



Selected thyreology problems during the COVID-19 pandemic. Hypothyroidism and hyperthyroidism — did anything change?

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Abstract

On March 11, 2020, the World Health Organisation (WHO) observed the scale of epidemic risk and declared the state of the COVID-19 pandemic. Most countries, including Poland, implemented national and local emergency management plans to deal with the imminent threat of SARS-CoV-2 infection, one of the most serious in this century, according to many experts. In the era of pandemic, during which an epidemiological regime and social distancing are constantly recommended, and routine medical care and planned surgical procedures have been postponed or significantly reduced, patients and their physicians have to struggle on a daily basis with difficult access to diagnostic and therapeutic procedures. This is a great challenge for both groups. The aim of this study is to assess the current state of knowledge about thyreological diseases during the COVID-19 pandemic and to provide indications for the introduced therapeutic changes on the basis of recent scientific literature published up to December 2020 and searches of the PubMed, Google Scholar, EMBASE, and Web of Science databases, which searched for keywords related to SARS-CoV-2 and its influence on thyreology problems. The main focus was on diagnostic and therapeutic differences in the era of the COVID-19 pandemic, bearing in mind the most common endocrinopathies, i.e. hypothyroidism and hyperthyroidism, as well as advantages and disadvantages and possibilities of using telemedicine in the common practice of a specialist physician. (*Endokrynol Pol* 2021; 72 (2): 171–178)

Key words: COVID-19 pandemic; COVID-19; SARS-CoV-2; TSH; hypothyroidism; hyperthyroidism; orbitopathy; levothyroxine; antithyroid therapy; ATD

Introduction

On March 11, 2020, the World Health Organisation (WHO) observed the scale of epidemic risk, which at that time comprised more than 118,000 cases in 114 countries, including 4291 fatalities, and declared the state of the COVID-19 pandemic [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, which had a huge impact on China and the world. The disease caused by SARS-CoV-2 was named as coronavirus disease 2019 (COVID-19) [2].

Most countries, including Poland, implemented national and local emergency management plans to deal with the imminent threat of SARS-CoV-2 infection, one of the most serious in this century, according to many experts. From March 4, 2020, when the first coronavirus case was registered in Poland, until mid-December this year, more than 1,300,000 confirmed SARS-CoV-2 infec-

tions were reported, including more than 28 thousand fatalities [3, 4]. In the era of the pandemic, during which an epidemiological regime and social distancing are constantly recommended, and the routine medical care and planned surgical procedures have been postponed or significantly reduced, patients and their physicians have to struggle on a daily basis with difficult access to diagnostic and therapeutic procedures. This is a great challenge for both groups [5, 6].

The aim of this study is to assess the current state of knowledge about thyreological diseases during the COVID-19 pandemic and to provide indications for the introduced therapeutic changes.

How to treat hypothyroidism effectively

Hypothyroidism is one of the most common endocrinopathies. All these symptoms adversely affect the course of infection with the SARS-CoV-2 virus. The



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subclinical form represents between 3% and 15% of all diseases in the world, while explicit hypothyroidism occurs in 0.3–0.8% of the population [7–9]. It is characterised by a deficiency of peripheral thyroid hormones: thyroxine (FT4) and triiodothyronine (FT3), and although it generally seems quite easy to diagnose and treat, it can even be fatal in severe cases if the appropriate therapy is not implemented. Clinical symptoms vary individually, depending on age, gender, or cause. Most adults show signs of reduced metabolism, such as generalised fatigue, progressive drowsiness, cold intolerance, weight gain, gastrointestinal disorders, as well as reduced tone of voice or memory and concentration disorders. Dry, peeling, thick, and cold skin, hair, eyebrows, and eyelashes loss, and generalised swelling of the eyelids, face, or whole body occur. Moreover, it is possible to observe bradycardia, tachyarrhythmia, or diastolic hypertension. All these symptoms adversely affect the course of infection with the SARS-CoV-2 virus. As a result, among others, the comfort of life is deteriorated, occupational performance is reduced, and the risk of cardiovascular disease is increased. In the case of hypothyroidism, we also observe lipid and carbohydrate disorders [10–15]. The standard method of treatment is hormone replacement therapy with levothyroxine (L-T4), which is carried out chronically, until the end of life, in an endocrinology clinic or general practice [4,9].

Both the American Thyroid Association (ATA) and European societies — the European Thyroid Association (ETA) and the British Thyroid Association (BTA), state in their latest reports that so far no patients with hypothyroidism have been reported to be at greater risk of COVID-19 infection or of a more serious clinical course of the infection, especially if they are pharmacologically balanced. They emphasise that autoimmune thyroid disease does not cause immunosuppression, including that of the p/virus [16–18]. Additionally, BTA states that there is also no evidence of more frequent infections in patients with poorly controlled thyroid disease. Although there are currently no clear reports that the SARS-CoV-2 virus can in any way affect the function of the thyroid gland, in patients with unbalanced, explicit hypothyroidism, in case they become ill, it can be expected that the clinical course of disease may be more complex, and this is due to different systemic relationships. Therefore, it is important that patients do not interrupt L-T4 substitution treatment during the pandemic [17, 18].

The aim of hypothyroidism treatment is to relieve symptoms of the disease, normalise the TSH concentration, and avoid underdosing or overdosing of L-T4. As important as normalisation of the patient's clinical status is biochemical equalisation. Determination of the

thyroid-stimulating hormone (TSH) level is the most sensitive test in hypothyroidism of primary origin, and the sensitivity of measurement is estimated to be above 95%, while specificity is about 90%. The TSH is excreted by pulsation, with low pulse amplitude and long T1/2. However, its daily variations are very small and are not significant in routine diagnostics. It is recommended that the TSH determination is carried out in the morning, preferably after a good night's sleep, but it can be performed also during the day. It is necessary during fasting, because a meal inducing somatostatin secretion may inhibit TSH secretion in this mechanism [19–21]. On the other hand, the change of the TSH level after taking L-T4 dose (half-life = 7–8 days) occurs with some delay; thus, it is not important whether the TSH determination will be carried out after the morning drug administration or on a completely empty stomach [14, 19]. However, it is important for the determination of FT4, and therefore in this case it is recommended that the test be performed before taking the morning L-T4 dose. In fact, the reference values of TSH levels, for the whole population, range from 0.25–0.4 mIU/L to 4.2–4.9 mIU/L, depending on the laboratory method used; however, the target TSH levels should vary depending on the age and clinical status of the patient, as shown in Table 1. Therefore, individualisation of the treatment target for hypothyroidism is an important part of the therapy in the present day. Moreover, medicinal products containing L-T4 are characterised by a narrow therapeutic range. For this reason, in choosing an appropriate dose of L-T4, a personalised approach

Table 1. Target thyroid-stimulating hormone (TSH) concentration depending on the age and clinical status of the patient according to Biondi et al. [19]

Age [years]/Clinical status	Serum TSH concentration [mIU/L]
Planned pregnancy	Lower norm range < 1.2
Pregnancy I trimester	< 2.5
Pregnancy II and III trimester	< 2.5 or < 3.0
Children with congenital hypothyroidism	< 5.0, optimally 0.5–2.0 with FT4 concentration in the upper normal range at 1 year of age
Young adults	1.0–2.5
Middle age	1.0–3.0
≤ 65	> 4.5
60–70	> 6.0
70–80	> 7.0–8.0
Central hypothyroidism	FT4 in the upper half of the norm
Thyroid cancer	According to the principles of thyroid cancer stratification

FT4 — free thyroxine

to each patient should be adopted to avoid under- or overdosing.

For several years in the United States and in some European countries, and recently also in Poland, a new preparation containing a liquid form of L-T4 produced as an oral solution of L-T4 sodium in purified water and glycerol has been available. Many scientific papers published so far have pointed out that the liquid L-T4 was more effective than the previously commonly used pill form of L-T4, especially in patients with absorption disorders as a result of taking other drugs, diseases of the digestive system, or undergoing bariatric surgery. Better pharmacokinetics of liquid L-T4 in patients without malabsorption syndrome have also been confirmed: patients undergoing replacement or suppressive therapy, who changed their tablet to liquid form in an equivalent dose, achieved better hormone control and required less frequent TSH measurements. The drug also proved to be effective and easy to use in patients fed through an enteral probe. Interestingly, liquid L-T4 seems to be equally effective when taken just before or during the first meal of the day. The analysis of usefulness of the drug in particular groups of patients, including newborns, pregnant women, and the elderly, confirmed the high value and safety of L-T4 liquid therapy. However, it should be emphasised that in the population of examined newborns, a higher incidence of TSH suppression was observed with an equivalent dose of liquid L-T4 compared to tablet therapy. Therefore, special attention should be paid to this group of patients in order to avoid an excessive drug dose [22–30].

Also, in view of this group of patients, who, despite an appropriate dose of L-T4 tablet form, did not achieve satisfactory effects of biochemical equalisation, the change to liquid form of the preparation should be considered. It is also important to remember that in spite of proper biochemical equilibrium in about 10% of patients, unfortunately, no satisfactory clinical equilibrium, i.e. improvement in quality of life (QOL), is achieved in the subjective assessment of a patient [14, 31]. So far, despite the fact that the brain is considered a target organ for thyroid hormones, it has not been proven that there is a reference concentration for TSH that would improve the patient's mood or cognitive function. Samuels MH et al. have shown that despite the objective lack of benefit, patients who received higher doses of L-T4, with lower TSH values, reported an improvement in mental function, which is undoubtedly very important in the era of the COVID-19 pandemic, when the sanitary regime and social distancing play key roles in the fight against SARS-CoV-2 infections [32].

However, it should not be forgotten that preparations of dried thyroid, FT3, or complex FT4 with FT3 are also available on the market. Many randomised studies

indicate that therapy with a mixture of synthetic doses of liothyronine (L-T3) and L-T4 in different proportions, although non-physiological, is safe and seems to be effective in controlling the symptoms of hypothyroidism. Patients report faster improvement of mood as well as cessation of depressive disorders. In particular, this is observed in patients with a genetic defect in deiodinase activity. On the other hand, this type of therapy may induce side effects, such as a higher risk of drug overdose and the appearance of symptoms of hyperthyroidism, including cardiac arrhythmias and hypertension. In addition, it is impossible to maintain the most physiologically similar level of free thyroid hormones, thus making it difficult to individualise the dose for each patient, and it may also adversely affect the course of SARS-CoV-2 virus infection [19, 32–35].

A preparation containing FT3 alone in the form of synthetic L-T3 sodium is also available on the market. However, L-T3 has a short half-life and is rapidly absorbed, resulting in large non-physiological variations in its serum concentration. In addition, twice-a-day supply of the drug is required. Although dried thyroid preparations, FT3, or complex FT4 with FT3 are also available on the market, a number of scientific societies, including the ETA, ATA, and the American Association of Clinical Endocrinologists (AACE), do not recommend their use. In the lack of available studies confirming higher efficacy of combined therapy with FT3 and FT4, it seems that the synthetic sodium of levorotatory thyroxine in oral supply, whether in tablet or liquid form, should now be the standard treatment for hypothyroidism, regardless of its cause [32–35].

In light of the epidemiological recommendations during the COVID-19 pandemic, including social distancing, as well as limitations in access to personal visits to specialist clinics and additional examinations, it is recommended that patients with recently diagnosed hypothyroidism, despite the lack of knowledge of the exact diagnosis of this disease, should implement an appropriate L-T4 substitution therapy as part of online telephone advice or videoconferencing [5, 6], bearing in mind that full diagnostics should be supplemented as soon as possible as the availability of laboratory and imaging tests is restored.

It should be emphasised that L-T4 substitution treatment in full due dose should be implemented in pregnant women, newborns, and young adults with a short history of disease, while in elderly patients over 50–60 years of age and those at risk of cardiovascular diseases the therapy should be started with a small dose with a plan to increase it in the following days and weeks of treatment. The most stable absorption of L-T4 in tablet form occurs during fasting from 30–60 minutes before breakfast or at least 3–4 hours after the last meal. Given

the limited access to specialist outpatient clinics, and thus less control over the enforcement of therapeutic recommendations, even in non-cooperative patients, a full weekly substitution dose can be administered once a week [19, 36]. In addition, it is important to note that the e-prescription formula allows for the prescription of a 12-month treatment, although the patient receives the drug in 2 doses every 6 months.

In the times before the outbreak of pandemic, it was recommended to assess the serum TSH levels 6–8 weeks after the inclusion of treatment and every 6–12 months after the equalisation. During pregnancy, monthly TSH monitoring with fT4 was recommended [17, 19]. However, in the current epidemiological situation, if regular monitoring of TSH levels is not possible and the patient taking the previously recommended dose of L-T4 feels well, it is possible to extend the time of TSH control. If, on the other hand, there is a feeling of malaise or a significant change in body weight, TSH determination seems to be necessary. A special group of patients included in the current recommendations are pregnant women. During pregnancy, the dose of L-T4 should be increased, even if monitoring of thyroid function becomes difficult, with the recommendation to follow the principle “Stay at home to protect yourself and your baby” [5, 18].

In the period of difficult access to general practitioners and specialists, as well as laboratory tests, it is not recommended to discontinue the existing therapy. In the absence of a personal visit, a video conference or telephone advice should be preferred. If possible, a long-term therapeutic plan should be scheduled, informing the patient about the possibilities of safe purchase of drugs and the principle of not collecting excessive medical devices during a pandemic [17].

Selected aspects of hyperthyroidism diagnostics and treatment

Hyperthyroidism is a much greater thyreological challenge compared to hypothyroidism. It is estimated that this endocrinopathy occurs in Europe in about 0.8% of the population, while in the United States of America the rate is 1.3%. The number of cases increases with age and more often affects women. It should be emphasised that from the moment of diagnosis, it requires an in-depth examination by an experienced endocrinologist. Both recently diagnosed and already treated, but poorly controlled, hyperthyroidism is a risk of severe SARS-CoV-2 infection. It is also worth highlighting that changes in the cardiovascular system, including cardiac arrhythmias, thrombotic events, and exacerbation of circulatory or coronary insufficiency, which constitute a serious threat to the health and life

of patients, may also increase the risk of severe course of COVID-19 infection. Therefore, a proper diagnosis should be made as soon as possible, and appropriate therapy should be undertaken [37–39].

In the times before the outbreak of the pandemic, when access to a specialist and laboratory tests was much easier, it was not very difficult to make a proper diagnosis of hyperthyroidism. The clinical symptoms vary according to age, gender, incidence of coexisting diseases, and duration of the disease and its cause. In most patients with explicitly defined thyrotoxicosis, elevated concentrations of free thyroid hormones FT3 and/or FT4 and TSH suppression are observed [37, 40, 41].

There is no evidence to date that patients with poorly controlled hyperthyroidism are at greater risk of systemic viral infection. However, it cannot be excluded that these patients have a higher risk of complications, including the development of thyroid crisis, caused by any infection, including SARS-CoV-2 [6]. Therefore, in such a situation, patients with recently diagnosed hyperthyroidism should be quickly diagnosed and covered with appropriate treatment.

The diagnostic and aetiological process will certainly be helpful: medical history (pregnancy, iodine contamination, use of antiarrhythmic medicinal products including amiodarone, exposure to iodine-contrasting agents and genetic burden), physical examination, hormonal tests (TSH, FT4, FT3), immunological determinations: thyrotropin receptor antibodies (TRAbs), thyroid peroxidase antibodies (TPOAbs), thyroglobulin antibodies (TgAbs), human chorionic gonadotropin (hCG), and imaging. On the basis of an individual analysis of each case of hyperthyroidism, the physician should be able to decide on the best way to carry out the medical service in a specialist clinic, taking into account the current possibilities of telemedicine (teleconferencing, videoconferencing), make a personal visit, and even consider referring the patient directly to the hospital for hospitalisation. However, it is important to remember that it may be difficult or impossible to objectify the patient's ailments with a clinical examination during a distance visit. Therefore, any suspicion of thyrotoxicosis based on the clinical symptoms observed by the patient should be confirmed by laboratory tests [5, 42, 43]. However, always, regardless of the availability of tests in every patient in whom we have confirmed or suspected hyperthyroidism, the severity of symptoms should be assessed, as well as the risk of exacerbation of coexisting diseases. In all cases of life- and/or health threatening conditions, the patient should be urgently referred to hospital [5].

Beginning antithyroid therapy (ATD) (methimazoles, MMI) and propylthiouracil (PTU), and its de-

rivative carbimazole, it is necessary to remember that the use of this group of medications requires special attention. Approximately 13% of patients, especially in the first 3 months of treatment, experience side effects, and their frequency depends on the dose of thyrostatic medicine used. The most frequent reports are itchy generalised or localised rash on the torso, joint pain, fever with symptoms suggestive of pharyngitis, and less frequently nausea, abdominal pain, or melaena with accompanying dark urine [44–46]. However, the greatest risk during oral ATD is agranulocytosis, as this is a life-threatening condition and is an urgent indication for hospitalisation, although it is observed in less than 0.5% of patients. Neutropaenia is usually characterised by fever and sore throat, sometimes accompanied by oral ulceration, which in the era of COVID-19 pandemic may suggest a mild form of SARS-CoV-2 infection (fever, dry cough, fatigue, flu-like symptoms). These symptoms may be difficult to distinguish, both for the patients and their physicians; thus, in the case of a justified suspicion of neutropaenia, the patient should be advised to immediately discontinue ATD and perform an urgent peripheral blood morphology. It is worth noting that in COVID-19 infection lymphopaenia and thrombocytopenia are observed, but they are not contraindications for anti-thyroid therapy [5, 6, 17]. The

absolute contraindications are agranulocytosis, toxic liver damage, and vasculitis [44]. Therefore, prior to the inclusion of ATD the blood count should be examined with a smear and the transaminase activity should be determined. If, due to epidemiological reasons and limited access to primary healthcare resources, it is not possible to perform these tests, it is recommended that ATD treatment be discontinued and the patient be observed. If symptoms disappear within a week, treatment may be continued, and if they become more severe during discontinuation or relapse after re-admission, the patient should be advised to contact his/her endocrinologist or primary care physician immediately [5,17].

In the era of the SARS-CoV-2 pandemic, the “Block-Replace Regimen (BRR)” combination therapy scheme may be considered, given the reduced availability of laboratory tests. It allows for less frequent control of thyroid function and prevents enlargement and the occurrence of hypothyroidism phase. However, it is important to remember that it brings a higher risk of side effects. The exact scheme of combination treatment of BRR is shown in Figure 1 [5, 43].

In selected cases where, despite the use of oral ATD therapy or due to its side effects, it has not possible to obtain the disease control, it is recommended to try to

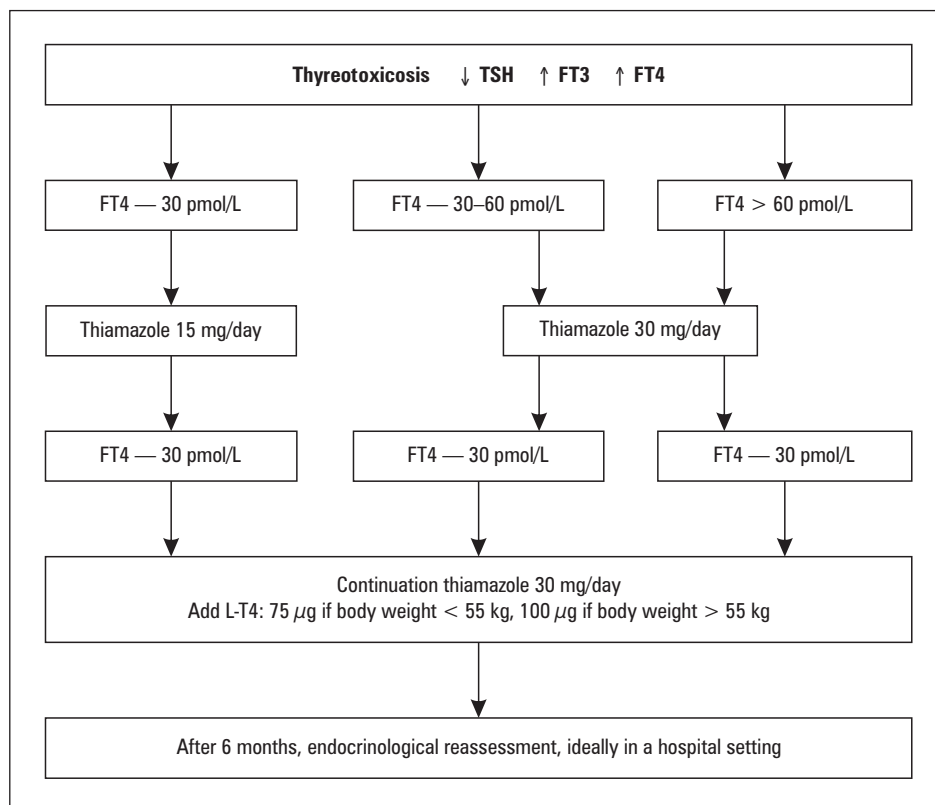


Figure 1. Combination therapy “Block-Replace Regimen (BRR)” in the treatment of hyperthyroidism in adult patients during the COVID-19 pandemic, according to Boelaert et al. [5]

refer the patient to urgent surgery or to use radioactive iodine therapy [46].

Graves' disease is one of the main symptoms of hyperthyroidism, and one of its non-thyroidal complications is a syndrome of ophthalmic symptoms caused by immunological inflammation of muscles, as well as adipose tissue and connective tissue of orbits — so-called thyroid-associated orbitopathy. In anti-inflammatory therapy, weekly intravenous glucocorticosteroids (GKS) are usually used [47]. Unfortunately, due to the immunosuppressive effect of GKS, the patients treated by us are more exposed to SARS-CoV-2 infection, and this also applies to the therapy with modern drugs such as mycophenolate, azathioprine, or antibody-class drugs: rituximab, teprotumumab, and tocilizumab [48]. Therefore, together with the patient, we should try to minimise the risk of infection by adapting to the safety rules recommended by the Ministry of Health, as well as the European Endocrine Society, which advises 12-week isolation for these patients [49]. On the other hand, it is important to remember that immunosuppressive treatment should absolutely not be discontinued. The treating physician, considering the benefits and risks in a specific epidemiological situation, should be able to finally decide on the continuation of treatment. One option, if it is not possible to administer GKS IV, is to replace the therapy with an oral form, for the patient to receive treatment at home. Additionally, in preventing the progression of orbitopathy, it is recommended that smoking be avoided, both actively and passively, and/or to enhance the effects with selenium preparations [50]. In the paper Xia J et al. it was indicated that conjunctivitis may be one of the symptoms of COVID-19 infection, because the presence of SARS-CoV-2 mRNA was detected in tears. Therefore, patients with orbitopathy in whom COVID-19 has been confirmed represent a significant risk of infection, especially when soft tissues of the orbit are also occupied. It is necessary to make these patients aware of the recommended precautions to prevent infection with the SARS-CoV-2 virus. The WHO recommends keeping a safe distance from other people, i.e. social distancing, covering the nose and mouth, as well as washing and disinfecting hands thoroughly and regularly [51].

An equally important group of patients with hyperthyroidism are pregnant women. This particular group of patients should be particularly careful and should, as much as possible, implement all personal protective equipment to protect against SARS-CoV-2 infection [52]. During the COVID-19 pandemic, it is recommended that the therapy of hyperthyroidism in pregnant women should be carried out according

to the current standards of management. In the first trimester of pregnancy (up to 16 weeks), the PTU and then MMI should be treated with the lowest possible dose of ATD [53]. When starting MMI therapy, it is important to remember to inform the patient about possible teratogenic effects of the drug on the foetus [54]. It is important to point out that BRR therapy is contraindicated in pregnant women.

Conclusions

Many international scientific societies, including the International Thyroid Federation, emphasise that there is currently no evidence that patients with thyroid diseases are more likely to be infected with SARS-CoV-2. There is also no evidence that people with poorly controlled thyroid disease are more likely to be infected. However, it is important to remember that the pandemic and resulting epidemiological regime may cause difficult access to basic and specialist health care. In order to prevent the spread of the SARS-CoV-2 virus, it is recommended that the need for personal visits to a specialist physician be minimised, with contacting a telemedicine provider being preferred. Direct visits should be dedicated only to selected groups of patients requiring personal contact with the physician.

Due to the possibility of difficult access to specialised laboratory and imaging tests, it is recommended that patients with recently diagnosed hypothyroidism or hyperthyroidism start treatment as soon as possible, with the possibility of postponing additional tests to establish the full aetiology of the disease. In the case of patients already treated, it is important to emphasise the necessity of continuing the existing treatment. It is recommended that the physician providing treatment be contacted on a regular basis via telecommunication. Physicians, including endocrinology specialists, should educate their patients in the use of virtual advice and various social platforms, and thus limit personal visits during the pandemic.

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