

## **Nifedipine-induced gingival hyperplasia – electron microscopic study**

T. DZHEMILEVA<sup>1</sup>, I. YANCHEV<sup>2</sup>, T. BOLYAROVA<sup>1</sup>

<sup>1</sup>*Department of Periodontology and Diseases of Oral Mucosa, Faculty of Stomatology, University of Medicine, Sofia, Bulgaria*

<sup>2</sup>*Institute of Experimental Pathology and Parasitology, Bulgarian Academy of Sciences*

### **Abstract**

One of the basic means for treatment of the cardiovascular diseases are the calcium antagonists. Their less known undesired effect is the gingival hyperplasia.

This study is aiming at enlightening of some pathogenetic mechanisms of the gingival hyperplasia, induced by calcium antagonists, through characterization of the changes in the epithelium and in the underlying connective tissue.

Subject of the study were hyperplastic gingival papillae with globular overgrowth of 3<sup>rd</sup> degree plaque index = 2 after S i l n e s s , L ö e (1964) and gingival index = 2 after L ö e , S i l n e s s (1963). They were found in 8 patients (6 women and 2 men) of average age 61 (56 - 63) with heart and vascular diseases, treated with nifedipine in the course of at least 9 months with no data about other gingival hyperplasia-inducing medications.

Electron microscopy. The epithelium is noticeably thickened and with a strongly expressed acanthosis and a deep penetration into the connective tissue. In the connective tissue abundant and frequent extravasates near dilated blood vessels with strongly thinned and even broken walls can be seen as well as degraded collagen fibrils, numerous cells of the immune system (granulocytes, lymphocytes, Langerhans cells). Such cells are sometimes observed also in the dilated intercellular epithelial spaces.

The electron microscope findings give the grounds for discussion of the effect of two groups of factors: system ones, generated by the daily therapy of cardio-vascular diseases with calcium antagonists (nifedipine), and local factors, related to the dental plaque and its metabolic products (enzymes, toxins and allergens) and to plaque-induced inflammation.

### **Introduction**

The cardiovascular and brain-vascular diseases - arterial hypertension, cardiac arrhythmia, ischaemic cardiac disease, spasm of cerebral arteries etc. have strong health and social after-effects (N a c h e v, 2003). They are the main reason of the sudden death and of over 60% of the general death-rate in Bulgaria (N a c h e v, 2002).

In the medical treatment of the arterial hypertension basically calcium antagonists, ACE-inhibitors, beta-blockers, diuretics and others are used. The calcium antagonists (blockers of calcium canals), used for control of arterial pressure as a monotherapy, exceed the effect of any of the mentioned group of medicaments (JNC VI, 1997). They are used in the treatment of over 500 millions inhabitants of our planet (N a c h e v,

2003), over 1 700 000 Bulgarians, nearly 60 000 of them living in Sofia, with reimbursement of over 8 000 000 levs per year.

Those data are explicit, concerning the great number of patients having diseases treated with calcium antagonists, as well as with respect to the necessary expenditures for the purpose. These diseases and their control are indeed a great social problem. Its importance increases with the aging of the population and on the background of the other accompanying senior diseases in Bulgaria.

Among the various undesired effects of the calcium antagonists the gingival hyperplasia is the less known side effect, although it does trouble the patients: it makes the mastication and speech more difficult, acts on the psychics and limits the social contacts.

In order to prove the role of some local cofactors in the appearance and progressing of the gingival hyperplasia we estimated with the aid of index systems the clinical picture, the gingival inflammation, the preliminary parodontal destruction etc.; we determined as well the composition of the complex subgingival micro-flora and characterized the histological picture.

The goal of the present study was to throw light upon some pathogenetic mechanisms of the gingival hyperplasia, induced by calcium antagonists, by characterizing the changes in the epithelium and in underlying connective tissue.

## Materials and Methods

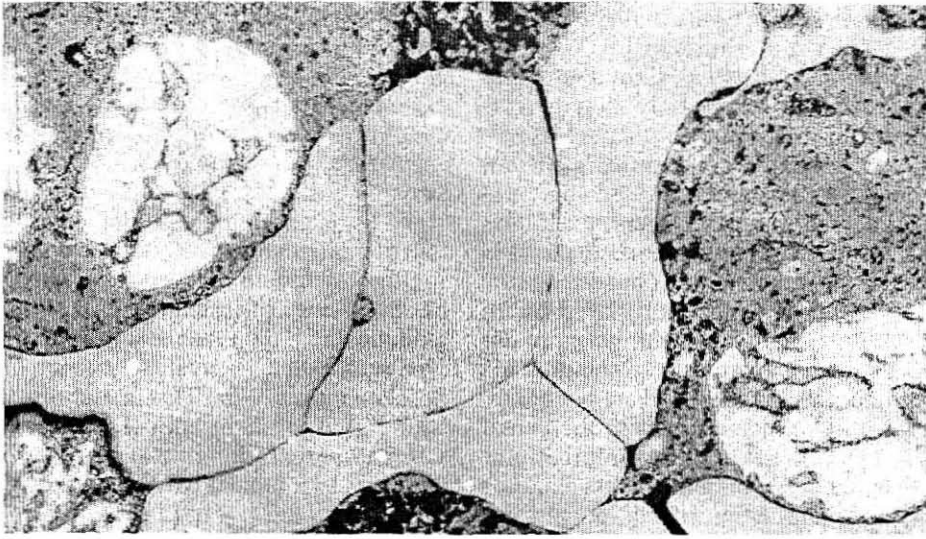
*Excision.* Subject of the study were hyperplastic gingival papillae with globular overgrowth of 3<sup>rd</sup> degree after, plaque index = 2 after Silness and Løe (1964) and gingival index = 2 after Løe and Silness (1963). They were found in 8 patients (6 women and 2 men) of average age 61 (56 - 63) with heart and vascular diseases, treated with nifedipine in the course of at least 9 months with no data about other gingival hyperplasia-inducing medicaments. The gingival papillae were excised in the course of

a planned gingivectomy under infiltrational anaesthesia with Ultracain DS (Hoechst) and vasoconstrictor epinephrin 1:200 000. Anaesthetic was not introduced intrapapillary in order not to break the structure of the papilla under study. The biopsic tissue was cut into small pieces with a sharp scalpel. They were oriented in such a way as to make possible to investigate oral and/or the sulcular part of the hyperplastic gingival papilla.

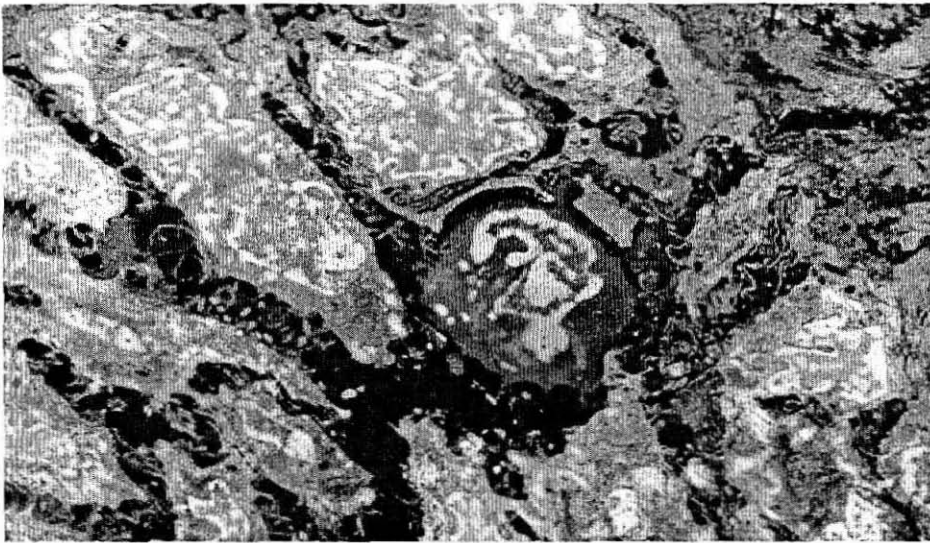
*Electron microscopical preparations.* Immediately after the excision the tissue was fixed in 4% glutaraldehyde solution and additionally in 2% solution of osmium tetroxide. After dehydration in an ascending alcohol series the material was embedded in Durcupan. The sections were made by ultramicrotome Reichert and then additionally contrasted with 1% water uranyl acetate solution and with plumbum citrate. For the observations an electron microscope JEM 1200 was used.

## Results and Discussion

Under the electron microscope dilated, sometimes broken blood vessels, numerous extravasates and collagen fibrils as well as the presence of the immune system cells (granulocytes, lymphocytes, Langerhans cells) in the gingival connective tissue can be observed (fig. 1). Sometimes such cells are seen in the dilated intercellular epithelial spaces (fig. 2). The immune system cells, described in our country in the gingiva of experimental gingivitis and in the hyperplastic gingiva as a result of nifedipine therapy, do not differ from the type of cells described by other authors as inflammatory cells, found in the underlying connective tissue. We observed these in the connective tissue, but in the dilated intercellular epithelial spaces they were found as well. In our opinion it would be more correct to define them as cells of the immune system, since these cells in cases of inflammation as well as in hyperplasia (and our data suggest an inflammation reaction in the hyperplastic gingiva) play a protective role. A comparison of these data



**Fig. 1. Hemorrhage in the gingival connective tissue. × 4000**



**Fig. 2. Granulocyte in the dilated intercellular spaces of the epithelium. × 5000**

with findings in studies of cyclosporine-induced gingival hyperplasia show that while in the case of cyclosporine cells of lymphocyte series prevail, in nifedipine therapy besides them there are granulocytes and Langerhans cells which are usually occasionally found.

The results of investigation of gingival papillae in experimental and spontaneous catarrhal inflammation in humans (Djemileva-Konova, 1976; Yanchev and Djemileva, 1990) show that the parakeratose layer of the gingival epithelium becomes thinner, acanthosis is not observed,

and the proliferation of the underlying layers in lateral direction causes epithelial bends inward, relatively shallow, but broad, with participation of not only the germinative layer. In drug-induced gingival hyperplasia, on the contrary, the epithelium is noticeably thickened, and with a strongly expressed acanthosis and a deep penetration into the connective tissue. It is quite possible all these findings to be caused by the nifedipine action, all the more that they are found also in other drug- and hormone-induced gingival hyperplasias (including after our unpublished data) and are not the result of an independent effect of the dental plaque. The dilation of the intercellular spaces in the deep epithelial layers could be attributed to the action of microorganisms and their products (enzymes, toxins and allergens), which brings to an increased flux of gingival fluid and swelling of the tissue (Djemileva-Konova, 1976, Djemileva, 1988). Migration of immune cells is observed also in a healthy gingiva, caused most probably by the permanent contact of the microorganisms from the dental plaque (and their chemotactic potential) with the gingiva, but to a very slight degree, in the framework of the physiological (Djemileva-Konova, 1976). Their presence at an expressed higher frequency in experimental human gingivitis could be the result of gingival reaction to the bacterial action. It could be suggested that in drug-induced gingival hyperplasia immune mechanisms could be the result of a high plaque index respectively of the great number of more virulent microorganisms (the ecosystem of the formed deep parodontal pockets and pseudopockets allows the development of anaerobic microorganisms near the gingival). But they could be due also to the still unclear action of nifedipine and other calcium antagonists. The connective tissue, lying immediately under the basal lamina, is rich in blood vessels in normal conditions too. In experimental gingivitis in humans under the action of dental plaque microorganisms the vacuolization increases, but hemorrhages are observed very rarely. Be-

sides, clinically the bleeding from the gingiva in experimental gingivitis is provoked and not spontaneous (Djemileva, 1999, Djemileva-Konova, 1976). On the contrary, the abundant and frequent extravasates along the dilated vessels (with strongly thinned and even broken walls) could be taken for a morphological substratum of a spontaneous bleeding, accompanying the nifedipine-induced gingival hyperplasia. Besides, the calcium antagonists have a dilating action on the vessels of periphery type such as the gingival ones which has to be taken into account. This is supported also by the cited before in a pilot Djemileva's investigation sensation of a strong tension in the gums by a patient half an hour after taking nifedipine (Djemileva, 1993).

## Conclusion

The observed electron microscope picture in study of the nifedipine-induced gingival hyperplasia gives the grounds for discussion of the effect of two groups of factors: system ones, generated by the daily therapy of cardio-vascular diseases with calcium antagonists (nifedipine), and local factors, related to the dental plaque and its metabolic products (enzymes, toxins and allergens) and to plaque-induced inflammation.

## References

- Djemileva, T. Periodontal diseases. Acer, Sofia, 1999 (In Bulgarian).
- Djemileva-Konova, T. Clinical-experimental data on the effect of dental plaque on the gingiva. PhD Thesis, Stom. Faculty, Sofia, 1976, p. 250 (In Bulgarian).
- Djemileva, T. Nifedipine-induced hyperplasia of the gingiva. – A pilot study. Quintessence Dent., Year II, 5, 1993, 1520 (In Bulgarian).
- Djemileva, T. Some pathogenetic mechanisms of the gingival and parodontal diseases. In "Complex treatment of parodontal diseases". Ed. E Atanasova. Med. And Sports, 1988, 40-52 (In Bulgarian).
- Nachev, C. Criteria for the choice of a given calcium antagonist. CXXII BNAM symposium, BAS, BLH, 2003, Sofia, lecture.

- N a c h e v, C. New ideas in the control of arterial hypertension. CI BNAM symposium, BAS, BLH., 2002, Sofia, lecture.
- Y a n c h e v I., T. D j e m i l e v a. Ultrastructural morphometric studies of the epithelium of healthy and chronically inflamed gingiva. I. Desmosomal contacts. – General and Comparative Pathology, BAS, **28**, 1990, 10-18 (In Bulgarian).
- L ö e , H., J. S i l n e s s. Periodontal disease in pregnancy. I. Prevalence and severity. – Acta Odont. Scand., **21**, 1963, 533-551.
- S i l n e s s , J., H. L ö e. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. – Acta Odont. Scand., **22**, 1964, 112-135.

Received 31 March 2004