EFFECT OF CALCIUM CHANNEL-BLOCKERS ON CLINICAL OUTCOMES OF IMPLANT RETAINED OVERDENTURE IN HYPERTENSIVE PATIENTS

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ABSTRACT

Purpose: Calcium channel-blocking agents are used extensively for the management of hypertension. Gingival overgrowth around natural teeth has been previously reported in the literature with patients taking calcium channel-blocking agents. There are limited scientific documentations illustrating its effects around dental implants. This study compared the effects of Calcium channel-blocking agents (Amlodipine) and angiotensin receptor blockers (Valsartan) on dental implants retaining overdentures in hypertensive patients clinically and radiographically after two years of function.

Materials and Methods: Twenty completely edentulous male hypertensive patients wearing mandibular overdentures retained by two implants **(3.6*12mm Dentium Two– piece (Ball type) dental implant, Dentium Implant System, Korea)** were included in this study, Patients were equally and randomly divided into two groups, Group (I) were managed by Amlodipine according to their physician to control the hypertension. Group (II) were managed by Valsartan according to their physician to control the hypertension. Each case was evaluated clinically concerning plaque index, gingival index, probing depth and implant stability by using OSSTELL ISQ and radiographically concerning marginal bone loss at baseline (overdenture insertion) and after 6, 12 and 24 months. Data were collected, tabulated and statistically analyzed using t-Student test.

Results: No statistical significant difference was found between the two groups (P≥0.05).

Conclusions: Based on the limitations of the present study and although no statistical difference was found between the effect of Amlodipine and Valsartan on dental implants under overdentures. Peridontium around implants in hypertensive patients managed by calcium channel blockers Amlodipine was affected more than that managed by Valsartan.

KEYWORDS: Dental implant, Hypertension, Overdenture.

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INTRODUCTION

Gingival overgrowth (enlargement, hyperplasia) is benign painless condition, characterized by massive enlargement of the interdental papillae, which can range from mild to extremely severe [1, 2]. It may be accompanied by swelling of the gingival margin and partial cover of the occlusal surface of teeth, causing aesthetic limitations and functional difficulties in swallowing, speaking, and mastication [1,3].

Gingival overgrowth (GO) is usually more conspicuous at labial/buccal surface of both upper and lower anterior teeth [4]. GO can be caused by various factors, such as inflammatory changes, mouth breathing, vitamin C deficiency, heredity, malignancies, hormonal alterations (seen in puberty and pregnancy), and the adverse effects associated with the systemic administration of certain drugs/ drug induced gingival overgrowth (DIGO) [4].

The prevalence of the DIGO is 3–20% compared to other gingival enlargements [4]. DIGO was firstly observed in patients who were taking phenytoin for epilepsy; with approximately 50% having GO [1, 5]. Currently, more than 20 drugs, mainly among anticonvulsants (e.g., phenytoin), immunosuppressants (e.g., cyclosporine A), and various calcium channel blockers (e.g., nifedipine, verapamil, and diltiazem), are associated with gingival enlargements [2, 6].

Hypertension is a crucial risk factor for cardiovascular diseases; the World Health Organization classifies hypertension as "a silent killer" and "a global public health crisis"[7, 8]. Hypertension was responsible for 45% of deaths due to coronary heart diseases and for 51% of deaths due to stroke. Mortality due to hypertension was reported as 9.4 million annually. Moreover, hypertension was the leading risk factor for death, followed by tobacco use and diabetes mellitus [9]. On the other hand, improvements in diagnosis and follow-up, the presence of numerous

options for antihypertensive medication, and an increased awareness and patient participation in treatment in this age of rapid communication are promising developments in the management of hypertension [10].

The joint guideline by the European Society of Hypertension and the European Society of Cardiology (the 2013 guideline on arterial hypertension) recommends five main drug groups [(diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs)] equally in monotherapy together with lifestyle changes, unless any compelling indication[11].

Valsartan, which is one of the first members of the ARBs group, has been used since 1996 in Europe and since 1997 in the United States of America. It can be combined with hydrochlorothiazide (HCTZ), amlodipine, and aliskiren. The efficacy and reliability of valsartan in hypertension, post-myocardial infarction, and heart failure have been revealed by large clinical trials [12, 13, 14].

Among calcium channel blockers, the dihydropyridines (e.g., nifedipine, felodipine, amlodipine, nitrendipine, nicardipine, and manidipine) tend to be more commonly associated with gingival enlargement [6].

Amlodipine is a third generation dihydropyridine calcium channel blocker that is frequently used in therapy of hypertension and angina pectoris. The prevalence of GO associated with amlodipine is reported to be 3.3%, which is significantly lower than that associated with nifedipine, ranging from 14 to 83% [15].

Complete edentulism affects the psychological, oral, general health and the quality of life. While many patients are satisfied with ordinary complete denture, others prefer implant-retained prostheses[16].

Complete maxillary and mandibular dentures have been used as a conventional treatment of

edentulous patients for longer than a century. Suitable complete maxillary dentures are usually well tolerated but many patients struggle to chew and swallow with the complete mandibular denture because it is too unstable. Previous studies have shown that a mandibular two-implant retained overdenture is superior to the conventional denture in terms of retention and stability[17]. Thereby, the two-implant assisted mandibular overdenture should be the first treatment option for mandibular edentulous patients[18].

Since the exact pathogenesis of amlodipine-induced gingival hyperplasia (AIGO) is not well-understood, it has become a serious challenge for the patients and dentists/ periodontists to diagnose and manage the cases effectively. The first line management of AIGO is withdrawal or substitution of amlodipine with the patient's physician consent. Unfortunately, in most of the cases, withdrawal is not possible and drug substitution alone is not enough to overcome the AIGO effects[1–4].

To date reports related to AIGO are very rare. Majority of available literature are case studies/ presentations which demonstrated that the AIGO occurs within 2-3 months of onset at a dose of 10 mg/day and rarely within first 6months of onset at a lower dose of 5 mg/day [2].

The aim of this study was to compare the effects of Calcium channel-blocking agents (Amlodipine) and angiotensin receptor blockers (Valsartan) on dental implants retaining mandibular overdenture in hypertensive patients clinically and radiographically after two years of function.

MATERIALS AND METHODS

This study was carried out on twenty completely edentulous, hypertensive male patients with a mean age of 50 years old.

Patient's general health was evaluated by taking full medical history. Laboratory investigations were done to ensure that all selected patients free from any other systemic diseases that might have an effect on implants osseointegration.

Patients were equally and randomly divided into two groups, Group (I) were managed by Amlodipine dose (5 mg) for a period of about 4 years according to their physician to control the hypertension. Group (II) were managed by Valsartan dose (60 mg) for a period of about 4 years according to their physician to control the hypertension.

Patients whose alcoholic, drug abuse, poor oral hygiene were excluded from this study.

Preoperative panoramic radiographs were taken for all patients to show the height of bone in the interforaminal area, the position of the mental foramen and inferior alveolar canal and to check for any clinically undetectable pathology or bone abnormality.

An informed consent approved by the ethics committee was signed by each patient after discussing the treatment plan with them and prior to initiation of treatment.

An acrylic complete denture was fabricated for each patient with the conventional technique using semi-anatomic acrylic teeth set on semi-adjustable articulator. For each patient, two mandibular immediately-loaded **(3.6*12mm Dentium Two–piece (Ball type) dental implant, Dentium Implant System, Korea)** were placed at the anterior region using flapless technique, with ball and socket attachments to retain mandibular overdenture (**Figure 1 and Figure 2**).

Twenty four hours after implant insertion; patients were recalled and each mandibular denture was relieved at implant locations, the metallic caps were placed on the implants making sure that the dentures were securely seated, the head of each implant was then covered with a small shim to prevent excess acrylic resin from engaging any undercuts. The relieved areas of the fitting surface

Fig. (1): Clinical picture showing the two implants inserted in the mandibular edentulous arch.
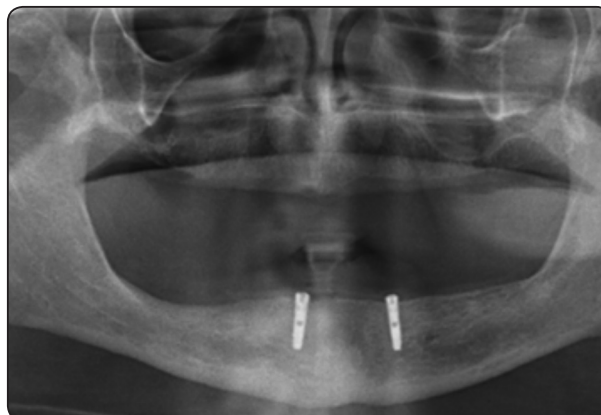

Fig. (2): Radiographic picture showing the two implants inserted in the mandibular edentulous arch.

of the denture were filled with autopolymerized acrylic resin, denture was seated and the patient was instructed to bite gently during setting of the acrylic resin. After the resin set, the denture was removed, the metallic caps inside the denture were examined, excess resin trimmed then inserted in patient mouth. Patients were then instructed on how to clean the denture and were asked to return on the following day to examine the denture bearing area and check for signs of tissue irritation. All patients were then scheduled for clinical and radiographic follow-up visits.

Patients were evaluated clinically and radiographically at baseline (complete denture insertion) and at 6, 12 and 24 months after complete denture insertion as follows:

Plaque index:

Plaque adherent to implants' surfaces was quantified at four sites, buccal, lingual, mesial and distal, using a mouth mirror and a plastic dental explorer after air drying of the implant and gingiva. Each of the four areas was scored on a 4-point scale of 0-3 as described by Mombelli and Lang[19]:

0 = No plaque is visible

1 = A film of plaque adhering to the free gingival margin and adjacent area of the implant, seen only after application of disclosing solution or by running the explorer across the implant surfaces.

2 = Moderate accumulation of soft deposits within the gingival pocket and on the gingival margin and/or adjacent to implant surface that can be seen by the naked eye.

3 = Abundance of soft matter within the gingival pocket and/or the gingival margin and adjacent implant surface.

The PI score was obtained by taking the average of the four plaque scores for the single implant.

Gingival index (GI)[20]:

The Gingival Index was created for the assessment of the gingival condition and records qualitative changes in the gingiva. It scores the marginal and interproximal tissues separately on the basis of 0 to 3. The criteria are:

0= Normal gingiva;

1= Mild inflammation – slight change in color and slight edema but no bleeding on probing;

2= Moderate inflammation – redness, edema and glazing, bleeding on probing;

3= Severe inflammation – marked redness and edema, ulceration with tendency to spontaneous bleeding.

The bleeding is assessed by probing gently along the wall of soft tissue of the gingival sulcus. The scores of the four areas of each implant can be summed and divided by four to give the GI for each implant. The GI of the individual can be obtained by adding the values of each implant surfaces and dividing by the number of each implant examined.

Probing depth [21]:

The probing depth was measured using a plastic periodontal probe **(CPITN, R.O.R. international, Copenhagen, Denmark)** around the surfaces of the implants in four areas (mid-buccal, mid-lingual, mid-mesial and mid-distal). The score was obtained by taking the average of the four scores for the single implant and. Measurements of probing depth ≤1 mm was recorded as 1mm, measurements exceeding 1mm, but less than 2 mm was recorded as 2 mm, and so on.

Stability test by using OSSTELL ISQ (Osstell Mentor Göteborg, Sweden) [22]:

➤ Smart peg was inserted inside the fixture and firmly screwed into it.

➤ The probe of Osstell was directed toward the smart peg without touching it (3mm away from it) in two directions bucco- lingual and mesio-distal.

➤ The average of two readings was calculated .

➤ Values less than 50 ISQ have a higher risk of failure. An increase in ISQ value during long-term examination implies that the implant became more stable [23]. Reports indicate that ISQ values are proportional to the extent of bone formation [24].

➤ Reading above 50 ISQ indicate stable implants **(Figure 3).**

Periapical and Panoramic radiographs[25]:

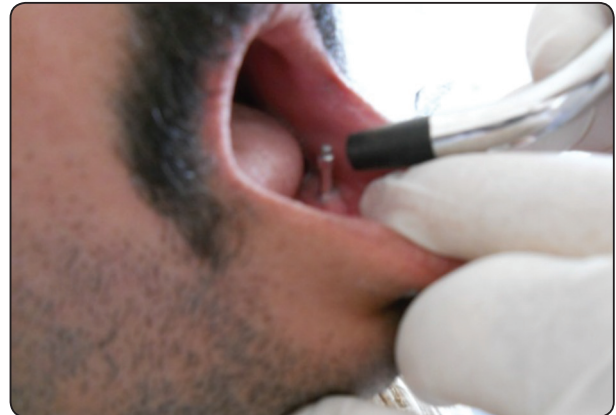Periapical and Panoramic X-ray films were used to measure the marginal bone loss around the im-

Fig. (3): Stability meter

plants. The long cone paralleling technique using the Rinn XCP instrument **(Rinn Co. Dentsply division, York, PA, USA)** was used. It included the use of standardized periapical radiographs to detect changes in alveolar bone surrounding the implants during the follow-up period. The standardized periapical radiographs were taken by the Xerograph Coping Process holder with a personalized bite registration record, made from putty rubber base impression material for extension cone (35 cm) paralleling technique. Every X-ray film was inserted into a slot in the bite-block. To ensure accurate repositioning of the film every time the radiograph was taken, the putty rubber base impression material **(Express XT VPS, 3M ESPE AG, Germany)** was folded around the bite-block, then a bite registration was obtained for each film in closed mouth position, the putty bite-block with the occlusal registration was kept aside for the follow-up recall visits. Repeatable standardized periapical radiographs were made for each implant to measure the mesial and distal bone heights. The measurements were made from the base of the implant to the most coronal point of bone adjacent to the implant surface.

All radiographs were exposed using ultra speed periapical film **(Kodak, Paris, France)** with X-ray grid and X- ray unit set at 70 KV and 10 mA. With similar exposure times, the radiographs were devel-

oped under standardized condition using automatic process. The scanning settings were adjusted and noted down in order to be used each time with all the radiographs before each scan, 2600 DPI (dot per inch) high quality resolution, 100% (1:1) scaling, fixed brightness and contrast setting, and no filter or other modifications were selected. The images were displayed on a 17 inches View sonic (3) colored monitor **(1024 x 768 DPI)**. The digital image was then saved in an uncompressed format on the patient file. The stored images of each patient were then interpreted at the end of the follow-up period.

The marginal bone-level measurements were made from the reference point to the lowest observed point of contact of the marginal bone with the fixture. The reference point for the fixture was the fixture–abutment interface. The distance was measured to the nearest 0.01 mm. These measurements were done using an analysis software program **(Adobe Photoshop, Adobe Systems Incorporated, San Jose, CA, USA)**. The actual implant length served as a standard to calculate the bone height, calculations were made according to the following formula:

$$CBL = IL*BR/MIL$$

Where **CBL** is the calculated bone resorption, **IL**: Actual implant length, **BR**: measured bone resorption (mean mesial and distal) and **MIL**: measured implant length.

Data analysis:

All clinical and radiographic data were tabulated for each individual and group. Summary statistics (mean, standard deviation) were calculated and also tabulated; data were statistically analyzed using t-Student test.

RESULTS

Plaque Index:

Figure (4) shows the mean plaque index values at different periods of follow up and Table (1) lists

the results of the t-Student test analysis for plaque index over time. On the initial examination after prosthesis insertion, mean±standard deviation (SD) of plaque index scores of group I patients was (4.54±0.37), while mean±standard deviation (SD) of plaque index scores of group II patients was (4.42±0.33). During the follow-up period there was a non-significant statistical decrease of the plaque index ($P > 0.05$) between the two groups.

Gingival Index:

Figure (5) shows the mean gingival index values at different periods of follow up and Table (2) lists the results of the t-Student test analysis for gingival index over time. On the initial examination after prosthesis insertion, mean±standard deviation (SD) of gingival index scores of group I patients was (6.01±0.26), while mean±standard deviation (SD) of gingival index scores of group II patients was (5.99±0.21). During the follow-up period there was a non-significant statistical increase of the gingival index ($P > 0.05$) between the two groups.

Probing Depth:

Figure (6) shows the mean probing depth values at different periods of follow up and Table (3) lists the results of the t-Student test analysis for probing depth over time. On the initial examination after prosthesis insertion, mean±standard deviation (SD) of probing depth scores of group I and group II patients was (1±0). During the follow-up period there was a non-significant statistical increase of the probing depth ($P > 0.05$) between the two groups.

Stability Test (Osstell ISQ):

Figure (7) shows the stability test values (Osstell ISQ) at different periods of follow up and Table (4) lists the results of the t-Student test analysis for stability test (Osstell ISQ) over time. On the initial examination after prosthesis insertion, mean±standard deviation (SD) of stability test scores (Osstell ISQ) of group I patients was

(55.625 ±4.428), while mean±standard deviation (SD) of stability test scores (Osstell ISQ) of group II patients was (56.025 ±3.206). During the follow-up period there was a non-significant statistical increase of the stability test values (Osstell ISQ) (P > 0.05) between the two groups.

Marginal bone loss:

Figure (8) shows the mean marginal bone loss values at different periods of follow up and

Table (5) lists the results of the t-Student test analysis for marginal bone loss over time. On the initial examination after prosthesis insertion, mean±standard deviation (SD) of marginal bone loss scores of group I patients was (0.91±0.32), while mean±standard deviation (SD) of marginal bone loss scores of group II patients was (0.82±0.28). During the follow-up period there was a non-significant statistical increase of the marginal bone loss scores (P > 0.05) between the two groups.

TABLE (1): Comparison of plaque index at different follow up periods.

Plaque Index	Group I			Group II			T-test	
	Mean	±	SD	Mean	±	SD	t	P-value
Insertion	4.54	±	0.37	4.42	±	0.33	1.63	0.413
After 6 Months	4.24	±	0.35	4.19	±	0.31	1.43	0.368
After 12 Months	3.98	±	0.34	3.88	±	0.29	1.67	0.423
After 24 Months	3.77	±	0.27	3.66	±	0.25	1.35	0.493

TABLE (2): Comparison of gingival index at different follow up periods.

Gingival index	Group I			Group II			T-test	
	Mean	±	SD	Mean	±	SD	t	P-value
Insertion	6.01	±	0.26	5.99	±	0.21	1.66	0.439
After 6Months	6.06	±	0.32	6.04	±	0.29	1.82	0.573
After 12Months	6.11	±	0.35	6.09	±	0.31	1.74	0.546
After 24Months	6.13	±	0.42	6.11	±	0.39	1.78	0.483

TABLE (3): Comparison of probing depth at different follow up periods.

Probing Depth	Group I			Group II			T-test	
	Mean	±	SD	Mean	±	SD	t	P-value
Insertion	1	±	0	1	±	0	0	1
After 6Months	1.37	±	0.65	1.29	±	0.55	1.88	0.683
After 12Months	1.79	±	0.68	1.66	±	0.57	1.64	0.389
After 24Months	1.87	±	0.87	1.71	±	0.64	1.56	0.431

TABLE (4): Comparison of implant stability at different follow up periods.

Osstell (ISQ)	Group I			Group II			T-test	
	Mean	±	SD	Mean	±	SD	t	P-value
Insertion	55.625	±	4.428	56.025	±	3.206	0.168	0.869
After 6 Months	57.75	±	3.238	58	±	3.424	0.072	0.943
After 12 Months	58.075	±	6.442	58.975	±	5.223	0.231	0.82
After 24 Months	60.1	±	2.768	60.2	±	3.4	0.343	0.735

TABLE (5): Comparison of marginal bone loss at different follow up periods.

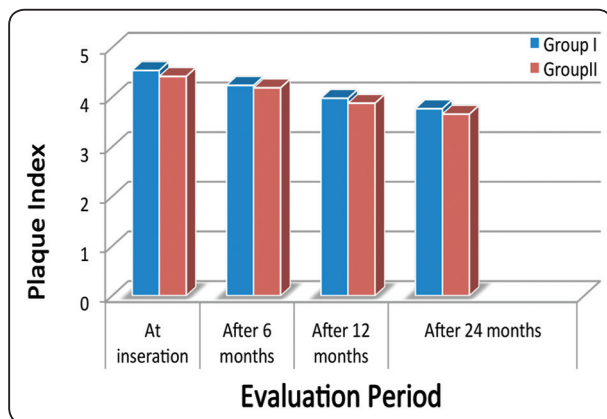| Marginal bone loss	Group I			Group II			T-test	
	Mean	±	SD	Mean	±	SD	t	P-value
Insertion	0.91	±	0.32	0.82	±	0.28	1.64	0.375
After 6 Months	1.28	±	0.37	1.17	±	0.32	1.85	0.259
After 12 Months	1.59	±	0.49	1.46	±	0.39	1.52	0.376
After 24 Months	1.74	±	0.57	1.61	±	0.45	1.77	0.383

Fig. (4): Distribution of mean value of plaque index between the two groups at different follow up periods.
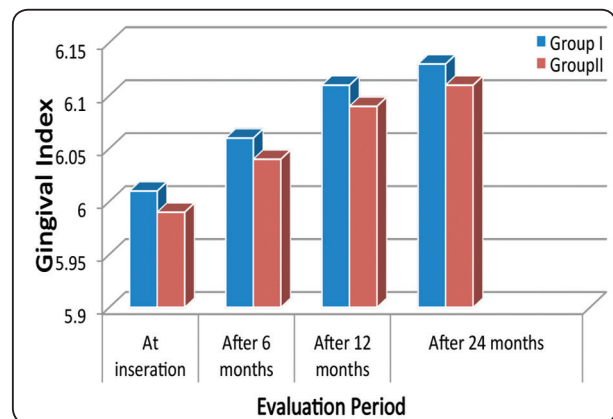

Fig. (5): Distribution of mean value of gingival index between the two groups at different follow up periods.
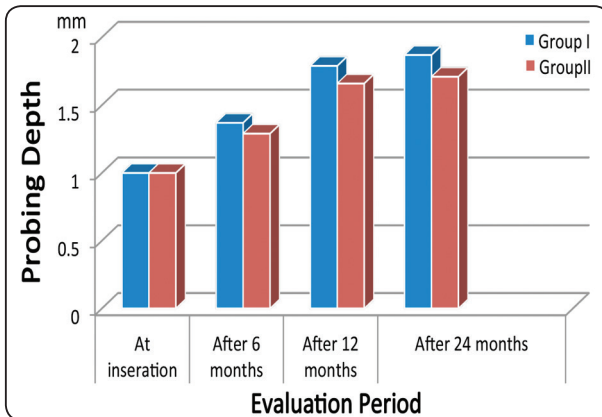
Fig. (6): Distribution of mean value of probing depth between the two groups at different follow up periods.
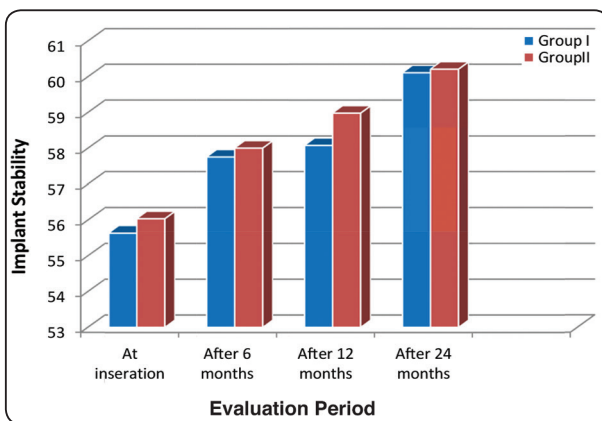

Fig. (7): Distribution of mean value of implant stability between the two groups at different follow up periods.
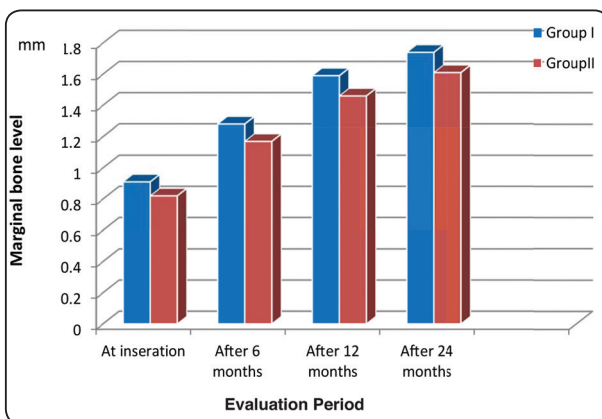

Fig. (8): Distribution of mean value of marginal bone loss between the two groups at different follow up periods.

DISCUSSION

Today relatively high percentages of elderly population suffer from different cardiovascular diseases and are on permanent antihypertensive therapy. One of the most frequently used drugs is the calcium channel blockers prescribed against high blood pressure. The most common oral side effect of these drugs is the gingival enlargement that might develop even on otherwise healthy gingiva [26-28].

Usually GO are traps for debris and plaque, causing difficulties in maintenance of oral hygiene, further enhancing secondary inflammation and susceptibility of periodontal disease and caries [1-3].

Amlodipine is a third generation relatively newer of calcium channel blockers that is frequently used in therapy of hypertension, exhibit adverse effect of gingival enlargement in middle to older aged adults[29,30]. Valsartan is angiotensin receptor blocker used in therapy of hypertension but with no side-effects observed with these calcium channel blockers [31, 32].

In this study, a significant decrease in plaque index was observed over two years of follow-up and may be attributed to routine hygienic recall visits and to the patients' efforts in maintaining a high level of oral hygiene. This matches the results from previous studies which reported successfully osseointegrated implants in patients who followed regular oral hygiene instructions [33, 34].

Slight increase in the gingival index was found in both groups during the follow up period. There is no evidence to support a single factor as responsible for gingival hyperplasia, this may be due to our patients did not have a habit of regular/daily brushing at the beginning of treatment [34]. Further, possible explanation is the fact that our patients were men, and AIGO occurs three times more often in men than in women [35]. Another potential explanation could be a patient's sensitivity to a specific drug's metabolic pathway [35] or patient's sensitivity to a

specific amlodipine concentration in the crevicular gingival fluid [36].

In addition, prosthetic restorations, by movement of the denture base during function which may exert pumping action of the gingival margin. This was decreased after relief in acrylic resin of the overdenture over the inflamed gingival tissue [37].

Gingival hyperplasia may occur when oral hygiene procedures are discontinued, so plaque accumulation leads to gingivitis in 10-21 days or peri-implant mucositis [38, 39].

There was no significant difference in the gingival index between the two groups. The increases of Amlodipine may be due to that Amlodipine exhibit adverse effect of gingival enlargement in middle to older aged adults[29, 30], but this increase is non-significant, which may be due to lower dose of Amlodipine (5 mg/day) and these results are in agreement with Seymour et al. reported that gingival hyperplasia could be a side effect of amlodipine even with a very short term and low dose administration [40], or may be due to sharp oral hygiene instruction these is agreed with Thompson et al and Prisant and Herman , where they say drug-induced gingival enlargement can be minimized, but not prevented by meticulous oral hygiene, and regular recall [26, 41].

It was also observed a slight trend of non-significant increasing of probing depth around the implants between the two groups during the follow-up periods, although it did not reach statistical significance. These findings could be attributed to bone resorption during the first year after implant placement; the increases were within acceptable values and are in agreement with previously reported results of a probing depth increase after one year follow-up period and explanation that this phenomenon of up to 1 mm marginal bone loss is related to maturation of bone after implant placement and adaptation of bone to withstand functional forces [42].

Implant stability is a critical factor that determines the long-term success of dental implants [43]. In this study, all the Osstell ISQ values are more than 50 and there was insignificant increase in implant stability between the two groups, this was in agreement with Atsumi et al [44]. On the other hand there was significant increase of implant stability within the same group, this indicates successful Osseointegration [45].

The difference between the bone loss around the implant fixtures in the two groups was not statistically significant during the follow-up periods.

The difference between the bone loss around the implant fixtures in the two groups was not statistically significant during the follow-up periods. Loss of marginal bone height after the onset of implant function is a phenomenon that is normally observed around dental osseointegrated implants. This has been described as either a plaque- related and/or as a load- related effect [46].

In this study, crestal bone resorption related to implant abutments in both groups after one year follow-up did not exceed 1mm, hence all implants were considered successful, this was in agreement with Albrektsson [47].

Also, this was in agreement with Adell et al [48], who found that crestal bone loss around dental implants, typically seen during the first year of implant function was about 1.2 mm up to the end of the first year of function, and a mean loss of 0.1 mm annually thereafter. From the study of Albrektsson, success criteria for osseointegrated dental implants were proposed to include a level of marginal bone loss of up to 1.5 mm in the first year, and then no more than 0.2 mm annually [47].

The amount of bone level changes in this study was within the criteria for implant success suggested by Albrektsson and coworkers [49].

In this study, the use of immediately-loaded flapless one-stage implants without a second surgical

phase might be a reason of the success rate of the implants. The flapless implant surgery "minimally invasive" preserves maximum amount of blood supply to the bone. On the other hand, reflection of flap in the second stage will compromises part of blood supply coming from soft tissue to bone and interfere with the tissues vascularization [50].

Due to the limitations of this study, the authors suggest that the small sample size may have affected the power to show a statistical significant change in the clinical and radiographical evaluations. Also longer evaluation period may be needed to asses success of immediately-loaded implants in hypertensive patients.

CONCLUSIONS

Based on the limitations of the present study and although no statistical difference was found between the effect of Amlodipine and Valsartan on dental implants under overdentures. Dental implants can be immediately loaded successfully to retain mandibular overdentures in controlled hypertensive edentulous patients. Peridontium around implants in hypertensive patients managed by calcium channel blockers Amlodipine was affected more than that managed by Valsartan. Also we need more research about more doses and longer periods.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The Authors declare that they have no conflict of interest, have full control of all primary data.

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