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REVIEW ARTICLE

EndoBridge 2023: highlights and pearls

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Abstract

EndoBridge 2023 took place on October 20–22, 2023, in Antalya, Turkey. Accredited by the European Council, the 3-day scientific program of the 11th Annual Meeting of EndoBridge included state-of-the-art lectures and interactive small group discussion sessions incorporating interesting and challenging clinical cases led by globally recognized leaders in the field and was well attended by a highly diverse audience. Following its established format over the years, the program provided a comprehensive update across all aspects of endocrinology and metabolism, including topics in pituitary, thyroid, bone, and adrenal disorders, neuroendocrine tumors, diabetes mellitus, obesity, nutrition, and lipid disorders. As usual, the meeting was held in English with simultaneous translation into Russian, Arabic, and Turkish. The abstracts of clinical cases presented by the delegates during oral and poster sessions have been published in JCEM Case Reports. Herein, we provide a paper on highlights and pearls of the meeting sessions covering a wide range of subjects, from thyroid nodule stratification to secondary osteoporosis and from glycemic challenges in post-bariatric surgery to male hypogonadism. This report emphasizes the latest developments in the field, along with clinical approaches to common endocrine issues. The 12th annual meeting of EndoBridge will be held on October 17–20, 2024 in Antalya, Turkey.

Keywords Pituitary · Adrenal · Thyroid · Bone · Diabetes mellitus · Obesity

Introduction

EndoBridge is an international organization with the vision of bridging the field of endocrinology on a global scale (https://endobridge.org). The annual meetings of EndoBridge have taken place every October in Antalya, Turkey, since its foundation. Accredited by the European Accreditation Council for Continuing Medical Education (EACCME), the 3-day scientific program with a well-established format includes state-of-the-art lectures along with interactive small group discussion sessions led by experts and featuring intriguing and challenging clinical cases. The meetings are held in English and are attended by a diverse audience, hence the simultaneous translation into Russian, Arabic, and Turkish. The abstracts of clinical cases presented by the delegates during oral and poster sessions are published annually in a supplementary issue of JCEM Case Reports.

EndoBridge has partnered with several prominent organizations including the Endocrine Society, the European Society of Endocrinology, the American Thyroid Association, the Pediatric Endocrine Society, the European Association for the Study of Obesity, the Society of Endocrinology and Metabolism of Turkey, and the Brazilian Society of Endocrinology and Metabolism. This year, EndoBridge brought together 481 delegates from over 40 countries.

In the current report, we present pearls and highlights of the scientific presentations of EndoBridge 2023 which covered a wide spectrum in endocrinology and metabolism, detailing for each section of endocrinology, the current state of the field along with contemporary diagnostic and therapeutic approaches.

Extended author information available on the last page of the article

Pituitary disorders

Advances in the treatment of acromegaly

A.J. van der Lely

Treatment options for acromegaly include surgery, medical therapy, and/or radiation therapy. Surgery is usually the preferred treatment and, the smaller the tumor, the more likely surgery will be curative. If surgery is contraindicated or not curative, somatostatin analogs (SSAs), dopamine agonists, or GH receptor antagonists (GHRAs) may be used. Long-acting somatostatin analogs, both first- and second-generation, are administered as monthly injections. Upcoming treatments are the oral somatostatin analogs. Among the latter, the first kid-on-the-block will be MYCAPSSA® octreotide. MYCAPSSA® (a delayed-release oral capsule) is the first and only FDA-approved oral somatostatin analog for appropriate patients with acromegaly providing effective and consistent biochemical control, while (according to the company) freeing patients from the burden of injections. MYCAPSSA is powered by patented Transient Permeability Enhancer (TPE®) technology. It has been shown to maintain normal IGF-I levels in most patients who switched from injectable SSAs. BID oral dosing leads to consistent biochemical control in a significant proportion of subjects in the registration studies. Paltusotine is another new oral SSA analog. It is an investigational, potential first-in-class, oral non-peptide sst2 agonist, currently being developed in phase 3 trials. Once approved, it will join the ranks, along with MYCAPSSA, of the most up-to-date means of administering SSAs [1, 2].

To date, pegvisomant is the only available GH receptor antagonist. However, John Kopchick and colleagues recently presented the design, synthesis, and characterization of a 16-residue peptide (site 1-binding helix [S1H]) that inhibits hGH-mediated STAT5 phosphorylation in cultured cells. Other research groups and companies are also active in the field of developing new GHRAs. For instance, Amolyt Pharma SA recently reported positive preclinical data on their compound AZP-3813, a 16 amino acid, bicyclic peptide antagonist of the hGH receptor. Cimdelirsen, formerly known as IONIS-GHR-LRx, is a ligand-conjugated (LICA) investigational antisense medicine designed to reduce the production of the growth hormone receptor (GHR) as a means of decreasing the circulating levels of IGF-I [3, 4]. However, the company that owns it has discontinued this project for unknown reasons. In any case, the modification of GH activity by blocking the GH-receptor has become a rapidly evolving area of science.

Thyroid disorders

Subclinical hypothyroidism: to treat or not to treat

Robin P. Peeters

Subclinical hypothyroidism is a biochemical diagnosis defined as an elevated concentration of circulating TSH in combination with a serum free T4 level within the reference range. The incidence ranges from 3 to 15% depending on the age, sex, and iodine status of the population. A TSH cutoff level of 10 mIU per liter is commonly used to distinguish between mild and more severe subclinical hypothyroidism, with the majority of patients having a TSH of less than 10 mIU/L.

Levothyroxine is one of the most commonly prescribed drugs worldwide with, for example, approximately 7% of the U.S. population being estimated to be using levothyroxine [5]. Different studies show that the median TSH at which levothyroxine is started is only very mildly elevated, suggesting substantial overuse of levothyroxine. This is particularly relevant since a substantial number of levothyroxine treated patients are at risk of having a suppressed TSH [6], known to be associated with negative health outcomes. In addition, the largest clinical trial on subclinical hypothyroidism shows no beneficial effects of LT4 on a wide range of health outcomes when mild subclinical hypothyroidism is treated [7]. For this reason, we discussed two cases of mild subclinical hypothyroidism. The first case concerned a 78-year-old female patient with mild complaints possibly related to subclinical hypothyroidism and a TSH of 9 mIU/L. We concurred that there is no evidence that her symptoms or clinical outcome will improve, while unwarranted treatment of mild subclinical hypothyroidism may result in a suppressed TSH. The other main conclusions drawn from this case were not to rely on a single TSH measurement, generally to initiate no treatment when TSH < 10 mIU/L, and also in general not to initiate treatment in patients above 70 years old. This case was discussed based on the treatment algorithm published in [8].

The second case involved a 25-year-old patient who was 10 weeks pregnant with a TSH of 4.9 mIU/L and positive TPO antibodies. We discussed the importance of pregnancy-specific references ranges [9], concluding that this TPO antibody positive woman required treatment for her elevated TSH in early pregnancy. The other main conclusions were that when in doubt, re-measurement of thyroid function tests within a few weeks is a good alternative and that once treatment is started, a moderate dose of levothyroxine should be given.

Updates on thyroid nodule risk stratification

Jennifer Sipos

The evaluation of a thyroid nodule should be conducted via a holistic approach that incorporates the sonographic appearance, cytologic features, molecular characterization, and patient factors in order to carry out malignancy risk assessment and thereby adopt the optimal approach to management. All sonographic stratification systems have their respective limitations and strengths. When comparing these various systems, the performance characteristics (sensitivity/specificity) are driven by the size thresholds used for fine needle aspiration (FNA) [10]. Smaller size thresholds for FNA are associated with improved sensitivity, but specificity is lower. The use of a higher size threshold improves specificity, but does so at the cost of sensitivity. As we become more adept at classifying nodules sonographically, we have begun to see a decrease in the prevalence of benign cytologic results and a concomitant increase in the proportion of indeterminate cytology readings [11].

The ability to predict malignancy risk with ultrasound (US) is based on the underlying nodule histopathology. Nodules that represent papillary thyroid carcinoma are generally easier to identify based on the presence of suspicious sonographic features. These tumors also have a characteristic genomic profile, falling into the category of BRAF-like tumors in The Cancer Genome Atlas (TCGA). Follicular tumors, on the other hand, are less likely to display these suspicious features and more often have an intermediate or low-risk sonographic pattern. These tumors tend to have a genomic profile that is more RAS-like on the TCGA [12].

Nodules with a cytologic diagnosis of atypia of undetermined significance or follicular neoplasm have a risk of malignancy (ROM) of 20–30% [13]. Molecular testing has become a major component of the evaluation of these indeterminate nodules. However, when using molecular testing, it is important first to consider the US pattern and its associated ROM. Low and intermediate risk US patterns have a ROM of 5–20%, whereas high sonographic suspicion nodules have a ROM of > 50%. The use of molecular testing in cytological indeterminate nodules with a high-risk US pattern does not further enhance the malignancy risk prediction because the ROM is already elevated due to the suspicious US findings. In these scenarios, the risk of malignancy is sufficiently elevated to justify immediate referral to surgery, the addition of a suspicious molecular test does not further augment clinical decision-making. In contrast, the identification of a suspicious molecular testing result in cytological indeterminate nodules with a low or intermediate risk US pattern increases and improves the malignancy risk prediction and warrants surgical intervention [14].

Challenges in optimizing treatment of low-risk thyroid cancer

Megan R. Haymart

In recent years, clinical guidelines have encouraged less intensive treatment of low-risk thyroid cancer. These recommendations include greater use of lobectomy instead of total thyroidectomy, less use of radioactive iodine, and less use of suppressive doses of levothyroxine. Despite this shift, there has not been uniform uptake. The barriers to uptake of these recommendations include lack of physician buy-in, lack of patient buy-in, the difficulty of long-term follow-up after less intensive treatment, and the uncertainty of the impact on patient worry. Solutions to these barriers include more high-quality research to improve the quality of the data behind clinical guideline recommendations, providing patients with more time to make informed decisions, clinician competence and confidence in use of neck ultrasound during long-term surveillance, and providing patients with additional resources to address worry [15–20].

Bone disorders

Controversies regarding the impact of vitamin D supplementation on health outcomes

Ghada El-Hajj Fuleihan

The activated form of vitamin D is a steroid hormone that controls several hundred genes. It modulates a wide range of molecular and cellular functions, including immune functions, inflammation, cellular senescence, and telomere biology [21]. Vitamin D plays a critical role in musculoskeletal health through its effects on mineral homeostasis and bone metabolism, while its efficacy in preventing and healing rickets and osteomalacia is undisputable. However, its effect in reducing fracture risk has been the subject of debate over recent years, several meta-analyses having led to contradictory results. In a recent umbrella review of meta-analyses of vitamin D RCTs, our group demonstrated that the only consistent significant protective effect concerned the ability of calcium and vitamin D (Ca/D), not vitamin D alone, to reduce the risk of hip fractures, by 16 to 39% in 8/13 meta-analyses, and of any fracture by 5 to 26% in 8/14 meta-analyses (Fig. 1) [22]. Subgroup analyses by residential status suggested a reduction in hip fractures in two meta-analyses and in any fractures in four meta-analyses, but only with Ca/D and in institutionalized but not community-dwelling adults. These findings were driven by two trials in older institutionalized vitamin D–deficient individuals. Earlier systematic reviews had

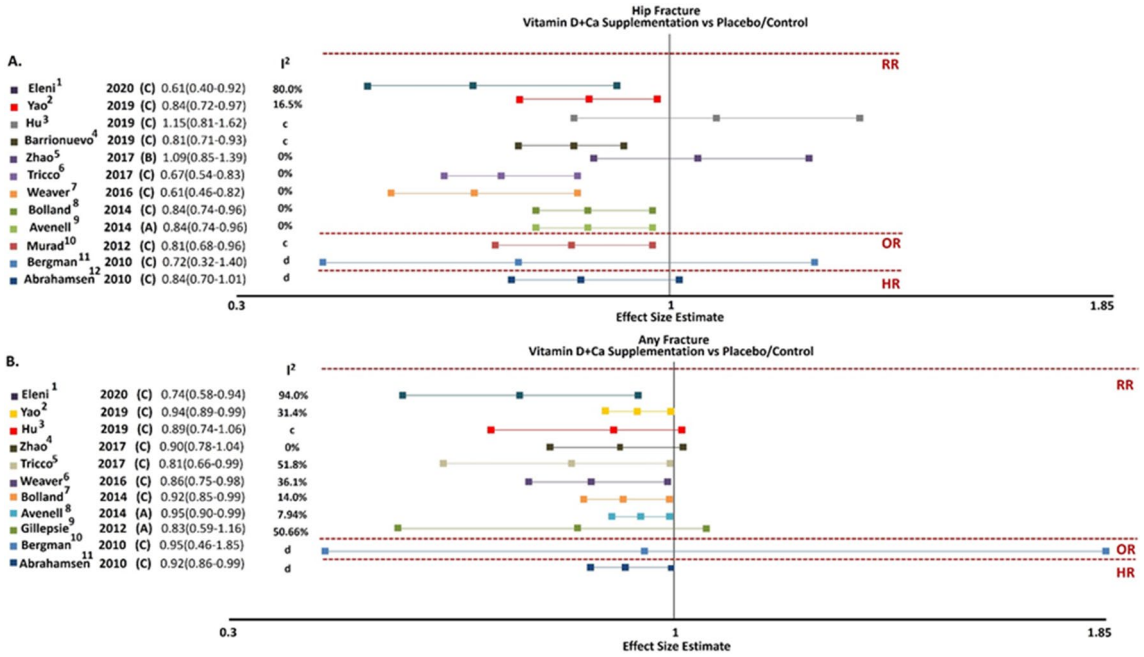

Fig. 1 Effect size estimates and 95% CI for hip and any fracture risk with vitamin D and calcium supplementation vs placebo/control. Footnote: **A.** [1]Eleni A. Clin Rheumatol. 2020;39(12):3571–3579. [2]Yao P. JAMA Netw Open. 2019;2(12):e1917789. [3]Hu ZC. BMJ Open. 2019;9(10):e024595. [4]Barrionuevo P. J Clin Endocrinol Metab. 2019;104(5):1623–1630. [5]Zhao JG. JAMA. 2017;318(24):2466–2482.[6]Tricco AC. JAMA. 2017;318(17):1687–1699. [7]Weaver CM. Osteoporos Int. 2016;27(1):367–376. [8]Bolland MJ. PLoS One. 2014;9(12):e115934. [9]Avenell A. Cochrane Database Syst Rev. 2014;2014(4):CD000227. [10]Murad MH. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. J Clin Endocrinol Metab. 2012;97(6):1871–1880. [11]Bergman GJ. Curr Med Res Opin. 2010;26(5):1193–1201. [12]DIPART Group. BMJ. 2010 Jan 12;340:b5463. **B.** [1]Eleni A. Clin Rheumatol. 2020;39(12):3571–3579. [2]Yao P. JAMA Netw Open. 2019;2(12):e1917789. [3]Hu ZC. BMJ Open. 2019;9(10):e024595. [4]Zhao JG. JAMA. 2017;318(24):2466–2482. [5]Tricco AC. JAMA. 2017;318(17):1687–1699. [6]Weaver CM. Osteoporos Int. 2016;27(1):367–376. [7]Bolland MJ. PLoS One. 2014;9(12):e115934. [8]Avenell A. Cochrane Database Syst Rev. 2014;2014(4):CD000227. [9]Gillespie LD. Cochrane Database Syst Rev. 2012(9):CD007146. [10]Bergman GJ. Curr Med Res Opin. 2010;26(5):1193–1201. [11]DIPART Group. BMJ. 2010 Jan 12;340:b5463. https://doi.org/10.1136/bmj.b5463. Quality assessment using a MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR-2): A, moderate quality; B, low quality; and C, critically low quality. [a]HR, hazard ratio; OR, odds ratio; RR, risk ratio. [b]Meta-analyses that included institutionalized trials. [c]Network meta-analyses. [d]Not available. Figure reproduced with permission from Chakhtoura M et al. J Clin Endocrinol Metab 2022; 107(3):882–898

demonstrated that older age and 25-hydroxyvitamin D (25(OH)D) levels < 20 ng/mL may be predictors of fracture reduction in response to vitamin D [22]. In our recent umbrella review of meta-analyses on the efficacy of vitamin D in fall prevention, vitamin D ± Ca had no effect on reducing the number of fallers. Its potential in preventing the number of falls in institutionalized participants was suggested but remains uncertain given the low quality of evidence (manuscript in submission process). Mega-trials have investigated the impact of vitamin D on several primary outcomes, including fractures, cancer incidence, diabetes, hypertension cardiovascular disease, and mortality, with null findings (Table 1) [23]. This could be explained by the vitamin D replete status of subjects at study entry. The above null findings were confirmed in meta-analyses, with the exception of mortality [23]. Two large meta-analyses including one from the Cochrane group revealed a mild decrease in all-cause mortality [23].

The 2024 Endocrine Society Clinical Practice Guidelines on Vitamin D in the Prevention of Disease issued a conditional recommendation for empiric vitamin D supplementation in the general population ages 75 years and older because of the potential to lower mortality [24]. The RCTs and meta-analyses published to date do not have adequate power to evaluate important subgroups, and specifically those at high risk of adverse outcomes. This includes subjects with low 25(OH)D levels, men, the oldest old, ethnic groups other than White individuals, and those from low-income countries [22, 25]. In addition, many studies lacked measurement of vitamin D levels during treatment and used non-standardized assays. Vitamin D supplementation should be targeted to subjects with hypovitaminosis D and not to the general population who is likely to be vitamin D replete, such as those from Western, developed countries [25].

Table 1 Major placebo-controlled megatrials*, trials of vitamin D therapy and impact on major outcomes

Trial	N	Baseline 25OHD ng/ml	Age years/Gender	Doses & frequency	Median duration	Primary outcomes
Trivedi Bmj, 2003 326(7387):469	2,686	NA**	65–85; both	Monthly 100 000 IU oral vitamin D3	5 years	Vitamin D reduced any first fracture (RR = 0.78 [0.61—0.99] and first hip, wrist or forearm, or vertebral fracture (RR = 0.67 [0.48—0.93]) and did not significantly reduce mortality (RR = 0.88 [0.74—1.06]
RECORD Grant *Lancet, 2005* *365(9471):1621–1628*	5,292	15.2 ± 6.5 [*n* = 60]	> 70; both	Daily 800 IU oral vitamin D3	45 months	Vitamin D did not significantly reduce the incidence of new, low-trauma fractures (HR = 1.02 [0.88–1.19])
WHI Jackson *NEJM, 2006* *354(7):669–683*	36,282	NA**[1]	50–79; women	Daily 400 IU oral vitamin D3	7 years	Vitamin D with calcium did not significantly reduce hip fracture (HR = 0.88 [0.72–1.08]), clinical spine fracture (HR = 0.90 [0.74–1.10]), and total fractures (HR = 0.96 [0.91–1.02])
CAPS Lappe Jama, 2017 317(12):1234–1243	2,303	32.8 ± 10.5	≥ 55 women	Daily 2,000 IU oral vitamin D3	4 years	Vitamin D did not reduce cancer incidence (difference of 1.69% [-0.06—3.46])
ViDa Study Scragg *JAMA Cardiol, 2017* *2(6):608–616*	5,110	26.5 ± 9 [*n* = 5108]	50–84; both	Monthly 100,000 IU oral vitamin D3	3.3 years	Vitamin D did not significantly reduce the primary endpoint of incident cardiovascular disease (HR = 1.02 [0.87–1.20])
D2d Pittas *NEJM, 2019* *381(6):520–530*	2,423	28.0 ± 10.2	> 30; both	Daily 4,000 IU oral vitamin D_3	2.5 years	Vitamin D did not significantly reduce the risk of diabetes among persons at high risk for type 2 diabetes (HR = 0.88 [0.75 -1.04])
VITAL Manson *NEJM, 2018* *380(1):33–44*	25,871	30.8 ± 10.0 [*n* = 15,787]	Men ≥ 50 Women ≥ 55	Daily 2,000 IU oral vitamin D3	5.3 years	Vitamin D did not significantly reduce the co-primary endpoints of any invasive cancer incidence (HR = 0.96 [0.88–1.06]) or major cardiovascular events (HR = 0.97 [0.85–1.12])
DO-HEALTH Bischoff-Ferrari *Jama, 2020* *324(18):1855–1868*	2,157	22.4 ± 8.4 [*n* = 2,140]	≥ 70; both	Daily 2,000 IU oral vitamin D3	3 years	Vitamin D did not significantly reduce incident non-vertebral fractures, cognitive decline or rate of infections, or improve physical performance or systolic and diastolic blood pressure
D-Health Trial Neale *Lancet Diabetes Endocrinol, 2022* *10(2):120–128*	21,315	NA**[2]	≥ 60; both	Monthly 60,000 IU oral vitamin D3	5.7 years	Vitamin D did not significantly reduce mortality (HR = 1.04 [0.93–1.18])

Table 1 (continued)

Trial	N	Baseline 25OHD ng/ml	Age years/Gender	Doses & frequency	Median duration	Primary outcomes
FIND Virtanen *Am J Clin Nutr. May, 2022 115(5):1300–1310*	2,495	29.9 ± 7.3 [sub-cohort *n* = 551]	Men ≥ 60 Women ≥ 65	Daily 1,600 IU or 3,200 IU oral vitamin D3	5 years	Vitamin D did not significantly reduce the incidence of major cardiovascular events (HR = 0.90 [0.62–1.32]) or invasive cancer (HR = 1.04 [0.72–1.51])

*Megatrials are trials that included ≥ 2,000 study subjects. ** not available. **[1] Mean 25(OH)D in a nested case–control assessment was 18.42 ± 9.1 ng/ml for participants who had hip fracture and 19.39 ± 9.41 ng/ml among their controls ($P = 0.17$). **[2] Predicted de-seasonalized serum 25(OH)D concentration [N (%)]: < 50 [2562 (24·0)] vitamin D group; [2638 (24·8)] placebo group ≥ 50 [8099 (76·0)] vitamin D group; [8011 (75·2)] placebo group

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Secondary osteoporosis

Michael R McClung

Estrogen deficiency in women and aging in both men and women are the primary causes of osteoporosis. Many – perhaps most – diseases and myriad medications adversely affect skeletal health. These factors may directly alter bone metabolism by either increasing bone resorption (e.g., myeloma and acute immobilization) or impairing bone formation (glucocorticoid therapy and chronic immobilization). The skeleton may be affected indirectly by inflammation or abnormal nutrient intake. Conditions including phosphate wasting and chronic phenytoin therapy impair bone mineralization, causing low bone mass due to osteomalacia, while others (e.g., type 2 diabetes and proton pump inhibitors) increase fracture risk without altering bone mineral density (BMD).

Some conditions such as mild vitamin D deficiency or secondary hyperparathyroidism are common but have modest skeletal effects, while other diseases and drugs such as phosphate wasting or glucocorticoid therapy may have significant negative effects and may alter management decisions, including choice of therapy. Significant secondary contributions to bone health have been found in 5–20% of patients seen in osteoporosis clinics [26, 27].

There is no general test to identify patients with secondary contributing factors. Neither BMD Z- scores (compared to a healthy age-matched person) nor biochemical markers of bone turnover identify patients with underlying contributing factors. For these reasons, all patients found to have osteoporosis deserve a clinical evaluation before beginning osteoporosis treatment to identify disorders that can influence bone density, fracture risk, or responses to therapy. Key steps in the evaluation and appropriate laboratory tests are listed in Table 2 [28]. A thorough clinical history is the most important part of this evaluation, with an emphasis on personal and family history of fractures, details of known diseases and drugs, and symptoms of other disorders. Physical examination may reveal evidence of contributing diseases, such as hyperthyroidism, evidence of vertebral fractures (excessive historical height loss and kyphosis), or features of osteogenesis imperfecta or osteomalacia.

Routine laboratory testing should be augmented with measurement of serum phosphorus and evaluation of vitamin D status. A determination of 24-h calcium excretion can identify the many patients with hypercalciuria, who then need additional workup or treatment, and the few with hypocalciuria (< 100 mg/daily) in whom intestinal malabsorption (vitamin D deficiency, celiac disease) should be suspected. Spot measurement of urine calcium is not an adequate substitute. Additional tests may be needed to evaluate the significance of abnormalities found during the routine evaluation and laboratory testing.

Table 2 Clinical and laboratory evaluation of patients with osteoporosis

Evaluation
Complete medical history (fractures, family history, diseases, drugs, etc.)
Physical examination (evidence of height loss, kyphosis, or other diseases such as hyperthyroidism, Cushing's syndrome, osteogenesis imperfect, or osteomalacia)
Search for occult vertebral fractures with spinal radiographs or lateral vertebral assessment with DXA
Fracture risk assessment with an algorithm such as FRAX, including trabecular bone score
Laboratory testing
Basic: chemistry panel plus serum PO4 and 25(OH)D, CBC, testosterone for men, 24-h urinary calcium
Additional laboratory tests as indicated by routine evaluation: serum PTH, TSH, urine cortisol, serum and/or urine protein electrophoresis, etc

More sophisticated tests are used in certain situations. Trabecular bone score (an algorithm assessing heterogenicity of density distribution on a lumbar spine DXA scan) is an indirect measure of trabecular microarchitecture and can assist in fracture risk prediction but not in identifying secondary contributing factors. Trans-iliac bone biopsy after tetracycline labeling can identify patients with osteomalacia, while marrow-based diseases can be diagnosed with a bone marrow biopsy.

In summary, osteoporosis frequently coexists with other disorders that may influence skeletal health. Thorough medical evaluation should be performed and the presence of underlying contributing factors should be included in fracture risk assessment in deciding when to treat and in selection of therapy.

Diabetes mellitus

Perioperative management of hyperglycemia in hospitalized patients with diabetes for elective surgery

Anton Luger

Most consensus statements or guidelines recommend a perioperative glucose target range of 100/140 to 180/200 mg/dL (5.6/7.8–10.0/11.1 mmol/L) for patients with diabetes undergoing elective surgery and initiation of insulin therapy if blood glucose concentrations are > 180 mg/dL (10 mmol/L) [29–31]. In addition, HbA1c values ranging from < 7 to < 8% (53–64 mmol/mol) are recommended) [29–31]. Perioperative glucose control appears to be more important than preoperative HbA1c concentrations) [30] in preventing postoperative complications, but there is a lack of studies addressing this issue directly. Whereas some guidelines recommend that poor preoperative HbA1c values should not be grounds for deferring elective surgical interventions [30], others recommend deferring elective surgeries when HbA1c levels are > 8.5% (69 mmol/mol) and optimizing glycemic control [29–31]. Studies comparing tight glycemic control with differing target levels and observation periods to conventional control have not unanimously demonstrated improvement in postoperative outcomes. Of the oral antidiabetic drugs, only DPP-4 inhibitors and GLP-1 receptor agonists can be continued perioperatively without interruption [31]. Type, duration, and site of surgical intervention as well as type of anesthesia appear to influence the incidence and types of postoperative complications. It should be stressed, however, that almost all studies investigating the effect of pre-, peri- and postoperative glycemia on postoperative complications have been performed in patients with type 2 diabetes and most were retrospective analyses. The majority of studies have been conducted in patients undergoing cardiac surgery. There is a definitive need for prospective randomized controlled trials to determine the optimal perioperative management of patients with type 1 and type 2 diabetes.

Glycemic challenges after bariatric surgery

Hamayle Saeed MBBS, Mary-Elizabeth Patti

While the gap between medical therapies and the more potent surgical approaches to obesity is narrowing, long-term data demonstrate that bariatric surgery is a safe and highly effective approach to weight loss and obesity-associated comorbidities. Weight loss achieved through surgery has a significant impact on glucose metabolism as it improves insulin sensitivity, beta cell function, and adipose tissue biology, resulting in improved glycemic control, reduction in medication use, reduction in diabetes-related complications, and even diabetes remission [32, 33]. Favorable effects on glucose metabolism among patients with type 2 diabetes (T2D) are observed even when BMI is under 35 kg/m^2.

The impact of bariatric surgery on glucose metabolism is particularly striking in the postprandial state. Rapid delivery of nutrients to the foregut as a result of surgery-induced anatomy results in an early and increased peak in blood glucose and marked increases in postprandial levels

of glucagon-like peptide 1 (GLP1). Together, this results in very high levels of insulin in the postprandial state and rapid return of glucose levels to the pre-meal state. Indeed, glycemic variability is increased after surgery [34] (Fig. 2).

While these post-bariatric changes in glucose metabolism are very helpful for those with T2D, individuals without T2D also experience changes in glucose metabolism. Some even develop postprandial hypoglycemia, a condition termed post-bariatric hypoglycemia (PBH). PBH can occur after Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy or additional upper gastrointestinal surgeries, such as fundoplication. The prevalence of hypoglycemia in individuals who have had bariatric surgery varies according to the methods utilized and definition but ranges from < 1% for severe hypoglycemia requiring hospitalization to 10–30% with self-reported symptoms. Onset of this condition is typically observed at least 1 year postoperatively, but occasionally many years later [34].

In patients with PBH, increases in both GLP1 and insulin secretion in the postprandial state are even higher than in unaffected post-surgical patients. In addition, insulin-independent mechanisms can contribute, including decreased counter-regulatory hormones and changes in glucose production and uptake [34].

Unfortunately, PBH can be severe, resulting in episodes requiring the assistance of others and can be associated with hypoglycemia unawareness, a further threat to safety. Careful diagnostic evaluation is needed to rule out other causes of hypoglycemia. Long-term treatment options currently available are often unable to fully eliminate hypoglycemia, but include dietary modification to reduce high-glycemic index carbohydrate intake and ensure adequate protein and micronutrient intake [35], acarbose or miglitol to slow carbohydrate absorption, somatostatin analogs (e.g., octreotide or pasireotide) to reduce both incretin and insulin secretion, and diazoxide to reduce insulin secretion [36]. Additional strategies for therapy are under investigation.

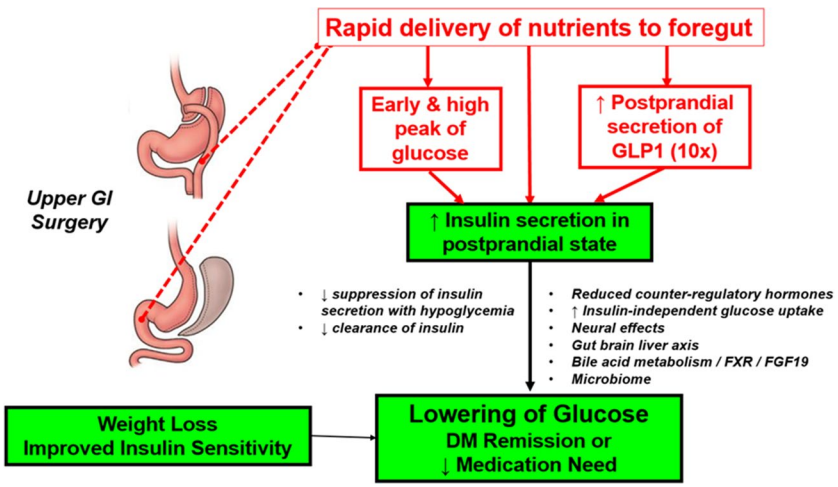

Fig. 2 Glycemic variability after bariatric surgery

Obesity

Sarcopenic obesity: diagnosis and management

Luca Busetto

Coexistence of excess fat mass and sarcopenia, defined as low skeletal muscle mass and function, defines sarcopenic obesity (SO). SO was described initially as a geriatric syndrome. However, SO can also occur at younger ages in people with obesity. The occurrence of SO in people with obesity is favored by the metabolic alterations characteristic of obesity itself (oxidative stress, inflammation, and insulin resistance), the coexistence of other chronic diseases, and sedentariness. Therapeutic weight loss that inevitably leads to loss of significant amounts of skeletal muscle can also be a cause of sarcopenia in people with obesity [37]. SO has been consistently demonstrated to be a strong and independent risk factor for disability and mortality in the older population [38], and the risk of disability is higher in SO than in sarcopenia or obesity alone [39].

The evaluation of SO in clinical practice and the accrual of data on its prevalence have been hampered by the absence of shared diagnostic criteria. A systematic review analyzing diagnostic criteria for SO applied so far in human studies confirmed a huge heterogeneity, including different definitions and cut-offs for both obesity and sarcopenia, and differences in methodologies for assessing body composition and physical functioning [40]. In view of this situation, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) promoted an international initiative aimed at reaching a consensus on the definition of SO, diagnostic procedures, and methodologies for its assessment [37].

The EASO-ESPEN consensus ultimately produced an algorithm for the screening, diagnosis, and staging of SO

applicable both in epidemiology and in clinical practice (Fig. 3) [37]. Screening for SO is based on the concomitant presence of elevated body mass index or waist circumference (using ethnicity-specific cut-offs) and risk factors for sarcopenia, including clinical symptoms, risk conditions, or testing positive on validated questionnaires. Table 3 lists the clinical symptoms or suspicion factors mandating a screening for SO [37]. Recent weight loss, including voluntary weight loss and weight cycling syndrome, is included. Diagnostic procedures to confirm or reject SO should always follow a positive screening result. Both altered skeletal muscle functional parameters and altered body composition are needed to establish the diagnosis. Skeletal muscle strength (hand-grip strength, knee extensor strength, or chair-stand test) is used for the assessment of skeletal muscle function. Dual-energy X-ray absorptiometry (DXA), or bioelectrical

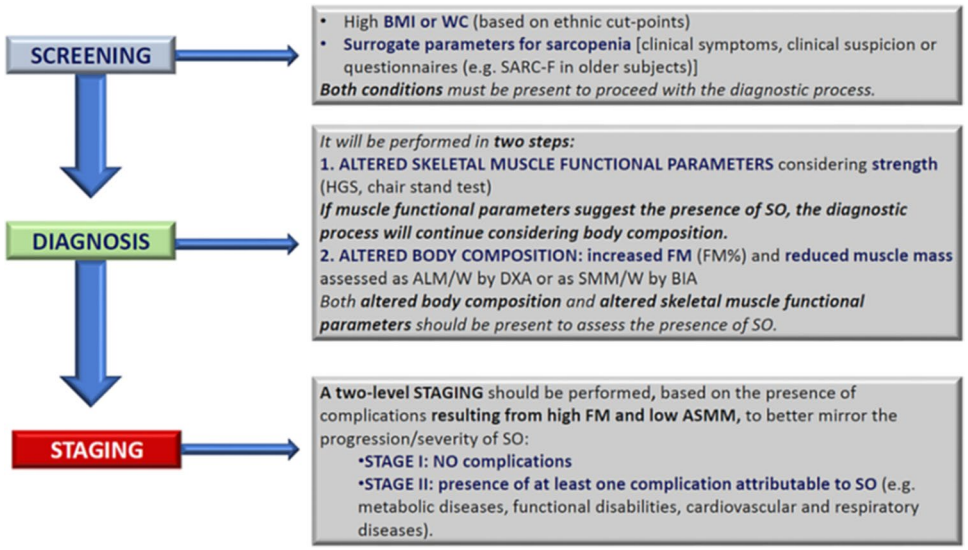

Fig. 3 Diagnostic procedure for the assessment of sarcopenic obesity according to EASO-ESPEN consensus. Footnote: ALM/W, appendicular lean mass adjusted to body weight; ASMM, absolute skeletal muscle mass; BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual X-ray absorptiometry; FM, fat mass; HGS, handgrip strength; SMM/W, total skeletal muscle mass adjusted by weight; SO, sarcopenic obesity; WC, waist circumference; SARC-F, strength, assistance with walking, rising from a chair, climbing stairs and falls. Adapted from reference [37]

Table 3 Clinical symptoms or suspicion factors mandating a screening for sarcopenic obesity according to EASO-ESPEN consensus [37]

Age > 70 years
Chronic disease diagnosis (e.g., inflammatory diseases and organ failure or chronic disease) including but not limited to:
Chronic heart failure
Chronic kidney disease (particularly renal replacement therapy)
Chronic bowel failure or dysfunction
Chronic liver disease (particularly NASH and liver cirrhosis)
Chronic respiratory disease
Chronic neurologic and neurodegenerative diseases
Chronic cognitive impairment
Depression
Organ transplantation
Endocrine diseases (e.g., metabolic syndrome, diabetes mellitus, hypercortisolism, hypogonadism, and corticoid treatment)
Osteoarthritis
Cancer (especially but not limited to chemotherapy of breast or prostate cancer)
Recent acute disease/nutritional events:
Recent hospitalization (particularly but not limited to COVID-19, ICU stay, and surgery)
Recent major surgery or trauma with/without complications
Recent sustained immobilization or reduced mobility (e.g., trauma, fracture, and orthopedic diseases)
Recent history of reduced food intake (e.g., < 50% for > 2 weeks)
Recent weight loss (including diet-induced voluntary weight loss and weight cycling syndrome)
Recent rapid increase in weight
Long-standing restrictive diets and bariatric surgery
History – complain of:
Repeated falls
Weakness, exhaustion
Fatigability
Perceived progressive movement limitations

impedance analysis (BIA) as alternative second choice, are utilized for body composition analysis, using appendicular lean mass adjusted to body weight (ALM/W) for DEXA and skeletal muscle mass adjusted by weight (SMM/W) for BIA. Cut-off points validated for sex, ethnicity, and age stratum should be used for both strength and body composition [37].

In the context of obesity management and weight loss, the risk of inducing SO should be considered, particularly when treating older people with obesity-related complications. So far, only resistance training physical exercise has been shown to be effective in reducing loss of strength and lean mass in dieting older adults with obesity [41]. More research is needed on therapeutic strategies able to prevent SO as a negative consequence of obesity management.

Pharmacotherapy for the treatment in obesity in 2023

Barbara McGowan

Obesity significantly increases the risk of various serious health conditions including T2D, hypertension, atrial fibrillation, dyslipidemia, sleep apnea, heart failure, and osteoarthritis.

Weight loss can significantly improve several of these conditions, with even a modest 5% weight loss achieving amelioration in hypertension and hyperglycemia, but a 15% weight loss is required to achieve remission of T2D in those with early disease.

Historically, there has been a treatment gap in the management of obesity, with lifestyle interventions achieving around 3–7% weight loss and bariatric surgery achieving 25–30%. This gap has recently been bridged by effective new gut hormone pharmacotherapy which is now able to play a significant role in the management of the disease.

The weekly injectable GLP-1 agonist semaglutide 2.4 mg (Wegovy) has demonstrated double digit weight loss, with the STEP-1 clinical trial showing an average weight reduction of 15.6% over 68 weeks [42]. The SELECT study has highlighted its cardiovascular benefits, reducing major adverse cardiovascular events (MACE) by 20% in subjects living with overweight or obesity with established cardiovascular disease and no T2D [43]. In patients with heart failure with preserved ejection fraction and obesity, treatment with semaglutide 2.4 mg has shown larger reductions in symptoms and physical limitations and greater improvements in exercise function.

Tirzepatide (Mounjaro), an injectable dual gastric inhibitory peptide (GIP) and GLP-1 receptor agonist, has demonstrated an even greater mean weight loss of over 20% at the highest dose of weekly tirzepatide 15 mg in the SURMOUNT-1 trial [44]. Both semaglutide 2.4 mg and tirzepatide are approved for the treatment of obesity.

Looking ahead, there are promising gut hormone therapies in Phase 2/Phase 3 clinical trials, including oral GLP-1 therapies such as semaglutide (25 mg and 50 mg) and the oral non-peptide GLP-1 agonist orforglipron [45]. Initial Phase 2 clinical trial results for dual/triple injectable incretin agonists are also arousing great interest, including those for the GLP-1/GIP/glucagon receptor agonist retatrutide [46], and those for the combination of the amylin analog cagrilintide with semaglutide 2.4 mg, both now in Phase 3 clinical trials.

Common side effects of these medications are mainly gastrointestinal and need to be managed via slow titration during an escalation phase. However, the medications are generally well-tolerated and thus far, no major safety concerns have arisen from the clinical trials.

These new gut hormone treatments for obesity are a welcome addition for patients living with obesity. However, supply has out-stripped demand for medications such as semaglutide 2.4 mg and tirzepatide, leading to global shortages of these drugs. Future medications, especially the non-peptide oral GLP-1 agonists, are exciting developments in the pipeline for obesity management and likely to significantly impact management of this disease over the coming years.

Combination of bariatric surgery with pharmacotherapy for the treatment of obesity

Amanda Yuan Ling Lim, Alexander Dimitri Miras

Greater weight loss leads to greater health benefits in patients with obesity. Metabolic and bariatric surgery (MBS) is currently the most effective treatment for obesity, although there is great heterogeneity in the response to MBS. There remains a significant clinical gap among patients who have undergone MBS and have experienced primary suboptimal response (i.e., suboptimal weight loss after surgery) or secondary suboptimal response (i.e., weight regain after initial weight loss after surgery).

Combination treatment of surgery with pharmacotherapy is a key component in filling this gap. In the past decade, there has been a revolution in obesity pharmacotherapy with safe and effective gut hormone analogs (e.g., liraglutide and semaglutide). In clinical practice, there are many practitioners prescribing medications to patients after MBS with suboptimal outcomes [47]. However, only a few randomized double-blind placebo-controlled trials have been conducted [48–50].

The GRAVITAS study investigated the use of liraglutide 1.8 mg for the treatment of persistent or recurrent T2D in patients with previous MBS. Liraglutide 1.8 mg use was associated with a HbA1c change of -13.3 mmol/mol over placebo and a total weight change of -5.26 kg from baseline to 26 weeks [48]. The BARI-OPTIMISE study investigated the effect of liraglutide 3.0 mg on weight in patients with

suboptimal weight loss and GLP1 response after MBS. Liraglutide 3.0 mg was associated with greater percentage weight change of -8.82% over placebo at 24 weeks [49]. Liraglutide was well-tolerated and there was no increase in rates of severe adverse events. In both trials, weight loss had not plateaued by the end of the trial period at approximately 6 months. The weight responses after both trials were probably higher than expected based on the use of these medications in unoperated patients. This raises the possibility of additive or synergistic effects between the two treatments.

In another randomized double-blind placebo-controlled trial conducted by Thakur et al., liraglutide 3.0 mg initiated 6 weeks post-operatively after sleeve gastrectomy was associated with a total weight loss of 28.2% at 6 months, which was 5.0% weight loss more than sleeve gastrectomy with placebo. This result was not statistically significant, possibly due to the small sample size [50]. Compared to the previous two studies, liraglutide was initiated early post-operatively and the selection of patients was not limited to patients with suboptimal metabolic or weight response to surgery.

The use of other obesity pharmacotherapy, particularly phentermine-topiramate, in patients with suboptimal response after MBS appears to be beneficial. However, most of the supporting literature is composed of observational cohort studies or case series [47]. There are as yet no published randomized controlled trials on the use of semaglutide in this population, although the BARI-STEP study (NCT05073835) investigating semaglutide in patients with suboptimal weight loss after MBS is currently underway. There are upcoming drugs, such as combination agonists, with even greater weight loss efficacy anticipated as primary obesity treatment.

As more patients undergo MBS, suboptimal weight loss and weight regain will inevitably become more prevalent. Pharmacotherapy seems to be an effective tool to support weight loss after MBS. Further studies are required to investigate various types of pharmacotherapy as well as patient and drug selection, long-term efficacy, and safety. This needs to be done while addressing the cost and access to novel therapies, which remain a significant barrier to patients and health systems.

Adrenal and gonadal disorders

Adrenal masses: When to be concerned about malignancy. What to do early on in work-up. What to do in the case of adrenocortical carcinoma

Gary D. Hammer

Adrenocortical masses are relatively common and can represent a wide array of either systemic or adrenal-specific diseases, some benign and others lethal. Management requires careful attention to systemic signs/symptoms. There are three key decisions that a clinician must make when confronted with adrenal masses, as follows: (**1**) evaluate the possibility (based on clinical history) of any systemic diseases that may manifest with unilateral or bilateral enlargement; (**2**) determine the risk of malignancy of the observed lesions; and (**3**) identify any adrenal hormone excess that would support a "primary" adrenal process, whether functional and/or anatomical, benign or malignant [51].

Adrenocortical carcinoma (adrenal cancer or ACC) is a rare malignancy which requires multidisciplinary care to manage the multiple endocrine and oncologic manifestations of the disease. We have used a variety of recently published international guidelines regarding adrenal masses to illustrate essential components of the standard of care work-up, diagnosis, and management of unilateral and bilateral adrenal masses, including ACC. Given that an understanding of genetics is becoming increasingly mainstream in cancer biology and care, including adrenocortical carcinoma, we discussed the burgeoning work in endocrine genetics and the current efforts to translate such work into better strategies for diagnosis and for the development of targeted therapies for the treatment of adrenal cancer.

The possibility must be borne in mind that any unilateral or bilateral enlargement might represent an adrenal primary hyper-functional state or, on the contrary, an extra-adrenal infiltrating disease that presents with adrenal insufficiency. The oncologic risk of malignancy must always be assessed. Given the significant variability in presentation and patient course, as well as the rarity of primary malignancies presenting as bilateral enlargement, these cases are best evaluated and cared for by the endocrinologist while also being referred at times to specialized centers. The initial differential diagnosis of adrenal enlargement, which is very wide, is guided in part by history, demographics, and coexisting medical conditions. While the full evaluation of adrenal masses was beyond the scope of this session, the nature of bilateral masses may become clear with a careful history, physical and biochemical testing, and careful imaging review with an expert radiologist. Bilateral adrenal masses represent the rare situation where biopsy is at times indicated in the diagnostic work-up [52–55].

In summary, this session was designed to cover a number of important issues regarding the diagnosis and treatment of solitary and unique bilateral adrenocortical masses through discussion of a number of cases seen in our multidisciplinary endocrine oncology clinics. Additional goals of this talk were to better understand the role of genetics in the pathobiology of adrenal cancer and to discuss

the ways in which such knowledge is transforming how we care for our patients. The answers to these questions are essential in the initial work-up of any adrenal "enlargement" and will guide how the endocrinologist, surgeon, and/or oncologist will proceed with additional diagnostic and/or therapeutic interventions. Cases were presented and discussed.

Diagnostic and therapeutic approach of male hypogonadism

Dimitrios G. Goulis

The two classical types of hypogonadism are the hypergonadotropic and the hypogonadotropic forms. However, symptoms and signs of low testosterone (T) concentrations in men become commoner with increasing age, presence of comorbidities, use of medications, and lifestyle choices. When confirmed by appropriate T assays, this condition is referred to as functional hypogonadism (Table 4). Three key studies enhanced our knowledge on functional hypogonadism, as follows: EMAS (the European Male Aging Study) quantified its prevalence, while the T-trials (Testosterone Trials) focused on the effect and the TRAVERSE study (Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men) was centered on the safety of testosterone replacement therapy (TRT).

Epidemiology EMAS [56] studied a random population sample of 3369 men (age 40—79 years) at eight European centers acquiring data on general, physical, sexual, and psychological health. The prevalence of hypogonadism in this population group was approximately 2%. These data imply that, for every million people of the general population, it is expected that 25 men will have Kallmann syndrome (1:20.000 in males), 500 Klinefelter syndrome (1:1000 in males), and more than 5000 functional hypogonadism (2:100 in middle-aged and elderly males).

Efficacy TRT constitutes the main treatment for men with any type of hypogonadism. The T-Trials [57] assigned 790 men (age ≥ 65 years) with a serum T concentration < 275 ng/dL (9.5 nmol/L) and symptoms of hypogonadism to receive either T gel or placebo gel for 1 year. TRT had a moderately beneficial effect on sexual function and some beneficial effect on mood and depressive symptoms but none on vitality or walking distance.

Safety TRAVERSE study [58] was a multicenter, randomized, double-blind, placebo-controlled, non-inferiority clinical trial. It recruited 5246 men (age 45—80 years) with pre-existing or a high risk of cardiovascular disease and confirmed hypogonadism, who were randomized to daily transdermal 1.62% T gel or placebo gel. The primary endpoint was the first occurrence of any component of a composite outcome (death from cardiovascular disease, non-fatal myocardial infarction, or non-fatal stroke). The study concluded that in men with hypogonadism and pre-existing or a high risk of cardiovascular disease, TRT was non-inferior to placebo concerning the incidence of major adverse cardiac events.

In conclusion, based on evidence from the EMAS, T-Trials and TRANVERSE studies, TRT is an effective and safe option for men with hypogonadism. Selection of patients with confirmed hypogonadism and appropriate monitoring constitute the pillars of a successful diagnostic and therapeutic approach.

Table 4 Causes of functional hypogonadism

Age
Ageing
Comorbidities
Chronic systemic disease
Acute or critical illness
Organ failure
Obesity
Type 2 diabetes
Sleep apnea
Medications
Drug-induced
Glucocorticoid excess
Lifestyle
Marijuana abuse
Alcohol abuse
Excessive exercise
Miscellaneous
Malnutrition
Iatrogenic

Considerations on the treatment of adults with Turner syndrome

Jennifer R Law

Turner syndrome (TS) affects up to 1:2,000 live female births and results when all or the distal p-arm of an X chromosome is missing [59]. Considering chromosome mosaicism, a 20-cell karyotype may be necessary for diagnosis [59]. In women over 50, up to 5% of cells can be 45 X due to aging. TS can affect nearly every organ system and TS phenotypes vary considerably. Comprehensive TS care guidelines by Gravholt et al. were published in 2017 [59]. A

suggested approach to comorbidity screening and treatment is summarized in Table 5. All individuals with TS should have comprehensive comorbidity screening for early detection and treatment and, hence, improved outcomes. The following are two illustrative, fictional cases that represent possible presentations of adult patients with TS.

Kendra is a 25-year-old woman who presents with her husband because she does not feel comfortable driving and wants help implementing her treatment plan. She was diagnosed with TS at age 10 years during a short stature evaluation and identified as having karyotype 45 X. Despite growth hormone use, she is 144.8 cm tall. She works in a childcare facility and desires to have children. She never had spontaneous puberty and labs have shown she has no ovarian reserve as her anti-mullerian hormone level is undetectably low and her follicle-stimulating hormone level is in the menopausal range. She uses continuous estradiol 0.1 mg transdermal patches and micronized progesterone 200 mg for 12 consecutive days each month. She has considered using a donor egg to conceive, but because a recent echocardiogram demonstrated a bicuspid aortic valve and moderately dilated aortic root, you counsel her that it would not be safe for her to carry a pregnancy. When reviewing her TS-related problem list, you see that she had recurrent ear infections as a child

Table 5 General overview of adult Turner syndrome comorbidities, suggested screenings, and suggested treatments[a]

Condition	Screening modality	Screening frequency	Treatment
Skeletal dysplasia	Physical exam	Annual	As per routine treatment of condition in otherwise healthy individuals
Premature ovarian insufficiency	FSH, AMH	Annual	Continuous use of estrogen, up-titrating every 6 months over 2–4 years (starting dose, possible final dose to normalize serum estradiol) - Estradiol patch (6.25, 100 mcg) - Micronized oral estradiol (0.25 mg, 2 mg) - Ethinyl estradiol (2 mcg, 20 mcg) - Monthly depot estradiol (0.2 mg, 2 mg) Oral progesterone added 10–14 continuous days per month after 2 years of unopposed estrogen: - Micronized progesterone 200 mg - Medroxyprogesterone 10 mg
Osteopenia	DXA, consider using Pediatric Bone Density Calculator tool to adjust bone mineral density results for short stature and age < 20 due to possibility of falsely low readings due to short stature [1, 2]	Every 5–10 years if normal	Optimize hormone replacement therapy, vitamin D supplementation, and treatment of other comorbid conditions such as hypothyroidism and celiac disease. Then manage per routine treatment of condition in otherwise healthy individuals
Cardiac anomaly	Echocardiography, Cardiac magnetic resonance imaging, or cardiac computed tomography	Every 5–10 years if normal	Per cardiology recommendations, hypertension management
Neurocognition and psychological differences	Neurocognitive testing, psychology screening	As needed	Clinical psychology and education support
Ear infections and hearing loss	Routine examination and audiogram	Every 3–5 years	Antibiotics, tympanostomy tubes, and hearing aids as needed
Autoimmune and skin conditions	Routine physical examination, TSH, tissue transglutaminase	Every 1–3 years	As per routine treatment of condition in otherwise healthy individuals
Renal anomaly	Renal ultrasound	Once at diagnosis	As per routine treatment of condition in otherwise healthy individuals
Hypertension	blood pressure monitoring, consider 24 h ambulatory blood pressure monitoring to detect loss of nocturnal dip in blood pressure	Every visit	As per routine treatment of condition in otherwise healthy individuals or cardiology recommendations
Metabolic and liver conditions	HbA1c, liver function tests	Annual	As per routine treatment of condition in otherwise healthy individuals

[a]Please refer to published comprehensive care guidelines for detailed recommendations [59]

and was diagnosed with mixed conductive and sensorineural hearing loss at 16 years. She also has hypothyroidism, diagnosed at age 19, and takes levothyroxine 75 mcg daily. She additionally has psoriasis but no history of celiac disease. Her DXA result trends have been followed with consideration that her baseline lumbar spine bone mineral density at age 19 was 0.74 gm/cm^2, which equaled a z-score of -3.0 but the Children's Hospital of Philadelphia Research Institute Pediatric Bone Density Calculator corrected the z-score to -1.5 when accounting for height and age [60].

Nadia is a 39-year-old female physician who was diagnosed with TS after her third pregnancy. During her most recent two pregnancies, she had abnormal noninvasive prenatal testing results that suggested sex chromosome aneuploidy. Further testing demonstrated normal fetal karyotypes. After the second incident of abnormal prenatal testing, Nadia was found to have 46,XX [22]/45,X[8] karyotype. She wears glasses for myopia and previously had surgery for strabismus. Nadia has never had an ear infection and has no concerns about her hearing. Her menses are normal. She has scoliosis but normal stature. She has chronic eczema, anxiety, and mild idiopathic hypertension. She had a normal renal ultrasound after TS diagnosis, but evidence of hepatosteatosis was found incidentally during the renal ultrasound. She also has prediabetes.

Neuroendocrine tumors

Congenital adrenal hyperplasia

Marina Tsoli, Djuro Macut, Gregory Kaltsas

The European Neuroendocrine Tumor Society (ENETS) has recently provided new guidelines for the management of gastroduodenal and appendiceal neuroendocrine tumors (NETs) as well as for carcinoid syndrome (CS) and carcinoid heart disease (CHD) [61–64]. The aim of these guidelines was to provide all relevant knowledge on these tumors and newly evolving data and to focus on areas of uncertainty and unmet needs.

Reporting of endoscopy in gastric NETs (g-NETs) should comprehensively characterize the neoplastic lesions (number, location, appearance, and size) and assess the surrounding gastric mucosa for the presence of atrophic gastritis and enterochromaffin-like (ECL) cells hyperplasia [64]. Evidence from several retrospective studies suggests that selected patients with g-NET type III and no lymph node involvement can be safely treated with endoscopic resection [61]. Hence, after adequate staging, endoscopic resection may be recommended in patients who have localized type III, grade 1, g-NETs $\leq$ 10 mm and, occasionally, larger tumors (< 15 mm) with Ki-67 < 10% [61].

A complete histological assessment is required in the case of appendiceal NETs (aNETs) [63]. Lymph node involvement in aNETs, when present, does not seem to be related to risk of recurrence or metastatic disease nor to overall survival per se. Conventional imaging may be suggested in patients with risk factors for residual or metastatic disease (> 2 cm in size and high G2 and G3 tumors), while functional imaging may be performed in the event of positive findings on conventional imaging. Tumor size, grade, and completion of surgery are the risk factors that need to be evaluated and guide the decision to proceed to right hemicolectomy (RHC) after the initial appendectomy. RHC is recommended in aNETs > 2 cm in size and in incomplete appendectomies (R1/R2) [63]. In resected 1–2 cm in size lesions, RHC may be suggested in high-grade aNETs, albeit these are relatively rare and, thus, a specific Ki67 cut-off value could not be recommended.

Carcinoid syndrome is predominately developed in patients with NETs of intestinal or lung origin and has a significant impact on the patient's quality of life. Carcinoid heart disease is a rare complication of CS characterized mainly by right heart failure [62]. Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) is considered an adjunct marker to echocardiography in screening for and monitoring of CHD [62]. Hence, NT-proBNP measurement is recommended as screening biomarker of CHD in all patients with increased urine 5-hydroxyindoleacetic acid (5-HIAA) levels and/or suspicious symptoms. Long-acting somatostatin analogs are considered the mainstay of treatment of CS, while prophylactic short-acting octreotide prior to and during invasive procedures is suggested to prevent carcinoid crisis. In the case of refractory CS, hepatic resection, locoregional therapies and peptide receptor radionuclide therapy (PRRT) are recommended to control the functioning syndrome and prevent CHD appearance or progression. Telotristat ethyl, an oral inhibitor of tryptophan hydroxylase, may be used for symptomatic improvement [62]. Surgical valve replacement is recommended for CHD treatment in the event of severe symptoms and at least 12 months of NET-related survival. The optimal timing of surgery should be individualized and decided under clear indication and optimal treatment [62].

Congenital adrenal hyperplasia: transition from pediatrics to adult care

Selma Feldman Witchel

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is an autosomal recessive disorder due to 21-hydroxylase *(CYP21A2)* gene variants. The spectrum of CAH ranges from classic forms with salt-loss and simple virilization to the non-classic form. Symptom severity and extent of enzyme dysfunction differentiate the various forms. The incidence of classic CAH is approximately 1 in 14,000,

whereas nonclassic CAH is more common with a reported incidence of 1 in 200 in American Whites [65].

Prenatal exposure to excessive adrenal androgens virilizes the external genitalia of affected female infants. When mineralocorticoid deficiency occurs, salt loss is generally apparent within the first 3 weeks of life. Treatment involves hormone replacement therapy with glucocorticoids and, if necessary, mineralocorticoids. Patient care involves monitoring auxologic parameters and clinical symptoms and taking hormone measurements. Hormone measurements include androstenedione, 17-hydroxyprogesterone, and 11-oxoandrogens. Current regimens fail to replicate the physiological cortisol circadian rhythm. Rather, treatment involves achieving a balance between under- and over-treatment [66].

Consequences of undertreatment include tall stature in childhood, excessive virilization, advanced skeletal maturation, hirsutism, infertility, adult short stature, and subfertility in adulthood. Overtreatment is associated with short stature, obesity, dysglycemia, and osteopenia in adulthood.

Eventually, infants and children with CAH transition to adult care providers. Transition is a pro-active planned process addressing medical, psychosocial, educational, and vocational needs. The health care paradigm shifts from active supervision to self-directed management while in the midst of fluctuating educational/work settings and an escalating propensity for risk-taking behaviors (Table 6). Relevant topics for review include fertility, sexuality, pathophysiology, knowledge of daily and emergency medications, medical alert ID, and potential chronic consequences such as obesity, osteopenia, dysglycemia, cardiovascular disease, and testicular adrenal rest tissue in boys and men (Fig. 4) [67].

Holistic patient-centered comprehensive care through the lifespan and especially during the transition from pediatric to adult care maximizes quality of life (QoL) and promotes the individual's independence [68]. Ongoing efforts to develop novel therapies will likely bolster therapeutic options and improve QoL for individuals with CAH [69].

Table 6 Factors relevant to transition in CAH

Patient factors
- Transition is a gradual planned process typically occurring concurrent with other developmental events
- Ascertain patient readiness and desire for transition recognizing the value of "a transition window" and individualized timing for transition
- Specific timetable for transition involves shared decision-making between patient and healthcare provider
- Assure that the patient has adequate knowledge regarding pathophysiology, medication needs, and past medical history
- Ensure that the patient can assume responsibilities for self-care and demonstrates the ability to call for medication refills, schedule appointments, and manage sick days
- Recognize dependency on parents/guardian and pediatric health care team
- Provide time for patient to talk to healthcare providers privately and confidentially
- Ascertain for poor adherence to recommended regimen
- Discuss and resolve unrealistic expectations of adult health care system
- Perform DEXA studies to assess bone mineral density
- Perform scrotal ultrasound in boys and young men to assess for testicular adrenal rest tissue (TART)
- For girls and emerging young women, gauge vaginal caliber regarding tampon use and sexual intercourse

Parent/Guardian factors
- Appreciate anxieties about new health care team, different hospital system, and other logistical issues
- Understand that patient and parents/guardians may be reluctant to leave pediatric health care team
- Acknowledge potential difficulties in identifying an appropriate adult health care provider/hospital
- Although parents/guardians often struggle to assume their new role as an advisor rather than the manager, they play an important role in encouraging youth to assume more responsibility
- Provide opportunities for parents/guardians to participate in educational events and discussions regarding their new roles

System factors
- Assure multidisciplinary health care across the health care system/team
- Patient and parent/guardian should meet adult health care providers prior to transition
- Assure mechanism to transfer/provide medical records to patient and new provider
- Provide a transition navigator/coordinator to help with scheduling initial appointment and to assure follow-up visits
- Increased flexibility with evening office hours and increased non-traditional communication via video-conferencing, email, patient portals, and texting
- Monitor outcomes

System issues
- Limited availability of adult providers with appropriate training
- Inadequate and inconsistent insurance coverage for follow-up visits and medications
- Imperfect infrastructure; need for adolescent/young adult friendly facilities
- Limited evidence-based guidelines for successful transitions
- Lack of adequate mental health/behavioral health services
- Insufficient communication among health care providers

Interactive case discussion session

Transitional neuroendocrinology

Cesar Luiz Boguszewski, Margaret Cristina da Silva Boguszewski

In this interactive session, medical management in the transition phase from childhood and adolescence to adulthood was discussed based on clinical cases of patients diagnosed with growth hormone deficiency (GHD), hypopituitarism, and Cushing disease.

The first case was a 5.5-year-old boy with slow growth and short stature exhibiting classical features of GHD on physical examination, such as frontal bossing, mid-facial hypoplasia ("doll-like" facies), and truncal adiposity. Other pituitary axes were normal. The case was used to explain the current algorithm to investigate a child with short stature, how to make the diagnosis of GHD, and the indications, therapeutic approach, and follow-up of GH therapy [70]. The second clinical case presented a 23-year-old female who complained of progressive chronic fatigue, asthenia, reduced muscle strength, and increased abdominal fat that started after discontinuation of GH therapy at the age of 15, which was started at the age of 6 due to growth retardation. She did not present spontaneous menarche and sex steroid replacement was initiated when she was 17, at the same time that she received the diagnosis of hypothyroidism and started treatment with levothyroxine. Her pituitary MRI was normal. From this case, the following topics were addressed based on published reviews and guidelines [71, 72]: (I) which patients should be investigated for GHD during transition; (II) how we should interpret IGF-1 levels and GH stimulatory tests to make the diagnosis of GHD in the transition; (III) which additional exams are required; (IV) how the initiation, maintenance, and follow-up of GH therapy should be pursued in these cases; and (V) how to manage the interaction between GH therapy with the replacement of other deficient pituitary hormones (Fig. 5A/B).

One additional case of a transitioning male patient diagnosed with isolated GHD at the age of 20 in consequence of a macroprolactinoma, with bone densitometry showing Z-scores of – 2.73 at the lumbar spine and – 2.51 at the femoral neck, associated with increased fat mass and decreased lean mass, was used to demonstrate the improvement and recovery of his body composition after 8 years of GH therapy. The latter case exhibited a positive effect of GH in attaining full skeletal maturation which we have demonstrated in a large group of individuals during the transition period [73].

The last clinical case was a 11-year-old girl who presented with slow growth in the last 2 years associated with weight gain, acne, mild hirsutism, hair loss, headache, and polydipsia. She had mild signs of hypercortisolism on physical examination (normal blood pressure, body mass index of 23.1 kg/m^2, truncal and cervical obesity, mild acanthosis on the neck, moon-like face, hirsutism, Tanner M1 P4). Her growth chart confirmed a deviation in the curve, from the 75th to the 10th percentile. Initial lab tests showed

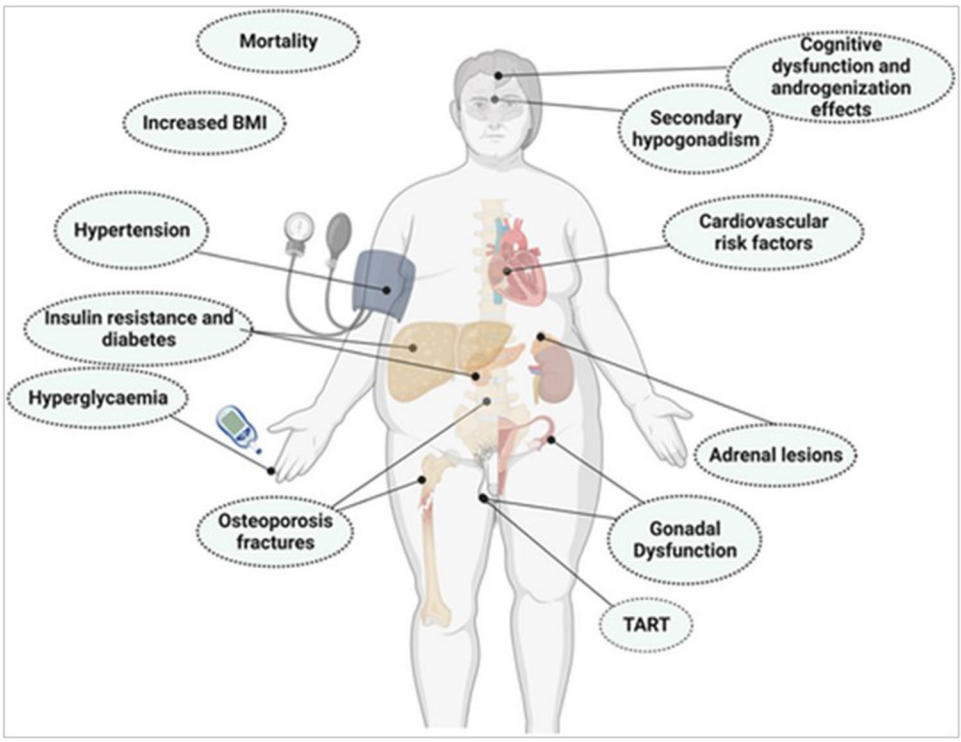

Fig. 4 Potential deleterious health consequences associated with classic CAH [67]

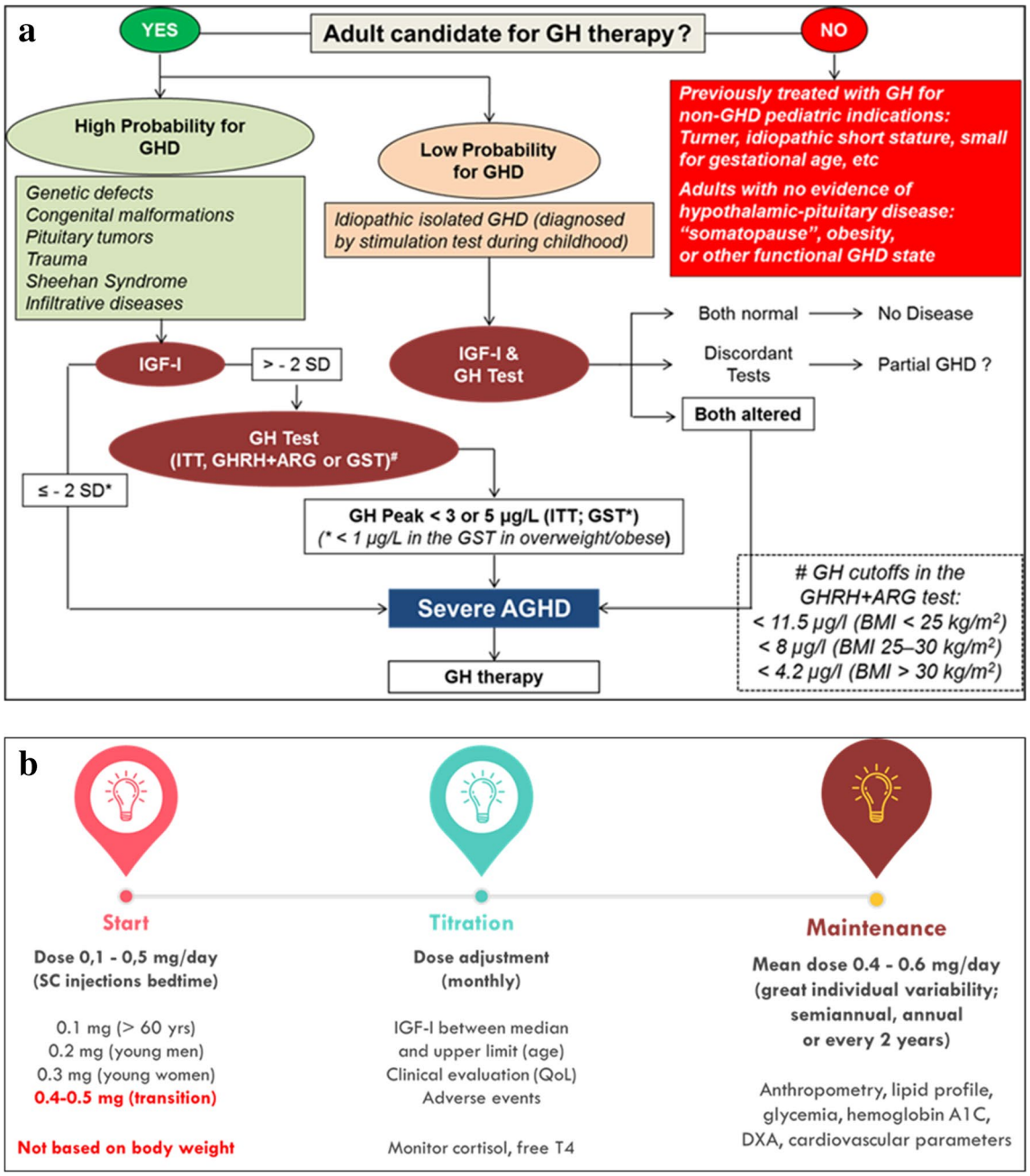

Fig. 5 Diagnostic (**A**) and therapeutic approach (**B**) of GH deficiency during transition phase. SD, standard deviation; ITT, insulin tolerance test; GHRH + ARG, GH releasing hormone + arginine; GST, glucagon stimulation test; BMI, body mass index; SC, subcutaneous; QoL, quality of life; DXA, Dual-energy X-ray Absorptiometry

normal urinary free cortisol (UFC) and loss of serum cortisol rhythm, but repeated tests confirmed the diagnosis of Cushing disease, with elevated UFC, no suppression of serum cortisol on the 1 mg dexamethasone suppression test, inappropriately normal ACTH levels, normal MRI, and inferior petrosal sinus sampling (IPSS) demonstrating a central source of ACTH secretion. At this point, the current recommendations were presented for the investigation and treatment of Cushing's syndrome during childhood [74]. The patient underwent transsphenoidal surgery with resection of a pituitary adenoma located in the posterior pituitary, developed deficiency of vasopressin (AVP), and GHD; she remained in remission for 4 years, when recurrence of hypercortisolism was detected. The pros and cons of the currently available therapies for recurrence of hypercortisolism were debated, including repeated pituitary surgery, radiotherapy,

medical therapy, and bilateral adrenalectomy [75]. She underwent a second transsphenoidal surgery, which resulted in permanent eucortisolism after 14 years of follow-up. She is now 29 years old, is on replacement therapy with GH, levothyroxine, sex steroids, and DDAVP, and is planning pregnancy. The session ended with discussions on fertility issues in women with hypopituitarism.

Adrenal disorders

Duarte Pignatelli, Selma Feldman Witchel

In this interactive session, several interesting cases were discussed mainly addressing CAH and adrenal cortex tumors. Although CAH in its most severe (classic) form is a rare disease, the non-classic form of the disease is fairly frequent, being one of the most common genetic diseases in humans in adulthood. Given that it is a genetic disease, the first important issue is when to perform genotyping in suspected cases. A consensus was reached that this was most important for genetic counseling in couples planning to attempt pregnancy. However, it can also be important for the confirmation of diagnosis and to be aware of the possibility of the patient's having a severely affected allele together with a mild mutation in the other allele. All of these situations result from the fact that these patients are usually compound heterozygotes with different genetic variants in the two alleles, which can result in the possibility of a progenitor with a milder form of the syndrome giving birth to a child with the classic form [76].

The second aspect that was discussed was how to deal with a pregnancy in a patient with a severe form of the disease. If the father does not have any mutation, the treatment only needs to be delivered to the mother and, for this purpose, the use of hydrocortisone (or another glucocorticoid that does not cross the placenta) is warranted as it is not able to affect fetal development. If however both parents have severe genetic variants as, for example, in a couple with the mother having the classical form and the father being a carrier of one of the severe mutations (which occurs in 1/60 persons in the general population), it will then be important first to identify the gender of the fetus, since, if it is male, there will be no need for treatment during pregnancy. If on the other hand the embryo is female, the need to treat should be considered, although only in specialized centers with the possible administration of dexamethasone, the only commercialized glucocorticoid that crosses the placenta and blocks excessive androgen secretion by the adrenals of a female fetus, which might lead to prenatal virilization. The problem is that this treatment should be started between 6 and 8 weeks of pregnancy and, at present, we are not able to determine the fetal genotype until later on during the pregnancy. Only at that time will we be able to know if the fetus carries the two severe genetic variants that their parents carry and only if they are not present can treatment with dexamethasone be interrupted [77].

Adrenal tumors are very frequent in the general population. They are rarely malignant or catecholamine-secretory and, therefore, the majority of patients do not need to undergo surgery. Most adrenal tumors are found incidentally and, in these cases, the presence of genetic variants of the 21-hydroxylase gene is only marginally augmented. The question of the existence of an increment of cardiovascular risk in adrenal incidentalomas is a complex one, since the existence of metabolic syndrome is, in its turn, considered as predisposing to these tumors. When tumors are cortisol-secreting, giving rise to clinical Cushing syndrome, they generally need to be surgically removed, and there is a post-operative risk that the patients will go through a period of hypocortisolism (known as an adrenal crisis). This leads most clinicians to prescribe glucocorticoid treatment after surgery, but, in fact, many cases do not need this treatment. In consequence, some patients may be exposed to hazardous treatments, which, besides involving well known risks, need to be tapered slowly before withdrawal can be done safely. A good rule to follow is to avoid unnecessary use of postoperative glucocorticoid treatments based on the fact that when a cortisol-secreting adrenal tumor is removed, there is no need to start replacement with glucocorticoids immediately. In fact, this can be postponed until the next morning, thus allowing a blood sample to be taken at 8.00 AM before starting glucocorticoid therapy; then, if the cortisol level is above 15 µg/dL, one can immediately stop the corticotherapy because the remaining adrenal has been demonstrated as secreting sufficient amounts of cortisol to avoid adrenal insufficiency. If, on the contrary, cortisol levels are below 5 µg/dL, there is a considerable risk of the development of an adrenal crisis resulting in the patient needing to continue to taking glucocorticoids for a period of time.

Conclusion

EndoBridge 2023 provided a valuable platform for exchange of the latest clinical knowledge and expertise in the field of endocrinology. Addressing a wide array of significant topics in the field, from treatment of acromegaly to subclinical hypothyroidism, from controversies on impact of vitamin D supplementation on health outcomes to sarcopenia or treatment of adult Turner syndrome, the scientific sessions of the annual meeting delivered the latest data and enabled thorough in-depth face-to-face discussions on a large number of interesting and challenging clinical cases—these composing a wide array of real highlights and pearls among the many issues that were incorporated.

Bringing together a diverse audience of over 6500 participants from 95 countries since its first launch in 2013, EndoBridge has evolved into a hub for the global sharing of knowledge among numerous physicians and scientists coming from all over the world and with interest in the broad field of endocrinology. In an era during which bridging connections matters more than ever, the unique and highly influential model of EndoBridge continues to serve as a invaluable platform for physicians and scientists worldwide to exchange experiences, share perspectives, and partake in discussions with global leaders in endocrinology. The 12th Annual Meeting of EndoBridge will be held on October 17–20, 2024 in Antalya, Turkey.

Declarations

Conflict of interest B.O.Y., O.C., D.G.G, M.R.H., J.R.L., A.Y.L.L., D.M., M.E.P., R.P.P., D.P., H.S., J.S., S.F.W., D.Y. have no relevant disclosures to report. C.L.B. has received consultant/speaker fees from Novo Nordisk, Recordati and Ipsen; participated as clinical investigator in international multicentric trials of Crinetics. M.C.D.B. has received consultant/speaker fees from Novo Nordisk and Pfizer. L.B. has received honoraria for lectures from Rhythm Pharmaceuticals and PronoKal as well as payment of honoraria for attendance to advisory boards from Lilly, Pfizer, Bruno Farmaceutici, and Novo Nordisk. G.E.F. has received travel support from Abiogen. G.D.H. is the founder of Millendo Therapeutics. G.K. has received honoraria from Ipsen, Sanofi, Recordati and research funds from Ipsen, Recordati, FARAN and Pfizer. A.L. has received consulting fees from Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk and Sanofi. B.M. is a shareholder and board member of Reset Health, has received advisory fees from Novonordisk, J&J Ethicon, Lilly, fees for educational work from Lilly, Novonordisk, BI, Janssen, MSD, Sanofi, Astra Zeneca, institutional research grant support from Novonordisk. M.M. has received honoraria for speaking and consulting fees from Amgen and honoraria for speaking from UCB and Alexion. M.M. is a member of the Boards of the International Osteoporosis Foundation and the American Society of Osteoporosis Practitioners and just completed a 6-year term as a Board member of the North American Menopause Society. A.D.M. has received research funding from the MRC, NIHR, Jon Moulton Charitable Foundation, Fractyl, Gila, Randox and Novo Nordisk. A.D.M. is a shareholder in the Beyond BMI clinic, which provides clinical obesity care. C.A.S. serves as a consultant to ELPEN, SteroTx, and Lundbeck pharmaceuticals; has received a research grant from Pfizer for the study and treatment of acromegaly; and holds patents on the defects and function of the PRKAR1A, PDE11A, and GPR101 genes. M.T. has received honoraria from Ipsen and FARAN. A.J.vdL has received consultancy fees or speakers fee of Amolyt Pharma SA, Crinetics Inc and Ipsen Pharma.

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