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Review

Management of Patients with Addison's Disease in Dentistry: An Overview

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Abstract: Adrenal crisis (AC) is an unexpected and possibly lethal situation of stressful interventions in patients with Addison's disease (AD). Despite being rare in dentistry, it is to be noted that evidence indicates that 5-8% of patients with AD necessitate emergency glucocorticoid administration to treat AC annually. For that, dentists must be aware of this condition and be prepared when the clinical signs and symptoms occur.

Keywords: Addison's disease; adrenal crisis; adrenal gland; corticosteroid; primary adrenal insufficiency.

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1. Introduction

The adrenal glands (AGs), part of the body's endocrine system, are two small organs located on top of the kidney. They are directly in relation with the central nervous system. The latter controls functions of the AGs via the hypothalamus and the pituitary gland [1].

The AGs produce many hormones involved in metabolism regulation, function of the immune system, as well as salt-water balance in blood; they function as well in body's response to stress. During embryonic maturity, the AGs differentiate into two structures anatomically, physiologically, histologically and functionally distinct: a) the adrenal cortex (peripheral) representing 80-90% of the gland and b) the adrenal medulla (central). A connective tissue capsule covers the gland [1, 2].

The adrenal cortex produces the majority of functional secretions of the AGs, including:

a) Mineralocorticoids, the major one being aldosterone whose role is to regulate homeostasis of sodium (Na+) and potassium (K+), and to help adjust blood pressure and volume. Aldosterone also affects the excretion of hydrogen ions (H+) in the urine; consequently, it plays a powerful role in acid-base balance, mainly regulation of acidosis [1-3].

b) Glucocorticoids, including predominantly cortisol (hydrocortisone), corticosterone, and cortisone. They increase blood sugar levels via gluconeogenesis, thus regulating glucose metabolism. Moreover, they help the body manage stress and they are part of the feedback mechanism in the immune system which reduces certain aspects of immune function, such as reduction of inflammation. Cortisol is secreted at a basal level and as a response to the release of adrenocorticotropic hormone (ACTH) from the pituitary gland.

Glucocorticoids help also in protein breakdown and lipolysis [3, 4].

c) Sex hormones such as androgen, a steroid hormone that have masculinizing effects. The main androgen is dehydroepiandrosterone (DHEA); it supplies the production of estrogen, progesterone, testosterone, and cortisol by the AGs [3, 5].

Aldosterone, androgen and glucocorticoids are essential for life. Unless hormone replacement therapy begins on time, total loss of such hormones is fatal, in a short time, due to dehydration and electrolyte inequality [3, 6].

The adrenal medulla produces catecholamines, mainly, epinephrine and norepinephrine that enhance the fight-or- flight response by increasing blood pressure, heart rate and modifying

other sympathetic responses. Consequently, they increase blood flow in major organs (liver, heart, adipose tissue and muscles), lead to airway dilation, and elevate glycemia and fatty acids in blood [3, 7]. Hormones of the adrenal medulla, unlike the adrenal cortex, do not present an indispensable element for life due to their limited role to increasing sympathetic response in the less-critical body parts [7].

The hypthalamo-pituitary-adrenal (HPA) axis directly regulates glucocorticoid secretions. Such process includes a set of complicated interactions and feedback systems between the AGs, pituitary gland, and hypothalamus. These organs' interactions present the main neuroendocrine control of stress, as well as other processes, such as immune system, digestion, emotions, sexuality, mood, energy and others [3, 8, 9].

In fact, considering HPA axis control of stress situations, the hypothalamus first secretes CRH – corticotropin-releasing hormone, acting upon the pituitary gland. The pituitary gland, in turn, produces ACTH into blood circulation which stimulates the AGs to produce cortisol. Cortisol, in addition to other less potent hormones, mobilizes body's energy stores through stimulating the release of stored glucose into blood, hence anticipating energy for the "fight-or-flight" reaction. Additionally, the AGs directly secrete epinephrine, ultimately increasing systolic blood pressure and heart rate and decreasing diastolic blood pressure [3, 6, 8, 9].

These interactions continue until the hormones reach the levels that the body needs, and then a series of chemical reactions begins to switch them off. This is just one of the automatic switches called negative feedback loops, and these loops make from the HPA axis a very complicated process [3, 6, 8, 9].

As for mineralocorticoids regulation, it is under the effect of renin–angiotensin–system (RAS) – also known as renin-angiotensin-aldosterone system and the potassium concentration. Renal juxtaglomerular cells contain blood pressure sensors releasing renin enzyme into blood; such enzyme causes a series of reactions ultimately producing angiotensin II. In the AGs, angiotensin receptors detect angiotensin II eventually leading to the secretion of aldosterone [10].

The overproduction of the AGs can concern one or all their secretions. However the most common is the cortisol manifested by the Cushing's syndrome [9].

As for the overproductions of aldosterone, catecholamines and androgens, they induce respectively the hyperaldosteronism (primary aldosteronism, Conn's syndrome), Pheochromocytome and virilization.

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Underproduction of the AGs (AGs insufficiency) is characterized by low production of mineralocorticoids, glucocorticoids, or both, in addition to androgens produces by the AGs.

AGs insufficiency is an uncommon but life-threatening condition. Because its clinical manifestations are non-specific, diagnosis can be mistakenly delayed until advanced adrenal failure represented by an acute crisis-adrenal crisis (AC). AGs insufficiency can be primary known as Addison's disease (AD), or secondary, resulting from long-term glucocorticoids treatments or more infrequently from pituitary disorders [11]. AC is common mainly in the primary type of the disease.

Adrenal insufficiency, leading to adrenal failure and crisis, has always been fatal before the introduction of replacement therapy; supplementing with synthetic glucocorticoids presents the mainstay of managing adrenal failure.

The main objective of this article was to review the AD and its repercussion on dental treatments.

2. Addison's disease

AD affects more often women mostly between 30 and 50 years. The presently estimated frequency of AD ranges between 4 and 11 per 100,000 of the population [12].

The most frequent etiology of AD is the autoimmune destruction of the AGs [12]. Other causes can be involved in primary adrenal insufficiency such as infections (sepsis, tuberculosis, etc.), adrenal hemorrhage, sarcoidosis, lymphoma etc. [12-14].

The diagnosis of AD is based on: a) a low cortisol level, b) a low aldosterone level, c) a high renin level, and d) a direct cortisol response with ACTH stimulation [12].

Clinically, AD manifests in a variable intensity depending on the degree of adrenal failure and the affection of mineralocorticoid production [12, 15]. Adrenal insufficiency may remain unnoticed due to the gradual nature of the onset, until an AC is induced in response to systemic dysregulation as in diseases or in acute stress [15].

Signs and symptoms of AD vary considerably, from generalized weakness and malaise to weight loss with/without anorexia, nausea and vomiting, diarrhea or constipation, abdominal pain, hypotension, electrolyte imbalance (from metabolic acidosis to hyponatremia and hyperkalemia), vitiligo and other autoimmune lesions, reduced pubic and/or axillary hair,

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decreased sexual drive, amenorrhea, and hyperpigmentation (including oral mucosa, palms, elbows…) [16-19].

Treatment of AD includes lifetime glucocorticoid (hydrocortisone) and mineralocorticoid (fludrocortisone) taken orally and adjusted by the physician because a surplus of exogenous steroids may lead to adrenal atrophy [20].

AC constitutes a medical emergency due to cortisol deficiency and is often fatal if immediate attention is not provided [21]. It has an estimated prevalence of 5-6% in primary adrenal insufficiency patients [22-24], and is characterized by a quick progression from the symptoms encountered in AD to metabolic encephalopathy (seizures, consciousness, etc.), hypovolemic shock, and coma and death [18, 22].

3. Management of patients with AD in dental clinic

AC is an unpredictable and probably lethal result of stressful situations in patients with AD. To date, a small number of cases have been reported, in the scientific literature, of AC occurring during dental treatments [25].

In a systematic review analyzing papers published over a period of sixty-six years (before 2013) on the risk of the AC related to dental treatments, Khalaf et al. found only 6 reports, thus confirming the uncommonness of this condition [25]. Nevertheless, to be noted that although AC is exceptional in dentistry, evidence indicates that 5-8 % of patients with AD require urgent administration of glucocorticoid for treating AC annually [21-23]. For Miller et al., general anesthesia, infections, stress, and pain augment the risk of AC in predisposed patients [26]. Therefore, dentists must remain alert for signs and symptoms of this condition.

There is no obvious indication for antibiotic prophylaxis before dental treatment for patients with AD. Nonetheless, being under systemic corticosteroids, patients may be subject to septicemia following localized oral infections; in such cases, prophylactic antibiotic may be needed.

According to Radfar and Somerman, no antibiotic prophylaxis is necessary if the daily dosage of steroid is inferior to 10 mg (prednisone) [27].

As for the patients' ability to tolerate dental care, dentists are required to apply a stress-free protocol in pre-, per- and post treatment and to make sure of long-acting anesthesia and postoperative pain control.

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Additionally, because patients on long-term daily corticosteroid treatment of ≥ 10 mg of prednisone are considered having sufficient level of corticosteroid, they do not necessitate supplementary steroid to overcome any possible stress during routine dental treatments, including minor surgical procedures. While in the case of patients who lately tapered off the exogenous steroid, a supplementary dose before a stressful treatment might be necessary; the same is applicable during and after dentistry performed under general anesthesia [26, 28].

In a classification adopted by the American Dental Association (Patton and Glick, 2016), Miller et al. classified the risk, from dental procedures, for patients with adrenal insufficiency into 3 categories, negligible, mild, and moderate/major risks [26, 29].

The risk's classification proposed by Miller et al. is summarized in Table 1.

Risk	Procedures	Supplementation
Negligible	Non surgical	Nothing required
Mild	Minor oral surgical procedures (few extractions, biopsy, minor periodontal treatment, etc.)	The glucocorticoid must be around 25 mg of hydrocortisone (5 mg of prednisone) the day of the intervention
Moderate /major	Major oral surgery (multiple extractions or impacted teeth, advanced periodontal surgery, bone surgery, cancer surgery, surgery under general anesthesia, interventions lasting more than one hour and/or associated with significant blood loss	The glucocorticoid must be around 50-100 mg per day of hydrocortisone the day of the intervention and at least one day after

Table 1: Guidelines of corticosteroids supplementation for dental interventions in patients with adrenal insufficiency as proposed by Miller et al. [26]

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4. Conclusion

The AC is indeed rare in dental settings; however, certain factors can raise its risk in patients with AD. In the scientific literature, perioperative glucocorticoid supplementation is controversial despite it being beneficial in avoiding the stress-induced crisis.

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