

# Prevalence and Severity of Amlodipine-induced Gingival Enlargement

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## ABSTRACT

**Background:** The administration of several classes of drugs; anticonvulsants, immunosuppressants, and calcium channel blockers can cause gingival enlargement. The aim of the present study was to evaluate the frequency and severity of gingival enlargement in patients taking calcium channel blocker drug amlodipine.

**Methods:** This descriptive cross-sectional study was conducted on 250 patients who visited the dental hospital at Nepal Medical College between November 2021 to April 2022. Using the Bokenkamp and Bornhorst Index, the patients who had been on amlodipine for at least three months were examined for gingival enlargement. Along with gingival and plaque index, medication dosage and duration were also assessed.

**Results:** The prevalence of gingival enlargement was 37%. Grade 1 gingival enlargement was present in 18% while grade 3 was seen in only 2%. Both individuals taking amlodipine alone and in combination with other antihypertensive drugs showed the same level of gingival enlargement. The dose and duration of amlodipine ingestion showed a significant correlation with the enlargement. The gingival and plaque index also showed a strong correlation with overgrowth.

**Conclusions:** The physicians prescribing amlodipine should well inform the patients about the potential side effects. In such cases, the maintenance of oral hygiene should be prioritized from the beginning. In severe cases, substitution of the drugs followed by oral therapeutic measures should be considered for complete regression.

**Keywords:** Amlodipine; gingival enlargement; prevalence; periodontology

## INTRODUCTION

Enlarged gingiva is one of the common symptoms of gingival disease. It is a commonly neglected condition when it occurs in association with commonly prescribed drugs like cyclosporin A- an immunosuppressant, calcium channel blockers like nifedipine, amlodipine, and anticonvulsants like phenytoin.<sup>1</sup> Usually drug-induced gingival enlargement affects the interdental and marginal gingiva on the maxillary and mandibular anterior teeth.<sup>2</sup> A normal healthy gingiva is pale pink, robust, firm, and has a thinly lobulated surface with no tendency to bleed. However, as the gingiva enlarges plaque gets accumulated which invites the onset of serious periodontal diseases such as periodontitis.<sup>3</sup> To prevent these complications maintenance of good oral hygiene is mandatory. The present study aims to evaluate the prevalence and severity of gingival enlargement in patients taking amlodipine.

## METHODS

This descriptive cross-sectional study was carried out in the dental hospital of Nepal Medical College Teaching Hospital (NMCTH) Attarkhel, Nepal from November 2021 to April 2022. Ethical clearance was obtained from the Institutional Review Committee (IRC), Nepal Medical College [Reference No. 036-078/079]. Informed consent was taken from the patients prior to conducting the study.

The patients taking amlodipine for at least the previous three months and who provided informed consent were included in the study. Patients under orthodontic therapy, with a previous history of periodontal surgery within the last six months, patients with systemic diseases like leukemia, granulomatous diseases like Wegeners, and patients who have stopped taking their medication for more than four weeks were excluded

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from the study. Also, pregnant women, smokers, and people with diabetes mellitus were not included.

The demographic variables were recorded along with the intake of any medications known to enlarge the gingiva. Additional information related to a drug such as a dosage and duration of usage was also noted.

Patients under Amlodipine medication for at least 3 months were examined for the presence of gingival enlargement using the Bokenkamp and Bornhorst Index (1994)<sup>4</sup> indicated below:

Grade 0 - No indications of gingival enlargement.

Grade 1 - Only interdental papilla is enlarged.

Grade 2 - The papilla and marginal gingiva are enlarged.

Grade 3 - Three-quarters or more of the crown is enlarged.

The Loe and Sillness gingival index (1963) was used to record the gingival index.<sup>5</sup> Similarly; Sillness and Loe plaque index (1964) was used to record the plaque index.<sup>5</sup>

The sample size was calculated using the Cochran statistical formula ( $N = Z^2pq/d^2$ ) where  $Z = 1.96$  at a 95% confidence interval,  $p$  (the prevalence of gingival enlargement in patients taking 5mg of Amlodipine)<sup>6</sup> was set at 80.4%,  $q$  was equal to  $1 - p$ , and  $d$  was a minimum acceptable degree of error which was set at 5%. Thus, the minimum sample size calculated for the study was 244. Statistical analysis was done using SPSS version 20. Means and standard deviations were calculated for all the variables. The difference in proportions was calculated using the Chi-square test.

## RESULTS

A total of 250 patients were recruited for the present study out of which 117 (47%) were male and 133 (53%) were female. The mean age of the patients was  $56.13 \pm 11.75$ . Among the patients, 176 (70%) took only amlodipine, whereas 74 (30%) also took other antihypertensive medications. None were encountered who were under concomitant use of phenytoin and cyclosporine- A.

The prevalence of drug-induced gingival enlargement was 93 (37%) out of 250 patients. The frequency of drug-induced gingival enlargement was 46 (39%) in males and 47 (35%) in females respectively. There was no

statistically significant association between gender and gingival enlargement ( $p=0.600$ ) (Figure 1.)

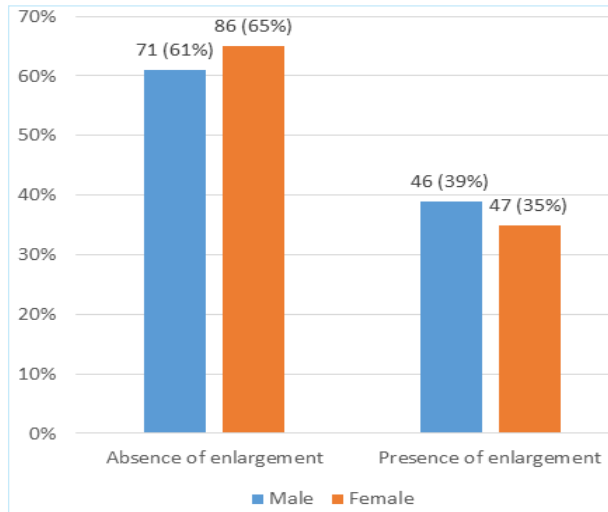


Figure 1. Prevalence of gingival enlargement.

Amlodipine-induced gingival enlargement was seen in 66(37%) out of 176 patients. Amlodipine in combination with other antihypertensive drugs induced gingival enlargement was seen in 27 (36%) out of 74 patients. However, there was no statistical difference between the two groups ( $p=1.00$ )

Grade 1 gingival enlargement was predominantly seen in 45 (18%), Grade 2 was seen in 43 (17%) and only 6 (2%) had grade 3 gingival enlargement out of 250 patients.

Significant association ( $p=0.007$ ) existed between the amlodipine dosage and gingival enlargement. Gingival enlargement was more prevalent with an intake of higher doses. Individuals ( $n=28$ ) who were taking 10 mg of the drug were found to have enlarged gingiva in 16 (57%) individuals, as opposed to those consuming 2.5 mg in which 10 (20%) had gingival enlargement (Table 1).

Table 1: Gingival enlargement according to the dose of Amlodipine.

Dose of Amlodipine	Study population	Gingival enlargement (%)	p-value
2.5mg	49	10 (20%)	0.007
5mg	161	61 (38%)	
7.5mg	12	6 (50%)	
10mg	28	16 (57%)	

Table 1 Distribution of patients with gingival enlargement according to different doses of Amlodipine intake.

Gingival enlargement was present in 26 (84%) of those

who had been using the medication for more than 10 years, as opposed to 37 (32%), who had been taking it for less than 5 years. The duration of drug use was significantly associated with gingival enlargement ( $p < 0.001$ ) (Table 2).

**Table 2. Association of gingival enlargement with the duration of drug therapy.**

Duration of the medication consumption	Absence of gingival enlargement (-) n(%)	Presence of gingival enlargement (+) n (%)	p-value
<5 years	78 (68%)	37 (32%)	<0.001*
5-10 years	74 (71%)	30 (29%)	
>10 years	5 (16%)	26 (84%)	

Chi square test,  $p$ -value < 0.05 statistically significant\*

There was a statistically significant difference in mean gingival index score ( $p$ -value < 0.001) and mean plaque index score ( $p$ -value < 0.001) between those with and without gingival enlargement. The gingival enlargement was seen in those with higher gingival and plaque index scores (Table 3).

**Table 3. Comparison of mean GI and PI between patients with and without gingival enlargement.**

Variables	Absence of Gingival enlargement (Mean)	Presence of Gingival enlargement (Mean)	p-value
Gingival Index (GI)	0.66±0.66	1.36±0.56	<0.001*
Plaque Index (PI)	1.10±0.75	1.84±1.41	<0.001*

Independent  $t$ -test,  $p$ -value < 0.05 statistically significant\*

## DISCUSSION

The prevalence of drug-induced gingival enlargement was 93 (37%) out of 250 patients. There was no statistically significant association between gingival enlargements and gender. In view of severity of gingival enlargement, grade 1 and grade 2 was more prevalent with 45 (18%) and 43 (17%) prevalence respectively, while only 6 (2%) had grade 3 gingival enlargement. The duration of drug use was significantly associated with gingival enlargement as the enlargement was present in 26 (84%) of those who had been using the medication for more than 10 years, as opposed to 37 (32%), who had been taking it for less than 5 years. More gingival enlargement occurred with an intake of higher doses as there was significant association between amlodipine dosage and gingival enlargement. Also there was a statistically significant difference in mean gingival

index score and mean plaque index score between those with and without gingival enlargement as gingival enlargement was seen in those with higher gingival and plaque index scores.

There was no statistically significant correlation between gingival enlargement and the sexes. This was in accordance with the other studies.<sup>7,8</sup>

The prevalence of amlodipine-induced gingival enlargement in the present study was similar to Gopal et al. (31.4%).<sup>7</sup> However, studies by Jorgensen et al. (3.3%)<sup>9</sup> and Ellis et al. (1.7%) varied.<sup>8</sup> The prevalence of amlodipine in combination with other drugs was lower in our study compared to Pintor et al. (58.1%).<sup>10</sup>

The prevalence may be affected by the heterogeneity of the gingival fibroblasts, which may be induced or repressed based on the genetic predisposition of the individual. Thus, the normal inflammatory response of gingival fibroblasts responsible for the growth of the connective tissue matrix may vary in each individual.<sup>11</sup>

The other factors which may influence the degree and severity of gingival enlargement are inhibition of cation influx, bacterial plaque, and folic acid (FA) uptake by gingival fibroblasts resulting in altered matrix metalloproteinase metabolism and failure to activate collagenase, all contributing to gingival enlargement.<sup>12</sup>

The present study showed a significant correlation of the drugs with the duration of consumption similar to Pradhan et al.<sup>13</sup> and Sharma et al.<sup>14</sup> But in contradiction to other studies.<sup>15,16</sup> This could be due to the fact that Amlodipine may accumulate over time in plaque, saliva, gingiva, and gingival crevicular fluid, leading to higher rates of gingival overgrowth.<sup>17</sup>

Also, the dose of the drug consumption showed a correlation with the gingival enlargement similar to Jayanthi et al.<sup>6</sup> and others<sup>18</sup> who reported 10 mg amlodipine to cause enlargement at a higher rate. This correlation can be explained by the pharmacokinetics of the inducing drugs and the gingival binding affinities of these drugs. The drug concentrations in whole blood and saliva may have a significant role in determining how gingival overgrowth manifests itself.<sup>9</sup>

The present study showed a correlation of gingival enlargement with gingival and plaque index similar to Tejnani et al.,<sup>18</sup> Taib et al.,<sup>16</sup> and Gopal et al.<sup>7</sup> but in contradiction to Kothari et al.<sup>19</sup> The plaque index (PI) and gingival index (GI) were seen to be moderately high for most subjects in the present study. It has been

suggested that calcium channel blockers inhibits the intracellular uptake of calcium across cell membranes, and may therefore interfere with the synthesis and function of collagenases, thus resulting in gingival fibroblast proliferation.<sup>20</sup> Calcium channel blockers are also known to cause decrease in salivary flow.<sup>21</sup> It is however believed that inflammation is a prerequisite for development of gingival enlargement and its hypothesized that in non- inflamed gingiva, fibroblast are less active or quiescent even in the presence of drug.<sup>22</sup> So this could explain higher PI and GI in our study with gingival enlargement because plaque leads to gingival enlargement in these patients and enlarged gingiva in turn hinders proper plaque control.

This implies that in any susceptible patient taking amlodipine, inflammation should be prevented. This can be achieved by proper oral hygiene care. In addition, periodic oral prophylaxis will favor the outcome. However, the actual role of drug in the increase in the amount of plaque in the present study need to be tested by further studies using control subjects.

Amlodipine has a distinct physiochemical profile that is characterized by nearly full absorption, late peak plasma concentrations, high bioavailability, and slow hepatic biodegradation. Only one dose per day is necessary due to amlodipine's slow excretion and the lengthy duration of its action. Better patient compliance follows, and up until now, this has been linked to side effects that are similar to or less severe than those caused by nifedipine.<sup>1</sup> These favorable properties of Amlodipine may avoid the physicians and the patient themselves from drug substitution. In such cases, the physicians should understand the consequences and advocate drug substitution.

## CONCLUSIONS

In the present study, 37% of patients taking Amlodipine drug were seen to have gingival enlargement. Both individuals taking amlodipine alone and in combination with other antihypertensive drugs have shown the same level of gingival enlargement. The dose and duration of amlodipine ingestion showed a significant correlation with enlargement. The gingival and plaque index also showed a strong correlation with gingival overgrowth.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest

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