hypertension and T2D, and statins could be useful to maintain or optimize lipid management and improve endothelial dysfunction in this clinical setting [166]. In animal models, statins inhibit the myeloid differentiation primary response 88 (MYD88) [167]. MYD88 is a protein adaptor for inflammatory signalling pathways downstream of members of Toll-like receptors and IL-1 receptor families, and plays a critical function in the activation and amplification of innate immune response [168]. The inhibition of MYD88 seems to reduce pulmonary inflammatory damage, and to improve survival in SARS-CoV and MERS-CoV infected mice [167]. Patients with established cardiovascular disease, and those at higher risk of atherosclerotic cardiovascular disease including T2D (also in primary prevention) should be advised to maintain current statin treatment also in case of confirmed COVID-19. In patient with active COVID-19, an increased risk of muscular damage has been described and statin therapy could be interrupted for a short period of time in order to favour muscular recovery [169].

Discussion and conclusions

T2D should be considered as a risk factor for poor prognosis in COVID-19 due to several reasons, including poor baseline glucose control and high glycaemic variability, diabetes-related immune dysfunction and concurrent comorbidities, also proven to act as independent risk factors for poor prognosis in this clinical setting. Considering that respiratory system remains essentially the leading way for SARS-CoV-2 entering in host, and given that immune barriers are weaken in T2D patients, including resident pulmonary macrophages, neutrophils and T cells [70], diabetologists could improve clinical outcomes in COVID-19 simply by the use of such a medication with potential for positive immune-modulation and anti-inflammatory effects. Unfortunately, inconclusive deductions are currently available for considering concomitant medications favourable (as well as detrimental) factors in COVID-19 patients with T2D. Despite some putative mechanisms have been identified and some speculative hypothesis have also been formulated indicating that some anti-diabetes medications may improve clinical course in COVID-19 (pioglitazone, gliflozins, DPP-IV inhibitors, GLP-1RA), further studies are needed to clarify the issue. A timely glucose control should be obtained in diabetic patients during pandemic for the purpose to avoid potentially harmful outcomes in case of SARS-CoV-2 infection [170]. Anti-diabetic medications should be used with caution, also considering their impact on patient safety in case of complications related with COVID-19 infection (renal failure, cardio-respiratory burden, ketoacidosis, etc). Oral and non-insulin injectable medications (GLP-1RAs) should be considered to maintain or intensify household glucose control, while insulin treatment is currently known to be safer in case of hospitalized and seriously ill patients [171].

Given this consideration, in seriously ill patients, immune response should be adequately monitored in order to carefully predict or precociously diagnose a severe disease [172] and cytokines, including IL-6, may be considered as a goal for novel and more specific target therapies particularly in T2D individuals [173–175].

Beyond the risks strictly related with COVID-19 infections in diabetic patients, further concerns should be taken into account. Social distancing and lockdown have been proposed as the most effective action to prevent and reduce spread of SARS-CoV-2 infection [176]. Consequently, more time has been spent in household and access to public and private services has been consistently reduced. Thus, several barriers exist for diabetic patients to maintain an adequate fitness status and weight management as well as access to ambulatory care for obtaining adequate treatment adjustments [177]. In the last few months, home confinement led to physical inactivity and low exposure to sunlight,

with possible detrimental effects particularly in diabetic and obese patients [119]. Physical exercise should be encouraged also at home or outdoor, even respecting social distancing rules, since it promotes weight loss, and improves cardiorespiratory fitness [121]; reduces levels of cortisol thus reinforcing immune response against infections; induces T-cell differentiation and maturation [178].

Importantly, patients should be advised about risks and supported regarding pandemic-related concerns. Particularly, they should be elucidated about general hygienic tips to protect themselves and others from SARS-CoV-2 spread; promptly recognize COVID-19 signs and symptoms; access orderly to approved testing if exposed; furthermore, it is important to avoid unnecessary routine appointment in person especially for elderly patients [179]. Closely monitoring of glucose control should be recommended at home and glucose reports should be periodically sent to the diabetologist for proper therapy adjustments [180].

The hard lesson form Lombardy disaster probably teaches to change prospective in the conception of patients care during the present and in case of further pandemic. Implementation of community-centred care system (home care and mobile clinics) may result in a prompt detection and better management of infected patients particularly for frail individuals. Moreover, it might contain an unnecessary hospital workload, letting hospital activities to focus mainly on acute cares and limiting contagion risks among inpatients and healthcare personnel. Finally, it could provide at home special cares for elderly and comorbid patients [181]. In this historical moment, the use of technologies appears certainly appropriated to better manage chronic clinical conditions, including DM [182–184]. Diabetic outpatients should be conveniently managed by means of telemedicine that includes several services such as emergency phone calls, social media messaging, teleconsulting and ambulatories should be fitted with technological tools according to patients ability, healthcare personnel characteristics and available economic resources [62].

Compliance with ethical standards

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