

Anti-resorptive therapy and MRONJ. A survey of the Italian Society of Periodontology and Implantology

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Abstract

Objectives: Anti-resorptive agents have been linked to the development of MRONJ in patients undergoing dental surgical procedures. This survey aims to explore the level of knowledge and experience of Italian Society of Periodontology and Implantology members in the management of patients treated with anti-resorptive agents and with the risk of developing MRONJ.

Materials and Methods: An 18-item questionnaire was submitted by e-mail to the SIdP members. Statistical analyses were carried out. Continuous variables were described as mean \pm standard deviation (SD) or median, and first and third quartile according to distribution's normality. Normality of data was checked with Shapiro–Wilk test.

Results: Four hundred and fifty-one questionnaires were returned by e-mail (32%). Most of the respondents were private practitioners (81.8%). Only 47.7% declared to be highly confident in managing patients on anti-resorptive therapy while 92.5% reported to have performed tooth extractions and 52.3% implant surgery in patients under anti-resorptive therapy for osteometabolic disorders. One or more MRONJ-affected patients were encountered by 63.2% of the respondents.

Conclusions: This survey highlights the need to develop a “dedicated” program both for dentists and prescribers to improve the level of cooperation and to increase the level of awareness of patients treated with anti-resorptive agents.

KEYWORDS

anti-resorptive therapy, bisphosphonates denosumab, dentists, medication-related osteonecrosis of the jaws, periodontitis

1 | INTRODUCTION

Anti-resorptive (AR) agents (i.e. bisphosphonates and denosumab) are widely used and are the first-line option in patients at risk of fragility fracture due to osteoporosis (Gregson et al., 2022; Nuti et al., 2019). These drugs are also used in patients affected by solid tumor cancer (breast, prostate) and multiple myeloma (Campisi et al., 2020).

Medication-related osteonecrosis of the jaw (MRONJ) is a rare condition defined as an exposed bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that persist for more than 8 weeks in patients with a history of treatment with AR or anti-angiogenetic drugs and no history of radiation therapy or metastatic diseases of the jaws (Ruggiero et al., 2022). MRONJ if left untreated may lead to several complications including pain, purulent secretion from the area, general malaise, malodor, paresthesia and

in the more severe cases also fracture of the jawbone affecting the patient's quality of life (Cuozzo et al., 2022). Early diagnosis followed by a conservative treatment including control of periodontal inflammation, antiseptic and antibiotic treatment may lead to MRONJ resolution without the need of surgical resection of the necrotic bone area that may have severe consequences in terms of function and aesthetic (Nisi et al., 2018; Ramaglia et al., 2018).

The incidence of MRONJ in osteoporotic patients treated with AR drugs is reported to be quite low ranging from 0.02 to 0.9% (Everts-Graber et al., 2022; Fujieda et al., 2020; Ruggiero et al., 2022). Among cancer patients treated with AR or anti-angiogenetic drugs (SDCEP, 2017) these figures are nearly 10 times higher (8%) (Yamori et al., 2021). Dento-alveolar surgery, periodontal disease, diabetes, steroids treatment, and the duration of AR therapy may be considered risk indicators for developing MRONJ although it may occur spontaneously (Gaudin et al., 2015; Lo et al., 2010; Ramaglia et al., 2018).

Although MRONJ is a rare condition, it should be considered that in 2019, in Italy, around 5,000,000 individuals were affected by osteoporosis of whom 80% were post-menopausal women (Willers et al., 2022). These data are confirmed by the National Institute of Statistics (ISTAT) data relating to the year 2021, as 7.8% of the Italian population (13.2% of females and 2.1% of males) declared they were suffering from osteoporosis (<https://www.salute.gov.it/portale/donna/dettaglioContenutiDonna.jsp?area=Salute+donna&id=4491&menu=patologie#:~:text=Si%20stima%20che%20in%20Italia,sono%20donne%20in%20post%20menopausa>).

Furthermore, in terms of prevalence, in Italy, 3,600.00 individuals were affected by a form of cancer in 2020 (AIOM, 2022). Those numbers are deemed to increase in the next few decades as a consequence of the aging of the population, with an expected increase in the number of patients affected by osteoporosis, cancer and chronic diseases. Moreover, periodontitis, a worldwide highly prevalent chronic inflammatory disease, if left untreated, is the major cause of tooth loss in the adult population (Kassebaum et al., 2014). The previous can lead to partial or complete edentulism with a significant impact on masticatory function, aesthetics and the need of complex rehabilitation (Cairo et al., 2018). A recent population-based survey done by SIdP showed that in spite of the prevalence of periodontitis in Italy is estimated to be as high as 50% (Aimetti et al., 2015) only 17% of the respondents reported to have received a diagnosis of periodontitis (Raspini et al., 2021), underlying the need to increase diagnostic accuracy and patient awareness about this disease.

Within this scenario, dental professionals will be asked to face an increasingly higher number of patients with periodontitis and systemic diseases that may require the use of AR therapy, and, therefore, the risk of developing MRONJ, albeit low, may become significant in absolute numbers. We must also keep in mind that the risk of developing MRONJ as a consequence of AR therapy for osteometabolic disorders is much lower than the risk of a bone fragility fracture and, therefore, an objective and evidence-based information should be provided to the public. All these things

considered, dentists are likely to play a fundamental role in the primary prevention of MRONJ and in the patient's education about the beneficial role of AR therapy. Therefore, in order to promote and reinforce a tighter cooperation with prescribers to properly treat patients who undergo AR therapy, SIdP (Italian Society of Periodontology and Implantology) and SIOT (Italian Society of Orthopaedics and Traumatology) recently proposed algorithms for the management of patients affected by both osteoporosis and periodontitis (Landi et al., 2023).

One of the major issues in the prevention of MRONJ is the level of the awareness among prescribers, dentists and patients about the possible complication derived by using AR therapy. Dental students, general dental practitioners (GDP), oral and maxillofacial surgeons, prescribers and patients have been included in several surveys, carried out in different geographic areas, in the attempt to identify the level of knowledge, awareness and clinical experience about MRONJ (Al-Eid et al., 2020; Al-Samman & Al-Ani, 2019; Escovedo et al., 2018; Levin et al., 2020; Tanna et al., 2017). A wide range of results were collected indicating that more information and clear guidelines are needed in tackling this issue. As Italian data on this topic are missing, the Italian Society of Periodontology and Implantology (SIdP) carried out a survey aiming to investigate the knowledge, experience and training needs in a cohort of Italian dentist SIdP members in relation to the use of anti-resorptive therapy and MRONJ.

2 | MATERIALS AND METHODS

The cross-sectional study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. No personally identifiable data were collected, and responses were anonymous from the point of entry.

A 18-item questionnaire (Table 1) was prepared by the Italian Society of Periodontology and Implantology (SIdP) ad hoc committee and by the Board of directors to explore the level of knowledge, experience and training needs of SIdP members. The questionnaire was sent out by e-mail in June 2022 to all the dentists SIdP members in good standing with the membership for the year 2022. The members were asked to reply within a month and a reminder was sent 15 days after the starting of the survey. Questions involved single-choice and multiple-choice answers and were completely anonymous. The answers to the questionnaire were grouped in 5 different items and analyzed according to the goals of the survey:

- Demographic characteristics;
- Knowledge about indications, mechanisms of action of AR therapy and awareness of MRONJ as possible oral complication;
- Clinical experience in managing a patient under AR therapy;
- Frequency of MRONJ cases encountered in clinical activity;
- Need of clinical guidelines and training path for the dental and periodontal management of patients under AR therapy.



TABLE 1 Study questionnaire (translated from Italian).

<i>Demographic data</i>	
Age	
Biological sex	
Region in which the profession is practiced	
<i>Specific questions</i>	
1. Number of years of professional activity	
2. Type of professional activity	Public or private and public practice; Exclusively private practice
3. I update patients' medical history	
a. with regard to pathologies and/or multipathology	Occasionally; Frequently; All the time
b. with regard to the current pharmacotherapy	Occasionally; Frequently; All the time
4. In relation to any current pharmacological therapies I regularly take note	
	Medications taken; Reasons for taking medication; Medication dosages; The method and routes of administration of prescribed drugs; The duration of the therapy
5a. Have you ever treated patients on anti-resorptive drugs	Never; Occasionally; Frequently
5b. If so, patients took those drugs for reasons	Especially related to osteoporosis; Especially related to oncology
6. My level of general expertise regarding the pathologies for which drugs most related to medication-related osteonecrosis of the jaws (MRONJ) are used is	Insufficient; sufficient; good; very good
7. My main source of information regarding MRONJ are	PubMed and/or Databases of scientific literature; Guidelines proposed by national or international organizations; Participation in Conferences or Conferences on the topic; Documents proposed by CAO, FNOMCeO or other organizations; Other
8. I believe that my level of expertise on medication-related osteonecrosis of the jaws (MRONJ) is	
a. with regard to drugs that may induce it	Insufficient; sufficient; good; very good
b. with regard to the mode of administration of drugs that can induce it	Insufficient; sufficient; good; very good
c. regarding the suspicion or clinical diagnosis of MRONJ	Insufficient; sufficient; good; very good
d. with regard to the protocols to be used in the event a patient on anti-resorptive therapy for osteoporosis needs invasive dental intervention (for example the extraction of one or two teeth)	Insufficient; sufficient; good; very good
9. I believe that my level of familiarity in the dental management of a patient taking MRONJ-related drugs is	Insufficient; sufficient; good; very good
10a. Have you ever performed extractions in patients on anti-resorptive therapy	Never; Yes, but only in osteoporotic patients; Yes, but only in cancer patients; Yes, both in osteoporotic patients and in cancer patients
10b. Have you ever placed implants in patients on anti-resorptive therapy	

TABLE 1 (Continued)

	Never; Yes, but only in osteoporotic patients; Yes, but only in cancer patients
11. Have you ever come in contact with a patient affected by MRONJ in your practice?	Never; Once; Two/Three Times; More Than Three Times
a. In case of a positive response, have you ever had cases of MRONJ in patients taking anti-resorptive drugs for osteoporosis?	Never; Once; Two/Three Times; More Than Three Times
b. In case of a positive response, have you ever had cases of MRONJ in patients taking anti-resorptive drugs for oncological reasons?	Never; Once; Two/Three Times; More Than Three Times
c. In case of a positive response, can you identify a potential trigger for MRONJ? (Multiple answers are possible)	No; Tooth extraction; Implant placement; Prosthetic trauma; Other
d. In case of a positive response, did you treat the patient with MRONJ in the office or did you refer him to an external health center?	Treated in office; Referred to an external health center
12. Have you ever received letters from the doctors treating your patients, before starting treatment with bisphosphonates or Denosumab for oncological or osteometabolic conditions, asking for an evaluation and possible dental treatment?	Never; Once; Occasionally by oncologists; Occasionally by the general practitioner; Occasionally by other specialists; Several times
13. In your experience, are patients receiving bisphosphonates or Denosumab aware of the possible risk of developing MRONJ in relation to invasive dental procedures?	
a. In case of osteoporotic patients	No, in my experience; Occasionally, because informed by the prescribing doctor; Occasionally, for reading the leaflet of the drug; Often
b. In case of cancer patients	No, in my experience; Occasionally, because informed by the prescribing doctor; Occasionally, for reading the leaflet of the drug; Often
14. Have you ever independently suggested patient to discontinue bisphosphonates or Denosumab therapy before invasive dental therapy?	No; Yes; Yes, but only on the recommendation of the prescriber
15. Which of the following diseases is considered, in a subject treated with bisphosphonates or Denosumab, an additional risk factor for the development of MRONJ	Hypertension; Oral Lichen Planus; Degenerative neuropathy; Diabetes
16. Which of the following drugs is considered, in a subject treated with bisphosphonates or Denosumab, an additional risk factor for the development of MRONJ	Antihypertensives; Beta blockers; Corticosteroids; Benzodiazepines
17a. Would you consider useful for the Italian Society of Periodontology and Implantology and the Italian Society of Orthopedics and Traumatology to collaborate and develop training material for dentists on the subject of MRONJ?	I don't think it can be useful; Useful; Very useful

(Continues)

TABLE 1 (Continued)

- 17b. Would you consider useful and appropriate that specific Italian recommendations or guidelines on MRONJ were developed and disseminated?
- Not particularly useful; Useful; Very useful
- 17c. If you answered yes to the previous question, in what format could this material be structured?
- With a poster; With a guideline from the Ministry of Health; With a free FAD course that awards CME credits; With all three methods described above
18. With reference to Medication-Related Osteonecrosis of the Jaws, would you like to make personal considerations or comments?

2.1 | Statistical analysis

Continuous variables were described as mean \pm standard deviation (SD) or median, and first and third quartile (q1-q3), according to distribution's normality. Normality of data was checked with Shapiro-Wilk test. Dichotomous variables, including numbers of answers to the questionnaire, were expressed as numbers and percentages. In order to analyze whether age of responders, responders' years of professional activity, and responders' type of professional activity (public or private and public vs. exclusively private practice) influenced the responses some sub-analyses were carried out. Forty-one years of age was chosen as the cut-off to identify two groups. The threshold (41 years of age) was consistent with the age limit to be included in the "SIdP Young category." In relation to responders' years of professional activity, the respondents were divided into two categories: professionals with ≤ 25 years of professional activity, and professionals with ≥ 26 years of professional activity, choosing this threshold since it is the median. Therefore, to compare whether professionals belonging to different categories gave significantly different answers, we performed contingency tables and compared answers using Pearson's χ^2 or Fisher's exact test, as appropriate. Statistical analysis was performed using Stata software, StataCorp, 4905 Lakeway Drive, College Station, Texas 77,845 USA. Statistical significance was set at $p \leq 0.05$.

3 | RESULTS

A total of 1410 dentists were counted as SIdP members at the end of May 2022. The questionnaire was sent by e-mail, and they were asked to reply within a month. The survey was closed on June 28th, 2022, and 451 members filled out the questionnaire with a redemption rate of 32.0%.

3.1 | Item 1: Demographic characteristics

Demographic characteristics of the sample can be seen in Table 2. Briefly, the average age of the respondents was 54 and 80.7% were male and 19.3% female. Most of the dentists (369, 81.8%) were

TABLE 2 Socio-demographic data of study participants.

Characteristic	
Total, <i>n</i> (%)	451
Age, median (q1-q3), years	54 (42-60)
Male, <i>n</i> (%)	364 (80.7)
Female, <i>n</i> (%)	87 (19.3)
Years of professional activity, median (q1-q3), years	26 (16-34)
Type of professional activity	
Public or private and public practice, <i>n</i> (%)	82 (18.2)
Exclusively private practice, <i>n</i> (%)	369 (81.8)
Region in which the profession is practiced	
Abruzzo, <i>n</i> (%)	15 (3.3)
Basilicata, <i>n</i> (%)	3 (0.7)
Calabria, <i>n</i> (%)	3 (0.7)
Campania, <i>n</i> (%)	33 (7.3)
Emilia-Romagna, <i>n</i> (%)	48 (10.6)
Friuli-Venezia Giulia, <i>n</i> (%)	15 (3.3)
Lazio, <i>n</i> (%)	65 (14.4)
Liguria, <i>n</i> (%)	11 (2.4)
Lombardia, <i>n</i> (%)	74 (16.4)
Marche, <i>n</i> (%)	12 (2.7)
Molise, <i>n</i> (%)	3 (0.7)
Piemonte, <i>n</i> (%)	42 (9.3)
Puglia, <i>n</i> (%)	27 (6.0)
Sardegna, <i>n</i> (%)	5 (1.1)
Sicilia, <i>n</i> (%)	12 (2.7)
Toscana, <i>n</i> (%)	35 (7.8)
Trentino-Alto Adige, <i>n</i> (%)	8 (1.8)
Umbria, <i>n</i> (%)	9 (2.0)
Valle d'Aosta, <i>n</i> (%)	1 (0.2)
Veneto, <i>n</i> (%)	30 (6.7)

Abbreviations: q1, first quartile; q3, third quartile.

involved only in private practice, while 82 (18.2%) were working both in public and private facilities. While SIdP members are distributed along the entire country, over 2/3 of the respondents were based in the center and north of Italy.

3.2 | Item 2: Knowledge about indications, mechanisms of action of AR therapy and awareness of MRONJ as possible oral complication

A high percentage (85.5%) of SIdP dentists updated the patient's past medical history frequently. As for medications in particular, the update was carried out on a regular basis by an even larger number of dentists (94.2%).

Almost all the respondents (98.4%) dealt with patients undergoing AR therapy in their practice and 186 (41.2%) encountered those type of patients frequently. Most of the time the

patients were on AR therapy for osteometabolic disorders (93.9%) (Questions 5a, b).

As for the indications for AR therapy, 49.9% of the sample claimed to have a good level of knowledge about the diseases and conditions that may require those medications, while the other half of the sample considered their level inadequate or nearly sufficient.

In terms of understanding the MRONJ, about half of the respondents stated they have good or optimal level of knowledge while the rest of the sample declared they have insufficient or barely sufficient background on MRONJ (Questions 8 a, b, c). However, 413 (91.6%) dentists indicated diabetes as an additional risk factor for MRONJ in case on AR therapy (Question 14) and 87.6% of the respondents also considered the use of corticosteroid an issue for the development of an MRONJ (Question 15).

3.3 | Item 3: Clinical experience in managing a patient under AR therapy

Two Hundred and fifteen dentists (47.7%) declared to be highly confident in managing patients assuming drugs potentially related to MRONJ (Question 9), while 92.5% of the respondents declared to have performed at least one tooth extraction in patients undergoing AR therapy mainly for osteometabolic disorders (Question 9a). In the case of implant surgery, the figures were quite different as 215 dentists (47.7%) never performed an implant surgery in a patient undergoing AR therapy. It is worth noting that only 5 out of the total number of the respondents placed implants in patients taking AR therapy for oncologic reasons (Question 9b).

3.4 | Item 4: Frequency of MRONJ cases encountered in clinical activity

Interestingly when the dentists were asked if they have ever encountered a MRONJ-affected patient, 63.2% of the respondents stated they managed at least one patient with MRONJ. Seventy-two (16.0%) more than 3 patients, while 213 (47.2%) between 1 and 3 patients (Question 11), [Figure 1](#).

In those cases, the patient was most frequently referred to the hospital for treatment (169) 59.3%, while 40.7% of the dentists decided to manage the patient in their office.

3.5 | Item 5: Need of clinical guidelines and training path for dental and periodontal management of patients under AR therapy

Domestic or international guidelines offered by scientific entities were considered as the primary source of information for 51.4% of the respondent (Question 7), [Figure 2](#).

The patient's level of awareness regarding the MRONJ as a possible complication of the AR therapy was perceived as quite low by the respondents. In case of AR therapy for metabolic bone diseases,

60.3% of the dentists reported the information received by the patients were sporadic, while for 23.3% of the sample of patients were not at all informed about the possible side effects of AR therapy. Almost the same figures could be seen in the case of AR therapy for oncologic reasons, although patients were more often considered well informed (26.2%) compared to those treated for osteoporosis (16.4%) (Questions 13 a, b), [Figure 3](#).

Suspension of the AR therapy was decided autonomously by 10.6% of the dentists, while 52.8% never asked the patient to stop AR therapy. A tight collaboration with the prescribers to suspend AR therapy before dental treatment was carried out was reported by 36.6% of the sample. (Question 13).

The level of cooperation among specialists was also investigated and only 30.6% of the respondents professed a good level of collaboration between bone specialists, endocrinologists, oncologists, family doctors, and dentists. In most of cases this joint effort was only occasional and 20% of the time it was totally absent.

3.6 | Sub-set analyses

In order to evaluate the impact of age and years of professional activity on the different items, a sub-set analysis was also performed. Young SIdP category dedicated activities with specific training and education programs and the results might also indicate special needs of this younger clinicians in this matter. The results of sub-set analyses are reported in the [Appendix S1](#).

In short, 96 (21.3%) dentists were under 41, and 355 (78.7%) were equal or older than 41. Although the two groups were not homogenous, this sub-set analysis revealed some statistically significant differences. The younger group included more women (39.6%) than men compared to those in the >40-year-old group (13.8%).

As expected, the younger group had been in practice for an average of 8 years (q1-q3: 4-12), much less than the more experienced dentists who had been in practice for an average of 30 years (q1-q3: 22-35).

Younger dentists worked more frequently in private and public facilities (33.3%) compared to the older group (14.1%) and the difference is statistically significant ($p < 0.01$). This result must be interpreted with caution as some of the younger dentists may be involved in specialty programs and not be employed in a public facility.

More experienced dentists belonging to the >41-year group updated the past medical history more frequently than their younger colleagues ($p < 0.01$) and treated more patients undergoing AR therapy either for extraction or dental implant placement ($p < 0.01$) (Questions 5a, b, 10, a, b). Furthermore, this group stated a higher patients' awareness of MRONJ as a possible consequence of AR therapy compared to the group of younger dentists. This difference was mainly related to oncologic patients who were undergoing AR therapy.

Younger respondents seemed to be more confident in dealing with AR therapy and MRONJ compared to their older colleagues although this difference was not statistically relevant ($p < 0.17$). No other statistically significant differences were reported.

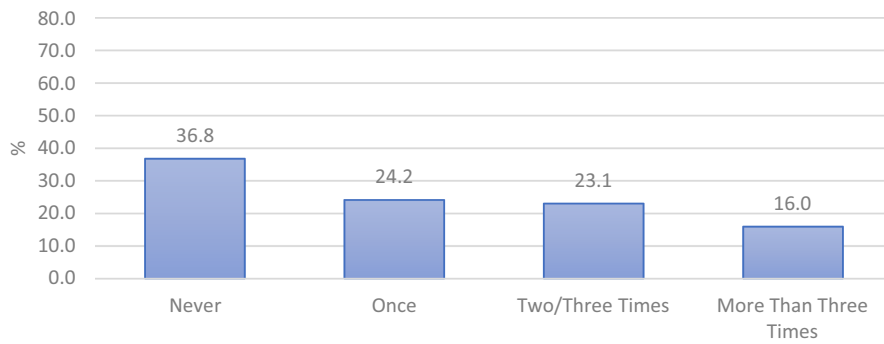


FIGURE 1 Answers related to question 7: responders' source of information regarding MRONJ.

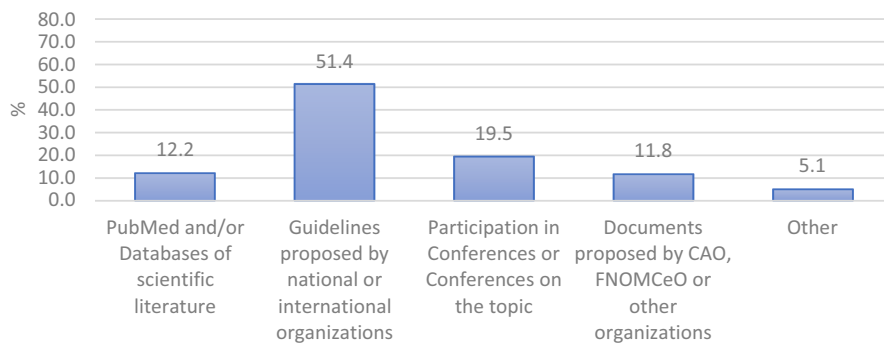


FIGURE 2 Answers related to question 11: responders' number of contacts with patients affected by MRONJ.

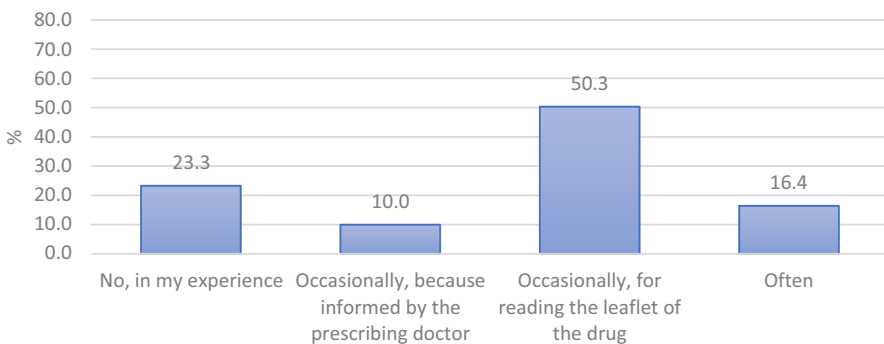
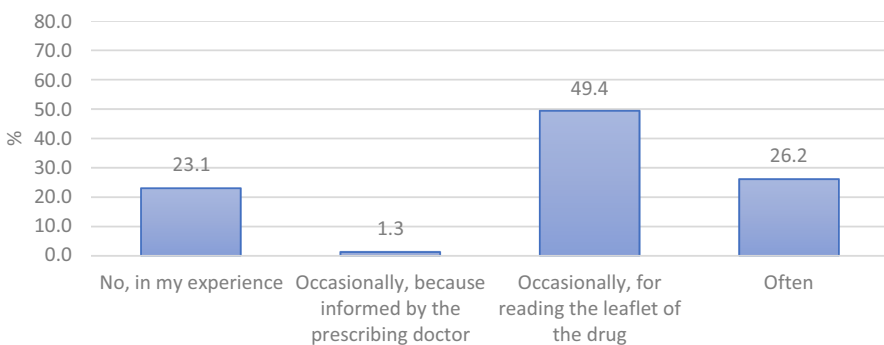


FIGURE 3 Answers related to question 13a, and 13b: patients' awareness, according to responders, of possible risk of developing MRONJ in relation to invasive dental procedures. Upper: in case of osteoporotic patients; Lower: in case of cancer patients.



4 | DISCUSSION

The current survey was designed to assess both the awareness and the knowledge that dentists and periodontists, SIdP members, could offer in terms of the use of anti-resorptive therapy and the risk of MRONJ. The response rate obtained (32%) is in line with those described in previous similar surveys (Yamori et al., 2021).

The big picture arising from the current data depicts professionals that are frequently exposed to the management of patients

undergoing anti-resorptive medications potentially related to MRONJ and who are in need to improve their knowledge and expertise in dealing with this clinical issue.

The history of knowledge and awareness on anti-resorptive and ONJ is complex and dramatically evolved during the last two decades.

Although the first report about AR-related osteonecrosis of the jaws dates back over 20years (Marx, 2003), it was only after 4years later (2007) that the first position paper on the subject was

published by the American Association of Oral and Maxillofacial Surgeons (AAOMS).

In those early years the level of information of both patients and dental care professionals was reasonably low.

In 2010, Migliorati and coworkers shed light upon the knowledge of patients on bisphosphonate regarding both their indications for therapy and the presence of possible adverse reactions.

They reported that 82% of the patients could not recall if they had been told about the risk of experiencing adverse reactions, including oral osteonecrosis, by their physicians. (Migliorati et al., 2010). The authors suggested that: "...a more effective communication process between prescribing physicians, dentists and patients using bisphosphonates is needed..."

Where are we now? Since then, many position papers were published providing detailed information on MRONJ diagnosis and treatment (Campisi et al., 2020; Chang et al., 2017; Hilder et al., 2020; Landi et al., 2023; Mauceri et al., 2022; Yoneda et al., 2017).

In our cohort, Scientific Society Position Papers represent indeed the most used tool for the improvement of knowledge among dentists (Item 2, question 7).

Over the years, the evolving evidence from literature registered a heterogeneous level of interest and awareness in the clinical community involved in the control of the oral and dental ONJ risk factors before starting AR therapy.

While several previous reports highlighted that a low proportion of prescribers still do not routinely refer their patients to dentists before initiating AR therapy (Taguchi et al., 2016), a recent survey surprisingly showed that 90% of a sample of urologists from Austria and Germany declare they implemented referrals to dentists for oral examination before initiating AR (Calderaro et al., 2023).

Unfortunately, the crosstalk between prescribers and dentists is only partially represented in the current dental survey in which only 30% of the respondents receive on a regular basis request for a dental evaluation from the prescriber before starting AR therapy (Item 12).

The need to establish a closer collaboration with the prescribers and to improve the knowledge on this issue emerged clearly from our survey with about half of the cohort of the interviewed dentists admit an insufficient or barely sufficient knowledge of the matter.

This proportion is higher than that found in a similar previous survey (Al-Samman & Al-Ani, 2019) in which only 33% of general dental practitioners claim to have adequate knowledge about MRONJ.

Promisingly, in the current research, the subgroup analysis shows that younger dentists (<41 years old) are more aware of patients undergoing AR therapy and their clinical implications.

According to the results of our survey, about 60% of the respondents reported to have encountered and managed at least 1 case of MRONJ. This proportion is rather high compared with the low incidence of this complication reported in a recent retrospective survey

where MRONJ cases ranged from 0,55 to 0,9% (Everts-Graber et al., 2022).

Our results are in line with previous reports (Campisi et al., 2020; Mauceri et al., 2022) and support the hypothesis that a significant number of MRONJ cases may not be notified to the national regulatory agencies of drugs (e.g., FDA in the United States or AIFA in Italy), therefore, underestimating both the prevalence and incidence of this condition.

Furthermore, this finding is partially corroborated by the high proportion of dentists (50%) that in the current survey treat the osteonecrosis in a private practice facility (Item 4, Question 11d).

Patients' awareness is undoubtedly an important component of the medical alliance for both prevention and treatment of MRONJ.

In the current survey, the level of the patient's knowledge about the clinical implications of being under AR therapy was very low (Item 2, question 13a), and the cohort of involved dentists recognized an insufficient level of education in more than 60% of their patients; moreover 20% of them were perceived as "completely unaware."

Even if these data represent the dentist's perception and not the actual level of information of the patients, they still suggest the need to improve the patient's level of education (Acharya et al., 2022). Evidence confirms that the level of communication among physicians, dentists and patients is fairly inappropriate (Choi et al., 2022). In this regard, a recent paper from the United Kingdom performed a qualitative evaluation of the patient's attitude and perception toward the multidisciplinary approach in the prevention of MRONJ. Patients demonstrated positive attitudes toward a multidisciplinary approach to care; however, they perceived prescribers as having the key role in articulating risk. Moreover they perceived the need of interprofessional patient education to mitigate the risk of developing MRONJ (Sturrock et al., 2019).

Nevertheless, the above reported results must be interpreted with caution: even if the geographical distribution of professionals was homogeneous throughout the entire country, it is not representative of the entirety of the Italian dental practitioners (more than 60.000 in 2022). In fact, the source from which the final sample was obtained is a scientific society (i.e., SidP), which includes specialists in periodontology and general dentist with specific training in periodontology. These last characteristics may have increased the level of sensitivity and knowledge of the interviewees.

Ultimately, this selection bias might have led to more promising results with an underestimation of MRONJ risk and an overestimation of competence and knowledge from the professionals.

Eventually, an important critical aspect that emerged from the survey is represented by the limited frequency of adverse drug reactions events reported by dental professionals.

Prevention and early diagnosis of MRONJ are critical to reduce incidence and complications of this pathological condition. There is very low evidence that periodontal treatment may be associated with MRONJ occurrence, but periodontal diseases was reported as the trigger for MRONJ in some cases (Ramaglia et al., 2018). However,

the treatment of periodontal disease combined with a supportive periodontal care program have shown to reduce gingival inflammation and tooth loss in the long term, which are considered risk factors for MRONJ. The establishment of early conservative treatment approaches has been shown to be effective in reducing the need for an extensive surgical resective approach, and stage-specific therapy should be promoted (Ramaglia et al., 2018).

For these reasons, continuing education programs involving both physicians and dental professionals (dentists and dental hygienists) are required for competent stakeholders (academic institutions, scientific societies, medical associations, regulatory agencies of drugs) to promote the culture of pharmacovigilance in oral and periodontal health.

5 | CONCLUSIONS

It is now well established that MRONJ, in subjects taking anti-resorptive drugs for osteoporosis, is a rare event. However, MRONJ, albeit rarely, is a severe side effect of Bisphosphonates and Denosumab, which are, after Vitamin D, the most frequently prescribed drugs for the treatment of osteoporosis in Italy (Osservatorio Nazionale per l'Impiego dei Farmaci, 2022).

Dentists should be more aware and updated regarding this issue, given the increasing number of patients undergoing AR therapy. Moreover, it is also important that patients treated with these drugs should be informed by the prescriber regarding this rare side effect and it is desirable that a greater collaboration between the prescriber and the dentist could be established.

There is a need, from the data obtained from this cross-sectional study, to provide in Italy interventions aiming to develop major awareness, training, and updating for dentists on this issue.

AUTHOR CONTRIBUTIONS

L. Landi: Conceptualization; writing – original draft; writing – review and editing; supervision. **G. Oteri:** Writing – original draft; writing – review and editing. **L. Barbato:** Writing – original draft; writing – review and editing. **N. Discepoli:** Writing – original draft; writing – review and editing. **A. M. Carrassi:** Writing – review and editing; conceptualization; writing – original draft. **M. Rigoni:** Formal analysis; data curation; writing – review and editing. **F. Cairo:** Writing – review and editing. **R. Cavalcanti:** Writing – review and editing; supervision. **A. Crea:** Writing – review and editing; supervision. **R. Gianserra:** Writing – review and editing; supervision. **N. M. Sforza:** Conceptualization; writing – original draft; writing – review and editing; supervision.

ACKNOWLEDGEMENTS

The Authors would like to thank Manuela Bertelli, Lorenzo Benedetti and Roberta Nastasi from the SIdP office for their invaluable help in the dissemination and collection of the questionnaire.

CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Luca Landi at <http://www.surveymronjsidp.it> and in the Appendix S1.

CONSENT FOR PUBLICATION

All the authors gave their consent for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Landi, L., Oteri, G., Barbato, L., Discepoli, N., Carrassi, A. M., Rigoni, M., Cairo, F., Cavalcanti, R., Crea, A., Gianserra, R., & Sforza, N. M. (2024). Anti-resorptive therapy and MRONJ. A survey of the Italian Society of Periodontology and Implantology. *Oral Diseases*, 00, 1–10. <https://doi.org/10.1111/odi.14907>