

RELATIONSHIP BETWEEN CIRCULATING LEVELS OF SEX HORMONES AND PERIPHERAL GIANT CELL GRANULOMA

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Abstract- Giant cell granuloma is a relatively common, benign, non odontogenic lesion of oral cavity. It is a reactive response to local irritations and trauma that may be of central or peripheral type. It predominantly affects women and occurs most frequently in first 4 decades of life when hormonal changes are prominent. Therefore, hormonal effects are considered as a main factor in the etiology of this lesion. Purpose of this descriptive study was evaluating the relationship between circulating levels of sex hormones (testosterone, estrogen and progesterone) and presence of giant cell granuloma. We measured circulating levels of these hormones in 20 patients with giant cell granuloma utilizing radio immunoassay (RIA). Our sample included 12 females and 8 males from 10 to 65 years of age. Results were compared with normal range by means of *t* test. There were no significant differences between testosterone, progesterone and estrogen levels in patients with normal ranges. Our findings suggest that giant cell granuloma does not depend on sex hormones directly and role of sex hormones in development of this lesion is secondary to local factors such as trauma and poor oral hygiene.

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INTRODUCTION

There are two types of giant cell granuloma: peripheral and central. The peripheral giant cell granuloma is a benign lesion and histologically composed of proliferating mononuclear cells admixed with varying numbers of multinucleated giant cells. Frequently, a prominent vascularity is identified and is often accompanied by moderate amounts of hemosiderin pigment. Scattered foci of metaplastic bone may also be observed. A putatively related lesion arising centrally in the jaws is the central giant cell granuloma. The two appear similar histologically and presumably have the same cell

origin. The origin of the lesional cells is still incompletely understood; however, some feel the mononuclear cells represent transformed histiocytes and are derived from the mononuclear-macrophage system (1, 2). It is believed that the giant cells may be formed by fusion of the mononuclear cells (3), however, some feel them to essentially represent osteoclasts (4). Indeed, Bonetti *et al.* used a panel of immunohistochemical stains and concluded that the multinucleated giant cells of the closely related peripheral giant cell granuloma were osteoclasts (5).

One of the more common lesions of the oral cavity, peripheral giant cell granuloma always occurs on the gingiva or alveolar process and tends to present anterior to the molar teeth. A slight predilection for the mandible has been noted (1). The peripheral giant cell granuloma also has a distinct gender predilection where most series report a female predominance (6-8). As such it has been suggested that hormonal influences may play a role

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in the development of some lesions (6). Indeed, the majority of lesions present in the first 4 decades, when hormonal changes are most pronounced (6-8). In order for a lesion to be responsive to the major female hormones (estrogen and progesterone) it is presumed that the lesional cells would exhibit receptors for those hormones (9).

In the present study, we have attempted to ascertain whether presence of peripheral giant cell granuloma is related to circulating levels of sex hormones: testosterone, estrogen and progesterone.

MATERIALS AND METHODS

A total of 20 patients referred to the Department of Oral and Maxillofacial Surgery of Dentistry Faculty of Tehran Medical Science University with peripheral giant cell granuloma entered the study. The study was approved by Ethics Committee of Tehran University of Medical Sciences and written informed consent was obtained from all subjects.

Lesions in all cases had arisen in the gingiva or alveolar mucosa. Periodontium of patients was examined to specify gingival index (GI) and history of trauma was obtained. The patients with previous record of trauma were excluded.

Patients were sent to laboratory for specifying blood hormonal levels (progesterone and estrogen in females, estrogen and testosterone in males) with radio immunoassay (RIA) method. Hormonal titers were compared to normal range with one sample *t* test. The software that we used was SPSS. $P < 0.05$ was considered statistically significant.

RESULTS

The patient/lesion profiles of all cases are listed in Table 1.

Our 20 patients included 12 females (60%) and 8 males (40%) with average age of 31.1 years. From 12 females, 4 were in luteal phase and 4 in follicular phase, 2 in premature period and 2 in postmenopausal period. In 8 patients the gingiva was

Table 1. Patient/ lesion profiles of 20 peripheral giant cell lesions of the jaws

	Age (years)	Sex	Progesterone (ng/ml)	Estrogen (ng/ml)	Testosterone (ng/ml)
1	18	female	6.8	190	
2	10	female	0.4	20	
3	32	female	0.3	120	
4	63	male		28	7.8
5	16	female	3.1	132	
6	23	female	0.5	128	
7	50	female	2	70	
8	17	female	7.5	170	
9	45	male		12.5	4.7
10	41	male		14.7	5
11	19	male		25.6	7.6
12	29	female	0.1	135	
13	17	male		65.6	4.9
14	13	female	0.5	109	
15	65	male		37.1	5.1
16	25	male		9.4	6.4
17	37	male		23.7	5.3
18	17	female	5.7	149	
19	47	female	18.4	67.4	
20	38	female	0.1	174	

Table 2. *t* test value for measurement of testosterone

	Test value= 6.2					
	<i>t</i>	df	Sig.(1-tailed)	Mean difference	95% CI of the difference	
					Lower	Upper
Testosterone	0.672	7	0.523	0.3125	-1.4121	0.7871

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normal and in 10 patients light inflammation and in the rest moderate inflammation was seen. Periodontal examination showed normal gingiva in 40% (GI = 0), light inflammation in 50% (GI = 1) and moderate inflammation in 10% (GI = 2). None of the patients had severe inflammation (GI = 3). Overall, 60% of patients didn't have healthy gingiva and had some degree of gingivitis.

From 12 measured progesterone samples, 4 were higher than normal and 8 were normal, and from 20 measured estrogen samples just 1, in a male, was higher than normal.

Comparison of hormonal levels in patients to normal ranges using *t* test showed no significant differences. Mean testosterone level in patients was 5.8875 ± 1.31523 ng/ml which didn't have any statistically significant difference with normal quantities ($P = 0.523$) (Table 2). Mean progesterone level in patients was 3.7833 ± 5.36111 ng/ml with no statistically significant difference with normal quantities ($P = 0.072$) (Table 3). Mean estrogen level in patients was $84.05 \pm 61/7666$ ng/ml which didn't have any statistically significant difference with normal quantities ($P = 0.246$) (Table 4).

DISCUSSION

Giant cell granuloma is a benign and prevalent lesion of oral cavity. Several authors have shown the relationship between sex hormones and giant cell granuloma (1, 4, 10-14). Most articles detailing the age/sex characteristics of peripheral giant cell granuloma have reported a marked female predilection with a mean age in the early 30s (1, 7,

8). The reason for this distribution is not yet well known. A hormonal influence could be postulated, and indeed other lesions with a female predilection have been examined for a possible influence by estrogen and progesterone (1). Present research in accordance with previous researches shows that peripheral giant cell granuloma has predilection to females and occurs more frequently in first 4 decades of life when hormonal changes are prominent.

The presumed intraosseous counterpart to the peripheral giant cell granuloma (central giant cell granuloma) is also thought to be possibly under the influence of these hormones as these lesions also have a marked female predilection. Indeed several cases of central giant cell granuloma occurring in pregnancy have been documented in the literature (15-17).

McGowan was the first to suggest that the central giant cell granuloma could be under the influence of the ovarian hormones (9). Similarly, a case of rapidly enlarging peripheral giant cell granuloma in pregnancy has been reported by Cailluette and Mattar (18). The lesion had to be removed before parturition but recurred rapidly and necessitated termination of the pregnancy at 38 weeks by Caesarean section. The lesion subsequently regressed and did not return. Of further interest is an article by Flaggert *et al.*, who reported a case of central giant cell granuloma in a patient undergoing high dose estrogen therapy for Soto's syndrome (12). These findings would suggest that both the peripheral giant cell granuloma and central giant cell granuloma could be under the influence of the ovarian hormones (1).

Table 3. *t* test value for measurement of progesterone

	Test value= 0.7					
	<i>t</i>	df	Sig.(1-tailed)	Mean difference	95% CI of the difference	
					Lower	Upper
Progesterone	1.992	11	0.72	3.0833	-3230	6.4896

Table 4. *t* test value for measurement of estrogen

	Test value= 0.7					
	<i>t</i>	df	Sig.(1-tailed)	Mean difference	95% CI of the difference	
					Lower	Upper
Estrogen	-1.155	19	0.262	-15.9500	-44.8577	12.9577

Chambers, discussing Caillouette and Mattar's paper, suggested that peripheral giant cell granuloma is probably enhanced by pregnancy rather than being "pregnancy-dependent" (19). He felt that the lesion was not specifically hormone dependent, but that factors such as the responsiveness of the gingiva to these hormones coupled with the immunosuppressive actions of these hormones could have contributed to the growth of the lesion.

It would appear that although the marked female predilection in all these lesions suggests a possible hormonal influence, a true direct influence on lesional tissue can only be strongly suggested in the peripheral giant cell granuloma. This is not to say that the ovarian hormones play no part in the development/growth of these lesions, but the evidence suggests that they may influence them only secondarily.

In order to be directly under hormonal influence, it is presumed that the particular tissue would contain receptors for these hormones. Studies have shown that many tissues/organs and certain tumors contain receptors for the ovarian hormones, and are responsive to fluctuations in hormone levels. Breast carcinomas are routinely examined for these receptors where their presence usually implies a better prognosis. Other tumor types have also been examined for steroid receptors and given positive results. Clearly, these hormones do play a role in the biology of many types of tumor (1).

ElAtter and Hugoson on 1974 showed estrogen metabolism in unhealthy gingiva was 3 times more than normal gingiva and the activity of responsible enzyme of these reactions increased gingival inflammation (20). Mohamed showed absorption of progesterone by rabbit's gingiva (21). In 1982, Vittek could find progesterone receptors in rabbit's gingiva and progesterone and estrogen receptors in human's gingiva (22), and in 1992 Forabasco showed estrogen receptors in oral mucosa (13).

In addition to hormonal factors, trauma, poor oral hygiene and local stimulation are effective on prevalence of these lesions. We used Silness gingival index to consider oral hygiene. In our cases 40% had normal gingiva and 60% showed light to moderate degrees of inflammation. These results confirm the role of poor oral hygiene in initiation of peripheral giant cell granuloma.

Since we were unable to demonstrate direct action of sex hormones on peripheral giant cell granuloma, we measured the levels of estrogen, progesterone and testosterone in our research. The results showed no significant difference between blood levels of these hormones and normal quantities but clinical aspects confirmed the relationship between these lesions and sex hormones. It is important to note that higher frequency of these lesions on maturity, pregnancy and menstruation periods doesn't mean that patients with peripheral giant cell granuloma have high blood level of these hormones.

Since we know estrogen and progesterone receptors are present in oral mucosa (1, 10, 11, 14), we could conclude that secondary influences of sex hormones with background of low oral hygiene or other stimulation factors are important factor in etiology of peripheral giant cell granuloma. In our research mean levels of hormones didn't differ from normal quantities so we can't conclude that blood levels of these hormones in patients with peripheral giant cell granuloma differ from normal people, but our results shows the clinical relationship of peripheral giant cell granuloma with progesterone.

In conclusion, patients under hormone therapy with sex hormones or during pregnancy have a higher chance for peripheral giant cell granuloma. It seems that more attention must be paid to oral hygiene of people on these special periods and this factor is more important than hormonal control.

Conflict of interests

The authors declare that they have no competing interests.

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