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Immunoendocrinology: When (neuro)endocrinology and immunology meet

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It is with great pleasure to introduce Professor Antonelli as the Guest Editor for this special issue of *Reviews in Endocrine & Metabolic Disorders*. Prof. Antonelli is board certified in Internal Medicine, Endocrinology, and Oncology, and the Director of the Immuno-Endocrine Section of Internal Medicine, Head of the Laboratory of Primary Human Cells and Associate Professor in the Department of Clinical and Experimental Medicine at the University of Pisa, Italy. For this guest issue, Prof. Antonelli assembled a panel of international expert contributors to discuss current aspects of immunoendocrinology.

There is increasing awareness of the intricate and intertwined relationship between the endocrine and immune system. In part, this is caused by an explosion of various immunotherapies including cellular immunotherapy (for instance, sipuleucel-T (Provenge), tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta)), antibody-based therapy (i.e. rituximab (Rituxan, Mabthera), atezolizumab (Tecentriq), avelumab (Bavencio), ofatumumab (Arzerra), alemtuzumab (Campath-1H), durvalumab (Imfinzi), ipilimumab (Yervoy), tremelimumab, pembrolizumab, nivolumab (Opdivo)), cytokine therapy (i.e. interferon, interleukin-2), combination immunotherapy, and others. Among antibody based immunotherapies are the checkpoint inhibitor antibodies with ipilimumab being the first antibody approved by the Federal Food and Drug Administration (FDA). More and more immune-related adverse events of immune checkpoint inhibitor treatment are being unraveled and algorithms for acute management of endocrine complications have been proposed [1–8].

My first encounter with immunology occurred while studying at the Friedrich-Alexander University of Erlangen-Nuremberg in the 1980s and rotating through the Department of Medicine headed by Professor Joachim R. Kalden, who in 1970 reported on the effect of hypophysectomy on the immune system in male Sprague-Dawley strain rats [9]. Many fellow immunologists and rheumatologists trained under Prof. JR Kalden have risen to the top of the field [10–12]. My next immunological encounters, including the occurrence of bullous pemphigoid after treatment with furosemide, happened during residency training at the Ohio State University Medical Center [13] followed by the National Institutes of Health (NIH) which had the largest impact on my education in immunology and its intersection with endocrinology [14]. At the NIH I met many immunology and other experts, including Profs. George Chrousos, Ronald Wilder, Esther Sternberg, Ilias Elenkov, Philip Gold, Julio Licinio, and Thomas Fleisher [15–17]. After departing the NIH and spending a few years in Germany, I had the pleasure to collaborate with visceral and thoracic surgeon expert Prof. Ott and we published a study showing that converting liver transplant recipients from cyclosporine A therapy to steroid-saving tacrolimus monotherapy caused a decline in mean serum cholesterol and high density cholesterol levels but an increase in low density cholesterol serum concentrations, apparently without beneficial effect on the atherogenic lipid profile [18].

After joining the University of Mississippi Medical Center in 2006, I had the honor to be invited by Profs. Julius Cruse and Robert Lewis in the Department of Immunopathology, both being Editors of the Atlas of Immunology (ISBN 9781439802687) and Historical Atlas of Immunology (ISBN-13: 978–1,842,142,172 and ISBN-10: 1842142178), to provide lectures outlining the intersection between

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immunology and endocrinology: https://www.researchgate.net/publication/270161648_Autoimmune_Syndromes_Endocrine_Autoimmunity_Potpourri).

Profs. Cruse, Lewis, and I always had very informative and entertaining discussions until recently, when Prof. Cruse sadly passed away [19–22]. Based on these intellectual interactions with these two wonderful colleagues I learned more about immunoendocrinology and in 2013, I had the honor to present a lecture at the Southern States Chapter of the American College of Endocrinologists (https://www.researchgate.net/publication/329124524_When_Neuroendocrinology_and_Immunology_Meet_Practical_Considerations), illustrating how the immune system controls endocrine organs and function and reviewing how sex steroids control neuro-inflammatory processes in the brain. As usual, caring for patients often makes me think about why people have certain afflictions. Acknowledging that Mississippi is one of the US states with the highest percentage of obese individuals, it is conceivable that persistent organic pollutants impact the immune system. Persistent organic pollutants have high lipid solubility and bioaccumulate in fatty tissues of not only animals but also humans (https://en.wikipedia.org/wiki/Persistent_organic_pollutant). Furthermore, contamination of groundwater and drinking (tap) water with micropollutants and pharmaceuticals, including antibiotics, can impact health of animals and humans and their (intestinal) microbiome [23–27].

Such an environmental impact can lead to molecular mimicry. In predisposed individuals, a microbial antigen would then trigger autoimmunity because of structural similarity to an autoantigen of the host [28–36]. Being born and growing up in such an obesogenic and polluted environment may be more challenging for changing the deleterious course on health than coming into such an environment from outside as an adult, although both situations will alter the gut microbiome [37–41]. The question arises when the time has come to act on limiting endocrine disrupting chemicals (https://www.researchgate.net/publication/292335196_Endocrine_Disruptors_is_it_time_to_act and https://www.researchgate.net/publication/270161477_Endocrine_Aspects_in_Obesity_What_the_Non-Endocrinologist_Should_Know/download). The FDA has published pamphlets on how to dispose of unused medicines and the risks associated with the environmental release of pharmaceuticals on the United States FDA "flush list" [42].

As a simple rule, in my opinion, one should read about the ancient Greek philosophers and their concept of the four elements, earth, fire, water, and air, and put that into contemporary context in hopes of identifying what people need to do to preserve life on the planet Earth (https://en.wikipedia.org/wiki/Classical_element).

The complex interaction between environmental, hormonal, immune, and genetic factors has been coined as a "mosaic of autoimmunity" [43]. The autoimmune/inflammatory syndrome is induced by adjuvants including aluminum and silicone. Medical conditions of this syndrome are vaccination-induced autoimmunity, silicone implants-induced autoimmunity, Gulf War syndrome, macrophagic myofasciitis with chronic fatigue syndrome, and the sick building syndrome [44–46].

The presence of autoantibodies alone is not sufficient to define a disease as autoimmune. According to Whitebsky there also should be a demonstration of lymphocytic infiltration in the target organs, identification and characterization of auto-antigens, and induction of the disease in animal models with the injection of auto-antigens and passive transfer by serum or lymphocytes [47]. Interestingly, (only) approximately 30% of patients with stiff person syndrome develop diabetes mellitus, although auto-antibodies directed to the 65-kDa isoform of glutamic acid decarboxylase (GAD) are present [48]. In the TrialNet pathway to prevention study, 994 relatives with normal glucose tolerance and being positive for a single "diabetes" autoantibody, were followed prospectively and tested for antibodies against islet cells, zinc transporter 8, insulin, insulinoma associated antigen 2, and GAD. After a median follow-up of 2 years, 141 relatives were found to have at least one additional autoantibody [49]. When comparing identical twins and full siblings in the TrialNet pathway to prevention study including 17,226 subjects, the risk of type 1 diabetes at 3 years was high (>69%) for identical twins who were positive for initially multiple and single "diabetes" autoantibodies and for non-identical twins with multiple "diabetes" autoantibodies. For initially "diabetes" autoantibody negative identical twins, the risk of developing type 1 diabetes was 1.5% [50].

Similarly, euthyroid individuals may have very high titers of antithyroid peroxidase antibodies [51]. Analyzing more than 16,000 individuals in the National Health and Nutrition Examination Survey (NHANES) revealed a prevalence of approximately 10% of people with anti-thyroglobulin antibodies and approximately 11% of subjects with antithyroperoxidase antibodies. Positivity for both antithyroidal antibodies increased the odds ratio of developing hypothyroidism from 6.9 (anti-thyroperoxidase antibody alone) to 23.5. The presence of anti-thyroglobulin antibody alone was not a risk factor of hypothyroidism. Interestingly, no anti-thyroid antibodies were detected in 31% of men and in 11% of women who had unequivocal elevations (> 10 mIU per liter) of thyroid stimulating hormone/TSH [https://www.thyroidmanager.org, 52, 53]. 1184 Western Australian subjects were followed for 13 years while checking serum concentrations of thyroid stimulating hormone (TSH) and antibodies directed to thyroid peroxidase and thyroglobulin. In 112 subjects, overt

hypothyroidism developed. In women with positive antithyroidal antibodies, 55% became hypothyroid when the initial TSH was between 2.5 and 4.0 mU per Liter [54].

Guest Editor Prof. Antonelli whose roots of endocrinology and immunology go back into the 1980's and I myself have met at one of the annual Endocrine Society meetings via introduction by Prof. Salvatore Benvenga who has also worked at the NIH in Bethesda, MD, in the past [55–61]. This guest issue begins with a review on the immune cell-adipocyte crosstalk as an important regulator not only of adipose tissue function, but also of systemic metabolism and homeostasis [62]. The group around Professor Chavakis has made major contributions on inflammasome pathways [63]. The second article will then focus on the role of microbiota in maintaining nutritional, metabolic, and immunologic homeostasis with an emphasis on thyroid autoimmunity [39]. Next will be a review of the increasing prevalence of chronic lymphocytic thyroiditis in papillary microcarcinoma. Hashimoto' s thyroiditis coexists in approximately one third of patients with papillary thyroid microcarcinoma [64]. At my present clinical practice location, I see many patients with autoimmune skin disorders referred by dermatologists. In particular, women with alopecia areata and/or totalis suffer from this appearance. Unfortunately, no universal therapy exists, although successful hair regrowth after certain immunotherapies, with ustekinumab, has been reported [65–67]. A retrospective study showed that 12 of 70 patients (17%) with alopecia totalis had complete hair regrowth but 30 patients with alopecia universalis (65%) remained in an alopecic state without improvement long term [68]. The epidemiology, clinical manifestations, and pathogenesis of the main autoimmune skin disorders such as alopecia, vitiligo, pemphigus, bullous pemphigoid, and their association with thyroid disease will be reviewed by Dr. Baldini and colleagues [69], followed by a review on thyroid disorders induced by checkpoint inhibitors such as monoclonal antibodies directed to cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed death receptor-1 (anti-PD-1), and programmed death-ligand 1 (anti-PD-L1) [8]. Checkpoint inhibitor therapy, especially with anti-CTLA-4, is also associated with hypophysitis [1]. Dr. Gubbi and colleagues from the NIH review the topic primary hypophysitis and other autoimmune disorders of the sellar and suprasellar regions with an emphasis on lymphocytic hypophysitis [70].

Myoinositol is involved in intracellular thyroid-stimulating hormone signaling, has immunomodulatory effects, and may be effective in protecting thyroid cells from reactive oxygen species such as hydrogen peroxide and pro-inflammatory cytokines which will be reviewed by the group around Prof. Antonelli [71, 72].

Immunomodulatory effects can also be observed in/with many other substances and medications. The role of the peptide hormone somatostatin has been recently reviewed in an issue on neuroendocrine neoplasms, including its impact on the immune system [73]. Somatostatin receptor subtype 1 and subtype 2 are both expressed on fibroblast-like synovial cells and somatostatin analog therapy may be effective in treating patients with rheumatoid arthritis [74]. Of 175 patients with sarcoidosis, all but one patient showed uptake when undergoing somatostatin receptor scintigraphy. In 6% of these patients, exclusive extrapulmonary disease was identified [75].

Besides their well established role in reducing cardiovascular risk, statins also exert immunomodulatory effects. This topic including statins, metformin, pro-protein-convertase-subtilisin-kexin type-9 (PCSK9) inhibitors, angiotensin converting enzyme inhibitors and sex hormones will be reviewed by me with colleagues Dr. Hehmke and Prof. Krabbe, who have extensive experience with immunodiagnostics methods utilized at the Institute of Diabetes "Gerhardt Katsch" in Karlsburg, Germany [76]. Statins are known to be associated with myopathy and many patients with muscle complaints have these complaints in the absence of prior statin use [77]. Myalgia is reported in approximately 9% of patients on atorvastatin and in approximately 5% of placebo patients when using self-reported symptoms and there have not been validated scales to diagnose statin-associated myalgia [77]. Interestingly, discontinuation of statin therapy for 2 weeks caused improvement in musculoskeletal symptoms in 75% of patients with statin-associated muscle side effects. After stopping initial statin therapy, 92% of patients are able to tolerate a second statin. A skeletal muscle biopsy is recommended for persistent tenderness and myalgia with moderate to severe elevations of creatine kinase. Major autoimmune myopathies include dermatomyositis, polymyositis, myositis associated with antisynthetase syndrome, inclusion body myositis, and immune-mediated necrotizing myopathy. Typically, glucocorticoisteroids are considered first-line therapy, although intravenous immunoglobulin has also been used, especially in patients with immune-mediated necrotizing myopathy related to statin use [78]. The detection of anti-3-hydroxy-3-methyl-glutaryl-coenzyme A reductase antibodies with prior or current statin use can assist in diagnosis and management, as timely treatment with immunosuppressive agents can increase the likelihood of a favorable outcome [77]. In an Australian population-based case-control study, using the South Australian Myositis Database, of all histologically confirmed cases of idiopathic inflammatory myositis and controls from the North West Adelaide Health Study, statin exposure at the time of diagnosing idiopathic inflammatory myositis occurred in 31% of patients and in 22% of matched controls [79].

This issue will be concluded by 2 articles related to infection with hepatitis C virus, one article by Dr. Colaci and colleagues, reviewing endocrine disorders in such patients and the final article, a systematic review and meta-analysis, by Prof. Antonelli and colleagues focusing on the development of diabetes mellitus [80, 81].

As I conclude my term as the Editor-in-Chief of this journal, I wish to say farewell and thank the readership, guest editors, associate editors, Editorial Board, and the current and past Springer staff, especially Laura Walsh, Elizabeth Dziubela, Mitchelle Joseph, Rosario Gramatica, and John Rafael Patricio, for their support which has helped the journal maintain its excellent Impact Factor.

Compliance with ethical standards

Conflict of interest Profs. Koch and Antonelli declare no direct conflict with this article.

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References

1. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr Rev. 2018. https://doi.org/10.1210/er.2018-00006.
2. Piranavan P, Li Y, Brown E, Kemp EH, Trivedi N. ImmuneCheckpoint inhibitor-induced Hypoparathyroidism associated with calcium-sensing receptor-activating autoantibodies. J Clin Endocrinol Metab. 2018. https://doi.org/10.1210/jc.2018-01151.
3. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. Diabetes. 2018;67(8):1471–80.
4. Moseley KF, Naidoo J, Bingham CO, Carducci MA, Forde PM, Gibney GT, et al. Immune-related adverse events with immune checkpoint inhibitors affecting the skeleton: A seminal case series. J Immunother Cancer. 2018;6(1):104. https://doi.org/10.1186/s40425-018-0417-8.
5. Casey RT, Giger O, Seetho I, Marker A, Pitfield D, Boyle LH, et al. Rapid disease progression in a patient with mismatch repair-deficient and cortisol secreting adrenocortical carcinoma treated with pembrolizumab. Semin Oncol. 2018;45:151–5.
6. Higham CE, Olsson-Brown A, Carroll P, Cooksley T, Larkin J, Lorigan P, et al. Society for endocrinology endocrine emergency guidance: Acute management of the endocrine complications of checkpoint inhibitor therapy. Endocr Connect. 2018;7(7):G1–7.
7. Paepegaey AC, Lheure C, Ratour C, Lethielleux G, Clerc J, Bertherat J, et al. Polyendocrinopathy resulting from Pembrolizumab in a patient with a malignant melanoma. J Endocr Soc. 2017;1(6):646–9.
8. Ferrari SM, Fallahi P, Galetta F, Citi E, Benvenga S, Antonelli A. Thyroid disorders induced by checkpoint inhibitors. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9463-2.
9. Kalden JR, Evans MM, Irvine WJ. The effect of hypophysectomy on the immune response. Immunology. 1970;18(5):671–9.
10. Voll RE, Herrmann M, Roth EA, Stach C, Kalden JR, Girkontaite I. Immunosuppressive effects of apoptotic cells. Nature. 1997;390(6658):350–1.
11. Manger K, Wildt L, Kalden JR, Manger B. Prevention of gonadal toxicity and preservation of gonadal function and fertility in young women with systemic lupus erythematosus treated by cyclophosphamide: The PREGO-study. Autoimmun Rev. 2006;5(4):269–72.
12. Breedveld FC, Kalden JR, Smolen JS. Advances in targeted therapies 2017. Clin Immunol. 2018;186:1–2.
13. Koch CA, Mazzaferri EL, Larry JA, Fanning TS. Bullous pemphigoid after treatment with furosemide. Cutis. 1996;58(5):340–4.
14. Koch CA, Robyn JA, Pacak K. How do levels of (endogenous) glucocorticoids, interleukin-10 and interleukin-12 relate to multiple sclerosis relapse before, during and after pregnancy? Clin Endocrinol. 1999;50(6):818–9.
15. Sternberg EM, Wilder RL, Gold PW, Chrousos GP. A defect in the central component of the immune system–hypothalamic-pituitary-adrenal axis feedback loop is associated with susceptibility to experimental arthritis and other inflammatory diseases. Ann N Y Acad Sci. 1990;594:289–92.
16. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332(20):1351–62.
17. Elenkov IJ, Chrousos GP, Wilder RL. Neuroendocrine regulation of IL-12 and TNF-alpha/IL-10 balance. Clinical implications. Ann N Y Acad Sci. 2000;917:94–105.
18. Ott R, Bussenius-Kammerer M, Reck T, Koch CA, Kissler H, Hohenberger W, et al. Impact of changing immunosuppressive monotherapy from Cyclosporin a to Tacrolimus in long-term, stable liver transplant recipients. Transpl Int. 2004;17(1):39–43.
19. Lewis RE. Julius M. Cruse, Mentor and mensch. Exp Mol Pathol. 2012;93(3):288–90.
20. Cruse JM, Lewis RE. Immunologic research: Publishing knowledge of the future today!: the first three decades. Immunol Res. 2012;52(1–2):1.
21. Ejaeidi AA, Craft BS, Puneky LV, Lewis RE, Cruse JM. Hormone receptor-independent CXCL10 production is associated with the regulation of cellular factors linked to breast cancer progression and metastasis. Exp Mol Pathol. 2015;99(1):163–72.
22. Melcescu E, Hogan RB 2nd, Brown K, Boyd SA, Abell TL, Koch CA. The various faces of autoimmune endocrinopathies: Non-tumoral hypergastrinemia in a patient with lymphocytic colitis and chronic autoimmune gastritis. Exp Mol Pathol. 2012;93(3):434–40.
23. Elliott SM, Erickson ML, Krall AL, Adams BA. Concentrations of pharmaceuticals and other micropollutants in groundwater downgradient from large on-site wastewater discharges. PLoS One. 2018;13(11):e0206004.
24. Camiré A, Espinasse J, Chabot B, Lajeunesse A. Development of electrospun lignin nanofibers for the adsorption of pharmaceutical contaminants in wastewater. Environ Sci Pollut Res Int. 2018. https://doi.org/10.1007/s11356-018-3333-z.
25. Kibuye FA, Gall HE, Elkin KR, Ayers B, Veith TL, Miller M, et al. Fate of pharmaceuticals in a spray-irrigation system: from wastewater to groundwater. Sci Total Environ. 2018;654:197–208.
26. Li J, Zhao H, Xia W, Zhou Y, Xu S, Cai Z. Nine phthalate metabolites in human urine for the comparison of health risk between population groups with different water consumptions. Sci Total Environ. 2019;649:1532–154.
27. Leusch FDL, Neale PA, Arnal C, Aneck-Hahn NH, Balaguer P, Bruchet A, et al. Analysis of endocrine activity in drinking water, surface water and treated wastewater from six countries. Water Res. 2018;139:10–5.
28. Guarneri F, Benvenga S. Environmental factors and genetic background that interact to cause autoimmune thyroid disease. Curr Opin Endocrinol Diabetes Obes. 2007;14(5):398–409.
29. Benvenga S, Guarneri F. Molecular mimicry and autoimmune thyroid disease. Rev Endocr Metab Disord. 2016;17(4):485–98.
30. Melcescu E, Kemp EH, Majithia V, Vijayakumar V, Uwaifo GI, Koch CA. Graves' disease, hypoparathyroidism, systemic lupus erythematosus, alopecia, and angioedema: autoimmune polyglandular syndrome variant or coincidence? Int J Immunopathol Pharmacol. 2013;26(1):217–22.
31. Koch CA. How can environmental factors contribute to the incidence of Thyroid Cancer? Horm Metab Res. 2017;49(3):229–31.
32. Koch CA. Editorial: a journey from brain to muscle across the thyroid continent. Rev Endocr Metab Disord. 2016;17(4):465–9.

33. Melcescu E, Horton WB, Pitman KT, Vijayakumar V, Koch CA. Euthyroid Graves' orbitopathy and incidental papillary thyroid microcarcinoma. Hormones (Athens). 2013;12(2):298–304.
34. Newman BD, Maher JF, Subauste JS, Uwaifo GI, Bigler SA, Koch CA. Clustering of sebaceous gland carcinoma, papillary thyroid carcinoma and breast cancer in a woman as a new cancer susceptibility disorder: A case report. J Med Case Rep. 2009;3:6905. https://doi.org/10.4076/1752-1947-3-6905.
35. Antonelli A, Benvenga S. Editorial: the Association of Other Autoimmune Diseases in patients with Thyroid autoimmunity. Front Endocrinol (Lausanne). 2018;9:540.
36. Benvenga S, Antonelli A, Vita R. Thyroid nodules and thyroid autoimmunity in the context of environmental pollution. Rev Endocr Metab Disord. 2015;16(4):319–40.
37. De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. Clin Exp Immunol. 2018. https://doi.org/10.1111/cei.13158.
38. Vatanen T, Franzosa EA, Schwager R, Tripathi S, Arthur TD, Vehik K, et al. The human gut microbiome in early-onset type 1 diabetes from the TEDDY study. Nature. 2018;562(7728):589–94.
39. Virili C, Fallahi P, Antonelli A, Benvenga S, Centanni M. Gut microbiota and Hashimoto's thyroiditis. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9467-y.
40. Koch CA. Editorial: "The Koch's" view on the sense of taste in endocrinology. Rev Endocr Metab Disord. 2016;17(2):143–7.
41. Langer-Gould A, Brara SM, Beaber BE, Koebnick C. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. Neurology. 2013;80(6):548–52.
42. Khan U, Bloom RA, Nicell JA, Laurenson JP. Risks associated with the environmental release of pharmaceuticals on the U.S. Food and Drug Administration "flush list". Sci Total Environ. 2017;609:1023–40.
43. Colafrancesco S, Agmon-Levin N, Perricone C, Shoenfeld Y. Unraveling the soul of autoimmune diseases: Pathogenesis, diagnosis and treatment adding dowels to the puzzle. Immunol Res. 2013;56(2–3):200–5.
44. Watad A, David P, Brown S, Shoenfeld Y. Autoimmune/inflammatory syndrome induced by adjuvants and Thyroid autoimmunity. Front Endocrinol (Lausanne). 2017;7:150. https://doi.org/10.3389/fendo.2016.00150.
45. Segal Y, Dahan S, Sharif K, Bragazzi NL, Watad A, Amital H. The value of Autoimmune syndrome induced by adjuvant (ASIA) - shedding light on orphan diseases in autoimmunity. Autoimmun Rev. 2018;17(5):440–8.
46. Freiberger SN, Leuthard DS, Duda A, Contassot E, Thallmair M, Kündig TM, et al. Intraperitoneal administration of aluminium-based adjuvants produces severe transient systemic adverse events in mice. Eur J Pharm Sci. 2018;115:362–8.
47. Witebsky E, Rose NR, Terplan K, Paine JR, Egan RW. Chronic thyroiditis and autoimmunization. JAMA. 1957;164:1439–47.
48. Hänninen A, Soilu-Hänninen M, Hampe CS, Deptula A, Geubtner K, Ilonen J, et al. Characterization of CD4+ T cells specific for glutamic acid decarboxylase (GAD65) and proinsulin in a patient with stiff-person syndrome but without type 1 diabetes. Diabetes Metab Res Rev. 2010;26(4):271–9.
49. Bosi E, Boulware DC, Becker DJ, Buckner JH, Geyer S, Gottlieb PA, et al. Type 1 diabetes TrialNet study group. Impact of age and antibody type on progression from single to multiple autoantibodies in type 1 diabetes relatives. J Clin Endocrinol Metab. 2017;102(8):2881–6.
50. Triolo TM, Fouts A, Pyle L, Yu L, Gottlieb PA, Steck AK, et al. Identical and nonidentical twins: risk and factors involved in development of islet autoimmunity and type 1 diabetes. Diabetes Care. 2018. https://doi.org/10.2337/dc18-0288.
51. Ehlers M, Jordan AL, Feldkamp J, Fritzen R, Quadbeck B, Haase M, et al. Anti-Thyroperoxidase antibody levels >500 IU/ml indicate a moderately increased risk for developing hypothyroidism in Autoimmune thyroiditis. Horm Metab Res. 2016;48(10):623–9.
52. Spencer CA, Hollowell JG, Kazarosyan M, Braverman LE. National Health and Nutrition Examination Survey III thyroid-stimulating hormone (TSH)-thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction. J Clin Endocrinol Metab. 2007;92(11):4236–40.
53. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2):489–99.
54. Hershman JM, Cheng SY, Gianoukakis AG. Update in thyroidology 2010. J Clin Endocrinol Metab. 2011;96(1):9–14.
55. Benvenga S, Cahnmann HJ, Rader D, Kindt M, Robbins J. Thyroxine binding to the apolipoproteins of high density lipoproteins HDL2 and HDL3. Endocrinology. 1992;131(6):2805–11.
56. Mondello P, Mian M, Pitini V, Cuzzocrea S, Sindoni A, Galletti M, et al. Thyroid hormone autoantibodies: Are they a better marker to detect early thyroid damage in patients with hematologic cancers receiving tyrosine kinase inhibitor or immunoregulatory drug treatments? Curr Oncol. 2016;23(3):e165–70.
57. Benvenga S, Bartalena L, Antonelli A, Li Calzi L, Di Pasquale G, Trimarchi F, et al. Radioimmunoassay for human thyroxine-binding prealbumin. Ann Clin Lab Sci. 1986;16(3):231–40.
58. Antonelli A, Carmassi F, Neri S, Saracino A, Gambuzza C, Alberti B, et al. Inappropriate antidiuretic hormone secretion in a patient with systemic sarcoidosis. Recenti Prog Med. 1992;83(9):492–5.
59. Antonelli A, Navarranne A, Palla R, Alberti B, Saracino A, Mestre C, et al. Pretibial myxedema and high-dose intravenous immunoglobulin treatment. Thyroid. 1994 Winter;4(4):399–408.
60. Baschieri L, Antonelli A, del Guerra P, Fialdini A, Gasperini L. Somatostatin effect in postprandial hypoglycemia. Metabolism. 1989;38(6):568–71.
61. Pacini F, Antonelli A, Lari R, Gasperini L, Baschieri L, Pinchera A. Unsuspected parathyroid cysts diagnosed by measurement of thyroglobulin and parathyroid hormone concentrations in fluid aspirates. Ann Intern Med. 1985;102(6):793–4.
62. Chung KJ, Nati M, Chavakis T, Chatzigeorgiou A. Innate immune cells in the adipose tissue. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9451-6.
63. Kourtzelis I, Li X, Mitroulis I, Grosser D, Kajikawa T, Wang B, et al. DEL-1 promotes macrophage efferocytosis and clearance of inflammation. Nat Immunol. 2018. https://doi.org/10.1038/s41590-018-0249-1.
64. Vita R, Ieni A, Tuccari G, Benvenga S. The increasing prevalence of chronic lymphocytic thyroiditis in papillary microcarcinoma. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9474-z.
65. Aleisa A, Lim Y, Gordon S, Her MJ, Zancanaro P, Abudu M, et al. Response to ustekinumab in three pediatric patients with alopecia areata. Pediatr Dermatol. 2018. https://doi.org/10.1111/pde.13699.
66. Cranwell WC, Lai VW, Photiou L, Meah N, Wall D, Rathnayake D, et al. Treatment of alopecia areata: an Australian expert consensus statement. Australas J Dermatol. 2018. https://doi.org/10.1111/ajd.12941.
67. Mikhaylov D, Pavel A, Yao C, Kimmel G, Nia J, Hashim P, et al. A randomized placebo-controlled single-center pilot study of the safety and efficacy of apremilast in subjects with moderate-to-severe alopecia areata. Arch Dermatol Res. 2018. https://doi.org/10.1007/s00403-018-1876-y.
68. Jang YH, Hong NS, Moon SY, Eun DH, Lee WK, Chi SG, et al. Long-term prognosis of alopecia Totalis and alopecia Universalis: a longitudinal study with more than 10 years of follow-up: Better than reported. Dermatology. 2017;233(2–3):250–6.
69. Baldini E, Odorisio T, Tuccilli C, Persechino S, Sorrenti S, Catania A, et al. Thyroid diseases and skin autoimmunity. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9450-7.

70. Gubbi S, Hannah-Shmouni F, Stratakis CA, Koch CA. Primary Hypophysitis and Other Autoimmune disorders of the Sellar and Suprasellar regions. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9480-1.
71. Fallahi P, Ferrari SM, Elia G, Ragusa F, Paparo SR, Caruso C, et al. Myoinositol in autoimmune thyroiditis and hypothyroidism. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9477-9.
72. Ferrari SM, Elia G, Ragusa F, Paparo SR, Caruso C, Benvenga S, et al. The protective effect of myoinositol on human thyrocytes. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9476-x.
73. Bhanat E, Koch CA, Parmar R, Garla V, Vijayakumar V. Somatostatin receptor expression in non-classical locations - clinical relevance? Rev Endocr Metab Disord. 2018;19(2):123–32.
74. Sakane T, Suzuki N. The role of somatostatin in the pathophysiology of rheumatoid arthritis. Clin Exp Rheumatol. 1998;16(6):745–9.
75. Kamphuis LS, Kwekkeboom DJ, Missotten TO, Baarsma GS, Dalm VA, Dik WA, et al. Somatostatin receptor scintigraphy patterns in patients with sarcoidosis. Clin Nucl Med. 2015;40(12):925–9.
76. Koch CA, Krabbe S, Hehmke B. Statins, metformin, proprotein-convertase-subtilisin-kexin type-9 (PCSK9) inhibitors and sex hormones: Immunomodulatory properties ? Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9478-8.
77. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. The National Lipid Association's muscle safety expert panel. An assessment by the statin muscle safety task force: 2014 update. J Clin Lipidol. 2014;8(3 Suppl):S58–71.
78. McGrath ER, Doughty CT, Amato AA. Autoimmune Myopathies: Updates on evaluation and treatment. Neurotherapeutics. 2018;15(4):976–994. https://doi.org/10.1007/s13311-018-00676-2.
79. Caughey GE, Gabb GM, Ronson S, Ward M, Beukelman T, Hill CL, et al. Association of Statin Exposure with Histologically Confirmed Idiopathic Inflammatory Myositis in an Australian population. JAMA Intern Med. 2018;178(9):1224–9.
80. Colaci M, Malatino L, Antonelli A, Fallahi P, Giuggiolo D, Ferri C. Endocrine disorders associated with hepatitis C virus chronic infection. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-018-9475-y.
81. Fabiani S, Fallahi P, Ferrari SM, Miccoli M, Antonelli A. Hepatitis C virus infection and development of type 2 diabetes mellitus: Systematic review and meta-analysis of the literature. Rev Endocr Metab Disord. 2018. https://doi.org/10.1007/s11154-017-9440-1.

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