Endocrinology and Covid-19: A Multifaceted Interaction

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Abstract

Women with diabetes, obesity and other endocrine or metabolic disorders form a distinct vulnerable group, who are at increased risk during the COVID-19 pandemic, either due to increased risk of severe infection or due to challenges in healthcare delivery during the pandemic.

Diabetes is a major risk factor for increased morbidity and mortality from COVID-19. Optimal cardiometabolic control and preventive measures to reduce risk of infection are needed in people afflicted with diabetes. Women with diabetes are at greater risk as they have limited access to diabetes care facilities even outside the time frame of a pandemic and this gender gap in care is likely to widen during the pandemic. Moreover, the care of pregnant women with pre-existing diabetes or gestational diabetes mellitus (GDM) also cannot be compromised. While alternate screening strategies for GDM such as the use of fasting plasma glucose and glycosylated hemoglobin are being considered, telemedicine services can offer a platform for remote monitoring and delivery of optimal diabetes care to pregnant women.

Telemedicine services can also be used for delivery of long-term care for other endocrine disorders. Elective surgery or evaluation of endocrine disorders that are not immediately life-threatening can be deferred till appropriate safety precautions can be taken. At the same time, there is a need ensure that care of endocrinopathies such as diabetes, obesity, thyroid disorders and osteoporosis, all of which affect women more severely, is not compromised during the pandemic.

Many endocrine organs, including pancreas, thyroid, testis, ovary, adrenals and pituitary, express the angiotensin-converting enzyme 2 (ACE2) that is the receptor for SARS-CoV-2 virus. Since ACE2 expression is different in men and women, there is a need to evaluate the impact of the virus on endocrine system and assess whether this is gender-specific.

Keywords
- adrenal insufficiency
- COVID-19
- diabetes
- endocrine disorders
- glucocorticoids
- thyroid disorders
- women

Introduction

The coronavirus 2019 (COVID-19) pandemic has created significant challenges for healthcare systems worldwide, especially impacting the management of chronic disorders. Persons with metabolic disorders such as obesity, diabetes, hypertension and cardiovascular disease (CVD) are at greater risk of morbidity and mortality from the infection.[1]

Women with diabetes, obesity and other endocrine or metabolic disorders form a distinct vulnerable group who are at increased risk. The limitations imposed by the pandemic on routine healthcare services is also likely to impact women with chronic noncommunicable diseases more.

The gene for angiotensin-converting enzyme 2 (ACE2), which is the binding protein for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is X-linked. There have been reports that the expression of ACE2 seems to be different in men and women, with higher expression reported in men.[2] The transmembrane protease serine 2 (TMPRSS2) that

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is involved in viral internalization is also androgen-regulated and its higher expression in lungs in men could also create gender differences in susceptibility to infection, although this has not been established.[3,4]

Many endocrine organs, including pancreas, thyroid, testis, ovary, adrenals and pituitary, express ACE2, which is the receptor for SARS-CoV-2 virus. Therefore, there is a possibility that COVID-19 infection may impact endocrine health.[5]

Although no gender-specific relationship of COVID-19 with endocrine disorders has yet been reported, it is worth exploring if the differences in susceptibility to infection have any gender-specific impact on endocrine health. The long-term care of women with thyroid disorders, osteoporosis, reproductive dysfunction, or other endocrinopathies is also likely to be compromised during the pandemic, and there is a need to ensure that gender disparities in care do not get widened by the socioeconomic impact of the pandemic.

Diabetes Mellitus and Metabolic Syndrome

Diabetes mellitus, old age, obesity, hypertension, CVD, chronic kidney disease, and chronic respiratory disease are associated with significantly increased risk of severe COVID-19 infection.[6]

Diabetes is associated with defects in innate and adaptive immunity, delayed viral clearance as well as increased inflammatory response that increases the risk of cytokine storm.[7] In addition, ACE2 expression has been reported to be increased in persons with type 1 or type 2 diabetes.[8] Diabetes has, in fact, emerged as a major risk factor for severity of COVID-19 infection and complications such as acute respiratory distress syndrome (ARDS), cardiac or renal injury, need for hospitalization and intensive care as well as mortality.[1,6]

Studies have not evaluated gender differences in severity and fatality of COVID-19 infection with respect to the prevalence of underlying comorbidities.[9] However, while gender-specific data are not available at present, women with diabetes remain a vulnerable group. Women with diabetes often have a higher burden of complications of diabetes including cardiovascular and microvascular complications, which further their risk of severe COVID-19 infection.[10] In addition, women have poor access to healthcare services, which is likely to impact diabetes care during the pandemic.[11]

Diabetes Management during the Pandemic

The management of diabetes during the pandemic should follow the general principles with focus on patient-centered care.[12] It is important to ensure diabetes-specific medical education (DSME) and empower women with skills for self-care. This includes education and motivation about balanced nutrition and physical activity, self-monitoring of blood glucose (SMBG), and adherence to treatment.[13]

The pandemic is likely to impact routine clinic visits; telemedicine and remote consultation platforms provide an opportunity to ensure continuity of care. The impact of telemedicine services on diabetes care is already well-established.[14,15] However, telemedicine may not always be feasible; it is important for diabetes care providers to ensure distancing and appropriate safety measures in clinics.

Optimal glycemic control may reduce the risk of severe disease in people afflicted with diabetes.[16] While the factors determining the choice of medications or insulin for diabetes management remain the same, it is important to emphasize the need for optimal cardiometabolic control. The access to medications and the direct cost of treatment are likely to emerge as important variables, as the pandemic continues to have widespread economic impact.

Metformin may have gender-specific immunomodulatory effects. A recent observational study suggested that women but not men with diabetes who had been taking metformin regularly had lower mortality.[17] Antidiabetic medications should therefore be continued and insulin should be considered in those with inadequate glycemic control. Patients should be counseled about the need for regular SMBG, especially if they are taking insulin. They should also be educated about sick day guidelines.

In addition, there is a need to provide psychological support to women, as women are more prone toward psychological distress. Women with diabetes are already coping with the demands of diabetes self-care, and diabetes distress puts them at greater risk of suboptimal control and worse outcomes.[18]

Management of Hyperglycemia in COVID-19 Infected Patients

People afflicted with diabetes constitute a large proportion of patients hospitalized for severe COVID-19, and appropriate inpatient management of hyperglycemia is important for improved outcomes.[19,20] Uncontrolled hyperglycemia has been linked to increased morbidity and worse outcomes in recent studies.[21]

Severe COVID-19 infection may result in significant hyperglycemia not only in those with pre-existing diabetes but also in patients who have prediabetes, obesity or no previous risk factors. This is due to multiple mechanisms: increased secretion of counter-regulatory hormones, increased inflammatory response, medications such as glucocorticoids, inotropes and dextrose-containing fluids, inadequate and unpredictable oral intake, and a direct effect of SARS-CoV-2 on pancreatic islets.[21]

The management of hyperglycemia in infected individuals follows the general principles of hyperglycemia management during acute illness.[22-24] Regular point-of-care blood glucose monitoring is recommended in all sick patients including those with pre-existing diabetes. Care should be taken to ensure adequate hydration and optimal nutrition. Titration of antidiabetic medications and insulin takes into account blood glucose levels, nutritional status, age, severity of infection, complications, and underlying comorbidities.

Noninsulin therapies can be continued in mild-to-moderate infection for patients who are at home or in quarantine.[23,24] However, they should be instructed about regular SMBG, hypoglycemia prevention and care and sick day guidelines.

Correction doses of rapid acting insulin can be used in addition to ongoing antidiabetic medications, but in case of any worsening of symptoms or persistent hyperglycemia, they should contact the medical team immediately.

Small studies have reported that DPP4 inhibitors are safe for use in hospitalized patients with type 2 diabetes and can be considered for mild hyperglycemia.[19] Drugs such as sitagliptin or linagliptin, which do not increase the risk of hospitalization for heart failure, are preferred. Sulfonylureas may increase the risk of hypoglycemia while metformin may increase the risk of lactic acidosis, especially in unstable patients who have hypoxia or renal impairment. GLP1-RAs can result in significant nausea and vomiting during acute illness if patients are not taking regular meals. SGLT2 inhibitors may increase the risk of DKA and volume depletion and are best discontinued in sick patients. Pioglitazone may result in fluid retention and increase the risk of heart failure.[23,24] Careful monitoring of blood glucose is required in patients on hydroxychloroquine, as it can have glucose-lowering effect.[25]

Insulin forms the mainstay of treatment for patients who have severe symptoms, significant hyperglycemia, complications and severe infection.[23,24] Standard guidance on inpatient management of hyperglycemia using IV and basal-bolus insulin regimens is available.[22] Intensive glycemic control with IV insulin infusion is associated with better outcome and reduced inflammatory and procoagulant state.

Targets for glycemic control include blood glucose of 140 to 180 mg/dl in critically ill patients and 100–180 mg/dl in noncritically ill patients.[22] Intravenous insulin infusion is recommended in those who are critically ill, while other patients can be optimally managed with basal-bolus insulin regimen.

Vasopressors and glucocorticoids may significantly increase the requirement of insulin. Most patients on glucocorticoids will require insulin for management of hyperglycemia.[23] Basal-bolus regimens are optimal but most of these patients require a higher bolus dose than basal insulin. NPH insulin has been used as its pharmacokinetic profile parallels the hyperglycemic effect of prednisolone or methylprednisolone.[26] Tapering of glucocorticoids and acute kidney injury can increase risk of hypoglycemia. This may require frequent adjustment in insulin plan.

However, there are several challenges in care posed by shortage of resources such as personal protective equipment (PPE), ICU beds, and healthcare staff. Remote monitoring and guidance by diabetes care specialists can improve care and inpatient glycemic management.

Early reports suggest that severe COVID-19 infection may be associated with increased risk of diabetic ketoacidosis, which is associated with a grave prognosis.[27] This calls for greater vigilance with regard to acute hyperglycemic emergencies in patients with COVID-19 infection and their prompt diagnosis and aggressive management. In resource-limited settings, where use of IV insulin infusion is not feasible, frequent subcutaneous injections of rapid-acting insulin analogs can be considered along with IV fluids in mild-moderate DKA.[27]

Pregnancy with Diabetes

The pandemic has significantly impacted healthcare services, including antenatal care delivery.[28] Pregnant women with pre-existing diabetes and gestational diabetes mellitus (GDM) are a vulnerable group at increased risk of adverse maternal and fetal outcomes and require close vigilance. However, there is a need to minimize the risk of inadvertent transmission of infection from frequent visits.

A small case series of pregnant women with COVID-19 suggested that the presence of gestational diabetes or gestational hypertension did not increase the risk of life-threatening infection in the mother.[29] The risk of fetal transmission is another factor to consider.

Some recent guidelines suggest that the standard 2-hour oral glucose tolerance test (OGTT) may be avoided during the pandemic and instead recommend use of fasting plasma glucose, random plasma glucose and HbA1c.[30,31] Underdiagnosis of GDM remains a major concern, as these criteria have not been validated but may be useful alternatives during the pandemic.[32]

As per the recent guidelines from the International Federation of Gynecologists and Obstetricians, the management of diabetes during pregnancy should follow established standards of care using lifestyle modification, medical nutrition therapy, SMBG and insulin.[33] Video consultations for management of diabetes during pregnancy may improve care while limiting the need for hospital visits, with clinic visits limited to ultrasound and retinal scans, laboratory monitoring and emergency evaluation.[34]

Some antenatal women with diabetes may be administered glucocorticoids to promote fetal lung maturation if there is a risk of preterm delivery. This may result in hyperglycemia requiring insulin dose adjustment.[34]

Thyroid Disorders

Autoimmune thyroid disorders are more common in women, especially during the reproductive age. It does not seem that thyroid disorders increase the risk of severe infection or an adverse outcome.[35] Telemedicine services can be used for regular follow-up of patients with thyroid disorders in most cases. Women with thyroid disorders who are planning pregnancy or are pregnant should be managed as per standards of care.

In patients with hyperthyroidism who are being treated with antithyroid drugs (carbimazole, methimazole or propylthiouracil), there have been concerns that these medications may cause agranulocytosis. However, agranulocytosis is rare and no studies have reported an increased risk of COVID-19 with the use of antithyroid drugs.[36] The Endocrine Society suggests that hyperthyroid patients can be managed with antithyroid drugs and elective surgery or radioiodine ablation, as hyperthyroidism may be deferred during the pandemic if access to these services is limited.[16,36] The clinical presentation of agranulocytosis may mimic COVID-19 with fever and sore throat; therefore, it is important to be vigilant, and to detect and treat agranulocytosis promptly. In patients with hyperthyroidism who develop COVID-19 infection,

antithyroid drugs should be continued unless there is neutropenia.[37] A block-and-replace regimen using antithyroid medications and levothyroxine has been suggested in hyperthyroid subjects in case frequent biochemical monitoring of thyroid functions is not possible.[13] There may be an increased risk of thyroid storm in COVID-19 infected patients if there is underlying uncontrolled thyrotoxicosis, although this has not been documented so far.[13,35]

It is also not yet known whether COVID-19 infection results in thyroid dysfunction, although there have been a few case reports of subacute thyroiditis in infected patients.[38] Therefore, screening for thyroid functions may be advised in COVID-19 infected patients who present with significant tachycardia and neck or ear pain. Whether COVID-19 can cause direct damage to thyroid tissue should be evaluated in prospective studies. During the previous SARS epidemic, reversible hypophysitis and central hypothyroidism have been reported.[39]

Severe infection may also result in abnormal thyroid functions due to nonthyroidal illness (or sick euthyroid state). The underlying mechanisms include decreased cellular uptake of T4 and reduced conversion to T3, alterations in thyroid binding proteins and receptor binding as well as increased catabolism.[37] Many patients with severe infection may have low-T3 levels.[35] In a recent study of 50 patients with COVID-19 infection and no prior history of thyroid dysfunction, thyroid stimulating hormone (TSH) was lower than normal in 56% patients and serum TSH as well as total T3 levels were lower than in healthy controls and inversely correlated with severity of COVID-19 infection.[40] Following recovery, no difference in serum levels of T3, T4 or TSH was noted compared with controls.

Clinicians must be aware of this possibility, and assessment of thyroid function results should take into account careful history and examination. However, routine screening for thyroid functions is not warranted in infected patients unless there is a strong suspicion of thyroid disorder.

During the pandemic, the evaluation of thyroid nodules and elective surgery or radioiodine ablation can be deferred if there are no worrisome signs (rapid increase in size, large nodule, compressive symptoms such as hoarseness of voice, difficulty in breathing or swallowing).[41] Since most thyroid cancers are well-differentiated, surgery and radioiodine ablation can be postponed in these cases while keeping a close vigil.

Adrenal Disorders

There is no data on the impact of adrenal disorders such as adrenal insufficiency, Cushing's syndrome (CS), pheochromocytoma or primary hyperaldosteronism on the risk of COVID-19 infection.

Adrenal Insufficiency

There is no evidence at present to suggest that patients with adrenal insufficiency who are on glucocorticoid replacement or patients being treated with glucocorticoids for other systemic diseases are at an increased risk from COVID-19 infection or that glucocorticoids protect them.[5,15,42] However, people on glucocorticoids (such as those with inflammatory diseases, malignancy, transplant recipients, etc.) represent a group with greater risk of comorbidities and immune disorders which makes them vulnerable.

The Endocrine Society have provided guidance for patients with primary or secondary adrenal insufficiency and for patients on long-term glucocorticoids.[16] Patients who are on long-term glucocorticoids as replacement (adrenal insufficiency) or immunosuppressive agents are at risk of adrenal crisis during acute illness and must be instructed on "sick day rules" and stress doses of glucocorticoids.[5]

In case of fever, cough, diarrhea or any acute illness, they should be advised to double the dose of oral glucocorticoids till symptoms resolve or take oral hydrocortisone 20 mg every 6 to 8 hours.[13,16] If there is inadequate supply of oral hydrocortisone, patients should be instructed to use equivalent doses of oral prednisolone. Intravenous or intramuscular hydrocortisone (100 mg bolus followed by infusion or 50 mg every 6–8 hours) should be used in case of any worsening of symptoms or occurrence hypotension, altered sensorium or recurrent vomiting. Timely diagnosis and management of adrenal failure with parenteral glucocorticoids is required.

Critically ill COVID-19 infected patients may develop critical illness-related corticosteroid insufficiency (CIRCI) due to impaired activation of the hypothalamic–pituitary–adrenal (HPA) axis in response to stress.[37] CIRCI has been associated with increased inflammatory and procoagulant markers, greater morbidity and ICU stay. Patients with altered sensorium, refractory hypotension and dyselectrolytemia (hyponatremia, hyperkalemia and normal anion gap metabolic acidosis) should be considered for short-term intravenous glucocorticoids (hydrocortisone 100 mg 8 hourly). Such HPA axis suppression was documented in SARS patients, and it would be prudent to assess if patients who continue to complain of significant malaise and fatigue following recovery from COVID-19 have altered cortisol dynamics.[43]

Recent studies have demonstrated that dexamethasone reduces mortality in critically ill COVID-19 infected patients by preventing cytokine storm and multiorgan failure.[42,44] Low-dose dexamethasone reduced the risk of mortality by 35% in ventilated patients and by 20% in those on supplemental oxygen in the RECOVERY trial. No benefit was seen in mild cases.[42] This needs to be balanced against the risk of delayed viral clearance, superadded infections and hyperglycemia due to glucocorticoids. Dexamethasone has shown benefits in severe COVID-19 infection. However, there is potential concern of its abuse, as it is a nonexpensive medication that is easily available, even over-the-counter in some countries. For COVID-19 patients who are being treated with glucocorticoids, glucocorticoid therapy may be discontinued if the use has been short-term (less than 3 weeks). However, among patients in whom glucocorticoids are used for longer duration of time, a gradual tapering down of the dose is advisable, as these patients may have adrenal suppression due to exogenous glucocorticoid therapy.[45]

Cushing's Syndrome (CS)

Patients with CS, both exogenous and endogenous, are at an increased risk of morbidity and mortality from COVID-19 infection due to immunocompromised state along with occurrence of comorbidities such as diabetes, hypertension, central obesity, cardiovascular disease, endothelial dysfunction, and procoagulant state. Therefore, they constitute a highly vulnerable group.[37] Specific data on COVID-19 infection in patients with CS is currently unavailable, but these patients should be instructed to follow strict preventive measures. Treatment should focus on optimal cardiometabolic control as well as rapid normalization of cortisol levels.[13]

Trans-sphenoidal surgery (TSS) can result in aerosol formation; therefore, presurgical testing for COVID-19 and use of PPE by surgical team should be considered. In cases where surgery is deferred, inhibitors of steroidogenesis such as ketoconazole or metyrapone should be considered to tide over the waiting period.[13]

Primary Hyperaldosteronism and Pheochromocytoma

There is no data related to risk of COVID-19 infection in patients with primary hyperaldosteronism or pheochromocytoma, but the underlying hypertension and dysglycemia increases the risk in these individuals. Evaluation and treatment of these endocrine disorders should not be delayed or compromised.

Pituitary Disorders

Special care is needed in COVID-19 infected patients with underlying hypopituitarism along with close monitoring of fluid-electrolyte balance and stress doses of glucocorticoids. Additionally, those with diabetes insipidus require close monitoring of water and electrolyte balance to prevent hyponatremia and hypernatremia, especially when there is significant insensible fluid loss due to fever and tachypnea.[16] If patients are not able to take oral or intranasal desmopressin (DDAVP), IV or intramuscular route of administration should be considered during acute illness.

In addition, central hypothyroidism and secondary adrenal insufficiency have been reported following SARS-CoV infection[13] and clinicians need to be vigilant of this possibility with SARS-CoV-2 infection as well. SARS-CoV-2 may also result in immune-mediated hypophysitis, although currently there is no data available.

Patients with pituitary disorders such as CS, acromegaly or hyperprolactinemia may have underlying comorbidities that make them vulnerable and need continued care. TSS should not be delayed if there is visual compromise or apoplexy but may be deferred in other cases till suitable preventive measures can be implemented. Long-acting somatostatin receptor ligands and/or dopamine agonists should be considered for the medical management of acromegaly in the interim period.[13]

Osteoporosis and Disorders of Bone Mineral Metabolism

There is no evidence of increased risk of COVID-19 in patients with metabolic bone disorders, although hypocalcemia may result in impaired immune response. Vitamin D has immunomodulatory effects, and vitamin D deficiency has been linked with increased risk of viral respiratory infections, and morbidity and mortality related to them. However, no studies have systematically looked at the effect of vitamin D supplementation in COVID-19.[43] In the absence of clear evidence, it would be prudent to ensure routine supplemental doses of 800 to 1000 IU of vitamin D daily.

Osteoporosis remains an underdiagnosed and inadequately treated disorder in postmenopausal women. There is a need to ensure optimal calcium and vitamin D intake. Circumstantial evidence suggests that vitamin D deficiency may predispose to COVID-19 infection and related mortality.[13] Appropriate nutrition, regular weight-bearing exercises, and fall prevention is important to reduce fracture risk. While oral bisphosphonates and subcutaneous teriparatide can be continued as such, there may occur delays in administration of IV bisphosphonates or denosumab.

The management of parathyroid and other metabolic bone diseases remains the same. Surgery for primary hyperparathyroidism (PHPT) may be delayed if needed, provided serum calcium levels can be maintained at < 11 mg/dl. In patients with hypoparathyroidism, it is important to ensure serum calcium levels are maintained in the normal range. They should also be instructed to increase the dose of calcium and vitamin D during any acute illness, and hyperventilation and respiratory alkalosis may reduce ionized serum calcium levels.[13,16]

Hypocalcemia and hypomagnesemia may occur in critically ill patients with COVID-19 due to multiple factors such as vitamin D deficiency, impaired parathyroid hormone (PTH) secretion, hypoalbuminemia and acid-base imbalance.[43] A recent single-center study documented hypocalcemia in a significant proportion of COVID-19 infected patients, and it was a risk factor for the need for hospitalization, ICU admission and mortality.[46] Therefore, in sick patients, measurement of serum calcium and appropriate supplementation should be considered.

Reproductive and Gonadal Disorders

The higher risk of severe disease and mortality in men could result from both biological factors (sex-related immunological and sex hormone differences) and gender-specific behavior (lifestyle and preventive measures).[9] Estrogen receptors on the endothelium increase the production of nitric oxide and reduce the production of reactive oxygen species (ROS). This apparently protects the vasculature from the effects of angiotensin-II (vasoconstriction, inflammation and oxidative stress).[47]

ACE2 protein expression is sex-specific with males showing higher renal expression, and estrogen may further reduce the ACE2 activity.[9] A sex-difference in ACE2 expression in lungs and other tissues is not yet clear. Innate immune response to viral infections appears to be more robust in females than males, with greater inflammatory and humoral immune response resulting in greater viral clearance.[9]

While some studies suggest that SARS-CoV-1 infection was associated with impaired sperm function and lymphocytic infiltration of testis, the impact of SARS-CoV-2 on female reproductive health has not been evaluated. Management of hypogonadism and other female reproductive disorders should follow general practice during the pandemic. Reproductive and maternal-fetal health services are likely to be compromised, as healthcare resources are diverted toward the pandemic. There is an urgent need for policymakers to focus on women as a vulnerable group and ensure that the gender gap in care is not widened.

Conclusion

There is a need to assess the impact of the virus on endocrine system and ensure that care of endocrinopathies such as diabetes, obesity, thyroid disorders and osteoporosis, all of which affect women more severely, is not compromised during the pandemic.

Conflicts of Interest
None declared.

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