Journal of Mind and Medical Sciences

Volume 7 | Issue 2 Article 3

2020

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Journal of Mind and Medical Sciences

https://scholar.valpo.edu/jmms/
https://proscholar.org/jmms/

ISSN: 2392-7674

Oral pathology induced by excess or deficiency of glucocorticoids in adults

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ABSTRACT

Oral manifestations are present both in Cushing's syndrome and in adrenal insufficiency. Possible oro-dental pathology in patients with Cushing's syndrome include jawbone loss, tooth loss, and periodontal diseases. Professional societies did not include Cushing's syndrome as being part of systemic diseases associated with loss of periodontal supporting tissues. The comorbidities of Cushing's syndrome such as obesity, osteoporosis, and diabetes are conditions that influence periodontal attachment apparatus. In patients with adrenal primary insufficiency, the most specific sign is the melanic pigmentation of the skin and mucosal surfaces due to increments of corticotropin and pro-opiomelanocortin peptide levels that occur as a result of decreased cortisol feedback. The oral mucosa develops black plaques that can also be present on the gums, palate, tongue, and lips. The pallor may occur in patients with adrenocortical insufficiency secondary to corticotropin deficiency. Patients with primary adrenal insufficiency need to increase their glucocorticoid doses during physical activity, intercurrent illnesses, surgery, and medical procedures. Current evidence indicates that routine, nonsurgical, or minor surgical procedures do not need supplemental glucocorticoids in diagnosed patients who are in a stable condition. However, for major oral surgery, glucocorticoid supplementation is necessary for the surgery day and for at least one postoperative day.

Category: Review

Received: April 05, 2020
Accepted: July 02, 2020

Keywords:

Cushing's syndrome, adrenal insufficiency, oral pathology

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Introduction

Periodontal diseases, also known as gum diseases, are being detected more frequently in patients undergoing routine dental control. This type of pathology is linked to several metabolic imbalances but can also originate from hormone level fluctuations. Understanding the connection between glucocorticoid levels and several characteristic manifestations of oro-dental pathologies can help dentists develop better therapeutic protocols. The endocrinologist and the dentist need to be familiar with the oral manifestations of endocrine conditions and must have good communication to maintain patient oral health in Cushing's syndrome and to prevent a possible adrenal crisis in the case of major oral surgery in patients with adrenal insufficiency.

Discussions

Cushing's syndrome

Cushing's syndrome is a disorder characterized by chronic exposure to glucocorticoid excess. The etiology of this syndrome includes exogenous or endogenous hypercortisolism [1]. The exogenous (or iatrogenic) Cushing's syndrome is the most common cause of hypercortisolism and is generated by administration of supraphysiologic doses of steroid therapy for inflammatory, autoimmune, or neoplastic disorders [2]. The endogenous Cushing's syndrome includes adrenocorticotropic hormone (ACTH) dependent or ACTH independent forms. ACTH dependent Cushing's syndrome is generated by ACTH production by a pituitary adenoma or nonpituitary tumors and excess of corticotropin-releasing hormone producing tumors [3]. Ectopic ACTH

To cite this article: Rucsandra Elena Dănciulescu Miulescu, Loreta Guja, Bogdan Socea, Anca Dumitriu, Stana Paunica, Emil Ștefănescu. Oral pathology induced by excess or deficiency of glucocorticoids in adults. *J Mind Med Sci*. 2020; 7(2): 141-147. DOI: 10.22543/7674.72.P141147

production derives from pulmonary carcinoid tumor, pancreatic or thymic neuroendocrine tumors, medullar thyroid cancer, pheochromocytoma etc. [4]. Păun et al. described ectopic ACTH-dependent Cushing's syndrome arising from a Meckel diverticulum [5]. ACTH-dependent Cushing's syndrome accounts for 80 % of cases [1]. With a much lower frequency (15-20%), ACTH-independent Cushing's syndrome can by generated by adrenal unilateral tumors, macronodular adrenal hyperplasia, or primary pigmented nodular adrenal disease [1].

The most common signs of disease are represented by progressive weight gain, moon face, supraclavicular and dorsocervical fat pads, hirsutism or alopecia, facial plethora, violaceous striae, acne, depression, and mania. The clinical presentation is influenced by age, sex, and the severity and duration of hypercortisolism [1,6,7]. However, it should be mentioned that no signs or symptoms are pathognomonic. The chronic glucocorticoid exposure is associated with comorbidities such as obesity, cardiovascular diseases, hypercoagulability, impaired glucose tolerance or diabetes mellitus, dyslipidemia, osteoporosis, and increased susceptibility to infection with common or unusual agents [8].

Possible ***oro-dental pathology in patients with Cushing's syndrome*** can include jawbone loss, tooth loss, and periodontal diseases. The jawbone supports the teeth; when bone becomes less dense the tooth mobility is increased [9]. Periodontal disease is a set of inflammatory conditions affecting the tissues surrounding the teeth. In 2017, the "*American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP)*" recommended a classification for periodontal and peri-implant disease and conditions. Periodontal disease and conditions comprise three major categories [10]:

"*1. Periodontal health and gingival diseases: periodontal and gingival health, gingivitis caused by biofilm, gingivitis not caused by biofilm.*

2. Periodontitis: necrotizing diseases, periodontitis, periodontitis as a manifestation of systemic disease.

3. Other conditions affecting the periodontium: systemic diseases affecting the periodontal supporting tissues, periodontal abscess, or periodontal and endodontic lesions, mucogingival deformities and conditions, traumatic occlusal forces, tooth, and prosthesis related factor."

The peri-implant disease and conditions include peri-implant health, peri-implant mucositis, peri-implantitis and peri-implant soft- and hard-tissue deficiencies [10].

The proceedings of the workshop conducted by AAP and EFP did not include Cushing's syndrome among the systemic diseases associated with loss of periodontal supporting tissues. Comorbidities of Cushing's syndrome such as obesity, osteoporosis, and diabetes are mentioned among the conditions that affect periodontal attachment apparatus [11]. In Cushing's syndrome, the prevalence of obesity varies between 70% and 95%, that of osteoporosis between 50%-80%, and that of diabetes mellitus between 20%-50% [1,12]. The possible mechanisms by which obesity increases periodontitis, periodontal disease progression, and loss of periodontal attachment risk include immune response and increased production of proinflammatory cytokines. A systematic review regarding the association between obesity and periodontitis was published in 2010 in the *Journal of Periodontology* by Chaffee and Weston. After systematic analysis of databases, the authors conclude that obesity increases susceptibility to infection and *"obesity is a risk factor for periodontal disease or that periodontitis might increase the risk of weight gain"* [13]. The likelihood of periodontitis in obese patients varies between 50% to 80% compared with normal-weight subjects, and the risk is higher among obese women compared with obese men [13,14]. The response to periodontal treatment does not differ for obese patients versus normal-weight subjects [15].

Osteoporosis is associated with a higher prevalence of alveolar bone loss but the association with periodontitis is not clear [11]. Beetaka and coworkers published in 2013 in *Dental Research Journal* a study about the oral health of patients under long-term corticosteroid therapy. 100 patients who received corticosteroid therapy for a minimum of 3-months duration and 100 healthy subjects were included in the study. The results showed that *"Patients on steroids exhibited significantly higher levels of candidiasis and clinical attachment loss of the periodontal ligament, probing pocket depth. Bone density was significantly lower in the study group than that in the control group. Random blood glucose was significantly higher and significant lower levels of calcium were observed in patients on steroids"* [16].

Oral health in patients on inhaled corticoid therapy was investigated in 30 patients with chronic obstructive pulmonary disease by Komerik *et al.* Results were compared with those of 30 healthy subjects. The study revealed that in patients on steroid treatment, bone density of the mandible was lower than in the control group, and the patients had more missing teeth [17]. Bisphosphonates are the first line options for treatment of osteoporosis but do not directly address the decreased bone characteristic of the glucocorticoid-induced bone disease [18]. Treatment with bisphosphonates can generate osteonecrosis of the jaw, typically diagnosed after an invasive procedure, and associated with poor dental hygiene and infection. Other risk factors for bisphosphonates-associated osteonecrosis of the jaw are cancer and anti-cancer therapy, duration of exposure to therapy, glucocorticoids, pre-existing dental or periodontal disease, tobacco and alcohol abuse, etc. [18,19]. Before prescribing bisphosphonates, the "*American Society for Bone and Mineral Research"*

recommends communication between physicians and dentists, informing patients about the benefits and risks of bisphosphonates, including the risk for developing jaw osteonecrosis and the signs and symptoms of jaw osteonecrosis (pain, swelling, suppuration, soft tissue ulceration, intra-or extraoral sinus tracks, loosening of teeth). Patients in treatment with bisphosphonates should be encouraged to maintain good oral hygiene and to have regular dental visits and to report any oral problems [19].

There is information on potential pathways which support the association between diabetes mellitus and periodontitis. The presence of hyperglycemia in gingival crevicular fluid can generate the growth of certain bacterial species in the subgingival environment which may increase susceptibility to periodontitis. The hyperinflammatory response to bacterial challenge can generate hyperinflammatory response of monocytes, increased release of proinflammatory cytokines, and oxidative stress reactions [11,20]. In patients with type 1 diabetes mellitus there is evidence that monocytes have a hyperinflammatory phenotype and cells are responding to periodontal bacteria, producing higher levels of interleukin 1β, prostaglandin E2, and tumor necrosis factor alpha, suggesting that this phenomenon may be involved in the pathogenesis of periodontitis in diabetes [21,22]. Increasing nonenzymatic protein glycation characteristic of diabetes mellitus can generate the advanced glycation end products (AGEs). Several studies have shown that AGEs contribute to the diabetic complications and, regarding the periodontal tissue, AGEs contribute to increase of alveolar loss in diabetic mice [23]. Diabetes is a redox imbalance disease [24-26]. The oxidative stress is involved in the pathogenesis of diabetes complications and there is evidence showing increased local and systemic alterations in the redox balance of periodontitis [27].

Diagnostic of Cushing's syndrome. In 2008, the Endocrine Society Guidelines recommended exclusion of exogenous doses of glucocorticoid therapy before conducting biochemical testing. Testing for Cushing's syndrome is recommended in the following situations: patients with unusual features for age, with multiple and progressive features predictive of the syndrome, adrenal incidentaloma, or children with decreased height and increased weight. For the initial testing, the Endocrine Society guidelines recommend urine free cortisol, late–night salivary cortisol, 1-mg overnight dexamethasone suppression test, and long low dose dexamethasone suppression test (2 mg). In individuals with abnormal test results, the following investigations are recommended: random serum cortisol or ACTH levels, urinary 17-ketosteroids, pituitary and adrenal imaging, and 8 mg dexamethasone suppression test [28].

Management of Cushing's syndrome. The Clinical Practice Guidelines of the Endocrine Society published in 2015 in "*The Journal of Clinical Endocrinology & Metabolism"*, recommend that effective treatment should include normalization of cortisol levels or action. *"Surgical resection of the causal lesion(s) is generally the first-line approach. The choice of second-line treatments, including medication, bilateral adrenalectomy, and radiation therapy (for corticotrope hormone), must be individualized to each patient"* [29]. Treatment of comorbidities is important to reduce mortality. Management of exogenous Cushing's syndrome involves: dose and duration of glucocorticoid therapy should be kept as low as possible, pulse glucocorticoid therapy should be used only when absolutely indicated, use of highly potent and long-acting glucocorticoid should be restricted to acute setting only, and short-acting glucocorticoid is preferred for long-term treatment [30].

Adrenocortical insufficiency

Adrenal insufficiency can be generated by destruction of adrenal cortex (primary adrenocortical insufficiency) or can be secondary to pituitary or hypothalamic diseases. The condition can manifest as a chronic or acute form [31,32]. Primary adrenal insufficiency is a relatively rare disease. Its etiology includes autoimmune adrenalitis, infectious diseases (tuberculosis, fungal, viral), neoplastic diseases, adrenal hemorrhage or thrombosis, drug, infiltration, and neonatal or genetic conditions. Secondary adrenocortical insufficiency can be generated by pituitary or metastatic tumors, craniopharyngioma, pituitary surgery or irradiation, infiltration, empty sella syndrome, Sheehan syndrome, lesions of the pituitary stalk, hypothalamic tumors, and exogenous corticosteroids [33]. In primary adrenal insufficiency there is a deficiency of the glucocorticoid and mineralocorticoid hormones. Cortisol deficiency manifests as fatigue, anorexia, nausea, weight loss, diminished resistance to infection, and hyperpigmentation as a consequence of cessation of inhibition at pituitary level with increments of ACTH and melanocyte stimulating hormone. Aldosterone deficiency generates sodium and liquid depletion, increased diuresis, and secondary hypotension and dehydration. In secondary adrenocortical insufficiency, the mineralocorticoid function is preserved [34].

Oro-dental pathology in patients with adrenal insufficiency. The most specific sign of primary adrenal insufficiency is the melanic pigmentation of the skin and mucosal surfaces as a consequence of increments of corticotropin and pro-opiomelanocortin peptide levels that result from decreased cortisol feedback. The oral mucosa develops black plaques that can be also present on the gums, palate, tongue and lips. Pallor may occur in patients with secondary adrenocortical insufficiency secondary to corticotropin deficiency [35,36].

Diagnostic of adrenal insufficiency. Serum ***cortisol*** is a test used in the screening and diagnosis of adrenal

insufficiency and can be measured in early morning between 08.00 and 09.00 h. Betterle C*et al.* mention that *"Hormonal pattern of morning plasma cortisol concentrations of less than 3 μg/dl (83 nmol/liter) are indicative of clinical adrenal insufficiency whereas concentrations of more than 19 μg/dl (525 nmol/liter) rule out the disorder"* [33]. Measurement of serum cortisol may represent the first laboratory test in patients evaluated for hypothalamic, pituitary, and adrenal insufficiency [37]. Determining values of plasma ACTH is used to differentiate between primary and secondary adrenal insufficiency. The Clinical Guidelines Subcommittee of the Endocrine Society recommends confirmatory testing with corticotropin for diagnosis of primary adrenal insufficiency. The guidelines suggest the standard dose of 250 ug for adults, 15 μg/kg for infants and 125 μg for children under 2 years of age, in intravenous administration. The low dose (1μg) corticotropin test is recommended when the substance itself is in short supply. To assess the presence of mineralocorticoid deficiency, the simultaneous measurement of plasma renin and aldosterone is recommended. After an endocrinological diagnosis has been established by hormonal testing, the etiology of the disease should be determined [38].

Management of adrenal insufficiency. The Clinical Guidelines of the Endocrine Society published in 2016 recommend glucocorticoid and mineralocorticoid replacement in all patients with confirmed adrenal insufficiency. In adults, glucocorticoid replacement can be achieved by administering hydrocortisone 15-25 mg/day or cortisone acetate 20-35 mg/day in two or three divided doses administered via oral route; the highest dose should be given in the morning. In patients with reduced compliance an alternative is prednisolone 3-5 mg once or twice per day administrated orally. In children, glucocorticoid replacement can be achieved by oral intake of hydrocortisone in three or four doses, with total starting dose of 8 mg/m^2 body surface area. It is recommended to monitor glucocorticoid therapy by clinical assessment. Patients with primary adrenal insufficiency need to increase glucocorticoid doses during physical activity, intercurrent illnesses, surgery, and medical procedures. In adults, mineralocorticoid replacement can be achieved by administering fludrocortisones with a starting dose of 50-100 μg/day without restricted salt intake. In children, the starting dose is of 100 μg/day with supplements of sodium chloride in the newborn up to the age of 12 months. Dehydroepiandrosterone replacement may be recommended in women with low libido, depressive symptoms, and asthenia which has not been optimized by glucocorticoid and mineralocorticoid treatment. In the absence of a beneficial effect of therapy after 6 months, the dehydroepiandrosterone should be discontinued [38,39].

The management of adrenal insufficiency secondary to hypothalamic-pituitary failure conventionally is based on the long-term replacement of hydrocortisone (20 mg in the morning and 10 mg in the evening); the mineralocorticoid replacement is not required in patients with secondary adrenal insufficiency [40]. Education of the patient is essential for the management of this condition. Patients should be instructed to increase the dosage of glucocorticoids during intercurrent illness, fever, and stress, and promptly identify suggestive signs and symptoms of acute adrenal crisis is especially important.

The acute adrenal crisis is an emergency that requires prompt recognition and therapy. Symptoms of an acute adrenal crisis are major impairment of general health, hypotension, nausea, vomiting, abdominal pain, and impaired cognitive function. Treatment of patients with possible acute adrenal crisis must be initiated immediately and should not be delayed by diagnostic investigations. Important is intravenous administration of 100 mg hydrocortisone followed by 100-300 mg/day as continuous infusion or frequent intravenous or intramuscular boluses every 6 hours, isotonic saline infusion, and treatment of the precipitating condition [38, 39].

Dental management of the patients with adrenal insufficiency. In dental practice, patients experience pain or stress generated by procedures, and anxiety control is important for the dental management of these patients [39]. Current evidence indicates that the routine, nonsurgical, or minor surgical procedures do not need supplemental glucocorticoids in diagnosed patients in a stable condition [38]. Invasive procedures increase the plasma cortisol levels during and after a surgery. In a review published in 2001 in the "*Journal of the American Dental Association*", Miller and coworkers mention that *"For major oral surgical stress (for example, multiple extractions, quadrant periodontal surgery, extraction of bony impactions, osseous surgery, osteotomy, bone resections, oral cancer surgery), surgical procedures involving the use of general anesthetic, procedures lasting more than one hour, or procedures associated with significant blood loss, the glucocorticoid target is about 50 to 100 mg per day of hydrocortisone equivalent for the day of surgery and for at least one postoperative day"* [34]. The adrenal crisis related to dental treatment is rarely mentioned in the literature. Miller *et al* searched the literature from 1966 to 2000 for information that addressed adrenal insufficiency and adrenal crisis in dentistry; 4 reports were identified over 35 years [34, 41-44]. Features in 3 reports included patients who had multiple extractions performed with administration of general anesthetic or oral infection [30]. The authors identified four risk factors that contribute to the risk of adrenal crisis during the perioperative period of oral surgery: magnitude of surgery, general anesthetic, health of the patient, and the degree of anxiety control; they

concluded that perioperative glucocorticoid supplementation *"can be prescribed in a more rationale manner than is currently the case"* [34, 45].

Highlights

- ✓ Oro-dental pathology is linked to both glucocorticoid excess and deficit.
- ✓ Identifying the specific periodontal symptoms associated with either Cushing's syndrome or adrenocortical insufficiency is essential for good dental management in these particular patients.

Conclusions

Oral manifestations are present in the case of glucocorticoid excess but also in the case of glucocorticoid deficiency. The endocrinologist and the dentist need to be familiar with the oral manifestations of these conditions and must ensure good communication to maintain patient oral health in Cushing's syndrome and prevent a possible adrenal crisis in the case of major oral surgery in patients with adrenal insufficiency.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Acknowledgments

All authors contributed equally to this manuscript.

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