

# Measurement of Interleukine-6 and C-reactive Protein in Serum of Patients on Amlodipine Therapy

**Nahla O. Tawfik**  
BDS, MSc, PhD. (Lect.)

**Rana Kh. Atarbashe**  
BDS, MSc (Asst. Lect.)

**Dental Basic Science Department**  
College of Dentistry, University of Mosul

**Dental Basic Science Department**  
College of Dentistry, University of Mosul

## الخلاصة

**الاهداف:** تهدف الدراسة إلى المقارنة بين المؤشرات المناعية (الانترلوكين ٦) ، البروتين التفاعلي (سي) في المصل) للمرضى الذين يعانون من أمراض القلب المزمنة المعالجين بالاملوديبين ومجموعة السيطرة لتحديد تأثير الدواء على هذه المؤشرات . **المواد و طرائق العمل:** أجريت هذه الدراسة على (٤٢) مريضاً (٢٧) مريضاً يعانون من أمراض الاوعية الدموية (ارتفاع ضغط الدم) كانت تستخدم العلاج لفترة طويلة وكانت أعمارهم تتراوح بين (٣٤-٧٠) سنة وتم اعتماد (١٥) مريضاً من الفئات العمرية نفسها للمشاركة في هذه الدراسة كمجموعة ضابطة . لقد تم قياس تضخم اللثة و بعض المتغيرات المناعية (الانترلوكين ٦) ، البروتين التفاعلي (سي) في المصل . **النتائج:** لقد أظهرت ألتائج بأن الاملوديبين سبب تضخم في اللثة وهناك فرق معنوي في حدوث تضخم اللثة و المتغيرات المناعية مابين مجموعة الدراسة والمجموعة الضابطة وكذلك اظهرت الدراسة زيادة في مستوى المتغيرات المناعية مابين المرضى الذين يعانون من ذلك التأثير المرضى الذين لم يظهر عندهم التأثير كما لوحظ ارتباط إيجابي غير معنوي مابين الانترلوكين (٦) والبروتين (سي) . **الاستنتاجات:** نستنتج من هذه الدراسة إن دواء الاملوديبين تسبب في ظهور تضخم في اللثة وهناك فرق معنوي في حدوث تضخم اللثة و المتغيرات المناعية مابين مجموعة الدراسة والمجموعة الضابطة وكذلك اظهرت الدراسة زيادة في مستوى المتغيرات المناعية مابين المرضى الذين يعانون من ذلك التأثير المرضى الذين لم يظهر عندهم التأثير.

## ABSTRACT

**Aims:** The aims of this study were to compare between the immunological parameters (serum interleukin-6 (IL-6) and c-reactive protein (CRP) of patients suffering from chronic cardiovascular diseases with amlodipine therapy and control group to determine the effects of the drug on those parameters. **Materials and Methods:** The study was conducted on 42 subjects, 27 patients already on amlodipine therapy, aged ranged between 34-75 years. Fifteen healthy subjects of the same age group participated in this study as a control group. The screening by medical history, examination (gingival enlargement scores) and blood samples to measure serum IL-6 and CRP was done once at base line visit. **Results:** The results obtained showed that amlodipine trtherapy group had higher gingival overgrowth scores and immunological parameters than control group with significant difference at ( $p < 0.05$ ), also there was positive correlation but not significant between CRP in serum and IL-6 ( $p < 0.05$ ). **Conclusion:** The study concluded that there is a significant difference in the GO score and immunological parameters in amlodipine therapy group as compared with healthy group.

**Key words:** amlodipine, gingival overgrowth, interleukin-6(IL-6), C-reactive protein (CRP).

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## INTRODUCTION

Amlodipine is a dihydropyridine calcium channel blocker (CCB), used for treatment of hypertension and angina pectoris (stable and Prinzmetal's angina<sup>(1,2)</sup>). It is given orally in a dose of (2.5-10 mg once daily). It is well absorbed following oral administration, it exhibits very slow kinetics of onset and offset of blockade; with peak blood concentration occurring after 6 to 12 hours. It has a prolonged terminal elimination half life of 30 to 50 hours and extensively metabolized in the liver.<sup>(1,2)</sup>

Gingival overgrowth (GO) is one of the side effects which had been reported<sup>(1,2)</sup>.

Drugs associated with GO can be broadly divided into three categories; Anticonvulsants, CCBs, and immunosuppressant<sup>(3)</sup>.

It is hypothesized that non inflamed gingival fibroblasts are less active or even quiescent and do not respond to circulating drugs. While the fibroblasts within inflamed tissue are in an active state, as a result of inflammatory mediators and endogenous growth factors<sup>(4)</sup>.

Gauldie et al.,<sup>(5)</sup> founded that IL-6 is a potent inducer of the acute-phase reactant including CRP, a response of the organism to several pathological conditions, which is believed to constitute a rapid and general

defense mechanism against injury prior to the onset of the immune response. C-Reactive protein is an abnormal specific glycoprotein which is primarily derived via IL-6 dependent hepatic biosynthesis<sup>(6)</sup> and is secreted in increased amounts within six hours of an acute inflammatory stimulus<sup>(7)</sup>.

The aims of this study were to compare between the immunological parameters of patients with amlodipine therapy and control group to determine the effects of the drug on those parameters.

**MATERIALS and METHODS**

This study was conducted at outpatient clinic in Ibn Sina Teaching Hospital in Mosul City. The study includes patients already on amlodipine therapy (more than 12 weeks of therapy). This group consisted of 27 patients accepted to participate in this study, their age ranged between (34-75) years and mean age was (53.33±10.674) years. All patients had professional diagnosis for which they had prescribed the drug.

Any patients taking anticonvulsants, immunosuppressants, or any other medications known to produce gingival enlargement were excluded from the study. Female patients

enrolled in this study were not pregnant, lactating nor taking oral contraceptive pills.

The screening by medical history, gingival enlargement examined by vision if there is enlargement involve interdental papilla, marginal gingival or enlargement covers three quarters or more of the crown<sup>(8)</sup> and blood samples was done once at base line visit.

The determination of IL-6 in human serum was done using Enzyme immunoassay Kit (IMMUNOTECH, France) and for C-reactive protein was done using high sensitivity CRP enzyme immunoassay kit (Biocheck, USA).

Statistical analysis of data were conducted using SPSS 17 for windows software. A p-value of ≤ 0.05 was considered statistically significant, the The t test was used for the analysis of data<sup>(12)</sup>. Pearson correlations were used to evaluate correlations between parametric variables.

**RESULTS**

Table (1) demonstrates that the mean values of IL-6, CRP in the amlodipine therapy group were significantly higher than control group.

Table (1): Comparison between amlodipine therapy group and control group

Parameters	Chronic group	Control group	p-value
	Mean ± SD	Mean ± SD	
GO score	0.560 ± 0.801	0.00 ± 0.00	0.008**
IL-6 pg/ml	524.1 ± 121.57	260.5 ± 152.8	0.000**
Serum CRP .mg/l	9.937 ± 1.3077	5.738 ± 2.394	0.000**

\*\* significant at the 0.01 level.

Table (2) shows that serum CRP was positively but not significantly correlated

with serum IL-6 .

Table (2): Correlation between IL-6 and CRP

Parameters	IL-6
Serum CRP Pearson correlation	0.164
p-value	0.299

**DISCUSSION**

There are higher GO in mlodipine therapy group than control group (Table (1)). Osterberg<sup>(9)</sup> reported that CCB causes significantly higher GO scores

Gingival enlargement can be observed after a few weeks or after a few years from the beginning of the treatment, being reversible after interruption of the drug that

is generating it, a fact that underlines the necessity of periodic, specialized examinations, because the real definition of GO is represented by the increase, with more than 1 mm of the inter-dental papilla<sup>(10,11)</sup>.

Inflammation of the gingival tissue from the bacterial plaque and the subsequent development of gingival crevicular fluid may allow sequestration of the amlodipine,

thus predisposing the tissue to a localized, toxic effect and to the development of GO<sup>(11)</sup>. Apoptosis is a process that acts in concert with mitosis to preserve cellular homeostasis or to facilitate tissue remodeling during development. It involves a cascade of biochemical steps, which require a rise in the level of intracellular calcium. Amlodipine was well known as a CCB and inhibits the calcium influx from extracellular fluid. Blockade of one or more steps in the cascade by amlodipine results in a decrease in apoptosis rate. This inhibition of apoptosis in the epithelium leads to cell accumulation, resulting in GO<sup>(12)</sup>.

When we are dealing with important tissue destruction and the presence of a periodontal pouch, there is a clear association with many markers of inflammation: high sensitivity CRP, homocysteine, fibrinogen, proinflammatory cytokines plasmatic concentration<sup>(13)</sup>. This inflammatory process represents the result of the interaction between pathological agents and the reactivity of the host<sup>(14)</sup>.

The highest prevalence of periodontal disease (PD) and cardiovascular disease (CVD) is encountered in middle and old age people. During the last years, CCB reached the first line of treatment, a level of evidence recommendation in treating coronary heart disease, the most fearful and most frequent expression of atherosclerosis<sup>(15)</sup>. So, the problem became more complicated: first to demonstrate a causal link between periodontal disease (PD) and cardiovascular disease (CVD) and, then, to find if CCB, although they have a beneficial effect in coronary heart disease, could have a deleterious effect on the periodontium<sup>(14,16)</sup>.

There is higher serum IL-6 in amlodipine therapy group than control group. These elevated inflammatory factors may increase inflammatory activity in atherosclerotic lesions and potentially increasing the risk for cardiovascular events<sup>(17)</sup>.

There is higher serum CRP level in amlodipine therapy group than control group (Table 1) with significant difference. Hirasaki et al.,<sup>(18)</sup> found that blood CRP level increased in patients with CVD, and that CVD is accompanied by oral infection such as periodontal disease compared to that in healthy patients. Megson et al.<sup>(19)</sup> reported CRP in the gingival crevicular fluid (GCF) appears to be of systemic origin, and therefore may be indicative of systemic inflammation from either a

periodontal infection or inflammatory disease elsewhere.

In the present study (Table 2), serum CRP is positively correlated with IL-6. Heinisch et al.,<sup>(20)</sup> reported that there is a positive correlation between IL-6 and CRP, but not with the other cytokines in patients with acute coronary syndromes were compared with patients with stable angina and with control volunteers. This study is in contrast to other studies which examined the inter-relationships of the different inflammatory markers in hypertension. For example, Bautista et al.,<sup>(21)</sup> examined the cross-sectional relationship between IL-6, TNF-a, and hsCRP and hypertension in a random sample of 196 healthy subjects and showed that after adjusting for other risk factors, IL-6 and TNF-a, high sensitivity CRP are not significantly associated with hypertension. Whilst this was a relatively small study and only include 79 hypertensive patients, it is the only study to date to specifically analyze the potentially confounding relationship between several inflammatory markers and hypertension.

## CONCLUSIONS

The study concluded there is a significant difference in the GO score and immunological parameters in chronic group as compared with healthy group.

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