Multiple immune function impairments in diabetic patients and their effects on COVID-19

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Abstract
Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2, poses a significant threat to public health worldwide, and diabetes is considered a risk factor for the rapid progression and poor prognosis of COVID-19. Limited immune function is a clinical feature of COVID-19 patients, and diabetes patients have defects in innate and adaptive immune functions, which may be an important reason for the rapid progression and poor prognosis of COVID-19 in patients with diabetes. We review the possible multiple effects of immune impairment in diabetic patients on the immune responses to COVID-19 to provide guidance for the diagnosis and treatment of diabetic patients with COVID-19.

Key Words: COVID-19; Diabetes; Immune function; SARS-CoV-2

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Core Tip: Diabetes is an important predictor of coronavirus disease 2019 (COVID-19) morbidity and mortality. The immune response impairment presented by diabetes mellitus (DM) may be among the underlying mechanisms of the association between diabetes and COVID-19. DM patients with uncontrolled hyperglycemia are more prone to develop severe COVID-19 due to T cell dysfunction. Therefore, DM is often associated with impaired innate and adaptive immune function, thus greatly increasing the risk of severe acute respiratory syndrome coronavirus 2 infection in DM patients.

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INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has been declared a global pandemic. As of January 18, 2021, there were 93805612 COVID-19 cases and 2026093 COVID-19-related deaths worldwide. Diabetes mellitus (DM) is an important risk factor for the occurrence and development of COVID-19 and has caused a heavy economic burden on global health[1,2]. Diabetic patients often have impaired immune function, which significantly increases the susceptibility of patients to respiratory tract, urinary tract, and soft tissue infections[3-5] and increases the risk of death caused by infection. Some studies have found that 10% to 18.3% of COVID-19 patients have diabetes[6,7], and the mortality rate among these patients is as high as 26.4%[6,7]. To further understand the role of the abnormal immune function of patients with diabetes in the development of COVID-19, we review the literature as follows (Table 1).

IMPAIRED INNATE IMMUNITY AGAINST COVID-19 IN PATIENTS WITH DIABETES

Impact of dendritic cells on COVID-19 in patients with diabetes

Dendritic cells (DCs) play unique roles as antigen-presenting cells in response to both bacterial and viral infections in diabetic patients, and poor control of diabetes and glucose metabolism leads to reduced numbers and abnormal function of DCs. Studies have shown that the percentage of mononuclear plasmacytogenic DCs (pDCs) in peripheral blood is significantly reduced in patients with recent-onset and long-term type 1 DM (T1DM)[8]. The relative numbers and absolute ratios of peripheral blood myeloid DC1s and pDCs were significantly lower in type 2 DM (T2DM) patients with poor metabolic control than in healthy subjects[9]. Women with T2DM with poor glycemic control had fewer circulating pDCs than women with T2DM with good glycemic control and healthy women. The study also found that tumour necrosis factor (TNF-α) production by healthy pDCs was significantly increased, suggesting that poor glycemic control in patients with T2DM could lead to a decrease in the number of pDCs and their production of TNF-α[10]. It has been suggested that patients with obesity and COVID-19 have higher serum TNF-α concentrations and are more likely to develop acute respiratory distress syndrome (ARDS) and, even worsen, are more likely to die from COVID-19[11]. The number and function of circulating DCs are reduced in patients with T2DM and the complication of atherosclerosis, and the spontaneous secretion of interleukin (IL)-6 and TNF-α by monocytes and CD16+ DCs is also significantly reduced in these patients[12]. In addition to TNF-α, patients with T2DM have increased serum levels of TNF superfamily 14 (TNFSF14). TNFSF14 may exacerbate T2DM by reducing insulin secretion by pancreatic islet cells and promoting vascular inflammation. In a study of NK cell-DC interactions, activated NK cells induced DC maturation in a TNFSF14-dependent manner[13]. The study found that the serum TNFSF14 levels of hospitalized patients with COVID-19 were significantly higher than those in age- and sex-matched healthy controls. Among hospitalized patients over 60 years of age, the mortality rate was 82%, and the TNFSF14 levels were significantly higher in the patients who died than in those who survived[14], suggesting that increased TNFSF14 levels may in turn promote the maturation of DCs.

High glucose-induced DC maturation and apoptosis may be an important factor in the immunosuppression observed in COVID-19 patients. Studies have shown that high glucose can induce the secretion of the proinflammatory cytokines IL-6 and IL-12 by human DCs, lead to the increased expression of CD86 and CD83 by DCs, promote the maturation of DCs, and increase the expression of the DC scavenging receptors SR-A, CD36, and LOX-1, thus increasing the ability of DCs to absorb oxLDL[15]. Lipopolysaccharide (LPS) can induce DC maturation[16], while high glucose concentrations may promote the LPS-induced apoptosis of DCs by upregulating the expression of Bax and downregulating the expression of Akt, ERK, and Bcl-2[17]. Activation of the PI3K/Akt and ERK signalling pathways induced immunosuppression during infection with SARS-CoV-2, while further activation of this pathway induced DC apoptosis in patients with DM[17], which may be an important factor in the reduction in DCs in patients with DM with COVID-19.

The release of a large amount of interferon alpha subtype (IFN-α), which is an important proinflammatory factor, in patients with DM promotes COVID-19 pneumonia-mediated injury. Infection induces DCs and other cells to produce large...
Table 1 Impaired immunity against coronavirus disease 2019 in patients with diabetes

| Type of immune response | Immune cell type | Immune cell abnormalities that cause COVID-19 exacerbation in diabetes |
|-------------------------|------------------|---------------------------------------------------------------|
| Innate immunity         | Dendritic cells  | (1) Hyperglycemia promotes DC maturation and apoptosis\[^{[15-17]}\]; (2) Reduction in quantity\[^{[17]}\]; and (3) Abnormal function: IFN-α\[^{[18]}\] |
|                         | Macrophages      | (1) Macrophages accumulate in the lungs\[^{[26,29]}\]; (2) Increased numbers of M1-type macrophages\[^{[29]}\]; and (3) Macrophages may promote inflammatory storms and DIC of COVID-19\[^{[20]}\] |
| Neutrophils             |                  | (1) Neutrophils are more prone to NETosis in diabetes\[^{[34]}\]; and (2) Diabetes may increase ACE2 expression, which mediates enhanced neutrophil infiltration\[^{[36,37]}\] |
| NK cells                |                  | NK cell levels increase but activity decreases and function abnormally in diabetes\[^{[41,42]}\] |
| NKT cells               |                  | NKT cells were inversely associated with diabetes progression or COVID-19 severity\[^{[46]}\] |
| Adaptive immunity       | B cells          | Changes in the number, phenotype, and function of B cells in diabetic patients may exacerbate the abnormal response to COVID-19\[^{[51]}\] |
|                         | T cells          | The higher correlation between CD4 T cells and antibodies targeting the S1 domain of the spike protein leads to the worsening of COVID-19 in diabetes\[^{[33]}\] |

COVID-19: Coronavirus disease 2019; IFN-α: Interferon-alpha; ACE2: Angiotensin converting enzyme 2.

amounts of type I interferons, especially IFN-α, which can regulate the progression of autoimmune diabetes\[^{[18]}\]. By sequencing on bronchoalveolar lavage (BAL) fluid from COVID-19 patients, the expression of proinflammatory genes (especially chemokine genes) was shown to be significantly increased in COVID-19 patients. SARS-CoV-2 strongly induces the expression of a number of interferon-stimulating genes (ISGs), which lead to immunopathogenicity and are representative of the expression of genes involved in the hyperinflammatory response. Transcriptome data were also used to estimate the number of immune cells, and the results showed an increase in the numbers of activated DCs and neutrophils\[^{[19]}\], suggesting that in patients with COVID-19 at this stage, the increased activation of DCs and neutrophils\[^{[19]}\], which lead to immunopathogenicity and are representative of the expression of genes involved in the hyperinflammatory response, which may be an important mechanism underlying COVID-19-induced lung injury.

Decreased DC counts and impaired IFN-1 secretion may be important mechanisms of immune escape by SARS-CoV-2. Human infectious pathogens activate the autoimmune regulation system and stimulate the release a series of cytokines to resist virus invasion and replication; among these cytokines, the most effective is IFN. pDCs are an important source of IFN-1 production\[^{[20]}\], but pDC numbers are significantly reduced in patients with COVID-19. Therefore, although SARS-CoV-2 replicates more effectively in human lung tissue, it induces even less IFN-1 production than SARS-CoV\[^{[21]}\]. Therefore, the coronavirus may evade immune attack by decreasing the production of IFN-1 by pDCs, leading to the exacerbation of COVID-19. IFN inhibited viral replication by promoting the expression of some downstream ISGs (IFN-stimulated genes). These genes include Mx1, PKR, OAS, IFITM, APOBEC1, TRIM, etc. Compared with other respiratory RNA viruses, SARS-CoV-2 is a poor inducer of the IFN-1 response \textit{in vitro} and in animal models\[^{[22,23]}\], and the serum levels of IFN-1 in patients with COVID-19 are significantly lower\[^{[24,25]}\]. These results suggest that SARS-CoV-2 may escape the immune response caused by IFN-1.

**Impact of macrophages on COVID-19 in DM patients**

Increased numbers of M1-type macrophages in patients with diabetes may exacerbate lung injury in patients with COVID-19. The increase in the number of adipose tissue macrophages (ATMs) and the release of a large number of inflammatory cytokines are important mechanisms that mediate the development of obesity-related insulin resistance (IR) in T2DM patients\[^{[26]}\]. ATMs exhibit two highly heterogeneous phenotypes, M1 or M2\[^{[27]}\]. M1 macrophages are mainly induced by the Th1 signalling pathway, which involves LPS, IFN-γ, and other factors, and express high levels of inflammatory cytokines. M2 macrophages are induced by Th2 signalling, which involves factors such as IL-4 and IL-13, and are associated with anti-inflammatory responses. In addition to regulating the microenvironment in adipose tissue and controlling insulin sensitivity, M1/M2 ATMs also function in immune regulation\[^{[28]}\].
Macrophages and neutrophils are the main immune cell subsets involved in severe COVID-19. Cumulative data have shown a correlation between cytokine storms and the severity of COVID-19. The presence of immune cell subsets in BAL fluid was found to be correlated with COVID-19 disease severity. The presence of neutrophils and macrophage cluster-1 is a feature of severe COVID-19. Through genetic testing, IFITM2, IFITM1, H3F3B, SAT1, and S100A8 were found to be highly correlated with neutrophils, while in patients with severe COVID-19, CCL8, CCL3, CCL2, KLF6, and SPP1 were highly correlated with macrophage group-1. These data reveal the existence of neutrophils and macrophage cluster-1 as major immune cell subsets associated with severe COVID-19[29].

The severe form of COVID-19 is characterized by cytokine storm syndrome and disseminated intravascular coagulation (DIC). The hyperactivation of M1 macrophages with proinflammatory characteristics is related to aerobic glycolysis and causes monocytes, neutrophils, and platelets to be recruited from the blood to the lesion; these cells may play an important role in the excessive inflammatory response to COVID-19 and the process of DIC[30]. Activation of the prostaglandin E2 (PGE2) receptor EP4 alters the polarization of ATMs to the anti-inflammatory M2 phenotype, thereby inhibiting chronic inflammation. Studies have shown that activation of surface EP4 alters the inflammatory macrophages in the pancreas of patients with diabetes to inhibit islet inflammation and protect β-cell function[31]. SARS-CoV-2 causes an inflammatory storm, and multiple organs are affected, and this phenomenon may be related to the secretion of PGE2, which is involved in a variety of inflammatory and immune pathways. In addition, the association between PGE2 and thrombosis is very important. PGE2 can make platelets more sensitive to aggregation by reducing the activation threshold of platelets, which may be related to microthrombosis in patients with COVID-19[32]. Therefore, it is possible for the chronic inflammation in DM patients to be inhibited by activating EP4, but this condition may lead to an inflammatory storm and DIC in COVID-19 patients.

Impact of neutrophils on COVID-19 in patients with diabetes

Neutrophils are the primary immune cells in mammals that fight pathogens, recognize and phagocytose microorganisms, and then kill pathogens through a combination of cytotoxic mechanisms. These mechanisms include the production of reactive oxygen species, the release of antimicrobial peptides, and the recently discovered release of their nuclear contents to form neutrophil extracellular traps (NETs)[33], which are also involved in tissue injury healing. It has been reported that neutrophils isolated from humans and mice with T1 and T2DM produce NETs when activated (a process known as NETosis). The expression of peptide arginine deiminase 4 (PAD4, encoded by the Pad4 gene in mice), an enzyme that is important in chromatin densification, is increased in the neutrophils of diabetic patients. A large number of NETs were produced in the wounds of the skin excised from wild-type (WT) mice but not in the wounds of the skin excised from Padi4 (-/-) mice. Compared with WT mice, PADI4 (-/-) mice healed faster, and diabetes did not impair wound healing. NETs impair wound healing, especially in diabetes, in which neutrophils are more prone to NETosis [34]. It is speculated that the hyperglycaemic conditions in diabetes promote neutrophils to release NETs release though PAD4, which affects the repair of injured lungs and may be the mechanism by which DM promotes the COVID-19-induced inflammatory response and lung injury. In addition, neutrophil-derived S100 calcium-binding protein A8/A9 (S100A8/A9) interacts with advanced glycosylation end product receptor (RAGE) on liver Kupffer cells during the hyperglycaemia response, resulting in increased IL-6 production and increased inflammatory platelet production, which may be associated with increased microthrombosis in COVID-19 patients. During hyperglycaemia, neutrophil-derived S100 calcium-binding protein A8/A9 (S100A8/A9) interacts with advanced glycosylation end product receptor (RAGE) on liver Kupffer cells, resulting in increased IL-6 production and increased inflammatory platelets, which may be associated with increased microthrombosis in COVID-19[35]. Angiotensin converting enzyme 2 (ACE2) is a receptor that SARS-CoV-2 binds to in order to gain cellular access, and high expression of ACE2 may increase susceptibility to infection. Loss of ACE2 may contribute to the severity of ARDS during COVID-19 by increasing angiotensin II-mediated vascular permeability, pulmonary oedema, and neutrophilic infiltration[36,37]. Some studies have found that DM and its related characteristics may increase the expression of ACE2[38], so patients with both COVID-19 and DM may have a worse prognosis.
**Impact of NK cells on COVID-19 in patients with diabetes**

T1DM is characterized by the immune-mediated progressive destruction of pancreatic cells. NK cells have the ability to kill target cells and interact with antigen-presenting cells and T cells. It has been suggested that NK cells may be involved in one or more of the immune-mediated attacks that lead to T1DM[39]. NOD mice with autoimmune diabetes show a high frequency of inKTI7 cells, which are involved in the development of the disease[40]. Chronic immune activation and hyperglycaemia are hallmarks of T2DM, and a dysregulated NK cell response is associated with an increased risk of cardiovascular disease in patients with T2DM. A meta-analysis showed that NK cell levels were significantly elevated in adult patients with T2DM [41]. Kim et al[42] measured NK cell activity by detecting the level of interferon-γ secreted by circulating NK cells in T2DM patients and found that the NK cell activity in T2DM patients was lower than that in patients with prediabetes and those with normal glucose tolerance. In patients with T2DM, NK cell activity was significantly negatively linear with fasting blood glucose, glycated haemoglobin, and post-2-h blood glucose levels[42]. Berrou et al[43] showed that the NK cell-activating receptors NKG2D and NKP46 were lacking in patients with T2DM, and the expression level of NKG2D was negatively correlated with the level of HbA1c, suggesting that chronic hyperglycaemia may lead to NK cell dysfunction[43]. The NK cell count and percentage were significantly decreased in patients with severe COVID-19. The number of cytotoxic CD3-CD56dim CD16' cells was significantly decreased in patients with severe COVID-19, while the number of some CD3-CD56dim CD16- cell types was significantly increased. More importantly, the expression of CD244, programmed death-1, and other regulatory molecules on NK cells and T cells in the peripheral blood of COVID-19 patients was increased, while the expression of cytotoxic effector molecules, such as perforin and granulosin A, in the serum was decreased. The serum levels of IL-6, IL-10, and TNF-α were increased significantly in severe patients. By Lasso logistic regression analysis, CD3-CD56dim CD16- cells were identified as the influencing factor leading to severe disease[44]. Therefore, the functional failure of NK cells and T cells and the changes in other subsets may be related to the progression and prognosis of COVID-19.

**Impact of NKT cells on COVID-19 in patients with diabetes**

T1DM is an autoimmune disease caused by the T cell-mediated destruction of insulin-producing beta cells. iNKT cells induced pDCs to produce TGF-β in pancreatic lymph nodes in both virus-induced and spontaneous mouse T1DM models. These tolerant pDCs transform naive anti-islet T cells into Foxp3(+) CD4(+) regulatory T cells (Treg cells). These cells are then recruited to the islets to secrete TGF-β, which inhibits the activity of the virus- and islet-specific CD8(+) T cells, thus preventing T1DM development[45]. These findings suggest an important collaboration between NKT cells, pDCs, and Treg cells in the prevention of T1DM through viral infection. Zingaropoli et al[46] analyzed the characteristics of the T, NK, and NKT cells in the peripheral blood of patients with COVID-19, and the study showed that the proportion of CD57' and CD56dim NK cells was higher in patients with COVID-19, while the proportion of NKT and CD56bright cells was lower. In the severe group, the percentage of NKT cells was significantly lower. NKT cells were independently correlated with the severity of COVID-19[46].

**IMPAIRMENT OF ADAPTIVE IMMUNITY AGAINST COVID-19 IN DM**

**Impact of B cells on COVID-19 in patients with DM**

Patients with COVID-19 have had different clinical outcomes, and studies of neutralizing antibodies have shown rapid antigen-specific responses in severely ill patients and strong virus-specific responses capable of neutralizing the virus in vitro in patients recovering from COVID-19[47,48]. The rapid attenuation of anti-SARS-CoV-2-specific antibodies is characteristic of mild COVID-19[49]. These findings strongly suggest that there are important differences in the nature and regulation of effector B cell responses associated with mild and severe COVID-19. Patients with T2DM have disease-associated changes in B cell function, and B cells are associated with promoting systemic inflammation, inflammatory B cell and T cell cytokines, adipose tissue inflammation, and IR in diabetic mice[50]. The loss of islet autoantibodies and the significant changes in B cell phenotype and function in T1DM islet cells compared to healthy donor islet cells were correlated with higher CD95 expression in T1DM B cells[51]. Changes in the number, phenotype, and function of B cells in DM patients
may exacerbate the abnormal response to COVID-19 and the difference in the production of anti-SARS-CoV-2-specific antibodies, which may be responsible for the same clinical outcome in clinical patients. This phenomenon also suggests that COVID-19 immunotherapy targeting B cells may offer hope for a successful cure. In a study of convalescent plasma therapy in B cell-depleted patients with protracted COVID-19, it was found that convalescent plasma may contain large amounts of anti-SARS-CoV-2 antibodies produced by B cells, 90% of patients showed improvement in clinical symptoms after blood transfusion, inflammation syndrome was relieved within 48 h, and SARS-CoV-2 RNAemia decreased to levels below the sensitivity threshold within 1 wk[52].

**T cell immune response in patients with diabetes exacerbates COVID-19**

Studies have shown that comorbidities such as DM and obesity alter the CD4+ T immune response to SARS-CoV-2. The magnitude and functional breadth of virus-specific CD4 T cells and antibody responses continued to be higher in hospitalized subjects, especially in those with diabetes. However, there was a higher correlation between polyfunctional CD4 T cells and antibodies targeting the S1 domain of the spike protein among subjects who were not hospitalized, and this inflammatory response was reduced in patients with conditions, such as diabetes, with known risk factors for severe COVID-19[53]. This suggests that DM may play a greater role in severe COVID-19 by altering the immune function of CD4+ T cells. In a study of the phenotype of SARS-CoV-2-specific T cells in patients with COVID-19 acute respiratory distress syndrome, the strongest T cell responses targeted the spike (S) surface glycoprotein, and SARS-CoV-2-specific T cells predominantly produced effector and Th1 cytokines[54]. A study showed spike-reactive CD4+ T cells in 83% of COVID-19 patients[55]. Cell binding and entry of β-coronavirus occur via its surface spiking glycoprotein; SARS-CoV binds to metalloprotease ACE2, and Middle East respiratory syndrome coronavirus uses dipeptidyl peptidase 4 (DPP4)[56]. Recent modelling of the structure of the spike glycoprotein of SARS-CoV-2 predicted that it could interact with human DPP4 in addition to ACE2. DPP4 is a surface T cell-activated antigen that plays an important role in glucose metabolism through the truncation and inactivation of the N-terminus of enterotropin glucagon-like peptide-1 and gastric suppressor protein[57], and its inhibitors have been used in the treatment of T2DM. However, the apregulation of DPP4 in COVID-19 comorbidity may be a determinant of the severity of COVID-19 disease, and it is speculated that DPP4 treatment may block the invasion of SARS-CoV-2 virus. Patients with diabetes with uncontrolled glucose levels are more prone to develop severe COVID-19 due to T cell dysfunction[58]. SARS-CoV-2 infection triggers mitochondrial ROS production, which induces the translocation of hypoxia-inducible factor-1alpha (HIF-1α) and consequently promotes glycolysis. HIF-1α-induced changes in monocyte metabolism during SARS-CoV-2 infection directly inhibit the T cell response and reduce epithelial cell survival[58]. Therefore, DM may be the key to the establishment of an adaptive immune response and impaired immune memory during SARS-CoV-2 infection due to the effects of T cell function impairment.

**CONCLUSION**

DM is often associated with impaired innate and adaptive immune function, thus greatly increasing the risk of COVID-19 infection in DM patients. The information reviewed in this paper aims to provide guidance for the diagnosis and treatment of COVID-19 and DM comorbidity as well as underscores the need for further research on the mechanisms underlying the disordered immune cell function. Moreover, we hope it might further contribute to the development of appropriate immunotherapies.

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