

Comparison of nonexposed and exposed bisphosphonate-induced osteonecrosis of the jaws: a retrospective analysis from the Copenhagen cohort and a proposal for an updated classification system

Morten Schiodt, DDS, Dr.odont,^a Jesper Reibel, DDS, Dr.odont, PhD,^b Peter Oturai, MD,^c and Thomas Kofod, DDS, PhD^d
Rigshospitalet and University of Copenhagen, Copenhagen, Denmark

Objective. Nonexposed osteonecrosis of the jaws (NE-ONJ) does not fit into the current definition of osteonecrosis, which requires exposed bone. A modification of the classification of bisphosphonate-induced osteonecrosis of the jaws (ONJ) is proposed. This study aimed to test proposed criteria for NE-ONJ and compare NE-ONJ with exposed ONJ (E-ONJ) in a retrospective analysis.

Study Design. In 102 patients with E-ONJ diagnosed according to Ruggiero et al. (2006, 2009), criteria for NE-ONJ were developed. Subgroups of NE-ONJ and E-ONJ were tested against each other using nonparametric and parametric statistics.

Results. Among 102 patients with ONJ, 14 had NE-ONJ and 88 had E-ONJ. NE-ONJ and E-ONJ were similar in all important data ($P > .05$) except bone exposure.

Conclusions. NE-ONJ belongs to the same disease condition as E-ONJ. NE-ONJ may be otherwise classified as ONJ stage 1, 2, or 3 and is different from ONJ stage 0. We propose to include the criteria for NE-ONJ into the classification. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:204-213)

Bisphosphonates (BPs) are well-established medications for reducing skeletal morbidity in patients with multiple myeloma or metastases from breast cancer, prostate cancer, and other malignant diseases, as well as some benign skeletal conditions.¹⁻³ However, since 2003, osteonecrosis of the jaws (ONJ) has been widely identified as a complication to these medical treatments.⁴⁻⁹ The need for proper definition and classification of ONJ was soon recognized and addressed in a number of position papers.¹⁰⁻¹⁴ The clinical definition of ONJ by Ruggiero et al. in 2006¹⁰ (exposed bone for more than 8 weeks in a patient treated with a BP and without irradiation for head and neck cancer), as well as the ONJ classification into 3 stages, has been widely accepted.⁹⁻¹⁰ The definition is, however, not inclusive, as ONJ cases may occur where bone is not clinically

exposed.¹⁵⁻²² Such cases have been named “nonexposed osteonecrosis.”²⁰⁻²²

The proportion of nonexposed ONJ (NE-ONJ) may vary and be as high as 29% to 45%.¹⁹⁻²⁰ This fact may lead to potential underreporting in epidemiologic studies. Ruggiero et al.¹⁴ introduced the term “stage 0” in their revision of the American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper and assigned stage 0 to cases with no clinical evidence of necrotic bone (see details in Table I). Stage 0 cases are by definition characterized by nonspecific changes, whereas the proposed group of NE-ONJ includes symptoms and findings that in combination are believed to represent “true” ONJ. Thus, Bagan et al.²¹ reported 6 cases of NE-ONJ that could not be classified even after the revised AAOMS definition. Stage 0 includes some cases that will qualify as NE-ONJ but also some that presumably are not true ONJ (for example, widening of lamina dura around teeth). The details of

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^aConsultant Oral and Maxillofacial Surgeon, Department of Oral & Maxillofacial Surgery, Rigshospitalet, University Hospital of Copenhagen.

^bProfessor, Section of Oral Medicine, Clinical Oral Physiology, Oral Pathology and Anatomy, Department of Odontology, University of Copenhagen.

^cDepartment of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, University Hospital of Copenhagen.

^dHead, Consultant Oral and Maxillofacial Surgeon, Department of Oral & Maxillofacial Surgery, Rigshospitalet, University Hospital of Copenhagen.

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Statement of Clinical Relevance

Nonexposed osteonecrosis of the jaws (ONJ) does not fulfill the current definition of ONJ, but it belongs to the same disease as exposed ONJ. A classification that includes nonexposed ONJ is proposed. This classification may improve reliability of epidemiologic studies by identifying the full spectrum of ONJ.

similarities and differences between stage 0 ONJ and the proposed group of NE-ONJ appear in [Table I](#).

It is imperative that clinicians and researchers have access to a disease definition and classification that include all the relevant patients who are assumed to have the same disease. However, if NE-ONJ is to be included in the group of ONJs, we need to establish that there is every probability that NE-ONJ and E-ONJ belong to the same biologic disease condition.

In Copenhagen we have established a cohort of patients with ONJ since November 2005. A large number of systematic data have been collected prospectively in the charts, and the patients have been followed up longitudinally with treatment interventions (Schiodt et al. 2013, International Association of Oral & Maxillofacial Surgery Congress, Barcelona, Spain, October 2013, abstract No. 1180). Based on a retrospective review of the charts, we propose the hypothesis that NE-ONJ and E-ONJ belong to the same biologic disease group and should be classified together. Furthermore, we propose a modified classification that includes NE-ONJ (see [Table I](#)).

The main purpose of the present study was to develop criteria for NE-ONJ and to examine if the subgroups of NE-ONJ and E-ONJ differed from each other with regard to demographic parameters, oral symptoms, clinical features, imaging characteristics, and life survival. The secondary purpose was to propose a classification based on the new findings.

MATERIALS AND METHODS

A retrospective chart review was performed of all patients with ONJ examined from November 1, 2005, to January 1, 2013, referred to the Department of Oral & Maxillofacial Surgery at Rigshospitalet, Copenhagen University, Denmark. Patients were included if they met the following criteria: (1) present or previous BP or other antiresorptive treatment; (2) no previous radiation to the jaws; and (3) presence of exposed bone for 8 weeks or more.^{10,14} This group is referred to as “exposed ONJ (E-ONJ)” (see [Table I](#)).

Patients were also included if they met the following criteria: (1) present or previous bisphosphonate or other antiresorptive treatment; (2) no previous radiation to the jaws; (3) no exposed bone in the oral cavity; (4) one or more of findings 4a to 4d, which are (4a) intraoral or extraoral fistula; (4b) jaw pain; (4c) swelling; and (4d) sequestrum formation on imaging (odontogenic causes such as periapical inflammation or cysts were ruled out); plus (4e) necrotic bone on histopathology. If a specimen is available, item 4e is mandatory. This group is referred to as “nonexposed ONJ” (NE-ONJ) (see [Table I](#)).

Ethics

All patients in this study have been examined, diagnosed, and treated according to the standards and ethical

principles for Rigshospitalet and the Capital Region of Denmark. This study is a retrospective study based on existing chart data, anonymized to patient identification, and does not involve any experimental component.

Chart review

Each patient had a routine chart recorded. The data included demographic parameters; basic disease; and type, dose, and duration of BP treatment or other antiresorptive agents. BP treatment was further grouped into either “high-dose BP” (for patients with cancer) or “low-dose BP” (for patients with osteoporosis), regardless of whether the drug administration was intravenous, subcutaneous, or oral with tablets. Oral symptoms and jaw pain using a visual analog scale (VAS) (0-10) were recorded. VAS was recorded since 2010. Presence of dental/oral trauma such as tooth extraction before onset of ONJ was recorded, including the time from the trauma to referral. Panoramic radiographs were taken for all patients. Bone scintigraphy (using Tc-99m-oxidronate [Technescan; Mallinckrodt, St Louis, MO, USA] as radiotracer and often including SPECT/CT) and cone beam computed tomography were performed when possible. All patients who had surgery done also had bone tissue specimens submitted for histopathologic examination with regard to vitality of bone marrow and exclusion of malignancy. Oral symptoms (VAS) and ONJ stage were recorded at the initial visit and at each follow-up visit. Each patient was classified as either E-ONJ or NE-ONJ. In addition to this, each patient was classified as having ONJ stage 1, 2, or 3.^{10,14} No patients with ONJ stage 0¹⁴ were included in this study. No patients were referred to us with stage 0 without symptoms.

The subgroup of NE-ONJ was analyzed with regard to possible development into E-ONJ within the observation time. The time from enrollment to development into E-ONJ or surgical treatment was recorded. Life survival analyses were calculated on the basis of date of inclusion (date of referral) into the ONJ cohort and by using January 1, 2013, as the cutoff date for all patients. Patients were followed up in the cohort for variable time, but information on life status was obtained for all patients by January 1, 2013. If a patient had died before January 1, 2013, the date of death was recorded and life table analyses were performed that spanned from the date of referral to either the date of death or, for the living patients, January 1, 2013.

Statistics

The 2 subgroups of NE-ONJ and E-ONJ were compared using nonparametric statistics (Fisher exact test or χ^2 test) for frequencies of characteristics ([Tables II to VIII](#)) and using the Student independent *t* test to calculate the mean values of parametric data.

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