Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

SARS-CoV-2-related atypical thyroiditis

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1,2] has seriously affected northern Italy. Preliminary data analysis of patients with COVID-19 who required high intensity of care at our institution (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy) showed that these individuals commonly had low or suppressed serum thyroid stimulating hormone, with and without elevated free thyroxine concentrations, which suggests thyrotoxicosis. Patients who are critically ill can have alterations of thyroid function tests, known as non-thyroidal illness syndrome.[3,4] Alternatively, thyrotoxicosis could result from SARS-CoV-2 directly infecting the thyroid gland, as described in other viral infections. Infection of the thyroid gland is known as subacute thyroiditis and is characterised by self-limiting thyrotoxicosis of variable duration—lasting a period of weeks or months—followed by hypothyroidism with final restoration of euthyroidism.[5,6]

We aimed to assess the prevalence of thyrotoxicosis, suggestive for subacute thyroiditis, in patients admitted to high intensity of care units (HICUs) in relation to the presence or absence of COVID-19. To this end, we compared patients admitted to HICUs in 2020 because of COVID-19 (HICU-20 group), with those admitted to the same HICUs in 2019, thus SARS-CoV-2 negative (HICU-19 group). Estimating a prevalence of subacute thyroiditis of 0·5% in the HICU-19 group, in line with the general population,[5] and of 10% in the HICU-20 group, a total of 166 patients were needed to obtain a 80% statistical power and a significance of 0·05 (two tails).

Thyroid function was assessed at hospital admittance (within an average of 2 days) in 93 consecutive patients in the HICU-20 group and 101 consecutive patients in the HICU-19 group. 52 patients with COVID-19 who were admitted to low intensity of care units (LICU-20 group) were also studied (appendix p 4). Patients in the HICU-20 group were younger than those in the other two groups (65·3 [SD 12·9] years in the HICU-20 group, 73·0 [15·2] years in the HICU-19 group, and 70·3 [18·1] years in the LICU-20 group; p=0·0019). The HICU-20 group had more men than the other two groups (64 [69%] of 93 in the HICU-20 group, 57 [56%] of 101 in the HICU-19 group, and 25 [48%] of 52 in the LICU-20 group; p=0·038). Thyroid diseases are more common in women, which was reflected in the number of patients with pre-existing thyroid disorders: 23 (23%) of 101 in the HICU-19 group, 11 (21%) of 52 in the LICU-20 group, and 8 (9%) of 93 in the HICU-20 group (p=0·017). These patients were excluded from the thyroid function analysis (appendix p 4). As many as 13 (15%) of 85 patients in the HICU-20 group were thyrotoxic, compared with one (1%) of 78 patients in the HICU-19 group (p=0·002) and one (2%) of 41 patients in the LICU-20 group (p=0·025). Of the 14 patients with COVID-19 and thyrotoxicosis, more were men (nine [64%] men and five [36%] women; p=0·017). Patients in the HICU-20 group had lower serum thyroid stimulating hormone concentrations than did patients in the HICU-19 and LICU-20 groups (p=0·018; figure 1A). Mean serum free thyroxine concentrations were higher in the HICU-20 group than in the LICU-20 group (p=0·016), but not the HICU-19 group (p=0·38; appendix p 4). Stratification for sex and age did not affect the results (data not shown).

Although the dramatic increase in the number of patients requiring hospitalisation because of the COVID-19 pandemic emergency might have meant that patients in the HICU-20 group were admitted in more critical conditions compared with those in the HICU-19 group, the thyroid dysfunction observed in the HICU-20 group is unlikely to be related to non-thyroidal illness syndrome only. There was no significant difference between the free tri-iodothyronine concentrations, the main non-thyroidal illness syndrome indicator, which were low in all groups (p=0·71; appendix p 4). In patients with non-thyroidal illness syndrome, normal or low serum concentrations of thyroid stimulating hormone and low concentrations of tri-iodothyronine are usually associated with low concentrations of thyroxine;[3,4] however, in our cohort of patients

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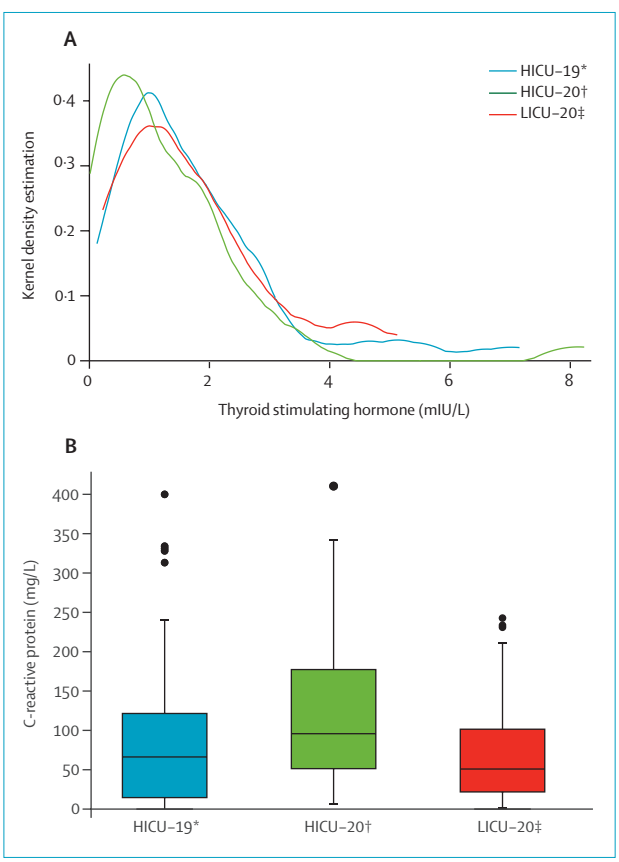

Figure 1: **Distribution of serum thyroid stimulating hormone (A) and box plots of C-reactive protein (B) concentrations in patients admitted to high or low intensity of care units**

Date are expressed as median (IQR). (A) Patients with known thyroid disorders at hospitalisation were not included. Serum thyroid stimulating hormone was 1·43 (0·88–2·37) mIU/L in the HICU-19 group; 1·04 (0·47–1·80) mIU/L in the HICU-20 group; and 1·43 (0·71–2·28) in the LICU-20 group (p=0·018). The HICU-20 group had a lower thyroid stimulating hormone concentration than the HICU-19 group (p=0·009) and the LICU-20 group (p=0·045). (B) C-reactive protein concentrations were 66 (15–121) mg/L in the HICU-19 group; 96 (51–177) mg/L in the HICU-20 group; and 52 22–103 mg/L in the LICU-20 group (p=0·0038). HICU=high intensity of care unit. LICU=low intensity of care unit. *78 patients admitted to HICUs in 2019. †85 patients admitted to HICUs in 2020. ‡41 patients admitted to LICUs in 2020.

with COVID-19, low concentrations of thyroid stimulating hormone and tri-iodothyronine were associated with normal or elevated concentrations of thyroxine. A transient thyroxine increase over a period of hours can occur in acute conditions, usually associated with normal or high serum thyroid stimulating hormone concentrations,[3] but not low concentrations as observed in this study. It is plausible that our patients might have had a combination of thyrotoxicosis and non-thyroidal illness syndrome, described as thyroxine thyrotoxicosis.[4]

To test this hypothesis, eight patients with COVID-19 and any thyroid dysfunction observed at hospital admission were followed-up after a mean of 55 (SD 8) days following discharge when negative for SARS-CoV-2 (appendix p 6). Two (25%) patients were confirmed to have hypothyroidism and had marked diffuse hypoechogenicity and heterogeneity at thyroid ultrasound, characteristic features of autoimmune thyroiditis. The six (75%) patients with low or suppressed thyroid stimulating hormone concentrations or thyrotoxicosis at baseline had normal thyroid function and were negative for thyroid autoantibodies at follow-up; none reported neck pain ever. The six patients had a diffuse mild hypoechoic pattern at thyroid ultrasound. Three patients had focal markedly hypoechoic areas. Such areas corresponded to focal reduced Technetium-99m uptake at single-photon emission CT imaging, and the thyroid gland showed a general low to normal or reduced Technetium-99m uptake, which suggested subacute thyroiditis (appendix p 7). It is plausible that we might have missed some typical imaging features of subacute thyroiditis in the other three patients because of the time elapsed between hospital admission and follow-up and the anti-inflammatory treatments received.

Our work suggests that a substantial proportion of patients with COVID-19, requiring high intensity of care, present with thyrotoxicosis and low serum thyroid stimulating hormone concentrations, possibly as a consequence of subacute thyroiditis induced by SARS-CoV-2, in an underlying setting of non-thyroidal illness syndrome. Patients in the HICU-20 group also had a lower prevalence of both autoimmune and non-autoimmune pre-existing thyroid disorders compared with the HICU-19 group; this suggests that such conditions are not a risk factor for SARS-CoV-2 infection or severity of COVID-19. In patients with COVID-19 requiring high intensity of care and presenting with subacute thyroiditis, serum free thyroxine concentrations were not as elevated and serum thyroid stimulating hormone concentrations not as suppressed, as described in the classic subacute thyroiditis.[6] These patients also did not complain of neck pain (consistent with silent thyroiditis), did not have leucocytosis, but did have lymphopenia, as observed with COVID-19 infection (appendix p 6).[2] These features differ from those described in the first case report of late-onset thyroiditis after mild SARS-CoV-2 infection,[7] and reports of classic subacute thyroiditis, characterised by a pathognomonic infiltration of giant cells (congregates of lymphocytes, histiocytes, and colloid), with swelling of thyroid follicles, stretching of the thyroid capsule, and consequent neck pain.[6] In SARS-CoV-2 related thyroiditis, giant cells might not form because of lymphopenia and thyroid cells might be damaged by apoptosis, as observed with severe acute respiratory syndrome coronavirus (SARS-CoV).[8] The angiotensin-converting enzyme 2 (ACE2) is a host-cell entry receptor for both SARS-CoV and SARS-CoV-2,[1] and it might be partly responsible for a common pathogenic pathway. ACE2 is more highly expressed in thyroid cells than in lung cells, and in women such expression negatively correlates with signatures of immune cell enrichment.[9] This expression profile might explain why in this study the most severe forms of COVID-19 pneumonia[2] and associated thyroid dysfunction were predominantly reported in men in the HICU-20 group, but not women as in the classic viral subacute thyroiditis.[6]

Serum C-reactive protein concentration is a general non-specific marker of inflammation, subacute thyroiditis,[10] and COVID-19 disease severity.[2] Median serum C-reactive protein concentrations were significantly higher in the HICU-20 group compared with the HICU-19 ad LICU-20 groups (p=0·0038; figure 1B; appendix p 4). In patients with COVID-19, median serum C-reactive protein, but not median thyroid stimulating hormone and mean free thyroxine concentrations, were significantly higher in patients that died than in survivors (median 190 mg/L [IQR 94–256] in patients that died *vs* 73 mg/L [33–133] mg/L in patients that survived; p=0·0052; not shown). This difference was not observed in the HICU-19 group (p=0·27). It could be speculated that patients with higher serum C-reactive protein concentrations might have a systemic spread of SARS-CoV-2 that is more likely to affect the thyroid gland.

This is the first comprehensive description of thyroid alterations in hospitalised patients with COVID-19 with initial longitudinal follow-up available; however, this work has limitations. Serum free thyroxine and free tri-iodothyronine concentrations were measured when thyroid stimulating hormone concentrations were less than 0·45 mIU/L and thyroxine concentrations were measured when thyroid stimulating hormone concentrations were more than 3·50 mIU/L (appendix p 2), thyroid imaging was done nearly two months after baseline thyroid stimulating hormone measurement because of prolonged post-discharge persistence of SARS-CoV-2 positivity,

and serum thyroid stimulating hormone analysis was not available in all patients in the LICU-20 group.

In conclusion, we suggest routine assessment of thyroid function in patients with COVID-19 requiring high intensity care, because they frequently present with thyrotoxicosis due to a form of subacute thyroiditis related to SARS-CoV-2. Considering the currently ongoing pandemic emergency, future studies are encouraged to confirm, or counter, these results. Thyroid cytology or histology and longitudinal studies of thyroid (dys)function in these patients would be particularly informative.

We declare no competing interests.

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Bariatric and metabolic surgery during and after the COVID-19 pandemic

In *The Lancet Diabetes & Endocrinology*, Francesco Rubino and colleagues discussed the prioritisation of bariatric and metabolic surgery during and after the COVID-19 pandemic.[1] We congratulate the authors for bringing up this important discussion, since difficulties around future care of obesity and type 2 diabetes might be a major problem within this context.

We would like to point out, however, our disagreement with the algorithm for prioritisation for bariatric and metabolic surgery in patients with type 2 diabetes. Many diabetes characteristics the authors suggest be prioritised are associated with reduced long-term benefits (which we previously discussed in a review[2]), but we would like to focus on one point here: established cardiovascular disease. This suggestion goes against current evidence.

Although many good-quality observational data suggest that cardiovascular disease risk and mortality are reduced after bariatric and metabolic surgery, the number of patients evaluated that already had cardiovascular disease is very small, and even smaller if we consider those with type 2 diabetes.[2] In the large Swedish Obese Subjects study, although similar benefits were suggested, only 1·5% of patients had a history of cardiovascular disease, and only 21 patients with cardiovascular disease were submitted to surgery.[3]

In randomised controlled trials of bariatric and metabolic surgery in diabetes, there are few mentions of patients with established cardiovascular disease, and in some of these studies, such as the large and highly cited STAMPEDE, previous cardiovascular disease was an exclusion criterion, according the details registered on ClinicalTrials.gov (NCT 00432809). Early this year, in a retrospective study of nearly 7000 patients who had bariatric and metabolic surgery for obesity, only 3·6% had a history of cardiovascular disease, and the rates of post-operative complications in those patients were significantly higher than in patients without previous cardiovascular disease.[4] The authors concluded that additional research is necessary to define the benefits of bariatric and metabolic surgery in this population. The exact number of patients with type 2 diabetes and a history of cardiovascular disease who have been submitted to bariatric and metabolic surgery and whose outcomes have been studied is unknown, yet is probably too small to draw any definitive conclusion to put such patients on a priority list.

Moreover, we should bear in mind that, on the contrary, this particular population with type 2 diabetes and a history of cardiovascular disease is the most studied regarding long-term safety and benefits in cardiovascular outcome trials with drugs (with more than 50 000 patients studied), and the known cardiovascular and renal benefits of both SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists are clear.[5]

Therefore, we agree with most of Rubino and colleagues' work[1] and that much effort will have to be made regarding evidenced-based therapies, including bariatric and metabolic surgery for obesity and type 2 diabetes following the COVID-19 pandemic, but it is still unwise and incorrect to