MRS Journal of Multidisciplinary Research and Studies
ISSN *(Online) 3049-1398*
Vol-3, Iss-2 (January-2026)
Journal homepage: https://mrspublisher.com/journals

Primary Adrenal Insufficiency (Addison's disease): Pathophysiology, Diagnosis, and Management – A Narrative Review

Mustafa Raheem Tuamah*

* DNA Research center, University of Babylon, Babylon, Hillah, 51001, Iraq

Corresponding Author: ***Mustafa Raheem Tuamah*** *(DNA Research center, University of Babylon, Babylon, Hillah, 51001, Iraq)*

Received: 15 / 12 / 2025	Accepted: 27 / 01 / 2026	Published: 08 / 02 / 2026

Abstract: Background: Primary adrenal insufficiency (PAI), commonly known as Addison's disease, is a rare but potentially life threatening endocrine disorder resulting from destruction of the adrenal cortex and consequent deficiency of glucocorticoids, mineralocorticoids, and adrenal androgens. Autoimmune adrenalitis represents the leading cause in developed countries.

Objective: This narrative review aims to summarize current knowledge regarding the epidemiology, pathophysiology, immunological mechanisms, clinical manifestations, diagnostic approach, and management strategies of Addison's disease.

Methods: A narrative literature review was conducted based on key articles, international clinical guidelines, and major reviews published in peer reviewed journals focusing on primary adrenal insufficiency.

Results: Addison's disease typically presents with nonspecific symptoms such as fatigue, weight loss, hypotension, and hyperpigmentation, often leading to delayed diagnosis. Laboratory findings include low serum cortisol, elevated adrenocorticotropic hormone (ACTH), electrolyte disturbances, and the presence of adrenal autoantibodies, particularly 21 hydroxylase antibodies. Lifelong hormone replacement therapy with glucocorticoids and mineralocorticoids remains the cornerstone of management. Failure to recognize or adequately treat the condition may result in adrenal crisis, a medical emergency associated with significant morbidity and mortality.

Conclusion: Early recognition of Addison's disease, appropriate diagnostic evaluation, and patient education regarding lifelong therapy and stress dose adjustment are essential to improve outcomes and quality of life.

Keywords: *Addison's disease; Primary adrenal insufficiency; Autoimmune adrenalitis; Cortisol deficiency; ACTH*

Cite this article: Tuamah, M. R. (2026). Primary Adrenal Insufficiency (Addison's Disease): Pathophysiology, Diagnosis, and Management – A Narrative Review.*MRS Journal of Multidisciplinary Research and Studies, 3(2),4-6.*

Introduction

Addison's disease, also referred to as autoimmune adrenalitis, is an acquired form of primary adrenal insufficiency characterized by progressive destruction of the adrenal cortex [1]. This destruction leads to impaired synthesis of cortisol, aldosterone, and adrenal androgens, resulting in significant metabolic, cardiovascular, and immunological consequences [2]. Although rare, Addison's disease is a potentially fatal condition if unrecognized or inadequately treated [3]. The disease often follows an insidious course, with early symptoms being nonspecific and gradually progressive, contributing to diagnostic delay [4]. In some cases, patients may present acutely with adrenal crisis precipitated by infection, trauma, or other physiological stressors [5]. This review aims to provide an updated and comprehensive overview of Addison's disease, focusing on its epidemiology, immunopathogenesis, clinical presentation, diagnostic strategies, and current management principles [6].

Epidemiology

Primary adrenal insufficiency is an uncommon disorder worldwide [2]. The reported prevalence ranges between 40–60 cases per million population in the United States and Europe [6]. In Great Britain, the prevalence is approximately 39 per million, while Denmark reports around 60 per million [4][7]. Higher prevalence rates have been documented in Scandinavian countries, with Iceland reporting 22.1 cases per 100,000 population [8]. In contrast, lower prevalence rates have been observed in Asian populations, such as Korea, where the prevalence is estimated at 4.17 per million population [9]. Autoimmune Addison's disease accounts for more than 80% of cases in developed countries and shows a female predominance, typically presenting in early to middle adulthood [3][10].

Pathophysiology

The adrenal cortex consists of three distinct zones: the zona glomerulosa, zona fasciculata, and zona reticularis, responsible for the production of mineralocorticoids, glucocorticoids, and adrenal androgens, respectively [11] [12]. In Addison's disease, immune-mediated destruction of these layers results in progressive hormonal deficiency [10]. Cortisol deficiency impairs glucose metabolism, stress response, and immune regulation, while aldosterone deficiency leads to sodium loss, potassium retention, hypovolemia, and hypotension [2][6]. Androgen deficiency may contribute to reduced libido and loss of secondary sexual hair, particularly in women [13].

Immunological Mechanisms

Addison's disease is most commonly caused by autoimmune destruction of the adrenal cortex [10]. Circulating autoantibodies against steroidogenic enzymes, particularly 21-hydroxylase, serve as key diagnostic markers [14]. The autoimmune process leads to gradual glandular atrophy and declining hormone secretion [4]. Elevated ACTH levels result from reduced cortisol-mediated negative feedback on the hypothalamic–pituitary–adrenal axis [2]. Increased production of proopiomelanocortin (POMC) derivatives, including melanocyte-stimulating hormone (MSH), explains the characteristic hyperpigmentation of the skin and mucous membranes [1]. Addison's disease frequently occurs as part of autoimmune polyglandular syndromes and may coexist with other autoimmune disorders such as type 1 diabetes mellitus, autoimmune thyroid disease, and pernicious anemia, reflecting a broader systemic immune dysregulation [15][16].

Clinical Manifestations

The clinical presentation of Addison's disease is variable and often nonspecific [13]. Common symptoms include chronic fatigue, weight loss, anorexia, nausea, abdominal pain, dizziness, and salt craving [2]. Physical findings may include hypotension, postural dizziness, and generalized or focal hyperpigmentation [1]. Electrolyte abnormalities such as hyponatremia and hyperkalemia are typical laboratory features [6]. In advanced cases or during stress, patients may develop adrenal crisis, characterized by severe hypotension, dehydration, hypoglycemia, and shock [5][17].

Diagnosis

The diagnosis of Addison's disease relies on a combination of clinical suspicion and biochemical testing [1]. Basal serum cortisol levels are typically low, accompanied by markedly elevated ACTH concentrations [2][13]. The ACTH (cosyntropin) stimulation test remains the gold standard for confirming adrenal insufficiency [6]. Additional investigations include measurement of plasma renin activity and aldosterone levels, electrolyte assessment, and screening for adrenal autoantibodies, particularly 21-hydroxylase antibodies [3][14]. Imaging studies such as computed tomography may be considered when non-autoimmune causes are suspected [4].

Management and Treatment

Lifelong hormone replacement therapy is essential in patients with Addison's disease [6]. Glucocorticoid replacement is commonly achieved using hydrocortisone in divided daily doses, while mineralocorticoid deficiency is treated with fludrocortisone [3][18]. Dose adjustments are required during periods of illness, surgery, or physiological stress [19]. Patient education plays a central role in disease management [19]. Individuals should be instructed on stress-dose steroid adjustment, emergency self-administration of injectable hydrocortisone, and the importance of wearing medical alert identification [5][20].

Adrenal Crisis

Adrenal crisis is a life-threatening complication of Addison's disease and represents a medical emergency [5]. Immediate treatment includes intravenous hydrocortisone, aggressive fluid resuscitation with isotonic saline, and correction of hypoglycemia and electrolyte abnormalities [6][17]. Prompt recognition and intervention are critical to reducing mortality [21].

Conclusion

Addison's disease is a rare but serious endocrine disorder requiring a high index of clinical suspicion for timely diagnosis. Advances in immunological testing and standardized treatment guidelines have improved patient outcomes. Nevertheless, lifelong follow-up, patient education, and appropriate stress management remain essential to prevent adrenal crisis and ensure optimal quality of life.

References

1. Nieman LK. Addison disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
2. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet. 2014;383(9935):2152–67.
3. Husebye ES, Allolio B, Arlt W, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275(2):104–15.
4. Erichsen MM, Løvås K, Skinningsrud B, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency. J Clin Endocrinol Metab. 2009;94(12):4882–90.
5. Hahner S, Ross RJ, Arlt W, et al. Adrenal crisis: Still a deadly event in the 21st century? J Clin Endocrinol Metab. 2021;106(3):e1078–e86.
6. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–89.
7. Dalin F, Nordling Eriksson G, Dahlqvist P, et al. Clinical and immunological characteristics of autoimmune Addison's disease: A nationwide Swedish multicenter study. J Clin Endocrinol Metab. 2017;102(2):379–89.
8. Olafsson AS, Sigurjonsdottir HA. Increasing prevalence of Addison disease: Results from a nationwide study. Endocr Pract. 2016;22(1):30–35.
9. Hong AR, Kim JH, Kim SW, et al. Epidemiology of primary adrenal insufficiency in Korea: A nationwide population-based study. Endocrinol Metab (Seoul). 2018;33(4):488–95.
10. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes. Endocr Rev. 2002;23(3):327–64.
11. Mescher AL. *Junqueira's Basic Histology: Text and Atlas*. 15th ed. New York: McGraw-Hill Education; 2018.
12. Hall JE, Guyton AC. *Guyton and Hall Textbook of Medical Physiology*. 14th ed. Philadelphia: Elsevier; 2021.
13. Arlt W, Allolio B. Adrenal insufficiency. *Lancet*. 2003;361(9372):1881–93.
14. Falorni A, Laureti S, De Bellis A, et al. Italian Addison Network Study: Update on autoantibodies in autoimmune adrenal insufficiency. *J Clin Endocrinol Metab*. 2004;89(2):594–600.

15. Husebye ES, Anderson MS, Kämpe O. Autoimmune polyendocrine syndromes. *N Engl J Med*. 2018;378(12):1132–41.

16. Betterle C, Zanchetta R. Autoimmune polyglandular syndrome type 1 and type 2. *Endocrinol Metab Clin North Am*. 2009;38(2):389–405

17. Rushworth RL, Torpy DJ, Falhammar H. Adrenal crisis. *Lancet Diabetes Endocrinol*. 2019;7(3):234–45.

18. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(2):364–89.

19. Choudhury S, Meeran K. Glucocorticoid replacement in Addison disease. *Nat Rev Endocrinol*. 2018;14(9):562.

20. Hahner S, Quinkler M, Fassnacht M, et al. Adrenal crisis: Prevention and management in adult patients. *J Clin Endocrinol Metab*. 2015;100(2):407–16.

21. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol*. 2015;3(3):216–26