MANAGEMENT OF ENDOCRINE DISEASE

Epidemiology, quality of life and complications of primary adrenal insufficiency: a review

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Abstract

In this article, we review published studies covering epidemiology, natural course and mortality in primary adrenal insufficiency (PAI) or Addison's disease. Autoimmune PAI is a rare disease with a prevalence of 100–220 per million inhabitants. It occurs as part of an autoimmune polyendocrine syndrome in more than half of the cases. The patients experience impaired quality of life, reduced parity and increased risk of preterm delivery. Following a conventional glucocorticoid replacement regimen leads to a reduction in bone mineral density and an increase in the prevalence of fractures. Registry studies indicate increased mortality, especially evident in patients diagnosed with PAI at a young age and in patients with the rare disease autoimmune polyendocrine syndrome type-1. Most notably, unnecessary deaths still occur because of adrenal crises. All these data imply the need to improve the therapy and care of patients with PAI.

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Incidence and prevalence

During the first half of the twentieth century, tuberculosis was the predominant cause of primary adrenal insufficiency (PAI) (1, 2). As the prevalence of tuberculosis declined, the aetiology pattern changed dramatically (3, 4, 5, 6, 7). Nowadays, autoimmunity is the most frequent cause (>90%) of PAI in industrialised countries (8, 9). Other causes include infectious, genetic, metastatic, haemorrhagic, and infiltrative disorders and surgery and drugs, but they are all rare in adult patients. The first prevalence rate of PAI, 39 cases per million, was reported from London in 1968 (3). Subsequent investigations have revealed increasing numbers up to 221 cases per million, as found recently on Iceland (10) (Fig. 1). However, lower prevalence rates have been reported outside Europe (11, 12, 13). The incidence has been estimated at 4–6 cases

per million per year and is probably on a rising course (5, 7, 8, 10, 14, 15, 16).

Autoimmune PAI occurs either as an isolated entity or as part of autoimmune polyendocrine syndromes type-1 and -2 (APS-1 and APS-2) (17, 18, 19) (Table 1). APS-1 is a rare, recessive monogenic disease that is caused by mutations in the autoimmune regulator (*AIRE*) gene, characterised by the presence of two of the three main components: PAI, hypoparathyroidism and chronic mucocutaneous candidiasis, which has been reviewed elsewhere (20). Recently, several monoallelic mutations in *AIRE*'s PHD1-domain were found to be associated with a milder form of APS-1 masquerading sometimes as APS-2, often with vitiligo and pernicious anaemia as disease components (21). Isolated PAI and APS-2 share the same

Figure 1

Historical overview of the epidemiology of primary adrenal insufficiency (PAI). Point prevalences of PAI in Europe. The prevalence rates were reported by A: Mason *et al.* (3), B: Nerup (4), C: Kong & Jeffcoate (5), D: Willis & Vince (6), E: Laureti *et al.* (14), F: Løvås *et al.* (7), G: Björnsdóttir *et al.* (15), H: Meyer *et al.* (16) and I: Olafsson & Sigurjonsdóttir (10).

pattern of complex inheritance. In more than half of the cases PAI is a part of APS-2 (8, 19).

Autoimmune PAI can start at virtually any age, but commonly occurs in young and middle-aged individuals and extremely rare in children. Women are more often affected than men, but below the age of 30, there is no gender difference. Conversely, among those with isolated PAI, there is a slight male predominance (8, 9, 19).

Health-related quality of life

The current replacement regimens do not reproduce the normal diurnal variations of the glucocorticoid levels, but the consequences for the patients' health remain unknown (22, 23). Demonstration of treatment effects is challenging because there is no 'gold standard' for assessment of treatment efficacy. Circulating hormone levels do not necessarily reflect the cellular effects of these hormones, and at best, assay of cortisol profiles can only roughly guide glucocorticoid replacement therapy (24, 25, 26, 27, 28). Several surveys undertaken by researchers or patient organisations have recorded common complaints before diagnosis and after treatment of PAI, but the majority of these studies do not give proper control data.

The most frequent symptoms at diagnosis are fatigue, loss of appetite, salt craving, vomiting and abdominal pain. Postural dizziness and pain in joints or muscles are also reported by a large number of patients. The most common signs are hyperpigmentation, hypotension and weight loss, which are observed in the majority. The frequencies of all the symptoms sharply diminish after replacement therapy is started, although many patients still report salt craving and postural dizziness while on replacement therapy (8).

Patients on replacement therapy reproducibly self-report impairment in particular dimensions of general well-being questionnaires such as SF-36 (8, 29, 30, 31, 32, 33, 34, 35, 36). General health and vitality perception are low for all patient subgroups, although the reductions are particularly pronounced for patients with concomitant type-1 diabetes (T1D). The quality of life (QoL) impairments have further been associated with female gender, increasing glucocorticoid dose, maladaptive personality traits, lower education and membership in patients' organisations (34, 35, 37). One registry study indicated increased prevalence of affective disorders associated with PAI (38), and a cross-sectional study including 54 patients with PAI reported more irritability and somatic arousal (34).

Table 1 Manifestations of APS-1 and APS-2 (main components appear in bold).

	APS-1	APS-2
Manifestations		
Endocrine	PAI Hypoparathyroidism Ovarian failure Type 1 diabetes mellitus Autoimmune thyroid disease	PAI Autoimmune thyroid disease Type 1 diabetes mellitus
Gastrointestinal	Autoimmune gastritis/pernicious anaemia Autoimmune hepatitis Intestinal malabsorption	Autoimmune gastritis/pernicious anaemia Coeliac disease
Ectodermal manifestations	Alopecia Vitiligo Enamel dysplasia Keratoconjunctivitis	Alopecia Vitiligo
Hematological	Asplenia	
Others	Chronic mucocutaneous candidiasis	

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In other clinical studies, the mental health indices are mostly comparable to the background population. Interestingly, a recent study demonstrated that illness perceptions are associated with beliefs regarding medical therapy, i.e. that stronger beliefs and concerns about the impact of the glucocorticoid replacement are related to the patients attributing more symptoms and perceiving more negative consequences of PAI (39).

Questionnaires containing disease-specific items are likely to be more sensitive to effects that clinicians wish to monitor. Recently, the disease-specific questionnaire AddiQoL was developed (40) and validated (41) as an evaluative tool in PAI, which might facilitate the detection of minor changes in well-being in future clinical trials and during routine follow-up of patients (42, 43, 44, 45).

The normal sleep cycle and the cortisol rhythm are tightly synchronised, and disruption of the cortisol rhythm in stress or glucocorticoid treatment clearly affects sleep. One study showed increased prevalence of sleep disturbances in Addison's disease (46), and another indicated that glucocorticoid replacement is permissive for rapid eye movement (REM) sleep (47). One study found that, although PAI had a noteworthy direct effect on QoL, the indirect effect of sleep disruption was significantly greater (48). However, sleep quality in PAI and the impact of various replacement therapies have never been properly studied, and it remains unanswered whether disturbed sleep contributes to deficits in QoL. Furthermore, the glucocorticoid and mineralocorticoid receptors play important roles in cognition and memory, and some studies in PAI have indicated impairment of various aspects of cognition, although inconsistently (49, 50).

Ultimately, reduced functioning in these patients is evidenced by limitation of working capacity and a higher percentage receiving disability benefits than in the general population (8, 29, 30).

Sexuality

Androgen deficiency is a hallmark of PAI in women. Although studies over the past few years have increased our knowledge on sexuality in patients with PAI, much is still not known. Sexual impairment could have various causes, including chronic fatigue, altered cortisol levels and androgen deficiency. The adrenals are a major source of androgens in women, and although the ovaries offer a significant contribution in healthy women, a contribution normally maintained after menopause (51),

their role in females with PAI is minor. Females with PAI lack androgen precursors from the adrenals, whereas those with concomitant autoimmune premature ovarian insufficiency (POI), which occurs in 10–20% of females with PAI, have a more complete androgen deficiency. The concentration of circulating androgens may, however, not reflect the effects at the cellular level, which may be better shown by the level of the testosterone metabolites (52). We have verified that the levels of 3 α -Diol-G are reduced, most significantly, in the subgroup of patients with POI (53).

One clinical trial demonstrated the beneficial effects of dehydroepiandrosterone (DHEA) replacement on sexual drive and satisfaction in females with adrenal insufficiency of primary and secondary aetiology (54). However, these effects were not replicated in studies that included only PAI patients (31, 55). Furthermore, despite the androgen depletion, female patients with PAI on a group level did not report impaired sexuality in any domain (53), which may however reflect subjective perception and not objective function. Miller and coworkers found improved sexual function with testosterone treatment (56) in severely androgen-deficient women with hypopituitarism, indicating that subgroups of PAI patients with complete androgen deficiency may possibly benefit from androgen replacement.

Parity and pregnancy outcome

A Norwegian postal survey found significantly fewer childbirths than expected from childbirth statistics after, but not before, the diagnosis of PAI, yielding a standardised incidence ratio (SIR) for birth of 0.69 (95% confidence interval [CI], 0.52–0.86, $n = 158$), after excluding patient with POI, 0.72 (95% CI, 0.52–0.92) (53). A Swedish population-based epidemiological study including 1188 women with PAI also found that parity was significantly reduced after, but not before, the PAI diagnosis was made (57). Furthermore, the likelihood of having three or more children was less than one-third in women diagnosed with PAI compared with controls. Consequently, we now have data from two populations showing that PAI influences the number of childbirths. The reasons are unclear, but social, psychological, physiological and biological factors probably contribute.

There are only a little more than 100 reported pregnancy cases in women with PAI in the literature, but clinical experience is extensive. Untreated or

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mismanaged PAI results in high rates of adrenal crisis, maternal deaths and negative foetal consequences, i.e. intrauterine deaths, suboptimal birthweight and reduced foetal growth (58, 59, 60). However, if provided adequate hormonal replacement, the majority of women can expect uneventful pregnancies of normal duration and without maternal or foetal compromise (61, 62, 63, 64). The first population-based epidemiological study on pregnancy outcomes in PAI was recently published, confirming that most pregnancies in women with PAI are uneventful (57). No maternal or infant deaths were reported, and there was no increase in risk of congenital malformations. However, more preterm deliveries (adjusted odds ratio (OR) 2.61; 95% CI, 1.69–4.05) and caesarean sections (adjusted OR 2.35; 95% CI, 1.68–3.27) were observed. Moreover, among 96 singleton infants born 3 years or less before their mothers were diagnosed with PAI had more frequent preterm births and lower birthweights. Notably, the risks were inversely correlated with time from delivery to the eventual PAI diagnosis. The underlying mechanisms are not known, but it is possible that suboptimal glucocorticoid levels before the diagnosis may alter the timing of delivery (65). Hormonal and immunoregulatory disturbances (more autoimmunity perhaps) preceding the diagnosis of PAI may account for the foetal growth retardation seen in infants born to mothers with undiagnosed PAI. The increased risk of a woman with PAI having a caesarean section may simply be treatment bias reflecting (unsubstantiated) concern for complications and possible adrenal crisis.

Bone

Glucocorticoids inhibit osteoblast activity, stimulate osteoclast activity and inhibit intestinal vitamin D-dependent calcium absorption, and osteoporosis is a feared complication of glucocorticoid therapy. Whether glucocorticoid-induced osteoporosis (GIOP) is also a problem with slight over-replacement, as commonly seen in patients with PAI, has not been well studied until recently. Some studies showed that reduction of glucocorticoid replacement doses improved markers of bone turnover (25, 66). A series of studies has shown an inconsistent correlation between bone mineral density (BMD) and disease duration, glucocorticoid type and dose in PAI (27, 67, 68, 69, 70, 71, 72). A study of 294 patients from Norway, the UK and New Zealand showed a moderate though significant reduction in BMD in PAI patients (73), as had been indicated in the earlier, mostly underpowered studies. Notably, a recent study in 81 German PAI patients

found no reduction in BMD (74). One likely explanation for the different findings is that the patients in the German cohort received lower doses of glucocorticoids (mean hydrocortisone equivalents: women 20.9 mg/day, men 24.2 mg/day) than the cohorts from Norway (women 31.5 mg/day, men 33.2 mg/day) and the UK and New Zealand (women 24.7 mg/day, men 29.1 mg/day).

The lack of adrenal androgens in patients with PAI could confer additional risk of osteoporosis. The largest DHEA trial so far in PAI suggested that 12-month DHEA replacement marginally but significantly increased BMD at the femoral neck but not at other skeletal sites (31). The German observational study showed that 17 female patients treated with DHEA had significantly lower markers of bone resorption and higher BMD Z-scores than those not receiving DHEA (74). One trial reported somewhat increased osteocalcin levels with DHEA treatment (75), whereas others found no effect of DHEA replacement on bone metabolism (76, 77).

Until recently, fracture data in PAI have been sparse. Thoracolumbar X-rays in 84 Norwegian patients older than 50 years did not show a higher prevalence of fractures than reported in the Norwegian reference population (73). However, a Swedish registry study that included 3219 patients over 30 years of age showed a significantly higher prevalence of hip fractures (6.9%) compared with a reference population of 31 557 age- and sex-matched controls (2.7%; hazard ratio (HR) 2.7; 95% CI, 1.6–4.5) (78). Interestingly, this study also indicated a significantly and unexplained increased risk of fractures in the patients before PAI diagnosis.

Little is known about individual susceptibility to GIOP in general or in patients with PAI. Using a candidate gene approach, Løvås *et al.* showed significant association between the common P-glycoprotein (*ABCB1*) SNP rs1045642 and BMD (73). Glucocorticoids are substrates for P-glycoprotein, and rs1045642 has previously been associated with reduced efficacy of this efflux transporter, which might increase intracellular glucocorticoid levels (79, 80). Most likely, individual susceptibility to GIOP is a multigenic and multifactorial challenge. The major clinical studies on bone and fractures are summarised in Table 2.

Metabolism

Glucocorticoids have profound effects on energy metabolism, but less is known about the metabolic status than bone status in PAI patients on replacement therapy. A study of 38 PAI patients on replacement therapy showed

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Table 2 Major clinical studies of metabolism, bone and fractures in primary adrenal insufficiency (PAI).

Reference	Study type	Sample	Result
Metabolism			
Giordano <i>et al.</i> (81)	Clinical study	PAI = 38 on conventional glucocorticoid treatment Controls = 38	Mean waist higher ($P < 0.05$) in PAI. No difference for mean gluco-lipid levels but a higher percentage of PAI patients had impaired glucose tolerance (8 vs 0%), hypercholesterolaemia (18 vs 8%) and triglyceridemia (18 vs 8%)
Meyer <i>et al.</i> (84)	Clinical study	PAI = 13 on conventional glucocorticoid treatment	Screening of hypoglycaemia using CGMS identified a nocturnal hypoglycaemic episode in one patient with blood glucose level clearly beneath the 95% tolerance interval of minimal glucose levels
Quinkler <i>et al.</i> (43)	Clinical study Open, prospective one-centre trial Baseline and at follow-up (median 202 days (85–498)).	PAI = 32, SAI = 18 21 PAI and 9 SAI patients switched by their own decision from conventional glucocorticoid treatment to once-daily modified release hydrocortisone	Patients on once-daily modified release hydrocortisone showed significant decreases in BMI (26.0 ± 0.75 to 25.6 ± 0.71 , P for change = 0.006) and HbA1c (6.04 ± 0.29 to 5.86 ± 0.28 , P for change = 0.005). No change in these parameters was seen in patients remaining on conventional glucocorticoid treatment
Johannsson <i>et al.</i> (85)	Clinical study Open, randomized, two-period, 12-week, crossover, multicentre trial	PAI = 64 The same daily dose of hydrocortisone was administered as once-daily modified release or thrice-daily conventional hydrocortisone treatment	Reduced mean body weight (difference = -0.7 kg, $P = 0.005$), reduced systolic BP (difference = -5.5 mmHg, $P = 0.0001$) and diastolic BP (difference = -2.3 mmHg, $P = 0.03$) and improved glucose metabolism (HbA1c (absolute difference = -0.1% , $P = 0.0006$)) were observed during once-daily modified release hydrocortisone treatment. A sustained serum cortisol profile 0–4 h after the morning intake and reduced late afternoon and 24-h cortisol exposure compared to thrice-daily conventional hydrocortisone treatment was also seen
Ross <i>et al.</i> (87)	Clinical study Cross-sectional nationwide study	PAI = 147 on conventional glucocorticoid treatment Controls = 147	Patients had elevated triglycerides ($P = 0.001$), reduced HDL ($P < 0.001$) and nonesterified fatty acids ($P < 0.001$), elevated hs-CRP ($P < 0.001$) and small dense LDL ($P = 0.002$) compared to controls
Björnsdóttir <i>et al.</i> (15)	Registry study Population-based cohort study	PAI = 1305 Controls = 11 996	More patients than controls were prescribed cardiovascular medicines (ATC C) (OER 1.14, 95% CI, 1.03–1.26). Patients <40 years of age used more antihypertensive drugs and diuretics than controls (OER 1.90, 95% CI, 1.20–2.75) Patients 40–49 years old were prescribed lipid-lowering agents more frequently than controls (OER 1.97, 95% CI, 1.15–3.01)
Ross <i>et al.</i> (88)	Clinical study	PAI = 110 (55 Swedish and 55 South African)	South African patients had higher median triglycerides ($P < 0.001$), total cholesterol ($P < 0.001$), LDL ($P < 0.001$), and median hs-CRP ($P < 0.003$) and lower HDL ($P < 0.001$) than the Swedish patients
Bone and fractures			
Løvås <i>et al.</i> (73)	Clinical study	PAI = 292	Moderately reduced BMD in the patients (mean Z-score reductions from -0.57 to -0.17 at various sites). No increase in fractures. Significant association between P-glycoprotein SNP and BMD reduction
Koetz <i>et al.</i> (74)	Clinical study	PAI = 81	No overall BMD reduction. Prednisolone associated with lower BMD and DHEA with higher BMD
Gurnell <i>et al.</i> (31)	Clinical trial Double-blind, randomized, placebo-controlled, 12-month, multicentre trial	PAI = 100 50 mg daily of oral DHEA or placebo	DHEA replacement reversed ongoing loss of bone mineral density at the femoral neck ($P < 0.05$) but not at other sites; DHEA enhanced total body ($P = 0.02$) and truncal ($P = 0.017$) lean mass significantly with no change in fat mass
Björnsdóttir <i>et al.</i> (78)	Registry study Population-based cohort study	PAI = 3219 Controls = 31 557	221 hip fractures (6.9%) in patients with PAI and 846 (2.7%) in the controls were observed, yielding increased risk of hip fracture in PAI (HR = 1.8; 95% CI, 1.6–2.1; $P < 0.001$). Women diagnosed with PAI ≤ 50 years old had the highest risk of hip fracture (HR = 2.7; 95% CI, 1.6–4.5)

CGMS, continuous glucose monitoring system; BP, blood pressure; HbA1c, glycated haemoglobin; hs-CRP, highly sensitive C-reactive protein; OER, observed to expected ratio.

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normal fasting glucose levels, but a higher percentage of impaired glucose tolerance than in controls (81). Studies in secondary adrenal insufficiency indicate that altered circadian cortisol patterns during replacement therapy affect both carbohydrate and lipid metabolism (82, 83), but the effects of glucocorticoid and growth hormone failure and their replacement are hard to distinguish. It is, however, likely that lack of night-time cortisol in patients on regular glucocorticoid replacement therapy confers risk of nocturnal hypoglycaemia, which may be a problem particular to patients with concomitant diabetes mellitus (84). Use of once-daily modified release hydrocortisone tablet (Plenadren, Viropharma Inc, Exton, PA, USA) resulted in decreased body mass index (BMI) and HbA1c compared with conventional hydrocortisone treatment (43, 85). Possibly, these findings were due to a beneficial reduction in 24-h hydrocortisone exposure, especially evident in the afternoon (85, 86).

Lipid status has been assessed in a number of DHEA replacement trials, but overall no significant baseline abnormalities or effects of the treatment have been noted. Some studies reported a slight increase in HDL cholesterol (76, 77), whereas others have found more dyslipidaemia in patients with PAI than in controls (81, 87). A description of the drug prescription patterns in Sweden showed a higher use of lipid lowering agents among PAI patients compared with population controls (15). Comparisons between different PAI cohorts are rare, but recently South African PAI patients were found to have a worse lipid profile than gender-, age- and BMI-matched Swedish PAI patients despite being treated with lower daily doses of hydrocortisone (88). This is interesting data and emphasises that environmental, dietary and/or genetic factors certainly contribute to regional differences in cardiovascular risk factors. The major clinical studies on metabolism are summarised in Table 2.

Cancer

Various autoimmune conditions have been associated with increased cancer incidence (89, 90, 91). Cancer mortality was slightly increased in the Swedish PAI population-based registry study but was not confirmed in a Norwegian cohort (92, 93). Data from other parts of the world do not exist. The cancer incidence pattern in Swedish PAI patients showed only a modest increase in cancer risk (93). When excluding cancers detected within the first year after PAI diagnosis, which may represent a potential detection bias, the risk remained elevated only in

patients with APS-1 and not in patients with isolated PAI or APS-2. Significantly higher incidences of oral cancers (ICD-7140–148), non-melanoma skin cancer (ICD-7191) and male genital system cancers (ICD-7177–179) were seen among patients. By contrast, less breast cancer (ICD-7170) than expected was observed.

Mortality

Before treatment with glucocorticoids and fludrocortisone became available in the 1950s, the majority of patients died shortly after diagnosis (2). The mortality in patients with chronic PAI on conventional therapy was for a long time considered similar to that of the background population (3). Recent studies, however, challenged this view (7, 92, 93, 94). Bergthorsdottir and coworkers performed a population-based epidemiological register study in Sweden (1987–2001) (94) and found an increased risk of death in both men (risk ratio (RR) 2.19; 95% CI, 1.91–2.51) and women (RR 2.86; 95% CI, 2.54–3.20). The excess mortality was ascribed to cardiovascular, malignant and infectious diseases. The risk was highest in the period close to diagnosis but remained elevated through the years. Concomitant diabetes mellitus contributed only to a limited extent (7%) to the reduced life expectancy. Bensing and coworkers corroborated a more than two-fold increased mortality in PAI investigating the same Swedish registers, but over an extended period (1964–2004) (93). A detailed cause-specific analysis showed an increased mortality from all disease categories. Notable high risks were observed from endocrine and infectious diseases. Furthermore, the highest mortality was observed in patients diagnosed before 15 years of age and in patients with APS-1. The Norwegian survey was a retrospective search of electronic in- and outpatient registries covering at least 15 years in 57 national hospitals (92). The diagnosis was verified by endocrinologists, identifying 811 patients with PAI and 147 deaths. Contrary to the Swedish studies, no overall increased mortality was found, but in line with Swedish data, an excess mortality was observed in patients diagnosed before the age of 40 (standardized mortality rate (SMR) 1.50; 95% CI, 1.09–2.01), particularly evident in men. Acute adrenal failure, infections and sudden deaths were all common causes of death.

A possible cause of the higher mortality observed in PAI is suboptimal replacement therapy. The conventional glucocorticoid doses may be too high, with possible negative metabolic and cardiovascular consequences, but low levels of androgens could also contribute.

Concomitant autoimmune disease, such as autoimmune thyroid disease, T1D, POI and APS-1, probably aggravate the higher mortality seen in PAI (93, 95, 96, 97, 98). At diagnosis, more than half of all PAI patients present with Addisonian crises and are critically ill with an increased risk of death (3, 92). Considering patients dying never diagnosed or diagnosed post-mortem, the mortality would be even higher than suggested by the recent studies.

A life-threatening adrenal crisis is, unfortunately, a common event in PAI on replacement therapy. Recent studies provide evidence of an annual incidence of adrenal crisis of 5–17% (16, 99, 100, 101, 102, 103) and show that 47% of PAI patients have experienced at least one acute adrenal crisis after diagnosis (100). In the first prospective study on adrenal crisis a total of 423 patients (PAI, $n=221$; secondary adrenal insufficiency (SAI), $n=202$) were followed up for 2 years; 10 patients died during follow-up (PAI, $n=5$; SAI, $n=5$), and at least 4 deaths were associated with adrenal crisis (0.5 adrenal-crisis-related deaths per 100 patients-years) (101). The most important precipitating causes of adrenal crisis are gastrointestinal infections with vomiting and/or diarrhoea, other infectious diseases and fever. Other listed causes are surgery, trauma, emotional stress and cessation of glucocorticoid substitution. Concomitant diseases (99, 100, 102) and previous adrenal crisis (101) increase the frequency. Even a minor stomach upset can provoke an Addisonian crisis, and in the event of an emergency medical staff must react with prompt administration of intravenous glucocorticoids and saline infusions. Education of patients and medical staff on how to adequately increase glucocorticoid doses, when to seek medical help and how to self-administrate parenteral hydrocortisone is important to prevent adrenal crisis (104, 105). All patients should be equipped with a hydrocortisone injection kit and a steroid card to improve safety. Recently, a European bilingual steroid emergency card has been designed to provide quick and potentially life-saving information to the healthcare worker in an emergency situation (106).

Concluding comment

In this article, we have summarised the current knowledge on the epidemiology, QoL and complications of PAI. There is a need for improvement of the treatment and monitoring of patients with PAI. Further epidemiological research and prospective follow-up of large unbiased cohorts are needed to unravel the medical and public health impacts of PAI.

Declaration of interest

S B, A-L H, E S H and K L declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review. O K is a board member of Olink AB.

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Author contribution statement

S B and K L wrote and revised the manuscript. A-L H, E S H and O K contributed in revising it.

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