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# Outpatient management of endocrine conditions during the COVID-19 pandemic

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## Abstract

Still very active COVID-19 pandemic demands continuous adjustment of our regular practices of delivering patient care. The aim of this manuscript is to provide practical suggestions for the management of the most common endocrinological conditions during ongoing COVID-19/SARS-CoV2 pandemic. We have conducted a literature review and present our own experience of treating endocrinology patients during the months of full COVID-19 lockdown and then phased partial reopening. The results of the literature review have demonstrated the utmost importance of excelling in a challenging task of maintaining the best possible control of such endocrinological conditions as diabetes mellitus and adrenal insufficiency, while also maintaining the universal social distancing and isolation. In the patients with diabetes mellitus Hemoglobin $A_{1C}$ level correlates with the risk of unfavorable outcomes of COVID-19 which makes optimization of diabetes mellitus control an even more significant during the pandemic. It is important to provide the patients with the specific instructions on self-titration of insulin and on the use of non-insulin antidiabetic medications, examples of which are shown in the manuscript. For the patients with adrenal insufficiency, it is essential to discuss the rules of dose increase of the glucocorticosteroids in case of development of COVID-19 or any other acute illness. The diagnosis and management of other endocrinological conditions as for example thyroid nodules and osteoporosis (with the exclusion of secondary osteoporosis associated with diseases requiring timely treatment) can be delayed for the sake of everybody's safety and partially also for prioritization of healthcare recourses utilization during these uneasy times. Since the beginning of the pandemic a considerable amount of new information regarding theoretical and practical aspects of connection of SARS-CoV2 and endocrinology is emerging almost weekly. In this manuscript, we have tried to gather the most clinically relevant data on the outpatient management of the patients with endocrine pathology.

**Keywords**: COVID-19, SARS-CoV2, endocrinological conditions, diabetes mellitus, adrenal insufficiency, thyroid gland, osteoporosis.

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**Background**. At present, there are still no reliable signs that the severe acute respiratory syndrome coronavirus 2/coronavirus disease 2019 (SARS-CoV-2/COVID-19) pandemic will be resolved in the foreseeable future. Moreover, historical experience warns of imminent subsequent waves of a pandemic. Quarantine measures aimed at combating the pandemic lead to an overall decrease in the frequency medical care consultations, which threatens the decompensation of chronic diseases. Thus, it becomes relevant to address the issue of maintaining high-quality medical care for patients with endocrinological disorders in the context of the ongoing pandemic and related isolation.

**Aim**. This review aimed to discuss important aspects of the outpatient management of patients with most common endocrine disorders during the COVID-19 pandemic. PubMed and Google Scholar databases were searched for scientific articles, including papers published before February 1, 2021. Search keywords were COVID-19, SARS-CoV-2, diabetes mellitus (DM) and separately all groups of antidiabetic drugs covered in this review, hypothyroidism, thyroid gland (thyroid) nodes, thyroid cancer, ultrasound examination of the neck, aspiration biopsy, adrenal insufficiency, vitamin D, and osteoporosis. Studies eligible for inclusion were selected by reviewing abstracts (97 studies). Then, full texts of articles selected at the abstract stage were evaluated, including studies that discussed direct outpatient treatment of endocrine pathologies during

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the COVID-19 pandemic. Finally, 49 studies on this topic were included in this review.

We also presented our experience of outpatient treatment during complete isolation of patients with endocrinological disorders while transitioning to telemedicine and subsequent staged resumption of outpatient visits. Clinical data were obtained from an outpatient clinic of an academic medical institution, which is a consultative center that provides services to patients living within more than 250-km radius. The patients had the following endocrinological nosologies: DM, thyroid pathologies (including thyroid cancer), osteoporosis, osteopenia, parathyroid gland pathology, adrenal diseases, hypercortisolism, and pituitary tumors. This study focused on the most relevant endocrine diseases, which are mostly presented to an endocrinologist and, in some cases, to a general practitioner.

*Outpatient treatment of DM.* Patients with DM have the highest risk for overall morbidity and adverse outcomes of COVID-19 [1, 2]. In a population-based cohort study by Holman et al., risk factors for an unfavorable outcome of COVID-19 in patients with type 1 and 2 DM are male sex, old age, overweight or underweight status, chronic renal failure, non-European race, low socioeconomic status, postponed stroke, and heart failure [3]. An independent risk factor is glycemic control: in patients with type 2 DM, the likelihood of an unfavorable outcome of COVID-19 increases by 22% at a glycated hemoglobin (HbA1C) level of 7.6%–8.9% and by 36% at an HbA1C level of 9.0%–9.9%, in comparison with HbA1C of 6.5%–7.0% [3].

In addition, the HbA1C level in nondiabetic values (<6.5%) is also a risk factor for an unfavorable outcome of SARS-CoV-2 in patients with type 2 DM. While data on the effect of SARS-CoV-2 on mortality in patients with type 1 DM is being investigated, recent studies have shown that in patients with type 2 DM with an increase in HbA1C content, mortality increases more sharply among those aged <70 years than among those aged >70 years. The same relationship is true for body mass index and mortality [3]. This may be due to the significantly larger number of comorbidities that influenced mortality in patients aged >70 years, independent of glucose and body weight control. The authors of this study also showed that body mass index and HbA1C level have a U-shaped relationship with mortality risk, when values below and above average are associated with an increased risk of mortality from COVID-19.

As regards blood pressure, Holman et al. reported that systolic pressure of 140 mmHg was associated with a decrease in mortality from COVID-19 in patients with type 2 DM, but not in patients with type 1 DM, while taking antihypertensive drugs was associated with an increased risk of mortality. The authors of the study found it difficult to explain this observation. Perhaps, the finding that only patients with blood pressure >140 mmHg and <140 mm Hg were identified does not allow us to assess whether this protective effect persists at extremely high systolic pressure and does not make it possible to determine the role of an increase in diastolic pressure.

Interestingly, smoking was associated with a lower risk of death from COVID-19 in patients with type 2 DM, but not in patients with type 1 DM. However, mortality from other causes was higher in smokers with type 1 and type 2 DM. Moreover, mortality from COVID-19 was higher in patients with both forms of DM and a history of smoking. At present, this controversial observation of the protective effect of smoking on mortality from COVID-19 in patients with type 2 DM can be explained by factors that complicate the interpretation, such as less frequent testing for SARS-CoV-2 in patients with smoking history, especially since this study was carried out in the early stages of the pandemic, when the prevalence of testing in general was still quite low. A more recent population-based study on this topic refuted this observation and showed that smoking is associated with a greater risk of mortality from COVID-19 in patients with DM [4].

Many attempts have been made to determine the relationship between SD and SARS-CoV-2 at the molecular level [5–8]. Angiotensin-converting enzyme 2, which plays an important role in key endocrinological process of blood pressure regulation and protection against inflammation, is also a receptor for the SARS-CoV-2 viral particle. During an infection, the virus decreases the activity of angiotensin-converting enzyme 2, thus inducing inflammation, death of respiratory epithelial cells, and respiratory failure. By contrast, DM, through chronic hyperglycemia, reduces the expression of angiotensin-converting enzyme 2, but through acute hyperglycemia, it can increase its expression, thus facilitating the penetration of SARS-CoV-2 into cells [5]. Some studies have also suggested that dipeptidyl peptidase-4 is involved in the process of penetration of SARS-CoV-2 into cells, and inhibitors of this enzyme may slow down this process [5, 7, 8]. At the moment, these theories still lack clinical confirmation.

The COVID-19 pandemic and its associated isolation also carry multiple factors that predispose patients with DM to impairment of glycemic control. These include an overall decrease in physical activity and an increase in calorie intake [9].

**Table 1**. Features of non-insulin antidiabetic drugs of various classes during the COVID-19 pandemic

| Drug class | Representatives | Features of treatment during the COVID-19 pandemic |
|---|---|---|
| Sulfonylurea preparations | Gliclazide, modified release gliclazide, glimepiride, gliquidone, glibenclamide, etc. | The risk of hypoglycemia in an acute infectious process. It is recommended to suspend therapy if an infection is suspected [7, 10] |
| Biguanides | Metformin, prolonged release metformin | The risk of lactic acidosis in cases of dehydration, especially in patients aged >65 years with impaired renal function [10, 11]. It is advisable to suspend therapy if an infection is suspected or if the glomerular filtration rate decreases to 30 ml/min/1.73 $m^2$ [5] |
| Thiazolidinediones | Pioglitazone | Conflicting data at this stage. It is advisable to suspend therapy if an infection is suspected or shortness of breath appears [5, 12] |
| Glucagon-like peptide-1 receptor agonists | Semaglutide, prolonged action exenatide, liraglutide, dulaglutide, etc. | Do not start therapy if it is not possible to see a doctor 6–8 weeks after the start of treatment [13]. Suspend therapy if nausea and vomiting develops, infection is suspected, and do not resume therapy if pancreatic complications develop [5, 7] |
| Dipeptidyl peptidase-4 inhibitors | Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin | Administration during an acute infectious process is safe [10, 14]. Evidence showed possible protective effect on COVID-19 [8, 15, 16]. It is recommended to suspend treatment if pancreatitis is suspected [13] |
| Type 2 sodium glucose cotransporter inhibitors | Dapagliflozin, empagliflozin, canagliflozin, ertugliflozin | Do not start therapy if it is not possible to monitor renal functions 4–6 weeks after the start of treatment. Do not start therapy in patients with a history of frequent urinary infections. Explain in detail to the patient the need to suspend treatment in case of suspected infection, nausea/vomiting, need for hospitalization, and preparation for planned outpatient procedures because of the risk of ketoacidosis [7, 13, 17] |
| Meglitinids | Repaglinide, nateglinide | Unlike sulfonylurea drugs, the risk of hypoglycemia is low due to the short half-life of drugs [18]. Research is underway to identify a possible positive modulating effect on the course of COVID-19 [19, 20] |
| ά-glucosidase inhibitors | Acarbose | Discontinue treatment if an infection is suspected owing to an increased risk of side effects from the gastrointestinal tract [21]. Research is underway to identify a possible positive modulating effect on the course of COVID-19 [22] |

Table 1 presents data on the characteristics of the most commonly used non-insulin antidiabetic drugs in the context of the COVID-19 pandemic.

When insulin is administered, patients should be given detailed instructions for the possible self-titration of insulin. In our practice, in accordance with accepted standards, we recommend that patients with type 2 DM independently increase the dose of basal insulin by 2 U every 3 days if the fasting glucose level is outside the target values (or by 10% every 3 days if the daily dose of basal insulin exceeds 40 U) [23]. Short-acting insulin is also titrated based on the preprandial glucose level. Basal and prandial insulin should not be titrated simultaneously. Since patients with type 1 DM have significantly higher insulin sensitivity, titration should be performed in smaller steps, for example, 1 U every 3 or 4 days.

An important practical aspect of COVID-19 treatment in patients with DM is a significant increase in resistance to antibodies if systemic steroids are prescribed (currently recommended for patients with COVID-19 experiencing a decline in blood oxygenation). In this case, as always with the use of systemic steroids, the need for prandial insulin increases disproportionately; therefore, the dose of insulin should be increased. Often, the normal ratio of prandial/basal insulin shifts from the usual 50%/50% toward an increase in the prandial component, for example, 60%/40% or 70%/20% or higher [24–26].

The COVID-19 pandemic also leads to adjustments in the screening process for the detection of DM in pregnant women. Since pregnant women constitute another high risk group, the emphasis is on reducing their need to visit health care facilities [27]. Instead of the standard 2-h glucose tolerance test, some authors have suggested using an HbA1C level of 5.9% or higher as a surrogate marker of DM in pregnant women. Moreover, some coun-

**Table 2**. Recommendations for modifying the dose of glucocorticoids (GCs) depending on the severity of COVID-19

| State severity | Body temperature | Symptoms | Recommended GC doses |
|---|---|---|---|
| Asymptomatic carriers | Normal | Uncomplicated upper respiratory tract infection, weakness, nasal congestion, no dyspnea or hypoxia | Leave a standard dose of GC |
| Mild infection | ≥37.5°C or cough | | Doubling the standard dose of GC while maintaining the dosing frequency (it is possible to switch to intramuscular GC administration) |
| Potential COVID-19-pneumonia | >38°C (hospitalization is required) | Lower respiratory tract symptoms: persistent cough, breathing rate >30 per minute, hypoxia, or arterial hypotension | Increase the dose to at least 100 mg/day of hydrocortisone (or equivalent), possibly by intravenous administration |
| Acute respiratory distress syndrome | | All of the above, severe arterial hypotension, and symptoms of acute adrenal insufficiency are possible | Increase the dose to at least 200–300 mg/day of hydrocortisone (or equivalent), possibly by intravenous drop infusion |

Note: adopted from COVID-19 infection and glucocorticoids: update from the Italian Society of Endocrinology Expert Opinion on steroid replacement in adrenal insufficiency [29].

tries have adopted a provision for the diagnosis of DM in pregnant women in the current pregnancy based on the detection of this diagnosis in a previous pregnancy, thus avoiding the need for additional tests.

Recommended methods to reduce in-person visits to the doctor are to increase the frequency of self-monitoring of glucose levels and possible symptoms of critical hyperglycemia with ketoacidosis and to use test strips to determine ketones in urine or capillary whole blood.

At every opportunity, patients can be taught strategies in case of positive results of home tests for ketones in the urine or blood, for example, depending on the general condition, an abundant intake of fluids (if there is no vomiting), light physical activity (walking), and immediate medical attention.

With the ongoing pandemic, patients are advised to start with a telephone call; this will allow a medical professional to identify those who need face-to-face treatment and who can continue treatment at home. The patient can also receive instructions by telephone on the necessary additional dose of insulin to correct hyperglycemia. Patients and medical workers are encouraged to increase the use of telemedicine capabilities and technologies for remote transmission of information, primarily remote monitoring of glucose indicators.

*Outpatient management of patients with adrenal insufficiency.* Patients with adrenal insufficiency are clearly at high risk for both COVID-19 disease and poor outcome. Patients taking supraphysiological immunosuppressive doses of glucocorticoids (GCs) are even at a higher risk. As in the case of DM, patients with adrenal insufficiency (primary, secondary, or iatrogenic) should be given clear instructions for self-regulation of the HA dose if COVID-19 or if other acute illness is suspected [28]. Recommendations of the Italian Society of Endocrinologists are given in Table 2 [29].

*Outpatient management of patients with thyroid disease.* Patients with various diseases of the thyroid gland constitute a significant portion of all patients with endocrinological disorders, and the COVID-19 pandemic will undoubtedly make adjustments on their management.

Since the beginning of the pandemic, small clinical studies have demonstrated various transient dysfunctions of the previously intact thyroid gland in patients with coronavirus infection, which is essentially a manifestation of non-thyroid diseases. Studies have suggested that pneumonia directly caused by SARS-CoV-2 predisposes patients to a more severe thyroid dysfunction than pneumonia, which is identical in severity, caused by other pathogens [30, 31]. Cases of thyroiditis associated with COVID-19 have also been described, which can develop within a few months after the infection resolves. In most cases reported, GC was used for treatment; however, non-steroidal anti-inflammatory drugs are also a possible treatment option [32,33].

With regard to existing thyroid diseases, the frequency of visits to the doctor during a pandemic should be reduced to monitor patients over time. In the treatment of hypothyroidism with a stable dose of levothyroxine in an unfavorable epidemiological setting, current treatment can be continued without frequent monitoring of thyroid-stimulating hormone. If active titration of levothyroxine dose is necessary, it is sufficient to determine the level of thyroid-stimulating hormone every 6–8 weeks and prescribe recommendations without a personal visit to the doctor.

*Outpatient treatment of patients with osteoporosis.* In patients with existing osteoporosis, drug

therapy can be started without waiting for the normalization of the epidemiological situation [37]. Densitometry, one of the components of monitoring existing osteoporosis, can be avoided during a pandemic, especially if there are no urgent indications and changes in the treatment plan.

Oral bisphosphonates (BP) (such as alendronic acid, risedronic acid, ibandronic acid) are the most commonly used drug group. They can be prescribed remotely, without the need for face-to-face admission and subject to the presence of baseline biochemical blood parameters, indicating normal kidney function and optimal levels of vitamin D and calcium. Similarly, when prescribing or continuing the intravenous administration of BP (zoledronic acid), biochemical blood test should be carried out first to determine the levels of total calcium and vitamin D and the glomerular filtration rate.

Optimally, before injections, each patient should take calcium and vitamin D supplements (e.g., calcium carbonate 500 mg 1–2 times a day and colecalciferol 2000 IU/day). In addition, before starting treatment with BP drugs to reduce the risk of developing avascular necrosis of the jaw, a rare but extremely unfavorable complication, patients are ensured to not have had remarkable medical history within the preceding 3–6 months or should not undergo dental procedures such as extraction of teeth or prosthetics [38].

During a pandemic, along with other side effects, patients should be advised about the following concerns. Up to 30% of people starting BP treatment may experience short-term flu-like symptoms and myalgias. This occurs most often with the intake of zoledronic acid, especially without prior treatment with oral BP. During the COVID-19 pandemic, warning patients about the development of such symptoms is relevant, since such symptoms can cause false stress and suspicion of COVID-19 and thus require medical consultation. It is also important to warn patients about possible occurrence of severe dizziness within a few days of zoledronic acid infusion, which is associated with falls and injury; especially, under social distancing conditions, when many elderly people, which is the main cohort of patients with osteoporosis, are isolated from their younger members, families should be able to help them [39].

Moreover, receptor activator of nuclear factor kappa-B ligand inhibitors are also commonly used, with the only representative being denosumab, which is administered subcutaneously every 6 months in medical institutions. This requires repeated biochemical blood test before each use. Recommendations for dental checkups are identical to those for BP, because denosumab also increases the risk of osteonecrosis of the jaws.

Moreover, patients should be advised about the increased risk of spine fractures if subsequent injection of denosumab is delayed by more than 2–3 months from the last injection — so-called paradoxical withdrawal effect. Thus, initiation of denosumab treatment during a pandemic is not recommended; other drugs that do not require visit to the doctor for continuous treatment are recommended. If denosumab treatment has already started and continuing on-site visits to the doctor is impossible, recommendations are to shift to oral BP or to inject denosumab at home. In the USA and some European countries, mobile stations and "drive-through" points are also used — patients drive up to a mobile clinic in a personal vehicle and receive an injection without leaving it, thus minimizing contact between medical workers and patients [37].

Contraindications for conversion to BP include chronic renal failure, severe gastroesophageal reflux disease, Berrett's esophagus, esophageal achalasia, and/or gastric and duodenal ulcer. Since denosumab is often chosen because patients have such conditions, only a few patients can shift to BP. In foreign countries, patients with gastrointestinal tract diseases experience "off-label"[1] monthly use of ibandronic acid or weekly/monthly intake of risedronic acid, and patients with a glomerular filtration rate <30–35 ml/min/1.73 $m^2$ reduced the dose of alendronic acid to 35 mg/week or received a full dose of 70 mg once every 2 weeks.

An open question is when is the optimal starting time of taking BP after the injection of denosumab. In our opinion, if it is impossible to continue denosumab administration, BP use can be started without waiting 6 months after the injection.

With regard to monitoring calcium levels and renal function in patients treated with zoledronic acid or denosumab in a particularly unfavorable epidemiological setting, the following can be observed: If the levels of calcium and vitamin D and glomerular filtration rate indicators have been stable over the past year, and if patients are also taking the recommended calcium and vitamin D supplements, a biochemical blood test before the administration of zoledronic acid or denosumab may not be performed. This decision is made by the attending physician on an individual basis.

Another important caveat concerns estrogens and selective estrogen receptor modulator raloxi-

[1] Off-label is defined as the use of a medicinal product not according to instructions approved by government agencies that control the use of medicinal products.

fene, which is used to treat postmenopausal osteoporosis in women. These drugs increase the risk of thromboembolic complications, and COVID-19 also leads to a significant risk of such complications; therefore, if COVID-19 is suspected, these drugs should be stopped immediately.

Other drugs for the treatment of osteoporosis are teriparatide and abaloparatide, which are synthetic analogs of parathyroid hormone, and romososumab, a sclerostin inhibitor. They are rarely used in Russia. Note that the termination of admission also leads to a rapid loss of positive results. Thus, therapy should not be started if there is a risk of disrupting access to these drugs.

Recently, numerous studies have focused on the relationship between vitamin D deficiency and SARS-CoV-2 infection [40–43]. Previous studies have revealed the effect of vitamin D intake on the occurrence of acute respiratory diseases, especially when the baseline vitamin D level is below 25 nmol/L [41]. Researchers have argued that the pandemic initially occurred during the winter months, when vitamin D levels are usually at their lowest. Several countries have issued guidance on essential vitamin replacement for the entire population during the summer and fall months as long as the pandemic continues. Pathophysiologically, several possible mechanisms for the involvement of vitamin D in the infection process of COVID-19 are being considered.

Vitamin D supports the synthesis of antibacterial proteins by the respiratory epithelium, thus increasing resistance to COVID-19, and vitamin D plays a role in the regulation of nonspecific and acquired immunity. Moreover, this vitamin helps in modulating the development of a cytokine storm. Despite the existing large amount of data and the absence of results from prospective randomized placebo-controlled trials, experts in this field suggest that the clinical relationship of vitamin D and COVID-19 is only hypothetical [40, 44].

**Conclusions**. The current global health crisis associated with an unprecedented pandemic that has led to more than a million death and has affected nearly 40 times more people requires the global medical community to rethink many of the usual approaches. The positive aspect of the pandemic is considered a powerful impetus for the development of telemedicine in many countries. At present, there are speculations about the lessons learned from life during a pandemic; even after its resolution, this pandemic will lead to a stable transition to medicine given the prevalence of teleinformation technologies and minimization of patient's physical contact with the doctor among all medical specialties [45–48].

Despite the need to limit patient–physician contact, analysis of mortality data among patients with COVID-19 requires further improvement in the quality of outpatient care and monitoring of patients with endocrinological disorders [49]. With these difficult conditions, the primary responsibility is assigned to the doctor — as they should clearly and easily explain and discuss in detail instructions for taking medications and all possible side effects and provide recommendations on changing the dose of some drugs in the event of an acute illness.

An even more difficult task of the doctor is to determine the risk/benefit ratio in deciding whether to call patients for a personal visit, instead of monitoring laboratory parameters and making a phone call (a practice now often used in European countries and USA).

Under limited availability of medical care, patients should be more involved in their own health issues, to remember possible side effects of drugs they are taking, to avoid factors that can decompensate chronic conditions, to monitor (if possible) indicators such as whole blood glucose and blood pressure more often, and most importantly, to make a decision on a personal request for medical help in a timely manner, despite the recommended self-isolation.

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