Issue 55 Winter 2024

Endocrine Views

Opinion and news from the European Society of Endocrinology

ISSN 2752-8529 (online)

Managing endocrine cancer

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Editorial

This issue updates you on many important new ESE initiatives: 'State of Endocrinology 2025' is an ESE project in response to the developing shortfall in healthcare workers across Europe (**page 6**). You will soon be invited to complete a comprehensive survey. Please take part: we want to know the challenges you face.

You can also find out more about ESE's two new, open access journals: *Obesity and Endocrinology* and *Environmental Endocrinology*. Research in both these areas of our field is necessary, to improve patient health and education. The journals are already accepting submissions, and ESE members receive a 50% discount on article publishing charges. We interview Melania Manco, Editor-in-Chief of *Obesity and Endocrinology*, on **page 8**. An interview with Josef Köhrle, the Editor-in-Chief of *Environmental Endocrinology*, will appear in the next issue.

We herald the arrival of 'World Hormone Day' in 2025. This is the next step in the development of the highly successful European Hormone Day. World Hormone Day will take place annually on 24 April, to continue building awareness of hormone health among the public and policymakers. Read more on **page 6**.

We also cover a range of topics related to the management of endocrine cancer, starting with immunotherapy, courtesy of Anna Angelousi and Gregory Kaltsas, on **page 9**, followed by childhood thyroid carcinomas with Sarah Clement and Hanneke van Santen on **page 10**, and an update on phaeochromocytomas and paragangliomas by Ashley Grossman on **page 11**. No less topical is our review of developments in steatotic liver disease, provided by Emir Muzurović and Christos Mantzoros on **page 12**.

Excitingly, 2025 will also see another first for your Society – a Joint Congress with the European Society for Paediatric Endocrinology, to cover the whole life course at a single event for adult and paediatric endocrinologists. This will be a great opportunity to make new connections, exchange information and start collaborations. Find out more on **page 3**, and remember to submit your abstracts before 3 February.

Marek Bolanowski
Editor, *Endocrine Views*

Areas of interest in this issue:

- Adrenal and Cardiovascular Endocrinology
- Diabetes, Obesity, Metabolism and Nutrition
- Education
- Endocrine-related cancer
- Events
- Pituitary and Neuroendocrinology
- Publications
- Thyroid

Connecting Endocrinology Across the Life Course
Joint Congress of ESPE and ESE 2025
Copenhagen, Denmark, 10-13 May 2025

Copenhagen, location of the 2025 Joint Congress

Key deadlines

Abstract submissions:
3 February 2025

Early Bird registration:
27 March 2025

Standard registration:
24 April 2025

www.espe-ese-congress2025.org

Endocrinology across the life course

The **2025 Joint Congress** will see adult and paediatric endocrinologists learn from one another, and spark new collaborations and friendships.

On 10–13 May 2025, ESE will meet together with ESPE (the European Society for Paediatric Endocrinology) in Copenhagen, Denmark. The Congress will provide opportunities to bring members of the two organisations together, in a way that has not happened previously.

Entitled 'Connecting Endocrinology Across the Life Course', the Congress aims to 'join up' our understanding of hormones in children, adolescents and adults, offering opportunities to enhance research and healthcare, especially across the transition from paediatric to adult care.

Anita Hokken-Koelega and Jérôme Bertherat are the Presidents of ESPE and ESE respectively. We took this opportunity to ask them how they felt about the Congress.

Why is holding a Joint Congress so important?

Jérôme: We will have, for the first time ever, a joint meeting between paediatricians and adult endocrinologists. Hormones matter throughout life, from birth to senescence. So it's really great to organise a meeting where we are going to discuss hormones throughout life, from the point of view of both physiology and disease.

Anita: It's not that you are a child with an endocrine disorder, and then there is a gap, and then you are an adult with an endocrine disorder. In many centres, there are still separate paediatric and adult endocrine departments – and actually sometimes people do not know each other. I hope that this joint meeting, with a lot of joint sessions, is the first step to becoming closer, not only for collaborative research, but also for patient care and to set up transitional care. Of course, there will be separate sessions for paediatric and adult endocrinology as well.

What are you particularly looking forward to?

Jérôme: The great thing is that there are some rare diseases that paediatricians know very well, but the adult endocrinologists know less well, and some disorders that are much more frequent in adults than in children; so we are all going to learn from our colleagues. Apart from education, the fact that the two societies are collaborating is also very important for endocrine research and healthcare in general, in terms of policy and advocacy. Both societies are concerned by endocrine disruptors, for instance, which is an area where we can jointly have an impact upon policymakers and society.

Anita: I think we realise that we are much stronger when we combine our efforts. I hope this Joint Congress inspires a lot of paediatric and adult endocrinologists to work more closely together in research and also in healthcare, because having separate departments is not the right way to continue.

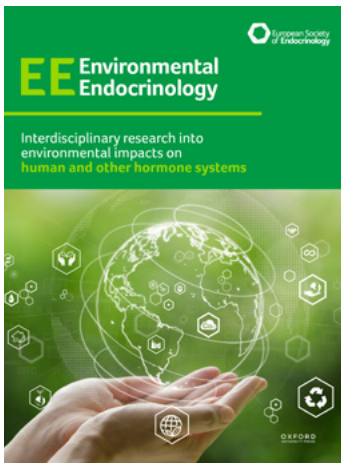
Jérôme: You come to a meeting for the science, for networking and to make new friends. My big hope is that we'll have new friends: adult and paediatric endocrinologists together. That could be one of the best outcomes of this meeting.

New Editor-in-Chief

We welcome Josef Köhrle, Senior Professor of Molecular Endocrinology at Charité-Universitätsmedizin Berlin, Germany, as the Editor-in-Chief of the new ESE journal ***Environmental Endocrinology***.

Environmental Endocrinology welcomes submissions across disciplines, including epidemiology, climate research, toxicological sciences, endocrinology and developmental biology. It is an open access, online journal dedicated to publishing high quality clinical, translational and basic research. and is dedicated to all aspects of environmental impacts on hormone systems in humans and living systems, incorporating the One Health perspective.

Enviro_Endo
environmental-endocrinology



EYES in Helsinki

Helsinki was the venue of the 11th Annual Meeting of the ESE Young Endocrinologists and Scientists (EYES) on 6–8 September 2024. A total of 165 participants from 25 countries enjoyed inspirational speakers and the chance to present their own work and to network.

Marc Philipp Schauer (Germany) won the award for best presentation, with Ana Rita Leite (Portugal) in second place. The **12th EYES Annual Meeting** will take place in Milan, Italy, on 26–28 September 2025.

Attendees at the 11th EYES Meeting

Are you affiliated?

If your organisation is **affiliated with ESE**, then please use this logo (rather than the ESE logo) on your digital and print materials, including your website. It is available for use by ESE National Partner Societies (ECAS) and Patient Advocacy Group Affiliate Members, and comes in a range of formats and colourways. You can request the logo from us at **info@ese-hormones.org**.

Affiliated with European Society of Endocrinology

From the ESE Office

It has been an exciting and busy time for ESE!

We will soon witness a ground-breaking moment in European endocrinology, when ESE and ESPE (the European Society for Paediatric Endocrinology) join forces on 10–13 May 2025 for a Joint Congress in the beautiful city of Copenhagen, Denmark (see **page 3**). This event will bring together the best minds in adult and paediatric endocrinology, offering an unparallelled opportunity to foster dialogue, share insights, and expand the horizons of what each society can achieve, by working together.

With an agenda spanning child and adult endocrine disorders, we aim to make connections that will enable seamless care throughout a patient's lifespan. Both ESE and ESPE are immensely proud to bring this meeting into reality and look forward to strong engagement by all of our members! Don't miss the deadline to **submit your abstracts by 3 February 2025** or the **Early Bird registration deadline of 27 March 2025**. Discounted rates and grants are available for ESE members, so make sure your membership is up to date!

ESE is committed to a collaborative, interdisciplinary approach. To reinforce this, we have launched two new journals that will become key platforms for cutting-edge research. ***Obesity and Endocrinology*** addresses one of the most pressing health challenges of our time, recognising the intricate relationship between obesity and hormonal health. The journal will publish high quality clinical and translational research and reviews on all aspects of obesity, both with regard to the complexity of obesity as an endocrine disease, and considering its biology, diagnostics, treatment and relationship with other endocrine and metabolic diseases.

Our second new journal, ***Environmental Endocrinology***, explores the growing impact of environmental factors on endocrine systems, publishing high quality clinical, translational and basic research on all aspects of environmental impacts on hormone systems in humans and living systems, incorporating the One Health perspective.

Both open access journals are open for submissions, with a 50% discount on the publishing rate for ESE members: we welcome your contributions! You can read more from the inaugural Editors-in-Chief: Melania Manco (*Obesity and Endocrinology*) on **page 8**, and Josef Köhrle (*Environmental Endocrinology*) in the next issue of *Endocrine Views*.

We hope you enjoy these new developments within the endocrine community. I'm always available to discuss any ESE matters at **helen.gregson@ese-hormones.org**.

Helen Gregson
Chief Executive Officer, ESE

Keep up to date with ESE on social media

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BecauseHormonesMatter

Endocrinology: spreading the word

The endocrine community has an accurate view of the major role of hormones in virtually all biological processes, in health and/or life. The medical community at large acknowledges endocrinology's importance, but often perceives it as a very complex, sophisticated domain to invest in. Scientists who work every day on hormones in biological processes in non-endocrine tissue usually do not identify their research as endocrinology. Among the general public, the word hormone is well known, but not the words endocrinology or endocrinologist (both providing an endless source of misspelling or mispronunciation).

This situation limits the use of our knowledge of hormones to optimise health, not only of endocrine patients but also generally across the population. It is also not ideal for stimulating the progress of research in endocrinology.

It is our Society's mission to advance endocrinology and to shape its future. For this reason, we are developing many activities to improve the knowledge of researchers, healthcare professionals, patients and – more broadly – the general public. For the largest audience, European Hormone Day has been a growing success story since it started in 2022. You can read more about its next chapter on **page 6**.

We have identified two endocrine domains that are particularly important for the health of the general population, which warrant education and research; these are obesity and the environment. To advance endocrinology in these areas, this year ESE has launched two new journals, namely *Obesity and Endocrinology* and *Environmental Endocrinology*. They are both open access journals aiming at disseminating and promoting clinical, translational and basic endocrine research in these fields.

Hormones play a major role in the development of many aspects of obesity and its co-morbidities. If those outside our community still need to be convinced, the explosion of medical treatments for obesity that target hormone receptors provides highly visible evidence. We are delighted to welcome Melania Manco from Italy as the first Editor-in-Chief of *Obesity and Endocrinology*. You can read an interview with her on **page 8**.

There is a strong link between health and the environment, and hormones are a key part of the way in which living organisms respond to the major environmental changes that are challenging human health and life in general. Research in this field is a priority, with endocrine-disrupting chemicals being just one example, among many, of an area where endocrine science is needed. We welcome Josef Köhrle from Germany as Editor-in-Chief of *Environmental Endocrinology*.

These journals will be instrumental in advancing and promoting endocrinology in two rapidly evolving, major areas, and we are proud to launch them. Our expectations and ambition are high. Starting a journal is a great endeavour and deserves a lot of energy and support. It is essential to tell you, so that you and all clinicians and scientists working in these fields are aware of this great opportunity to disseminate your impactful results and to advance science. You can count on our efforts to make your research visible to the largest audience.

Jérôme Bertherat
President, ESE

Renew your membership for 2025

There are just **4 easy steps** to renew your ESE membership:

1. Log into your **'My ESE' area**
2. Click **'Renew my ESE membership'** — Renew
3. Check and correct the **pre-filled form**
4. **Submit the form and pay** using your preferred method — €

Thank you for a fantastic year! 2024 was a huge success for our community, and we look forward to a landmark 2025, with the first Joint Congress with ESPE 'Connecting Endocrinology Across the Life Course', two new journals, and plenty more.

Did you know?
You can now set up an annual direct debit for your renewal. This option is available at the payment stage (step 4). **Find out more**.

World Hormone Day 2025

After three successful years of raising awareness around hormones and the importance of good hormone health through European Hormone Day, we're going global!

The first-ever World Hormone Day will take place on **24 April 2025**. Moving forwards, it will be held annually on the same date, making it easier to plan.

The 2025 campaign has two main goals. The first is **to raise public awareness of the importance of good hormone health**, focusing on the small steps we can all take towards this goal. The second is **to improve national political engagement** with the policymakers who can lay the groundwork for better prevention, diagnosis and treatment of endocrine disease.

As before, ESE will provide a public outreach toolkit with materials to support awareness-raising activities, such as infographics and social media graphics on 'Why Hormones Matter' and '10 Recommendations for Good Hormone Health', and a policy toolkit with tips on engaging with political representatives. We'll also be running three workshops in early 2025 to help participants plan their activities. These will cover media and news outreach, social media, and policy and advocacy.

Participants can choose whatever themes and activities are most relevant to their community, uniting behind the #BecauseHormonesMatter message. National and partner societies may also like to identify 'endocrine champions' – public figures with a particular interest in speaking about hormone health.

We hope you'll join us to spread the word! More information and resources will follow at **www.worldhormoneday.org**.

#BecauseHormonesMatter

Have your say: State of Endocrinology 2025

The World Health Organization predicts that, by 2030 (just five years away), there will be a shortfall of four million healthcare workers in Europe, and ten million globally.

This shortfall has been building over the last 20 years due to lack of investment in the healthcare workforce. It became painfully visible during the Covid-19 pandemic. Anecdotally, several countries have indicated that the shortfall is already visible, noting issues associated with identifying sufficient candidates for open positions for specialisation. This also affects endocrinology.

As demand for healthcare increases still further, the solution to the workforce issue needs to be multifactorial. The so-called battle for the 'young and brightest' must be supplemented by better and longer retention of the existing workforce, a better integrated and multidisciplinary workforce, and increased use of new technology.

It is important that, as a discipline, we are informed and equipped. Our President, Jérôme Bertherat, explains that, 'Given this landscape, ESE is launching a Europe-wide "fitness test" to assess how the discipline of endocrinology is equipped for the future. This project – named the "State of Endocrinology 2025" – will consider the clinical aspects of endocrinology, as well as the infrastructures and capabilities needed to address the scientific opportunities and challenges of the future.'

Part of the fitness test will be a comprehensive survey. This will be launched in early 2025 and sent to all ESE members and the members of the National Partner Societies in Europe that are participating in this project. The project is being overseen by the ESE Council of Affiliated Societies (ECAS), with the presidents of the National Partner Societies taking part in the working groups that are preparing the survey and other strands of the project.

Respondents will be asked to provide details of the professional environment they work in, challenges and expectations in the future, and also their satisfaction with present working conditions. Members with departmental responsibility (clinical or research) will be asked to provide information about the department and the challenges faced.

Retiring ECAS Representative Anton Luger said, 'Across the National Partner Societies that make up ECAS, we see a strong interest in, and commitment to, this project. Doing this "fitness test" and collecting data will give us a strong basis to develop recommendations specific to our discipline. It is important that we take our future in our own hands."

Stay tuned to provide your input to this project through the survey, and have your voice heard in building the future of European endocrinology.

Provide your input through the State of Endocrinology survey in early 2025

Watch out for further details

'Given this landscape, ESE is launching a Europe-wide "fitness test" to assess how the discipline of endocrinology is equipped for the future. This project – named the "State of Endocrinology 2025" – will consider the clinical aspects of endocrinology, as well as the infrastructures and capabilities needed to address the scientific opportunities and challenges of the future.'

Jérôme Bertherat *President, ESE*

Meet Charlotte Höybye

Charlotte Höybye is a Senior Consultant at the Department of Endocrinology, Karolinska University Hospital, and Associate Professor at Karolinska Institute, both in Stockholm, Sweden. She chaired the Local Organising Committee for ECE 2024. Charlotte recently became the representative for ECAS, the **ESE Council of Affiliated Societies**. Here, we talk to her about her career and her perspective on endocrinology in Europe.

Charlotte with a photo of her inspirational mentor, Professor Anna-Lena Hulting

Please tell us about your work

I came to the Karolinska University Hospital and Institute in 1994, as part of my training in endocrinology. I am also a specialist in internal medicine. Most of my patients have hypothalamic/pituitary diseases, and my major research interests focus on those. I have also been very interested in adults with Prader–Willi syndrome ever since I worked on my thesis, which was on the endocrine and metabolic aspects of the condition. I participate in the education of medical students and young doctors in training, and I am the main supervisor for three PhD students and co-supervisor for two.

How were you inspired to become an endocrinologist?

When I came to the Department of Endocrinology for my training, I met Professor Anna-Lena Hulting (now emeritus), and she introduced me to the pituitary/hypothalamic field. Anna-Lena is a very nice, engaged person, and I soon became convinced that this was what I wanted to focus on; I have never regretted my choice.

What do you most enjoy about your work?

Most of all, I enjoy meeting my patients. I learn a lot from them, and it is a gift to work with potentially curable and/or treatable diseases and to be able to improve quality of life for most of them. The diagnostic work up, integrating biochemistry, dynamic endocrine testing, radiology and pathology, is also very stimulating.

If not medicine, what might you have done?

I love animals, especially dogs. Throughout my childhood, I wanted to become a vet like my father. The last dog I had was a big mastiff. He was my friend, and the first thing I will do when I retire is to get a dog.

What challenges face people working in endocrinology in Europe?

There are several. Healthcare resources are decreasing and the number of patients with multisymptomatic and complex conditions is increasing. This, combined with too few endocrinologists and an increasing administrative workload, creates a lack of time and stressful working conditions. Another challenge is the development of medical technology and new, advanced treatments at high speed. To manage this, education is crucial for us all, and must be prioritised. Moreover, all clinicians are struggling with the many shortages in drugs and the immense time it takes to find available replacements.

Endocrine researchers face similar challenges. Grant funding is decreasing and so many researchers must undertake other work, such as teaching, clinics and administration, instead of research. In the long run, this will probably affect the quantity and quality of research.

What opportunities should the endocrine community embrace?

There is ongoing, big and rapid development in technology, genetics, pharmacology, laboratory science, pathophysiology and translational endocrinology. This gives us new tools for investigation and treatment, and fantastic opportunities, but we must learn how and when to use them. Continuous education is necessary, including attending conferences such as ECE to learn, discuss, connect and establish collaborations.

> ‘Most of all, I enjoy meeting my patients. I learn a lot from them.’

What attracted you to taking a leading role in ECAS?

I have been on the board of the Swedish Endocrine Society for many years. It gave me a good insight into the issues and challenges facing endocrinologists. Through this position, I also became a member of ECAS, playing a part in its important work. I think endocrinologists in Europe have much in common, and I am attracted by the possibility of leading and uniting our knowledge to improve patient care, and the working conditions of endocrinologists and endocrine researchers.

Why are ECAS and the partner societies important?

They form a network for discussion and collaboration. It is important to identify challenges and issues in the work environment and find areas for further investigation and development. Several projects are ongoing, and I am looking forward to seeing the results.

How would you like the role of ECAS to develop?

The former ECAS lead, Anton Luger, undertook fantastic work on many important projects including, with UEMS (the European Union of Medical Specialists), an updated curriculum. I hope I can continue this positive development, and intensify the collaboration with Endo-ERN and UEMS, so improving the profile of endocrinology and the best care for patients in Europe.

What is your advice for the European endocrine community?

Technology and treatment have developed enormously and not all of us are exposed to patients with the more complex and rare diseases. It is easy to become insecure, but take the opportunity to get help and advice through discussions with your colleagues. It is important to have highly specific knowledge, but it is also important to have a broader perspective. To keep the balance, focus on continuous education and networking.

What else would you like to add?

It is an honour for me to become the representative for ECAS, and I thank all colleagues who voted for me. I also thank Anton Luger for his excellent work in the role and for making it easier for me to take over. I am looking forward to this exciting work.

ECAS
ESE Council of Affiliated Societies

Meet Melania Manco

Melania Manco is Senior Scientist and Consultant Endocrinologist at the Bambino Gesù Children's Hospital in Rome, which is the largest paediatric hospital in Italy and a research institute for paediatrics. Her research focuses on obesity and insulin metabolism in children and young adults.

Melania has just been appointed as Editor-in-Chief of ESE's exciting and topical new journal, *Obesity and Endocrinology*. Here, she tells us about her work in the fields of endocrinology and obesity, and her vision for the future of the journal.

Melania Manco

What inspired your interest in medicine, obesity and hormones?

It was the search for harmony. The human body works perfectly, like solving a puzzle, when all the pieces are placed in the right place and interact with each other, creating a harmonious whole. The endocrine system is clearly proof of harmony.

What do you like most about your job?

I enjoy the possibility of applying research results in the clinic in a continuous and virtuous process for the patients' benefit.

What would you have done if not medicine?

I would have studied architecture.

What excites you about being the first Editor of *Obesity and Endocrinology*?

I am especially excited by the unique opportunity to shape and define the direction of a new, specialised journal at the intersection of endocrinology and obesity research.

This journal has the potential to become a key resource for professionals dedicated to tackling the global obesity epidemic through an endocrine lens.

I am particularly thrilled at the prospect of fostering a platform that highlights innovative research, promotes multidisciplinary approaches, and drives impactful discussions that can lead to better clinical practice and public health policies.

What are the journal's most important aims?

We have a consensus that obesity is an adipose tissue-based chronic disease, with adipose tissue being the largest endocrine organ in the body. The focus of this new journal is on obesity as an endocrine disease, and the journal will speak for endocrinologists who want to share their clinical experience or contribute to research in the field from all over Europe.

Why is this new journal needed at the moment?

We live in a time of profound change in the management of obesity. Let's think about the redefinition of the disease and the new drugs available.

Why should ESE members submit their papers to *Obesity and Endocrinology*?

European endocrinologists must be actors of this change. Spreading their thoughts and their research by publishing them in this new journal is a way of being an active part of this change. *Obesity and Endocrinology* will be their voice.

How can the biggest current challenges in your field be addressed?

The challenge of decisively overcoming the obesity epidemic persists. There is a continued need for a deeper understanding of the mechanisms that regulate food intake and energy expenditure in humans, as well as a broader comprehension of the complex causes that contribute to the disease in the real world. Only through this knowledge can we achieve early, holistic and effective prevention and treatment of obesity.

What is your advice to people considering a career in the field?

Be passionate and never give up.

Where are we likely to find you on a day off?

Sailing along the Sorrento coast, my birthplace.

Is there anything else you would like to say?

The launch of this new journal, *Obesity and Endocrinology*, will be a team effort. The role of the Editor-in-Chief is crucial, but, much like the captain of a ship, they need the entire crew – the editorial board, the reviewers, and the contributors – to truly make the journey successful. The next step will be to attract leading experts, researchers and clinicians in the field, who are committed to bringing the journal to life, with their research, insights, and dedication.

Immunotherapy for endocrine tumours

Anna Angelousi and Gregory Kaltsas discuss the use of immune checkpoint inhibitors in a range of endocrine tumours where immunotherapy is less well understood.

Immunotherapy is a novel cancer treatment, developed to enhance the immune system of oncology patients. Immune checkpoint inhibitors (ICIs) are designed to restore immune homeostasis and the response against tumour cells that aim to evade immune system activation by expressing specific molecules on their surface and acquiring distinct genetic alterations.[1]

Programmed death-1 (PD-1) functions as a T-cell surface receptor and binds to two ligands, programmed death ligands-1 and -2 (PD-L1 and PD-L2), which may be found on cancer cells and which negatively regulate T-cell effector functions. A monoclonal antibody against PD-1 can block PD-1/PD-L interaction, resulting in upregulation of immune response and inhibition of tumour growth.

Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) is also expressed on regulatory T-cells. It competes with T-cell surface protein CD28 for binding to CD80 or CD86 on antigen-presenting cells. Anti-CTLA-4 antibodies block CTLA-4, so restoring the T-cell activation and proliferation that result from CD80 or CD86 binding to CD28.[1]

The choice of ICIs for the treatment of neoplasms is based on various tumour-specific features, including the expression of PD-1 and PD-L1 proteins, the presence of microsatellite instability/mismatch repair deficiency, the *BRAF* proto-oncogene status, the tumour mutational burden (TMB) and the somatic copy number alteration.[2]

We recently reviewed the clinical application of ICIs in various endocrine tumours, where immunotherapy is less well studied compared with other solid tumours, such as melanoma, lung cancer or renal cell carcinoma.[3]

Adrenocortical carcinoma

Adrenocortical carcinoma (ACC) has an overall 5-year survival of only 15%. ICIs have been studied as an alternative regimen, and the anti-PD-1 agent pembrolizumab has been introduced in the National Comprehensive Cancer Network guidelines for patients with metastatic/progressive ACC on standard treatments.[4] Monotherapy with pembrolizumab exhibited a response rate (RR) between 14 and 23%. In comparison, nivolumab (another PD-1 agent) and avelumab (an anti-PD-L1) gave RRs of 26% and 6% respectively.[4]

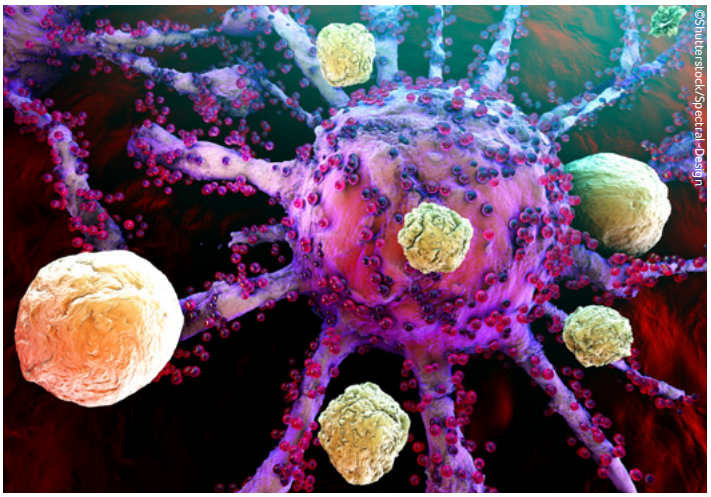
Current data on combined treatments with tyrosine kinase inhibitors (TKIs), chemotherapy, mitotane or anti-vascular endothelial growth factor have shown no additional benefit. However, there are still several ongoing studies, such as the SPENCER multicentre phase I/II trial, which is the first-in-human trial evaluating the EO2401 vaccine against ACC in combination with nivolumab, and the ACCOMPLISH study assessing the efficacy of pembrolizumab and lenvatinib (TKI). Preliminary data from the ongoing trial of the TKI cabozantinib and the anti-PD-L1 atezolizumab combination (CABATEN study) have shown modest responses, with a median progression-free survival of 2.9 months and overall survival of 13.5 months.

Phaeochromocytoma/paraganglioma

Patients with metastatic phaeochromocytoma (PC)/paraganglioma (PGL) treated with pembrolizumab or a combination of the anti-CTLA-4 ipilimumab and nivolumab or cabozantinib and nivolumab showed a modest RR, independently of PD-L1 expression. The RR in PC/PGL was <9%, although the number of patients treated was small.[5] The CABATEN study in advanced endocrine tumours, including PGL, is ongoing.

Thyroid cancer

ICIs have shown moderate activity in differentiated thyroid cancer, with an RR ranging from 9 to 62% and a progression-free survival of 9% at 6 months to 74% at 12 months.[3] The combination of ICIs with TKIs showed higher efficacy. ICIs have been evaluated in advanced medullary thyroid carcinoma in two phase II trials (NCT03246958 and NCT02834013), with preliminary results showing a lack of response except in tumours with high TMB.



Anaplastic thyroid cancer (ATC) is an aggressive tumour with poor response to conventional treatment.[3] The efficacy of immunotherapy alone in ATC resulted in RRs between 16 and 30%. A phase II, single-arm, open-label trial (NCT02688608) showed more promising results, reporting an RR of 60%. Pembrolizumab or spartalizumab (anti-PD-1) can be utilised in patients with a high TMB in ATC. Better RRs are obtained in patients with high PD-L1 expression.

Parathyroid carcinoma

Parathyroid carcinoma is rare, accounting for approximately 1% of primary hyperparathyroidism cases, with only two patients being treated with ICIs, generating equivocal responses.

Neuroendocrine neoplasms

The RR in neuroendocrine neoplasms is rather variable, mostly encountered in higher grade tumours. Patients with an advanced neuroendocrine neoplasm achieve an overall response rate of 15%, which varies according to the primary tumour site, degree of differentiation, and therapeutic regimen utilised.

For aggressive pituitary tumours (APT)/pituitary carcinomas, there is a relative paucity of data regarding the efficacy of ICIs. A combination of ipilimumab and nivolumab exhibited an RR of 26.6%, mostly in APT and corticotroph tumours.[3]

Conclusions

The common point that emerged from the majority of the studies that were included was the need to identify molecular, genetic and pathological markers for selecting those patients who could benefit from immunotherapy. The immunohistochemical expression of anti-PD-L1 or other proteins is not a prerequisite for response in many endocrine tumours. The main limitation of the majority of existing studies is the small number of patients treated, the lack of prospective design and the absence of treatment-naïve patients.

Current guidelines endorse the utilisation of pembrolizumab in some endocrine tumours with microsatellite instability or elevated TMB based on a tissue-agnostic approach. However, international multicentre randomised controlled studies are notably lacking. Promising data in treatment-naïve patients should be validated through randomised prospective studies that employ a more refined patient selection process, based on predictive markers and well designed combination treatments.

Anna Angelousi and **Gregory Kaltsas**
National and Kapodistrian University of Athens, Greece

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Personalising treatment for childhood thyroid carcinoma

This recent European collaboration on paediatric differentiated thyroid carcinoma seeks to enable personalised treatment.

Although rare, paediatric differentiated thyroid carcinoma (ped-DTC) is the most common endocrine malignancy in children, accounting for 2–4% of all paediatric malignancies.[1] The incidence of thyroid cancer is increasing worldwide, most likely as a result of (a) earlier and better detection of small and early stage papillary tumours, probably due to improved diagnostic tools and clinical awareness, and (b) changes in environmental risk factors resulting in an absolute increase in paediatric thyroid carcinoma.

Of all ped-DTC, the papillary form is most common (80–90%). There are important differences between adult and ped-DTC in terms of clinical, molecular and pathological characteristics. Compared to adult DTC, patients with ped-DTC are more likely to present with advanced disease at diagnosis, with larger tumour sizes, more frequent lymph node involvement, distant metastases and multifocal disease. Despite this more aggressive presentation, ped-DTC has an excellent prognosis in terms of survival (overall 10-year mortality rate <2%), although tumour recurrence/persistence is not uncommon.

Unmet medical needs

The therapeutic approach for adult and ped-DTC is classically based on surgery (i.e. total thyroidectomy, with or without lymph node dissection), followed by postoperative treatment with ^{131}I.[2,3] The 2022 European Thyroid Association guideline for ped-DTC recommends total thyroidectomy and ^{131}I treatment in nearly all patients.[2]

The consequences of total thyroidectomy include the need for lifelong thyroid hormone replacement therapy, and the risk of endocrine and non-endocrine complications of surgery (i.e. hypoparathyroidism and recurrent laryngeal injury). Adverse effects of ^{131}I treatment have been widely reported in survivors of ped-DTC, affecting up to 35% of treated patients, probably depending on the cumulative activity/dose administered. Late complications of ^{131}I treatment include permanent salivary gland dysfunction, permanent nasolacrimal duct obstruction, permanent bone marrow suppression, pulmonary fibrosis, and possibly secondary primary malignancies (SPM).[4]

Although the overall disease-free survival of ped-DTC patients is excellent with the current treatment strategies described above, there is ongoing controversy about the necessity of the treatments applied. Central to this debate is the question of whether ped-DTC is currently over-treated, potentially leading to unnecessary adverse effects, particularly in the management of patients at low-risk of recurrence.

The current 'one-size-fits-all' approach could be improved by moving towards more personalised treatment. This may include less extensive surgery (lobectomy versus total thyroidectomy), more limited use of postoperative ^{131}I, and less intensive follow-up protocols. We hypothesise that modification of current treatment protocols will not affect disease-specific morbidity and mortality, yet may reduce treatment-related adverse outcome.

The ped-DTC registry: a unique European collaboration

Due to the rarity of the disease in childhood and adolescence, current treatment guidelines are based mainly on the results of small retrospective observational studies. However, such results should be interpreted with caution, due to their inherent limitations and potential bias. Given the important differences in the behaviour of DTC in children compared with adults, evidence from large studies conducted in adults cannot be directly extrapolated to children and, therefore, ideally should not be. To improve the management and outcomes of patients with ped-DTC, there is thus an unmet need for consistent prospective data collection from larger cohorts and randomised-controlled clinical trials.

As ped-DTC is a rare disease, no single study site is able to generate clinical data in sufficient quantities to conduct conclusive studies. So, in January 2024, we launched the European ped-DTC registry, in collaboration with the European Registries for Rare Endocrine Conditions (EuRRECa).[5,6] To date, at least 30 clinical sites in 13 different European countries are participating in this unique project. This collaborative effort will provide clinical datasets that are large enough to answer questions conclusively through well powered studies. The registry will provide detailed demographic information on each patient and will serve as an umbrella for linked studies.

First linked study: ped-DTC STRATIFY

With the support of the Dutch Cancer Society (KWF; who have provided a Young Investigator Grant), we started the first linked study in October 2024. In this prospective cohort study (n= 200), we aim to investigate prognostic factors of persistent/recurrent disease in children with DTC, and to establish prediction models based on these prognostic factors.

We believe that the first step towards personalised treatment protocols will be the development of accurate pre- and post-surgical prognostic stratification tools. We hypothesise that (a) a preoperative model consisting of a combination of patient characteristics, ultrasound and cytology/biopsy features will be able to predict the behaviour of ped-DTC and thus help to guide the extent of surgery, and (b) the addition of clinical, pathological and genetic features to the current American Thyroid Association risk stratification will lead to a more accurate postoperative prediction of recurrent/persistent disease in children with DTC and thus guide the need for adjuvant ^{131}I treatment. A more personalised approach to staging and treatment may reduce unnecessary exposure to extensive surgery or to ^{131}I in patients with ped-DTC, potentially reducing short and long term complications and toxicity.

Sarah C Clement and **Hanneke M van Santen**
Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, University Medical Center Utrecht, and the Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

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SDH-B mutations and PPGL management

Ashley Grossman discusses new guidance for management of phaeochromocytomas or paragangliomas in patients with germline mutations of *SDH-B*.

Phaeochromocytomas and paragangliomas (formerly known as extra-adrenal phaeochromocytomas, jointly referred to as PPGLs), remain an infrequent cause of hypertension, but are increasingly diagnosed following investigation of incidentally discovered adrenal masses – adrenal incidentalomas – even in the absence of hypertension or of the classic triad of headache, palpitations and sweating.

However, they have become of increasing interest in endocrinology as, over the past few years, a very significant minority have been associated with germline mutations, which are of considerable importance in terms of their prognosis and family counselling and testing.[1] We have almost reached a new era in the study of these fascinating tumours, but one which has developed so fast that many who are not intimately involved in the field may not have realised the massive changes in diagnosis and management.

New guidelines

In general, phaeochromocytomas show specific germline mutations in around 30% of patients, rising to 50% for paragangliomas and approaching 80% in children. These phenomenal discoveries have recently led to the publication of a series of guidelines in major journals, based on detailed assessment of the published literature by an international panel of experts. Most recently, there has been new guidance for patients with germline *SDH-B* mutations.[2]

The original studies by Patricia Dahia and her colleagues[3] showed how PPGLs could be divided into clusters based on the underlying pathway aberrations, cluster 1 showing abnormalities in hypoxia signalling, often involving the Krebs cycle, and cluster 2 dependent on changes in kinase signalling. A much less common cluster 3 set of defects has now been added.[1] Of the cluster 2 germline mutation sets, those for succinate dehydrogenase type B are the subject of the most recent guideline,[2] following on from guidelines for *SDH-D*[4] mutations and for surveillance of asymptomatic patients.[5]

Diagnosis and assessment

Patients with *SDH-B* mutations show a penetrance of around 30% and a relatively high rate, around 35–40%, of metastases (the WHO recommend that we abandon the term 'malignant' in this context, and just refer to metastases). Diagnosis of index patients may be assessed on clinical suspicion, while biochemical confirmation should depend on metanephrines, preferably in plasma, including metanephrine, normetanephrine and (for plasma) 3-methoxytyramine. Imaging can be by computed tomography or magnetic resonance imaging (MRI) but, wherever possible, radionuclide imaging (preferably with ^{68}Ga-dotatate positron emission tomography) is encouraged to assess multifocal or metastatic disease.

Treatment and management

Surgery should always be considered as first-line therapy, with the emphasis on an experienced surgeon and full adrenoceptor blockade. Laparoscopic surgery may be appropriate, but usually an open approach is preferred to remove all associated disease, and cortical-sparing adrenalectomy is not recommended.

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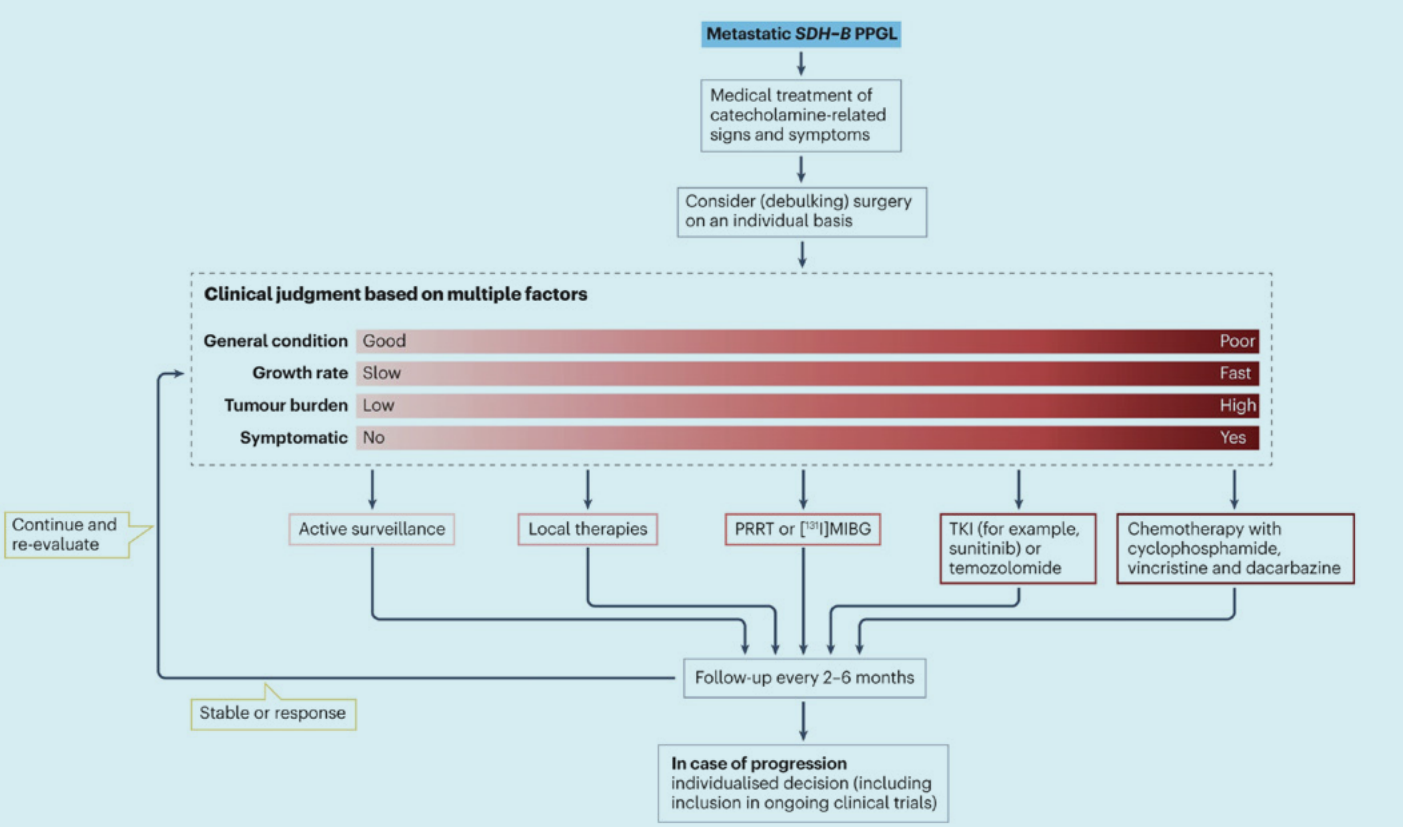

An algorithm for the treatment of metastatic *SDH-B* PPGLs. After medical treatment of catecholamine-related signs and symptoms, surgery is considered on an individual basis, depending on several clinical factors that can vary from mild to severe. When considering debulking surgery, note that surgery should be performed if all tumoural lesions can be removed. However, debulking surgery could be considered only in patients with symptoms and signs related to notable catecholamine excess or mass effect. Treatment options depend on the condition of the patient, severity of progression, tumour load and presence of catecholamine-related signs and symptoms. Treatment must be followed up and the patient should be re-evaluated depending on treatment results. Local therapies include radiotherapy, radiofrequency ablation, cryoablation, microwave ablation, embolisation, chemoembolisation and palliative surgery. Reproduced by permission from Taïeb *et al.* 2024 *Nature Reviews Endocrinology* **https://doi.org/10.1038/s41574-023-00926-0**.[2]

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For progressive metastatic disease with minor progression, radionuclide therapy is effective and well-tolerated. Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-octreotate is generally recommended, especially as high specific activity ^{131}I-meta-iodobenzylguanidine ([^{131}I]MIBG) is no longer available. There may be a place for 'cold' somatostatin analogues such octreotide LAR or lanreotide Autogel, although their use has not been validated.

For patients with more rapid progression, especially with extensive visceral disease, chemotherapy with CVD (cyclophosphamide, vincristine, dacarbazine) has been most studied, although temozolomide may play a role in some with slower progression. For further progression, use of a tyrosine kinase inhibitor (TKI) can be attempted, with most experience with sunitinib; other TKIs are under trial.

However, for any patients with stable disease, even when widely metastatic, close surveillance may be the best and safest option, as in many patients the disease may be indolent and stable for many years. It should be emphasised that, for head and neck paragangliomas, extensive surgery can lead to significant, debilitating cranial nerve palsies. Pre-embolisation may be useful, and frequently some form of radiotherapy may be preferred. Careful discussion in an interdisciplinary group is required, with input from surgeons and radiotherapists. Often, simple observation and surveillance provide the safest approach.

All patients require regular clinical and biochemical follow-up, with periodic imaging, usually with MRI to minimise radiation exposure. Routine repeat radionuclide scanning is unnecessary, but can be useful if there are changes in imaging and especially if radionuclide therapy is planned, i.e. as a 'theranostic'.

It is important to refer all such patients for careful genetic counselling, with at least all first-degree relatives offered screening. There is evidence that prophylactic screening can reduce later morbidity and probably mortality. Follow-up should be life-long.

SDH-D mutations

The general rules for patients with *SDH-D* mutations are broadly similar, with an emphasis on close clinical and biochemical follow-up, and regular imaging, preferably with MRI in the first instance. The major differences are that patients with *SDH-D* mutations have a lower rate of metastasis than those with *SDH-B* mutations, show maternal imprinting, and have a propensity for head and neck paragangliomas. The imprinting indicates that paternal inheritance is most likely, but children of female patients still have a low but significant (~5%) risk of a tumour, and will nevertheless be carriers for future generations.

Ongoing care

Surveillance protocols for both index patients and mutation carriers define recommended biochemical and imaging intervals, usually for life.[5] For all patients, discussion in a multidisciplinary group is vital to optimise care, with specialists including endocrinologists, surgeons, pathologists, radiologists, nuclear medicine physicians and, where appropriate, clinical geneticists. A specialist nurse practitioner is an essential team member. Decisions and suggestions regarding therapy should be rapidly fed back and communicated to patients, and advice given regarding patient support groups in the relevant country.

It is to be hoped that these guidelines, while by no means definitive, but based on the best current evidence, will allow all patients to receive the best clinical care available.

Ashley Grossman
NET Unit, Royal Free Hospital; Centre for Endocrinology, Barts and the London School of Medicine, Queen Mary University of London; and Green Templeton College, University of Oxford, UK

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Steatotic liver disease: a fresh understanding

Emir Muzurović and Christos Mantzoros review the journey to new nomenclature and improved knowledge.

Steatotic liver disease (SLD) is a public health threat, affecting more than one third of the adult population globally.[1] Along with rising rates of obesity and type 2 diabetes mellitus (T2DM), the global burden of SLD is increasing worldwide, already reaching the status of the most common cause of chronic liver disease.[1–3]

Revised nomenclature

During the last decade, there have been several attempts to change the nomenclature, necessitated by our evolving understanding of fatty liver disease. This led to replacement of 'non-alcoholic fatty liver disease (NAFLD)' with 'metabolic dysfunction-associated SLD (MASLD)'.[1,4] The term 'non-alcoholic' did not accurately capture the aetiology and pathophysiology of the disease, and the term 'fatty' has been considered to be stigmatising.[4]

An independent committee of experts published 'A multi-society Delphi consensus statement on new fatty liver disease nomenclature', and SLD was chosen as an overarching term to encompass the various aetiologies of steatosis, while MASLD was chosen to replace NAFLD.[4] More precisely, MASLD is defined as the existence of SLD in patients with at least one additional cardiometabolic criterion (e.g. overweight/obesity, prediabetes/T2DM, hypertension, hypertriglyceridaemia or low plasma high-density lipoprotein cholesterol; HDL-C). Similarly, metabolic dysfunction-associated steatohepatitis (MASH) became the replacement term for non-alcoholic steatohepatitis.[1,4] Therefore, the renaming ended the previous non-specific, broad and negative classification of NAFLD, and turned it into a positive and targeted SLD/MASLD/MASH nomenclature that describes what the disease is rather than what it is not.

New understanding

There is a growing body of evidence linking T2DM with SLD.[2] The global prevalence of MASLD in the general population is about 30%, while in patients with T2DM, the prevalence is up to 70%.[5] The majority of patients with T2DM who have MASLD have MASH (66.44%), and the proportion of patients with significant and advanced fibrosis is very high (40.78% and 15.49% respectively).[5] Thus, nowadays, MASLD is often referred to as diabetic hepatopathy. Although some people use the term 'diabetic hepatopathy', the true underlying cause is excessive ectopic fat deposition that accompanies obesity, T2DM and dysmetabolic disorders. This link brings this pathology deeper into the field of diabetology and endocrinology.

While the association of obesity, insulin resistance, metabolic syndrome and T2DM with MASLD and MASH is widely appreciated, there is a host of complex interactions between the liver and other endocrine axes.[6] Although research investigating the relationship between MASLD and endocrinopathies is increasing, there are still insufficient data to form strong recommendations regarding screening for comorbid endocrine disorders in patients with SLD/MASLD. The current joint European Association for the Study of the Liver–European Association for the Study of Diabetes–European Association for the Study of Obesity guideline[7] only suggests thyroid evaluation and polycystic ovary syndrome (PCOS) work-up as part

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of the extended MASLD diagnostic algorithm, while other guidelines do not even recommend screening for non-diabetic endocrine disorders.

Endocrine dysregulation and MASLD

There is evidence for both direct and indirect effects of endocrine dysregulation on the severity of MASLD, which should be considered in clinical practice. More specifically, low levels of thyroid hormones, growth hormone deficiency and panhypopituitarism promote the development and progression of MASLD, a condition that may show responsiveness to hormone replacement or agonist therapy.[6]

The influence of steroid hormones, e.g. cortisol, is much more divergent.[6] MASLD demonstrates marked sexual dimorphism, probably influenced by the pivotal role of sex hormones in regulating carbohydrate, protein and lipid metabolism within and beyond the liver.[6] In addition, elevated androgen levels characteristic of women with PCOS increase the risk of SLD.[6] Therefore, understanding the involvement of endocrine axes in the pathobiology of MASLD has been and will continue to be instrumental in paving the way for novel pharmacotherapies. It is important to emphasise that research on the impact of reproductive endocrine axis disorders on the development or progression of MASLD is particularly rare; more is needed.

Diagnosis and management

In addition, endocrinologists should screen and identify patients with advanced MASH fibrosis, and are indeed on the front line of recognising MASLD and treating comorbidities that may lead to its progression. Sequential algorithms of the fibrosis-4 (FIB-4) index followed by transient elastography (Fibroscan) or use of blood-based biomarkers can help diagnose SLD.[1] The FIB-4 index, calculated using age, platelet count and levels of alanine aminotransferase and aspartate aminotransferase, is a non-invasive indicator for the presence of advanced liver fibrosis, with scores categorised as low (<1.30), indeterminate (1.30–2.67) or high (>2.67) risk of fibrosis.[1] Non-invasive testing, such as Fibroscan or the enhanced liver fibrosis test, is used to further risk-stratify patients for advanced liver fibrosis.[1] However, more sensitive and specific non-invasive diagnostic criteria are needed.

The understanding that distinct subgroups of patients exist under the umbrella of SLD should guide more personalised treatment recommendations.[1] Recently, resmetirom, a thyroid hormone receptor-β liver selective agonist, has become the first agent approved for the treatment of adults with non-cirrhotic MASH with moderate to advanced liver fibrosis. After the impressive effects of glucagon-like peptide-1 (GLP-1) and dual gastric inhibitory polypeptide/GLP-1 receptor agonists in patients with T2DM and obesity, and significant cardiovascular benefits, there are also high expectations from existing and emerging incretin-based drugs in the treatment of MASLD/MASH.[1] Survodutide, a GLP-1/glucagon receptor agonist, has received Breakthrough Therapy status from the US Food and Drug Administration (FDA), and similar designation by European and Chinese authorities, to proceed to phase 3 randomised clinical trials for MASH. Several studies have proven the efficacy of pioglitazone and/or vitamin E in diabetics and non-diabetics respectively, despite lack of formal US FDA or European Medicines Agency approval specifically for MASH. These are inexpensive and should be considered where otherwise indicated.[1]

In the future, the mainstay of the pharmacological treatment of SLD/MASLD will be combined therapies that include liver-specific medications, such as resmetirom, in addition to diabetes and anti-obesity medications with proven benefits in MASLD/MASH. Endocrinologists and diabetologists have considerable experience with the latter.

Emir Muzurović
Department of Internal Medicine, Endocrinology Section, Clinical Center of Montenegro, Faculty of Medicine, University of Montenegro, Podgorica, Montenegro

Christos Mantzoros
Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

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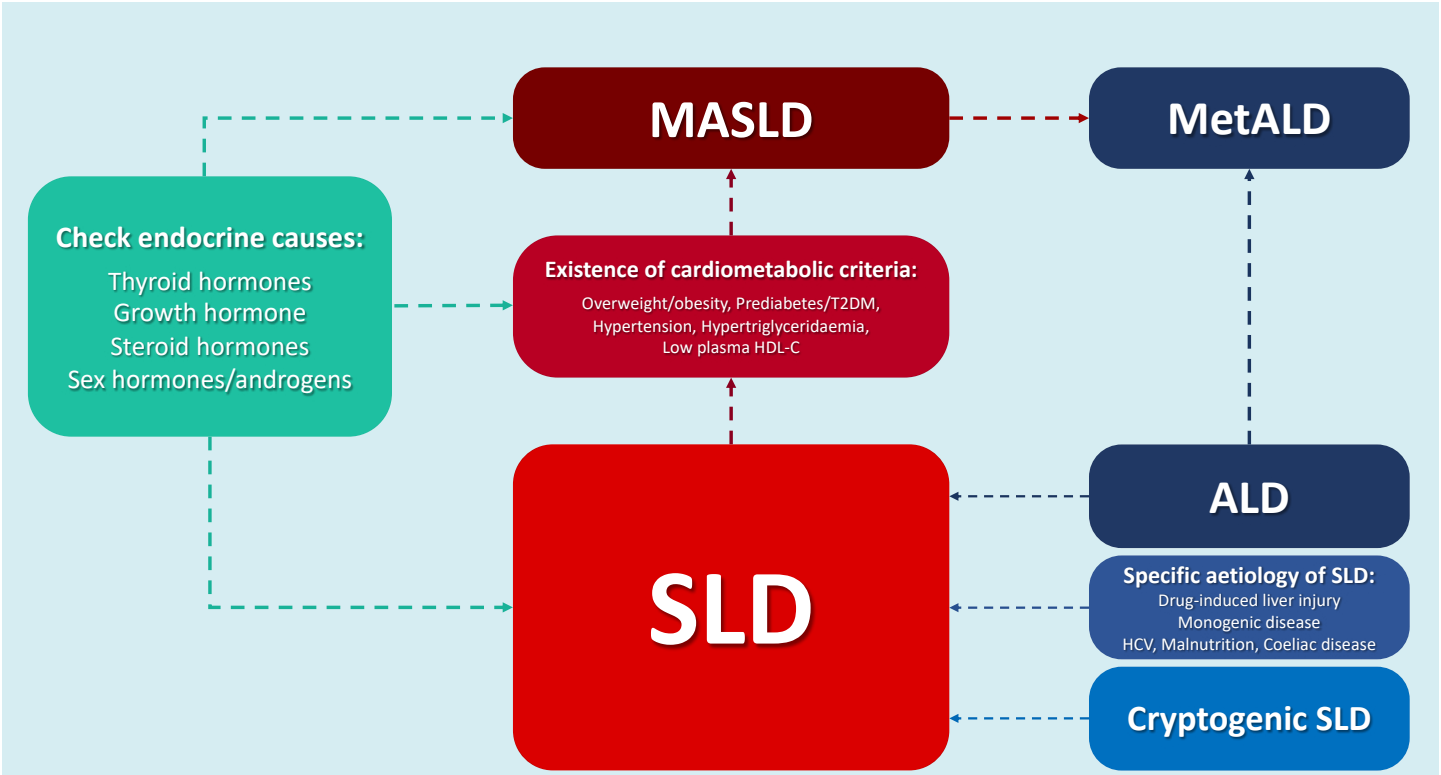


Understanding steatotic liver disease (SLD). ALD, alcohol-associated liver disease; HCV, hepatitis C virus; HDL-C, high density lipoprotein cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction-associated and alcohol-associated liver disease; T2DM, type 2 diabetes mellitus.

EJE Combined LT3 and LT4 after thyroidectomy

European Journal of Endocrinology reports one of the largest studies to date on the efficacy of combined therapy.[1]

There remains a debate regarding the best therapy for hypothyroidism. Treatment is routinely with levothyroxine (LT4), which is activated to tri-iodothyronine (T3) at the tissue level by deiodinases. However, a significant percentage of patients treated with LT4 complain of persistent symptoms, despite normalisation of serum thyrotrophin (TSH).[2,3]

It has been suggested that, after thyroidectomy, LT4 therapy alone is unable to recreate the balance of circulating thyroid hormones that existed when the thyroid was functioning. In particular, the action of deiodinases in the periphery fails to produce the necessary dose of T3, accumulating T4.[4] Thus, LT4 guarantees euthyroidism at the pituitary level, with TSH normalisation, but probably not at the periphery.

Adding liothyronine (LT3) to LT4 is a theoretical solution. However, it has not shown convincing results, also due to methodological limitations in studies to date: (a) administration of LT3 once daily in the morning, not respecting the half-life and circadian rhythm of T3, (b) a lack of adequate washout period in crossover studies, (c) fixed LT3 doses, with the risk of over- or undertreatment, (d) hypothyroidism of any nature, with varying degrees of residual function, and (e) evaluation of quality of life (QoL) using questionnaires not specific to hypothyroidism.

Finally, some evidence suggests that combination therapy may be indicated for subjects with a particular genotype, with variants of the *DIO2* and *MCT10* genes, involved in thyroid hormone metabolism and transport.[5]

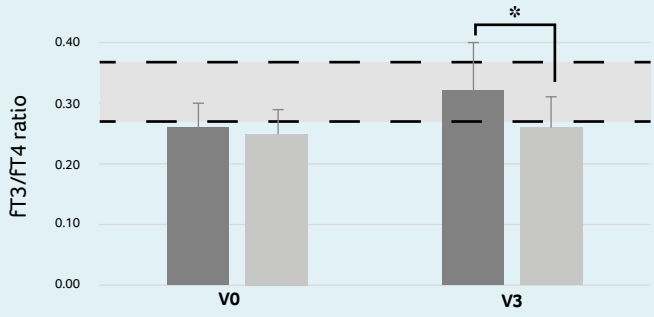
Our study

We conducted a longitudinal, prospective, double-blinded, randomised, placebo-controlled study, enrolling thyroidectomised patients with undetectable thyroglobulin, in good compensation during replacement LT4 at stable dosage for at least 3 months. Patients (n=141) were treated with LT4 and LT3 twice daily at a personalised dose (recreating a physiological T4/T3 ratio) or LT4 and placebo, and were followed for 6 months. To test the efficacy of the combination therapy, we measured TSH, free T3 (fT3), fT4, body mass index (BMI), heart rate, blood pressure and tissue markers of thyroid function (sex hormone-binding globulin (SHBG) as the primary endpoint, serum lipids, bone markers), and gathered ThyPRO questionnaire results for QoL in thyroid patients. *DIO2* and *MCT10* single nucleotide polymorphisms were genotyped.

Our findings

The combination therapy was found to be safe, with no significant adverse events, except for a greater lowering of TSH. It required greater dose adjustments than placebo, but this never led to signs of thyrotoxicosis. It probably arose from the interesting observation that only subjects treated with combination therapy reached levels of fT3 that normalised the fT3/fT4 ratio. Conversely, subjects receiving LT4 alone had significantly lower fT3/fT4 compared with the group treated with LT3 (see Figure).

However, after 6 months, neither SHBG nor other tissue markers of thyroid hormone function, BMI, heart rate or blood pressure differed significantly between groups. Although a trend towards improvement in some QoL parameters was observed in those treated with LT3, there was no significant difference from the group receiving placebo at the end of the study. No preference for combination therapy was found, mainly because of the complex therapeutic scheme, drop counting and twice-daily administration. Genetic variants did not influence any outcomes.



Comparison of fT3/fT4 ratio between groups receiving LT4+LT3 (dark grey) and LT4+placebo (mid-grey) at baseline (V0) and after 6 months (V3); *P<0.001, data are means±SD. The physiological range of the fT3/fT4 ratio (mean=0.32, interquartile range 0.27–0.37, pale grey band) in the presence of physiological TSH levels has been proposed in the consensus document.[6]

Discussion and conclusion

This is one of the largest studies to date on the efficacy of combined therapy. After 6 months of customised, twice daily, periodically adapted, physiological doses of hormones, only subjects receiving combination therapy normalised fT3/fT4, while those treated with LT4 and placebo still had reduced values, despite normal TSH. But this biochemical benefit did not lead to significant changes in tissue markers of thyroid hormone action or QoL. Perhaps 6 months was insufficient to see an improvement in these endpoints, or other, more specific, tissue markers are needed to measure the effect of thyroid hormones outside the hypothalamus–pituitary unit.

Giulia Brigante
University of Modena and Reggio Emilia, and Azienda Ospedaliero-Universitaria of Modena, Italy

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Insights from the Editor

This well-designed study addresses the long-standing debate on the optimal treatment of primary hypothyroidism. A combination of levothyroxine and liothyronine, or levothyroxine alone, when offered for 6 months did not differ in their effects on tissue markers of thyroid hormone action or on the quality of life of the patients.

Undoubtedly these are interesting results and a useful addition to the relevant literature. Could assessment of other markers reflect more accurately the impact of each approach? Until this question is clarified, the debate is likely to continue!

Niki Karavitaki
Deputy Editor, *European Journal of Endocrinology*

EJE Clinical & translational endocrinology **from around the globe**

Smoking and IgG production in Graves' disease

A recent study in *Endocrine Connections* investigated the mechanism of smoking's impact on Graves' disease.[1]

Graves' disease (GD) and Graves' ophthalmopathy (GO) are autoimmune disorders influenced by environmental factors such as smoking, stress and dietary iodine intake.[2,3] GD affects the thyroid, causing hyperthyroidism, while GO involves inflammation and tissue expansion in the orbit, leading to eye symptoms. Smoking is a significant risk factor for the development and worsening of GO.[4] In our recent study,[1] we investigated how cigarette smoke worsens these conditions by promoting inflammation and immune cell proliferation, and whether simvastatin mitigates these effects.

Performing the study

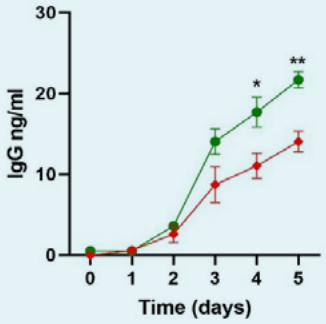
Twelve blood samples from newly diagnosed patients with GD and 10 healthy controls were collected at Skåne University Hospital, Malmo, Sweden. Both groups were selected based on the absence of prior GD treatment and other autoimmune diseases.

Peripheral blood mononuclear cells (PBMCs) were isolated and treated with various compounds, including cigarette smoke extract (CSE), simvastatin and diclofenac. The cells were incubated, and their RNA and protein expression were analysed using reverse transcription–polymerase chain reaction and enzyme-linked immunosorbent assay respectively. Flow cytometry was conducted to assess cell viability and proliferation. Statistical analysis was performed using one-way analysis of variance and Tukey's multiple comparisons test.

Our findings

The results showed that exposure to CSE significantly increased the expression of the inflammatory markers interleukin-1B (IL-1B), IL-6 and prostaglandin–endoperoxide synthase 2 (PTGS2) in PBMCs from patients with GD. Specifically, *IL-1B* expression increased 6-fold, *IL-6* 10-fold and *PTGS2* 5.6-fold compared with untreated cells. The corresponding protein levels also rose, with IL-1B, IL-6 and prostaglandin E_2 (PGE_2) showing 4-fold, 16-fold and 3.7-fold increases respectively. Moreover, CSE exposure enhanced the proliferation of B and T lymphocytes, immune cells that play crucial roles in autoimmune responses, by 1.3-fold and 1.4-fold respectively.

Interestingly, we found that PBMCs from patients with GD exposed to CSE produced significantly higher levels of IgG compared with those from healthy individuals (see Figure). This is surprising, as smoking usually decreases IgG production[5] and is linked to immunosuppressive effects.[6] There is limited research on how CSE affects IgG production in B lymphocytes from patients with GD. The findings suggest that B lymphocytes in patients react differently to CSE than those in healthy individuals. Further research into epigenetic changes in B lymphocytes could clarify these unique responses, and aid development of targeted treatments for GD and related conditions.



IgG levels in the supernatants of PBMCs isolated from patients with GD (green) and healthy controls (red) after 1–5 days of exposure to 10% CSE. Values are the means±SD of three independent experiments; $^{*}P \leq 0.05$, $^{**}P \leq 0.01$. Reproduced under **CC BY-NC 4.0 licence** from **Shahida *et al.***[1] ©2024 The Authors.

This suggests that smoking not only promotes inflammation but also enhances the production of autoantibodies that drive the disease.

We also explored the potential therapeutic effects of simvastatin and diclofenac in mitigating the harmful impact of CSE on PBMCs. Combined treatment with simvastatin and diclofenac significantly downregulated expression of *PTGS2*, *IL-6* and *IL-1B*, as well as their corresponding protein levels, suggesting that these drugs could potentially be used to counteract the inflammatory effects of smoking in GD.

Moreover, simvastatin alone was found to decrease the proliferation of B and T lymphocytes by 0.7-fold, indicating its potential to reduce the autoimmune response in GD. This effect of simvastatin on immune cells further supports its use in managing the inflammatory and autoimmune aspects of GD and GO, particularly in patients who smoke.

In conclusion

Our study found that CSE increases inflammatory markers, IgG levels, and B and T lymphocyte proliferation, explaining the link between smoking and severe GO and GD. Diclofenac and simvastatin reduced these effects, suggesting a possible role as treatments for GD and GO.

Bushra Shahida
Lund University and Skåne University Hospital, Malmö, Sweden

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Insights from the Editor

The interaction between smoking and thyroid eye disease, specifically Graves' ophthalmopathy, is a very interesting and important topic.

In the research reported in this paper, the authors analysed blood samples from patients with Graves' disease and healthy controls, to evaluate the effects of cigarette smoke extract. Not only did they show some markers that were associated with a worsening immune response, they also showed that simvastatin and diclofenac reduced inflammation and immune cell activity, suggesting their therapeutic potential for Graves' disease in smokers.

The study underscores smoking's harmful impact on thyroid eye disease and the need for specific treatments to counter these effects.

Faisal Ahmed
Editor-in-Chief, *Endocrine Connections*

Endocrine CONNECTIONS

Welcoming the new ESE Curriculum

Over the last year, ESE and UEMS (the European Union of Medical Specialists) have worked jointly to produce an **ESE Curriculum and European Training Recommendation in Endocrinology**.

This new initiative replaces the previous curricula formulated by ESE (last updated in 2019) and the UEMS Training Requirement (published in 2018). It includes an updated detailed list of the requested areas of knowledge, experience and training in endocrinology. It also specifies attitudes that are expected from an endocrinologist, and provides recommendations on the duration and structure of training, the governance of training, including assessment, and the requirements for trainers and training centres.

'The overall goal is to harmonise training in endocrinology.'

The document does not specifically address the skills and competencies required for clinical and basic research. This is beyond of the scope of this curriculum. However, understanding the pathophysiology, diagnostic procedures and treatment of endocrine diseases will form the basis for addressing relevant areas for research.

Since not all centres will be able to offer training possibilities in all specific core domains, they are encouraged to form training units with other training hospitals.

The authors and ESE representatives who have been involved are well aware that it will not be possible to meet all the listed competencies within the broad discipline of endocrinology during the postgraduate training period. Training after accreditation, as required by national continuous medical education/continuous professional development programmes is fundamental, and will enrich both the number and the level of competencies.

The aim of the new ESE curriculum is not to be imposed over established national curricula, but it may complement them by offering a comprehensive training framework. The overall goal is to harmonise training in endocrinology and, thereby, to contribute to best care of subjects with endocrine diseases across Europe, and to facilitate professional mobility.

You can find the new **ESE Curriculum and European Training Recommendation in *European Journal of Endocrinology***.

The new initiative was led by former ESE Education Committee Chair Mirjam Christ-Crain and the President of the UEMS Section and Board of Endocrinology (SBE) Maeve Durkan, together with ESE Scientific Programmes Project Manager Pedro Marques and myself as former representative of the ESE Council of Affiliated Societies (ECAS).

The input of ESE Focus Areas, the ESE Young Endocrinologists and Scientists (EYES) Committee, the ESE Education Committee, the ESE Executive Committee, UEMS delegates from the SBE, and ECAS was greatly appreciated. This Curriculum and Training Recommendation was ratified by the ESE Executive Committee and by the General Assembly of the UEMS SBE, and then endorsed by all 48 members of ECAS.

This work is further supported by another joint initiative of the ESE and the UEMS Section and Board of Endocrinology: the **European Board Examination in Endocrinology, Diabetes and Metabolism**. In 2023, the exam was sat by 158 candidates from 42 countries, with a pass rate of 69%. The 2024 exam is scheduled for 13 December.

Anton Luger

EJE Read the new curriculum in ***European Journal of Endocrinology***

Gdańsk Update

The 5th Polish–Romanian–Hungarian Endocrine Symposium took place in Gdańsk, Poland, in October. In total, 120 participants enjoyed presentations by colleagues, including guest speaker Djuro Macut (Serbia). The next event will be Iasi, Romania, in 2026.

Save the date

For more information about any ESE event see www.ese-hormones.org.

ESE Talks...Obésité et hormones: vers une médecine de précision
5 December 2024
Online

35th ESE Postgraduate Training Course
20–23 February 2025
Bucharest, Romania/Online

Connecting Endocrinology Across the Life Course

Joint Congress of ESE and ESE 2025
10–13 May 2025
Copenhagen, Denmark

ESE Summer School 2025
22–25 June 2025
Innsbruck, Austria

12th ESE Young Endocrinologists & Scientists (EYES) Meeting
26–28 September 2025
Milan, Italy

Deadlines

3 February 2025 (23.59 CET)
Joint Congress of ESPE and ESE 2025
Abstract submission deadline

28 February 2025
ESE Awards 2026:
- Geoffrey Harris Award
- *European Journal of Endocrinology* Award
- European Hormone Medal
- European Endocrine Nurse Award
- Clinical Endocrinology Journal Foundation Award
- Jens Sandahl Christiansen Award

Nomination deadline

27 March 2025
Joint Congress of ESPE and ESE 2025
Early Bird registration deadline

24 April 2025
Joint Congress of ESPE and ESE 2025
Standard registration deadline