MANAGEMENT OF ENDOCRINE DISEASE

Disease burden and treatment challenges in patients with both Addison's disease and type 1 diabetes mellitus

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Abstract

Concurrent type 1 diabetes (T1D) and Addison's disease (AD) is a rare combination of diseases and, in approximately one third of these patients, it is also combined with an autoimmune thyroid disease. Recently, it was shown that patients with both T1D and AD have a higher risk of premature death compared to patients with T1D alone, the most common causes of death being due to diabetic complications and cardiovascular disease. These patients receiving replacement therapies with both insulin and glucocorticoids face an increased risk of hypo- and hyperglycemia and diabetic ketoacidosis and have a higher risk of adrenal crisis than patients with AD alone. Treatment challenges include the opposing effects of insulin and glucocorticoids on glucose homeostasis and the need to balance and synchronize these two treatments. The rarity of this disease combination may explain the paucity of data on outcome and specific treatment strategies in this patient group. Based on this review, we suggest management strategies for their insulin and glucocorticoid replacement therapies and indicate future areas of research.

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Introduction

Patients with one autoimmune disease are at an increased risk of developing another autoimmune disorder (1). In the developed world, type 1 diabetes (T1D) and approximately 85% of the cases with Addison's disease (AD) or primary adrenal insufficiency are both considered to result from autoimmune destruction of the pancreatic insulin-producing beta cells and the adrenal cortex, respectively (2, 3).

T1D and autoimmune AD, when they occur simultaneously, belong to the family of inherited autoimmune polyendocrine syndromes (APSs) (4). APS-1, also named autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a monogenic disease

caused by mutations in the *AIRE* (autoimmune regulator) gene. Its main manifestations during childhood (with or without T1D) are autoimmune AD, chronic mucocutaneous candidiasis, and hypoparathyroidism (at least two of three). APS-2, which is more common and usually has a later onset than APS-1, is a polygenic disease characterized by T1D, autoimmune AD, and thyroid disease (at least two of three). Some of the other manifestations in APS-2 are autoimmune gastritis, alopecia, vitiligo, celiac disease, and primary ovarian insufficiency.

In the group of patients with T1D and positive 21-hydroxylase antibodies, immunological studies have shown that those who were homozygous for the MICA5.1

allele or had MHC class II haplotypes DR3 and DR4 had higher risk of progression to overt AD (5, 6). Details on underlying molecular mechanisms in patients with APSs including T1D have been reviewed before (7), and the natural history and risk factors for autoimmune AD in patients with other APS components have been described (8).

Diabetes was one of the first described diseases when, in 1500 BC, the ancient Egyptians mentioned a condition that appears to have been T1D (9). The basis for the scientific understanding of T1D and AD was laid in the mid-1800s. For diabetes, Claude Bernard, a French physiologist, first showed between 1845 and 1855 in dogs that the liver produces glucose without glucose ingestion by an 'enzyme' that he isolated and named glycogen (10). In a monograph dated 1855 (11), Thomas Addison, a British physician, reported on six patients in a morbid state with concomitant pathological changes in the adrenals, which he named 'suprarenal capsules'. The first patient diagnosed with both diseases simultaneously was reported in 1890 by West (12). Later, a more detailed description was provided in 1962 by Christy *et al.* (13). Further back in 1943, Thorn *et al.* reported the progressive decrease in glucose tolerance in a patient with AD receiving treatment with sodium chloride and i.m. desoxycorticosterone acetate until the development of insulin-dependent diabetes (14). This report described a striking decrease in glucose tolerance after a single dose of cortisone (also called compound E) supplied by Edward Kendall, who was the first to purify

cortisone. Based on their observations (14), Thorn *et al.* were the first to suggest that cortisone can induce glucose intolerance by increased gluconeogenesis and inhibition of glucose utilization or storage, and that cortisone may promote lipolysis.

Despite T1DM being well described and characterized, and that there is growing evidence on outcome in patients with AD, outcome data in patients with both diseases are very limited. In the current review, we focus on the disease burden with the combination of T1D and AD and its management challenges. We searched PubMed, Scopus, Web of Science, and Cochrane database for articles published in English until September 2019 with the following terms in title, abstract, or keywords: diabetes mellitus, diabetes, Addison's disease, primary adrenal insufficiency, primary hypoadrenalism, and Addison, which identified a total of 1660 records (Fig. 1). An additional study by Giordano *et al.* (15) was not identified by the electronic database search (due to the absence of the terms diabetes or diabetes mellitus in the title, abstract, or keywords), but was added after independent identification by experts. Of these 1661 records, 1634 remained after removal of duplicates. Review of the 1634 unique articles revealed three treatment studies on patients with both T1DM and AD, which included one observational treatment study on patients with concomitant T1D and AD, one treatment study where the T1D and AD patient group was reported as a subgroup of patients with AD, and the additional study by Giordano *et al.* (15) that was independently identified by experts.

Figure 1

Review flow chart. Articles published in English until September 2019 were searched with the following terms in title, abstract, or keywords: diabetes mellitus, diabetes, Addison's disease, primary adrenal insufficiency, primary hypoadrenalism, and Addison. They were then screened for treatment studies in patients with both T1D and AD, AD, Addison's disease; T1D, type 1 diabetes.

Incidence and prevalence

Epidemiological studies in populations with AD have shown that 10.8–14.1% also have T1DM. A local study in Western Norway reported 18 patients with T1D among 128 patients with autoimmune AD between 1970 and 1999 with a prevalence of 20 cases per million inhabitants at the end of 1999 (16). A nationwide Norwegian study identified 49 patients with T1D among 426 patients with autoimmune or idiopathic AD between 1993 and 2007 (17). A study based on German health insurance data reported 85 patients with T1D among 712 patients with autoimmune AD in 2012 and, thus, a prevalence of ten cases per million inhabitants (18). Finally, a study based on the Swedish Addison Registry identified 71 patients with T1D among 660 patients with autoimmune AD between 2008 and 2014 (19).

From the alternative perspective, a meta-analysis has recently shown that the prevalence of autoimmune AD among patients with T1D was 0.2% (95% CI: 0.0–0.4) (20). A local study in a US population identified 76 patients with AD among 25 759 patients with T1D between 2010 and 2016 (21). In another study based on Swedish National Registries (22), 105 patients with AD were identified among 30 790 patients with T1D between 1987 and 2012 (0.3%); after matching each case with T1D that developed AD to five controls without T1D that developed AD, there was a prevalence of 3410 cases of AD per million persons with T1D (95% CI: 2759–4061). The same study found a more than ten-fold higher risk for patients with T1D to develop AD (22). In conclusion, up to 0.4% of patients with T1D also have AD, while up to 14.1% of patients with AD also have a diagnosis of T1D.

Mortality and morbidity

Outcome data in patients with both T1D and AD are scarce. Swedish National Registries data have shown a four-fold higher risk of premature death in patients with both T1D and AD compared to matched T1D controls (hazard ratio 4.3 (95% CI: 2.6–7.0)) (Fig. 2) (23, 24). The most common cause of death in this cohort was due to diabetic complications followed by cardiovascular disease, cancer, unknown cause of death, and infection or sepsis. Interestingly, in a US based epidemiological study of patients with T1D, no obvious cause of death was found in 4% of the patients as determined by a mortality classification committee reviewing death certificates and additional records surrounding the death (25). It is

Figure 2

(A) Cumulative overall mortality and (B) main causes of death in patients with T1D and AD vs controls with T1D. AD, Addison's disease; T1D/T1DM, type 1 diabetes (reprinted with permission from Chantzichristos D, doctoral thesis: Addison's disease and type 1 diabetes mellitus, Gothenburg, Sweden, 2018 (23)).

possible that among these patients were patients included who had died because of undiagnosed AD and that adrenal crisis was impossible for the committee to detect retrospectively.

Based on the higher susceptibility for additional autoimmune diseases, patients with both T1D and autoimmune AD may present additional autoimmune co-morbidities, such as autoimmune thyroid disease, celiac disease, pernicious anemia, and rheumatic diseases, which may also influence patient outcomes. Patients with both T1D and AD have shown a higher frequency of infections and hospital admissions due to infections compared with patients with AD alone (26), suggesting that adrenal crisis may be more common. Adrenal crisis is a potentially life-threatening event in patients with AD. A study based on

German health insurance data showed that the subgroup of patients with both T1D and AD indeed had a higher prevalence of adrenal crises (12.5/100 patient-years) compared to patients with AD alone (7.6/100 patient-years) (27). Assessment of health-related quality of life using Short Form 36 in 426 of all 664 (64%) of patients diagnosed with AD in Norway between 1993 and 2007 showed that the subgroup with both T1D and AD ($n=50$) had the most pronounced impairment of quality of life (17).

Treatment challenges

The main treatment challenges in patients with both T1D and AD are the need to mimic the diurnal changes in both insulin and glucocorticoids and accommodate their opposing effects on glucose homeostasis.

Endogenous insulin and glucocorticoid metabolism

For the management of patients with both T1D and AD, different types of insulin and insulin analogs (short- to long-acting) are administered either subcutaneously at different times or by continuous s.c. insulin infusion (CSII) in combination with different oral glucocorticoid preparations. Figure 3 shows the diurnal profiles of plasma cortisol, glucose, and insulin in healthy individuals during circadian alignment during wake, sleep, and in relation

Figure 3

Diurnal profiles of plasma cortisol, glucose, and insulin levels in ten healthy subjects in relation to four meals (breakfast (B), lunch (L), dinner (D), and supper (S)) during normal circadian alignment between behavioral cycles (fasting/feeding and sleep/wake cycles) and endogenous circadian cycles (reproduced and adapted with permission from Scheer *et al.* (28)).

Figure 4

(A) Circadian profile of serum cortisol in healthy subjects (reproduced with permission from Kerrigan *et al.* (29)), (B) serum cortisol concentration after oral administration of hydrocortisone three times daily (TID) or dual-release hydrocortisone once daily (OD) in patients with Addison's disease (reproduced with permission from Johannsson *et al.* (30)), and (C) salivary cortisol concentration after oral administration hydrocortisone three times daily (black line) or after continuous s.c. infusion of hydrocortisone (gray line) with an insulin pump in patients with Addison's disease (reproduced with permission from Oksnes *et al.* (31)).

to four meals. In the post-prandial state, plasma cortisol, glucose, and insulin increase (28). Figure 4 shows the circadian variation of serum cortisol in healthy individuals (daily peak on waking and a nadir during sleep) (29) and the achieved levels of serum or salivary cortisol

concentration in patients treated with oral hydrocortisone three times daily, oral dual-release hydrocortisone once daily (30), and an experimental treatment using circadian s.c. hydrocortisone infusion using an insulin pump (31).

Both insulin and glucocorticoid metabolism are governed by circadian mechanisms that are synchronized internally by the rhythmic expression of *CLOCK/BMAL1* in central clock mechanisms (oscillators) and externally by environmental factors (32, 33). The most powerful external synchronizers are the 12 h light:12 h darkness cycle and the timing of food intake. Glucocorticoid secretion and glucocorticoid receptors are also regulated by clock genes not only in peripheral tissues, such as the adrenal glands, but also in tissues such as liver and muscles more directly regulating glucose homeostasis. Experimental data show that the sensitivity of the glucocorticoid receptor is also affected by clock genes with the highest sensitivity to glucocorticoid stimulation occurring during the hours of darkness. Desynchronization between these regulatory components has various adverse effects on the immune system, cardiovascular system, and metabolism, including glucose metabolism. These mechanisms could explain the observation that the insulin resistance induced by glucocorticoids is more pronounced when administration occurs in the evening (34). Chronic elevated glucocorticoid concentrations in the evening have also been associated with glucose intolerance, type 2 diabetes, abdominal obesity, and coronary arteriosclerosis (35, 36).

Other factors involved in insulin and glucocorticoid metabolism are gastric emptying, physical activity, emotional stress, stressful events (including infections), macronutrient distribution in meals, and hormonal factors. Macronutrient distribution (percentage of calories from carbohydrate, protein, and fat) in meals plays a

role in the post-prandial increase of both insulin and glucocorticoids (37). Other endocrine systems integrating with both insulin and glucocorticoids on glucose metabolism are catecholamines and growth hormone (38). How these systems are affected in patients with both T1D and AD has not been studied specifically.

Insulin, glucocorticoids, and glucose metabolism

In patients with both T1D and AD, replacement therapies with insulin and glucocorticoids have, in many respects, opposing effects on glucose metabolism, with insulin lowering and glucocorticoids increasing plasma glucose levels. Glucocorticoids induce insulin resistance, glucose intolerance, and overt diabetes in susceptible individuals. Conversely, in the absence of physiological levels of circulating glucocorticoids, the sensitivity to insulin is increased; this is why patients with T1D may present clinically with reduced insulin requirement during the development of AD (39, 40). The normal physiology of insulin and cortisol on skeletal muscle, liver, and adipose tissue, including cortisol-induced insulin resistance, are summarized in Fig. 5 (41).

Synchronizing insulin and glucocorticoid replacement

Misalignment between the two treatments can lead to hypo- or hyperglycemia, diabetic ketoacidosis, and adrenal crisis. Patients with both T1D and AD need to make daily decisions on the doses of both insulin and glucocorticoids based on their capillary or interstitial glucose measurements and/or symptoms.

Elbelt *et al.* (42) studied the insulin requirement in patients with T1D with or without AD treated twice or

Figure 5

Schematic view of the opposing effects of cortisol and insulin on glucose, lipid, and protein metabolism in skeletal muscle, liver, and adipose tissue. NEFAs, non-esterified fatty acids; TGs, triglycerides.

Table 1 Summary of treatment studies in patients with both T1D and AD.

Reference	Study design	Study subjects	Intervention	Findings
Elbelt <i>et al.</i> (42)	Single-center, retrospective, matched-cohort	Cases with both T1D and autoimmune AD ($n = 10$) vs controls with T1D alone ($n = 10$)	Treatment with immediate-release oral hydrocortisone or cortisone acetate twice or thrice daily and intensive conventional or CSII insulin	Prandial insulin requirement was higher and increased throughout the day in T1D + AD vs T1D. Mean ($\pm$ s.d.) insulin/carbohydrate ratio for carbohydrate 10 g in T1D+AD vs T1D, respectively, was: – morning 1.9 ± 1.0 (range 1–3.6) vs 1.4 ± 0.5 (range 0.8–2.3) ($P = 0.191$) – noon 2.0 ± 0.9 (range 1–3.3) vs 1.1 ± 0.5 (range 0–1.8) ($P = 0.018$) – evening 2.1 ± 1.1 (range 1–4.6) vs 1.3 ± 0.5 (range 0.3–2.0) ($P = 0.039$). No difference in glycemic control was observed.
Johannsson <i>et al.</i> (30)	Multicenter, open-label, randomized, crossover	Subgroup studied: subjects with diabetes and AD ($n = 11$, 9 of them with T1D and AD)	Same daily dose of oral hydrocortisone dual-release (once daily) vs immediate-release (3 times daily) for 12 weeks	Improved glycemic control after 12 weeks treatment with dual-release vs immediate-release hydrocortisone ($\Delta = -0.6\%$, $P = 0.004$). Treatment preference in favor of dual-release hydrocortisone (10 of 11 subjects).
Giordano <i>et al.</i> (15)	Single-center, prospective, open-label	Subgroup studied: subjects with T1D and autoimmune AD ($n = 3$)	Oral immediate-release hydrocortisone 20 mg/day in three divided doses switched to dual-release hydrocortisone 20 mg/day for 12 months	Reduced insulin requirement after 6 months treatment with dual-release compared to conventional hydrocortisone.

AD, Addison's disease; CSII, continuous s.c. insulin infusion; T1D, type 1 diabetes; Δ , difference.

three times daily with oral hydrocortisone or cortisone acetate using either intensive conventional insulin treatment or CSII (Table 1). A lower percentage of basal insulin requirement and an increase in prandial insulin requirement throughout the day was seen in patients with both T1D and AD compared to those who had T1D alone. This may be explained by lower sensitivity to glucocorticoids in the early morning and for a period after the ingestion of oral glucocorticoids and increased sensitivity of the glucocorticoid receptor in the evening (43). The time-window of increased requirement of insulin due to reduced insulin sensitivity after ingestion of oral hydrocortisone is not known. An indication comes from a study administering oral hydrocortisone 100 mg (supraphysiologic exposure) in the fasting state in healthy men that demonstrated reduced insulin sensitivity after 4–6 h, which persisted for more than 16 h (44).

Subjects with AD, without diabetes, treated with conventional hydrocortisone tablets have a continuous fall in plasma glucose during the night and until the morning and may even have nocturnal hypoglycemic episodes (45, 46). Whether this has a specific clinical relevance in patients with concomitant T1D has

not been studied. The counter-regulatory endocrine response to hypoglycemia does not only need cortisol action but also glucagon, which is also impaired in patients with T1D. In particular, an earlier case study had identified glucagon deficiency in an APS-2 patient with AD prior to manifestation of T1D (47). Better understanding of the glucose metabolism in patients with both T1D and AD and the risk of nocturnal hypoglycemia is needed.

Additional treatment challenges may also be present in patients with both T1D and AD who suffer from other concomitant autoimmune manifestations of APS-1 or APS-2. These include subjects with the triad T1D, AD, and autoimmune thyroid disease. Whether these concomitant autoimmune manifestations affect mortality and/or morbidity is not known.

Strategies to improve outcome

The increased mortality and increased risk of adrenal crisis observed in patients with both T1D and AD call for improvement in the management of these patients.

Timely detection

Reduced insulin requirement is a well-known clinical indicator of adrenal insufficiency in patients with T1D (39, 40). In a nationwide Swedish registry study in adults with T1D who then developed AD, four early clinical indicators that can alert patients and healthcare professionals for the development of AD were identified: autoimmune thyroid disease (T), diabetic retinopathy (R), severe infections (I), and glucagon prescription (G) (48). These indicators can be summarized under the acronym T.R.I.G. and 'trigger' the suspicion of an underlying AD during the follow-up of patients with T1D. Since routine screening for AD in patients with T1D is not currently recommended (49, 50, 51), reduced insulin requirement and/or the four early clinical indicators noted can alert for the possibility of AD development. Potentially, laboratory measurements for this assessment would be those recommended in AD with the reservation that these methods are poorly studied or have not been validated in the context of adrenal insufficiency in patients with T1D. In patients with T1D and recurrent hypoglycemia, adrenocorticotrophic hormone (ACTH) stimulation test identified AD in 0.4% (52, 53). In adults with T1D and positive 21-hydroxylase autoantibodies, ACTH levels greater than 60 pg/mL (13.2 pmol/L) had a 100% sensitivity and 98% specificity for the diagnosis of AD (54). The occurrence of hyponatremia is also an early biochemical finding in autoimmune AD (55). It could therefore be argued that a screening method for AD among patients with T1D should be morning serum cortisol and ACTH. Confirmatory studies using T.R.I.G. for the timely detection of AD in patients with T1DM are currently lacking.

Glucocorticoid treatment

Oral immediate-release hydrocortisone (15–25 mg/day) or cortisone acetate (25–37.5 mg/day) taken in divided doses twice or thrice daily are considered first-line therapy in adults with AD (56). New developments in replacement therapy for patients with AD include a dual-release hydrocortisone preparation and experimental studies have used continuous s.c. hydrocortisone infusion using an insulin pump.

Replacement therapy with once-daily administration of dual-release hydrocortisone tablets in contrast to administration of conventional immediate-release hydrocortisone tablets three times daily has shown: (1.) decrease in glycated hemoglobin A1c (HbA1c); (2.) reduced body weight, waist circumference, and blood pressure; (3.)

improvement in health-related quality of life; (4.) reduction of recurrent infections; and (5.) normalization of the immune cell profile (15, 30, 57, 58, 59). In addition, dual-release hydrocortisone has been recently shown to improve insulin secretion and sensitivity in patients with pre-diabetes (60). A two-period, crossover study comparing these two hydrocortisone preparations in 11 patients with diabetes and AD (nine of them with T1D) showed improved HbA1c after a 12-weeks treatment with dual-release hydrocortisone tablets once daily (30) (Table 1). In a prospective, open-labelled study in 19 patients with AD using conventional immediate-release hydrocortisone 20 mg/day in three divided doses who switched to the same dose of dual-release hydrocortisone once daily for 12 months, reduced insulin requirement were observed after the first 6 months in the three patients with both T1D and AD (15) (Table 1). These data indicate that dual-release hydrocortisone can be considered a better choice in patients with both T1D and AD. The data is, however, limited to few patients and the mechanism for these observations remains to be explained as they could be driven by the change in the serum cortisol profile or the reduction in total cortisol exposure when switching from thrice daily immediate-release to once daily dual-release hydrocortisone. Another preparation with delayed absorption containing microparticulate hydrocortisone has been developed (61) but has not been studied in patients with both T1D and AD.

Replacement therapy with continuous s.c. hydrocortisone infusion using an insulin pump in contrast to the administration of conventional immediate-release hydrocortisone tablets three times daily has shown advantages in: (1.) metabolic profile by both providing a more circadian-based salivary cortisol profile and preventing a continuous decrease in glucose during the night and (2.) in health-related quality of life (31, 45, 62). Continuous s.c. hydrocortisone infusion has, however, not shown advantages in other metabolic outcomes such as bodyweight and blood pressure. There is no available data on how this experimental treatment can affect patients with both T1D and AD.

The observation that glucocorticoids have more pronounced diabetogenic effects when administered in the evening is in favor of the use of dual-release hydrocortisone tablets or continuous s.c. hydrocortisone infusion, as both provide a more circadian-based cortisol profile compared to conventional hydrocortisone tablets in patients with both T1DM and AD. Another glucocorticoid, prednisolone, is recommended at a dose of 3–5 mg/day divided as one or two doses in adults with AD and poor

compliance when using multiple daily dose regimens (56). Theoretically, as prednisolone is a longer-acting glucocorticoid compared to conventional hydrocortisone tablets, it can be considered as an alternative in patients with both T1D and AD and poor compliance or frequent fluctuations of glucose levels.

Mineralocorticoid and adrenal androgen treatment

There is currently no evidence that the mineralocorticoid replacement therapy in patients with both T1D and AD should be managed differently to those with AD alone. The current standard treatment in adults with AD consists of fludrocortisone 50–200 µg as a single daily dose in the morning (49). A real-world, nationwide Swedish study has shown that the rate of fludrocortisone prescription in patients with both T1D and AD was lower than in matched controls with AD. The authors suggested that this was a result of the increased use of antihypertensive drugs due to over-replacement with glucocorticoids in those with both diseases (48).

Replacement of adrenal androgens in females with AD has not shown consistent benefit (49), while replacement therapy with dehydroepiandrosterone 50 mg for 12 weeks in 28 hypoadrenal women (from various causes) has shown an increase in insulin sensitivity (63). Treatment studies with this preparation in patients with both T1D and AD are lacking.

Prevention and management of adrenal crises

Patients with both T1D and AD have an increased risk of adrenal crises compared to patients with AD alone. A mortality study in patients with T1D and AD showed that adrenal crisis (acute adrenal failure in Fig. 2B) was one of the main causes of death and there was also evidence for deaths due to untreated/inadequately treated adrenal crisis (23). This is why it is important, as in patients with AD alone (49), to prevent adrenal crises by patient education, steroid cards, and adjustment of the glucocorticoid treatment in case of surgery or medical procedures, as well as to identify and treat adrenal crises in a timely manner.

Insulin treatment and diabetes care

The current standards of medical care in patients with T1D are also applicable to patients with both T1D and AD (51). Diabetes care should address glycemic targets, screen for diabetes complications (especially as they are

the most common main cause of death in this patient group), evaluate potential co-morbidities including other autoimmune diseases, and provide risk management of cardiovascular disease. Bearing in mind the outcome data in patients with both T1D and AD, a particular emphasis should be on the understanding of the interactions between insulin and glucocorticoids. Besides the standards in the adjustment of insulin treatment in patients with T1D and glucagon as rescue therapy in hypoglycemia, healthcare professionals who treat patients with T1D and AD must consider the risk of increased insulin sensitivity and hypoglycemia in the early morning hours and increased insulin resistance related to the pharmacodynamic/pharmacokinetic properties and administration timing of the glucocorticoid preparation used. We recommend, as shown experimentally by Elbelt *et al.* (Table 1) and depending on the actual individual insulin treatment regimen, lower daily basal insulin doses and slightly higher doses of prandial insulin for a period after the ingestion of glucocorticoids, which become higher for the same glucocorticoid dose throughout the day.

The use of CSII could be considered more liberally in patients with both T1D and AD because of the higher risk for severe hypoglycemia and the evidence that CSII reduces the rate of severe hypoglycemia in patients with T1D (64). Due to the previously described outcomes and treatment challenges in patients with both T1D and AD, healthcare professionals may also consider a more liberal use of self-monitoring of plasma glucose, as well as flash or continuous glucose monitoring. There are no treatment studies on the use of non-insulin treatments (injectable and oral glucose-lowering drugs) as adjuncts to insulin treatment in patients with both T1D and AD.

Conclusions and future perspectives

Timely detection of AD in patients with T1D is essential. Patients with both T1D and AD struggle to balance the two replacement therapies with insulin and glucocorticoids in the presence of constantly changing factors such as timing of food, macronutrient distribution in food, physical activity, emotional stress, and stressful events in order to prevent misalignment between them. The potentially deleterious outcomes of such misalignment are hypoglycemia, diabetic ketoacidosis, and adrenal crisis. Treatment studies have shown that once-daily administration of dual-release oral hydrocortisone may have advantages over conventional immediate-release oral hydrocortisone in this patient group, but more safety

data are needed before a general conclusion can be made. Otherwise, in the absence of other treatment studies, adoption of and adherence to treatment guidelines in T1D and in AD are recommended. A more liberal use of CSII, self-monitoring of blood glucose, and continuous glucose monitoring should also be considered in this patient group. Finally, development of targeted patient education programs may be considered specifically for patients with both T1D and AD.

Declaration of interest

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References

- Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, Manji N, Allahabadia A, Armitage M, Chatterjee KV *et al*. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *American Journal of Medicine* 2010 **123** 183.e1–183.e9. (<https://doi.org/10.1016/j.amjmed.2009.06.030>)
- Pociot F & Lernmark Å. Genetic risk factors for type 1 diabetes. *Lancet* 2016 **387** 2331–2339. ([https://doi.org/10.1016/S0140-6736\(16\)30582-7](https://doi.org/10.1016/S0140-6736(16)30582-7))
- Winqvist O, Karlsson FA & Kämpe O. 21-Hydroxylase, a major autoantigen in idiopathic Addison's disease. *Lancet* 1992 **339** 1559–1562. ([https://doi.org/10.1016/0140-6736\(92\)91829-W](https://doi.org/10.1016/0140-6736(92)91829-W))
- Husebye ES, Anderson MS & Kämpe O. Autoimmune polyendocrine syndromes. *New England Journal of Medicine* 2018 **378** 1132–1141. (<https://doi.org/10.1056/NEJMra1713301>)
- Triolo TM, Baschal EE, Armstrong TK, Toews CS, Fain PR, Rewers MJ, Yu L, Miao D, Eisenbarth GS, Gottlieb PA *et al*. Homozygosity of the polymorphism MICA5.1 identifies extreme risk of progression to overt adrenal insufficiency among 21-hydroxylase antibody-positive patients with type 1 diabetes. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 4517–4523. (<https://doi.org/10.1210/jc.2009-1308>)
- Baker P, Fain P, Kahles H, Yu L, Hutton J, Wenzlau J, Rewers M, Badenhop K & Eisenbart G. Genetic determinants of 21-hydroxylase autoantibodies amongst patients of the Type 1 Diabetes Genetics Consortium. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E1573–E1578. (<https://doi.org/10.1210/jc.2011-2824>)
- Husebye ES & Anderson MS. Autoimmune polyendocrine syndromes: clues to type 1 diabetes pathogenesis. *Immunity* 2010 **32** 479–487. (<https://doi.org/10.1016/j.immuni.2010.03.016>)
- Naleto L, Frigo A, Ceccato F, Sabbadin C, Scarpa R, Presotto F, Dalla Costa M, Faggian D, Plebani M, Censi S *et al*. The natural history of autoimmune Addison's disease from the detection of autoantibodies to development of the disease: a long follow-up study on 143 patients. *European Journal of Endocrinology* 2019 **180** 223–234. (<https://doi.org/10.1530/EJE-18-0313>)
- Poretsky L (ed). *Principles of Diabetes Mellitus*. Springer, 2010. (<https://doi.org/10.1007/978-0-387-09841-8>)
- Bernard C. *Du Suc Pancréatique, et de Son Role dans les Phénomènes de la Digestion*, pp 1–24. Paris: Rigoux, Imprimeur de la Faculté de Médecine, 1849.
- Addison T. *On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules*, pp 1–43. London: Samuel Highley, 1855.
- West S. Diabetes mellitus associated with Addison's disease. *Transactions of the Pathological Society of London* 1890 **41** 271–273.
- Christy NP, Holub DA & Tomasi TB. Primary ovarian, thyroidal and adrenocortical deficiencies simulating pituitary insufficiency, associated with diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism* 1962 **22** 155–160. (<https://doi.org/10.1210/jcem-22-2-155>)
- Thorn GW & Clinton Jr M. Metabolic changes in a patient with Addison's disease following the onset of diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism* 1943 **3** 335–344. (<https://doi.org/10.1210/jcem-3-6-335>)
- Giordano R, Guaraldi F, Marinazzo E, Fumarola F, Rampino A, Berardelli R, Karamouzis I, Lucchiari M, Manetta T, Mengozzi G *et al*. Improvement of anthropometric and metabolic parameters, and quality of life following treatment with dual-release hydrocortisone in patients with Addison's disease. *Endocrine* 2016 **51** 360–368. (<https://doi.org/10.1007/s12020-015-0681-z>)
- Løvås K & Husebye ES. High prevalence and increasing incidence of Addison's disease in western Norway. *Clinical Endocrinology* 2002 **56** 787–791. (<https://doi.org/10.1046/j.1365-2265.2002.t011-01552.x>)
- Erichsen MM, Løvås K, Skinningsrud B, Wolff AB, Undlien DE, Svartberg J, Fougner KJ, Berg TJ, Bollerslev J, Mella B *et al*. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 4882–4890. (<https://doi.org/10.1210/jc.2009-1368>)
- Meyer G, Neumann K, Badenhop K & Linder R. Increasing prevalence of Addison's disease in German females: health insurance data 2008–2012. *European Journal of Endocrinology* 2014 **170** 367–373. (<https://doi.org/10.1530/EJE-13-0756>)
- Dalín F, Nordling Eriksson G, Dahlqvist P, Hallgren Å, Wahlberg J, Ekwall O, Söderberg S, Rönnelid J, Olcén P, Winqvist O *et al*. Clinical and immunological characteristics of autoimmune Addison's disease: a nationwide Swedish multicenter study. *Journal of Clinical Endocrinology and Metabolism* 2016 **102** 379–389. (<https://doi.org/10.1210/jc.2016-2522>)
- Nederstigt C, Uitbeijerse BS, Janssen LGM, Corssmit EPM, de Koning EJP & Dekkers OM. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. *European Journal of Endocrinology* 2019 **180** 137–146. (<https://doi.org/10.1530/EJE-18-0515>)
- Hughes JW, Riddlesworth TD, DiMeglio LA, Miller KM, Rickels MR, McGill JB & T1D Exchange Clinic Network. Autoimmune diseases in children and adults with type 1 diabetes from the T1D Exchange Clinic Registry. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 4931–4937. (<https://doi.org/10.1210/jc.2016-2478>)

Review	D Chantzichristos and others	Type 1 diabetes plus Addison's disease	183:1	R10
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- 22 Chantzichristos D, Persson A, Eliasson B, Miftaraj M, Franzén S, Svensson AM & Johannsson G. Incidence, prevalence and seasonal onset variation of Addison's disease among persons with type 1 diabetes mellitus: nationwide, matched cohort studies. *European Journal of Endocrinology* 2018 **178** 115–122. (<https://doi.org/10.1530/EJE-17-0751>)
- 23 Chantzichristos D. Addison's disease and type 1 diabetes mellitus. PhD Thesis, University of Gothenburg, Sweden, 2018.
- 24 Chantzichristos D, Persson A, Eliasson B, Miftaraj M, Franzén S, Berghthorsdottir R, Gudbjörnsdottir S, Svensson AM & Johannsson G. Mortality in patients with diabetes mellitus and Addison's disease: a nationwide, matched, observational cohort study. *European Journal of Endocrinology* 2017 **176** 31–39. (<https://doi.org/10.1530/EJE-16-0657>)
- 25 Secrest AM, Becker DJ, Kelsey SF, Laporte RE & Orchard TJ. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes. *Diabetes* 2010 **59** 3216–3222. (<https://doi.org/10.2337/db10-0862>)
- 26 Smans LC, Souverein PC, Leufkens HG, Hoepelman AI & Zelissen PM. Increased use of antimicrobial agents and hospital admission for infections in patients with primary adrenal insufficiency: a cohort study. *European Journal of Endocrinology* 2013 **168** 609–614. (<https://doi.org/10.1530/EJE-12-0879>)
- 27 Meyer G, Badenhop K & Linder R. Addison's disease with polyglandular autoimmunity carries a more than 2.5-fold risk for adrenal crises: German Health insurance data 2010–2013. *Clinical Endocrinology* 2016 **85** 347–353. (<https://doi.org/10.1111/cen.13043>)
- 28 Scheer FA, Hilton MF, Mantzoros CS & Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *PNAS* 2009 **106** 4453–4458. (<https://doi.org/10.1073/pnas.0808180106>)
- 29 Kerrigan JR, Veldhuis JD, Leyo SA, Iranmanesh A & Rogol AD. Estimation of daily cortisol production and clearance rates in normal pubertal males by deconvolution analysis. *Journal of Clinical Endocrinology and Metabolism* 1993 **76** 1505–1510. (<https://doi.org/10.1210/jcem.76.6.8501158>)
- 30 Johannsson G, Nilsson AG, Berghthorsdottir R, Burman P, Dahlqvist P, Ekman B, Engström BE, Olsson T, Ragnarsson O, Ryberg M *et al.* Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 473–481. (<https://doi.org/10.1210/jc.2011-1926>)
- 31 Oksnes M, Björnsdottir S, Isaksson M, Methlie P, Carlsen S, Nilsen RM, Broman JE, Triebner K, Kämpe O, Hulting AL *et al.* Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of Addison's disease: a randomized clinical trial. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 1665–1674. (<https://doi.org/10.1210/jc.2013-4253>)
- 32 Oster H, Challet E, Ott V, Arvat E, de Kloet ER, Dijk D-J, Oster H, Rund D & Neumann D. The functional and clinical significance of the 24-hour rhythm of circulating glucocorticoids. *Endocrine Reviews* 2017 **38** 3–45. (<https://doi.org/10.1210/er.2017.38.issue-2.edboard>)
- 33 Cedernaes J, Waldeck N & Bass J. Neurogenetic basis for circadian regulation of metabolism by the hypothalamus. *Genes and Development* 2019 **33** 1136–1158. (<https://doi.org/10.1101/gad.328633.119>)
- 34 Plat L, Leproult R, L'Hermite-Baleriaux M, Fery F, Mockel J, Polonsky KS & Van Cauter E. Metabolic effects of short-term elevations of plasma cortisol are more pronounced in the evening than in the morning. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 3082–3092. (<https://doi.org/10.1210/jcem.84.9.5978>)
- 35 Gangwisch JE. Epidemiological evidence for the links between sleep, circadian rhythms and metabolism. *Obesity Reviews* 2009 **10** (Supplement 2) 37–45. (<https://doi.org/10.1111/j.1467-789X.2009.00663.x>)
- 36 Matthews K, Schwartz J, Cohen S & Seeman T. Diurnal cortisol decline is related to coronary calcification: CARDIA study. *Psychosomatic Medicine* 2006 **68** 657–661. (<https://doi.org/10.1097/01.psy.0000244071.42939.0e>)
- 37 Stimson RH, Mohd-Shukri NA, Bolton JL, Andrew R, Reynolds RM & Walker BR. The postprandial rise in plasma cortisol in men is mediated by macronutrient-specific stimulation of adrenal and extra-adrenal cortisol production. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 160–168. (<https://doi.org/10.1210/jc.2013-2307>)
- 38 Cryer PE. Hierarchy of physiological responses to hypoglycemia: relevance to clinical hypoglycemia in type I (insulin dependent) diabetes mellitus. *Hormone and Metabolic Research* 1997 **29** 92–96. (<https://doi.org/10.1055/s-2007-978997>)
- 39 Dunlop D. Eighty-six cases of Addison's disease. *BMJ* 1963 **2** 887–891. (<https://doi.org/10.1136/bmj.2.5362.887>)
- 40 Armstrong L & Bell PM. Addison's disease presenting as reduced insulin requirement in insulin dependent diabetes. *BMJ* 1996 **312** 1601–1602. (<https://doi.org/10.1136/bmj.312.7046.1601>)
- 41 van Raalte DH, Ouwens DM & Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *European Journal of Clinical Investigation* 2009 **39** 81–93. (<https://doi.org/10.1111/j.1365-2362.2008.02067.x>)
- 42 Elbelt U, Hahner S & Allolio B. Altered insulin requirement in patients with type 1 diabetes and primary adrenal insufficiency receiving standard glucocorticoid replacement therapy. *European Journal of Endocrinology* 2009 **160** 919–924. (<https://doi.org/10.1530/EJE-08-1003>)
- 43 Lamia KA, Papp SJ, Yu RT, Barish GD, Uhlenhaut NH, Jonker JW, Downes M & Evans RM. Cryptochromes mediate rhythmic repression of the glucocorticoid receptor. *Nature* 2011 **480** 552–556. (<https://doi.org/10.1038/nature10700>)
- 44 Plat L, Byrne MM, Sturis J, Polonsky KS, Mockel J, Féry F & Van Cauter E. Effects of morning cortisol elevation on insulin secretion and glucose regulation in humans. *American Journal of Physiology* 1996 **270** E36–E42. (<https://doi.org/10.1152/ajpendo.1996.270.1.E36>)
- 45 Björnsdottir S, Øksnes M, Isaksson M, Methlie P, Nilsen RM, Hustad S, Kämpe O, Hulting AL, Husebye ES, Løvås Kristian *et al.* Circadian hormone profiles and insulin sensitivity in patients with Addison's disease: a comparison of continuous subcutaneous hydrocortisone infusion with conventional glucocorticoid replacement therapy. *Clinical Endocrinology* 2015 **83** 28–35. (<https://doi.org/10.1111/cen.12670>)
- 46 Meyer G, Hackemann A, Reusch J & Badenhop K. Nocturnal hypoglycemia identified by a continuous glucose monitoring system in patients with primary adrenal insufficiency (Addison's Disease). *Diabetes Technology and Therapeutics* 2012 **14** 386–388. (<https://doi.org/10.1089/dia.2011.0158>)
- 47 Starke AA, Valverde I, Bottazzo GF, Tsotsalas M & Zimmermann H. Glucagon deficiency associated with hypoglycaemia and the absence of islet cell antibodies in the polyglandular failure syndrome before the onset of insulin-dependent diabetes mellitus: a case report. *Diabetologia* 1983 **25** 336–339. (<https://doi.org/10.1007/BF00253197>)
- 48 Chantzichristos D, Persson A, Miftaraj M, Eliasson B, Svensson A-M & Johannsson G. Early clinical indicators of Addison disease in adults with type 1 diabetes: a nationwide, observational, cohort study. *Journal of Clinical Endocrinology and Metabolism* 2019 **104** 1148–1157. (<https://doi.org/10.1210/jc.2018-02064>)
- 49 Husebye ES, Allolio B, Arlt W, Badenhop K, Bensing S, Betterle C, Falorni A, Gan EH, Hulting AL, Kasperlik-Zaluska A *et al.* Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. *Journal of Internal Medicine* 2014 **275** 104–115. (<https://doi.org/10.1111/joim.12162>)
- 50 Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA

Review	D Chantzichristos and others	Type 1 diabetes plus Addison's disease	183:1	R11
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- et al.* Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 364–389. (<https://doi.org/10.1210/jc.2015-1710>)
- 51 American Diabetes Association. Standards of medical care in diabetes-2019. *Diabetes Care* 2019 **42** (Supplement 1) S1–S186. (<https://doi.org/10.2337/dc19-S004>)
- 52 Likhari T, Magzoub S, Griffiths MJ, Buch HN & Gama R. Screening for Addison's disease in patients with type 1 diabetes mellitus and recurrent hypoglycaemia. *Postgraduate Medical Journal* 2007 **83** 420–421. (<https://doi.org/10.1136/pgmj.2007.058321>)
- 53 Kristensen PL, Diemar SS, Bay C, Pedersen-Bjergaard U, Beck-Nielsen H, Christiansen JS, Norgaard K, Perrild H, Tonny J, Parving HH *et al.* ACTH stimulation test in patients with type 1 diabetes and recurrent severe hypoglycaemia. *Clinical Endocrinology* 2015 **82** 155–156. (<https://doi.org/10.1111/cen.12545>)
- 54 Barker JM, Ide A, Hostetler C, Yu L, Miao D, Fain PR, Eisenbarth GS & Gottlieb PA. Endocrine and immunogenetic testing in individuals with type 1 diabetes and 21-hydroxylase autoantibodies: Addison's disease in a high-risk population. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 128–134. (<https://doi.org/10.1210/jc.2004-0874>)
- 55 Saevik ÅB, Åkerman A-K, Grønning K, Nermoen I, Valland SF, Finnes TE, Isaksson M, Dahlqvist P, Bergthorsdottir R, Ekwall O *et al.* Clues for early detection of autoimmune Addison's disease – myths and realities. *Journal of Internal Medicine* 2018 **283** 190–199. (<https://doi.org/10.1111/joim.12699>)
- 56 Pearce SH. Insufficient evidence to favour prednisolone over hydrocortisone in glucocorticoid replacement. *BMJ* 2014 **349** g5510. (<https://doi.org/10.1136/bmj.g5510>)
- 57 Johannsson G, Lennernäs H, Marelli C, Rockich K & Skrtic S. Achieving a physiological cortisol profile with once-daily dual-release hydrocortisone: a pharmacokinetic study. *European Journal of Endocrinology* 2016 **175** 85–93. (<https://doi.org/10.1530/EJE-15-1212>)
- 58 Isidori AM, Venneri MA, Graziadio C, Simeoli C, Fiore D, Hasenmajer V, Sbardella E, Gianfrilli D, Pozza C, Pasqualetti P *et al.* Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. *Lancet Diabetes and Endocrinology* 2018 **6** 173–185. ([https://doi.org/10.1016/S2213-8587\(17\)30398-4](https://doi.org/10.1016/S2213-8587(17)30398-4))
- 59 Quinkler M, Miodini Nilsen R, Zopf K, Ventz M & Øksnes M. Modified-release hydrocortisone decreases BMI and HbA1c in patients with primary and secondary adrenal insufficiency. *European Journal of Endocrinology* 2015 **172** 619–626. (<https://doi.org/10.1530/EJE-14-1114>)
- 60 Guarnotta V, Ciresi A, Pillitteri G & Giordano C. Improved insulin sensitivity and secretion in prediabetic patients with adrenal insufficiency on dual-release hydrocortisone treatment: a 36-month retrospective analysis. *Clinical Endocrinology* 2018 **88** 665–672. (<https://doi.org/10.1111/cen.13554>)
- 61 Verma S, Vanryzin C, Sinaï N, Kim MS, Nieman LK, Ravindran S, Calis KA, Arlt W, Ross RJ & Merke DP. A pharmacokinetic and pharmacodynamic study of delayed- and extended-release hydrocortisone (Chronocort™) vs. conventional hydrocortisone (Cortef™) in the treatment of congenital adrenal hyperplasia. *Clinical Endocrinology* 2010 **72** 441–447. (<https://doi.org/10.1111/j.1365-2265.2009.03636.x>)
- 62 Løvås K & Husebye ES. Continuous subcutaneous hydrocortisone infusion in Addison's disease. *European Journal of Endocrinology* 2007 **157** 109–112. (<https://doi.org/10.1530/EJE-07-0052>)
- 63 Dhatariya K, Bigelow ML & Nair KS. Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. *Diabetes* 2005 **54** 765–769. (<https://doi.org/10.2337/diabetes.54.3.765>)
- 64 Yeh HC, Brown TT, Maruthur N, Ranasinghe P, Berger Z, Suh YD, Wilson LM, Haberl EB, Brick J, Bass EB *et al.* Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Annals of Internal Medicine* 2012 **157** 336–347. (<https://doi.org/10.7326/0003-4819-157-5-201209040-00508>)

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