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Diseases having an influence on inhibition of angiogenesis as risk factors of osteonecrosis of the jaw

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Abstract (J Korean Assoc Oral Maxillofac Surg 2016;42:271-277)

Objectives: The objective of this study was to retrospectively investigate the association of diseases having an influence on inhibition of angiogenesis such as hypertension, diabetes mellitus type II, hypercholesterolemia, and rheumatoid arthritis (RA) with the development of osteonecrosis of the jaws.
Materials and Methods: The 135 patients were allocated into 4 groups of bisphosphonate-related osteonecrosis of the jaw (BRONJ) group (1A); non-BRONJ group (1B); osteonecrosis of the jaw (ONJ) group (2A); and control group (2B), according to histologic results and use of bisphosphonate. This retrospective study was conducted with patients who were treated in one institute from 2012 to 2013. Fisher's exact test and logistic regression analysis were used to analyze the odds ratios of diseases having an influence on inhibition of angiogenesis for development of ONJ.
Results: The effects of diabetes and hypertension were not statistically significant on development of ONJ. When not considering bisphosphonate use, RA exhibited a high odds ratio of 3.23 (P=0.094), while hyperlipidemia showed an odds ratio of 2.10 (P=0.144) for development of ONJ. More than one disease that had an influence on inhibition of angiogenesis showed a statistically significant odds ratio of 2.54 (P=0.012) for development of ONJ.
Conclusion: Patients without diseases having an influence on inhibition of angiogenesis were at less risk for developing ONJ.

Key words: Bisphosphonate-associated osteonecrosis of the jaw, Angiogenesis inhibitors, Rheumatoid arthritis, Hypercholesterolemia
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I. Introduction

The concept of bisphosphonate-related osteonecrosis of the jaw (BRONJ) has evolved recently into medication-related osteonecrosis of the jaw (MRONJ). A recent position paper introduced two modifications to the definition. More specifically, anti-angiogenic agents were added to the list of medications, and "bone that can be probed" was considered equivalent to exposed bone.

Although the first case of BRONJ was reported several decades ago, the pathophysiology of MRONJ is not fully understood. There is controversy about the potential mechanisms underlying BRONJ pathophysiology among clinicians and researchers[1]. The most widely accepted pathophysiology is that bisphosphonates and other antiresorptives such as denosumab inhibit osteoclast differentiation and function and increase apoptosis, which all lead to decreased bone resorption and remodeling[2,3]. The main role of bone remodeling inhibition is further authenticated by a similar prevalence of osteonecrosis of the jaw (ONJ) observed with other anti-resorptive medications such as denosumab[4]. However, to explain the exclusive localization of BRONJ to the jaws, several hypotheses were suggested, such as inhibition of angiogenesis, consistent microtrauma, suppression of immunity, vitamin D deficiency, soft tissue toxicity of bisphosphonate, and inflammation or infection[1,5]. Among these hypotheses, recent studies have noted that angiogenesis suppression can result in the development of ONJ, and that serum vascular endothelial growth factor (VEGF) level might be a predictive marker of ONJ[6]. Also, bisphosphonates demonstrate anti-angiogenic properties due to their ability to significantly decrease VEGF and

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circulating level of the potent angiogenic factor, as shown in breast cancer patients with bone metastases[7,8]. Bisphosphonates decrease the density of microvasculature. Accumulated bisphosphonates in bone with a long half-life can interact with non-moving vessel cells and inhibit the release of endothelial progenitor cells from the bone marrow niches[9].

Angiogenesis is a process that involves growth, migration, and differentiation of endothelial cells to form new blood vessels. Angiogenesis depends on the binding of signaling molecules such as VEGF to receptors on the endothelial cells; new vessel growth is advocated by this signaling. It is classically considered that osteonecrosis is avascular necrosis or an interruption in vascular supply. Therefore, it is not extraordinary that inhibition of angiogenesis is a dominant hypothesis in ONJ pathophysiology[5,10]. Blood vessels arise from endothelial precursors, which share an origin with haematopoietic progenitors. VEGF has a predominant role in angiogenesis. The inhibition of VEGF seems to create an anti-angiogenic effect[11]. VEGF and endothelial nitric oxide synthase (eNOS) have been thought to be important factors for the induction of angiogenesis and the mobilization and release of endothelial progenitor cells[12]. *In vitro* experiments have demonstrated that zoledronic acid has an effect on the reduction of angiogenesis[13,14]. This data is supported by studies about cancer patients treated with zoledronic acid who exhibited decreased circulating VEGF level[15]. In addition, there is literature on the osteonecrosis of the jaw and other bones in patients taking novel anti-angiogenic drugs (monoclonal antibody targeting VEGF and tyrosine kinase inhibitors). However, there are not enough studies on the relationship between inhibition of angiogenesis and denosumab.

Peripheral resistance is developed by vascular rarefaction and results in the development of hypertension[16]. A substantial number of data have shown that microvascular abnormalities, such as reduction in blood flow and capillary rarefaction, are clear evidence of disturbance of the angiogenic process and result in increased vessel destruction from hypertension[17,18]. Hypertension might be the main cause of endothelial progenitor cell dysfunction. During the destruction of the vessels, the mobilized or transplanted endothelial progenitor cells are recruited into the foci of neovascularization and contribute to the re-endothelialization of injured vessels as well as new blood vessel formation[12,19]. Other studies have reported that the number of endothelial progenitor cells decreased and their senescence processes were accelerated in patients with hypertension and in experimental hypertensive rats[20,21].

Diabetes, known to be associated with decreases of VEGF and VEGF receptor 2 (VEGFR2), causes dysfunction of endothelial cells and reduces arterial remodeling[22-24]. The modern administration of glucose to wounds of non-diabetic rats leads to inhibition of normal angiogenesis. This treatment decreases angiogenesis through the critical role of high glucose level in diabetes[25]. Also, diabetes is associated with ONJ in rats undergoing alendronate therapy and subjected to tooth extractions[26]. In addition, clinical studies have shown that higher doses of bisphosphonate cause osteonecrosis in patients with diabetes[27].

Hypercholesterolemia is also known to inhibit angiogenesis by suppressing endothelial function and VEGF expression[28-30]. There is a relationship between hypercholesterolemia and serum level of VEGF[31]. The endothelial replication necessary for vascular growth is markedly impaired in the presence of hypercholesterolemia[32]. This finding suggests a close correlation between hypercholesterolemia and inhibition of angiogenesis.

In patients with rheumatoid arthritis (RA), bisphosphonates have been predominantly used to inhibit bone loss, especially in patients who develop osteoporosis. This is a common feature in this rheumatic disease[33]. Cyclooxygenase COX-2 inhibitors such as celecoxib are prescribed for arthritic patients due to their mediation of systemic antitumor activity through the inhibition of angiogenesis[34,35]. Celecoxib suppresses VEGF gene expression both *in vitro* and *in vivo*[36]. Vascular endothelial cells express COX-2, and the inhibition of its enzymatic activity by celecoxib prohibits angiogenesis. Treatment with celecoxib was shown to reduce vascularization, lower VEGF level, and induce apoptosis in angiogenic endothelial cells[34].

Anti-angiogenic agents such as sunitinib, bevacizumab, and sorafenib have been reported to have an association with osteonecrosis[37,38]. As mentioned above, few studies have been conducted on the correlation of osteonecrosis and COX-2, which is considered to have an influence on VEGF inhibition. Therefore, COX-2 inhibitors are used for diabetes, hypertension, and RA associated with angiogenesis suppression. As a result, these drugs are used to examine the association with ONJ. Since patients with RA suffer a substantial amount of bone loss, anti-resorptive agents like bisphosphonate have been overprescribed to prevent this phenomenon. However, there are few studies related to celecoxib, RA treatment drugs, or the occurrence of ONJ.

The aim of this study was to compare the systemic diseases known to inhibit angiogenesis between patients who were

Table 1. The classification of patients according to use of bisphosphonate and existence of osteonecrosis of jaw (n=135)

	Taking BPs (Group 1)	Not taking BPs (Group 2)
Histology revealed ONJ (Group A)	Group 1A (n=32)[1]	Group 2A (n=32)
Histology did not reveal ONJ (Group B)	Group 1B (n=27)	Group 2B (n=44)

(BPs: bisphosphonates, ONJ: osteonecrosis of the jaw)
[1]Bisphosphonate-related osteonecrosis of the jaw.
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or were not histologically diagnosed with ONJ and to distinguish very hazardous diseases that have an influence on the development of ONJ.

II. Materials and Methods

This retrospective study was conducted with patients who were referred to Wonkwang University Dental Hospital from January 2012 to December 2013 and underwent operations under general anesthesia. This paper was approved by the Institutional Review Board of Wonkwang Dental Research Institute (WKDIRB201409-01).

Based on the medical records, the patients were classified into four groups. Group 1 was patients who were taking bisphosphonate at the first visit, while Group 2 patients did not. Group A comprised patients who were histologically diagnosed with ONJ after the operation, and Group B was patients who were not histologically diagnosed with ONJ after the operation.(Table 1)

At the beginning of the study, the data of all the patients included in Groups 1A, 2A, 1B, and 2B were reviewed. For Group 2B, the authors randomly selected 44 patients who were approximately the same age and had not taken bisphosphonates, anti-resorptive agents such as denosumab or anti-angiogenic agents and were not histologically diagnosed with osteonecrosis. Patients who had been administered intravenous bisphosphonates were excluded from this study.

Since the osteonecrosis incidence and drug potency of intravenous bisphosphonates are different from those of oral bisphosphonates, only intraoral bisphosphonates were studied[39,40]. All patients' medical histories were reviewed with medical records at the first visit, with a focus on hypertension, diabetes mellitus type II (DM), hyperlipidemia, and RA.

To investigate the correlation of hypertension, DM, hyperlipidemia, and RA with the incidence of ONJ in patients taking bisphosphonates, the odds ratio of ONJ was calculated according to the presence of diseases having an influence on inhibition of angiogenesis. For example, to calculate the odds ratio for hypertension, the odds ratios of Group 1A divided by Group 1B in the hypertensive group and in the non-hypertensive group were calculated. The overall odds ratio was then determined by dividing the odds ratio in the hypertensive group by the odds ratio in the non-hypertensive group. To investigate the correlation between these diseases and ONJ in patients who were not taking bisphosphonate, the odds ratio of ONJ was calculated according to the presence of diseases having an influence on inhibition of angiogenesis. The odds ratio of ONJ in Group A compared to Group B was calculated to investigate the correlation between these diseases and ONJ in patients without consideration of bisphosphonate use.

Multivariable logistic regression was used to measure study-specific odds ratios, and Fisher's exact test determined the association of diseases having an influence on inhibition of angiogenesis with the development of ONJ. All statistical tests were two-sided, and *P*-values less than 0.05 were considered statistically significant. All analyses were performed using STATA software version 9.1 (StataCorp LP, College Station, TX, USA).

Table 2. The epidemiological information of the patients

Age (yr)	Female	Male
<60	20	0
60-69	32	2
70-79	56	2
≥80	23	0

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III. Results

Group 1A consisted of 32 patients, Group 1B consisted of 27 patients, Group 2A consisted of 32 patients, and Group 2B consisted of 44 randomly selected patients.(Table 1) A description of the ages and genders of the total study population (total of 135 patients) is shown in Table 2. The median age of all patients was 72 years, and the average oral bisphosphonate dosing period was 41.9±30.8 months.

Comparing the patients who were taking bisphosphonates (Groups 1A and 1B), the history of hypertension had a low odds ratio of 0.55 (*P*=0.254) in ONJ, with no statistically

significant difference between groups. The diseases that were studied did not have any significant relationship with development of BRONJ.(Table 3)

However, the proportion of patients who had no disease influencing the inhibition of angiogenesis was higher in Group 2B compared to the other groups (54.6%; $P<0.05$). Group 2B patients had an especially low proportion of RA among the diseases having an influence on inhibition of angiogenesis.(Table 4) Comparing the patients who were not taking bisphosphonates (Groups 2A and 2B), the history of hyperlipidemia had a low odds ratio of 1.41, with no significant different between groups. Group 2A patients had an especially higher proportion of one or more of the diseases mentioned above. In the groups with patients who did not take bisphosphonates (Groups 2A and 2B), it was found that one or more disease had a significantly high odds ratio for development of ONJ (odds ratio 3.06; $P=0.024$).(Table 4) Without consideration of bisphosphonate use, the relationship of diseases having an influence on inhibition of angiogenesis with development of ONJ was analyzed (Group A vs B). Patients who were at risk of RA and hyperlipidemia exhibited high odds ratios of 3.23 ($P=0.094$) and 2.10 ($P=0.144$), respectively, with marginal statistical significance. Diseases having an influence on inhibition of angiogenesis showed a statistically significant odds ratio of 2.54 for development of ONJ.(Table 5)

Table 3. Proportions and odds ratio of anti-angiogenic diseases in relation to ONJ in the groups of patients taking bisphosphonates

Anti-angiogenic disease	Group 1A (n=32)		Group 1B (n=27)		Odds ratio	*P*-value
	Yes	No	Yes	No		
DM	6 (18.8)	26 (81.3)	5 (18.5)	22 (81.5)	1.01	0.982
Hypertension	13 (40.6)	19 (59.4)	15 (55.6)	12 (44.4)	0.55	0.254
RA	5 (15.6)	27 (84.4)	2 (7.4)	25 (92.6)	2.31	0.341
Hyperlipidemia	9 (28.1)	23 (71.9)	4 (14.8)	23 (85.2)	2.25	0.226
More than 1 disease	24 (75.0)	8 (25.0)	17 (63.0)	10 (37.0)	1.76	0.319

(ONJ: osteonecrosis of the jaw, DM: diabetes mellitus type II, RA: rheumatoid arthritis, More than 1 disease: existence of more than one of the anti-angiogenic diseases mentioned above)

Group 1A: bisphosphonate-related osteonecrosis of the jaw (BRONJ) group, Group 1B: non-BRONJ group.

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Table 4. Proportions and odds ratio of anti-angiogenic diseases in relation to ONJ in the groups of patients not taking bisphosphonates

Anti-angiogenic disease	Group 2A (n=32)		Group 2B (n=44)		Odds ratio	*P*-value
	Yes	No	Yes	No		
DM	6 (18.8)	26 (81.2)	6 (13.6)	38 (86.4)	1.46	0.548
Hypertension	19 (59.4)	13 (40.6)	18 (40.9)	26 (59.1)	2.11	0.114
RA	3 (9.4)	29 (90.6)	1 (2.3)	43 (97.7)	4.45	0.206
Hyperlipidemia	3 (9.4)	29 (90.6)	3 (6.8)	41 (93.2)	1.41	0.684
More than 1 disease	23 (71.9)	9 (28.1)	20 (45.5)	24 (54.6)	3.06	0.024

(ONJ: osteonecrosis of the jaw, DM: diabetes mellitus type II, RA: rheumatoid arthritis, More than 1 disease: existence of more than one of the anti-angiogenic diseases above)

Group 2A: ONJ group, Group 2B: control group.

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Table 5. Proportions and odds ratio of anti-angiogenic diseases in relation to ONJ without consideration of bisphosphonates

Anti-angiogenic disease	Group 1A and 2A (n=64)		Group 1B and 2B (n=71)		Odds ratio	*P*-value
	Yes	No	Yes	No		
DM	12 (18.8)	52 (81.3)	11 (15.5)	60 (84.5)	1.26	0.616
Hypertension	32 (50.0)	32 (50.0)	33 (46.5)	38 (53.5)	1.15	0.683
RA	8 (12.5)	56 (87.5)	3 (4.2)	68 (95.8)	3.23	0.094
Hyperlipidemia	12 (18.8)	52 (81.3)	7 (9.9)	64 (90.1)	2.10	0.144
More than 1 disease	47 (73.4)	17 (26.6)	37 (52.1)	34 (47.9)	2.54	0.012

(ONJ: osteonecrosis of the jaw, DM: diabetes mellitus type II, RA: rheumatoid arthritis, More than 1 disease: existence of more than one of the anti-angiogenic diseases above)

Group 1A: bisphosphonate-related osteonecrosis of the jaw (BRONJ) group, Group 2A: ONJ group, Group 1B: non-BRONJ group, Group 2B: control group.

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IV. Discussion

There have been attempts to investigate the relationships between BRONJ and concomitant therapies, although associative medication did not exhibit statistically significant results[41-43]. In those studies, the prevalence of concomitant diseases, such as hypertension, DM, and lung disease, was high (n=129) but showed no significant relationship with occurrence of BRONJ. This study attempted to focus on systemic diseases that are known to be related to inhibition of angiogenesis and found little significant risk for development of ONJ.

Angiogenesis can be inhibited by four types of diseases: hypertension, DM, RA, and hyperlipidemia. In this study, however, the effects of DM and hypertension were not statistically significant with regard to development of ONJ.

Hypertension appears to be the main cause of endothelial progenitor cell dysfunction. Transplanted or mobilized endothelial progenitor cells are recruited into the foci of neovascularization where they contribute to the re-endothelialization of injured vessels and angiogenesis[12,19,44]. In this study, the mean blood pressure of hypertensive patients was low compared to the average blood pressure of 122/79 mmHg. Since most hypertensive patients take medications and maintain low blood pressure, hypertension might have little effect on the development of ONJ.

There is a likelihood of diabetes potentiating osteonecrosis risk during alendronate use. This supposition is supported by bone metabolism changes related to high blood glucose level[26]. In a study using Wistar rats, the incidence of ONJ was significantly greater in the diabetes group[45]. The high frequency of ONJ occurring concomitantly with diabetes has been reported to have several pathophysiologies. Diabetes is correlated with microvascular ischemia of the bone, decreased bone turnover and remodeling, endothelial cell dysfunction, and induced apoptosis of osteoblasts and osteocytes. Also, diabetes, which is known to be associated with decrease of VEGF and VEGFR2, causes dysfunction of endothelial cells and reduces arterial remodeling[22-24]. In 2007, a study attempted to investigate the relationship between BRONJ and diabetes. In the BRONJ patient group, more than half of the patients (58%) had DM or impaired fasting glucose. The proportion of diabetic patients was much higher compared to the proportion of diabetic patients in a control group of patients treated with bisphosphonates and without BRONJ (12%) (P=0.00003). However, there is still no clinical evidence of impaired vascularity under such conditions[46]. Unlike these studies, DM was not statistically significant with regard to development of ONJ in our study. Since all patients with diabetes mellitus were taking medications and exhibited almost normal glucose level, DM might have little effect on development of ONJ.

The high risk for development of ONJ was higher in the presence of hyperlipidemia and RA. Many patients with RA take bisphosphonates and anti-resorptive drugs that have been reported to be associated with occurrence of ONJ[47,48]. When patients with RA not taking bisphosphonates were investigated, no patients were prescribed anti-resorptive agents such as denoumab. Instead, most of the patients were taking celecoxib. Studies have shown that celecoxib might have an effect on inhibition of angiogenesis[44-48]. More studies are necessary to understand whether this effect is due to RA or celecoxib.

To our knowledge, there have been no reports that patients who have hyperlipidemia are at high risk for development of ONJ. However, there is not enough data about the status of disease because of the retrospective design of these studies.

In most reports, the prevalence of ONJ in patients who have used oral bisphosphonates is 1.04 to 1.69 per 100,000 patients per year. In a more recent report, Malden and Lopes derived an incidence of 0.004% (0.4 cases per 10,000 patients per year of exposure to alendronate) from 11 cases of MRONJ reported in a population of 90,000 patients living in southeast Scotland. The prevalence of osteomyelitis of the jaw in patients is 3 to 4 per 100,000 patients per year at the Dutch University Medical Center, which is similar to institutions in the Western world. It is believed that the prevalence of the two diseases has no significant difference. Among the patients who visited the center, the number of elderly patients was found to be high in our hospital. In addition, the patients who were selected for this study were over 60 years in age. Because of these points, the incidence of osteonecrosis seemed to be higher in our patients with systemic diseases.

Patients who had been administered intravenous bisphosphonates were excluded from this study. Intravenous medications are frequently administered to treat malignant diseases such as multiple myeloma, breast cancer, and prostate cancer and are sometimes prescribed simultaneously with anti-cancer chemotherapeutic medications. This means that there is a possibility that the preexistence of diseases such as metastatic tumors or myeloma in the jaw could skew the results of this study. Also, in our study, there was little number of patients who were administered intravenous bisphosphonates.

This study has several limitations that lack consideration

about the systemic diseases above whether it was adjusted like a normal person through a treatment or not. Since RA can affect the development of ONJ with its anti-angiogenic medications, another experimental study is recommended to show that RA actually contributes to the development of ONJ. In addition, in the groups taking bisphosphonates (Table 3) or not (Table 4), the presence of disease did not affect the development of ONJ. However, the presence of diseases with an influence on inhibition of angiogenesis was found to be significantly correlated with development of ONJ without consideration of bisphosphonates.(Table 5) These results might be due to the small number of patients in this study. We expect further studies on a greater scale to possibly reveal an association of the systemic diseases mentioned in this study with incidence of ONJ.

V. Conclusion

The effects of diabetes and hypertension were not statistically significant on development of ONJ. Patients without diseases having an influence on inhibition of angiogenesis are at less risk for development of ONJ. In addition, patients with hyperlipidemia or RA are at high risk for developing ONJ.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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References

1. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg 2014;72:1938-56.
2. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011;48:677-92.
3. Lacey DL, Boyle WJ, Simonet WS, Kostenuik PJ, Dougall WC, Sullivan JK, et al. Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. Nat Rev Drug Discov 2012;11:401-19.
4. Aghaloo TL, Felsenfeld AL, Tetradis S. Osteonecrosis of the jaw in a patient on Denosumab. J Oral Maxillofac Surg 2010;68:959-63.
5. Allen MR, Burr DB. The pathogenesis of bisphosphonate-related osteonecrosis of the jaw: so many hypotheses, so few data. J Oral Maxillofac Surg 2009;67(5 Suppl):61-70.
6. Vincenzi B, Napolitano A, Zoccoli A, Iuliani M, Pantano F, Papapietro N, et al. Serum VEGF levels as predictive marker of bisphosphonate-related osteonecrosis of the jaw. J Hematol Oncol 2012;5:56.
7. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res 2002;62:6538-44.
8. Marx RE, Cillo JE Jr, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg 2007;65:2397-410.
9. Pabst AM, Ziebart T, Ackermann M, Konerding MA, Walter C. Bisphosphonates' antiangiogenic potency in the development of bisphosphonate-associated osteonecrosis of the jaws: influence on microvessel sprouting in an in vivo 3D Matrigel assay. Clin Oral Investig 2014;18:1015-22.
10. Landesberg R, Woo V, Cremers S, Cozin M, Marolt D, Vunjak-Novakovic G, et al. Potential pathophysiological mechanisms in osteonecrosis of the jaw. Ann N Y Acad Sci 2011;1218:62-79.
11. Carmeliet P. Angiogenesis in life, disease and medicine. Nature 2005;438:932-6.
12. Urbich C, Dimmeler S. Endothelial progenitor cells: characterization and role in vascular biology. Circ Res 2004;95:343-53.
13. Wood J, Bonjean K, Ruetz S, Bellahcène A, Devy L, Foidart JM, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther 2002;302:1055-61.
14. Bezzi M, Hasmim M, Bieler G, Dormond O, Rüegg C. Zoledronate sensitizes endothelial cells to tumor necrosis factor-induced programmed cell death: evidence for the suppression of sustained activation of focal adhesion kinase and protein kinase B/Akt. J Biol Chem 2003;278:43603-14.
15. Santini D, Vincenzi B, Dicuonzo G, Avvisati G, Massacesi C, Battistoni F, et al. Zoledronic acid induces significant and long-lasting modifications of circulating angiogenic factors in cancer patients. Clin Cancer Res 2003;9:2893-7.
16. Humar R, Zimmerli L, Battegay E. Angiogenesis and hypertension: an update. J Hum Hypertens 2009;23:773-82.
17. Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? Circulation 2001;104:735-40.
18. Feihl F, Liaudet L, Waeber B, Levy BI. Hypertension: a disease of the microcirculation? Hypertension 2006;48:1012-7.
19. Asahara T, Masuda H, Takahashi T, Kalka C, Pastore C, Silver M, et al. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. Circ Res 1999;85:221-8.
20. Imanishi T, Moriwaki C, Hano T, Nishio I. Endothelial progenitor cell senescence is accelerated in both experimental hypertensive rats and patients with essential hypertension. J Hypertens 2005;23:1831-7.
21. Pirro M, Schillaci G, Menecali C, Bagaglia F, Paltriccia R, Vaudo G, et al. Reduced number of circulating endothelial progenitors and HOXA9 expression in CD34+ cells of hypertensive patients. J Hypertens 2007;25:2093-9.
22. Tousoulis D, Papageorgiou N, Androulakis E, Siasos G, Latsios G, Tentolouris K, et al. Diabetes mellitus-associated vascular impairment: novel circulating biomarkers and therapeutic approaches. J Am Coll Cardiol 2013;62:667-76.
23. Kolluru GK, Bir SC, Kevil CG. Endothelial dysfunction and diabetes: effects on angiogenesis, vascular remodeling, and wound heal-

ing. Int J Vasc Med 2012;2012:918267.
24. Chou E, Suzuma I, Way KJ, Opland D, Clermont AC, Naruse K, et al. Decreased cardiac expression of vascular endothelial growth factor and its receptors in insulin-resistant and diabetic states: a possible explanation for impaired collateral formation in cardiac tissue. Circulation 2002;105:373-9.
25. Brem H, Jacobs T, Vileikyte L, Weinberger S, Gibber M, Gill K, et al. Wound-healing protocols for diabetic foot and pressure ulcers. Surg Technol Int 2003;11:85-92.
26. Berti-Couto SA, Vasconcelos AC, Iglesias JE, Figueiredo MA, Salum FG, Cherubini K. Diabetes mellitus and corticotherapy as risk factors for alendronate-related osteonecrosis of the jaws: a study in Wistar rats. Head Neck 2014;36:84-93.
27. Molcho S, Peer A, Berg T, Futerman B, Khamaisi M. Diabetes microvascular disease and the risk for bisphosphonate-related osteonecrosis of the jaw: a single center study. J Clin Endocrinol Metab 2013;98:E1807-12.
28. Ozdemir BH, Akcali Z, Haberal M. Hypercholesterolemia impairs angiogenesis in patients with breast carcinoma and, therefore, lowers the risk of metastases. Am J Clin Pathol 2004;122:696-703.
29. Van Belle E, Rivard A, Chen D, Silver M, Bunting S, Ferrara N, et al. Hypercholesterolemia attenuates angiogenesis but does not preclude augmentation by angiogenic cytokines. Circulation 1997;96:2667-74.
30. Jang JJ, Ho HK, Kwan HH, Fajardo LF, Cooke JP. Angiogenesis is impaired by hypercholesterolemia: role of asymmetric dimethylarginine. Circulation 2000;102:1414-9.
31. Trapé J, Morales C, Molina R, Filella X, Marcos JM, Salinas R, et al. Vascular endothelial growth factor serum concentrations in hypercholesterolemic patients. Scand J Clin Lab Invest 2006;66:261-7.
32. Henry PD. Hypercholesterolemia and angiogenesis. Am J Cardiol 1993;72:61C-64C.
33. Breuil V, Euller-Ziegler L. Bisphosphonate therapy in rheumatoid arthritis. Joint Bone Spine 2006;73:349-54.
34. Leahy KM, Ornberg RL, Wang Y, Zweifel BS, Koki AT, Masferrer JL. Cyclooxygenase-2 inhibition by celecoxib reduces proliferation and induces apoptosis in angiogenic endothelial cells in vivo. Cancer Res 2002;62:625-31.
35. Masferrer JL, Leahy KM, Koki AT, Zweifel BS, Settle SL, Woerner BM, et al. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res 2000;60:1306-11.
36. Wei D, Wang L, He Y, Xiong HQ, Abbruzzese JL, Xie K. Celecoxib inhibits vascular endothelial growth factor expression in and reduces angiogenesis and metastasis of human pancreatic cancer via suppression of Sp1 transcription factor activity. Cancer Res 2004;64:2030-8.
37. Jain RK, Duda DG, Clark JW, Loeffler JS. Lessons from phase III clinical trials on anti-VEGF therapy for cancer. Nat Clin Pract Oncol 2006;3:24-40.
38. Christodoulou C, Pervena A, Klouvas G, Galani E, Falagas ME, Tsakalos G, et al. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. Oncology 2009;76:209-11.
39. Coleman R, Woodward E, Brown J, Cameron D, Bell R, Dodwell D, et al. Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE: BIG 01-04) for women with stage II/III breast cancer. Breast Cancer Res Treat 2011;127:429-38.
40. Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg 2010;68:243-53.
41. Assaf AT, Smeets R, Riecke B, Weise E, Gröbe A, Blessmann M, et al. Incidence of bisphosphonate-related osteonecrosis of the jaw in consideration of primary diseases and concomitant therapies. Anticancer Res 2013;33:3917-24.
42. Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS. Factors associated with osteonecrosis of the jaw among bisphosphonate users. Am J Med 2008;121:475-83.e3.
43. Yarom N, Yahalom R, Shoshani Y, Hamed W, Regev E, Elad S. Osteonecrosis of the jaw induced by orally administered bisphosphonates: incidence, clinical features, predisposing factors and treatment outcome. Osteoporos Int 2007;18:1363-70.
44. Kalka C, Masuda H, Takahashi T, Kalka-Moll WM, Silver M, Kearney M, et al. Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. Proc Natl Acad Sci U S A 2000;97:3422-7.
45. Maahs MP, Azambuja AA, Campos MM, Salum FG, Cherubini K. Association between bisphosphonates and jaw osteonecrosis: a study in Wistar rats. Head Neck 2011;33:199-207.
46. Khamaisi M, Regev E, Yarom N, Avni B, Leitersdorf E, Raz I, et al. Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. J Clin Endocrinol Metab 2007;92:1172-5.
47. Conte-Neto N, Bastos AS, Marcantonio RA, Junior EM. Epidemiological aspects of rheumatoid arthritis patients affected by oral bisphosphonate-related osteonecrosis of the jaws. Head Face Med 2012;8:5.
48. Grana J, Mahia IV, Meizoso MO, Vazquez T. Multiple osteonecrosis of the jaw, oral bisphosphonate therapy and refractory rheumatoid arthritis (Pathological fracture associated with ONJ and BP use for osteoporosis). Clin Exp Rheumatol 2008;26:384-5.