

Estimation of Prevalence of Gingival Enlargement - A Population Based Study

Running Title: Gingival enlargement in different age groups.

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Abstract:

Gingival enlargement is an increase in the size of the gingiva. It is also known as the gingival hyperplasia or hypertrophy. They can be categorised based on their etiology, pathogenesis, location, size and extent. Inflammatory gingival enlargement is a most common form and clinically present as soft and discolored gingiva. Drug induced gingival enlargement is a well recognised adverse effect of certain systemic medications. Calcium channel blockers, Anticonvulsants and Immunosuppressants are frequently implicated drugs in the etiology of drug induced enlargement. The aim of the study is to assess the prevalence of gingival enlargement and its distribution. The study was a retrospective, University based study. Case sheets of patients visiting the dental outpatient ward June 2019 to March 2020 were collected. Patients diagnosed with gingival enlargement were sorted and tabulated in Microsoft excel sheet and analysed using SPSS software. In the present study, out of 40,000 patients, the prevalence of inflammatory enlargement was found to be 0.1% and the drug induced enlargement was 0.03%. Drug induced enlargement was more prevalent in males than in females, whereas inflammatory enlargement was more prevalent in females than males, there was no statistically significant difference in the prevalence rate between age groups ($p=0.362$) and gender ($p=0.210$). On comparing the drugs, phenytoin was consumed by one third of the population (43%) but had a higher prevalence rate of 65% than antihypertensive drugs (28%) and immunosuppressants (7%).

Keywords: anticonvulsants, chronic and acute enlargement, calcium channel blocker, gingival enlargement, immunosuppressants, inflammation

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INTRODUCTION:

Gingival enlargement or gingival overgrowth - a common form of gingival disease is characterized by an increase in the size of gingiva. Gingival enlargement can be classified into various forms, based on their etiology, they can be classified as inflammatory, drug induced, those that are associated with systemic disease, neoplastic or false enlargement. Based on the location, they can be marginal, papillary or diffuse. Based on distribution it can be localised or generalized. (Agrawal, 2015)

Inflammatory gingival enlargement may be categorised as acute or chronic, whereas chronic changes are more common. Drug induced gingival enlargement remains a significant problem for the dentist in general and periodontologist. It may interfere with aesthetics, mastication, and even speech. An increasing number of medications are associated with gingival overgrowth. Currently more than 20 prescription medications are associated with gingival enlargement.

Drugs that are associated with gingival enlargement can be broadly classified into three categories - anticonvulsants, calcium channel blockers, immunosuppressants. The first case of phenytoin induced gingival enlargement was reported by Hassel et al. (Hassel, 1981) Other anticonvulsants like sodium valproate, phenobarbitone, have also been associated with gingival enlargement but have been rarely reported. (Hallmon and Rossmann, 1999) Calcium channel blockers induced gingival enlargement was first reported in 1984 by Hederman in patients treated with nifedipine. (Barclay et al., 1992; Ellis et al., 1999) Amlodipine induced gingival enlargement was first reported by Seymour in 1994. (Ellis et al., 2006) Cyclosporine induced gingival enlargement was first reported by Rateitschak in 1983. (Rateitschak-Plüss and Hefti, 1983) . Although the pharmacological effect of each of these drugs is different towards their primary target site, all of them seem to act similarly on their secondary target site that is the gingival connective tissue. Clinical manifestation of drug induced enlargement usually

appears within 1 to 3 months, after initiation of these medications. Gingival overgrowth normally begins in the interdental papilla and is more frequently found in the anterior segment of the labial surface.

The distribution of inflammatory enlargement is usually generalised or localised. Inflammatory enlargement can be plaque induced and non plaque induced. Plaque induced can be generalised and non plaque induced is localised to the contributing etiological factors like restoration that is impinging on the gingiva, prosthesis confined to a specific tooth. Whereas, drug induced enlargement is usually generalised. The gingival lobulations are formed gradually that may appear inflamed or fibrotic in nature. The presence of enlargement makes plaque control difficult, resulting in a secondary inflammatory process, this is known as combined gingival disease. The difficulty in maintaining oral hygiene leads to further plaque accumulation and inflammation, the presence of previous inflammatory factors like cytokines, TNF - alpha, endothelins and IL-21 favours the action of drugs on the gingival connective tissue, perpetuating this cycle. (Agrawal et al., 2017; Khalid et al., 2016, 2017; Mootha et al., 2016; Varghese et al., 2015)

Besides gingival enlargement being an entity in periodontal disease, it may appear as a clinical feature in periodontitis. Periodontitis is a multifactorial disease with primary etiological factors being plaque and microflora. The treatment of periodontitis is a multidisciplinary approach, starting from synthetic drugs like antibiotics to regenerative methods (Ravi et al., 2017) like PRF, (Panda et al., 2014; Thamaraiselvan et al., 2015) growth factors and stem cells. (Avinash et al., 2017) Disadvantages of these methods have led to plant based studies, where herbs are used as antimicrobials agents. Effectiveness of various herbal mouthwashes are being tested against periodontal disease. (Ramamurthy and Mg, 2018; Ramesh, Sheeja Saji Varghese, et al., 2016)

The prevalence rate of gingival enlargement in school children in Karnataka was assessed and found that it was predominantly inflammatory and was caused due to improper oral hygiene practices (Krishna et al., 2014). However, this findings may vary in individuals with different age groups and genders due to factors like hormones, stress etc. Hence, it is essential to assess the prevalence of gingival disease and its distribution in different populations and to assess the various etiological factors that caused enlargement.

MATERIALS AND METHODS:

Study setting:

This is a retrospective, university based study. Case sheets of 40,000 patients who reported to the dental outpatient ward from June 2019 to March 2020 were evaluated. Patients diagnosed with gingival enlargement were sorted. Ethical clearance was obtained from the Institutional Ethical Committee - Saveetha Dental College (SDC/SIHEC/2020/DIASDATA/0619-0320).

Sampling:

Patients diagnosed with gingival enlargement and those with under medication of anticonvulsants, antihypertensives and immunosuppressants were collected. Case sheets with incomplete data and repeated cases were excluded from the study. Further sorting was done with respect to age groups, gender distribution, drug used and type of enlargement. The data were cross verified by another reviewer to minimise the sampling bias.

Data Collection:

Datas collected were tabulated in Microsoft Excel sheet.

Statistical Analysis:

The Excel sheet was transferred to the host computer and processed in SPSS. Chi-square test was done to analyse the association and correlation with age and

gender as independent variables and type of enlargement, clinical site as dependent variables.

RESULTS AND DISCUSSION:

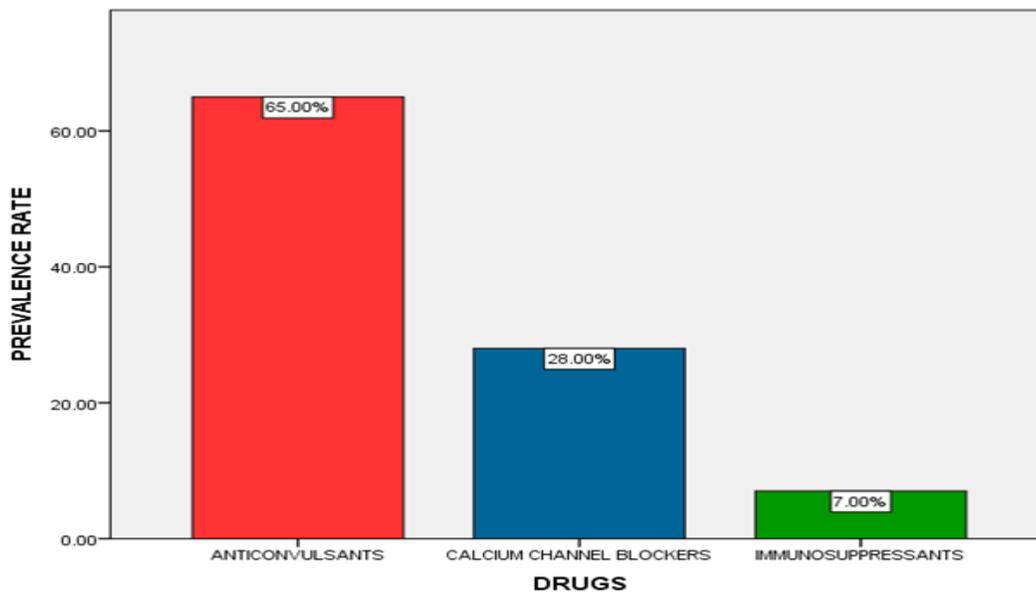
Out of 40,000 patients, the prevalence rate was calculated to be 0.1025%. The inflammatory enlargement was further categorised as generalised and localised, in which less than 40% had generalized gingival enlargement. This shows inflammatory enlargement is confined to a localised region.

On analysing the drug induced enlargement, 332 patients were under medication of anticonvulsant, calcium channel blockers and immunosuppressants. 33% patients were under phenytoin, 65% patients were under amlodipine, 0.6% patients under

nifedipine and 0.3% patients under cyclosporine. The prevalence rate was calculated to be 0.035%.

The prevalence of inflammatory enlargement is higher compared to drug induced enlargement because, out of 40,000 patients 0.83% of the patients consumed either of the listed drugs. Inflammatory enlargement may be due to a long standing bacterial plaque that produces constant irritation leading to continuous infiltration of neutrophils and their sequelae.

In the present, out of 332 patients, about one third (33%) consumed phenytoin and about 66% of the patients consumed antihypertensive drugs. In contrast, the gingival enlargement was prevalent in patients who consumed phenytoin with 65% frequency rate. Whereas enlargement induced by antihypertensive drugs is 28% (graph 1).



Graph 1: Bar chart shows the frequency rate of each drug that induced gingival enlargement. X axis represents the type of drug and Y axis represents the prevalence rate. From the above graph it is inferred that anticonvulsants induced gingival enlargement is more common.

Several theories have been put forward to explain the action of phenytoin on the gingiva that include, decreased collagen degradation. Generally, the mechanism of collagen degradation occurs in two pathways : By secretion of collagenase, Drugs like phenytoin reduces calcium influx into the cell ,leading

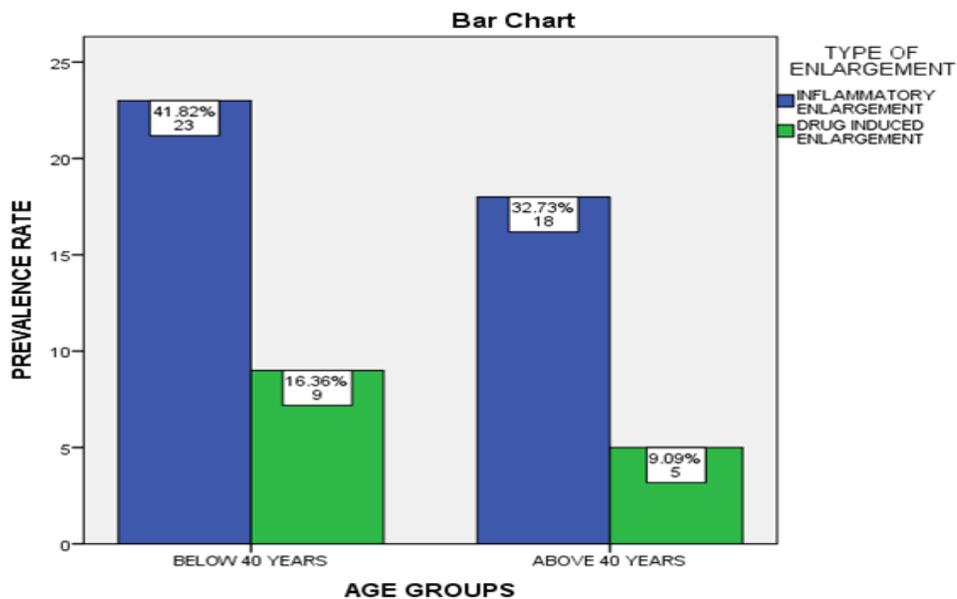
to the reduction in the uptake of folic acid, ultimately limiting the production of collagenases. 2. Intercellular pathway , where the alpha-2 beta-1 integrin acts as a specific receptor for the adhesion of fibroblast and collagen. Phenytoin is proved to diminish the expression of alpha-2 beta-1 integrin.

Hence, there is increased deposition of collagen leading to enlargement of the gingiva. In addition to the activity of phenytoin, most of the epileptic patients are not capable of maintaining proper oral hygiene. There will be increased deposition of plaque leading to a combined disease. (Corrêa et al., 2011)

In a study conducted by Jogersen et al, (Jorgensen, 1997) prevalence of amlodipine induced gingival enlargement was 3.3%. In another study conducted by Soumya et al, (Gopal et al., 2015) the frequency of occurrence of gingival enlargement in patients under medication of antihypertensive drugs was 27.1 %. In a study conducted by Ellios et al, the prevalence of amlodipine induced gingival overgrowth was 1.7%. The prevalence of hypertension is higher (29.8%) in India. Hence the patients under medication for hypertension is also higher. However not all patients under medication for hypertension have gingival

enlargement and may attribute to the vulnerability of an individual's gingival tissue. (Kavarthapu and Thamaraiselvan, 2018; Ramesh et al., 2017) The action of antihypertensive drugs on gingiva is similar to that of phenytoin. It has also been proposed that gingival fibroblast enhances the synthesis of collagenous proteins when exposed to antihypertensive drugs and other pro inflammatory cytokines like interleukin 1- beta. Moreover, periodontal disease as such is a risk factor for cardiac disease. Microflora Research has shown that the periodontal microflora is similar to that found in the atheromatous plaque. Hence, it is important to manage periodontal disease effectively. (Ramesh, Sheeja S. Varghese, et al., 2016)

The association between the age groups and type of enlargement was assessed (graph 2).



Graph 2: Bar chart represents the association of age group with type of enlargement.

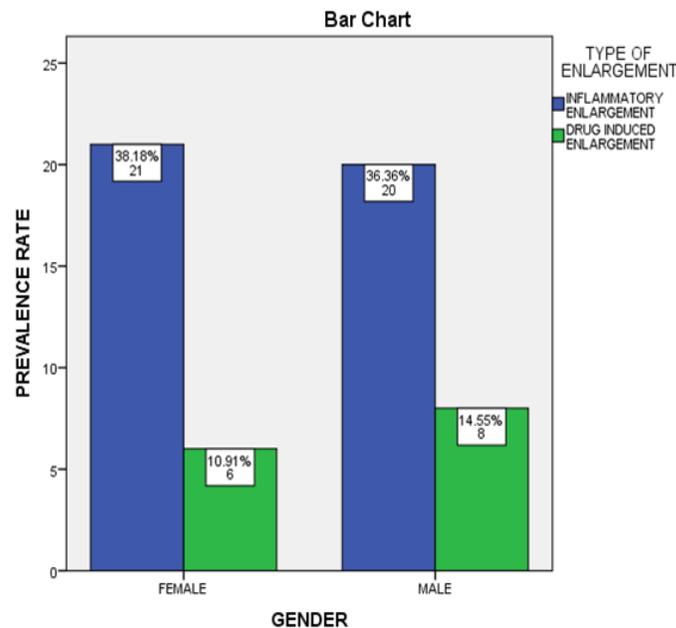
X axis represents the type of enlargement and Y axis represents the frequency rate, drug induced enlargement was more common in patients above 40 years whereas, inflammatory enlargement was more common in patients below 40 years. Chi

square test - Linear by linear association *p value = 0.362 (>0.05) , it can be inferred that the association of age groups with type of enlargement is statistically not significant.

There is no statistically significant association between the age groups and enlargement. However,

in drug induced enlargement phenytoin induced enlargement was prevalent in younger and calcium channel blockers induced enlargement was common in older age groups. In a study conducted by George et al (Goyal, 2017) it is stated that phenytoin induced gingival overgrowth was more susceptible to children and adults younger than 30 years of age. Another study conducted by Means et al states that phenytoin induced enlargement was more common in children

and young adults. These are similar to our present study. In a study conducted by Jayanti et al about amlodipine induced gingival enlargement, it was reported that amlodipine induced gingival enlargement was more prevalent in elderly people, which is also similar to our study. (Ramesh et al., 2019) The association of the type of enlargement and gender groups was assessed (graph 3).



Graph 3: Bar chart represents the association of gender distribution with type of enlargement.

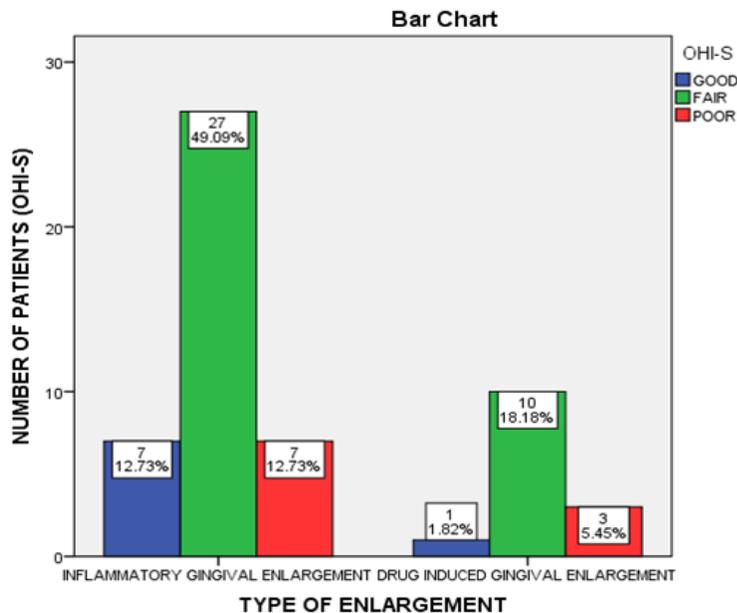
X axis represents the type of enlargement and Y axis represents the frequency rate. The drug induced enlargement was more common in males patients, whereas inflammatory enlargement was more common in female patients. Chi square test Linear by linear association *p value = 0.210 (>0.05) it can be inferred that the association of age groups with type of enlargement is statistically not significant. There is no statistically significant association between the gender and type of enlargement. The prevalence of drug induced enlargement was more common in males whereas inflammatory enlargement was increased in females. George et al stated that the drug induced enlargement

was more common in males than in females. Other studies conducted by Soumya et al, Barack et al (Barak et al., 1987), Thomson et al (Thomason et al., 1995) shows that males have increased prevalence and drug induced gingival enlargement. An animal study done in rats have also stated the prevalence of nifedipine induced gingival enlargement is more common in males. However puberty associated gingival enlargement is more common in females than males. Conditioned enlargement like enlargement in puberty and pregnancy are confined to the female population due to the influence of female sex hormones on the gingival connective tissue. Estrogen is mainly responsible for alterations in blood vessels

and progesterone stimulates the production of inflammatory mediators. The hormones increase the vascular permeability leading to gingival edema, an increased inflammatory response to dental plaque. The subgingival microbiota may also undergo changes, which include an increase in the *Prevotella intermedia*.

It is believed that *Prevotella intermedia* uses female sex hormones as a source of nutrients. (Khosla et al., 2012; Markou et al., 2009)

The oral hygiene status of patients with enlargement was assessed (graph 4).



Graph 4: Bar chart shows the association between the type of enlargement and Oral hygiene index.

X axis represents the type of enlargement and Y axis represents the number of patients. Most of the patients had fair oral hygiene status (green) in both the type of enlargement. Chi square test - linear by linear association p value = 0.649 (>0.05), it can be inferred that the association between type of enlargement and oral hygiene status is statistically not significant.

There was no statistically significant association between the oral hygiene status and the type of enlargement. However, we could see most of them had fair and poor oral hygiene status. Plaque and calculus is one of the main etiological factors for inflammatory enlargement, however on assessing the drug induced enlargement it can be a secondary factor. Inabilities of an individual to maintain proper oral hygiene can lead to plaque accumulation, studies have

proved that epileptic patients have poor oral hygiene due to improper maintenance. In these cases, the inability of the patients, gingival contour, gingival bleeding, pain can lead to poor oral hygiene status (Joshi et al., 2017).

OBJECTIVE:

- To assess the prevalence of inflammatory and drug induced enlargement.
- To compare the prevalence of gingival enlargement in different age groups.
- To compare the prevalence of gingival enlargement in male and female.
- To compare the prevalence of gingival enlargement in response to different types of drugs.

CONCLUSION:

From the present study, we can conclude that the prevalence of inflammatory enlargement is higher than drug-induced enlargement. Among the drugs included in our study, Gingival enlargement was more prevalent in individuals under medication of anticonvulsants. However there is no statistically significant difference in the prevalence rate of gingival enlargement with different age groups and gender.

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