



## Indonesian Society of Endocrinology

### Position Statement on How to Manage Patients with Diabetes and COVID-19

#### Epidemiology, clinical features, and mortality of COVID-19

In 31 December 2019, 27 cases of pneumonia of unknown aetiology were identified in Wuhan City, Hubei Province in China; and in 7 January 2020, The Chinese Centre for Disease Control and Prevention (CCDC) subsequently named the cause of this disease as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Thereafter, the World Health Organization (WHO) declared this outbreak as a Public Health Emergency of International Concern in 30 January 2020; and then in 11 February 2020 this disease was named Coronavirus Disease 2019 or COVID-19 by WHO.<sup>1,2</sup>

The most frequent clinical features of COVID-19 are fever, cough, and shortness of breath; although recently some unusual symptoms such as loss of smell and taste are reported. The incubation period of the disease is between 2-14 days.<sup>1</sup> Based on a review and meta-analysis by do Nascimento et al., of a total of 61 studies including 59,254 patients, it found that the most common disease-related symptoms were: fever (82%), cough (61%), muscle aches and/or fatigue (36%); dyspnea (26%), headache (12%), sore throat (10%), and gastrointestinal symptoms (9%).<sup>3</sup> Another systematic review and meta-analysis on data from Wuhan also showed very similar result that fever, cough, fatigue, and dyspnea were the most frequent clinical symptoms. It was found that the most prevalent co-morbidities were hypertension (17%), diabetes (8%), cardiovascular diseases (5%) and respiratory system disease (2%).<sup>4</sup>

Summary of a report of 72,314 cases from the CCDC revealed that spectrum of disease was mild 81% (36,160 cases), severe 14% (6,168 cases) and critical 5% (2,087 cases). The case-fatality rate (CFR) of the disease was 2.3% (1,023 of 44,672 confirmed cases), 14.8% in patients aged >80 years (208 of 1,408), 8.0% in patients aged 70-79 years (312 of 3,918), and 49.0% in critical cases (1,023 of 2,087). The CFR was elevated among those with pre-existing comorbid conditions, i.e.: 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer. Among diabetics, CFR is actually 3 times higher compared to general population.<sup>5</sup> Based on the latest global situation reported by WHO (April 20, 2020), there are 2,314,621 person with confirmed COVID-19 and 157,847 death (6.8%).<sup>2</sup> In Indonesia, the latest report from *Gugus Tugas Percepatan Penanganan COVID-19* (April 20, 2020) showed the number of people confirmed with COVID-19 were 6,760 with 590 death (8.7%) cases related to COVID-19.<sup>6</sup>

#### Diabetes and immune dysfunction

Patients with diabetes in general are categorized as immunocompromised hosts, which means there is dysfunction of immunity related to capability against infection. Therefore, infectious diseases are more frequent and more serious in patients with diabetes compared to those without diabetes. The course of the infection is also more complicated in diabetes patients. One of the possible causes of this increased prevalence of infections is defects in immunity. In patients with diabetes there are alterations in proliferation of T cells and macrophages and impairment in NK cells and B cells function, which represents abnormal innate and adaptive immunity.<sup>7,8</sup>

Other causes of reduced capacity against infection also involves other complications related diabetes such as depression of antioxidant system, micro- and macro-angiopathies, neuropathy, decrease in the antibacterial activity of urine, gastrointestinal and urinary dysmotility, and greater number of medical interventions.<sup>9</sup>

#### General and specific precautions for patients with diabetes during a pandemic

It is reasonable to assume that people with diabetes are at increased risk of developing infection including COVID-19. Coexisting heart disease, kidney disease, advanced age and frailty are likely to increase the severity of disease. The following measures are suggested for prevention of this disease in patients with diabetes as proposed by Gupta et al.:<sup>10</sup>

##### A. Specific measures in patients with diabetes:

1. Maintain good glycaemic control, as it might help in reducing the risk and severity of infection. More frequent self monitoring of blood glucose levels is required. Good glycemic control may lessen chances of superimposed bacterial pneumonia as well.

2. Patients with diabetes and co-existing heart disease or kidney disease need special care and attempts should be made to stabilise their cardiac/renal status.
3. Attention to nutrition and adequate protein intake is important. Any deficiencies of minerals and vitamins need to be corrected.
4. Exercise has been shown to improve immunity, though it might be prudent to be careful and avoid crowded places like gymnasias or swimming pools.
5. It is important to update influenza and pneumonia vaccinations. The latter may decrease chances of secondary bacterial pneumonia after respiratory viral infection, however, data in present viral epidemic is not available.

#### **B. General preventive measures:**

1. Thorough handwashing with soap and water should be encouraged since it kills the virus. Use of alcohol-based hand rubs is also useful.
2. Practice proper respiratory hygiene by covering of mouth and nose with bent elbow or tissue when coughing or sneezing. Touching of mouth, nose and eyes should be avoided.
3. Contact with an affected person needs to be minimised. Use face masks as advised if you have contact with someone with respiratory symptoms.
4. Avoid non-essential travel to major affected areas in order to restrict the spread of infection.

#### **Diabetes management in patients with COVID-19**

Patients with diabetes and COVID-19 may have more fluctuations in blood glucose levels due to conditions such as: irregular diet, reduced exercise or physical exercise, gastrointestinal symptoms; stress conditions like infection which increases glucocorticoid secretion; use of glucocorticoids in treatment can lead to a sharp rise in glucose; interruption or non-standard OAD treatment in isolation wards; fear, anxiety and tension; and COVID-19 itself can cause the human body to produce a large number of inflammatory cytokines and lead to extreme stress in some severe and critical patients.

People with diabetes are not more likely to get COVID-19 than the general population. The problem this group faces is primarily worse outcome, not a greater chance of contracting the virus. In China, where most cases have occurred so far, patients with diabetes had much higher rates of serious complications and death than those without diabetes. When sick with a viral infection, diabetes patients have an increased risk of diabetic ketoacidosis (DKA), commonly experienced by people with type 1 diabetes. Diabetic ketoacidosis can be a challenge for physician in managing fluid intake and electrolyte levels especially in sepsis and septic shock, which are serious complications found in COVID-19 patients.<sup>11</sup> A study by Guo et al., supported the notion that diabetes should be considered as a risk factor for a rapid progression and bad prognosis of COVID-19. They concluded that patient with diabetes should be given more attention especially in patients with rapid deterioration.<sup>12</sup>

The UK National Health Service (NHS) has proposed a clinical guide for the management of people with diabetes during the coronavirus pandemic.<sup>13</sup> There are the following categories of diabetes patients to consider:

1. Obligatory admissions and inpatients: Continue to require admission and medical management, eg., diabetic ketoacidosis (DKA). We must expedite treatment to avoid delay and expedite discharge to minimise length of stay.
2. Secondary care services: Outpatient attendances should be kept to the safe minimum. Consider using virtual clinics and remote consultations.
3. Primary care delivered diabetes services: Implications for routine diabetes care should be considered in the context of broader long-term condition management and prioritisation, taking into account individual risk factors and clinical needs.

Glucose control is key in the management of diabetes with COVID-19 because it impacts Infection control. Since COVID-19 patients with diabetes have higher mortality and also a higher proportion of critically ill adults, good glycemic control during hospitalization is particularly important in the comprehensive treatment of COVID-19. In diabetes patients, each patient should have individualized blood glucose target goals and treatment strategies.

Since there are currently no specific guidelines on plasma glucose targets in patients with diabetes and COVID-19, previous existing guideline can be implemented for them. For outpatients or inpatients in general ward, plasma glucose target in fasting or pre-prandial state is 80-130 mg/dL and 1-2 hour(s) post-prandial is <180 mg/dL. Whereas patients with critical illness who are treated with continuous intravenous insulin drip in Intensive Care Units, the plasma glucose target is between 140-180 mg/dL.<sup>14,15</sup>

Based on their experiences in China, Ma and Ran have proposed the target of blood glucose for patients with diabetes and COVID-19 based on the severity of COVID-19 (Table 1).<sup>16</sup> For patients with mild symptoms, a strict glycemic control target (fasting plasma glucose [FPG] 4.4-6.1 mmol/L [80-100 mg/dL], 2-hour postprandial plasma glucose (2 h PG) 6.1-7.8 mmol/L [100-140 mg/dL]) are recommended; a target for the glycemic control of common type patients (FPG 6.1-7.8 mmol/L [100-140 mg/dL], 2 h PG 7.8-10.0 mmol/L [140-180 mg/dL]) and subcutaneous insulin deliver therapy are recommended; a target non fasting blood glucose range of 10.0 mmol/L (180 mg/dL) or less for severe-type COVID-19 patients, a relatively less stringent blood glucose control target (FPG 7.8-10.0 mmol/L [140-180 mg/dL], 2 h PG 7.8-13.9 mmol/L [140-250 mg/dL]) for critically ill patients and intravenous insulin infusion therapy are recommended. Due to the rapid changes in the condition of some patients, the risk of DKA or hyperglycemic hyperosmolar status (HHS) may

occur during the treatment. Blood glucose monitoring, dynamic evaluation and timely adjustment of strategies should be strengthened to ensure patient safety and promote early recovery of patients.

In mild cases, both oral anti-diabetic (OAD) and insulin treatment can be maintained and it is not necessary to adjust original regimen. In moderate cases, the original treatment can be maintained if patient's mental condition, appetite and glucose control are within normal range. Patients who are previously on OAD with obvious COVID-19 symptoms that cannot eat regularly may be treated with insulin instead. Patients with premix insulin regimen may be switched to basal-bolus regimen or insulin pump to manage glucose more flexibly. In severe or critical cases, intravenous insulin should be the first-line therapy. In these cases, metformin may raise lactic acid levels, while the SGLT2 inhibitors cause volume contraction, fat metabolism, and acidosis. Glucagon-like peptide receptor-1 analogues should also be stopped since they can cause nausea and vomiting, and pioglitazone is also not recommended because it can cause fluid overload. Once the patient has recovered and stabilized even during hospitalization, the treatment can be switched back to the previous regimen and noninsulin therapy can be reintroduced.<sup>17</sup>

**Table 1.** Targets for the blood glucose management in COVID-19 patients with diabetes according to the severity of the COVID-19<sup>16</sup>

Severity of the COVID-19	Diabetic condition	Indicator	Glucose control recommendation
Mild-type	Younger patients or patients with a short duration of disease, long life expectancy, no complications, and no significant CVD, without significant hypoglycaemia.	FPG 2 h PG	4.4-6.1 mmol/L (80-100 mg/dL) 6.1-7.8 mmol/L (100-140 mg/dL)
Common type	Older patients or patients with a history of Severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions and long-standing diabetes	FPG 2 h PG	6.1-7.8 mmol/L (100-140 mg/dL) 7.8-10.0 mmol/L (140-180 mg/dL)
Severe type		FPG 2 h PG Non-fasting	6.1-7.8 mmol/L (100-140 mg/dL) 7.8-10.0 mmol/L (140-180 mg/dL) 7.8-10.0 mmol/L (140-180 mg/dL)
Critical type		FPG 2 h PG Non-fasting	7.8-10.0 mmol/L (140-180 mg/dL) 7.8-13.9 mmol/L (140-250 mg/dL) 7.8-11.1 mmol/L (140-200 mg/dL)

FPG = fasting plasma glucose, 2hPG = 2 hours postprandial plasma glucose.

## References

- Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg* 2020;76:71-6. PMID: 32112977. PMCID: PMC7105032. <https://doi.org/10.1016/j.ijsu.2020.02.034>.
- WHO Int. Coronavirus disease 2019 (COVID-19) Situation Report-92. Accessed 21 April 2020. [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200421-sitrep-92-covid-19.pdf?sfvrsn=38e6b06d\\_4](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200421-sitrep-92-covid-19.pdf?sfvrsn=38e6b06d_4).
- Do Nascimento IJB, Cacic N, Abdulazeem HM, et al. Novel coronavirus infection (COVID-19) in humans: A scoping review and meta-analysis. *J Clin Med* 2020;9(4):941. <https://doi.org/10.3390/jcm9040941>.
- Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91-5. PMID: 32173574. <https://doi.org/10.1016/j.ijid.2020.03.017>.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China summary of a report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA*. PMID: 32091533. <https://doi.org/10.1001/jama.2020.2648>.
- Gugus Tugas Percepatan Penanganan COVID-19. Covid19.go.id. Accessed in 21 April 2020.
- Zhou T, Hu Z, Yang S, Sun L, Yu Z, Wang G. Role of adaptive and innate immunity in type 2 diabetes mellitus. *J Diabetes Res*. 2018;7457269. PMID: 30533447. <https://doi.org/10.1111/j.1574-695X.1999.tb01397.x>.
- Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol*. 1999;26(3-4):259-65. PMID: 10575137. <https://doi.org/10.1111/j.1574-695X.1999.tb01397.x>.
- Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. *Indian J Endocrinol Metab*. 2012;16(Suppl.1):S27-36. PMID: 22701840. PMCID: PMC3354930. <https://doi.org/10.4103/2230-8210.94253>.
- Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Met Syndr*. 2020;14(3):211-2. PMID: 32172175. PMCID: PMC7102582. <https://doi.org/10.1016/j.dsx.2020.03.002>.
- American Diabetes Association. Diabetes and coronavirus. <https://www.diabetes.org/coronavirus-covid-19>. Accessed 16 April 2020.
- Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020;e3319. PMID: 32233013. <https://doi.org/10.1002/dmrr.3319>.
- National Health Service. Specialty guides for patient management during the coronavirus pandemic. Clinical guide for the management of people with diabetes during the coronavirus pandemic. 19 March 2020 version 2. Publications approval reference: 001559. <https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/speciality-guide-diabetes-19-march-v2-updated.pdf>. Accessed 16 April 2020.
- Ma WX, Ran XW. The management of blood glucose should be emphasized in the treatment of COVID-19. *Sichuan Da Xue Xue Bao Yi Xue Ban: Journal of Sichuan University Media Science edition*. 2020; 51(2): 146-50.
- Perkumpulan Endokrinologi Indonesia (Indonesian Society of Endocrinology). Pedoman pengelolaan diabetes melitus Tipe 2 dewasa di Indonesia. Penerbit PB Perkeni, 2019. ISBN 978-602-53035-2-4.
- American Diabetes Association. 15. Diabetes care in the hospital: Standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S193-202. PMID: 31862758. <https://doi.org/10.2337/dc20-S015>.
- Matthews R. Glucose control key with COVID-19 in diabetes, Say Experts. *Medscape Medical News*. Mar 18, 2020. <https://www.medscape.com/viewarticle/927044>. Accessed 16 April 2020.

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