International Journal of Community Medicine and Public Health
Alharbi SA et al. Int J Community Med Public Health. 2024 Dec;11(12):4990-4995
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20243414

Review Article

Recent developments in the diagnosis and treatment of Addison's disease

Samar Abed Alharbi[1]*, Rawdha Hameed Fardan[2], Mustafa Saeed Almahasnah[3], Nouf Ali Alsaeed[4], Hiba Hani Kashif[5], Nora Abdullah AlGhamdi[6], Amani Awadh Alharthi[7], Sara Abdullah Al Ghamdi[8], Amna Ayed Asiri[9], Dhari Ahmed Alharbi[10]

[1]Department of Internal Medicine, Al Thager Hospital, Jeddah, Saudi Arabia
[2]Endocrine and Diabetes Center, Salmaniya Medical Complex, Manama, Bahrain
[3]Department of Internal Medicine, Khafji General Hospital-Ministry of Health, Khafji, Saudi Arabia
[4]Department of Internal Medicine, East Jeddah Hospital, Jeddah, Saudi Arabia
[5]Department of Internal Medicine, Ministry of Health, Jeddah, Saudi Arabia
[6]Department of Internal Medicine, King Fahad General Hospital, Jeddah, Saudi Arabia
[7]College of Pharmacy, Taif University, Taif, Saudi Arabia
[8]Department of Pediatric Endocrinology, Maternity and Children's Specialized Hospital, Jeddah, Saudi Arabia
[9]Community Pharmacy, The World of Health and Beauty Pharmacy, Abha, Saudi Arabia
[10]Department of Internal Medicine, Farwaniya Hospital, Al Farwaniya, Kuwait

Received: 12 October 2024
Accepted: 28 October 2024

***Correspondence:**
Dr. Samar Abed Alharbi,
E-mail: Dr_sam1990@hotmail.com

ABSTRACT

Primary adrenal insufficiency (PAI), also referred to as Addison's disease (AD), is a rare but potentially life-threatening disorder marked by a deficiency in the production of hormones by the adrenal cortex. Despite significant advancements in diagnosis and treatment, challenges remain, particularly in pediatric cases where diagnostic delays are common. Autoimmune adrenalitis is the leading cause of AD in adults, while congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is the primary cause in children. Recent developments include dual-release hydrocortisone formulations designed to mimic circadian rhythms and improve patient outcomes, as well as continuous subcutaneous cortisol infusion using insulin pumps. Experimental therapies, such as immunosuppression, gene therapy, and cell replacement, are in early stages of research. Management focuses on hormone replacement therapy and preventing adrenal crises, often triggered by infections or surgery. Education on crisis prevention is crucial, and patients should regularly monitor hormone levels. Advances in treatment aim to improve quality of life, yet more research is needed to refine therapeutic approaches and long-term outcomes.

Keywords: AD, PAI, Glucocorticoid replacement, Hydrocortisone, Autoimmune adrenalitis, Adrenal crisis

INTRODUCTION

Primary adrenal insufficiency (PAI), first identified by Thomas Addison in 1855, is a rare disorder marked by the reduced production of all hormones from the adrenal cortex. Although glucocorticoid deficiency is the predominant characteristic, deficiencies in mineralocorticoids and androgen imbalances may also be present.[1] Despite its rarity, PAI is a life-threatening condition that requires prompt diagnosis and treatment, though this can be challenging, especially in children, often resulting in significant diagnostic delays. Both congenital and acquired conditions can cause PAI.[2,3] PAI is also often referred to as AD.[4]

The prognosis for the condition improved significantly with the introduction of steroid hormone therapies and the development of practical diagnostic methods. Following the isolation and characterization of cortisol and cortisone,[5] and the creation of synthetic glucocorticoid hormones,[6] the treatment and diagnosis of adrenal insufficiency advanced, largely due to the clinical efforts of Wilder in the 1930s, and later Thorn and Forsham in the 1940s and 1950s.[5]

In adults from industrialized countries, autoimmune Addison's disease (AAD) is the most common cause of PAI, while in children, the condition is primarily due to genetic defects.[7] CAH caused by 21-hydroxylase deficiency (21OH-D) is the leading cause of childhood-onset PAI. However, while 21OH-D has been well-researched, other causes of childhood PAI are not as thoroughly described, leaving gaps in the understanding of the epidemiology, etiology, and long-term outcomes of adrenal insufficiency in children. Autoimmune adrenal insufficiency can develop in isolation or alongside other autoimmune disorders, with clinical presentations varying depending on the underlying condition.

The prevalence of PAI continues to rise, particularly among women.[8] While this trend may reflect a genuine increase in cases, it is also possible that previous underestimation of PAI prevalence, alongside advancements in diagnostic methods and healthcare systems, plays a role in the observed increase.[9] Additionally, changes in the underlying causes of PAI may contribute to this trend.

In Addison's original description of PAI, based on 11 patients, over 50% of cases were caused by tuberculosis, 30% by neoplastic or metastatic disease, and about 10% by hemorrhage. In Western societies, autoimmune adrenalitis accounts for roughly 80% of PAI cases, while infections such as tuberculosis, HIV/AIDS, CMV, candidiasis, histoplasmosis, and syphilis, as well as malignancies like lung, breast, and colon cancer, are responsible for about 10% of cases.[5]

Autoimmune adrenalitis can occur as an isolated condition or as part of autoimmune polyglandular syndromes (APS), with over 50% of cases being linked to additional autoimmune disorders. Some forms of APS have a known genetic basis, such as autoimmune regulator (AIRE) gene mutations in APS type 1, and all forms of autoimmune adrenalitis are linked to specific gene variants in the major histocompatibility complex (e.g., HLA-DR3) or genes involved in immunological regulation (e.g., CTLA-4), highlighting the central role of T-cell mediated immunity in AD pathophysiology.[10,11]

METHODS

This study is based on a comprehensive literature search conducted on 15 October 2024, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed recent developments in the diagnosis and treatment of AD. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

In AD, adrenal failure leads to a decrease in cortisol production, followed by aldosterone deficiency, resulting in elevated adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH) levels due to the loss of negative feedback inhibition.[12] AD typically has an insidious and gradual onset of nonspecific symptoms, which can delay diagnosis. Symptoms such as fatigue, weight loss, nausea, vomiting, dizziness, and hypotension may worsen over time, and the disease is often diagnosed only after an acute adrenal crisis, triggered by stress, infection, trauma, or surgery, manifests with hypotension, hyponatremia, hyperkalemia, and hypoglycemia.[13] AD can occur at any age but most commonly presents in the second or third decade of life. Early signs include fatigue, generalized weakness, weight loss, nausea, vomiting, and abdominal pain. Due to the variable presentation, clinicians should maintain a high index of suspicion when evaluating patients with unexplained fatigue or chronic abdominal pain. An Addisonian crisis is characterized by severe dehydration, refractory hypotension, confusion, and shock, and it occurs more frequently in PAI than in secondary adrenal insufficiency.[14] The physical examination should focus on identifying hyperpigmentation of the skin and mucous membranes, a key feature of AD, particularly in sun-exposed areas and pressure points such as the palmar creases, gingival mucosa, lips, elbows, and nail beds.[15] Hyperpigmentation, caused by elevated ACTH and MSH, is absent in secondary adrenal insufficiency, as ACTH levels remain low.[16] Additional findings may include the development of new nevi, decreased axillary and pubic hair in females, and vitiligo.[17]

Etilogy of AD

AD arises from a variety of causes that impair the adrenal glands' ability to produce necessary hormones. These causes can be broadly categorized into primary and secondary adrenal insufficiency, with primary insufficiency involving direct injury to the adrenal cortex, and secondary insufficiency often linked to chronic glucocorticoid use.

Autoimmune processes represent the most common etiology, frequently occurring in conjunction with other autoimmune conditions. Infectious, hemorrhagic, infiltrative, and pharmacologic factors also contribute to adrenal failure (Table 1).[18]

Table 1: Common etiologies of AD and their mechanisms.[18]

Etiology	Description
Primary adrenal insufficiency	Caused by direct injury to the adrenal cortex, including autoimmune, infectious, hemorrhagic, pharmacologic, and infiltrative causes.
Autoimmune causes	Most common cause of Addison disease; involves antibodies against the adrenal cortex and can be linked to APS.
Associated autoimmune conditions	Autoimmune thyroiditis, type 1 diabetes, pernicious anemia, vitiligo, alopecia, and celiac disease.
Infectious causes	Sepsis, tuberculosis, cytomegalovirus, disseminated fungal infections (histoplasmosis, syphilis), and meningococcemia.
Adrenal hemorrhage	Can occur due to, trauma, meningococcemia, and neoplasms, with Waterhouse-Friderichsen syndrome being a severe form in children.
Infiltrative causes	Hemochromatosis, amyloidosis, sarcoidosis, lymphoma, and genetic disorders like Wolman disease.
Pharmacologic causes	Medications such as ketoconazole and etomidate can induce adrenal insufficiency by inhibiting cortisol synthesis.
Secondary adrenal insufficiency	More common than primary, resulting from exogenous steroid use, leading to suppressed ACTH synthesis and cortisol deficiency, while aldosterone remains normal.

Diagnosis for AD

The diagnosis of AD is confirmed by demonstrating low cortisol and aldosterone levels, high renin levels, and a diminished cortisol response following ACTH stimulation (Table 2 and 3).[18] A low random cortisol level is typically seen in AD, but cortisol follows a diurnal rhythm, with the highest levels in the early morning, so an early morning cortisol level should be obtained when possible. In emergency settings, this is often impractical, and results are not usually available during the visit.[18]

Table 2: Cortisol level interpretation.

Cortisol level	Interpretation
>18 mcg/dl	Normal (morning cortisol)
<3 mcg/dl	Adrenal insufficiency
3–19 mcg/dl	Equivocal (further evaluation recommended)

ACTH level is markedly elevated in PAI, but it is normal or low in central adrenal insufficiency. If the diagnosis is uncertain, an ACTH (cosyntropin) stimulation test is the first-line diagnostic test. Plasma cortisol levels should be measured at 0, 30, and 60 minutes after ACTH administration.

Table 3: Interpretation of the ACTH stimulation test.

Condition	ACTH Level	Cortisol Response
Primary adrenal insufficiency	Elevated ACTH	Peak cortisol <18 mcg/dl or no response
Central adrenal insufficiency	Normal or low ACTH	Peak cortisol <18 mcg/dl or no response
Normal response	Normal ACTH	Peak cortisol >18 mcg/dl

Serum aldosterone and renin levels are essential in assessing mineralocorticoid deficiency. In primary adrenal insufficiency, both cortisol and aldosterone levels are low, while plasma renin activity is elevated. In contrast, aldosterone levels remain normal in secondary adrenal insufficiency. A high renin level with low aldosterone suggests adrenal cortex dysfunction.[17,19,20]

A comprehensive metabolic panel in AD often shows hyponatremia, hyperkalemia, and hypoglycemia. Hyponatremia arises from cortisol and aldosterone deficiencies, leading to sodium wasting and increased water absorption. Hyperkalemia, due to aldosterone deficiency, is not typically seen in secondary adrenal insufficiency, distinguishing it from primary adrenal insufficiency. Hypoglycemia results from decreased gluconeogenesis due to glucocorticoid deficiency, and hypercalcemia may occur due to extracellular fluid loss.

A slight elevation in thyroid-stimulating hormone (TSH) may be observed in adrenal insufficiency, likely due to the effect of decreased cortisol on TSH's circadian rhythm. Persistent TSH elevation should prompt evaluation for hypothyroidism.[19]

Anti-adrenal antibodies, particularly 21-hydroxylase antibodies, are markers of autoimmune adrenal destruction and can help identify the cause of adrenal insufficiency. These antibodies are also useful in assessing for other autoimmune conditions.[17]

Diagnostic imaging should follow biochemical confirmation, as radiographic findings tend to be nonspecific. Abdominal CT scans may show bilateral adrenal enlargement in cases of adrenal hemorrhage, and adrenal calcifications may indicate tuberculosis. Small adrenal glands on imaging suggest autoimmune destruction. If ACTH is low, MRI of the hypothalamic-pituitary region is recommended to evaluate for central causes of adrenal insufficiency.[20]

Further diagnostic testing may be needed to identify the underlying cause of adrenal insufficiency. A purified protein derivative (PPD) test can be used to evaluate for tuberculosis, and a serum very long-chain fatty acid profile may be necessary if adrenal leukodystrophy is suspected. Complete blood count (CBC) may reveal neutropenia, lymphocytosis, and eosinophilia, while ECGs should be performed in cases of hyperkalemia. Histologic studies can help identify infiltrative causes, with caseating granulomas indicative of tuberculosis and non-caseating granulomas suggestive of sarcoidosis.[20,21]

Diagnosis of pediatric AD

In diagnosing pediatric AD, the evaluation starts with cortisol and ACTH measurements, with low cortisol and elevated ACTH levels confirming PAI. The short synacthen stimulation test (SDSST) is useful for unclear cases, though updated cortisol cutoffs for children require further validation. High renin and low aldosterone confirm mineralocorticoid deficiency, often an early marker of autoimmune adrenalitis. The presence of adrenal autoantibodies, particularly 21-hydroxylase (21-OH), supports an autoimmune etiology and helps predict the progression of PAI. Monitoring adrenal function and screening for APS ensures early diagnosis and management.[7]

Treatment of AD

The primary treatment for autoimmune PAI involves hormone replacement therapy and managing complications. Once PAI is confirmed or if severe symptoms strongly suggest the condition, hormone replacement with glucocorticoids and mineralocorticoids should be initiated immediately, without waiting for etiological confirmation.[1] The adrenal cortex typically produces around 10 mg/m² of cortisol daily, following a circadian rhythm, with peak levels in the morning and lower levels at night. Oral hydrocortisone is the standard glucocorticoid replacement for children with PAI. For patients with autoimmune AD, a recommended hydrocortisone dose is 8-10 mg/m² per day, divided into 3-4 doses, with half to two-thirds of the total dose taken in the morning. Mineralocorticoid deficiency, which is almost always present in AAD patients, should be treated with fludrocortisone (9-alpha-fluorohydrocortisone) at a dose of 0.05-0.2 mg/day taken in the morning.[7]

In the event of an adrenal crisis, treatment includes intravenous administration of saline and glucose, along with an initial intravenous dose of hydrocortisone at 50-100 mg/m², followed by 50-75 mg/m² per day, either divided into four doses or administered as a continuous infusion.[2,3]

Preventing adrenal crises, which continue to be a major cause of death for PAI patients, is essential to the management of AAD patients. Triggers include infections, surgery, intense physical activity, or the withdrawal of treatment.[22,23] Educating parents and patients is essential and should be revisited regularly during clinical evaluations.[24] Caregivers must understand the importance of increasing glucocorticoid doses during illness, physical or psychological stress, or minor surgeries, and how to administer intramuscular glucocorticoids if needed. They should also be equipped to manage an impending adrenal crisis.[24,25]

Additional care for patients with APS (APS-1 or APS-2) involves treating problems and substituting other hormones that are insufficient.[7] A pediatric endocrinologist or other healthcare professional with endocrinology experience should be in responsible for managing children with AAD.[1] At a specialist center, patients with APS-1 should preferably be managed by a multidisciplinary team under the direction of an endocrinologist, with at least two follow-up visits per year. The frequency of monitoring visits varies with age and associated disorders.[26]

At present, no single biomarker is available to monitor glucocorticoid treatment. The adequacy of treatment is assessed through clinical evaluations, observing for signs of overtreatment or undertreatment, overall well-being, and growth. For monitoring mineralocorticoid therapy, indicators such as salt cravings, blood pressure, electrolyte levels, and renin concentrations/activity are used. Renin concentration is regarded as a more reliable marker than renin activity for evaluating biochemical status and adjusting fludrocortisone dosage.[7]

Patients with AAD, especially those with APS, are at higher risk for other autoimmune diseases. Regular screening for autoantibodies or clinical signs of conditions like thyroid dysfunction, diabetes, or celiac disease is recommended, though optimal screening frequency depends on clinical assessments and disease complexity.[3,22,27]

Novel aspects for treatment of primary adrenal insufficiency

While steroid replacement therapy for patients with PAI is generally effective, glucocorticoid replacement has notable pharmacological limitations, making it difficult to fully replicate normal physiology with oral hydrocortisone. To improve this, a dual-release hydrocortisone formulation has been developed, mimicking circadian cortisol levels by providing a morning peak with a single oral dose taken in the morning.[28] Early clinical data are promising, showing the drug's efficacy and safety.[29]

In addition to improved patient satisfaction due to the convenience of single-dose administration, favorable effects on body weight, blood pressure, and glycemic control have been observed compared to standard therapy.[5] Other modified-release hydrocortisone formulations are also in development.[30]

A particular challenge is glucocorticoid replacement in children, and to address this, hydrocortisone capsules have been developed and successfully tested to facilitate dosing and oral administration.[31] Another approach to restore normal circadian cortisol concentrations, as opposed to oral regimens, is continuous subcutaneous cortisol infusion using insulin pumps. Although this method is complex and only applicable to selected patients, initial reports are promising.[32-34]

In addition, several experimental treatments are in very early stages of development. These include immunosuppression for patients with early forms of autoimmune adrenalitis, gene therapy for monogenic forms of PAI, transplantation, cell replacement therapies, and reprogramming techniques to induce steroidogenic cells from other cell types.[5]

Future directions

Future research should focus on improving the precision of glucocorticoid replacement therapies, including the development of personalized, circadian-based treatments. Further exploration of continuous subcutaneous cortisol infusion and gene therapies for monogenic forms of PAI is needed. Additionally, early detection strategies, including biomarkers for autoimmune adrenalitis, and better patient education on crisis prevention, are crucial for enhancing long-term outcomes.

CONCLUSION

Despite advancements in the management of AD, challenges remain in achieving effective hormone replacement and preventing adrenal crises. Ongoing research into improved therapies, such as circadian-based treatments and innovative approaches like gene therapy, holds promise for enhancing patient care and long-term outcomes.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Bornstein SR, Allolio B, Arlt W, Andreas B, Andrew DW, Gary DH, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metabol. 2016;101(2):364-89.
2. Kirkgoz T, Guran T. Primary adrenal insufficiency in children: Diagnosis and management. Best Pract Res Clin Endocrinol Metabol. 2018;32(4):397-424.
3. Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. The Lancet. 2021;397(10274):613-29.
4. Addison T. On the constitutional and local effects of disease of the supura-renal capsules. Highley, London; 1855.
5. Barthel A, Benker G, Berens K, Sven D, Burkhard M, Matthias G, et al. An update on Addison's disease. Exp Clin Endocrinol Diabetes. 2019;127(02/03):165-75.
6. Sarett L. The synthesis of hydrocortisone from desoxycholic acid. J Biol Chem. 1946;162:601.
7. Capalbo D, Esposito A, Gaeta V, Paola L, Sara V, Raffaella DM, et al. The multiple faces of autoimmune Addison's disease in children. Frontiers in Endocrinology. 2024;15:1411774.
8. Meyer G, Neumann K, Badenhoop K, Linder R. Increasing prevalence of Addison's disease in German females: health insurance data 2008-2012. Eur J Endocrinol. 2014;170(3):367-73.
9. Laureti S, Vecchi L, Santeusanio F, Falorni A. Is the prevalence of Addison's disease underestimated? J Clin Endocrinol Metabol. 1999;84(5):1762.
10. Mitchell AL, Pearce SH. Autoimmune Addison disease: pathophysiology and genetic complexity. Nature Rev Endocrinol. 2012;8(5):306-16.
11. Husebye ES, Løvås K. Immunology of Addison's disease and premature ovarian failure. Endocrinol Metabol Clin N Am. 2009;38(2):389-405.
12. Burton C, Cottrell E, Edwards J. Addison's disease: identification and management in primary care. Brit J General Pract. 2015;65(638):488-90.
13. Bouachour G, Tirot P, Varache N, Gouello JP, Harry P, Alquier P. Hemodynamic changes in acute adrenal insufficiency. Intensive care medicine. 1994;20(2):138-41.
14. Ho W, Druce M. Quality of life in patients with adrenal disease: A systematic review. Clin Endocrinol. 2018;89(2):119-28.
15. Hirota Y, Matsushita T. Hyperpigmentation as a clue to Addison disease. Cleveland Clin J Med. 2022;89(9):498-9.
16. Thawabteh AM, Jibreen A, Karaman D, Thawabteh A, Karaman R. Skin Pigmentation Types, Causes and Treatment-A Review. Molecules (Basel, Switzerland). 2023;28(12):10.
17. Giannakopoulos A, Sertedaki A, Efthymiadou A, Chrysis D. Addison's disease without hyperpigmentation in pediatrics: pointing towards specific causes. Hormones (Athens, Greece). 2023;22(1):143-8.
18. Sadaf M, Bryan SQR, Muhammad W. Addison Disease. StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
19. Samuels MH. Effects of variations in physiological cortisol levels on thyrotropin secretion in subjects with adrenal insufficiency: a clinical research center study. J Clin Endocrinol Metabol. 2000;85(4):1388-93.
20. Herndon J, Nadeau AM, Davidge-Pitts CJ, Young WF, Bancos I. Primary adrenal insufficiency due to bilateral infiltrative disease. Endocrine. 2018;62(3):721-8.

21. Takahashi K, Kagami S, Kawashima H, Kashiwakuma D, Suzuki Y, Iwamoto I. Sarcoidosis Presenting Addison's Disease. Internal Med (Tokyo, Japan). 2016;55(9):1223-8.
22. Hahner S, Ross RJ, Arlt W, Irina B, Stephanie BS, David JT, et al. Adrenal insufficiency. Nature Rev Dis Primers. 2021;7(1):19.
23. Saverino S, Falorni A. Autoimmune Addison's disease. Best Pract Res Clin Endocrinol Metabol. 2020;34(1):101379.
24. Worth C, Vyas A, Banerjee I, Wei L, Julie J, Helen S, et al. Acute Illness and Death in Children With Adrenal Insufficiency. Fronti Endocrinoly. 2021;12:757566.
25. Kienitz T, Bechmann N, Deutschbein T, Stefanie H, Jürgen H, Matthias K, et al. Adrenal crisis–definition, prevention and treatment: results from a Delphi survey. Hormone Metabol Res. 2024;56(01):10-5.
26. Autoimmune Polyendocrine Syndromes. N Eng J Med. 2018;378(26):2542-4.
27. Paparella R, Menghi M, Micangeli G, Lucia L, Giovanni P, Francesca T, et al. Autoimmune Polyendocrine Syndromes in the Pediatric Age. Children. 2023;10(3):588.
28. Johannsson G, Nilsson A, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, 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. J Clin Endocrinol Metabol. 2012;97(2):473-81.
29. Nilsson AG, Bergthorsdottir R, Burman P, Per D, Bertil E, Britt EE, et al. Long-term safety of once-daily, dual-release hydrocortisone in patients with adrenal insufficiency: a phase 3b, open-label, extension study. Eur J Endocrinol. 2017;176(6):715-25.
30. Mallappa A, Sinaii N, Kumar P, Martin JW, Lori-Ann D, Dena D, et al. A phase 2 study of Chronocort, a modified-release formulation of hydrocortisone, in the treatment of adults with classic congenital adrenal hyperplasia. J Clin Endocrinol Metabol. 2015;100(3):1137-45.
31. Whitaker MJ, Spielmann S, Digweed D, Hiep H, David E, Trevor NJ, et al. Development and testing in healthy adults of oral hydrocortisone granules with taste masking for the treatment of neonates and infants with adrenal insufficiency. J Clin Endocrinol Metabol. 2015;100(4):1681-8.
32. Gagliardi L, Nenke MA, Thynne TR, Jenny B, Wayne AR, David EH, et al. Continuous subcutaneous hydrocortisone infusion therapy in Addison's disease: a randomized, placebo-controlled clinical trial. J Clin Endocrinol Metabol. 2014;99(11):4149-57.
33. Øksnes M, Björnsdottir S, Isaksson M, Paal M, Siri C, Roy MN, et al. Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of addison's disease: a randomized clinical trial. J Clin Endocrinol Metabol. 2014;99(5):1665-74.
34. Russell GM, Durant C, Ataya A, Ragini B, Wolfram W, Stafford L, et al. Subcutaneous pulsatile glucocorticoid replacement therapy. Clin Endocrinol. 2014;81(2):289-93.

Cite this article as: Alharbi SA, Fardan RH, Almahasnah MS, Alsaeed NA, Kashif HH, AlGhamdi NA, et al. Recent developments in the diagnosis and treatment of Addison's disease. Int J Community Med Public Health 2024;11:4990-5.