Numerous treatments are recommended for the replacement of lost teeth, because despite scientific progress in oral health promotion, tooth loss remains prevalent in the population, causing esthetic, phonetic, and masticatory damage to patients.

One of the most successful and effective treatments is the placement of osseointegrated implants, with survival rates above 90%. However, some failures can still occur.

Implant failures can occur during two periods: before or during the abutment connection surgery (early failure) or after the functional loading of the implant through the prostheses (late failure). Failures during these periods are associated with different etiologic factors. Early failure can be due to the inability to establish osseointegration, thus compromising bone tissue repair, resulting in fibrous tissue between the implant surface and the bone, causing mobility and implant loss. Local and systemic factors can influence bone repair and result in early failure. As for late failure, its etiology is related to the oral microbial environment (peri-implantitis caused by plaque accumulation), parafuctional habits, or rehabilitation variables, such as occlusal overload.

Hypertension is the main cause of premature diseases in the world. It has multifactorial etiology and is associated with other systemic comorbidities, such as chronic renal failure, stroke, and alterations in skeletal structure, such as decreased body bone mass index and other bone abnormalities (abnormal calcium metabolism, impaired alveolar bone quality, and delayed bone healing). In addition, hypertension influences bone regeneration and alveolar bone quality, as it is associated with decreased bone mineral density (BMD).

In general, antihypertensive β-blockers inhibit β-2 receptors, reducing the catabolic effect of osteoclasts; diuretics increase calcium absorption and may improve bone neoformation; and angiotensin receptor blockers (ARB) and conversion enzyme inhibitors (CEI) block the renin-angiotensin system by altering the balance of bone formation.

With the increase in life expectancy of the population and the high prevalence of hypertension, more and more hypertensive patients are receiving rehabilitation.
treatments with implants. Considering that the ability to repair bone tissue is extremely important for implant integration, it is necessary to assess the influence of hypertension and the use of antihypertensive drugs on the clinical success of osseointegrated implants.

The hypothesis of this study was that hypertension and the use of antihypertensive drugs may cause predisposition to the loss of osseointegrated implants in rehabilitation treatments, both in the early and late stages.

The objective of this study was to evaluate the influence of hypertension and the use of antihypertensive drugs on the success rate of osseointegrated implants.

**MATERIALS AND METHODS**

The study was approved by the Research Ethics Committee (CEP) of the Faculty of Dentistry of Araçatuba, UNESP (CAEE 37546620.4.0000.54.20). This is a retrospective study based on analysis of data obtained from medical records of patients treated at the Center for Continuing Education at NEC (Araçatuba, São Paulo, Brazil) between 2000 and 2017. This study followed the ethical principles of the Medical and Ethical Protocols of the Helsinki Declaration, 2013 (World Medical Association, 2017) and the guidelines of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology).

The medical records selected for the study had the following inclusion criteria: a correctly filled-out form of a patient who received dental treatment for oral rehabilitation with conventional loading of osseointegrated implants (after 3 months), where the treatment must have been completed and have been followed up for 1 year. Medical records were excluded if patients received immediate loading implants, had periodontal disease, or if they abandoned treatment. There were no exclusions due to age, sex, race, systemic illnesses, or medication use.

For the tabulation of the variables of this study, anamnesis and treatment description data were used.

Anamnesis data were age (grouped into age groups), sex (male, female), presence or absence of hypertension, use or not of antihypertensive drugs, and identification of them grouped into categories.

Regarding treatment, data collected were as follows: the number of implants placed, the number of implants lost, and the type of prostheses implanted.

The criteria for considering a lost implant were clinical (presence of pain, peri-implant infection, or mobility) and/or presence of peri-implant radiolucency.

The data were stored and organized in the Launch Epi Info 7 software, which is aimed at epidemiologic studies in the health area.

All data collected were organized and tabulated in Microsoft Office Excel spreadsheets. Statistical analysis was performed using the SigmaPlot 12.0 software; the chi-square test or Fisher exact test were used to investigate possible associations between sex, age group, presence of hypertension, use of antihypertensive drugs, or type of prosthesis with the condition of implant loss. All tests were performed with a significance level of $P < .05$. To compare the success rate between hypertensive and normotensive patients according to the type of prosthesis used, the $t$ test was performed with a significance level of $P < .05$.

**RESULTS**

In this study, a total of 3,000 medical records of patients who received oral rehabilitation treatment with osseointegrated implants of different brands, but all with an external hexagon platform and conventionally loaded, were analyzed; 602 were included in the study because they met the inclusion criteria (Fig 1).

The sample consisted of 207 men and 395 women, and the most prevalent age groups were 50 to 54 years, 60 to 64 years, and older than 70 years (Fig 2).

It was observed that 71.59% of the patients (431 patients) were normotensive, and 28.41% (171 patients) were hypertensive (Fig 3).

A total of 1,887 osseointegrated implants were placed with a 97.51% success rate (47 implants lost in 41 patients).

Of the 41 patients who lost implants (15 male and 26 female), 12 were hypertensive and 29 were normotensive. Of the 561 patients who did not lose implants, 159 were hypertensive and 402 were normotensive. The success rate of implants in the normotensive group was 93.28%, and in the hypertensive group, it was 92.99% (Fig 4).

Comparing the success rate of normotensive and hypertensive patients, it can be seen that there is no statistically significant difference ($P = .958$). In other words, hypertension does not seem to have been a determinant factor in implant loss (Fig 4).
In the hypertensive group who lost their implants, nine used antihypertensive drugs and three did not. One patient used more than one antihypertensive medication (Fig 5 and Table 1). There was no statistically significant difference between the success rates of implants of patients using or not using antihypertensive drugs ($P = .939$; Fig 6).

According to the type of prosthesis placed, the success and loss rates for each group (unitary, partial, protocol, and overdenture) in normotensive and hypertensive patients were analyzed (Table 2).

There was no statistically significant difference between the hypertensive and normotensive patients regarding the success rate of the implant treatment, according to the type of prosthesis placed ($P = .092$).

It is noted that the age groups in which there was a greater loss of implants in hypertensive patients was between 60 and 64 years and older than 70 years (Fig 7). The comparison of the success rate between the age groups of hypertensive patients did not show statistical similarity ($P = .894$). When comparing the loss of implants between the normotensive and hypertensive groups, in relation to their age, a statistically significant difference was found ($P = .001$).

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DISCUSSION

Despite the high success rates of rehabilitation treatments using osseointegrated implants, clinicians and researchers try to understand why losses occur. Several factors can be related to the failure of an implant in both the early and late stages.

The present study aimed to investigate 17 years of care at a specialized level, where the same treatment philosophy was used in all cases. When investigating 602 medical records, it was observed that the most cited systemic disease was hypertension. Throughout the 17 years of the study, different brands of implants were used, but all with external hexagon and placed at two surgical times; ie, cases of immediate loading did not participate in the study.

Among the possible failure causes of dental implant treatment, the presence of hypertension deserves a special mention, since its high incidence affects one in three adults in the world, and there is a tendency for this proportion to increase. Therefore, the investigation of the influence of this condition is scientifically relevant.

Hypertension is a multifactorial systemic condition, a result of the increase in peripheral vascular resistance to blood flow. One should always be aware of the likelihood of developing hypertension, because it is an asymptomatic disease that often has a delayed diagnosis and is associated with other diseases. The diagnosis of hypertension is performed by medical evaluation according to the criteria of the American Society of Cardiology. In this study, the diagnosis of hypertensive patients was previously performed by specific cardiovascular medical examination. Patients attended the dental office already diagnosed and, when necessary, received prescriptions from the doctor. Thus, blood pressure was measured only to confirm its control.

Hypertension is related to decreased bone mineral density (BMD), which affects bone regeneration and the quality of alveolar bone. The mechanisms that cause hypertension to change bone metabolism are still unknown. The existent hypotheses are that hypertension causes increased mobilization of calcium from bone, increased renal excretion of calcium, activation of parathyroid hormone, changes in

Table 2 Access Rate of Implants in Hypertensive and Normotensive Patients According to Type of Prosthesis

<table>
<thead>
<tr>
<th>Type of prosthesis</th>
<th>Normotensives</th>
<th>Hypertensives</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Success</td>
<td>Loss</td>
<td>Success</td>
</tr>
<tr>
<td>Single</td>
<td>106 (97.3%)</td>
<td>3 (2.7%)</td>
<td>36 (97.3%)</td>
</tr>
<tr>
<td>Partial</td>
<td>204 (91.1%)</td>
<td>20 (8.9%)</td>
<td>76 (92.7%)</td>
</tr>
<tr>
<td>Protocol</td>
<td>66 (92.9%)</td>
<td>5 (7.1%)</td>
<td>34 (87.2%)</td>
</tr>
<tr>
<td>Overdenture</td>
<td>26 (96.3%)</td>
<td>1 (3.7%)</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>402</td>
<td>29</td>
<td>159</td>
</tr>
</tbody>
</table>

Fig 6 Success and failure rates in hypertensive or antihypertensive patients.

Fig 7 Implant loss according to age group.
activity, and differentiation of cells mediated by angiotensin II.\textsuperscript{17,38–42}

Although there are not many studies in the literature that demonstrate the impact of hypertension on implant osseointegration, there are studies that have investigated the relationship between hypertension and alveolar bone repair and bone tissue in general. One such study is by Manrique et al,\textsuperscript{43} who compared alveolar repair in normotensive and hypertensive rats. A gradual increase in BMD was observed in normotensive rats. In the alveoli of hypertensive rats, BMD was shown to be lower, revealing a smaller amount of mineralized bone tissue and alteration of the alveolar repair process, with the presence of immature bone tissue. Bastos et al\textsuperscript{27} observed that critical defects in hypertensive rats had a smaller formation of trabecular bone area compared with normotensive rats.\textsuperscript{27}

Studies with histomorphometric analysis and immunohistochemistry have established a correlation between the bone repair process and the activity of important proteins for bone remodeling. Osteoprotegerin proteins (OPG) and nuclear factor κB (RANK and RANKL) regulate bone remodeling. OPG induces bone formation and has the ability to bind to RANKL and block the RANKL/RANK receptor in preosteoclasts, which are responsible for stimulating bone resorption by osteoclasts; ie, OPG is in charge of bone formation, and RANKL is in charge of bone reabsorption. An increase in RANKL secretion and a decrease in OPG would result in impaired bone repair.\textsuperscript{38,44–46} Osteoblasts produce OPG and RANKL at the beginning of bone healing and maintain bone metabolism balance.\textsuperscript{38,47,48} Studies that compared these proteins in the bone tissue of normotensive and hypertensive rats during the bone healing process found that normotensive rats showed inversely proportional quantities of OPG and RANKL, whereas hypertensive rats had a lower marking of OPG and greater RANKL marking, interfering in the repair process. Those findings suggest that hypertension modulates osteoclast activity and induces bone resorption, decreasing bone neoformation and trabecular thickness.\textsuperscript{17,38}

These studies on alveolar repair are not compatible with the present results, since the present findings revealed loss of implants in hypertensive patients; however, a statistically significant difference was not found ($P = .958$). Clinical studies have shown that hypertension does not influence the failure of osseointegrated implants. Khadivi et al,\textsuperscript{49} in a retrospective study comprising 148 patients with systemic health conditions, 39 of whom had heart diseases, including hypertension, and 98 healthy patients, found 13% implant failure for the diseased group and 12% for the healthy group. Alsaadi et al\textsuperscript{50} observed, in their retrospective study of 412 patients and 1,514 placed implants, that systemic conditions, one of which was hypertension, had no influence on the loss of implants. Other retrospective cohort studies found that the implant survival rate in patients with systemic conditions, such as hypertension and coronary artery disease, were not related to failure rates of implant treatment.\textsuperscript{12,51,52}

This study showed that of 171 hypertensive patients, 51 patients did not use any antihypertensive. In these cases, hypertensive patients did not use medication because some had mild to moderate hypertension and chose (on their own) not to adhere to the proposed medical treatment. Thus, it was possible to compare groups that used or did not use medication, and no difference was found in the loss of implants between the groups ($P = .939$).

Some drugs can alter bone metabolism, as is the case of antihypertensive drugs.\textsuperscript{23,53} In general, antihypertensive β-blockers inhibit β-2 receptors, reducing the catabolic effects of osteoclasts; angiotensin receptor blockers (ARB) and angiotensin converting enzyme (ACE) inhibitors end up blocking the renin-angiotensin system, thus altering the balance of bone formation.\textsuperscript{23,24}

Angiotensin II is responsible for increasing RANKL levels and osteoclastic activity and also has an effect on the osteoblastic lineage, decreasing osteogenesis through the AT1 receptor, influencing the transcription factor related to Runx2 and osteocalcin. All these factors end up triggering greater bone resorption.\textsuperscript{13,38,52–57} Thus, antihypertensive drugs of the class of blockers of angiotensin II receptors have created interest for their potential effects on bone metabolism. Angiotensin II receptor blockers, such as Losartan, were the most-used antihypertensive drugs in the present study (Table 2). Antihypertensives did not seem to influence the success rate of the implants, since no statistically significant difference was found ($P = .939$). As observed by Mulinari-Santos et al\textsuperscript{13} in their study that evaluated the repair of alveolar bone in normotensive rats, normotensive rats with Losartan administration, hypertensive rats without Losartan administration, and hypertensive rats with Losartan administration, it was observed that the group of normotensive rats with drug administration had a higher calcium marking, with high values of bone volume formed and more mineralized surfaces and with higher rates of bone formation compared with other groups. Therefore, Losartan can improve bone mineralization under normal physiologic conditions, but the same does not occur in the presence of hypertension. Gealh et al\textsuperscript{20} evaluated the effect of Losartan on bone metabolism during the autogenous graft repair process in normotensive and hypertensive animals and found no statistically significant difference in the OPG marking between the groups and found that the RANKL marking was higher in the groups of hypertensive animals with and without Losartan administration, but they were not significantly different between each other. Even though the group
of normotensive and hypertensive animals treated with Losartan showed greater bone formation compared with the other groups, there was no statistically significant difference, indicating that Losartan has no effect on bone metabolism from a clinical point of view.

On the other hand, a prospective study of 1,499 implants, of which 327 had been placed in 142 patients using antihypertensive drugs, had a 99.6% success rate for the group of patients using antihypertensive drugs and 96.9% for nonusers. The hypertensive patients who did not use medication had a failure rate of 4.7%, confirming the hypothesis that treatment with antihypertensive drugs was associated with higher implant success rates.23 There are animal studies that reveal that greater bone-to-implant contact has been observed in rats treated with antihypertensive drugs.53,58,59 Thus, further studies should be carried out to better understand the effects of antihypertensive drugs on bone metabolism.

Success rates of hypertensive and normotensive individuals were compared according to the different type of prosthesis used for the rehabilitation, and no statistically significant differences were found (P = .411).

External factors such as surgical technique, surgeon’s experience, occlusal trauma, and hygiene habits of the patient should also be taken into account since they can have a great influence on the prognosis of implants.60 Age proved to be an influential factor in the loss of implants, since a higher failure rate was found in patients older than 50 years of age, with the majority of losses occurring in patients older than 70 years of age. Cohort studies corroborate the present results, showing that patients older than 40 years of age are twice as likely to have implant loss and increasing age is directly proportional to the risk of implant loss, mainly in patients aged 60 to 79 years.14,32,51,60,61 However, when the present study compared the loss rates of the age groups, age did not seem to be a decisive factor (P = .894).

The limitations of this study include the lack of information related to patients regarding their oral hygiene, blood pressure classification, and the degree of hypertension control.

This study investigated the possible impact of hypertension on the failure of dental implant treatment, aiming to achieve more predictable results for this treatment. Apparently, the presence of hypertension and the use of antihypertensive drugs did not prove to be a contraindication to the placement of implants, judging by the success rate of the implants observed in this study. However, the present results should be interpreted with caution, and more studies are needed to assess the real impact of hypertension and antihypertensive medication on the result of implant-supported rehabilitation.

CONCLUSIONS

In this study, the presence of hypertension and the use of antihypertensive drugs were not associated with the failure of osseointegrated implants.

ACKNOWLEDGMENTS

The authors reported no conflicts of interest related to this study.

REFERENCES