

Prevalence and Risk of Gingival Enlargement in Patients Treated With Nifedipine

Jaume Miranda,* Lluís Brunet,* Pere Roset,† Leonardo Berini,‡ Magí Farré,† and Carlos Mendieta*

Background: Gingival enlargement is a known side effect of nifedipine use. This study was conducted to determine the prevalence and risk factors for gingival enlargement in nifedipine-treated patients.

Methods: A cross-sectional study was conducted in a primary care center. Data from 65 patients taking nifedipine were compared with 147 controls who had never received the drug. All patients were examined for the presence of gingival enlargement using 2 different indices: vertical gingival overgrowth index (GO) in 6 points around each tooth, and horizontal MB index in the interdental area. Gingival index, plaque index, and probing depth were also evaluated.

Results: The prevalence of gingival enlargement was significantly higher in nifedipine-treated cases than in controls (GO index, 33.8% versus 4.1%; MB index, 50.8% versus 7.5%, respectively). Higher gingival and plaque indices were observed in patients taking nifedipine. Among the possible risk factors, only the gingival index showed a significant association with gingival enlargement. The risk (odds ratio [OR]) of gingival enlargement associated with nifedipine therapy was 10.6 (3.8-29.1) for the GO index and 14.4 (6-34.6) for the MB index. Gingival index-adjusted ORs were 9.6 (3.3-28.1) and 9.7 (3.9-23.3), respectively. In the subset of high nifedipine exposure patients, the odds ratio for gingival enlargement increased to 17.4 (5.3-56.3) for the GO index and 23.6 (7.7-72.3) for the MB index. The concordance between GO and MB indices showed a kappa value of 0.689 in controls and 0.642 in patients treated with nifedipine.

Conclusions: Patients taking nifedipine are at high risk for gingival enlargement, and gingivitis acts as a predisposing factor. *J Periodontol* 2001;72:605-611.

KEY WORDS

Cross-sectional studies; gingival hyperplasia/epidemiology; nifedipine/adverse effects; risk factors.

Gingival enlargement or overgrowth has been associated with multiple factors including inflammation, adverse drug effects, and neoplastic conditions. Chronic inflammation due to dental plaque frequently causes gingival overgrowth.¹⁻⁴ Drugs associated with gingival enlargement include antiepileptics such as phenytoin;⁵⁻⁷ cyclosporin A;⁸⁻¹⁶ and calcium channel blockers, such as dihydropyridine,¹⁷⁻²² verapamil,²³⁻²⁷ and diltiazem.²⁷⁻³² The clinical and pathologic features in drug-induced gingival overgrowth are independent of the drug administered, which suggests a common pathway of induction.³³ The pathogenic mechanisms involve different factors, such as dental plaque, presence of genetically predetermined gingival fibroblasts (named responders), and effect of the drug itself, with all compounds affecting the transmembrane flow of calcium.^{12,34,35} This, in turn, changes the metabolism of connective tissue fibroblasts, causing an increase in the components of the extracellular matrix, i.e., collagen fibers and/or ground substance.^{22,36-43}

Nifedipine is a calcium channel-blocking agent of the dihydropyridine group widely used as a vasodilating agent for the treatment of hypertension and ischemic heart disease.^{44,45} Gingival enlargement in patients treated with this drug was originally reported in 1984 by Lederman et al.¹⁹ and Ramon et al.²¹ More recently, gingival enlargement also has been described in patients treated with other dihydropyridines, such as nitrendi-

* Periodontics Unit, Facultat d'Odontologia, Universitat de Barcelona, Barcelona, Spain.

† Unit of Pharmacology, Institut Municipal d'Investigació Mèdica, Facultat de Medicina, Universitat Autònoma de Barcelona.

‡ Oral Surgery Unit, Facultat d'Odontologia, Universitat de Barcelona.

pine, nifedipine, felodipine, and amlodipine.⁴⁶⁻⁵² Because the majority of studies are based on series of cases with a small number of patients, the true prevalence of nifedipine-induced gingival enlargement is unknown.^{17,27,53-56} On the other hand, predictors of gingival enlargement in patients treated with nifedipine have not been previously assessed. Therefore, the aim of the present study was to determine the prevalence, severity, and risk factors of gingival enlargement in a population of nifedipine-treated patients and to compare the results with those in a control group.

MATERIALS AND METHODS

Study Population

A cross-sectional study was carried out at the CAP-Rambal primary care center serving a population of 170,000 inhabitants in Terrassa, Barcelona, Spain. All patients over 18 years of age treated with nifedipine who were consecutively visited by their general practitioner or cardiologist were eligible. Patients were included if they were currently taking nifedipine in regular doses during at least the last 6 months. The presence of at least 16 permanent teeth, with a minimum of 10 anterior teeth, was required. Patients who had undergone periodontal treatment within the 6 months prior to the initiation of the study; with concomitant systemic disorders known to affect the gums (such as diabetes, endocrine disorders, leukemia, thrombocytopenic purpura, or immunodeficiency states); or taking anticonvulsant drugs, calcium antagonists other than nifedipine, cyclosporin A, oral contraceptives, and sexual hormones were excluded from the study.¹⁸ The control group included patients not treated with nifedipine who fulfilled the same inclusion and exclusion criteria. All patients agreed to participate in the study and gave their written informed consent.

Gingival enlargement was graded according to the index originally described by Angelopoulos and Goaz⁵ and later modified by Miller and Damm²⁴ (GO index). The height of gingival tissue was measured from the cemento-enamel junction (CEJ) to the free gingival margin. The following grades were scored in 6 points around each tooth: grade 0, normal gingiva; 1, minimal enlargement (≤ 2 mm in size, with gingiva covering the cervical third or less of the anatomic crown); 2, moderate enlargement (2 to 4 mm in size and/or gingiva extending into the middle third of the anatomic crown); and 3, severe enlargement (nodular growth >4 mm and/or gingiva covering more than two-thirds of the tooth crown). Gingival overgrowth was also measured in the buccal-lingual direction in all interdental papilla according to the index described by Seymour et al.⁵⁷ and modified by Miranda et al. (MB index).⁵⁸ The increase in size of the papilla was measured from the enamel surface, at the interdental contact point, to

the outer papillary surface. Two scores were obtained, one for the buccal papilla and another for the lingual/palatal papilla, according to the following criteria: grade 0, papillary thickness of less than 1 mm; 1, papillary thickness between 1 and 2 mm; and 2, papillary thickness >2 mm.

A standard periodontal probe (Michigan 8/11) was used to assess the extent of enlargement. For both indices, an average mean was calculated for the whole mouth, anterior and posterior areas, and buccal and lingual/palatal surfaces. Gingival enlargement was considered to be present when grades other than zero were recorded in one or in both GO and MB indices.

Other measures included the Loe and Silness gingival index (GI),⁵⁹ plaque index (PI),⁶⁰ and periodontal probing depth (PD).⁶¹ These indices were measured in 6 points around each tooth. All measurements were done by the same examiner (JM).

Statistical Analysis

The sample size was estimated considering a prevalence of gingival enlargement of 20% in nifedipine-treated patients and 4% in controls.^{27,62} Sixty-two patients treated with nifedipine would provide an 80% power to detect a difference in gingival enlargement of 5% at a $P < 0.05$ significance level.⁶³ The chi-square (χ^2) test and the Fisher's exact test were used to compare data in nifedipine-treated patients and controls. The influence of different factors such as age, gender, GI, PI, and other patient characteristics was assessed, exploring their associations with gingival enlargement in either treated or non-treated patients. A multiple logistic regression analysis was used to assess the risk associated with treatment (odds ratio [OR]) taking into account the above factors. The kappa index was calculated to assess the degree of concordance between the GO and MB indices.

RESULTS

The total study population was 212: 65 nifedipine-treated subjects and 147 controls. Demographic characteristics are shown in Table 1. The distribution by gender was similar in both groups. Nifedipine-treated patients were older than controls (61.5 years versus 50.5 years, $P < 0.0001$). Bruxism was slightly more prevalent in nifedipine-treated patients than in controls (30.8% versus 18.4%, $P = 0.0450$). Tobacco smoking was less prevalent in the nifedipine-treated group (6.2% versus 11.6%, $P = 0.0352$).

The prevalence of all clinical measurements was significantly higher in nifedipine-treated patients than in controls (Table 2): GO index = 1, 33.8% versus 4.1%, $P < 0.0001$; MB index = 1, 50.8% versus 7.5%, $P < 0.0001$; GI >1.5 , 49.2% versus 32.7%, $P = 0.0217$; PI >2.5 , 75.4% versus 56.5%, $P = 0.0088$; mean PD >3 mm, 40% versus 8.8%, $P < 0.0001$.

Table 1.
Patient Demographic Characteristics

Characteristic	Nifedipine-Treated (n = 65)		Controls (n = 147)		P Value
	N	%	N	%	
Male/female	23/42	65/35	69/78	53/47	NS
Mean age, years (SD)	61.5 (8.5)		50.5 (15.7)		<0.0001
Age					<0.0001*
18-28	0	0.0	18	12.2	
29-45	1	1.5	29	19.7	
46-62	34	52.3	66	45.0	
63-80	30	46.2	34	23.1	
Smokers (>20 cigarettes/day)	4	6.2	17	11.6	0.0352
Bruxism	20	30.8	27	18.4	0.0450
Oral breathing pattern	6	9.2	24	16.3	NS
Dental prosthesis	19	29.2	47	32.0	NS

* Chi-square analysis collapsing categories: age = ≤45, >45.

Table 2.
Periodontal Evaluation of Control and Nifedipine-Treated Patients

Criteria	Nifedipine-Treated (n = 65)		Controls (n = 147)		P Value
	N	%	N	%	
Vertical gingival enlargement (GO index)					<0.0001*
0	43	66.2	141	95.9	
1	22	33.8	6	4.1	
2	0	0.0	0	0.0	
3	0	0.0	0	0.0	
Horizontal nodularity-papilla enlargement (MB index)					<0.0001*
0	32	49.2	136	92.5	
1	33	50.8	11	7.5	
2	0	0.0	0	0.0	
Gingival index (GI)					0.0217*
≤1.5	33	50.8	99	67.3	
>1.5	32	49.2	48	32.7	
Plaque index (PI)					0.0088*
≤2.5	16	24.6	64	43.5	
>2.5	49	75.4	83	56.5	
Probing depth					<0.0001*
≤3	39	60.0	134	91.2	
>3	26	40.0	13	8.8	

* Chi-square analysis collapsing categories: GO = 0, >0; MB = 0, >0; GI = ≤1.5, >1.5; PI = ≤2.5, >2.5; PD = ≤3, >3.

About 50% of patients in the nifedipine group had been taking the drug for more than 2 years, with 85% of the patients at doses between 30 to 60 mg/day. According to the level of exposure (total accumulated dose) to nifedipine, patients were divided in 2 groups: high exposure = 10 to 32 g and low exposure = 2 to 9.9 g (Table 3). In the high exposure group, a higher prevalence of gingival enlargement (for both GO and MB indices) was shown, but the differences were not statistically significant.

The bivariate analysis in both groups with respect to quantitative (GI, PI, PD) and qualitative variables (gender, age, smoking, bruxism, oral breathing pattern, and the presence of dental prosthesis) only showed a significant association between gingival enlargement (GO and MB indices) and GI ($P < 0.001$).

Results of multivariate analysis showed that the risk (odds ratio) for gingival enlargement associated with nifedipine treatment was 10.6 (3.8 to 29.1) for the GO index and 14.4 (6 to 34.6) for the MB index. When the odds ratios were adjusted for GI values, the risk of gingival enlargement was 9.6 (3.3 to 28.1) for the GO index and 9.7 (3.9 to 23.3) for the MB index. In the subset of high nifedipine exposure patients, the corresponding figures were 17.4 (5.3 to 56.3) for the GO index, 23.6 (7.7 to 72.3) for the MB index, and 9.0 (2.5 to 32.7) and 9.4 (3 to 28.9) when adjusted for GI (Table 4).

The level of concordance between GO and MB indices in the control group and in nifedipine-treated patients showed a kappa value of 0.689 and 0.642, respectively.

DISCUSSION

In a sample of the general population (control group), we found a prevalence of gingival enlargement of 4.1% (GO index) and 7.5% (MB index). These findings are similar to those reported by Steele et al.²⁷ By contrast, patients treated with nifedipine showed a prevalence of gingival enlargement of 34% and 51% according to the GO and MB indices, respectively. Data reported by others vary between 24% to

Table 3.
Periodontal Evaluations According to Length of Nifedipine Use

Criteria	Low Exposure: Accumulated Dose 2 to 9.9 g (n = 32)		High Exposure Accumulated Dose 10 to 32 g (n = 33)		P Value
	N	%	N	%	
GO index					NS*
0	24	75.0	19	57.6	
>0	8	25.0	14	42.4	
MB index					NS*
0	19	59.4	13	39.4	
>0	13	40.6	20	60.2	
Gingival index (GI)					NS*
≤1.5	12	37.5	15	45.4	
>1.5	20	62.5	18	54.6	
Plaque index (PI)					NS*
≤2.5	9	28.1	7	21.2	
>2.5	23	71.9	26	78.8	

* Chi-square analysis collapsing categories: GO = 0, >0; MB = 0, >0; GI = ≤1.5, >1.5; PI = ≤2.5, >2.5.

Table 4.
Risk of Gingival Enlargement OR

	Nifedipine		Nifedipine High Exposure		Nifedipine Low Exposure	
	GO	MB	GO	MB	GO	MB
	11.8	13.1	17.3	19	7.8	8.4
	(4.5-30.6)	(6-28.3)	(5.9-50.8)	(7.4-48.5)	(2.4-24.8)	(3.3-21.7)
	10.6	14.4	17.4	23.6	7.5	9.9
	(3.8-29.1)	(6-34.6)	(5.3-56.3)	(7.7-72.3)	(2-27.1)	(3.2-30.5)
GI - Adjusted	9.6	9.7	9	9.4	29.1	14.7
	(3.3-28.1)	(3.9-23.3)	(2.5-32.7)	(3-28.9)	(3.5-240)	(4.2-50.8)

43%.^{27,56} In our study, like others, lesions predominated and were more severe in the anterior and inferior teeth, especially vestibular. They also have been described at other sites including edentulous areas.^{19,20,64,65}

With regard to the degree of gingival enlargement in association with cumulative doses of nifedipine, a greater prevalence of gingival overgrowth was found for both indices (GO and MB) in the high exposure group of patients, but the differences were not significant. Other studies have also failed to find a relationship between gingival enlargement and dose of the cal-

cium antagonist and reported only that gingival overgrowth usually develops after 6 months of treatment.^{17,22,53,62,66,67} By contrast, some authors have stated that gingival overgrowth is dose dependent.^{68,69}

The gingival index differed between groups and was associated with gingival enlargement. We did not find differences in the plaque index between groups. Other authors have found a relationship of gingival overgrowth with both the gingival and plaque indices.^{17,22,35,67} Because drug-induced gingival enlargement very often involves a combination of the effects of the drug and the inflammatory status, it is difficult to determine the contribution of each. In our study, the odds ratios (for all nifedipine-treated patients and for the subset of high nifedipine exposure) associated with inflammatory status (GI) were lower for both indices (GO and MB) than the OR associated with the effect of nifedipine. However, the ORs associated with the effect of nifedipine were higher in the subset of high nifedipine exposure than in the whole group of nifedipine-treated patients, while there were no differences with respect to the effect of the inflammatory status (GI) (Table 4). All together, this would suggest a possible dose/exposure-response associated with nifedipine treatment. To our knowledge, the risk of gingival enlargement attributable to nifedipine treatment has not been previously documented.⁷⁰

Gingival overgrowth, which normally begins in the region of the interdental papilla, may favor the appearance of clinical symptoms and signs that include pain, bleeding and friability of the tissue, abnormal movement of the teeth, changes of appearance, phonetics, and occlusion, as well as the appearance of dental caries and other periodontal disorders.^{2,71} Surprisingly, for most of our patients with gingival enlargement, the condition was not noticed by either themselves or their clinicians, probably due to the fact that the gingival overgrowth was minimal (Table 2). Although usually there are no differences in the clinical characteristics

of gingival overgrowth induced by different drugs, we previously reported a more severe degree of gingival enlargement in patients treated with phenytoin.⁷²

The majority of indices used to quantify gingival overgrowth are unreliable because of their subjectivity or reproducibility difficulties.^{73,74} The present study used 2 indices that recorded vertical (GO) and horizontal (MB) gingival enlargement. The MB index evaluates the nodularity papilla enlargement and results from a modification of the index.^{57,58,70,72} The Seymour index uses an indirect method based on a 3-dimensional study of plaster casts and evaluates only

5 gingival units of the upper and lower anterior segments (from the midpoint of the right canine to the midpoint of the left canine). The index scores for each gingival unit are the result of the addition of gingival thickening (graded 0 to 2) and gingival encroachment (graded 0 to 3).⁵⁷ The modification introduced in the present study (GO and MB index) offers the following advantages: 1) it permits the direct clinical recording of gingival enlargement (MB index) in the area of the interdental papilla, the region in which the dysmorphism first expresses itself, for the whole dentition, and 2) it records the 2 components of gingival enlargement at any site, differentiating between the degree of horizontal (MB index) and vertical (GO index) gingival enlargement.⁵⁸ There were differences in the prevalence of gingival enlargement according to the index used (vertical versus horizontal registers). This has also been described in other studies.^{17,29} One possible explanation is that the MB index detects gingival overgrowth at earlier stages of enlargement than the GO index. The concordance between both measurements, however, confirmed their reliability.

In our study, we found a significant difference between both groups in relation to age and tobacco smoking, which could be explained by the nature of cardiovascular diseases that affects older individuals and by the fact that most of the patients had quit smoking. Other authors consider that neither age nor gender appears to be a determinate factor of drug-induced gingival enlargement.^{19-21,53} A relationship between oral breathing patterns and gingival overgrowth was not observed in the present study, but it has been reported in patients treated with phenytoin.^{7,75}

It has been shown that nifedipine-induced gingival enlargement may be reduced or prevented by good plaque control, aimed at reducing gingival inflammation, and that in the most severe cases, resective periodontal surgery is used to eliminate excess tissue.⁷⁶⁻⁸⁰ Also, wherever possible, reducing the drug dose or replacing it with another agent should be considered.^{25,81} In our case, alternatives to nifedipine include the other dihydropyridines or non-dihydropyridine calcium antagonists, although verapamil^{24,25} and diltiazem^{29,30} also have been related to gingival enlargement. As an example, Westbrook et al.⁸² reported that replacing nifedipine by isradipine reduced the severity of gingival enlargement in 60% of patients. Metronidazole and azithromycin have been recently used to treat gingival enlargement induced by cyclosporin A, resulting in a reduction or even resolution of the overgrowth.⁸³⁻⁸⁶ It is unknown whether this effect is related to the antimicrobial action of these drugs or to other mechanisms.⁸³

Clinicians should be aware of the prevalence and risk of gingival overgrowth induced by nifedipine in order to implement preventive measures and estab-

lish an early diagnosis. Regular visits to a periodontist when this drug is used is highly advisable.

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Send reprint requests to: Dr. Carlos Mendieta, Periodontics Unit, Facultat d'Odontologia, Universitat de Barcelona, Feixa Llarga, s/n. E-08907-L'Hospitalet de Llobregat, Barcelona, Spain. Fax: 34-93-3304767; e-mail: mendieta@bellvitge.bvg.ub.es

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