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Pharmacogenomics in medication-related osteonecrosis of the jaw: a systematic literature review

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Abstract. – OBJECTIVE: Medication-related osteonecrosis of the jaw (ONJ) is an adverse, severe and debilitating effect, which although infrequent, affects patients with osteoporosis or neoplasm who take bisphosphonates, antiresorptive drugs, and/or antiangiogenic drugs. Its etiopathogenesis is unknown, although genetic causes have been postulated.

MATERIALS AND METHODS: This review analyzed articles published to date that have studied genetic factors associated with ONJ. Fifteen case-control studies were included, published between 2008 and 2018.

RESULTS: Five set out to determine genetic causes by means of genome-centered techniques, while ten do so by investigating gene-centered variants. Nine works found statistically significant associations between one or various single nucleotide polymorphisms (SNPs) and the appearance of ONJ. None of the studies coincided as to which genes present some association.

CONCLUSIONS: The review observed the moderate impact of genetic factors on the appearance of ONJ. It also showed the heterogeneity of the studies that have investigated ONJ to date. In future studies, involving international and inter-hospital collaboration will be necessary to recruit sample sizes of sufficient size, elaborate adequate study designs, obtain clear results, and advance our understanding of ONJ and make it possible to single out individual patients at risk.

Key Words:
Antiresorptive drugs, Osteonecrosis of the jaw, Pharmacogenomics, Single nucleotide polymorphisms, Genetic susceptibility.

Introduction

Osteonecrosis of the jaw (ONJ) is a recently described pathology of unknown physiopathology defined as the exposure of necrotic bone in the oral cavity that does not resolve within eight weeks in patients who are or have been in treatment with bisphosphonates (BF), and who have not received radiation in the craniofacial region. Although cases were first reported over a decade ago, the etiopathogenesis of ONJ is not yet completely understood, and various theories have been put forward to explain its appearance: bone remodeling disorders or over-inhibition of bone resorption, angiogenesis inhibition, constant microtrauma to the oral mucosa, innate or acquired immunity suppression, vitamin D deficiency, soft tissue toxicity, inflammation or infection derived from BPs[1].

In patients taking BPs orally, the risk of ONJ increases in relation to the duration of exposure to the drug, concomitant medication (corticosteroids, chemotherapy), smoking, badly fitting prostheses, and the presence of chronic inflammation of the oral tissues (periodontal disease and/or poor oral hygiene). The general health of the patient is also a very important factor[2].

The association between ONJ and BP administration has been well documented, although in recent years reports have been published on ONJ cases not only related to BPs but also to antiresorptive drugs such as denosumab. Denosumab is a monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK,

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which is responsible for the NF-κB activation in osteoclastic cells. Other works report the appearance of ONJ derived from drugs with antiangiogenic activity used in cancer treatment: i) bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor (VEGF), inhibiting attachment to its receptor; ii) sutinib, which inhibits multiple receptors of tyrosine kinase activity involved in tumor growth, neoangiogenesis, and the progress of cancer metastasis; and iii) sorafenib, which blocks RAF kinase avoiding cell division, cell growth, and blocking VEGF receptors, impeding neoangiogenesis and blocking the source that feeds tumor growth[3]. There have even been reports of cases of ONJ in patients in treatment with aflibercept, a drug that inhibits vascular growth in tumors, approved by the U.S. Food and Drug Administration in 2012 for treating colorectal cancer[4].

As a result of the numerous articles published that relate ONJ with different drugs, in 2014 the American Association of Oral and Maxillofacial Surgeons published a position paper proposing to change the term BRONJ (bisphosphonate-related osteonecrosis of the jaw) to MRONJ (medication-related osteonecrosis of the jaw)[1].

It is known that interindividual genetic variation can determine unequal responses to some drugs. So, genetic variants are a possible explanation for the fact that ONJ only appears in some patients. This genetic variability is based on the presence of genetic variants, known as polymorphisms that do not have any notable impact on health. These variations present in the general population could explain interindividual differences both in the varying therapeutic effects and toxicity deriving from certain drugs[5].

To study these variations, two main approaches have been proposed: i) hypothesis-free studies, otherwise known as genome wide association studies (GWAS), which analyze many points in the genome, and by means of powerful statistical methods, identify associations between variants and the pathology under investigation[6]; and ii) directed studies that only investigate genes or variants of interest, or whenever it is suspected or enough scientific evidence exists to suggest an association with variants in particular genes[7].

As ONJ only occurs among a minority of patients treated with these drugs, it has been suggested that there may be a genetic background predisposing the patient to its appearance. Given that ONJ is an adverse effect of very low prevalence but nevertheless severe, and compromises the sufferer's quality of life, it would be very useful to discover a means of identifying in advance patients who are susceptible. The key may reside in individual genetic susceptibility, and improved understanding of this association could help to minimize the appearance of ONJ and the consequent costs.

Materials and Methods

An electronic literature search was conducted in the following online databases:

1. MEDLINE.
2. EMBASE.

Key search terms were used to identify texts: Osteonecrosis of the jaw, Bisphosphonate-related osteonecrosis of the jaw (BRONJ), ONJ, gene, SNP, single nucleotide polymorphisms, and pharmacogenomics. The search also consulted the database Uptodate®, which located additional texts.

PICO criteria were as follows:

- Population: patients in treatment with antiresorptive and anti-angiogenic drugs.
- Comparison: development/non-development of osteonecrosis
- Intervention: genetic study
- Outcome: identify the presence of genetic differences between the two groups.

Inclusion criteria:

- The inclusion criteria applied admitted editorials, case control studies, retrospective studies, and randomized double-blind studies related to bisphosphonates, antiresorptives, antiangiogenics, and osteonecrosis of the jaw.
- Human/*in vivo* studies.
- Articles written in English.
- Published between 1999 and June 2018.
- Articles that identified genetic relations between patients who develop osteonecrosis and antiresorptive and/or antiresorptive drugs.

Exclusion criteria were:

- Articles reporting studies conducted before 1999.
- Non-indexed articles.
- Articles published in languages other than English.
- Case reports describing fewer than three cases.
- Animal studies.
- *In vitro* studies.
- Gene expression studies.
- Reviews with articles already selected.

The search was limited to human and *in vivo* studies published from January 1999 to June 2018.

The articles identified in the initial search were screened in duplicate (two reviewers, IOLC, and NBL) for inclusion in analysis. If any information was lacking in the abstract or any disagreement arose between the reviewers, the authors read through the full text before reaching consensus. Three geneticists (NBL, JSC, and RMI) monitored all molecular aspects. AAS, GGM, and JHV supervised the dental and bone aspects. The review was directed and supervised by JSC and GGM.

Results

The initial search identified 17 articles of which two did not fulfill the inclusion criteria, leaving fifteen articles, all published between 2008 and 2018. All the articles were case-control studies (Figure 1).

Genome-Centered Studies

Table I summarizes the five case-control, genome-centered studies reviewed. One used a second control group (a healthy population not exposed to BPs). Another used a control group of healthy subjects not in treatment with BPs but did not include patients administered BPs but without ONJ. Sarasquete et al[8] conducted a GWAS, analyzing 500,000 SNPs in 87 patients, of whom 22 developed ONJ. They concluded that individual carriers of TT nucleotides in SNP rs1934951 in the *CYP2C8* gene presented almost thirteen times greater probability of developing ONJ derived from BPs than non-carrier individuals.

Di Martino et al[9] analyzed 1,936 variants in 225 genes associated with phase I and II enzymes of drug transport, metabolism, and excretion. This analysis was performed in nine cases and ten control cases.

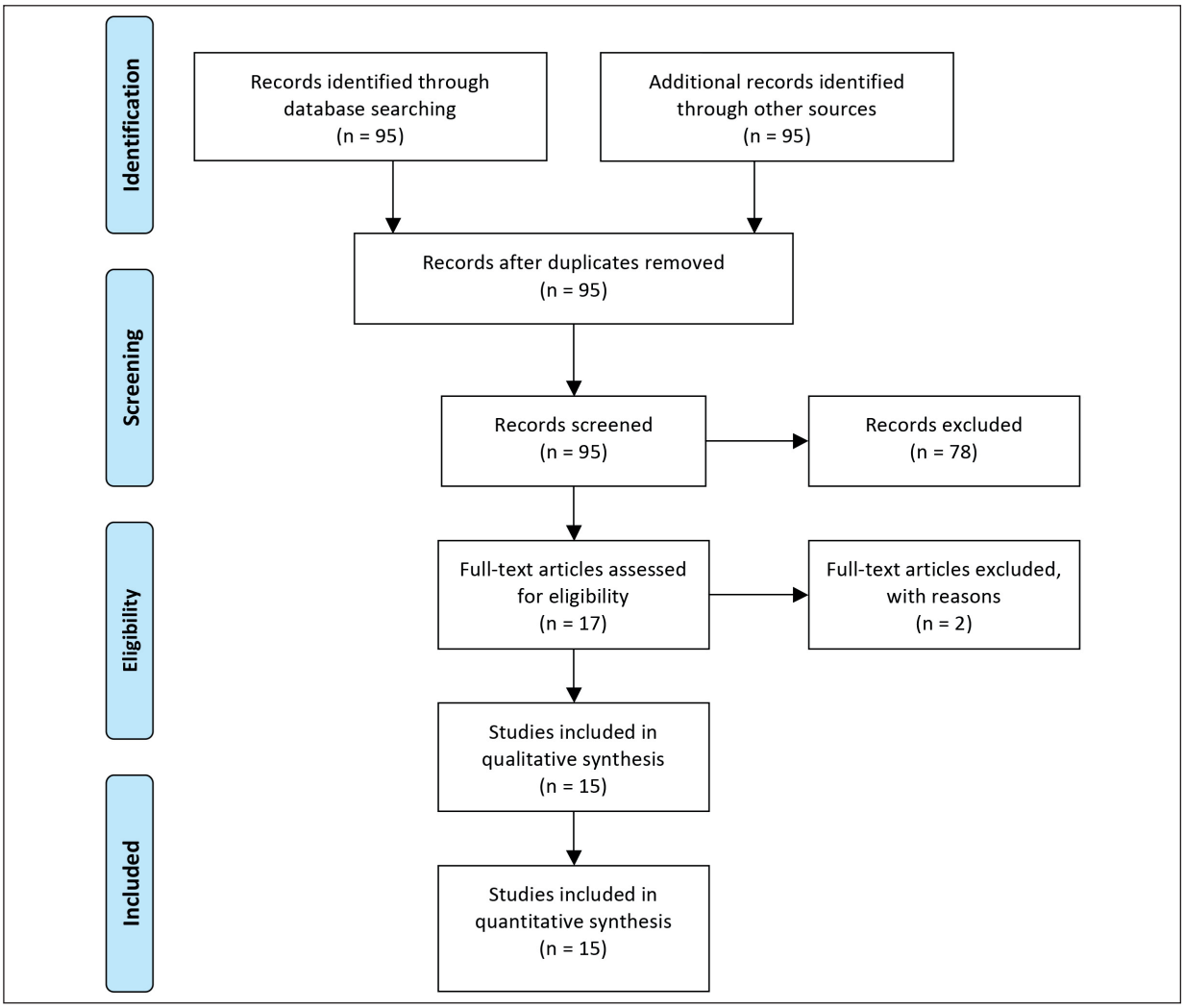

Figure 1. Selection of studies flowchart.

Table I. Summary of genome-centered studies.

Author	Year	Cases	Controls	Healthy controls	Primary disease	BP type	Gene	SNP	Biological Function
Sarasquete et al[8]	2008	22	65	NO	MM	Mostly pamidronate others zoledronate	*CYP2C8*	rs1934951	Arachidonic acid metabolism
Di Martino et al[9]	2011	9	10	NO	MM	Zoledronate	*PPARG*	rs1152003	Involved in adipocyte differentiation and angiogenesis
Nicoletti et al[10]	2012	30	17 +101	1743	Breast cancer	Zoledronate	*RBMS3*	rs17024608	Transcriptional factor that regulates Type I collagen in fibroblasts
Kim et al[12]	2015	16	NO	126	Unknown	Several	*PYGM* *ARSD* *SLC25A5* *CCNYL2*	10 SNPs	Only ARSD related to bone composition
Yang et al[13]	2018	58	51	NO	MM and solid tumor	Intravenous biphosphonate	*SIRT1*	rs7896005 rs3758391 rs7894483	NAD dependent deaceylase involved in several biological processes

MM: multiple myeloma, n/a: not applicable, SNP: single nucleotide polymorphism.

They concluded that individuals in treatment with zoledronic acid, carriers of CC nucleotides in the rs1152003 position in the *PPARG* gene presented 31 times greater probability of developing ONJ.

Nicoletti et al[10] published a second GWAS in which they studied over 733,000 genetic markers in the whole genome and particular genes in the *IGF* (insulin-like growth factor) family, genes related to vitamin D metabolism, and drug absorption, transport, metabolism, and excretion. They recruited 30 subjects with ONJ, 17 control subjects taking zoledronic acid, and 101 breast cancer patients exposed to BPs taken from the study by Ingle et al[11], who were included in control group, and another control group consisting of 1,743 healthy individuals not in treatment. They concluded that individual carriers of SNP rs17024608 in the gene *RBMS3* administered BPs presented almost six times greater probability of developing ONJ in comparison with healthy control subjects. But no significant differences were found in comparison with control group exposed to BPs.

Kim et al[12] analyzed the whole exome (all coding regions of genome) in 16 cases of ONJ by means of massive sequencing. These data were compared with variants found in 126 random samples drawn from a Korean population, considered a healthy reference population not in treatment, recruited from another study of thyroid cancer. They concluded that there were ten variants in four genes (*ARSD, SLC25A5, CCNYL2*, and *PGYM*) that showed significant association with the appearance of ONJ.

Lastly, Yang et al[13] studied exomes in 22 cases and 22 control subjects with multiple myeloma and 17 cases of solid stage-1 tumors. After *in silico* study of four SNPs obtaining significant association, three SNPs were selected from the *SIRT1* gene (rs7896005, rs3758391, and rs7894483) for later validation in all the samples selected: 39 cases and 22 control subjects at stage 1 and 19 cases and 29 controls in an independent sample. After multivariate logistic regression analysis, it was shown that the three SNPs were associated with odds ratios of 0.3, 0.26, and 0.26, respectively.

Gene-Centered Studies

Table II summarizes the ten gene-centered case-control studies reviewed. Four studied the association between ONJ and SNPs in the gene *CYP2C8*, two analyzed this association with the gene *VEGF*, another two SNPs in genes *CYP2C8* and *PPARG*, and the remaining four studied various genes.

Following the publication of the GWAS by Sarasquete et al[8], four research teams set out to replicate their results: English et al[14] sequenced the SNP rs1934951 in DNA samples from 100 patients with bone metastasis derived from prostate cancer in treatment with BPs. Of these, 17 were considered ONJ cases. Such et al[15], analyzed the same SNP in a population administered zoledronic acid for at least 18 months, subdivided as: 42 cases of multiple myeloma and ONJ, 37 with myeloma without ONJ, 45 healthy volunteers, and 120 reference control subjects taken from the Hap Map Project.

Balla et al[16] investigated the association between BP-related ONJ and the SNP rs1934951 in 46 cases who had been in treatment with BPs, of who 11 suffered osteoporosis and 35 presented various neoplasms. Control subjects comprised 224 healthy subjects. This was the only study to relate this variant with the localization of the ONJ lesion, which was found to be more probable in the mandibular region.

Katz et al[17] studied the SNPs described in the article by Sarasquete et al[8], as well as SNPs localized in other genes selected on the basis of their biological functions. This genetic study was performed in 78 patients with multiple myeloma taking zoledronic acid or intravenous (IV) pamidronate, of who 12 developed ONJ. Association with ONJ development was not found in any of the SNPs analyzed. Nevertheless, five combined SNPs of the genes *COL1A1, RANK, MMP2*, *OPG*, and *OPN* in relation to the smoking variable and the duration of BP treatment did present a significant association (OR, 11.2; $p<0.0097$).

Arduino et al[18] analyzed associations between ONJ and three SNPs of the *VEGF* gene (rs302539, rs699947, and rs2010963). The case/control group comprised 60 Italian women in treatment with zoledronic acid for both breast cancer and multiple myeloma, of whom 30 suffered ONJ while the others presented no ONJ symptoms. The control group consisted of 125 healthy subjects. No significant association was found, but applying statistical approximation by combining SNPs (haplotypes) the authors did detect a significant association between the AC genotype for SNPs rs699947 and rs2010963, respectively and ONJ in both treated group without complications (OR 3.11; $p<0.035$) and untreated group (OR 2.04; $p<0.008$).

Marini et al[19] studied the presence of SNP rs2297480 of the *FDPS* gene in 68 individuals taking zoledronic acid for multiple myeloma, breast cancer, and prostate cancer. Of the whole sample, 34 suffered ONJ and 34 did not.

Table II. Summary of gene-centered studies.

Author	Year	Cases	Controls	Healthy controls	Primary disease	BP type	Gene	SNP	Significance (variant number)	Biological Function
English et al[14]	2010	17	83	NO	Prostate cancer	Most zoledronate	*CYP2C8*	rs1934951	NO	Arachidonic acid metabolism
Such et al[15]	2011	42	37	45 + 120	MM	Zoledronate	*CYP2C8*	rs1934951	NO	Arachidonic acid metabolism
Katz et al[17]	2011	12	66	NO	MM	Zoledronate and/or pamidronate	*COL1A1*, *MMP2, RANK, OPG*, *OPN, TNF*, *CYP2C8*	10 SNPs	NO separately create an algorithm with 5 SNPs of genes COL1A1, MMP2, RANK, OPG, OPN	Related to osteoporosis, bone mineral density, osteonecrosis, osteoclastogenesis, bone resorption, and ONJ
Arduino et al[18]	2011	30	30	125	Breast cancer, MM	Zoledronic acid	*VEGF*	rs3025039 rs699947 rs2010963	YES (haplotype)	Angiogenesis
Marini et al[19]	2011	34	34	NO	Breast and prostate cancer, MM	Zoledronic acid	*FDPS*	rs2297480	YES (1)	Cholesterol metabolism
Balla et al[16]	2012	46	NO	224	Several	Combination of BPs	*CYP2C8*	rs1934951	NO Only related to the location of ONJ	Arachidonic acid metabolism
Stockmann et al[20]	2013	94	110	NO	Cancer	Various	*HLA-DRB1* *HLA-DQB1*	Multiple gene locus	YES (4)	Osteoimmunology metabolism
La Ferla et al[21]	2012	30	53	NO	Breast and prostate cancer, MM	Zoledronic acid	*ER* …….. *CYP19A1*	rs2234693 rs9340799 …….. rs10046	YES (4)	Fundamental role in osteoclast function and angiogenesis
Choi et al[22]	2015	26	19	NO	Mostly osteoporosis	Various	*VEGF*	rs3025039 rs699947 rs2010963	YES (1)	Angiogenesis
Kastritis et al[23]	2017	36	104	NO	MM	Zoledronic acid	*CYP2C8* *PPARG*	rs1934951 rs1152003	NO	Angiogenesis and bone remodeling

MM: multiple myeloma; BP: bisphosphonate; SNP: single nucleotide polymorphism.

They concluded that there is an association between ONJ and AA genotype carriers (p=0.033), while the non-appearance of ONJ is associated with CC genotype carriers (p=0.045).

Stockmann et al[20] analyzed the association between ONJ and the genes *HLA-DRB1* and *HLA-DQB1* of the major histocompatibility complex. This genetic study was performed with 94 patients with ONJ and 110 without. Four SNPs were found to present an association with ONJ with an OR ≥ 2 (DRB1*15 p=0.0014; DRB1*01 p=0.049; DQB1*05:01 p=0.05; DQB1*06:02 p=0.014).

La Ferla et al[21] investigated two SNPs, rs2234693 and rs9340799, in the estrogen receptor gene (*ER*) and another SNP, rs10046, in the *CYPI9A1* (aromatase) gene. The total sample consisted of 83 subjects of whom 30 were cases and 53 controls, all presenting different types of neoplasm. All subjects were taking zoledronic acid IV on a monthly basis. No significant differences were found in the allelic distribution of *ER* gene SNPs between the groups. But they did find a higher proportion of TT allele of the *CYPI9A1* gene among case subjects compared to controls, 36.67% and 16.98%, respectively (p=0.0439; OR=2.83).

Choi et al[22] analyzed three SNPs of the *VEGF* gene (rs3025039, rs699947, and rs2010963) in 44 individuals with osteoporosis, 26 of them with ONJ. Distribution of CC genotype in rs2010963 and rs302539 among case and control subjects was significantly different, p=0.04 and p=0.03, respectively. In addition, the authors noted that the combination of SNPs with CGT genotype for rs699947/rs2010963/rs302539 had a protective effect against developing ONJ.

Kastritis et al[23] analyzed the cosegregation of SNPs rs1934951 and rs1152003 of *CYP2C8* and *PPARG* genes in relation to the appearance of ONJ in 140 patients with multiple myeloma taking zoledronic acid. They concluded that the appearance of ONJ in 36 of the patients had no relation to the genotype analyzed in the study.

Summarizing the 15 articles reviewed, nine found associations between some SNPs and the appearance of ONJ, five in genome-centered[8-13], and four in gene-centered studies[19-22] (Table III). It is remarkable that none of the genome-centered works reflect or reiterate the findings of any of the gene-centered studies. Of all the works reviewed, only two – neither of them genomic studies – investigated patients with osteoporosis[16,22]. Lastly, two studies did not use patients with BP tolerance as control subjects[12,16], drawing data from databases[10,15,18], while one study used control data drawn exclusively from a healthy population[16].

Discussion

Pharmacogenomics is a part of what is known as personalized medicine, making it possible to optimize the therapeutic action of drugs and avoid any toxic effects. Interindividual differences together with the dynamic conditions of each specific case are responsible for the particular responses that each patient presents to each drug. Numerous studies have attempted to determine which genes are involved in the development of medication-related ONJ and to determine the impact that certain genetic variants have on the incidence of ONJ. To do so, some authors have investigated genes that participate in drug metabolism, while others have studied the genes involved in bone metabolism.

In 2008, Sarasquete et al[8] published the first study to explore a genetic association between the appearance of ONJ and BP administration. The study used molecular biology techniques that were avant-garde for the time, and powerful statistical analyses, finding a significant relation between the SNP rs1934951 of the *CYP2C8* gene and ONJ. Afterwards, other authors attempted to reproduce the study with different patient cohorts but none reached the same conclusion[14-17]. In 2013, Zhong et al[24] published a meta-analysis bringing together data drawn from most of the studies mentioned above, but failed to establish any statistically significant relations. These authors blamed a lack of homogeneity in the underlying pathology as the main cause for the failure to reach statistical power. Nevertheless, this approach did obtain significant results using data obtained exclusively from cases of multiple myeloma. It was concluded that further research should focus on the influence of BPs other than zoledronic acid, recruit larger patient samples to boost statistical power, and continue to investigate multiple myeloma to confirm the suspected association. It was not until 2017 that another study that met these criteria was published. Kastritis et al[23] studied the SNP rs1934951 of the *CYP2C8* gene in a cohort of 36 cases and 104 control subjects with multiple myeloma in treatment with zoledronic acid, but failed to find any statistical significance.

In parallel to these studies, other works have studied polymorphisms in the *VEGF* gene (vascular endothelial growth factor) in patients with osteonecrosis of the femoral head[25]. Several of these studies were analyzed by Hong et al[26] in their meta-analysis, which demonstrated the existence of an association between the SNP rs2010963 of the

Table III. Studies with significant association.

Type of study	Authors	Gene	SNP	Statistical significance	Association (Odds Ratio)
Genome centered	Sarasquete et al[8]	*CYP2C8*	rs1934951	$p=1.07 \times 10^{-6}$	12.75
	Di Martino et al[9]	*PPARG*	rs1152003	$p=0.0055$	31.5
	Nicoletti et al[10]	*RBMS3*	rs17024608	$p=7.47 \times 10^{-8}$	5.8
	Kim et al[12]	*ARSD*, *SLC25A5*, *CCNYL2*, *PYGM*	10 SNPs	$p<0.05$	–
	Yang et al[13]	*SIRT1*	rs7896005 rs3758391 rs7894483	$p=0.003$ $p=0.0004$ $p=0.004$	0.3 0.26 0.26
Gene centered	Marini et al[19]	*FDPS*	rs2297480	$p=0.03$	–
	Stockmann et al[20]	HLA-DRB1 HLA-DQB1 	DRB1*01 DRB1*15 DQB1*05:01 DQB1*06:02	$p=0.049$ $p=0.014$ $p=0.050$ $p=0.014$	2 2.3 2 2.3
	La Ferla et al[21]	*CYP19A1*	rs10046	$p=0.0439$	2.83
	Choi et al[22]	*VEGF*	rs3025039 rs2010963	$p=0.03$ $p=0.04$	0.17 17.66

VEGF gene and risk of developing osteonecrosis of the femoral head. However, the meta-analysis revealed a number of risks of bias, mainly the limited number of articles included for analysis, the absence of other risk factors that should be taken into account, and the study population, which was exclusively Asian. Following on from this hypothesis, Arduino et al[18] studied the same association in women with breast cancer. They demonstrated the relation between ONJ and AC haplotype (rs699947/rs2010963) of the *VEGF* gene, although they stressed the need for further research. Later, this study was repeated successfully among a Korean population by Choi et al[22], with a smaller number of cases and control subjects, a population of patients with osteoporosis. The authors found an association between the CC genotype of rs2010963 and the appearance of ONJ. However, when the study was repeated using haplotypes, it did not manage to replicate the same significance obtained by Arduino et al[18] for the AC haplotype. Vincenzi et al[27] studied VEGF in sera of patients in treatment with BPs and found that those who developed ONJ showed larger decreases in VEGF concentration 7 and 21 days after IV BP administration. BPs interact with the mevalonate pathway, which is necessary for bone remodeling, in which VEGF is an essential modulator[28]. VEGF induces neoangiogenesis, stimulating capillary proliferation, permeability, and migration, regulated by a series of angiogenic and antiangiogenic factors. Sustained and persistent angiogenesis appears in certain diseases such as diabetes mellitus, rheumatoid arthritis, psoriasis, and tumor progression. For this reason, therapy directed against VEGF is a widely used tool in antitumor strategy[29]. Studies[30] performed in oncological patients treated with zoledronic acid support this hypothesis, observing a decrease in VEGF levels in blood. Classically, osteonecrosis has been considered to constitute an interruption in the vascular supply or vascular necrosis, so it is not surprising that the hypothesis of angiogenesis inhibition is gaining ground as a pointer to the etiopathogenesis of ONJ[31]. Although it has been demonstrated that suppression of the angiogenic pathway could contribute to the development of ONJ, genetic studies that seek variants related to this pathway are scarce. In 2015, Fung et al[32] published a review of articles related to pharmacogenetics and the appearance of BP-related ONJ. The review included 12 articles, and pointed out the methodological limitations of the works, mainly due to small sample sizes.

None of the five works classified as full genomic studies coincide in their results[8-13]. All four had small sample sizes with fewer than 30 cases – a major statistical limitation. Nor did they investigate the same underlying pathology or the same BP regime. Moreover, two works used healthy populations not in treatment by BPs as control groups. As for the genetic studies reviewed, most focused on oncological populations. As patients were treated with BPs intravenously, it could be expected that

this would have greater impact on the appearance of ONJ. Nevertheless, this hypothesis is questionable as the duration of BP administration will be considerably shorter than that of patients in treatment for osteoporosis. Only two articles of the 15 cohort studies included patients with osteoporosis[16,22]. Given the high prevalence of osteoporosis in the general population, it could be expected that the incidence of complications such as ONJ would be comparatively high among this patient group, allowing recruitment of larger numbers of cases in retrospective studies, which would overcome one of the most noticeable limitations in all the works reviewed, namely, the small sample sizes.

Of the 15 studies reviewed, only one had more than 50 cases[20]. This work studied polymorphisms of the major histocompatibility complex, the first work to investigate this. Likewise, Marini et al[19] was the first to study *FDPS* genes and, La Ferla et al[21] the first to investigate ERα and CYP19A1. Although these three works did find statistically significant relations, they have had few repercussions as no further work has set out to reproduce the results.

The latest article by Yang et al[13] investigating genetic factors associated with the development of ONJ is of particular note. To increase the sample size, the authors made use of samples recruited in other projects and, applying cutting-edge technology on a large scale to investigate the exome, the experimental study was conducted in phases with a final validation of an independent sample[16,33]. The study affirmed the presence of three polymorphisms with a protective function in the *SIRT1* gene. Nevertheless, the impact of these SNPs was unclear, although the authors attributed them to *SIRT1* gene expression with possible involvement in the development of ONJ. So, this study adds a further hypothesis to the already extensive list of candidate genes, but without any relation with the others cited in earlier works.

Adequate experiment design is essential for obtaining reliable results. The appearance of ONJ has been clearly associated with BP administration, and so it is necessary to use a control group of BP-tolerant patients (in receipt of BPs but not presenting ONJ). To assess the role that genetic profile might play in predisposing individuals to ONJ, recruiting a control population of healthy subjects is clearly insufficient as it makes it impossible to isolate the variable (the effect of the drug) from statistical analysis of the genetic factor. For this reason, the drug-tolerant control group (in receipt of BP but ONJ-free) is essential for performing a robust study. The ideal would be to recruit a control group-taking BPs for the same pathology.

The introduction of new antiresorptive drugs such as denosumab and bevacizumab have been accompanied by increased concern over the role they might play in the appearance of complications such as ONJ[32,34,35]. There would appear to be some incipient evidence regarding the appearance of ONJ in relation to these drugs, which is similar to BP administration[1]. The use of these drugs remains infrequent due mainly to their recent introduction, the lack of clinical indications in support of their therapeutic use, and/or their cost. But it might be interesting to include these new drugs in future pharmacogenetic studies as the number of patients receiving them increases.

Conclusions

On the basis of the present review, which set out to determine the role played by genetic factors in predisposing individuals to a risk of developing medication-related ONJ, it is clear that future research will demand interhospital, and ideally international collaboration. Given the diversity of genes that have shown positive associations with ONJ and the lack of reproducibility of the studies, the role played by genetic causes would appear to be moderate and heterogeneous. For this reason, it is essential to recruit large patient cohorts to achieve relevant statistical power that would make it possible to reach definitive conclusions, and replicate studies that have obtained similar results. It is only by increasing sample sizes that the molecular mechanism that accompanies the appearance of ONJ will become clear, making it possible to establish clinical approaches of benefit to those patients at risk.

Conflict of Interests

The authors declare that they have no conflicts of interests.

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