



***Pediatric
Endocrinology
in the Time of
COVID-19***

COVID-19 has completely changed our daily clinical practice as well as our social relations.

Many organs and biological systems are involved in SARS-Cov-2 infection, either due to direct virus-induced damage or to indirect effects

increased vulnerability in specific population groups arise.

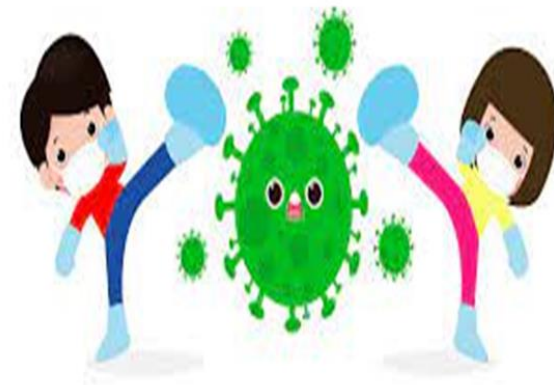
One of the high-risk populations is the pediatric population and particularly children with chronic diseases

Endocrine system is not only an exception but its involvement in COVID-19 is

so relevant that an “endocrine phenotype” of COVID-19 has progressively acquired clinical relevance.



To date, none of the endocrine conditions have been classified as predisposing factors for the Covid-19 infection and hence, children with endocrine diseases have not shown a different disease pattern compared to children without an endocrine disorder.

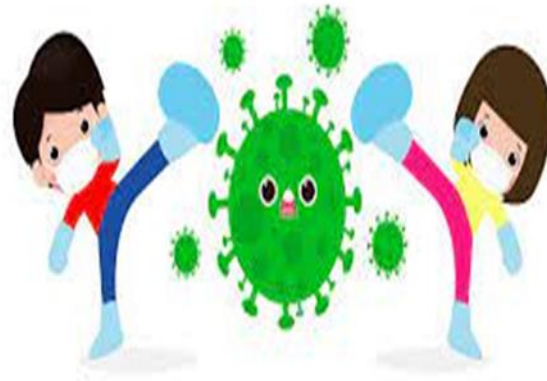


adhere to preventive and protective measures against viral spread

In the case of symptoms of infection medical advice should be sought

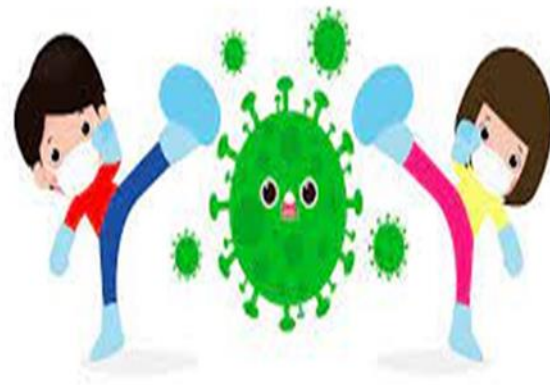
symptoms are of increasing severity, visiting the nearest hospital

important to maintain adequate hydration with frequent fluid intake.



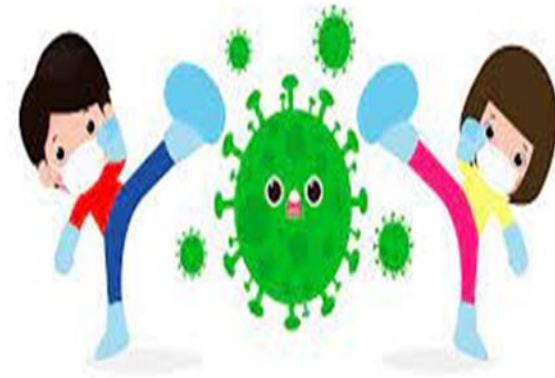
If COVID-19 is confirmed, recommended control measures should be promptly implemented together with supportive management of complications

If hospitalization is needed, the health care team should be aware so as to modulate management, particularly in endocrine diseases such as type 1 diabetes mellitus, hypoglycemia disorders and adrenal insufficiency.



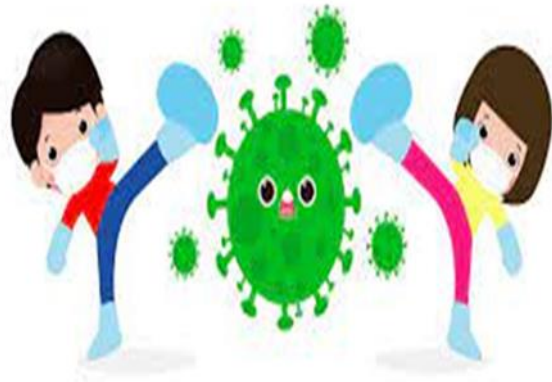
it is important that children with endocrine diseases who receive replacement or supplementation therapy maintain a euhormonal status.

The necessity of dose adjustment according to the individual needs no universal recommendation is applicable in all case.



sufficient supply of medications

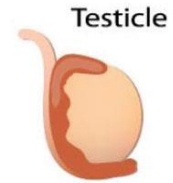
Routine hospital visits should be avoided for nonurgent reasons
and those should be replaced by telephone or video consultation



Possible transient
hypothalamopituitary
dysfuncon
Dysnatremias more
frequent



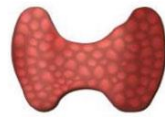
Pituitary
gland



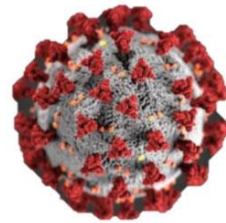
Testicle

COVIDHigher
susceptibility and
worse outcomes in
men

Sick euthyroid
syndrome



Thyroid

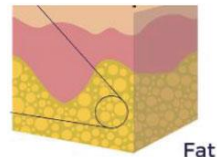


Low vitamin D
may be
linked to more
severe
disease -
Hypocalcemia

Probable
higher
susceptibility in
adrenal
insufficiency
and Cushing's
syndrome



Adrenal
gland



Fat

Worse outcomes in obese
paents

Pancreas

Worse outcomes in
diabec paents





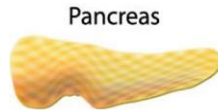
Pineal gland

Melatonin



Pituitary gland

Oxytocin



Pancreas

DPP4
GLP-1

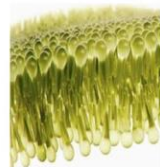


ACE-2



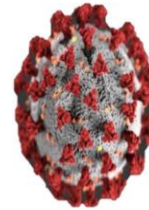
Ovary

Estrogens



Statins

Possible endocrine and metabolic targets that have been considered for COVID-19 therapy. Different hormones and drugs have been included as possible targets for COVI-19 including melatonin, oxytocin, DPP-4 (human dipeptidyl peptidase 4), ACE-2 (angiotensin converting enzyme-2), estrogens and statins



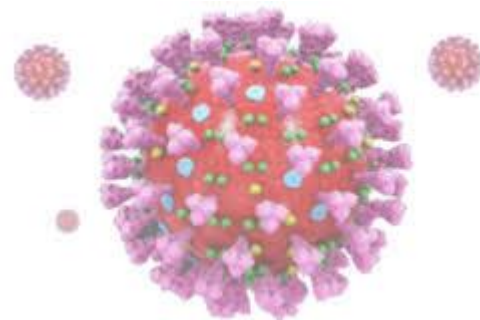
DIABETES



In adults, reports from China ,Italy , and USA indicate *that DM is a risk factor for severe COVID-19 disease.*

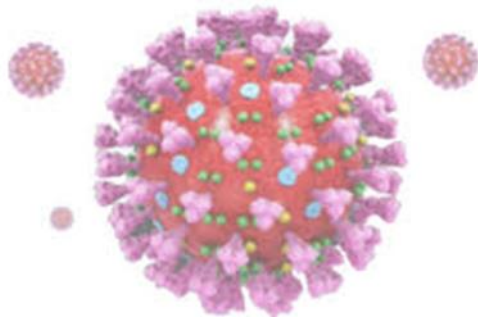
Longstanding DM involves *low-grade chronic inflammation*, which may promote the cytokine storm that seems to be implicated in the severe evolution of COVID-19, as inflammation markers (C-reactive protein, fibrinogen D-dimer, ferritin, erythrocyte sedimentation rate, IL-6) have been found higher in patients with DM

- While the restoration of normoglycemia seems to be related to a better prognosis for bacterial infections, in viral disease and especially in COVID-19 diabetic patients, is still under evaluation
- glucose exposure of pulmonary epithelial cells significantly increases influenza virus infection and replication
- elevated glucose levels impair the Antiviral immune response.



In viral disease animal models, diabetes is associated with numerous lung structural changes

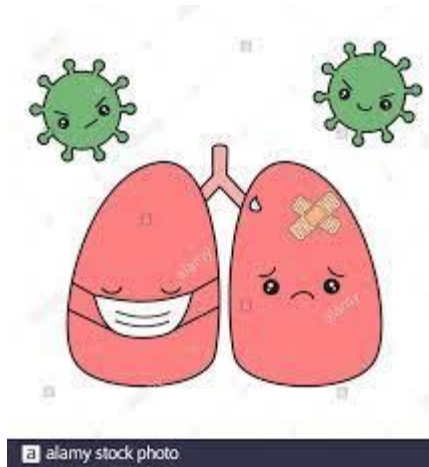
renin angiotensin system dysregulation
aberrant protein glycation
dysfunction of immunoglobulins and ACE2
increased coagulation activity,
potential bacterial super infection
direct pancreatic damage.
augmented permeability of the vasculature
collapsed alveolar epithelium



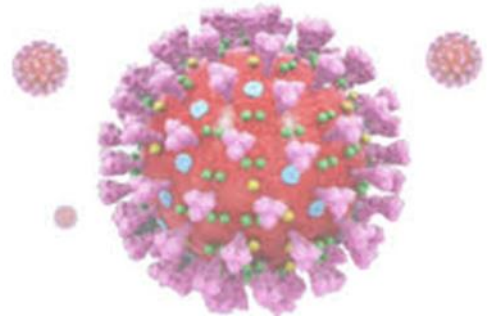
Hyperglycemia may also affect pulmonary function

respiratory dysfunction induced by COVID-19 is exacerbated in patients with diabetes.

In fact, COVID-19 pneumonia radiologic scores are worse in diabetic patients



Recently published data indicate that glycemic control is related to outcomes.



the last A1c previous to the development of COVID-19 has been reported to show

a linear relationship to outcomes and particularly to mortality when A1c is >10%

these latter figures equally applied to either type 2 and also type 1 diabetes.

Conversely, low A1c has also been related to mortality in type 2 diabetes

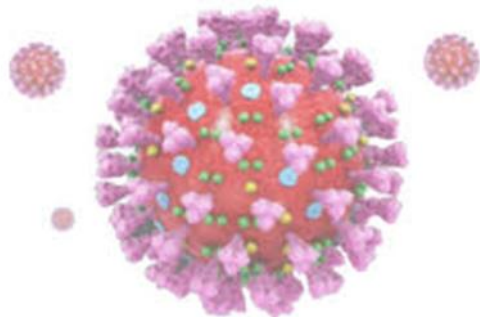
while the relationship is not statistically significant for type 1 diabetes.

Glycemic factors combined with **obesity** amplify the deleterious effects upon mortality and severe outcomes,

Besides the importance of the A1c previous to infection

glycemic control and glycemic fluctuations during the first days of hospital stay

have additionally been reported as important determinants of hospital length stay, ICU requirement, and mortality the strength of the association of these outcomes was higher if the patients received corticosteroid treatment, thus requiring intensive insulin treatment



COVID-19 and newly onset diabetes

Diabetes is one of the most frequent co-morbidities of hospitalized patients with severe COVID-19

bidirectional relationship between diabetes and COVID-19 may exist

pancreatic β -cells abundantly express ACE2 receptor, they may be damaged by SARS-CoV-2

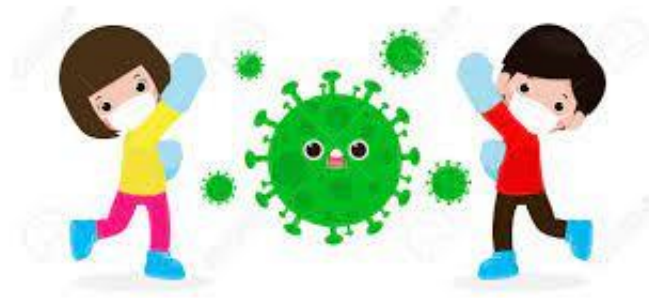
with consequent worsening of hyperglycemia in patients with known diabetes, often complicated by ketoacidosis or hyperosmolarity with high-dose insulin requirements.

new onset of diabetes in COVID-19 patients previously nondiabetic a **potential diabetogenic action of SARS-CoV-2**

The transient or persistent nature of this still not entirely known

children and adolescents with DM, it is expected that those with type 1 DM and good metabolic control will follow the same course of illness as their peers

Nonetheless, those with a poor control could have a debilitated immunity that puts them at a greater risk for contamination from SARS-Cov-2 , and a more severe presentation



The European Society for Paediatric Endocrinology (ESPE) recommends

maintaining the usual amount of back-up insulin supplies, for at least a week in advance

In the instance of symptoms that could be related to COVID-19 medical assistance is sought without delay

As during any other intercurrent illness, glycemic control may deteriorate following “sick day rules” also apply in the case of COVID-19



Recommendations from ISPAD

- ❖ monitor blood glucose and ketone bodies more frequently
- ❖ target blood glucose concentrations between 70-180 mg/dl (4-10 mmol/l) and negative ketones during illness
- ❖ never discontinue insulin administration, since increased insulin requirements are expected in case of fever;
 - ❖ watch and support hydration, especially in the presence of fever and/or vomiting/diarrhea
 - ❖ treat the underlying sickness and symptoms.





To date, there is no evidence that patients with adrenal insufficiency are at increased risk of contracting COVID-19.

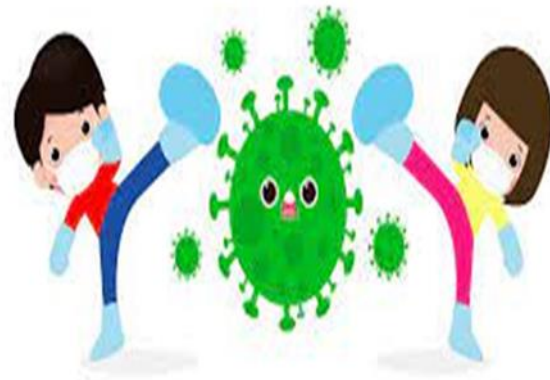
Nonetheless, patients with primary adrenal insufficiency are slightly more susceptible to infections in general.

This may partly be explained by the impaired natural immunity function characterized by a defective action of neutrophils and natural killer cells, which is known to be associated with primary adrenal insufficiency

susceptibility to infections may also be explained by an insufficient increase of the hydrocortisone dosage at the beginning of an infection.

Therefore, recommendations suggest that, if asymptomatic, children should remain on regular replacement doses of hydrocortisone and not increased doses.

If symptoms suggestive of COVID-19 develop (fever, cough, dyspnoea, vomiting, diarrhoea), the “sick day rules” are recommended



- ❖ including immediately increasing the hydrocortisone doses (e. g., > 38 °C: 2-fold increase, > 39 °C: 3-fold increase) until the fever has subsided and adding an extra doubled dose
 - ❖ Adequate hydration is also recommended
- ❖ In the case of more severe symptoms, if the medication cannot be orally received due to vomiting, parenteral glucocorticoids initiated, accompanied by glucose, preferably in the form of oral gel



- ❖ history of possible adrenal suppression secondary to prior exposure to glucocorticoids for more than 3 months, parenteral treatment with glucocorticoids is considered

Physiological stress doses of hydrocortisone

all the patients receiving corticosteroids for other medical reasons should be considered as high risk patients for contracting COVID-19 and experiencing more severe symptoms

Supraphysiologic doses of glucocorticoids may further increase susceptibility to COVID-19 due to their immunosuppressive effect.

Hypopituitarism

Children diagnosed with hypopituitarism are not at increased risk for COVID-19.

As a significant percentage of these patients have secondary adrenal insufficiency, the same recommendations apply as for children with adrenal insufficiency.

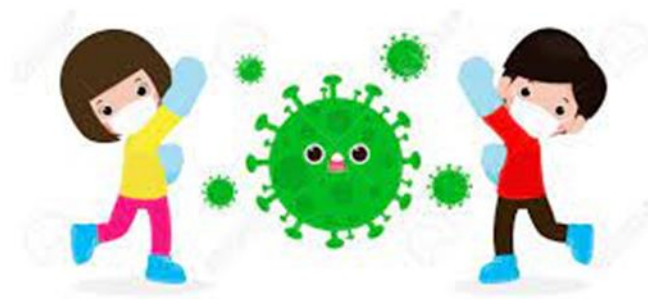
Identical advice applies for each of the endocrine deficiencies involved



Diabetes Insipidus

In addition, in the case of the presence of both secondary adrenal insufficiency and diabetes insipidus, it is important that medications for both conditions are always received.

Careful monitoring of fluid intake and urinary losses is important, as well as judicious replacement of water, in order to avoid hypo- or hypernatremia, particularly in the presence of fever, tachypnea and the co-existence of impaired ability for fluid intake due to altered level of consciousness



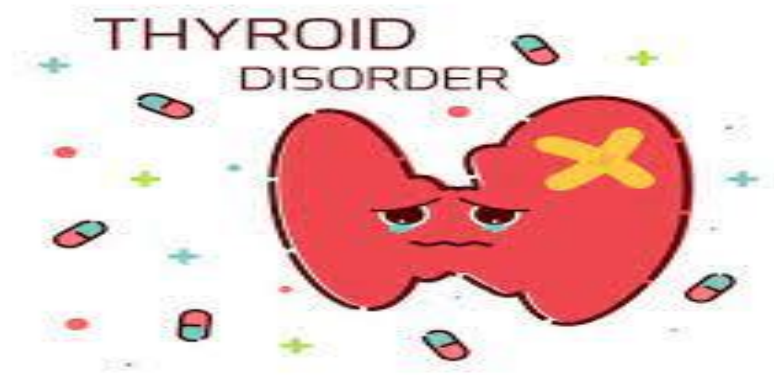
hydrocortisone should be administered at adequate doses to avoid accumulation of fluid urination should be monitored closely.

If the child has an intact thirst mechanism, fluid intake will be adequate.

If the thirst mechanism is not intact, maintenance fluids should be administered, with additional fluids to replace urinary losses.

The therapeutic team should be aware of the patient's condition in this scenario.





Children with thyroid disease, even if poorly controlled, are not at increased risk of COVID-19 and no extra measures are needed than those that apply to the general population

. However, patients with poorly controlled thyroid disease (e. g., thyrotoxicosis) may be at higher risk of complications from an infection

Medications used for the treatment of thyroid disease, including thyroxine, carbimazole, methimazole, and propylthiouracil do not affect the immune function and do not pose the patients at a heightened risk for COVID-

Recommendations from the **British Thyroid Association** about adults with thyroid eye disease who are on high-dose steroid or mycophenolate or rituximab and are considered as immunocompromised and susceptible to infections, include following the confinement and health protection measures very strictly
Depending on the severity of the eye problem, high-dose steroids or immunosuppressives might need to be suspended .



No different recommendations exist for the pediatric population for patients who had radioiodine therapy or thyroid surgery for benign thyroid disease, no evidence is available to suggest that these patients are at increased risk of a viral infection

With regard to the treatment when COVID-19 is confirmed in an adult or a pediatric patient, the normal dose of thyroxine should be continued.

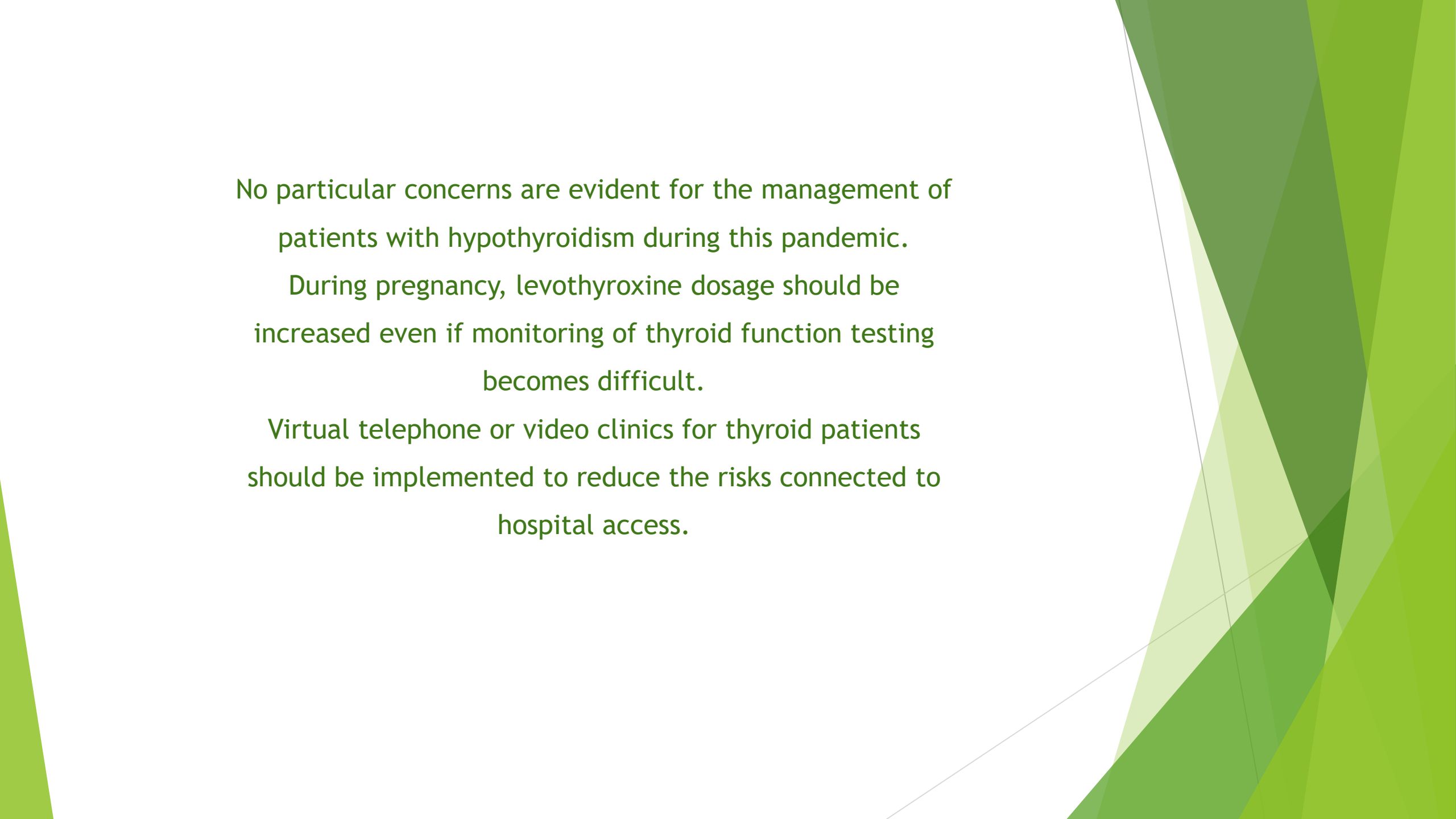
If gastrointestinal disturbances are severe, the dose may need to be repeated when feasible

In the case of symptoms that may be related to COVID-19, patients with hyperthyroidism who are on anti-thyroid drugs should immediately suspend the medication and be tested for possible agranulocytosis by performing a full blood count, as the symptoms of agranulocytosis (sore throat, mouth ulceration, fever, flu-like illness) may overlap with those from COVID-19



Thyroid dysfunction and COVID-19: key messages.

- ❑ Uncontrolled thyrotoxicosis may be associated with more severe complications from COVID-19.
- ❑ Symptoms of infection from COVID-19 are indistinguishable from those of antithyroid drug-induced neutropenia.
- ❑ Block-and-replace regimens are preferred for newlydiagnosed hyperthyroidism in adults and children.
- ❑ Conjunctival involvement of COVID-19 may make diagnosis of thyroid eye disease difficult and may present a particular risk of infection.
- ❑ Progression of thyroid eye disease should be prevented and advice to stop smoking and/or selenium supplementation should be reinforced.

The background of the slide features abstract, overlapping green geometric shapes, primarily triangles and polygons, in various shades of green, creating a modern and dynamic visual effect.

No particular concerns are evident for the management of patients with hypothyroidism during this pandemic.

During pregnancy, levothyroxine dosage should be increased even if monitoring of thyroid function testing becomes difficult.

Virtual telephone or video clinics for thyroid patients should be implemented to reduce the risks connected to hospital access.

Hypoglycemia

Receiving the proper medications and regular glucose monitoring should be ensured in children who are prone to have hypoglycemia during illness, especially those with ketotic hypoglycemia or hyperinsulinemic hypoglycemia.

These children are not considered vulnerable, with the exception of a minority that receive Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor with immunosuppressive action. For the latter, strict hygiene and confinement measures should be taken during the COVID-19 pandemic.

Adequate hydration (small volumes of fluid at frequent intervals) is also highly recommended



side effects of the medications used to treat hyperinsulinemic hypoglycemia

During this pandemic, children should follow the “sick-day rules” for hypoglycemia, which include

- close monitoring of glucose levels
- adequate hydration
- ensuring availability of medications and emergency regime
- contacting the medical



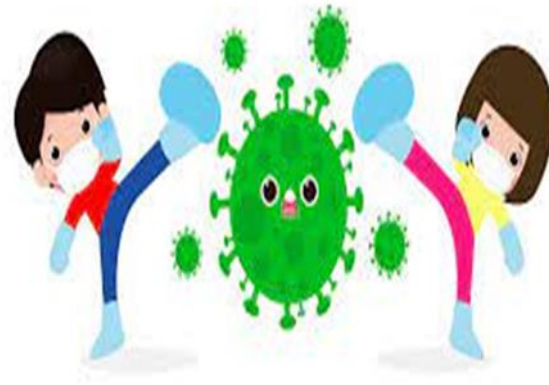
Cushing Syndrome

Cushing syndrome represents an immunocompromised state
increase susceptibility to infections, hence COVID-19 also .

Susceptibility to opportunistic infections

Glucocorticoids have a potent anti-inflammatory and immunosuppressive
action,

Hyperglycemia further contributes to immunosuppression.



The higher the concentrations of circulating cortisol, the more severe the infections.

Therefore, adherence to preventive self-protective measures, complying with the regular treatment and seeking medical advice in the case of even minor symptoms, is crucial



Hypoparathyroidism

Children with hypoparathyroidism have no susceptibility to infections

unless hypoparathyroidism exists in the context of 22q11.2

deletion syndrome

If COVID-19 is confirmed and the child is unable to receive oral tablets, parenteral treatment should be initiated with intravenous calcium.

Of note, hypocalcaemia may worsen breathing capacity due to weakening of the chest muscles



Hypocalcemia has become a major biochemical feature of COVID-19 hypocalcemia is highly prevalent ,associated with inflammatory parameters and independently predicted the need for hospitalization .

hypocalcemia may be a distinctive feature of COVID-19 since it is more frequently found in COVID-19 vs. non-COVID-19 patients hospitalized with acute respiratory disease Several studies have confirmed that calcium levels are lower in patients tested positive to SARS-CoV-2 vs. negative patients and hypocalcemia is independently associated with negative outcomes including ICU admission and mortality

From a pathophysiological perspective, calcium plays a key role in the action of different enveloped viruses and hypocalcemia has already been reported in patients with SARS.

Moreover, widespread lack of vitamin D may contribute relevantly to the high frequency with which hypocalcemia

Finally, since hypocalcemia may negatively impact on cardiac and neurologic outcomes calcium evaluation and monitoring in all patients admitted to the hospital with COVID-19 is recommended.



Several authors evidenced an association between COVID-19 prevalence and its severity with latitude and related sunlight exposure .

low vitamin D may negatively influence the outcome of patients admitted to ICU in whom vitamin D supplementation could reduce morbidity and mortality

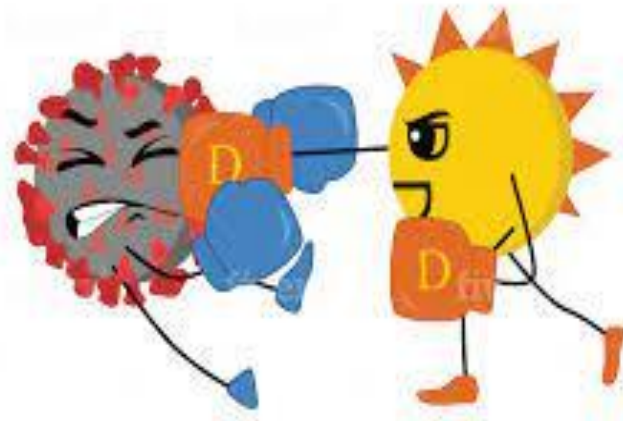
The specific role of vitamin D in COVID-19 may be due to

ACE2 down regulation and its ability to counteract the cytokine storm characteristic in severe COVID-19 cases by
modulating pro-inflammatory cytokines and
regulating T-
cell differentiation into Th2 phenotype



Poor vitamin D status has also been reported in the majority of the studies to predict disease severity including chest CT stage and mortality risk

In a Spanish pilot clinical trial, COVID-19 hospitalized patients with pneumonia were randomly assigned to standard of care combined or not with calcifediol, and this latter significantly reduced the requirement of ICU admission with no deaths .



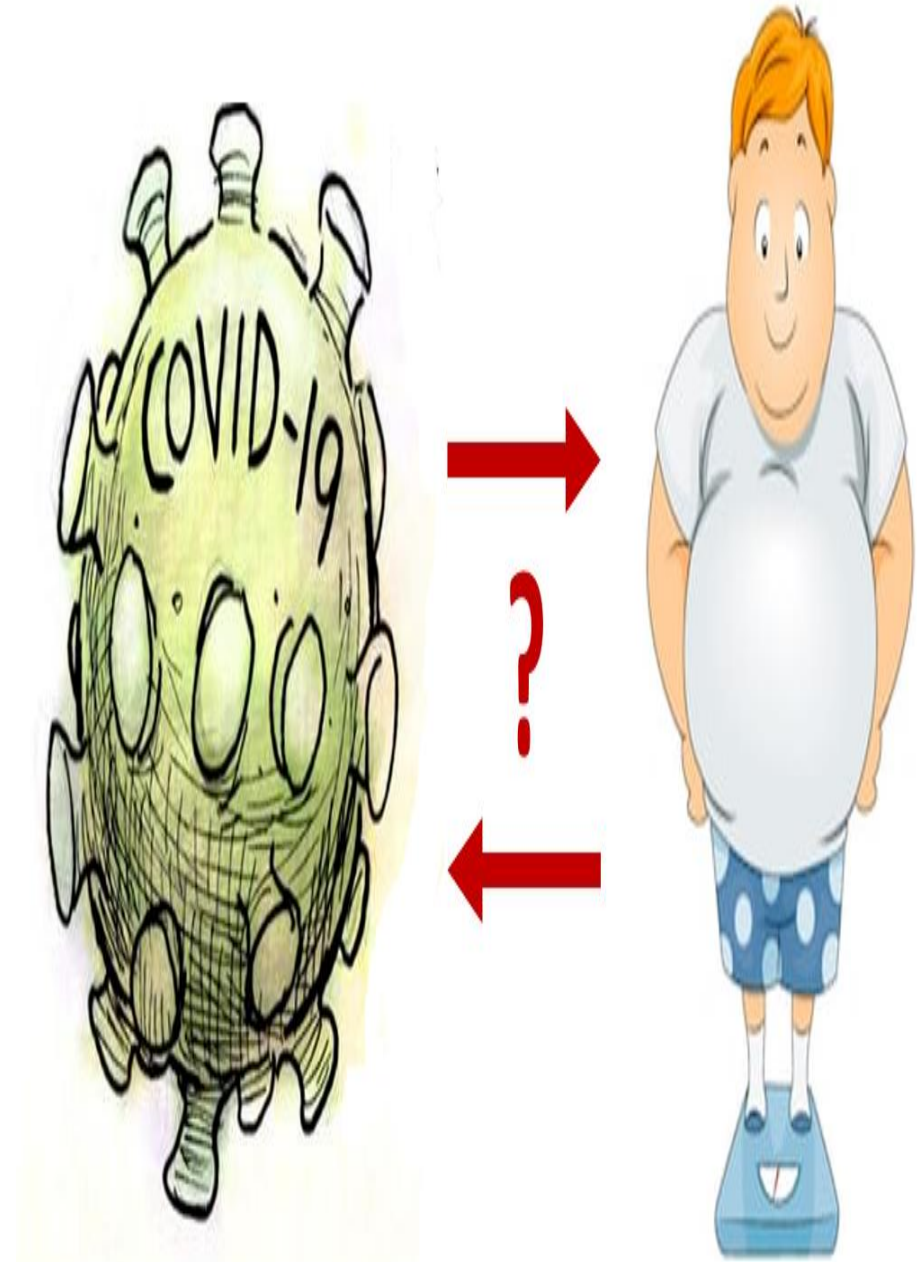
Based on the above, we recommend that granting adequate vitamin D levels in the general population but particularly in high risk (elderly with diabetes and obesity) should be a good clinical practice. Supplementation with vitamin D of elderly co-morbid persons at high risk of coexistent COVID-19 and hypovitaminosis D is suggested



Obesity

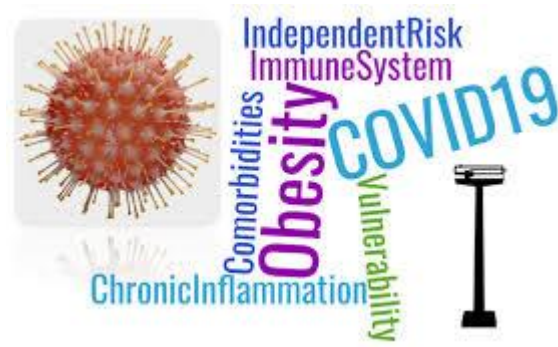
It is well established in the literature that excess weight promotes immune dysregulation and chronic inflammation, which result in the cytokine storm associated with the Acute Respiratory Distress Syndrome seen in influenza and other viral infections.

Limited data is available regarding the impact of COVID-19 in patients with obesity. It has been reported that severe obesity may be a risk factor for respiratory complications during the course of COVID-19.



- ❖ young people suffering from severe obesity may develop destructive alveolitis resulting in respiratory failure and death
- ❖ obesity is associated with sleep apnoea syndrome and surfactant dysfunction

Therefore, it is important that children with obesity, and those with severe obesity in particular, strictly follow self-protective strategies to avoid COVID-19.



For these patients, COVID-19 may have an additional negative impact on obesity itself.

For these reasons, it is estimated that the COVID-19 pandemic may result in exacerbation of childhood obesity.

It is important that these patients continue exercise through home-based exercise programs and that they follow a well-balanced diet

COVID-19 and Psychological Consequences in Children and Adolescents with Endocrine Disorders

It becomes evident that as the COVID-19 pandemic peaks, it is causing widespread concern, fear and stress. This is understandable due to the high morbidity and mortality rates of the disease in adults, the restrictive preventive measures that result in a drastic change of everyday life, affecting work, education, social life, entertainment, and the long period sustained fear of the unknown outcome of this outbreak



The impact of the COVID-19 pandemic to the pediatric population may be worsened by the co-existence of a chronic disease.

It is well established that a chronic illness may impair the immunologic reaction of an individual to infections.

Specifically, chronic stress from a permanent disease may erode immunologic mediators, increase risk of infections and cytokine production and decrease antibodies and defensive mechanisms

On the other hand, children suffering from a chronic disease are already experiencing higher stress and additional pressure compared to healthy children due to the need for compliance to chronic medication and regular doctor visits, but also because of school disruption and fear of death.

Children's stress due to a chronic endocrine disease can be magnified by a pandemic, as children are likely to experience anxiety and fear of death or of their relatives dying and they may also see the supportive family structure previously provided, to fall apart.

Of note, parental anxiety about children exposure to COVID-19, potentially further complicating their chronic endocrine disease, should not be ignored.

This may lead to retaining children out of school, thereby adding to social marginalization of the patients as well as aggravating their feeling of distress and impacting their wellbeing.



Hence, therapeutic teams should be aware of the possible psychological consequences of the current pandemic and monitor psychological responses, even screen for psychological distress using psychometric tools, such as validated questionnaires. This could promote the implementation of stress management strategies and interventions in order to avoid potential future psychological distress that may affect the feeling of wellbeing and adherence to treatment, allowing an optimal control and outcome of the endocrine disease

conclusion

The COVID-19 pandemic represents the greatest global public health

care crisis since the influenza outbreak in 1918. Thus far, the available data on the impact of COVID-19 on patients with endocrine disorders is reassuring for the majority of the cases.

In case of COVID-19 infection “sick day” rules apply.

However, lack of sufficient and reliable data, particularly for the pediatric population, should prompt health care providers to be more vigilant in the assessment of children with endocrine disorders and concerning symptoms, such as fever and dyspnea.



