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Complications of Treatment

Endocrine-metabolic assessment checklist for cancer patients treated with immunotherapy: A proposal by the Italian Association of Medical Oncology (AIOM), Italian Association of Medical Diabetologists (AMD), Italian Society of Diabetology (SID), Italian Society of Endocrinology (SIE) and Italian Society of Pharmacology (SIF) multidisciplinary group

Maria Chiara Zatelli [a,1,*], Antongiulio Faggiano, MD [b,1], Antonella Argentiero [c], Romano Danesi [d], Stella D'Oronzo [e], Stefano Fogli [f], Tindara Franchina [g], Francesco Giorgino [h], Nicola Marrano [h], Dario Giuffrida [i], Stefania Gori [j], Giampiero Marino [k], Rossella Mazzilli [b], Matteo Monami [l], Monica Montagnani [m], Lelio Morviducci [n], Annalisa Natalicchio [h], Alberto Ragni [o], Valerio Renzelli [p], Antonio Russo [q], Laura Sciacca [r], Enzo Tuveri [s], Gianluca Aimaretti [t], Angelo Avogaro [u], Riccardo Candido [v], Massimo Di Maio [w], Nicola Silvestris [g,2], Marco Gallo [o,2]

[a] *Section of Endocrinology, Geriatrics and Internal Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy*
[b] *Endocrinology Unit, Department of Clinical & Molecular Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy*
[c] *Medical Oncology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy*
[d] *Oncology and Haematology Dept, University of Milano "La Statale", Milano, Italy*
[e] *Interdisciplinary Department of Medicine, University of Bari Aldo Moro, Bari, Italy*
[f] *Clinical Pharmacology and Pharmacogenetics Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[g] *Medical Oncology Unit, Department of Human Pathology "G. Barresi", University of Messina, Messina, Italy*
[h] *Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari, Italy*
[i] *Department of Oncology, Istituto Oncologico del Mediterraneo, Viagrande, Catania, Italy*
[j] *Oncologia Medica, IRCCS Ospedale Don Calabria-Sacro Cuore di Negrar, Verona, Italy*
[k] *Internal Medicine Department, Ospedale dei Castelli, Asl Roma 6, Ariccia, RM Italy*
[l] *Diabetology, Careggi Hospital and University of Florence, Italy*
[m] *Department of Precision and Regenerative Medicine and Ionian Area, Section of Pharmacology, University of Bari Aldo Moro, Bari, Italy*
[n] *Diabetology and Nutrition Unit, Department of Medical Specialties, ASL Roma 1 – S. Spirito Hospital, Rome, Italy*
[o] *Endocrinology and Metabolic Diseases Unit, Azienda Ospedaliero-Universitaria SS Antonio e Biagio e Cesare Arrigo of Alessandria, Alessandria, Italy*
[p] *Diabetologist and Endocrinologist, Italian Association of Clinical Diabetologists, Rome, Italy*
[q] *Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy*
[r] *Department of Clinical and Experimental Medicine, Endocrinology Section, University of Catania Catania, Italy*
[s] *Diabetology, Endocrinology and Metabolic Diseases Service, ASL-Sulcis, Italy*
[t] *Endocrinology, Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy*
[u] *Department of Medicine, Section of Diabetes and Metabolic Diseases, University of Padova, Padova, Italy*
[v] *Department of Medical Surgical and Health Sciences, University of Trieste, 34149 Trieste, Italy*

* Corresponding author at: Section of Endocrinology, Geriatrics and Internal Medicine, Department of Medical Sciences, University of Ferrara, Via Fossato di Mortara, 64/B - 44121 Ferrara, Italy.

E-mail addresses: ztlmch@unife.it (M.C. Zatelli), antongiulio.faggiano@uniroma1.it (A. Faggiano), argentieroantonella@gmail.com (A. Argentiero), danesi.romano@gmail.com (R. Danesi), stella.doronzo@uniba.it (S. D'Oronzo), stefano.fogli@unipi.it (S. Fogli), tindara.franchina@unime.it (T. Franchina), francesco.giorgino@uniba.it (F. Giorgino), nicola.marrano@uniba.it (N. Marrano), dgiuff57@gmail.com (D. Giuffrida), stefania.gori@sacrocuore.it (S. Gori), giampiero.marino@aslroma6.it (G. Marino), rossella.mazzilli@gmail.com (R. Mazzilli), matteo.monami@unifi.it (M. Monami), monica.montagnani@uniba.it (M. Montagnani), leliomorviducci@gmail.com (L. Morviducci), annalisa.natalicchio@uniba.it (A. Natalicchio), alberto.ragni@ospedale.al.it (A. Ragni), valerio.renzelli@gmail.com (V. Renzelli), antonio.russo@usa.net (A. Russo), laura.sciacca@unict.it (L. Sciacca), enzo.tuveri@gmail.com (E. Tuveri), gianluca.aimaretti@med.uniupo.it (G. Aimaretti), angelo.avogaro@unipd.it (A. Avogaro), riccardo.candido@yahoo.it (R. Candido), massimo.dimaio@unito.it (M. Di Maio), nicola.silvestris@unime.it (N. Silvestris), marco.gallo@ospedale.al.it (M. Gallo).

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[w] Department of Oncology, University of Turin, Turin, Italy

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ABSTRACT

Immunotherapy with immune checkpoint inhibitors (ICI) is increasingly employed in oncology. National and international endocrine and oncologic scientific societies have provided guidelines for the management of endocrine immune-related adverse events. However, guidelines recommendations differ according to the specific filed, particularly pertaining to recommendations for the timing of endocrine testing. In this position paper, a panel of experts of the Italian Association of Medical Oncology (AIOM), Italian Association of Medical Diabetologists (AMD), Italian Society of Diabetology (SID), Italian Society of Endocrinology (SIE), and Italian Society of Pharmacology (SIF) offers a critical multidisciplinary consensus for a clear, simple, useful, and easily applicable endocrine-metabolic assessment checklist for cancer patients on immunotherapy.

Introduction

Immunotherapy has revolutionized tumour treatment by harnessing the power of the immune system to fight cancer. Anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimumab and tremelimumab), anti-programmed cell death protein 1 (PD-1) (nivolumab, pembrolizumab, cemiplimab, and dostarlimab), and anti-programmed death-ligand 1 (PD-L1) (atezolizumab, avelumab, and durvalumab) monoclonal antibodies are among the most widely used immunotherapeutic agents for a variety of malignancies [1,2]. These agents block inhibitory immune checkpoints allowing T-cells to recognize and attack cancer cells [3]. Based on the tumor immune-microenvironment complexity, the immune checkpoint inhibitors (ICI) were approved either as single agents or as combination therapy with a further ICI or other chemotherapy and targeted therapies, uncovering a broader toxicity landscape [4]. Indeed, although immunotherapy has shown impressive clinical responses, it also has the potential to activate significant autoimmune "off-target" effects, including endocrine adverse events (AEs). These endocrine toxicities are relatively frequent and can affect thyroid, parathyroid glands, pituitary, adrenal, and pancreas, resulting in hypothyroidism, hyperthyroidism, thyroid eye disease, hypoparathyroidism, hypophysitis, adrenal insufficiency, or hyperglycemia [5]. Usually, immune-related (ir) endocrinopathies appear after 3–6 weeks of therapy, but they can develop at any time, even after the end of treatment [6,7]. The complexity of endocrine ir AEs (irAEs) management also includes the less known role of possible risk factors (such as family or personal history of autoimmune disease, preexistent endocrine dysfunction, genetic predisposition, etc…) that could facilitate their onset. In most cases endocrine irAEs are mild (grades 1 and 2 according to the Common Terminology Criteria for Adverse Events, CTCAE) but often lead to chronic damage and permanent loss of organ function. Thus, endocrine lifelong replacement therapy could be needed, even though a delay or interruption of ICI treatment is often not necessary [4].

Since endocrine AEs may overlap with symptoms related to the oncological disease or other associated cytotoxic treatment, the identification of endocrine toxicities can be difficult. Therefore, the development of a standardized checklist for endocrine assessment of cancer patients on immunotherapy is of outmost importance. This checklist would enable healthcare providers to identify and manage endocrine toxicities in a timely and effective manner, improving patient outcomes and quality of life.

To date, national and international endocrine and oncologic scientific societies have published at least seven guidelines for the management of endocrine irAEs [8–15]. However, there are disagreements among the guidelines, particularly pertaining to recommendations for the timing of endocrine testing. Furthermore, most guidelines primarily focus on baseline testing and clinical management of overt irAEs; recommendations for longitudinal endocrine surveillance during ICI treatment and through post-treatment follow-up are limited. Therefore, further refinement is still required to define optimal surveillance algorithms covering the entire continuum of care. Harmonizing consensus protocols for endocrine assessment across treatment and survivorship could help regulate early irAE detection while improving patient outcomes as well as healthcare resource utilization. Overall, pre-treatment and ongoing assessment of endocrine function should include a detailed medical history, physical examination, and laboratory tests, including thyroid function tests, hypothalamic–pituitary–adrenal (HPA) axis assessment, and glucose monitoring. Patients at higher risk for endocrine toxicities, such as those with pre-existing autoimmune diseases, should be more carefully monitored. Furthermore, a specialized management of endocrine conditions is critical to ensure timely diagnosis and appropriate treatment to prevent long-term complications. Thus, endocrine disfunctions should be managed by an endocrinologist, who has specialized training in the diagnosis and treatment of these conditions. Hence, a multidisciplinary approach involving oncologists, endocrinologists, and other healthcare professionals is necessary for effective disease management and optimal patient outcomes.

In this position paper, a panel of experts of the Italian Association of Medical Oncology (AIOM), Italian Association of Medical Diabetologists (AMD), Italian Society of Diabetology (SID), Italian Society of Endocrinology (SIE), and Italian Society of Pharmacology (SIF) provides a critical multidisciplinary consensus for a clear, simple, useful, and easily applicable endocrine-metabolic assessment checklist for cancer patients on immunotherapy.

Diabetes

ICIs-induced diabetes mellitus (DM) may appear because of treatment with CTLA-4, PD-1, PD-L1 ICIs [16]. Initially defined as an extremely rare but life-threatening side effect, more recent large case series confirmed rates ranging from 0.2 % up to 1.8 % [17]. Notably, all currently approved ICIs have been associated with an increased risk of incident DM. In fact, PD-1 and PD-L1 inhibitors, and to a less extent CTLA-4 inhibitors, have shown detrimental effects. Even if not fully clarified, genetic predisposition (HLA class II alleles and non-HLA susceptibility gene markers) may play a relevant role in the development of ICI-induced DM [18]. ICIs-induced DM occurs within days up to more than one year after starting ICIs and up to several months after ICIs discontinuation. Interestingly, ICIs-induced DM seems to be different from autoimmune type 1 DM (T1DM), such as older age at onset, lower HbA1c and low C-peptide levels at presentation, more frequent severe diabetic ketoacidosis (DKA), absence of 'honeymoon' periods, possible association with increased amylase and/or lipase plasma levels, suggesting a generalized pancreatic inflammation [19,20]. Moreover, in only 40–50 % of the cases T1DM-associated autoantibodies (against insulin, glutamic acid decarboxylase, islet antigen-2, and zinc

[1] Co-first authors.
[2] Co-last authors.

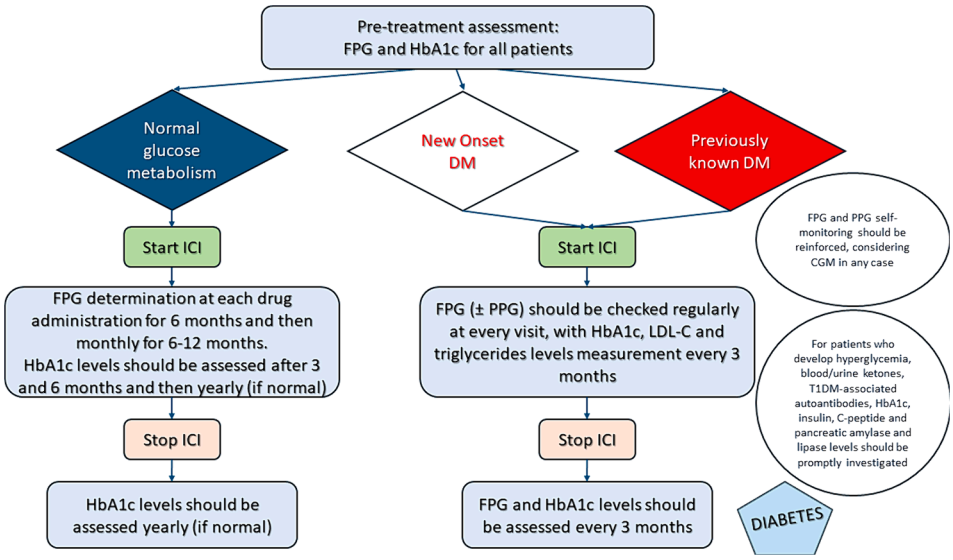

Fig. 1. Proposed flow-chart for the management of ICI-related diabetes. FPG: fasting plasma glucose. DM: diabetes mellitus. PPG: post prandial glucose. HbA1c: glycated hemoglobin. LDL-C: low density lipoprotein cholesterol.

transporter 8) have been reported, with anti-GAD antibodies as the most represented [21]. Risk factors for ICIs-induced T1DM appear to be pre-existing non-T1DM, younger age, combined use of ICIs. Almost all patients with ICIs-induced DM require lifelong insulin therapy [22]. In addition, ICIs seem associated with increased HbA1c levels in patients with pre-existing type 2 DM, often requiring the use of further hypoglycemic agents, including insulin [17].

Checklist for glucose disorders/diabetes

Since commonly ICIs-induced DM may present as fulminant diabetes associated with DKA, the onset of polyuria, polydipsia, weight loss, nausea, and/or vomiting should be promptly investigated in all patients independently of previously known DM. In addition, education for early recognition of signs and symptoms of hyperglycemia and DKA should be performed. Pre-treatment assessment includes fasting plasma glucose (FPG) and HbA1c levels evaluation for all patients. For patients without previously known DM, ongoing assessment consists of FPG determination at each drug administration for 6 months and then monthly for 6–12 months. HbA1c levels should be assessed after 3 and 6 months since the development of new-onset insulin-dependent diabetes often occurs after a median of four ICI cycles or 5 months [23]. After the first six months of follow-up, it appears conceivable to test HbA1c yearly (if normal) considering patients on ICIs at high risk for incident diabetes [24]. For patients with previously known DM, FPG (±post-prandial glucose, PPG) should be checked regularly at every visit, with HbA1c along with LDL-C and triglycerides levels measurement every 3 months. Self-monitoring of blood glucose (FPG and PPG) should be reinforced, considering continuous glucose monitoring (CGM) in any case [25]. For patients who develop hyperglycemia on ICI therapy, blood/urine ketones, T1DM-associated autoantibodies, HbA1c, insulin, C-peptide and pancreatic amylase and lipase levels should be promptly investigated (Fig. 1).

Thyroid disorders

Thyroid disorders are among the most common endocrinopathies related to ICIs therapy. They vary from overt hypothyroidism to overt hyperthyroidism, although the common pathophysiological basis seems to be destructive thyroiditis [26]. Therefore, thyroid function should be frequently monitored in patients treated with ICIs, even after therapy completion. Thyroid disorders appear more often in patients treated with anti-PD-1 agents or after combination therapy with ipilimumab and nivolumab, while they are less common after monotherapy with anti-CTLA-4 or anti-PD-L1 agents [26].

Usually, thyroid dysfunction presents as painless thyroiditis, which starts with a mild or asymptomatic thyrotoxic phase, progressing to euthyroidism or hypothyroidism [26]. In some other cases, subclinical or clinical hypothyroidism is the initial presentation, and it may be transient or permanent [26]. Notably, thyroid-related AEs have been associated with improved survival in cancer patients treated with ICIs [27,28], thus representing a possible predictive biomarker of treatment response [29].

Hypothyroidism is the most frequent manifestation of thyroid-related AEs in patients receiving ICIs, on average occurring ~63 days after initiation of ICI-combination treatment, and ~70 days after starting PD-1 inhibitors alone [30]. Hypothyroidism developed as ICIs treatment AE is often permanent and requires life-long levothyroxine replacement therapy [31,32]. On the other hand, patients who suffer from preexistent hypothyroidism should be closely monitored with thyroid function tests at all visits after initiation of ICIs to adjust levothyroxine replacement therapy doses [31,33]. New onset hypothyroidism is characterized by elevated TSH and low free T4 (fT4) levels, while subclinical hypothyroidism presents with elevated TSH and normal fT4 levels [34]. Importantly, primary hypothyroidism should be differentiated from central hypothyroidism, since hypophysitis should be always considered and assessed in these patients [26].

Conversely, thyrotoxicosis/hyperthyroidism is a less common endocrine AE than hypothyroidism among patients receiving ICIs and is mainly caused by the combination of different ICIs [30]. On average, it appears ~21 days after initiation of ICI-combination therapy, or ~47 days after starting PD-1 inhibitors alone, and often progresses to hypothyroidism after 3–6 weeks of treatment [30]. Overt thyrotoxicosis/hyperthyroidism is characterized by low TSH and elevated fT4 levels, while subclinical hyperthyroidism presents with low TSH and normal fT4 levels [34].

Differently from other symptomatic irAEs, treatment with ICIs should not be interrupted if thyroid disorders occur, unless severe symptoms or onset of ophthalmopathy occur. In those cases, ICIs therapy should be stopped until the symptoms disappear [30].

Checklist for thyroid disorders

Although the symptoms are usually mild and nonspecific, for early

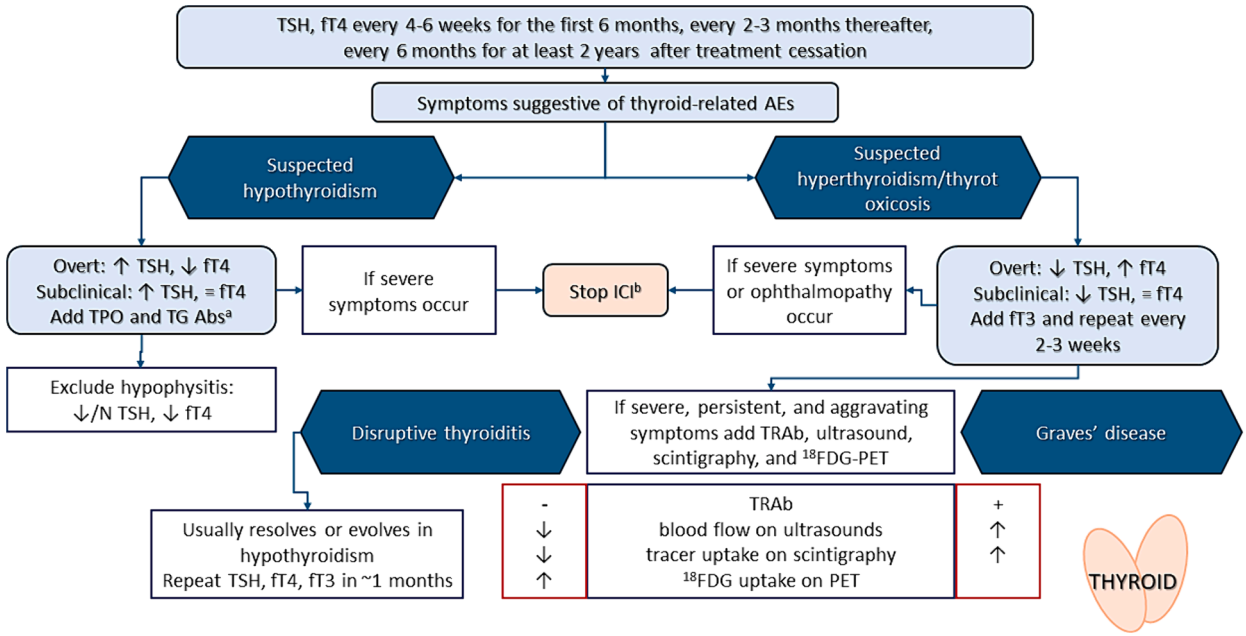

Fig. 2. Proposed flow-chart for the management of ICI-related thyroid alterations. ^{18}FDG-PET, 18-fluorodeoxyglucose uptake on positron emission tomography scan; Abs, antibodies; N, normal; TG, anti-thyroglobulin; TPO, anti-thyroid peroxidase; TRAb, anti-TSH receptor antibodies. [a]not necessary to confirm diagnosis but may represent a risk factor; [b]until the symptoms disappear.

detection of thyroid disorders as an AE developed after ICI treatment, an essential part of the routine monitoring should be the clinical investigation of symptoms suggestive of thyroid-related AEs (for hypothyroidism: weight gain, fatigue, cold intolerance, constipation, dryness of the skin, bradycardia, periorbital edema and tongue swelling; for hyperthyroidism/thyrotoxicosis: palpitations, heat intolerance, tremor, anxiety, emotional lability, weight loss in the presence of increased appetite, atrial fibrillation, hyperdefecation, oligo/amenorrhea in women, and erectile dysfunction in men) [24,28]. Additionally, TSH and fT4 levels should be screened before starting therapy, every 4–6 weeks after initiation of treatment for the first 6 months, every 2–3 months thereafter and every 6 months for at least two years after treatment cessation [11,15,26,35].

If hypothyroidism is suspected, anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) antibodies levels should also be measured. Elevated levels of thyroid autoantibodies are not necessary to confirm diagnosis, but they may represent a risk factor. On the other hand, if hyperthyroidism is suspected, fT3 may also be screened and, together with TSH and fT4, should be repeated every 2–3 weeks [12,15,26].

In patients with overt thyrotoxicosis with severe/persistent/aggravating symptoms, thyroid ultrasound, technetium or iodine scintigraphy, 18-fluorodeoxyglucose uptake on positron emission tomography scan (^{18}FDG-PET), and anti-TSH receptor antibodies (TRAb) evaluation might also be used for differential diagnosis [32,33,36]. Usually, diffuse enlargement, decreased blood flow, and low echogenicity of the thyroid gland could be observed in ICI-induced destructive thyroiditis [33,36]. Typically, reduced or absent tracer uptake on scintigraphy, and/or increased uptake ^{18}FDG-PET scan, associated with negative TRAb, confirm the diagnosis of destructive thyroiditis [36,37]. In contrast, high blood flow on Doppler ultrasound and high diffuse homogeneous iodine uptake, associated with high TRAb titers, are expected in Graves' disease, unlike destructive thyroiditis or toxic nodular goiter [26,33] (Fig. 2).

In patients with previously known thyroid disorder, the frequency of monitoring must be agreed with the endocrinologist based on the patient individual needs.

Parathyroid disorders

Even if rarely, the use of ICIs may also be related to primary hypoparathyroidism, characterized by acute hypocalcemia, with low or inappropriately normal levels of parathyroid hormone, and normal vitamin D, magnesium and phosphate plasma levels, and normal 24-hour urinary calcium excretion [38,39]. In some cases, autoantibodies against the calcium-sensing receptor have been identified [40,41]. In most cases, parathyroid dysfunction is irreversible, requiring continuous calcium and active vitamin D administration [30,39].

Checklist for parathyroid disorders

The possible presence of hypocalcemia should be evaluated before starting therapy, every 4–6 weeks after initiation of treatment for the first 6 months, every 2–3 months thereafter and every 6 months during the first 2–3 years post-therapy [26,38]. In case of hypocalcemia, parathyroid hormone levels should be monitored [39].

Primary adrenal insufficiency

Adrenal insufficiency (AI) can arise from a primary adrenal disorder, be secondary to adrenocorticotropic hormone (ACTH) deficiency, or a consequence of hypothalamus-pituitary axis suppression by exogenous glucocorticoids. It is a potentially life-threatening condition, which is increasingly recognized in malignancy [42,43]. Primary adrenal insufficiency (PAI) is characterized by low cortisol together with high ACTH levels. Clinical manifestations of PAI include hyponatraemia, hyperkalemia, hyperpigmentation, nausea, fatigue, non-specific symptoms that mimic other toxicities or disease manifestations: for this reason, the diagnosis is often delayed [42,43].

Even if ICI-associated PAI is a rare AE, it is very important to recognize this condition since it may impact on anti-tumor therapy efficacy and be life-threatening [15,26,43]. The pathophysiology is still not well defined but is likely mediated by autoimmune activation due to ICI [43]. A recent metanalysis analyzed 62 cohort studies and found 43 cases of any-grade PAI among 5831 patients (0.7 %), 14 of which (0.2 %) were graded 3 or higher [44]. More frequently, PAI was observed in

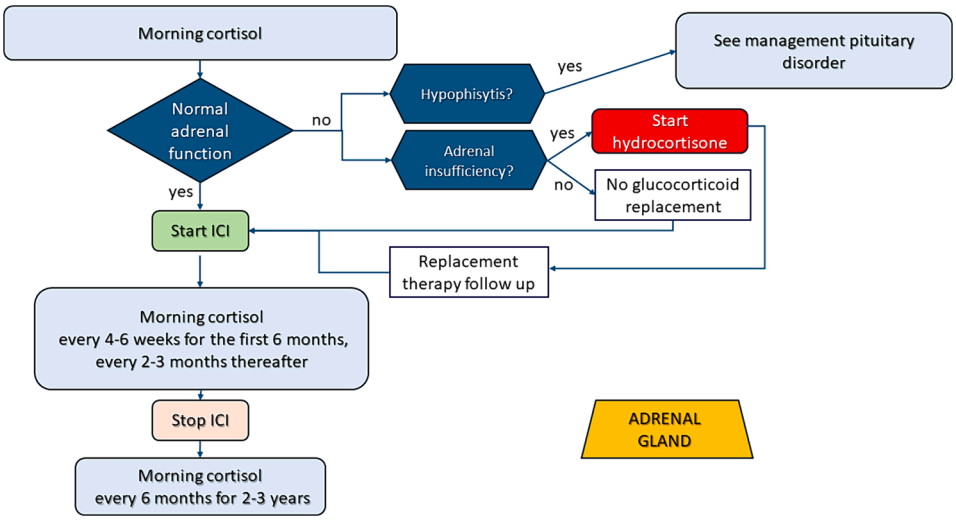

Fig. 3. Proposed flow-chart for the management of ICI-related adrenal gland alterations.

patients treated with ipilimumab, nivolumab and pembrolizumab, and in the subgroup of patients receiving a combination therapy, occurring, in the latter, in 4.2 % of cases [44–46]. Interestingly, the World Health Organization's (WHO) pharmacovigilance database of individual case safety reports analyzed a total of 50,108 ICI-associated adverse drug reactions (ADRs) from 2008 to 2018 [43]. Among them, 451 cases of PAI-irAE were identified, 45 of which were "definite PAI" and 406 "possible PAI". The mean age of the patients was 66 years (range, 30–95), 58.1 % were males, 41.2 % and 28.6 % had melanoma and lung cancer, respectively. Again, higher rates of PAI are reported after treatment with ipilimumab, nivolumab and pembrolizumab, or their combinations. Finally, PAI can occur with a median time to onset of 120 days (range, 6–576) [26]. This highlights the importance of thorough clinical monitoring throughout the entire treatment period.

Checklist for primary adrenal insufficiency

Morning plasma cortisol levels should be tested before starting ICI and every 4–6 weeks for the first 6 months of therapy. Then, testing should be carried out every 6 months for up to 2–3 years post-therapy [26]. If morning cortisol level is low (<5 μg/dl), this is indicative of AI and ACTH measurement should be performed, to differentiate between primary and secondary forms, together with basic metabolic panel (Na, K, glucose). Hormone assessment should be performed without interference of exogenous glucocorticoids; therefore, the cortisol level test is useless during chronic steroid administration. Finally, a glucocorticoid-induced AI should be always ruled out in cancer patients recently treated with steroids [41].

When basal cortisol levels range from 5 to 18 μg/dl, ACTH stimulation test (250 μg i.v.) is the gold standard tool to confirm diagnosis [24]. Peak cortisol levels below 18 μg/dl at 30 or 60 min indicate AI. In case of AI, precipitating causes of adrenal crisis such as infection should be checked, and adrenal CT should be performed to rule out adrenal metastasis/hemorrhage [26].

Of note, if AI is diagnosed together with hypothyroidism, cortisol must always be replaced before thyroid hormone therapy is initiated [15].

In case of asymptomatic or paucisymptomatic PAI, withdrawing ICIs until patient is stabilized on replacement hormone therapy (prednisone 5–10 mg daily or hydrocortisone 10–20 mg orally every morning and 5–10 mg orally in early afternoon) can be considered. The same path should be followed in case of moderate symptoms, with higher doses of replacement therapy (prednisone 20 mg daily or hydrocortisone 20–30 mg in the morning and 10–20 mg in the afternoon). In case of severe symptoms, ICIs withdrawal until patient is stabilized on replacement hormone plus normal saline infusion should be considered [15] (Fig. 3).

Primary hypogonadism

The potential impact of ICIs on gonadal function has not been adequately investigated [47], and the actual incidence of ICI-related hypogonadism remains unknown since gonadal hormone evaluations

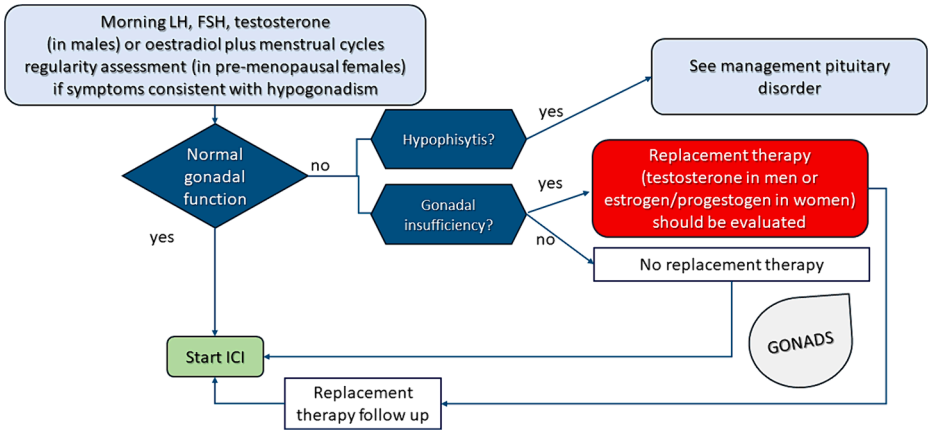

Fig. 4. Proposed flow-chart for the management of ICI-related gonadal alterations.

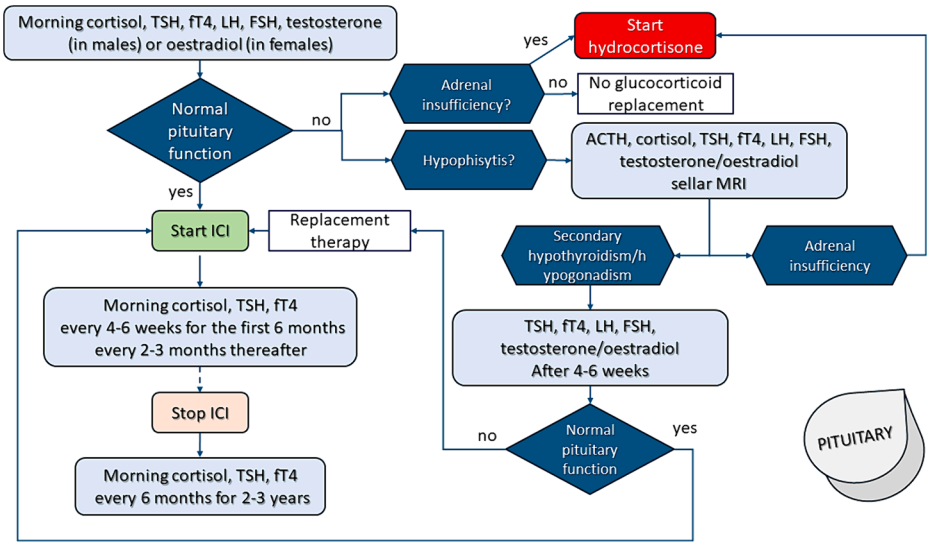

Fig. 5. Proposed flow-chart for the management of ICI-related pituitary alterations.

were not performed systematically [48]. A recent analysis of the WHO global database of individual case safety reports (between 2011 and 2019) found a significantly increased risk of hypogonadism because of ICIs therapy. Of the 13 reported cases, only 6 were carefully studied and, among them, 5 were defined as secondary and 1 as primary hypogonadism [47]. Though rare, orchitis and epididymo-orchitis were reported after therapy with ipilimumab-nivolumab and pembrolizumab, respectively [49–51]. Furthermore, an analysis of 13 patients with metastatic melanoma who underwent autopsy showed that 6 of the 7 men (86 %) treated with ICIs had impaired spermatogenesis, compared with the other 6 age-matched patients who did not receive ICIs [52]. Finally, no data are available on the potential effects on female gonadal function and fertility. Furthermore, teratogenic potential of ICIs in humans is not currently known. Data on pregnant mice show that treatment with ICIs dramatically increases the abortion rate [53].

Checklist for primary hypogonadism

Morning luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (in males) or oestradiol plasma levels plus menstrual cycles regularity assessment (in pre-menopausal females) should be evaluated before starting ICI in patients with symptoms consistent with hypogonadism (fatigue, loss of libido, and mood changes) [15,26]. If hypogonadism is confirmed, replacement therapy (testosterone in men or estrogen/progestogen in women) should be evaluated [26] (Fig. 4).

Pituitary disorders

Pituitary-related AE are among the firstly described ICI-related endocrine irAEs. A recent systematic review reports that, among 30,014 patients treated with ICIs, hypophysitis occurred in 3.20 % of the subjects (0–27.59 %) [53], more frequently in males and in the fifth decade, developing 4–5 months after treatment initiation[54]. Diagnosis is mostly based on clinical picture, hormonal evaluation and imaging studies, since assays measuring pituitary-related auto-antibodies are not performed in all centers. Pituitary gland enlargement, enhanced contrast uptake with swelling of the pituitary stalk and loss of neurohypophysial signal in the T1-weighed images are the main MRI findings [55]. Hypopituitarism is diagnosed in 0.42 % of patients (0–33 %) [56], being associated with symptoms including fatigue/malaise, nausea, weakness, headache, that could be difficult to differentiate from oncological symptoms. Visual disturbances, due to optic chiasm involvement, are rare [57]. These data indicate that, despite the incidence of hypophysitis is not negligible in ICI-treated patients, pituitary hormone deficits are rare. Nevertheless, attention should be paid to these patients, especially those undergoing combination therapy, since the most common hormonal changes are related to the corticotrophic, thyrotrophic and gonadotrophic axes. In severe cases, adrenal crisis can occur, which is a life-threatening condition requiring immediate medical attention. Therefore, early detection and management of pituitary-related AEs is crucial. Treatment typically involves the administration of hormone replacement therapy, that, in some cases, may be stopped thereafter. Indeed, pituitary axis function may recover, with total recovery being observed in 2–15 % of patients [58,59]. AI is frequently persistent, while hypothyroidism may recover [58]. High dose glucocorticoid therapy should be evaluated only in case of severe pituitary gland enlargement with mass effect symptoms (e.g. severe headache, visual disturbances related to optic chiasm compression, etc…). It should be emphasized that the development of pituitary-related AEs does not require ICI treatment withdrawal, if not otherwise indicated. It is important for healthcare providers and patients to be aware of these potential side effects when using ICIs, as early intervention can help mitigate the impact of pituitary-related issues and improve patient outcomes. Patients should also be educated about the signs and symptoms of these AEs to seek prompt medical attention if necessary. Treatment decisions should always be made in consultation with a qualified oncologist or endocrinologist, who can assess the risks and benefits of ICI therapy for each individual patient.

Checklist for pituitary disorders

Morning cortisol, TSH, fT4, LH, FSH, testosterone (in males) or oestradiol (in females) plasma levels should be checked before initiation of ICI therapy. Cortisol, TSH and fT4 levels should be checked every 4–6 weeks for the first 6 months of therapy and then every 2–3 months thereafter. After discontinuation of therapy (up to 2–3 years post-therapy), cortisol, TSH and fT4 levels should be checked every 6 months. In case of low cortisol levels, ACTH should be checked to differentiate between pituitary and adrenal involvement; when AI is suspected, a thorough clinical evaluation should be carried out to promptly initiate replacement therapy and other urgent treatments (e.g. iv hydration if needed). It is important to underline that, when suspecting AI, given its possible life-threatening consequences, prompt treatment should not be delayed while waiting for biochemistry test results. When hypophysitis is suspected, ACTH, cortisol, TSH, fT4, FSH,

Table 1
Proposal for an endocrine-metabolic assessment checklist in cancer patients on immunotherapy.

	ICI
Pre-treatment assessment*	
FPG, HbA1c	X
LDL-C, triglycerides	X
BP	X
Ca^{++}, P, Na^{+}, K^{+}	X
Cortisol (h 80.00)[ç]	X
TSH, fT4	X
Testosterone, LH, FSH (males)	X
FSH, LH, estradiol, menstrual cycles regularity (pre-menopausal females)	X
Antidiabetic therapy (if any)	X
Hormonal replacement therapy (if any)[§]	X
Ongoing assessment*	
Patients without previously known DM	
FPG & BP	at every drug administration for 6 months and then monthly for 6–12 months
HbA1c	after 3 months and then every year (if normal)
Other aspects	education for early recognition of symptoms of hyperglycemia **and DKA**
Patients without previously known endocrinopathies	
Ca^{++}, P, Na^{+}, K^{+}	every 4–6 weeks for 6 months, then every 2–3 months thereafter
Cortisol (h 8.00 am)[ç]	every 4–6 weeks for 6 months, then every 2–3 months thereafter If cortisol is low, check ACTH
TSH, fT4	every 4–6 weeks for 6 months, then every 2–3 months thereafter If hypothyroidism is suspected, add TPO-Ab and TG-Ab. If hyperthyroidism is suspected, add fT3, TRAb, and repeat TSH, fT3 and fT4 every 2–3 weeks. If persistent, consider thyroid ultrasound and/or scintigraphy
ACTH, LH, FSH, testosterone (men) or estradiol (premenopausal women) + Sellar MRI	If hypophysitis is suspected
Patients with previously known DM	
FPG (±PPG) & BP	Check regularly at every visit
HbA1c, LDL-C, triglycerides	every 3 months
Blood glucose monitoring	Reinforce SMBG (FPG & PPG); consider CGM in selected cases
Provide diabetes self-management education and support	X
Consider overall CV risk	X
Provide nutritional advices & support	
Patients who develop hyperglycemia during ICI therapy	
Urine/plasma ketones	X
Anti-GAD, anti-IA2, anti-ZnT8, and anti-insulin Ab	X
HbA1c, insulin, C-peptide	X
Pancreatic amylase & lipase	X
Patients with previously known endocrinopathies	
The frequency of monitoring must be agreed with the endocrinologist based on the patient individual needs	
Post-treatment assessment*	
Cortisol (h 80.00)[ç], TSH, fT4, Ca^{++}, P, Na^{+}, K^{+}	every 6 months for at least 2 years post-therapy

Abbreviations: AntiGAD, auto-antibodies against glutamic acid decarboxylase; anti-IA2, auto-antibodies against islet antigen-2; anti-ZnT8, auto-antibodies against zinc transporter 8; BP, blood pressure; CGM, continuous glucose monitoring; CV, cardiovascular; DKA, diabetic ketoacidosis; FPG, fasting plasma glucose; ICIs, immune checkpoint inhibitors; KI, kinase inhibitors; LDL-C, low density lipoprotein cholesterol; mTOR, mammalian target of rapamycin; PPG, post-prandial glucose; SMBG, self-monitoring of blood glucose; TPO-Ab, thyroid peroxidase antibodies; TG-Ab, thyroglobulin antibodies; TRAb, TSH receptor antibodies.

[*] Consider asking for an endocrine/diabetes consulting if 1 or more parameters are not normal.

[ç] If not on corticosteroid therapy (any formulation).

[§] eg, l-Thyroxin, hydrocortisone, testosterone, estrogens ± progestins.

LH and testosterone/oestradiol plasma levels should be evaluated and, although not necessary for diagnosis, a sellar MRI should be requested to rule out metastatic disease to the sellar structures. In case of secondary hypothyroidism and/or hypogonadism, given their frequent spontaneous recovery, thyroid and gonadal hormonal panel should be re-checked in 4–6 weeks before initiating replacement therapy. When initiating replacement therapy for one or more pituitary hormonal axes, the related hormonal panels should be checked regularly every 4–6 weeks during ICI treatment (Fig. 5).

Conclusions

Clinical development and approval of ICIs have revolutionized the natural history of several solid tumours. However, therapeutic targeting of immune-inhibitory pathways can lead to potentially life-threatening irAEs, not seldom pertaining the endocrine and metabolic system. Typically, irAEs occur within a few months from starting ICIs, but the possibility of a delayed effect of immunotherapy makes an ongoing and prolonged post-treatment evaluation mandatory. The purpose of this position paper, far from claiming to be definitive, is to propose to clinicians a multidisciplinary, clear, simple, useful, and easily applicable endocrine-metabolic assessment checklist of investigations to be carried out pre-treatment, during therapy, as well as post-treatment, with the aim to correctly suspect, identify, and manage irAEs as early as possible (see Table 1). Likewise, since diabetologists and endocrinologists are often requested to manage endocrine irAEs in cancer patients, in hospital clinical settings, this document aims to make them more and more familiar with ICIs and immunotherapy, as well. In addition, we also encourage multidisciplinary involvement in the management of cancer patients on immunotherapy.

Moreover, we think that our paper also has an important practical value, thanks to the brief and pragmatic checklists integrated in every paragraph and the structured table that could represent a reliable and feasible resource for the clinician, both oncologist and endocrinologist/diabetologist.

Considering the rapidly growing population of patients treated with immunotherapy, with increasingly broad indications, we believe that our scientific societies have the duty to share with clinicians an easy and practical guide for the management of irAEs, especially considering our long-lasting and demonstrated collaboration in producing documents for clinical practice. However, given the breadth of emerging immunotherapy field, together with the ever-evolving scenario of new approved drugs and new indications, clinicians must be aware that knowledge and experience are also continually changing, and that current recommendations may prove incomplete in the near future.

Several guidelines and dedicated papers on the management of endocrine irAEs already exist, drawn up and published by various scientific societies, differing from each other in terms of frequency, methods, and type of test to be requested [11,32,59]. This checklist intends to adapt the existing, authoritative recommendations to the Italian clinical setting, thus representing an agile guide for both oncologists and endocrinologists/diabetologists managing these increasingly common toxicities. Our contribution may improve the clinical management of ICI-related endocrine-metabolic toxicities providing simple and practical indications, with the added value of a multidisciplinary

evaluation.

A multidisciplinary approach involving oncologists, endocrinologists, diabetologists, pharmacologists and several other specialists is strongly recommended, as usual. Furthermore, the importance of patient education regarding endocrine irAEs should also be emphasized, so that the immediate reporting of symptoms can ease an early diagnosis and a rapid intervention.

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All authors have contributed to the conception and design of the manuscript. MG, MCZ, and NS conceived the document. All authors reviewed published literature, drafted the article, revised the manuscript critically, and approved the submitted version.

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CRediT authorship contribution statement

Maria Chiara Zatelli: Conceptualization, Project administration, Writing – original draft, Superivion. **Antongiulio Faggiano:** Investigation, Writing – original draft, Validation. **Antonella Argentiero:** Investigation. **Romano Danesi:** Investigation. **Stella D'Oronzo:** Investigation, Writing – original draft. **Stefano Fogli:** Investigation. **Tindara Franchina:** Investigation, Writing – original draft. **Francesco Giorgino:** Investigation. **Nicola Marrano:** Investigation, Writing – original draft. **Dario Giuffrida:** Investigation. **Stefania Gori:** Investigation. **Giampiero Marino:** Investigation. **Rossella Mazzilli:** Investigation, Writing – original draft. **Matteo Monami:** Investigation. **Monica Montagnani:** Investigation. **Lelio Morviducci:** Investigation, Writing – original draft. **Annalisa Natalicchio:** Investigation, Writing – original draft. **Alberto Ragni:** Investigation. **Valerio Renzelli:** Investigation, Writing – original draft. **Antonio Russo:** Investigation. **Laura Sciacca:** Investigation. **Enzo Tuveri:** Investigation. **Gianluca Aimaretti:** Investigation, Supervision. **Angelo Avogaro:** Investigation. **Riccardo Candido:** Reviewing. **Massimo Di Maio:** Methodology, Supervision. **Nicola Silvestris:** Conceptualization, Project administration, Review. **Marco Gallo:** Conceptualization, Supervision, Writing.

Declaration of competing interest

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