

Saudi Scientific Diabetes Society Position Statement: Management of Diabetes Mellitus in the Pandemic of COVID-19

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Abstract

About 10% coronavirus (COVID-19) infected patients are with diabetes comorbidity. Also, diabetes promotes severe progression in COVID-19 patients. Diabetes comorbidity is associated with significant mortality in those people with COVID-19. In this position statement, the management of diabetes in cases of COVID-19, has been presented. The impact of diabetes on the morbidity and mortality of COVID-19, as well as both the target glucose level and the method of blood glucose control have been presented in details.

Keywords

COVID-19, Diabetes Mellitus, Glycemic Target, Blood Glucose Control

1. Introduction

During our current era, the pandemic of coronavirus disease 2019 (COVID-19) has drawn the attention of every one all over the globe. In April 6th 2020, globally, according to the World Health Organization (WHO), CoVID-19 affected 1,210,956 confirmed cases with 67,594 deaths, with its unprecedented challenges to the global public health system [1]. This pandemic has disrupted the flow of everyday life as we know it. Healthcare systems started to experience some failure which led to reallocation of its resource in a new setting because of this crisis with a great difficulties for both healthcare personals and patients. Of course, people with comorbid diseases like diabetes mellitus are at a great risk for the hazardous consequences of this pandemic. Thus, the Saudi Society of Diabetes

would like to provide its recommendations for the clinical care of diabetes during this COVID-19 pandemic.

2. Diabetes Mellitus and COVID-19

2.1. Diabetes Mellitus and COVID-19 Morbidity and Mortality

Diabetes promotes severe progression in COVID-19 patients, the presence of coexisting diabetes was more common among COVID-19 patients with severe disease than among those with non-severe disease (16.2% vs. 5.7%), (Figure 1). Data was extracted regarding 1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in China through January 29th, 2020 [2]. Another nationwide analysis of comorbidity and its impact on 1,590 patients with COVID-19 in China, also, revealed that COVID-19 patients with diabetes had a worse prognosis (Figure 2) [3].

Diabetes is considered as a risk factor for mortality in cases with COVID-19. A large national study showed that the mortality of patients with diabetes was significantly higher than that of non-diabetic patients, (10% vs 2.5% P <0.001) [3]. In addition, WHO Joint Mission claimed that patients who reported no comorbid conditions had a CFR of 1.4%, patients with comorbid conditions had

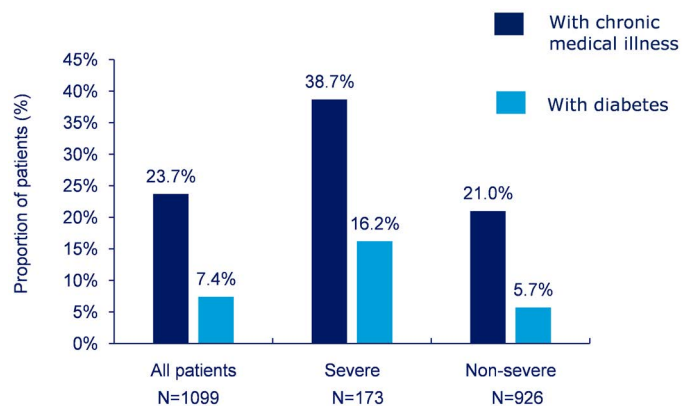
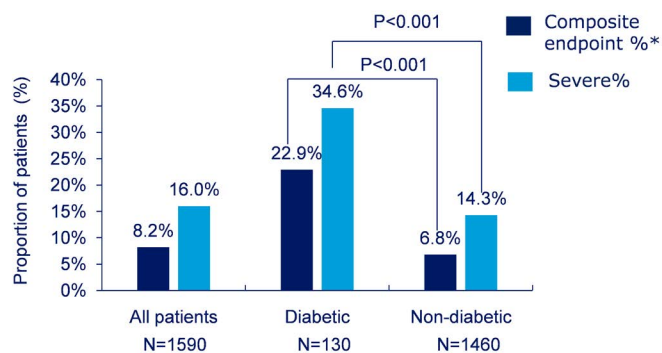


Figure 1. COVID-19 patients with comorbidities [2].



*Composite endpoint: admission to an intensive care unit (ICU), the use of mechanical ventilation, or death.

Figure 2. The risk of reaching to the composite endpoints and disease severity among patients with COVID-19 [3].

much higher rates—9.2% for diabetes [4]. Also, Chinese CDC declared that patients who reported no comorbid conditions had a case fatality rate (CFR) of 0.9%, while patients with comorbid conditions had much higher rates—7.3% for diabetes [5]. A research about clinical characteristics of 82 death cases with COVID-19 found that diabetic ketoacidosis is one of the causes of mortality [6].

2.2. How Does Diabetes Accentuate COVID-19 Morbidity?

High level IL-6, TNF- α and other inflammatory cytokines are expressed in the serum of individuals with diabetes [7]. Moreover, animal models suggested that diabetes significantly promoted the production of TLR4-induced IL-6 [8]. Also, studies have shown that coronavirus, including SARS, is highly likely to activate TLR3 and TLR4, leading to a runaway immune response [8], which in turn leads to IL-6-dominated cytokine storms, which have also been shown to be one of the leading causes of death from coronavirus pneumonia [9]. In addition, IL-6 were associated with death of COVID-19 patients, univariate regression showed increasing odds of in-hospital death associated with IL-6 (odds ratio 1.12, 95% CI 1.03 - 1.23, Per 1 unit increase; $p = 0.0080$) [10]. Therefore, it can be speculated that over activation of TLR4 signaling (**Figure 3**) in individuals with diabetes may contribute to the progression of the severity of the disease and even mortality.

Moreover, patients with diabetes may have bad glycemic control after viral

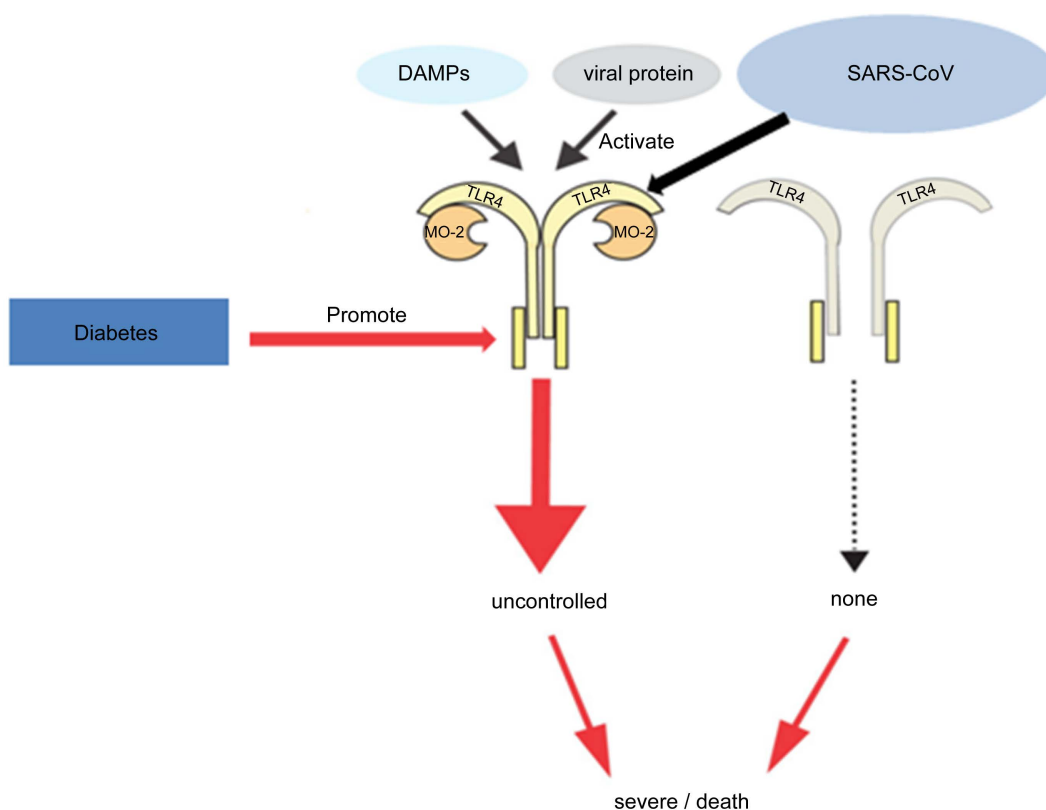


Figure 3. The potential mechanism of high severe/died risk in diabetic patients [10].

infection. It was suggested that SARS-CoV may cause pancreatic islets pathology because of the expression of angiotensin converting enzyme 2 (ACE2), the functional receptor of SARS-CoV, in the exocrine and endocrine tissues of the pancreas [11]. In addition, a recent study in China have found that SARS-CoV-2 is able to efficiently use human ACE2 as a receptor for cellular entry, which could potentially facilitate human-to-human transmission [12].

2.3. Glucose Level Fluctuation in Patients with COVID-19

Glucose level is fluctuating in patients with diabetes and COVID-19 because of irregular diet, reduced exercise, increased glucocorticoids secretion due to stress, the use of glucocorticoids in treatment, the interruption or non-standard treatment with oral antidiabetic drugs (OAD) in isolation wards. Also, COVID-19 can cause human body to produce a large number of inflammatory cytokines and lead to extreme stress in some severe and critical patients [13].

3. Management of Diabetes Mellitus in Patients with COVID-19

3.1. Glycemia Target in Patients with COVID-19

Stratification of cases with COVID-19 according to severity is the first step for better glucose management. For mild and moderate non-elderly COVID-19 patients, stick with strict high control target (**Table 1**). For mild and moderate elderly patients, or patients who have been using glucocorticoid, set up a low or strict control target. For severe and critical patients, elderly patients, hypoglycemia intolerable patients, or patients who have organ dysfunction or serious cardiovascular and cerebrovascular diseases, set up a low control target (**Table 1**). Also, hypoglycemia occurrence should be minimized during glucose management in diabetes patients with COVID-19. Medical care should be performed in time if hypoglycemia occurs [13].

3.2. Therapeutic Principle of Glucose Management in Patients with COVID-19

Insulin treatment is the first choice if diabetes combined with severe infection. For non-critical patients, insulin sc. injection is recommended, and basic dosage can refer to the out-of-hospital dosage. For critical patients, CSII is recommended. In case of serious glucose metabolism disorder with water and electrolyte and acid-base disorders, IV insulin treatment should be started, in combination with aggressive fluid infusion. If the clinical condition is stable and eating

Table 1. Target stratification of glucose management in hospitalized patients.

	High	Medium	Low
FPG/PPG, (mmol/L)	4.4 - 6.1	6.1 - 7.8	7.8 - 10.0
2hPPG/GLU, (mmol/L)	6.1 - 7.8	7.8 - 10.0	7.8 - 13.9

pattern is regular, patients can continue OAD treatment as before admission. Using NPH and long-acting insulin is recommended during glucocorticoid treatment to control the glucose level. Also, measure 7 point glucose (if necessary, plus nocturnal glucose) during insulin treatment [13]. Antidiabetic drugs and their use are shown in **Table 2**.

3.3. Management Plan of Diabetes in Patients with COVID-19 according to Disease Severity

Severity of COVID-19 can be based on the clinical classification released by the National Health Commission of China as shown in **Table 3** [14].

1) Mild cases

There is no need to adjust the original regime too much. Both OAD and insulin treatment can be maintained. The progress of COVID-19 can be rapidly,

Table 2. Anti-diabetic drugs and COVID-19.

Class	Comment
Metformin	Not recommended in severe/critical patients; patients with gastrointestinal symptoms or lack of oxygen.
Secretagogue	Mild/moderate patients using glucocorticoid: <ul style="list-style-type: none"> • Short-acting agents can be used in early stage; • Middle/long-acting agents if FPG and/or PPG increased or in advanced stage.
α -glucosidase inhibitor	Can be used to control PPG. Not recommended in severe/critical patients; or in patients with gastrointestinal symptoms.
TZD	Can be used during the process of glucocorticoid treatment. Regime should be adjusted according to treatment effect.
DPP-4i	Not recommended
SGLT-2i	Not recommended for COVID-19 patients having stress reaction at different levels.

Table 3. Severity classification of COVID-19.

Mild	Mild clinical manifestation None Imaging Performance
Moderate	Fever, respiratory symptoms, pneumonia performance on X-ray or CT
Severe	Meet any of the followings: <ol style="list-style-type: none"> 1. Respiratory distress, RR \geq 30/min; 2. Oxygen saturation \leq 93% at rest state; 3. Arterial partial pressure of oxygen (PaO₂)/Fraction of inspiration O₂ (FiO₂) \leq 300 mmHg, 1 mmHg = 0.133 kPa
Critically severe	Meet any of the followings: <ol style="list-style-type: none"> 1. Respiratory failure needs mechanical ventilation; 2. Shock; 3. Combined with other organ failure, patients need ICU monitoring and treatment

and can be worsen with hyperglycemia, thus, it is strongly recommend to increase the frequency of glucose monitoring, and consult with physicians to adjust treatment regime whenever needed even in diabetes patients with mild COVID-19.

2) Moderate cases

Original treatment regime is to be maintained if patient's cognitive condition, appetite and glucose control are within normal range. In patients with obvious COVID-19 symptoms who cannot eat regularly, OAD is to be switched to insulin. Premix insulin regime is to be switched to basal-bolus regime or insulin pump for better flexibility of glucose management.

3) Severe and critical cases

Intravenous insulin injection should be the first-line treatment. For patients who are in process of continuous renal replacement therapy (CRRT), the proportion of glucose and insulin in the replacement solution should be increased or decreased according to glucose monitoring result to avoid hypoglycemia and severe glucose fluctuations.

3.4. Management Plan of for Different Types of Diabetes in Patients with COVID-19

1) Type 1DM

Insulin pump or basal plus bolus insulin treatment is the optimal regimen. Insulin analogues are recommended as first choice. Insulin treatment regimen is to be individualized according to individual's profile.

2) Type 2DM

For mild COVID-19 patients with low-moderate glucose increase, non-insulin diabetes drugs can be used. For patients with fever or treated by glucocorticoid, insulin treatment is the first choice. For critical patients, insulin IV injection is recommended.

3) Glucocorticoid-associated diabetes

Glucocorticoids-induced glucose increase often occurs between after-lunch and before-sleep. Therefore, it is important to monitor blood glucose after lunch and before dinner. Insulin is the first choice.

3.5. Glucose Management of COVID-19 and Diabetes Treated with Glucocorticoids

Effect of glucocorticoids in COVID-19 is uncertain. However, some centers reported that glucocorticoids can be used in critical patients, or patients with fever and sporadic lesion in lungs, to reduce inflammatory lung injury. Thus, special consideration should be taken in management of glucose level in those cases [13].

3.6. Glucose Management of Children and Adolescents

In children, strengthen blood glucose monitoring (4 - 7 times/day) and individualize the exercise program. The total energy requirement in kcal/day = (Age *

70 - 100) + 1000 with carbohydrate: 50% - 55%, fat: 25% - 35% and protein: 15% - 20%. It is to be adjusted by nutrition, physical activity and stress of the children. Identify DKA and hypoglycemia in time. Target of blood glucose control is HbA1c < 7.5% [15] [16].

4. Recommendations

- Because of the more fluctuations of blood glucose level, strengthened dynamic glucose monitoring is necessary.
- As disease conditions of COVID-19 and diabetes can change rapidly, it is recommend to apply insulin therapy as soon as possible according to glucose level, and actively adjust treatment regime, to control glucose to a relatively ideal level.
- Insulin IV injection should be the first-line treatment in severe and critical patients.
- For fasting patients, the suggested ratio of glucose to insulin in IV infusion fluid is 2 - 4 G glucose: 1U insulin.
- Too much and too long course of glucocorticoid treatment are main risk factor for glucose deterioration.
- When gradually reduce glucocorticoid treatment, we should also pay attention to glucose fluctuation, and adjust insulin dosage according to glucose level.
- In principle, it is recommended to measure blood glucose 7 times a day.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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