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THE IMPACT OF CORTISOL HORMONE ON HYPOTHYROID PATIENTS WITH AND WITHOUT PERIODONTITIS

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ABSTRACT
Cortisol is a glucocorticoid hormone, known as a stress hormone. It is identified potent inhibitors of thyroid function at several points within the HPT axis. Abnormal increase of cortisol inhibits inflammation and impairs the immune system and host defense. This study aims to determine and compare serum and salivary levels of cortisol hormone in hypothyroidism patients (with and without periodontitis) and healthy control; as well as to estimate and study the effect of thyroid hormones on periodontitis. Serum and saliva samples were collected from 60 hypothyroid patients with age ranged between (20-64) years, 30 of patients were with periodontitis and 30 without periodontitis; compare with 30 subjects as control with age between (20-53) years. Detection of cortisol in serum and saliva, were done by using human cortisol enzyme-linked immunosorbent assay (ELISA). The results showed elevated serum and salivary cortisol levels significantly ($P<0.001$) in patients groups of hypothyroidism (with and without periodontitis) as compared to control. However, levels in serum and salivary hormone of patients group with periodontitis are increased significantly ($P<0.001$) than the levels in the group without periodontitis. The present findings suggested that cortisol may contribute to the pathogenesis of hypothyroidism and periodontal disease. Moreover, hypothyroidism may affect periodontal health indirectly through the effect of this hormone. Also, the salivary concentration of this hormone may usefully reflect the concentration of free cortisol in serum.

KEYWORDS: *cortisol, hypothyroidism, periodontitis, saliva.*

INTRODUCTION

Cortisol is a glucocorticoid hormone, a biomarker for numerous diseases in the body, secreted by the outer cortex of the adrenal gland. It is an end-product of the HPA axis (Levine *et al*., 2007; Gatti *et al.,* 2009). This steroid plays a principle role in the regulation of most vital physiological processes in the body (Gatti *et al.,* 2009). Cortisol, known as a stress hormone, has been used as an indicator in stress evaluation studies (Koray *et al*., 2003). Thyroid dysfunction is the second most common glandular disorder of the endocrine system which may rear its head in any system in the body including the mouth. The oral cavity is adversely affected by either an excess or deficiency of thyroid hormones (Chandna and Bathla, 2011; Babu and Patel, 2016). Hypothyroidism is the decrease in thyroid hormones production and thyroid gland function (Pinto and Glick, 2002). It most frequently reflects a disease of the gland itself as primary hypothyroidism, and it affects hundreds of millions around the world (Jonklaas *et al.,* 2014; Rowe *et al*., 2016).

Periodontitis is considered as one of the most common and severe types of oral infections. It is an inflammatory disease of the supporting structures of the teeth caused by specific microorganisms resulting in progressive destruction of periodontal ligaments and alveolar bone with pocket formation, recession or both. Periodontitis comprises a number of inflammatory and infectious conditions caused by the inflammatory host response to bacteria in the supragingival and subgingival biofilm (Pushparani, 2015; Gomes *et al.,* 2016). Cortisol, are known potent inhibitors of thyroid function at several points within the HPT axis (Cuerda *et al.,* 1991). The positive relationship between serum TSH and cortisol levels in a healthy population is a compelling new finding that is consistent with and extends the observation that frankly hypothyroid patients have frankly elevated cortisol levels (Iranmanesh *et al.,* 1990). However, Kelly (2000) suggested that high levels of cortisol might be responsible for altered T_4 peripheral metabolism to T_3 and rT_3 in those patients through decrease monodeiodination T_4 to T_3 and increase conversion T_4 to rT_3. Salivary cortisol is strongly correlated with plasma free cortisol, the biologically active form of circulating cortisol and the responsible for all cortisol-related activities in the body (Yaneva *et al*., 2009). The release of cortisol hormone impairs host defense which helps in the growth of opportunistic organisms in the gingival sulcus (Miller and O'Callaghan, 2002). This study was carried out to determine and compare serum and salivary levels of cortisol hormone in hypothyroidism patients (with and without periodontitis) and healthy control; as well as to estimate and study the effect of thyroid hormones on periodontitis.

MATERIALS & METHODS

This study was carried out on 60 (4 males and 56 females) Iraqi hypothyroid patients their age ranged (20- 64) years, were rounded up from Nuclear Medicine and Radiation Therapy Department, Educational Oncology Hospital.

Total patients divided into two groups; 30 patients without periodontitis and 30 patients were diagnosed with periodontitis [the diagnosis was made through specialized dentists in the department of periodontics, College of Dentistry, Baghdad University]. Besides 30 (3 males and 27 females) volunteers subjects who were considered as control, their ages and gender were matched with patients, their ages ranged between (20-55) years. Serum and saliva samples were collected from study groups. Approximately (4 ml) of human blood was collected intravenously from patient and control groups; also, unstimulated saliva (3 ml) was collected from studies groups. Both of them centrifuged at 3000 rpm for 10 minutes. Serum of blood was immediately separated, and the supernatant of saliva aspirated immediately, both divided into aliquots and kept at -20 °C until used. The diagnosis of hypothyroidism was based on the clinical features and biochemical tests that depended mainly on elevated serum levels of TSH, low T_4 level, and low or normal T_3. All patients had no complained of other chronic or systemic diseases, and pregnant women were excluded from the study. Detection of Cortisol level in serum and saliva were determined by using commercially available ELISA kit (Demeditec, Germany). The Statistical Analysis System- SAS (2012) program was used to identify the effect of difference factors in study parameters. The outcome quantitative variables were normally distributed, and therefore conveniently described by mean, standard error (SE) and tested for statistical significance by t-test and ANOVA test with least significant difference (LSD).

RESULTS

The age of hypothyroidism patients ranged between (20-64) years with a mean age of (39.88 ± 1.423) years. However, the majority (43.33%) of patients are in the age group of (35-45) years. Furthermore, there is a significant female's predominance among patients group. Males/females ratio is (1:14), and no statistically significant differences ($p>0.05$) in age or gender existed between patients and controls groups. The results of this study revealed that serum TSH levels are increased significantly ($P<0.001$) in patients group (10.26 ±0.36 µIU/ml) as compared to control group (5.99 ± 0.2552 µIU/ml). On the other hand, serum levels in patients of tT_4, fT_4, tT_3 and fT_3 (3.54 ± 0.17, 0.891 ± 0.04, 0.572 ± 0.02, and 1.227 ± 0.06 pg/ml) are decreased significantly ($P<0.001$) as compared to control of tT_4, fT_4, tT_3 and fT_3 (6.12 ± 0.37, 1.489 ± 0.08, 0.813±0.04 and 2.206 ± 0.16 pg/ml) respectively, as demonstrated in table (1).These result confirmed the diagnosis of hypothyroidism which is characterized by elevated TSH and declined T_4 and T_3 hormone levels as compared with control.

TABLE 1: Serum thyroid hormones level in study groups

Hormones in serum (Mean ± SE)	TSH (µIU/ml)	tT4 (µg/dl)	fT4 (µg/dl)	tT3 (ng/ml)	fT3 (pg/ml)
Patients N= 60	10.26 ±0.36	3.54 ± 0.17	0.891 ± 0.04	0.572 ± 0.02	1.227 ± 0.06
Control N= 30	5.99 ± 0.25	6.12 ± 0.37	1.489 ± 0.08	0.813±0.04	2.206 ± 0.16
t-test *(P-value)*	P<0.001**	P<0.001**	P<0.001**	P<0.001**	P<0.001**

**: Highly significant; SE: Standard error

TABLE 2: Serum and salivary Cortisol level in study groups

Hormones (Mean ± SE)	Serum Cortisol (ng/ml)	Salivary Cortisol (ng/ml)
Hypothyroidism N=30	163.39 ± 15.30 B	8.38 ± 0.97 B
Hypo. with Periodontitis N=30	234.68 ± 16.92 A	12.57 ± 1.46 A
Control N=30	91.63 ± 7.70 C	5.83 ± 0.35 C
LSD	47.68	2.385
ANOVA *(P-value)*	P<0.001**	P<0.001**

A, B: Different letters in the same column represent significant differences

The results in table (2) showed that serum cortisol levels are increased significantly ($P<0.001$) in hypothyroid patient without and with periodontitis (163.39 ±15.30 and 234.68 ±26.92 ng/ml) respectively, as compared to control group (91.63 ± 7.70 ng/ml), whereas mean levels of patients with periodontitis (234.68 ±26.92) are increased significantly ($P<0.001$) as compared with the levels in patients without periodontitis (163.39 ±15.30). Concerning cortisol levels in saliva, this study found that salivary hormone levels of hypothyroid patients without and with periodontitis (8.38 ± 0.97, 12.57 ± 1.46 ng/ml) respectively, are increased significantly ($P<0.001$) as compared to control (5.834 ± 0.35 ng/ml); and the level in patients with periodontitis is increased significantly ($P<0.001$) as compared to patients without periodontitis (8.38 ± 0.97).

DISCUSSION

This finding is in accordance with previous Iraqi study done by, Sultan and Jumma (2015) revealed that cortisol levels increased significantly in the hypothyroid patients in comparison with control. As well, Tomlinson *et al.* (2004)

and Iranmanesh and assistants (1990) found that hypothyroidism cause increase in serum cortisol levels, hence cortisol level was significantly elevated in hypothyroid patients when compared to control group. Interestingly, in a study conducted by Saxena and colleagues (2000) on depressed patients with elevated stress hormone (cortisol), appeared that serum T_3 and T_4 levels decrease and TSH levels increase in those patients than normal. However, Ranabir and Reetu (2011) explained that thyroid function is usually down-regulated during stressful conditions; and T_3 and T_4 levels decrease with stress. Whereas, there is a disparity with Kageyama (2000) showed hypothyroidism cause decrease in cortisol level.

On the other hand, Gonen *et al.* and Hoshiro *et al.* that studied the relationship between cortisol and thyroid hormones in hyperthyroid and hypothyroid patients and found no significant differences among all cases. Gonen and colleagues (2012) revealed that cortisol levels in saliva and serum were similar in overt and subclinical hypothyroidism, and the levels were similar in both hypo- and hyperthyroid patients. While Hoshiro and coworkers (2006) reported that there are no differences in cortisol levels in all stages of thyroid dysfunction; as well hypothyroidism has no effect on cortisol levels. They demonstrated that serum cortisol levels might be remained normal, because both production and degradation of cortisol are increased and THs stimulate conversion of cortisol to cortisone; which may explain the similar levels of salivary cortisol, serum and plasma cortisol, both in hypothyroidism and thyrotoxicosis. However, Perogamvros *et al.* (2010) found that salivary cortisol appears matched serum samples, and salivary cortisol seems to be valuable and convenient alternative method for free serum cortisol determination.

There are contrary reports with respect to cortisol levels in hypothyroid patients. There is substantial evidence that hypothyroidism may alter cortisol levels due to an imbalance between cortisol synthesis and degradation (Tomlinson *et al*., 2004; Hoshiro *et al*., 2006; Lizcano and Rodríguez, 2011). On the other hand, in the hypothyroid state, cortisol degradation is decreased; thus, 24-hour mean serum cortisol levels are higher than in healthy controls (Iranmanesh and assistants, 1990). Furthermore, increased TSH level raised cortisol levels among hypothyroid patients induce a conversion of T_4 to rT_3 with increased endogenous secretion of cortisol altered thyroid hormone metabolism. These findings suggest that hypothyroidism causes elevated cortisol levels, presumably due to both decreased clearance and diminished negative feedback of cortisol on the HPA axis (Sultan and Jumma, 2015).

In this study, the significant elevation of cortisol level in serum and saliva among patients of hypothyroidism with periodontitis than that in hypothyroid patients without periodontitis may be attributed to the presence of periodontitis. Several studies confirm the elevation cortisol levels in periodontitis patients (Rohini *et al*., 2015; Katuri *et al*., 2016) and reported significant differences in serum cortisol levels between the periodontitis patients group and control group. Moreover, Agarwa and his colleagues (2014) pointed out to that patient with periodontitis showed a statistically significant increase in serum cortisol level and their level significantly correlated with disease severity.

On the other hand, Mudrika *et al.,* (2014) found that salivary cortisol increased in coincidence with disease severity; and these levels are valuable biomarkers for evaluating a part of the etiopathogenesis of periodontitis. Whereas the result of Refulio and his assistants (2013) suggested that subjects with high salivary cortisol may be at increased risk for periodontitis, and the level of hormone was related to the disease severity.

The release of stress hormones impairs host defense which helps in the growth of opportunistic organisms in the gingival sulcus and eventually leads to periodontitis. As well, increased cortisol production suppresses the immune response and increases the potential of periodontal tissue destruction (Miller and O'Callaghan, 2002; Agarwa *et al*., 2014). In general, several stress markers are found in blood and saliva of patients with periodontitis and influence the development of periodontal diseases by several mechanisms including modifications of the inflammatory response and changes in the composition of the dental biofilm (Akcali *et al*., 2013).

Concluded from this study that increased the concentration of cortisol hormone significantly in the serum and saliva of hypothyroid patients with and without periodontitis, this adds to what is already known about hypothyroidism and cortisol demonstrates a potentially important relationship between TSH and cortisol in hypothyroid individuals. Furthermore, increased hormone level in the saliva of patients with periodontitis indicates that cortisol may contribute to the pathogenesis of periodontal disease, and hypothyroidism effect indirectly on periodontal health. Also, the salivary concentration of this hormone may usefully reflect the concentration of free cortisol in serum.

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