

Bangladesh Endocrine Society (BES)
Practical Recommendations for Management of
Diabetes and Other Endocrine Diseases in Patients with
COVID-19



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Preface

The world has been plagued with a deadly infection from a new virus- SARS-COV-2, with more than 300000 deaths worldwide. No effective drug or vaccine has been discovered till now. Personal hygiene and social distancing are considered to be the mainstay of infection control. All countries globally even the developed countries are facing shortage of health care personnel and resources in this unprecedented pandemic.

As diabetes is a global pandemic, it is presumed that a vast number of people affected with COVID-19 are having diabetes as a comorbidity. Diabetes increases the mortality and morbidity in COVID-19. Also, COVID-19 makes optimum control of diabetes difficult. Moreover many people are also suffering from other endocrine disorders like Hyperfunction and hypofunction of different endocrine glands. During the course of COVID illness patient badly experience gross electrolyte imbalance like hyponatremia, hypokalemia, hypocalcemia. Therefore, Bangladesh Endocrine Society has taken the initiative to publish an evidence based recommendation on management of patient with endocrine diseases and diabetes mellitus in COVID-19 pandemics.

Heartfelt gratitude to all the members of the BES guideline subcommittee and BES COVID-19 recommendations taskforce for their hard work, without which this recommendation couldn't be published in such a short time.

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Executive Summary

Glycemic targets:

- Diabetes Mellitus is an important common co-morbid condition for COVID-19 infection. Patients need optimum glycemic control without hypoglycemia in this pandemic.
- Glycemic target should be – 1) HbA1c < 7.0% (but <8% in some special cases), 2) fasting blood glucose (FBG) 4.4 -6.1 mmol/L and 2h postprandial blood glucose (PPG) 6.1-7.8 mmol/L in young patients with mild-moderate illness, 3) FBG 6.1 -7.8 mmol/L and 2h PPG 7.8-10.0 mmol/L in elderly patients with mild-moderate illness and in patients on steroids, 4) FBG 7.8 -10 mmol/L and 2h PPG 7.8-13.9 mmol/L in severely ill patients, and 5) random blood glucose (RPG) 7.8 – 10.0 mmol/L in ICU settings.

Diet and physical activity:

- At home, patients should follow 'Sick Day Rules', maintain healthy diet (containing adequate vitamin C, vitamin D and zinc), stay hydrated and perform home bound exercise.

Home vs. Hospital care:

- Mild cases can be managed at home. But moderate (especially with other co-morbidities), severe and critical cases need hospitalization.
- Following case need to contact hospital – 1) blood glucose persisting > 15 mmol/L, 2) ketonuria, 3) rapid breathing, abdominal pain, excessive thirst or reduced consciousness, 4) vomiting or diarrhea persisting for more than 6 hours, 5) unable to take food for > 6 hrs hours, 6) weight loss of ≥ 2.5 kg during the illness, and 7) co-existing serious morbidities
- Virtual appointments are preferred over face to face appointments except in case of emergency.

Treatment with anti-diabetic agents:

- Metformin and SGLT-2 inhibitors need to be stopped in cases of severely/critically ill patients or hypoxia or acute GI symptoms or dehydration. GLP-1RAs should be stopped in cases of acute GI symptoms or dehydration.
- Continue other anti-diabetic agents, but cautious for hypoglycemia in sulphonylureas and fluid overload in pioglitazone. Patient often needs high dose of insulin.
- For mild cases and moderate cases with normal appetite, taking food regularly and well controlled blood glucose → continue current antidiabetic regimen. For moderate cases not taking food regularly, switch → oral antidiabetic agents to insulin (premixed/split-mix/co-

formulated/basal-bolus) and → Premixed insulin to Split-mix/Basal-bolus SC insulin or IV insulin and adjust dose according to blood glucose profile.

- For severe and critical illness, IV insulin should be the 1st line treatment option, but SC insulin may be used in severe case, especially if insulin pump is not available.
- If the patient is on steroids, NPH/long acting insulin(/Premixed) is needed once/twice daily.

Drugs for co-morbid diseases of diabetes:

- ACEI/ARBs, aspirin and statins should be continued unless a specific contraindication arises.

Management of diabetes at hospital setting:

- On admission, check blood glucose and urine ketone for all patients. Consider using 10-20% glucose where ketosis persists despite treatment in line with usual protocols.
- For management of diabetes in hospital setting, DKA and HHS, standard protocol should be followed.
- Potassium balance needs to be considered carefully in the context of insulin treatment as hypokalemia is a common feature in COVID 19 and could be exacerbated following initiation of insulin. Potassium replacement should follow standard protocols and be guided by monitoring.
- After restoring the circulating volume the rate of fluid replacement regimen may need to be adjusted where evidence of “lung leak” or myocarditis.
- If insulin infusion pump is not available, use alternative IM/SC regimens to manage hyperglycaemia and mild DKA.

Management after discharge:

- After discharge, continue drugs according to discharge certificate. Do SMBG and contact endocrinologist/diabetologist if blood glucose is uncontrolled. For the patients who were on insulin prior to hospital stay, they will continue it. Insulin may be continued, if started during hospital stay.

Pre-existing diabetes

- For pregnant women with pre-existing diabetes at antenatal visit, additional test should include HbA1c, renal and thyroid function, and urinary albumin-creatinine ratio (ACR). If early face-to-face review is needed, this should coincide with the 11-14-week US scan and this review should cover about home blood glucose monitoring and the process for remote review of blood glucose control.

Gestational diabetes

- Two-hour oral glucose tolerance test (OGTT) may be postponed in this COVID 19 situation for GDM screening.
- For women considered to be at high risk of GDM, do HbA1c and RPG.
- If HbA1c > 6.5% or RPG > 11 mmol/L, manage as T2DM.
- If HbA1c > 6.0-6.5% or RPG > 9-11 mmol/L, manage as GDM.
- if HbA1c <6 % or RPG < 9 mmol/L, repeat at 28 wk of gestation and If HbA1c > 5.7% or FBG > 5.6 mmol/L or RPG > 9 mmol/L, manage as GDM.
- Postpartum screening for maternal dysglycemia should be deferred until after the COVID-19 pandemic is controlled.

Health-care professionals' safety:

- Health-care professionals with diabetes and those with age>60 years should be deployed away from front line clinical duties where possible. If not possible or desirable, high-grade protection or increased protection should be used.

Management of other endocrine diseases:

- Patients with adrenal insufficiency should double their usual glucocorticoid dose when minor symptoms appear, and/or switch to injectable steroid when patient can not take oral drug or adrenal crisis is suspected.
- Patients with hyperthyroidism and hypothyroidism should continue taking the respective drugs as suggested.
- Carbimazole induced agranulocytosis and subacute thyroiditis should be kept in mind as differentials in patients presenting with sore throat.

SECTION-1: Introduction

1.1: Background:

The year 2020 has witnessed a largely unprecedented pandemic of coronavirus disease (COVID-19), caused by the novel Corona virus SARS COV-2. Many people with COVID-19 have comorbidities, including diabetes, hypertension and cardiovascular diseases. These comorbidities are also significantly associated with worse outcomes [1]. Moreover COVID-19 itself is associated with worsening of hyperglycemia. Depending on the global region, 20-59% patients in COVID-19 pandemic had diabetes [2]. In Bangladesh, one in every 12 adult person has diabetes, with a prevalence of 8.4% [3]. Data suggest that only 22.5% patient with Diabetes has good glycemic control [3]. Significant number of Diabetes mellitus suffer from other comorbid conditions like HTN, Obesity, COPD. High prevalent Atherosclerotic CAD, CKD complicate the management. Therefore, Bangladesh Endocrine Society has formulated some practical recommendations for management of Diabetes and other endocrine diseases in patients with COVID-19 for use in both primary and specialist care settings.

1.2: Impact of COVID-19 Pandemic:

As on 06 June 2020, there were 66,44,011 confirmed cases of COVID-19 worldwide, with 3,91,839 confirmed deaths in 216 countries, areas or territories [5]. The highest number of cases were in USA with 18,57,872, followed by Brazil (6,14,941) and the Russian federation (4,49,834) [6]. The number of deaths were also highest in the USA (1,11,408), followed by the UK (40,465) and Brazil (35,047) [7].

In Bangladesh, there were 63,026 confirmed cases out of 3,84,761 tests upto 06 June 2020. Number of deaths till the date was 846, and 13,325 patients recovered. Case fatality rate was 1.34% [8].

1.3: Diabetes and COVID-19:

Data suggest that the risk of a fatal outcome from COVID-19 may be up to 50% higher in patients with diabetes than in non-diabetics [9]. According to a WHO Joint Mission statement, patients who reported no comorbid conditions had a case fatality rate (CFR) of 1.4%, whereas patients with diabetes had much higher rates-9.2% [10]. The data from Chinese CDC showed that CFR was 0.9% in patients who reported no comorbid conditions compared with 7.3% in patients with diabetes [11]. It is also suggested that diabetic ketoacidosis is one of the causes of mortality in COVID-19 [12].

There is wide fluctuation of blood glucose level in patients with diabetes and COVID-19 which may be due to irregular diet, reduced exercise, increased glucocorticoids secretion due to stress, use of glucocorticoids, interruption or non-standard treatment with oral antidiabetic drugs (OAD). Also, COVID-

19 can induce a large number of inflammatory cytokines leading to severe insulin resistance in some severe and critical patients [13]. The reason behind increased incidence and severity of COVID-19 in people with diabetes is complex. Apart from defective immunity in diabetes and higher prevalence of type-2 diabetes in the elderly population, Angiotensin-converting-enzyme 2 (ACE2) receptor dysregulation may play a role. ACE-2 has been identified as the receptor for the coronavirus spike protein. COVID-19 infection reduces ACE2 expression inducing cellular damage, hyperinflammation, and respiratory failure [14]. Chronic hyperglycemia downregulates ACE2 expression making the cells vulnerable to the inflammatory effect of the virus. But acute hyperglycemia upregulate ACE2 expression on cells which might facilitate viral cell entry. ACE-2 is also expressed on pancreatic β cells, which can lead to a direct effect on β cell function in COVID-19. Therefore it is possible that apart from diabetes being a risk factor of severe COVID-19, infection with SARS COV-2 may also induce new onset diabetes [15-17].

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SECTION-2: Glycemic Targets and Glucose Monitoring

2.1: Glycemic targets:

2.1.1: HbA_{1c}:

- < 7.0% for the majority of the patients.
- < 8.0% in those with multiple comorbidities, recurrent hypoglycemia or hypoglycemic unawareness and elderly with poor health status [1].

2.1.2: Target stratification of glucose management:

- Strict/tight control target: For mild and moderate illness in young COVID-19 patients.
- Low or medium control target: For mild and moderate illness in elderly, or patients on glucocorticoids and in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible.
- Low control target: For patients with severe illness, hypoglycemia intolerable patients, or patients having organ dysfunctions or serious cardiovascular or cerebrovascular diseases [2].
- For severe and critically ill patients who are on IV insulin infusion, the glycemic target should be 7.8 to 10 mmol/L.
- Plasma glucose targets [2]:

	Strict Control	Medium Control	Low Control
Fasting (mmol/l)	4.4-6.1	6.1-7.8	7.8-10.0
2h post-prandial (mmol/l)	6.1-7.8	7.8-10.0	7.8-13.9

- Hypoglycemia (<3.9 mmol/l) must be avoided [1,2].
- Continuous glucose monitoring/flash glucose monitoring targets (Ambulatory Glycemic Profile-AGP): Time-in-range (3.9-10.0 mmol/l) > 70% of time (or > 50% in frail and older people and moderate to severe cases) [3].

2.2: Glucose monitoring:

2.2.1: Self-monitoring of blood glucose (SMBG):

- SMBG of capillary blood is an acceptable alternative to plasma glucose estimation in present scenario [4].

- Attempts could be made to minimize exposure. Blood glucose readings can then be communicated on phone and necessary action taken [5].
- Availability of glucose strips could be a challenge in the current scenario. Taking help of online pharmacy stores and placing orders well before existing stocks dwindle could be the best solution in this regard [4].

2.2.2: SMBG frequency [4-6]:

Type of Diabetes	Patient category	Recommended frequency of SMBG
Type 2 DM	On Sulphonylureas or Meglitinides	<ul style="list-style-type: none"> ● Four times/day and should include preprandial, post prandial and bedtime levels. ● In well-controlled diabetes, daily fasting and after the major meal may be justified.
	On other OADs	<ul style="list-style-type: none"> ● Fasting and post-prandial capillary blood glucose once or twice a week.
	On Insulin ± OADs	<ul style="list-style-type: none"> ● At least 4 times/day and should include preprandial, post prandial and bedtime levels.
Diabetes in pregnancy	On lifestyle modifications	<ul style="list-style-type: none"> ● A day profile once a week ☐ FBG and 3 postprandial values at least once a week or staggered over the week.
	On insulin	<ul style="list-style-type: none"> ● At least 4 times/day (FBG and 3 postprandial values).
Type 1 DM	On multiple dose insulin injection	<ul style="list-style-type: none"> ● Pre- and post-meals, at bedtime, at 3am (if nocturnal hypoglycemia).

- In addition, capillary glucose should be checked at any clinical suspicion of hypoglycemia [4-6].
- Frequent monitoring of blood glucose (every hour or every 2 h) in patients with very poor oral intake or those in ICU or Non-ICU who are on mechanical ventilation who would require intravenous insulin infusion [4-6].

2.2.3: Continuous glucose monitoring (CGM):

- May confer additional benefit in terms of glycemic control in patients getting multiple dose insulin injections, continuous subcutaneous insulin infusion (CSII) or insulin pump or intravenous insulin syringe pump [4-7].

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SECTION-3: Nutrition Management and Physical Activity in Covid-19 and Diabetes

3.1: Conditions that may interfere a healthy regular diet [1]:

- Gastrointestinal symptoms like anorexia, nausea, diarrhea, vomiting
- Dehydration
- Irregular meals
- Lack of care in isolation ward
- Stress, anxiety, insomnia
- Anosmia

3.2: Diet during sick days [2,3]:

- Try to follow the regular calorie given before, in febrile stage calorie requirement may increase
- Stay hydrated, take at least half cup (~120ml) water or unsweetened drinks every hour
- Eat little but often, do not miss meal or do not fast
- If you are unable to eat much, try snacks or drinks with carbohydrates to get energy
- Try to sip drinks like fruit juice (rich in potassium), non-diet cola if unable to take food enough but be careful about hyperglycemia
- Maintain a regular schedule
- Keep glucose drink or lozenge or tablet with you in isolation room or ward
- Take plenty fruits and vegetables at least 2 or 3 servings a day
- If you are unable to eat due to vomiting or cannot remain hydrated, get medical help soon
- Protein and energy balance [4]:
 - Take enough lean protein like fish, meat, egg, milk, cheese, seeds or nuts
 - Daily 1 g protein per kg body weight/day in older persons, adjusted with regard to nutritional status, physical activity level, disease status and tolerance.
 - Daily ≥ 1 g protein per kg body weight/day in polymorbid medical inpatients in order to prevent body weight loss, reduce the risk of complications
- Critical/intensive care patients [4]:
 - In COVID-19 critical, intubated or ventilated ICU patients enteral nutrition (EN) should be started through a nasogastric tube.

- Isocaloric nutrition rather than hypocaloric nutrition can then be progressively implemented after the early phase of acute illness.
- During emergency times, the predictive equation recommending 20 kcal/kg/day could be used and energy increased to 50-70% of the predictive energy at day 2 to reach 80-100% at day 4.
- The protein target of 1.3 g/kg/day should also be reached by day 3-5.
- Blood glucose should be maintained at target levels along with monitoring of blood triglycerides and electrolytes including phosphate, potassium and magnesium.
- Vitamins and minerals:
 - A growing body of circumstantial evidence now also specifically links outcomes of COVID-19 and vitamin D status. There are recommendations for the population to take vitamin D supplements during this pandemic [5].
 - Zinc were shown to have inhibitory effects on H1N1 viral load, though their effect in COVID-19 is unknown and untested [6]. Vitamin C supplementation has some role in prevention of pneumonia and its effect on COVID-19 needs evaluation [7].

3.3: Physical activity and Exercise [8, 9, 10]:

- During sick days, vigorous exercise is not advised
- If the disease category is mild and you are at home isolation, you can do some home exercises
- Practice to do breathing exercise daily, and maintain prone position
- Walk for few steps or move your legs every 2 hourly to prevent thromboembolism during home isolation or in isolation ward
- In hospitals and ICU setting, specialist respiratory physiotherapists may be needed
- Ensure enough sleep

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SECTION-4: Home Management, Sick Days Rule and Indication for Hospital Care

Diabetes Mellitus with COVID-19 disease	
Who can be treated at Home [1]	Who should be treated at Hospital settings/ Indication for Hospitalization [1,2]
<ul style="list-style-type: none"> Mild COVID-19 cases that is patients having uncomplicated upper respiratory tract infection with non-specific symptoms (such as fever, fatigue, cough (with or without sputum production), sore throat, nasal congestion, anorexia, malaise, or headache) can be managed at home. 	<ul style="list-style-type: none"> Blood glucose > 15 mmol/l on repeated measurements. ketones in urine. Excessive Thirst. Vomiting or diarrhea persist for more than 6 hours. Unable to take food and drinks for 6 hours. Weight loss of ≥ 2.5 kg during the illness. Rapid breathing. Abdominal pain. Reduced level of consciousness (drowsiness). Co-existing serious morbidities. Clinical feature of moderate, severe and critical Covid-19 cases

4.1: At home, people with diabetes & COVID-19 infection should adhere to the ‘Sick Day Rules’ as following:

4.2: General Rules for DM Patients with COVID-19 Infection [1,2,3,4]:

- At home, patient should remain isolated in a separate single room.
- Patient should use a single toilet if possible.
- Patient should practice hand wash with soap-water 20 seconds each time frequently (1 to 2 hours) or before/after taking meal/using washroom/toilets, after using hand during coughing, sneezing.
- 60% alcohol-based sanitizer can be used for hand hygiene.
- Cough/sneezing etiquette should be maintained by using tissue paper, cloth or elbow of hand while doing so.
- Face mask should be used.

- Care should be given by a single healthy person who has to maintain protective measures as well.
- Home floor, furniture, door knobs, light switch, sink, toilet seat, handles should be cleaned and disinfected frequently and after use.
- Stress may adversely affect glycemic control. Meditation, prayer can help minimizing stress and anxiety. Reading or listening to news that could cause distress and anxiety should be minimized.
- Regular sleep routine should be maintained.
- Regular contact with relatives, friends and neighbors via telephone, online communication platforms can be practiced to reduce the effects of social isolation.
- An adequate supply/storage of prescribed anti-diabetic medications/refills at home should be ensured for at least 1 month.

4.3: General Rules for DM Patients to Prevent Exposure to COVID-19 [1,2,3]:

- People with DM should stay at home as much as possible to reduce risk of being exposed. If he/she needs to go out in public for essential purposes, crowd should be avoided and social distancing should be maintained by 1-2 meters.
- Face mask should be used when in Public for essential purposes.
- Routine clinic visits should be minimized while telemedicine/video consultations, telephone advice, online drug delivery should be considered.
- Non-emergency routine evaluations (for foot, disease, retinopathy etc.) should be deferred until cure.
- Medications and glucose testing kit and strips storage/supplies should be ensured for 1-3 months.
- Capillary blood glucose should be monitored regularly and dose of medication should be adjusted accordingly.

- Home-based exercise like treadmill, stationary cycling bike, free hand exercise or aerobics, walking in room if it is big, roof and in parking area or stair up-down should be maintained.
- Healthy diet with plenty of vegetables and citrus foods should be consumed. If needed multivitamins and multi-minerals (Fe, Cu, Zn, Selenium, Vit A) can be taken. Water or sugar-free drinks should be taken to avoid dehydration.
- People with DM should practice hand wash with soap-water 20 seconds each time frequently (1 to 2 hours) or before/after taking meal/using washroom/toilets/ touching outside objects or materials, after using hand during coughing, sneezing or after being in public. 60% alcohol-based sanitizer can be used for hand hygiene.
- People with DM should cover nose and mouth when coughing or sneezing with a tissue or a flexed elbow, then throw the tissue in the bin, should avoid touching eyes, mouth or nose when possible and avoid meeting with sick individuals.
- People with DM should not share food, tools, glasses, towels, unprotected contact with wildlife and farm animals.
- Vaccinate to prevent secondary infection (e.g.- influenza, pneumonia).

4.4: General Rules During Sickness [2,5,6]:

- Fluid balance should be carefully balanced with vomiting or diarrhea if any.
- Patient should take plenty of water or calorie-free drinks 120-180 ml per hour to avoid dehydration.
- If patient cannot take 50 grams of carbohydrates through food, it might also be necessary to drink sugary beverages. Amounts of sugary beverages should be carefully adjusted to prevent hyperglycemia.
- Weight should be measured every day. Losing weight while eating normally is a sign of high blood glucose.
- Temperature should be measured daily at morning and evening.

- Patient should have daily foot checks to ensure early detection of poor blood supply, infection.

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Section 5: Treatment of DM in COVID-19: Anti-diabetic Agents –Oral and Parenteral

5.1: Background

Treatment of type 2 diabetes in COVID-19 patients with oral or parental glucose lowering drugs depends on clinical severity of illness and associated co-morbid situations. But regarding use of antidiabetic agents, there are many controversies and misconceptions in COVID-19 pandemic. There is also recent recommendations from international panel of experts and organizations. Considering all these, this recommendation is made from Bangladesh Endocrine Society.

5.2: Considerations to use anti-diabetic drugs

Metformin is the widely used first-line antidiabetic agent for management of type 2 diabetes mellitus. It is responsible for the activation of the AMP-activated protein kinase (AMPK) in the liver and thereby decreases hepatic glucose output [1]. Historically, metformin was initially introduced as an anti-influenza drug and its well-known glucose lowering ability was actually a side effect [2]. It has been postulated that metformin may have an advantageous role in this COVID-19 pandemic. The activation of AMPK by metformin leads to phosphorylation of ACE2 which can lead to conformational and functional changes to this receptor [3]. Such changes may decrease the binding of SARS-CoV-2 and prevent entry of virus into target tissue. Once the virus enters into the host cells, it downregulates ACE2. This creates an imbalance in the rennin-angiotensin system promoting to unopposed activity of angiotensin-II which have deleterious proinflammatory and profibrotic activity which may induce lethal hyperinflammation and tissue damage [4]. However, metformin prevents this detrimental sequence by activation of ACE2 through the AMPK-signalling pathway [5]. Metformin also have indirect effect to decrease replication of this virus [6]. Considering all these, metformin can be a real game changer in COVID-19 pandemic [5]. It is evident that lactic acidosis with metformin use is rare events and predictable only in severe or critical COVID 19 illness with hypoxia [7].

Beside major role in carbohydrate metabolism, DPP4 enzyme also plays an important role in immune regulation, but this is not completely understood. DPP4 activate T cells and upregulate CD86 expression and NF- κ B pathway and increases inflammation in type 2 diabetes. So, DPP4 may represent a potential target for preventing and reducing the risk and progression of the acute respiratory complications of COVID 19 infection in type 2 diabetes [8]. A meta-analysis have showed that upper respiratory tract

infections does not increase significantly with DPP4 inhibitor treatment [9]. On the other hand, DPP4 inhibitors and GLP-1 receptor analogs have anti-inflammatory and anti-adipogenic effects [8]. In COVID-19 disease, there is cytokine Storm and excessive inflammatory response. So utilizing the protective role of DPP-4 inhibitors in decreasing the profound inflammation seems logical. But available evidence shows DPP4 inhibitors do not meaningfully modify immune response in human subjects [10].

Recently, it has been hypothesized that SGLT-2i, GLP-1RAs and pioglitazone might induce an over-expression of the ACE2 receptor, which may have more serious consequences if diabetic patient is infected [11,12]. GLP-1RA have shown over the years significant anti-inflammatory and anti-adipogenic effect.⁸ Similar evidence of anti-inflammatory effect is also seen with SGLT-2i and pioglitazone [13, 14].

The usefulness of both GLP-1Ra and SGLT-2i for the prevention of cardiovascular and kidney disease is well known. People with the presence of a cardiovascular or kidney disease show a worse prognosis during the COVID-19. Therefore it seems to be mandatory to preserve the integrity of kidney and of the cardiovascular system in people who could be affected by the SARS-CoV-2 [12]. Also euglycaemic or moderate hyperglycaemic DKA with SGLT-2i are rare events and predictable only in severe or critical COVID 19 illness [7].

Insulin is the most potent, appropriate and safest antidiabetic agent in any acute infection. COVID-19 infection is associated with multiple stresses including respiratory failure and sepsis that leads to defects in insulin secretion & action. So most patients will require insulin in high dose during this infection [7].

5.3: Recommendations to use oral or parental glucose lowering drugs:

Table-1: Recommendations for Anti-diabetic agents [7,15,16]

Therapy	Suggestions for practice
Metformin	Stop if severely/critically ill with hypoxia/ acute GI symptoms/dehydration
Sulfonylureas	Continue, adjust dose according to glycemic state, stop if unable to maintain regular oral food intake or at risk of hypoglycaemia or if insulin is started
SGLT2 inhibitors	Stop if severely/critically ill/acute GI symptoms/dehydration
GLP-1RAs	Stop if acute GI symptoms/dehydration, ensure adequate fluid and regular meal
DPP4 inhibitors	Continue
Pioglitazone	Continue care where volume overload and heart failure.
Insulin	Continue, adjust dose according to glycemic state, often require high dose

5.4: Management plan: according to severity of infection

Table-2: Recommendations for management of diabetes according to severity [15]

Severity of COVID-19	Treatment Regimen
Mild	Continue current treatment of oral antidiabetic agents (OAD) and/or insulin/GLP1-agonists. Monitor BG frequently and adjust regimen accordingly
Moderate	a) Continue current treatment regimen if appetite is normal, patient can take food regularly and blood glucose is controlled b) If patient can not eat regularly - If on OAD → switch to Insulin (Premixed/Split-mix/Co-formulated/basal-bolus) - If on Premixed insulin → switch to Split-mix/Basal-bolus SC insulin or IV insulin and adjust dose according to blood glucose profile. TDD premixed insulin is converted to same TDD of Split-mix/Basal-bolus insulin
Severe & Critical	IV insulin should be the 1 st line treatment, but SC insulin may be used in severe case, especially if insulin pump is not available
On steroid	NPH/long acting insulin(/Premixed) - 10-20 U once/two divided doses daily

Insulin initiation regimen from OAD:

- Follow BES Insulin Guideline for insulin initiation and intensification (section 3) [17]
- Basal-bolus regimen is preferable regimen, but require more frequent injections/monitoring. But in poor setting, Premixed/Split-mix/Co-formulated insulin regimen can be used
- Analog insulin is better than conventional human insulin, but is expensive.
- Total daily dose (TDD) of insulin is ~ 0.3 U/Kg body weight (decrease dose in elderly/renal impairment and increase dose if blood glucose is high) in insulin naïve patients
- Dose titration is done by monitoring SMBG.
- Continue DPP4i and pioglitazone.

Table – 3: Insulin initiation according to different insulin regimens [17]

Insulin initiation regimen	How to initiate
Split-mix insulin regimen	- 2/3 rd TDD as NPH with 2/3 rd at morning & 1/3 rd at dinner or ½ at morning and ½ at dinner - 1/3 rd TDD as short acting in 2 divided premeal doses
Pre-mixed insulin regimen	2/3 rd TDD at morning & 1/3 rd at dinner
Co-formulated insulin regimen	½ TDD before breakfast and ½ before dinner
Basal-bolus insulin regimen	- ½ TDD as basal in single/2 divided dose - ½ TDD as short/rapid acting in 2-3 divided premeal doses

5.5: Management of Co-morbidities of Diabetes in COVID-19:

Table-4: Recommendations for drugs used for co-morbid diseases of diabetes [12,16]

Therapy	Considerations for use during COVID-19	Suggestions for practice
ACEI/ ARBs	<ul style="list-style-type: none"> •Uncertain risk of increased susceptibility for infection - ACEis and ARBs could increase the expression of ACE2, which could accelerate the entry of the virus into the cells. • Uncertain benefit in mitigating inflammatory injury - ACE2 also has protective anti-inflammatory effect. As SARS-CoV-2 might impair the protective ACE2/Mas receptor pathway and increase deleterious angiotensin-2 activity, the use of ACEis and ARBs could protect against severe lung injury following infection. 	Continue use unless a specific contraindication arises
Aspirin	Risk of cardiovascular disease higher during COVID infection	Continue unless contraindications arise
Statins	<ul style="list-style-type: none"> •Restore the reduction of ACE2 induced by high lipids such as LDL or lipoprotein(a). •Have anti-inflammatory effects probably due to the upregulation of ACE2. •Possibility of increased risk of myositis with experimental antiviral agents/macrolides 	Continue use but monitor risk
Lifestyle	Smoking and obesity are co-morbid risk factors for increased morbidity and mortality in COVID-19 infection	Stop smoking Control body weight

5.6: Caution with investigational drugs for COVID-19:

Regarding use of investigational drugs for the treatment of COVID-19 in patients with diabetes, agents which interfere with glycemic status should be used with caution.

5.7: References:

1. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest* 2001;108:1167-74. <https://doi.org/10.1172/JCI13505>
2. Amin S, Lux A & O'Callaghan F. The journey of metformin from glycaemic control to mTOR inhibition and the suppression of tumour growth. *Br J Clin Pharmacol* 2019;85:37-46. <https://doi.org/10.1111/bcp.13780>.
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6. **Gordon D.E., Jang M.G., Bouhaddou M. et al.** A SARS-CoV-2-Human ProteinProtein Interaction Map Reveals Drug Targets and Potential Drug- Repurposing. *BioRxiv*. 2020; <https://doi.org/10.1101/2020.03.22.002386>
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9. Yang W, Cai X, Han X, Ji L. DPP-4 inhibitors and risk of infections: a meta-analysis of randomized controlled trials. *Diabetes Metab Res Rev*. 2016; **32**: 391-404

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11. Bhadada S.K. Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?. *Diab Res Clin Pract*. 2020; <https://doi.org/10.1016/j.diabres.2020.108146>
12. Ceriello A, Stoian AP, & Rizzo M. COVID-19 and diabetes management: What should be considered? *Diabetes Research and Clinical Practice* 163 (2020) 108151
13. Amin EF, Rifaai RA, Abdel-Latif RG. Empagliflozin attenuates transient cerebral ischemia/reperfusion injury in hyperglycemic rats via repressing oxidative-inflammatory/apoptotic pathway. *Fundam Clin Pharmacol* 2020. <https://doi.org/10.1111/fcp.12548>.
14. Ceriello A. Thiazolidinediones as anti-inflammatory and anti-atherogenic agents. *Diabetes Metab Res Rev* 2008;24:14–26.
15. Alshaikh A, Alsifri S, Alhozali A et al. Saudi Scientific Diabetes Society Position Statement: Management of Diabetes Mellitus in the Pandemic of COVID-19. *International Journal of Clinical Medicine*, 2020,11,199-206.
16. Royal Australian College of General Practitioners. Diabetes management during the coronavirus pandemic. <https://www.racgp.org.au/getmedia/97a5abb4-1290-42cb-91c0-eabcaa8ca590>
17. Bangladesh Endocrine Society Insulin Guideline 2018. (online published on website-bes.org.net).

SECTION-6: Diabetes Management in COVID-19 Patients in Hospital Setting

COVID-19 disease is a challenge for diabetic patients. Presence of diabetes increases disease severity and mortality in COVID-19 patients. Glycemic control needs to be very optimal during this pandemic situation. Diabetes management in hospital setup either in OPD and inpatient needs attention. Access of diabetes patients to outpatient clinics are limited during this pandemic and this urges alternative treatment options, particularly the implementation of telemedicine services. In spite of this situation even few required OPD visits and this can be prioritized as follows

6.1: Outpatient Appointment Prioritization for Specialist Diabetes Departments during the Coronavirus Pandemic

- **Urgent Face to Face:**
 - Newly diagnosed type 1 diabetes
 - Severe hyperglycemia requiring Insulin initiation
 - Teaching blood glucose monitoring in urgent situation as pregnancy or education about CGM
 - When blood test monitoring is needed (as in declining renal function or electrolyte imbalance)
 - Urgent physical examination is required (as in pregnancy and severe foot infection)
- **Virtual [Telephone, Video, Email]-**
 - Follow up of newly diagnosed type-1 DM
 - Vulnerable patient as history of recent hospital admission
 - Recurrent severe hypoglycemia
 - HbA_{1c}>11%
 - Diabetes follow up and insulin dose adjustment in pregnancy
 - Risk of face to face appointment is greater than benefit
- **Defer Appointment:**
 - Stable and well managed DM
 - Risk of attending OPD is greater than benefit
 - Health education sessions

6.2: Patients Requiring Hospital Admission:

- Subcutaneous insulin is reasonable for most general surgical and medical patients outside the ICU. Insulin analogues usually produce a lower incidence of hypoglycaemia than do regular human insulin or neutral protamine Hagedorn (NPH) insulin.
- Basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for noncritically ill hospitalized patients with poor oral intake or those who are taking nothing by mouth. An insulin regimen with basal, prandial, and correction components is the preferred treatment for noncritically ill hospitalized patients with good nutritional intake and also for patients requiring glucocorticoid. Use of only a sliding scale insulin regimen in the inpatient hospital setting is strongly discouraged.
- If Analogue insulin is unaffordable-conventional insulin can be continued but careful about more hypoglycemia, frequent monitoring is necessary.
- For management of diabetes in hospital setting, DKA and HHS, please refer to BES Insulin Guideline, Sections 4 and 5 [4].

Table-1: Protocol in COVID-19 suspected/positive people and those without COVID-19 disease when diagnosis of DKA has been confirmed

Fluid management	<p>Standard rate of fluid replacement with 0.9% saline (slower rate should be considered in those aged 18-25 and over 70, and who are pregnant or who have cardiac or renal failure).</p> <p>1st litre (given over 1 hr) 1000 ml/hour 2nd litre (given over 2 hr) 500 ml/hour 3rd litre (given over 2 hr) 500 ml/hour 4th litre (given over 4 hr) 250 ml/hour 5th litre (given over 4 hr) 250 ml/hour</p> <p>If a more cautious approach is required in COVID-19 positive/suspected, after an initial fluid bolus of 250 ml in 15 minutes. Glucose-containing fluid (e.g. 10% glucose at 125 ml/hour) should be infused when the glucose is less than 14 mmol/l and reviewed with insulin prescription. The 10% glucose usually runs alongside the 0.9% sodium chloride solution. For euglycaemic DKA 10% glucose should be used as the resuscitation fluid.</p>
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Insulin	Start insulin in infusion pump @ 6u/hour according to present blood glucose level and adjust according to hourly blood glucose level. To reduce to dose / units/hour every 2hours once glucose less than 14 mmol/l.
Potassium replacement	Potassium balance needs to be considered carefully in the context of insulin treatment as hypokalemia is a common feature in COVID 19 and could be exacerbated following initiation of insulin. Potassium replacement should follow standard protocols and be guided by monitoring
Monitoring	Blood glucose- check at least 2 hrly , Fluid balance - record hourly, regular review and adjustment according to clinical condition , Oxygen saturations - regular assessment as a potential marker of fluid overload.

Table-2: COVID-19 infection in people with or without previously recognised diabetes increases the risk of the EMERGENCY states of hyperglycemia with ketones, Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycaemic State (HHS) . Being acutely unwell requires adjustment to standard approaches to diabetes management according to following table.

WHERE CHANGE SEEN	KEY DIFFERENCE WITH COVID-19	SUGGESTED ACTION
Early in admission	People with COVID-19 infection appear to have a greater risk of hyperglycemia with ketones including: › People with type 2 diabetes (risk even greater if on a SGLT-2 inhibitor) › People with newly diagnosed diabetes COVID-19 disease precipitates atypical presentations of diabetes emergencies (eg, mixed DKA and hyperosmolar states)	Check blood glucose in everybody on admission › Check ketones in: » everybody with diabetes being admitted » everybody with an admission glucose over 12 mmol/l › Stop SGLT-2 inhibitors in all people admitted to hospital › Consider using 10-20% glucose where ketosis persists despite treatment in line with usual protocols
Severe illness on admission	Fluid requirements may differ in those with DKA/HHS and evidence of “lung leak” or myocarditis	After restoring the circulating volume the rate of fluid replacement regimen may need to be adjusted where evidence of “lung leak” or myocarditis ›

		Contact the diabetes specialist team early › Early involvement of the critical care team
All inpatient areas	Infusion pumps may not be available to manage hyperglycemia using intravenous insulin as these are required elsewhere (eg for sedation in ICU)	Use alternative I/M regimens to manage » Hyperglycemia » Mild DKA › Contact the diabetes specialist team for support
ICU	Significant insulin resistance seen in people with type 2 diabetes in ICU settings	IV insulin protocols may need amending (people seen requiring up to 20 units/hr) › Patients often nursed prone so feeding may be accidentally interrupted – paradoxical risk of hypoglycaemia

After the patient improves from the critical illness, when discontinuing intravenous insulin, a transition protocol is recommended. A patient being transitioned to a subcutaneous regimen should receive a dose of subcutaneous basal insulin 2–4 h before the intravenous infusion is discontinued. For more details, please follow BES Insulin Guideline Section 4 [4].

6.3: References:

1. Bornstein SR, Rubino F, Khunti K et al. Practical recommendations for the management of diabetes in patients with COVID-19. www.thelancet.com/diabetes-endocrinology Published online April 23, 2020.
2. Standards of Medical Care in Diabetes—2020, American Diabetes Association.
3. CONCISE ADVICE ON INPATIENT DIABETES (COVID:Diabetes): GUIDANCE, Diabetes UK. Professor Gerry Rayman (Chair), Dr Alistair Lumb, Dr Brian Kennon, Chris Cottrell, Dr Dinesh Nagi, Emma Page, Debbie Voigt, Dr Hamish Courtney, Helen Atkins, Dr Julia Platts, Dr Kath Higgins, Professor Ketan Dhatariya, Dr Mayank Patel, Dr Parth Narendran, Professor Partha Kar, Philip Newland-Jones, Dr Rose Stewart, Dr Stephen Thomas, Dr Stuart Ritchie Version 2.0, 20/4/2020
4. Bangladesh Endocrine Society Insulin Guideline 2018. (online published on website-bes.org.net.).

SECTION-7: Diabetes Management after Recovery from COVID-19

7.1: Advice at Discharge from Hospital

- During home isolation for diabetes management patient should start the drugs according to the advice of the discharge certificate. They should do SMBG 4 times per day in initial days and contact endocrinologist/ diabetologist as soon possible.
- The endocrinologist/ diabetologist will modify, if needed, the management plan gradually to achieve usual glycemic target of the patients.
- Insulin may be continued, if started in during hospital.
- But for the patients who were on insulin prior to hospital stay, they will continue it.
- When they feel well, they should start physical exercise.
- The patients should
 - Stop smoking
 - Try to reduce body weight, if overweight or obese
 - Check BP at home
 - Vaccinate for influenza and pneumonia, if not done as per schedule.

7.2: Isolation after Discharge from Hospital:

After discharge from hospital, the COVID-19 patients with diabetes should maintain home isolation for at least 3 weeks.

7.3: Prevention of COVID-19 in people with diabetes [2]

General precautions are mandatory for patients and caregivers, to prevent contracting COVID-19 (Text box: General precautions to prevent COVID-19 in people with diabetes).

7.3.1: General precautions:

- Hand hygiene
- Respiratory hygiene
- Social and physical distancing
- Avoid non-essential travels

7.3.2: Specific precautions:

- Frequent BG monitoring
- Good glycemic control
- Stabilize cardiac & renal status (control BP and lipid, stop smoking)

- Proper nutrition
- Regular Exercise
- Vaccinate if not taken previously (eg., influenza, pneumococcus)

7.4: References:

1. National Guidelines on Clinical Management of Coronavirus Disease 2019 (COVID-19), Version 6.0.
2. Diabetes UK Guidelines for the management of diabetes services and patients during the COVID-19 pandemic 2020. DIABETIC Medicin: DOI: 10.1111/dme.14316

SECTION-8: Pregnancy and Diabetes

According to the CDC, “Pregnant women experience immunologic and physiologic changes which might make them more susceptible to viral respiratory infections, including COVID-19. There have been cases of pregnancy loss, miscarriage, and stillbirth in women with SARS-CoV and MERS-CoV during pregnancy, but there are no studies yet of COVID-19. It’s important to note that high fevers (one of the symptoms of COVID-19) during the first trimester can cause or increase the risk of birth defects.

8.1: Pre-existing diabetes [1]

Adults with pre-existing diabetes have been identified as being more vulnerable to the severe effects of COVID-19. They have to stringently follow social distancing measures. Additional tests at antenatal visit for pregnant women with pre-existing diabetes should include HbA1c, renal and thyroid function, and urinary albumin-creatinine ratio (ACR) where possible. If early face-to-face review is needed, this should coincide with the 11-14-week scan and this review should cover: home blood glucose monitoring and the process for remote review of blood glucose control (insulin dose adjustment). All women with preexisting diabetes should have the-

- Provision of additional materials to support blood glucose monitoring, diet and sick day rules
- Information on hypoglycaemia avoidance and awareness for women using insulin.
- Prescription for folic acid and low dose aspirin.
- SMBG / urinalysis if available.

To reduce the number of hospital visits, retinal screening should only be done in women with known retinal changes prior to pregnancy. Consultations by the diabetes team for the purpose of reviewing SMBG levels should be done remotely, wherever possible.

Close and regular phone or email communication between obstetric, diabetic teams is essential to plan care and follow-up . Women affected by COVID-19 and who are symptomatic should be aware of the potential effects of infection on blood sugar control and should be advised to more frequent review of SMBG report, which can be arranged remotely by the diabetes team.

8.2: Gestational diabetes [2]

8.2.1: Screening:

In view of the prolonged waiting period in large groups at the hospital, and resource constraints, 2-hour oral glucose tolerance test (OGTT) may be postponed in this Covid 19 situation. For women considered to be at high risk of GDM the following modifications could be used as alternatives to OGTT. A screening pathway for gestational diabetes (GDM) can be followed as per figure 1

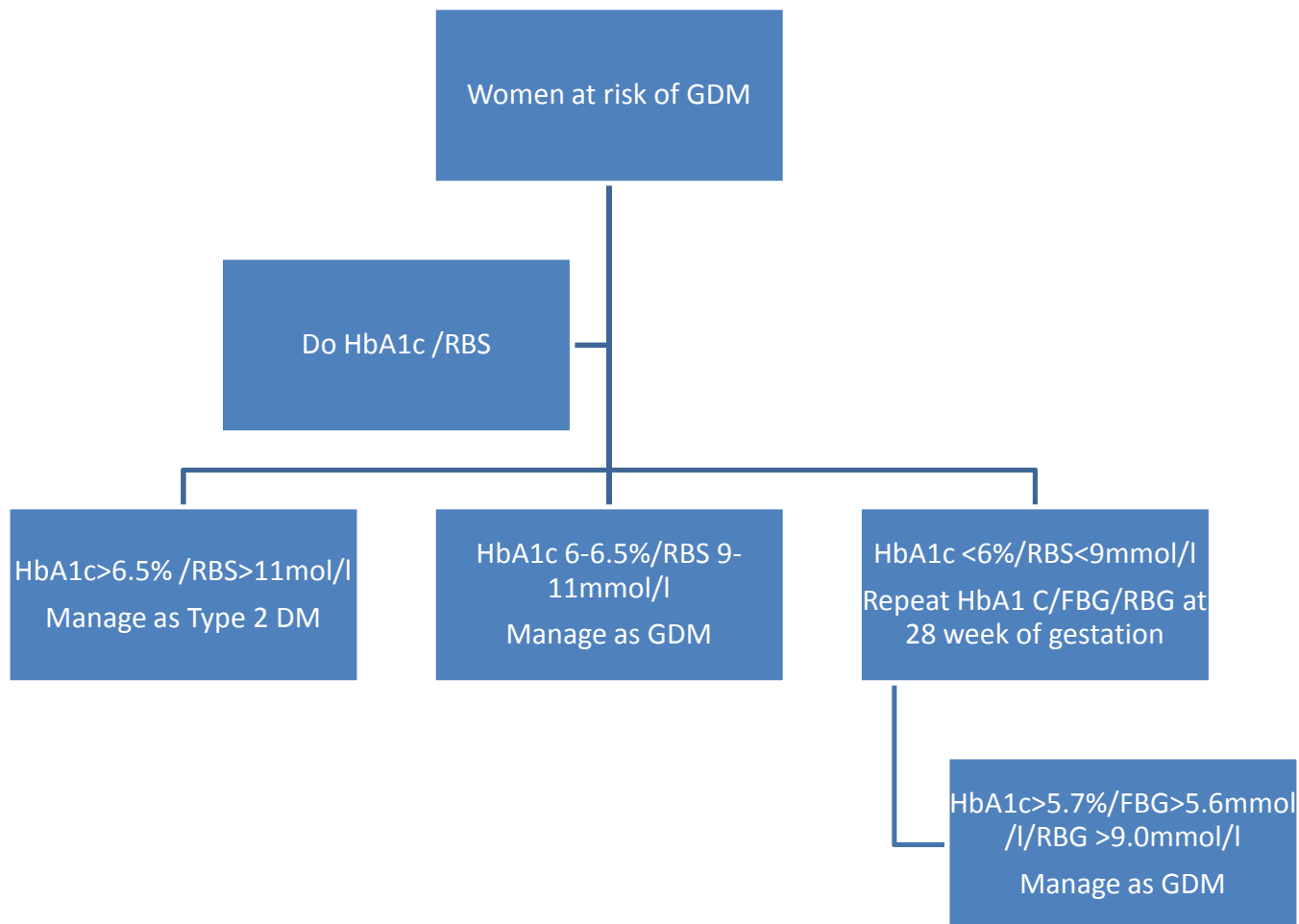


Fig-1: Screening for women with risk factors for GDM [2]

Note if following criteria is met with Test cutoff negative at 28-week gestation consider retesting if-

1. Heavy glycosuria
2. Highly suspicious classical symptoms of diabetes
3. Large for gestational age fetus /polyhydromnios

8.2.2: All women diagnosed with GDM should have an appointment with the diabetes team who will provide training in the use of a glucose meter. Where feasible, this should be done remotely via

video call. This visit should also be used as an opportunity to provide women with dietetic information and contact details of the dietician, where available.

8.2.3: Women should be followed-up remotely in the week after the glucometer training and all SMBG reports to be checked by the diabetes team. In women who have GDM managed by diet only, with blood glucose levels consistently in the target range no further hospital visits for diabetes test are needed. Women should be provided with advice to contact with diabetes team if they have >3 abnormal blood glucose levels in a week or >10-15% of all readings. If face-to-face review is required to start insulin it should be scheduled coinciding with obstetric follow up or planned ultrasound appointments.

8.2.4: Postpartum screening for maternal dysglycemia should be deferred until after the COVID-19 pandemic is over. It is not recommend bringing women to an in-person healthcare appointment solely for an OGTT postpartum.

8.3: References:

1. Guidance for maternal medicine in the evolving coronavirus (COVID-19) pandemic, Information for healthcare professionals, Royal college of obstetrics and gynecologist. Version 2.2: Published 13 May 2020
2. A Joint Consensus Statement from the Diabetes Canada Clinical Practice Guidelines Steering Committee* and the Society of Obstetricians and Gynecologists of Canada Jennifer M Yamamoto MD, Calgary, AB Lois E Donovan MD, Calgary, AB Denice S Feig MD, Toronto, ON Howard Berger MD, Toronto,

SECTION-9: Health Care Professional (HCP) and Diabetes

- Health-care professionals with diabetes and those with age>60 years should be deployed away from front line clinical duties where possible [1].
- For cases in which this is not possible or desirable, high-grade protection or increased protection should be used [1].
- All Healthcare personnel should adhere to standard precautions when caring for patients with SARS-CoV-2 infection, using respirator face mask, isolation gown, face shield or goggles, performing hand hygiene before putting on gloves [2].
- Patients with confirmed or possible SARS-CoV-2 infection should wear a facemask when being evaluated medically [2].
- Any HCP who develop fever or symptoms consistent with COVID 19 should immediately self-isolate and contact to arrange for medical evaluation and testing [2].

9.1: References:

1. Bornstein SR, Rubino F, Khunti K et al. Practical recommendations for the management of diabetes in patients with COVID-19. www.thelancet.com/diabetes-endocrinology Published online April 23, 2020.
2. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html>

SECTION-10: Management of Endocrine Diseases during COVID-19 Pandemic

10.1: Adrenal Insufficiency:

- Studies have reported that individuals with adrenal insufficiency have an increased rate of respiratory infection-related deaths, possibly due to impaired immune function [1].
- After diagnosis of COVID-19, a prompt modification of the replacement dose as indicated for the “Sick days” should be established when minor symptoms appear. In general, patients should double their usual glucocorticoid dose to avoid adrenal crisis.
- Additionally, patients are also recommended to have sufficient stock at home of steroid pills and injections, ideally a 90-day preparation [1].
- In case of inability to take oral glucocorticoids like vomiting/diarrhoea, injectable steroid should be initiated and hospital admission should be advised [3].
- If Adrenal crisis suspected (fever, hypotension) 100-200 mg Hydrocortisone IV 4-6 hourly should be initiated.

10.2: Cushing’s Syndrome :

- Individuals with uncontrolled Cushing’s Syndrome of any origin are at higher risk of infection in general [1].
- If experiencing fever, cough supportive treatment should be initiated. In case of shortness of breath, hospital admission should be advised.

10.3: Thyroid Disease :

- In COVID-19 patients admitted in hospital, routine Thyroid function tests is not recommended. There is no benefit of levothyroxine treatment in patients with Sick euthyroid syndrome [4].
- Patients with thyrotoxicosis should continue taking medications as prescribed as uncontrolled thyrotoxicosis may be at higher risk of complications (such as thyroid storm) from any infection.
- Patients on corticosteroids or immunosuppressive agents for thyroid eye disease are more susceptible and are at high risk of severe illness from COVID-19 and such patients need to take more precautions [2].

- Carbimazole induced agranulocytosis and Subacute thyroiditis should be kept in mind as differentials in patients presenting with sore throat. COVID-19 infection may cause Subacute Thyroiditis, according to recent case reports.
- Patients with hypothyroidism should continue taking levothyroxine treatment as suggested [2].

10.4: References :

1. AACE Position Statement: Coronavirus (COVID-19) and People with Adrenal Insufficiency and Cushing's Syndrome, <https://www.aace.com/recent-news-and-updates/aace-position-statement-coronavirus-covid-19-and-people-adrenal>
2. AACE Position Statement: Coronavirus (COVID-19) and People with Thyroid Disease, <https://www.aace.com/recent-news-and-updates/aace-position-statement-coronavirus-covid-19-and-people-thyroid-disease>
3. COVID-19 and endocrine diseases, A statement from the European Society of Endocrinology, <https://www.es-e-hormones.org/about-us/our-communities/clinicians/covid-19-and-endocrine-disease-clinical-information-and-comment-from-es-e>
4. Coronavirus disease 2019 and thyroid disease: Position statement of Indian Thyroid Society, <http://www.thetrp.net/article.asp?issn=0973-0354;year=2020;volume=17;issue=1;spage=4;epage=6;aulast=Rajput>.