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Optimal glucocorticoid replacement in adrenal insufficiency

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Adrenal insufficiency (glucocorticoid deficiency) comprises a group of rare diseases, including primary adrenal insufficiency, secondary adrenal insufficiency and congenital adrenal hyperplasia. Lifesaving glucocorticoid therapy was introduced over 60 years ago, but since then a number of advances in treatment have taken place. Specifically, little is known about short- and long-term treatment effects, and morbidity and mortality. Over the past decade, systematic cohort and registry studies have described reduced health-related quality of life, an unfavourable metabolic profile and increased mortality in patients with adrenal insufficiency, which may relate to unphysiological glucocorticoid replacement. This has led to the development of new modes of replacement that aim to mimic normal glucocorticoid physiology. Here, evidence for the inadequacy of conventional glucocorticoid therapy and recent developments in treatment are reviewed, with an emphasis on primary adrenal insufficiency.

Abbreviations: PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; CSHI, continuous subcutaneous hydrocortisone infusion; OHC, oral hydrocortisone; HRQoL, health-related quality of life.

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Conventional glucocorticoid replacement therapy

Adrenal insufficiency and adrenal crisis

In primary adrenal insufficiency (PAI), such as Addison's disease, the adrenal cortex produces insufficient amounts of glucocorticoids, mineralocorticoids and adrenal androgens. Primary adrenal insufficiency is rare, with a prevalence of 110–140 per million and an incidence of 4.4–5.6 per million with a female preponderance [1]. It may be isolated; however, more than 50% of patients have an autoimmune polyendocrine syndrome [2]. Symptoms may be non-specific, subtle and disease progress insidious, making diagnosis difficult. Acute adrenal failure, or Addisonian crisis, resulting from untreated cortisol and aldosterone deficiency, results in hypotension, hypovolemic shock, or both, often accompanied with abdominal pain, vomiting and fever [3]. It is a life-threatening complication of chronic adrenal insufficiency and is often the first presentation.

A historical perspective

Addison first described adrenal failure in 1955 [4]. Although efforts were made to produce adrenal extracts to prolong survival, the real treatment revolution came with the identification of the different adrenal steroids by two different researchers: Reichstein in Europe and Kendall in the USA. For their achievement, they won the Nobel Prize Award in 1950, see Fig. 1. Since then, the replacement therapy has remained almost unchanged. Oral hydrocortisone (OHC) is the most common treatment choice worldwide [5]. Cortisone acetate is considered equally effective and, in some countries, long-acting glucocorticoids, such as prednisolone and dexamethasone, are also used. Concerns, however, have been raised that the synthetic long-acting glucocorticoids result in continuous stimulation of the glucocorticoid receptor, probably increasing the risk of detrimental side-effects [6].

Prevention and treatment of adrenal crisis

Both the adrenocortical and the adrenomedullary stress responses are compromised in PAI [7], and strenuous exercise can trigger an adrenal crisis [8]. Patients are sometimes advised to use an additional dose of hydrocortisone 5–10 mg during strenuous or long-lasting exercise and long-lasting psychological stress [9]. Exercise studies in patients with congenital adrenal hyperplasia, however, have demonstrated

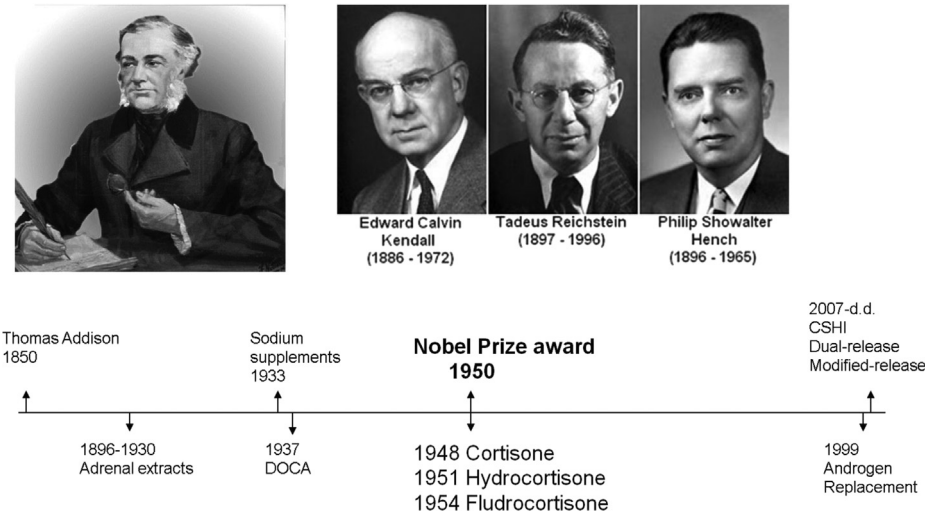

Fig. 1. Replacement therapy in adrenal insufficiency; a historical perspective.