

Position paper

Call for action to address the endocrine and metabolic consequences of COVID-19 for EU health

COVID-19 has inflicted large-scale change and challenges across all sectors and states. For the healthcare sector, the crisis has led to disruptions in diagnoses, delays in surgeries, therapeutic changes, the transition to virtual consultations, and even avoidance of medical consultation in fear of transmission, while staff and resource shortages have been felt around the world. Healthcare professionals have started to adapt to a “brave new world”. It is natural that policy efforts are currently focussed on crisis management and on the research and development of vaccines, treatment and urgent needs. Looking at the European Research Area (ERA) Corona platform, 72% of currently funded research is related to rapid diagnostic testing and responses, 16% is for the treatment and management of the disease, while only 11% is for research dedicated to long-term disease surveillance and diagnostics.

In parallel, we must not neglect the structural factors and underlying conditions that make populations vulnerable and exacerbate the COVID 19 pandemic and other healthcare crises. We must address these factors to help with the medium and longer-term management of the pandemic, and to ward off future ones. Prevention and research around the connection of COVID-19 to underlying health conditions – such as endocrine and metabolic conditions – are of critical importance in addressing this and in increasing the resilience and avoiding overburdening healthcare systems. The new EU4Health programme, proposed by the European Commission in response to the health crisis, shows promise in this area. The programme looks at addressing the long-term challenges facing the EU’s health systems, such as the burden from non-communicable diseases and the growing health burden from environmental pollution. Both these determinants have influenced the severity of COVID-19 and must be addressed to reduce the devastation of future pandemics.

The links between endocrine and metabolic conditions and the different stages of COVID-19

Endocrine-related conditions impact COVID-19 health outcomes. Emerging research¹ based on rapid expert consensus shows the relationship between COVID-19 and several endocrine and metabolic diseases. This paper gives a non-exhaustive overview of the many needs currently and in the years to come.

Prevention of COVID-19

When it comes to preventing the severe outcomes of COVID-19, there is evidence that people suffering from hormone conditions, such as **diabetes, obesity, adrenal insufficiency and Cushing’s syndrome**, face an increased risk of and/or from infection. Widely prevalent endocrine conditions such as obesity and diabetes deserve urgent attention. Studies show that 26% of COVID-19 patients with a symptomatic disease were obese and 15% had diabetes, and these individuals had worse outcomes and poorer survival compared to non-obese and non-diabetic subjects.² According to the Obesity Policy Engagement Network (OPEN-EU)

¹ <https://eje.bioscientifica.com/page/covid19-collection>

² Figures provided in the presentation of Professor Manel Puig Domingo, ESE Talks, 14/05/2020. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes.

initiative, obesity prevalence has tripled since 1980 – and as much as 8.4% of health budgets in developed countries could go towards treating the consequences of obesity and overweight by 2050.³ Around 10% of people in the European Region above the age of 25 are living with diabetes, a disease which kills 3.4 million people annually.

As the scientific community continues to evaluate which populations are most at risk of developing severe disease or dying from COVID-19, recent studies point towards **Vitamin D**, which is a hormone ingested and/or produced after sun-exposure that helps to control the concentration of calcium in the blood and is vital for the development of strong bones. It also plays a critical role in the functioning of the immune system.⁴ It seems that Vitamin D deficiency renders populations more vulnerable to infection and increases potential lung injuries.⁵ It is of high importance to further explore the association of Vitamin D levels with morbidity and mortality caused by COVID-19 ahead of a potential second wave.

Patients with (any form of) adrenal insufficiency could also be at an increased risk if their condition is exacerbated by infections. There is also evidence that pharmacological treatments could impact COVID-19 outcomes. In the case of adrenal insufficiency for example, glucocorticoids are used to replace the hormone **cortisol** and represent the only life-saving drugs in this setting. But glucocorticoids are widely used in the treatment of autoimmune, pulmonary and gastrointestinal disorders, as well as in patients after organ transplantation and with neoplastic diseases. Glucocorticoid overuse suppresses the production of cortisol and when these drugs are withdrawn (e.g., following completion of anti-inflammatory therapy), this could lead to a state of adrenal insufficiency which could be life threatening.

Endocrine Disrupting Chemicals (EDCs) in the environment could also be a contributing factor to underlying endocrine conditions. Recent studies⁶ show that “certain underlying conditions associated with exposures to EDCs are exacerbating the effects of COVID-19 in vulnerable populations”. EDC exposure with adverse impact on the immune system and their associations with obesity, diabetes and some endocrine cancer forms should not be separated or dismissed in this context. At the same time there is evidence that EDCs could contribute to the inflammatory response in patients with co-morbidities and those that are severely ill.

Treatment of COVID-19

Treatment of COVID-19 is considerably more complicated for patients with underlying endocrine-related diseases. Although not yet peer-reviewed and in an early phase, a recent study on hospitalised COVID-19 patients found good response to treatment with Dexamethasone (a **corticosteroid** used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects) proving strong evidence of the role of hormones within the context of COVID-19 that should not be overlooked⁷.

Zhu L. et al, Cell Metab. 2020 Jun 2;31(6):1068-1077.e3. doi: 10.1016/j.cmet.2020.04.021. Epub 2020 May 1. PMID: 32369736

Endocrine and metabolic aspects of the COVID-19 pandemic.

Marazuela M, Giustina A, Puig-Domingo M. Rev Endocr Metab Disord. 2020 Jul 9:1-13. doi: 10.1007/s11154-020-09569-2. Online ahead of print. PMID: 32643004

Obesity, the most common comorbidity in SARS-CoV-2: is leptin the link?

Rebello CJ, Kirwan JP, Greenway FL. Int J Obes (Lond). 2020 Jul 9. doi: 10.1038/s41366-020-0640-5. Online ahead of print. PMID: 32647360

³ <https://obesityopen.org/news/open-eu-press-release/>

⁴ Petre Cristian Ilie, Simina Stefanescu, Lee Smith et al. The role of Vitamin D in the prevention of Coronavirus Disease 2019 infection and mortality, 08 April 2020, PREPRINT (Version 1) available at Research Square [+<https://doi.org/10.21203/rs.3.rs-21211/v1>]

⁵ Lecture given by Dr. Anna Formenti in the context of ESE Talks, 28/05/2020

⁶ Endocrine Disrupting Chemicals and COVID-19 www.healthandenvironment.org/webinars

⁷ Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report, June 2020

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COVID-19 patients with **obesity, diabetes, and other chronic diseases** are more likely to suffer with severe symptoms, enter intensive care units, as well as have an increased risk of death. Specifically, 44% of COVID-19 patients in hospitals had cardiovascular diseases, 39% were obese and 31% had diabetes. A first study in *Diabetologia*, the journal of the European Association for the Study of Diabetes (EASD)⁸ showed that 10% of COVID-19 patients with diabetes die within seven days of hospital admission. Diabetes is present in 1 out of 3 patients that enter intensive healthcare units, require ventilators, or patients that are non-survivors. On the positive side, patients with good control of diabetes had significantly lower mortality rates due to COVID-19^{9,10}

Long-term quality of life following infection

Long-term quality of life following COVID-19 can also be impacted. Beyond the impact felt in all healthcare sectors of postponed and even cancelled or avoided care due to transmission fears, endocrine systems could suffer in the long term from the impact of COVID-19, because the hormone system is the key regulator of maintenance of body weight, energy expenditure and energy (food) intake.

COVID-19 is also associated with anorexia, dysgeusia, dysfunction of gastrointestinal absorption and severe weight loss, mostly from muscle mass. Within one-week COVID-19 patients could lose up to 10% of their weight while 30% of them require nutritional support, and about 10% need parenteral nutrition. From the experience of one hospital in Barcelona¹¹ that saw 1770 patients, 80% required nutritional support with high protein diet supplementation, even though all survivors at discharge had the status of undernutrition. In the same hospital, 15% of in-hospital patients show pancreatitis signs, weight loss during hospital stay, mostly from muscle mass, is followed by a rebound weight gain from adipose tissue.

Another very important point to note is how the COVID-19 pandemic has transformed every aspect of **endocrine/neuroendocrine cancer** care, postponing clinical activity, adopting less intensive and more innovative care regimens, and restraining specific research, aiming to maintaining cancer care with minimal risk to both patients and staff and shifting resources to COVID-19 care. Endocrine and neuroendocrine neoplasms (NENs) are a heterogeneous tumours of challenging diagnosis, clinical management and unique needs that requires a multidisciplinary approach, while each discipline is uniquely affected by the COVID-19 pandemic. Particular challenges include the requirement of specialized expertise at centres of excellence, the reliance on a multidisciplinary approach to ensure optimal care, and the lack of data to guide clinical decision making regarding the advantages/disadvantages of modifications to the standard of care during the pandemic. In the presence of rapidly changing data available on the effect of COVID-19, sharing collective experiences from multiple countries at different stages of the COVID-19 pandemic seems essential.

Rare diseases require additional funding and focus

Links to more prevalent disease groups are likely to be more easily discovered because of availability of data. Rare diseases therefore deserve heightened attention. The European Reference Networks (ERNs) are making a difference, but they could do more. Several of the rare diseases covered by ERN activities are relevant and

⁸ <https://diabetologia-journal.org/2020/05/29/first-study-of-covid-19-patients-with-diabetes-shows-that-10-die-within-seven-days-of-hospital-admission-and-two-thirds-are-men/>

⁹ [Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes.](#)

¹⁰ Figures provided in the presentation of Professor Manel Puig Domingo, ESE Talks, 14/05/2020.

¹¹ Personal communication, Prof Dr M Puig, Germans Trias i Pujol Research Institute (IGTP) Universitat Autònoma de Barcelona

related to the worse outcomes and poorer survival of COVID-19 patients as these rare diseases affect that the hormone system which is the key regulator of maintenance of body weight, energy expenditure and energy (food) intake, as well as response to stress, inflammation. ESE started a collaboration project on Rare Endocrine Diseases and COVID-19 and is collecting data on different subgroups of patients. e-Reporting of rare conditions (e-REC) is a part of the ERN puzzle, but more funding and focus on e-reporting is needed.

Endocrinology and Metabolism must be at the heart of EU policy

EU4Health is a very promising umbrella strategy for the next years. As this paper has outlined, this strategy needs a strong endocrine and metabolic element to achieve its objectives. In order to limit patient suffering and reduce mortality risk, help identify the connection between endocrinology and other viruses, and ensure that endocrinologists are equipped to handle diagnostic and management dilemmas, ESE recommends that the European institutions and EU Member States undertake the below actions without delay, with the aim to improve treatment and long-term health outcomes after the crisis is over by using the valuable experience gained during these challenging times.

- We call for **an urgent increase in research funding for the relationship between COVID-19 and hormones and metabolic factors** and the long-term health consequences of COVID-19 on endocrine and metabolic diseases. We urge the EU4Health programme to include sufficient efforts in this regard and encourage the ERA platform to increase funding for research into long-term solutions. We also encourage the Horizon 2020 and Horizon Europe calls to include funding for this crucial area. Holistic research across the board is needed, in areas including but not limited to translational research, epidemiological research, pharmacological research, as well as the funding of mechanistic research projects and endocrine networks, such as the EU's endo-ERNs.
- There also needs to be a coordinated effort for **global surveillance of cases and outcomes monitoring**. This calls for increased collaboration across the EU, within the WHO as well as with countries that are not members of the WHO. ERNs should receive sufficient funding to take up their share of this role, but ERNs cannot do it alone. EU should strongly promote this concept trying in guaranteeing common health care rights and providing "universal" standard of care.
- We also call for the development of new and effective models of **patient management** in order to improve long-term treatment, via telemedicine, use of digital solutions, and the optimisation of patient follow-up protocols. Endocrinologists are at the intersection of a broad range of diseases and would be well placed to take part in developing these models.
- Finally, **increased collaboration** is required between countries, policymakers, and other stakeholder groups such as patient groups, other societies, and pharmaceutical companies with endocrine/metabolic portfolios and digital solutions. COVID-19 has affected patients across the board, and only with a multi-stakeholder multidisciplinary approach will solutions be holistic enough to meet the challenge.

About ESE

The European Society of Endocrinology is at the centre of Europe's endocrine community. It is our vision to shape the future of endocrinology to improve science, knowledge and health. It is our mission to advance endocrinology. We unite, support and represent our specialty, promoting collaboration and best practice, and enable our community to develop and share the best knowledge in endocrine science and medicine.

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The ESE policy and advocacy task force aims to support EU policy decision making towards different areas where hormones and metabolism play a role – this includes, apart from addressing the impact of COVID-19, the prevention of prevalent diseases like obesity and diabetes, addressing the health inequalities in the care of rare diseases, developing better approaches towards cancer care and addressing the ubiquitous presence of endocrine disrupting chemicals and their consequences.

Chair:

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ANNEX: Current research and gaps + available resources

Research is still in its early stages and there are many gaps. Of notable importance are the interactions between Covid-19 and diabetes/obesity because of their high prevalence in and cost to society. Patient involvement to address all gaps is crucial. Some important research questions include:

Metabolic disease	What is needed to better ‘protect’ obese people from the impact of COVID-19? How does stress affect patients with diabetes and obesity?
	What longer term metabolic consequences can we expect from COVID-19?
	Are there any lung alterations produced by metabolic diseases that may impact COVID-19 outcomes? ¹²
	What is leading to the potentially higher rates of autoimmune thyroid diseases emerging due to Covid-19, and how can treatment be optimised? ¹³
	To what extent are patients using glucocorticoids impacted by COVID-19? ¹⁴
Vitamin D	What are the links between Vitamin D deficiency and COVID-19 morbidity and mortality rates?
Pharmacological research	What are the consequences of the use of certain pharmaceuticals – not just on COVID-19 but on the endocrine system?
Rare diseases	How can we address the needs for rare disease populations, building on the ESE and ENDO-ERN launch initiative to collect data on patients with rare endocrine conditions and COVID-19, including in specific patients with adrenal insufficiency and patients with Cushing’s syndrome?
Endocrine Disrupting Chemicals	What are the interlinkages between EDCs and COVID-19 or other diseases?
Long-term effects on hormones	What are the long-term consequences of having had COVID-19 on hormones and what would be the best treatment(s)?

¹² [The Diabetic Lung: An easy target for SARS-CoV-2?](#) Caruso I, Giorgino F. Diabetes Metab Res Rev. 2020 May 19:e3346. doi:

¹³ <https://www.thyroid.org/covid-19/coronavirus-frequently-asked-questions/>

¹⁴ Meijer OC, Pereira AM. Three Percent Annually on Systemic Glucocorticoids: Facts, Worries and Perspectives. Eur J of Endocrinology, December 2019

Available resources:

ESE has been engaged in developing resources to support clinicians throughout the COVID-19 period:

- ✓ 'COVID-19 and endocrine diseases – a statement from the European Society of Endocrinology' (23 March 2020).
 - ✓ Including the ESE decalogue for endocrinologists in the COVID-19 pandemic
 - ✓ COVID 19 statement from the ESE President
- ✓ ESE webinar series ESE Talks: Endocrine Conditions in the COVID-19 Era (7 May 2020).
- ✓ *European Journal of Endocrinology* (EJE) free review series: 'Endocrinology in the time of COVID-19' (21 April 2020). (already included above)
- ✓ ESE and ENDO-ERN launch initiative to collect data on patients with rare endocrine conditions and COVID-19 (24 April 2020).

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