Nationwide Multicentric Retrospective and Prospective Epidemiologic Survey of Bisphosphonate-related Osteonecrosis of the Jaws

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LIST OF PAPERS RELATED TO THE SUBJECT OF THE THESIS

I. **Vereb T**, Boda K, Czakó L, Vaszilkó M, Fülöp G, Klenk G, Janovszky Á, Oberna F, Piffkó J, Seres L.: Cloud-based multicenter data collection and epidemiologic analysis of bisphosphonate-related osteonecrosis of the jaws in a Central European population. J Clin Med 2020; 9: 426.
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II. **Vereb T**, Janovszky Á, Mucsi M, Piffkó J, Seres L.: Aktualitások a gyógyszer okozta állcsontelhalás primer és szekunder prevenciójának stratégiájában az evidenciák és a nemzetközi ajánlások tükrében. [Current evidence-based approaches and international guidelines in primary and secondary prevention strategies of medication-related osteonecrosis of the jaws] Orv Hetil 2020; 161: 214-223. [Hungarian]
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III. **Vereb T**, Vetró É, Piffkó J, Seres L.: A biszfoszfonát okozta állcsontnekrózisok. Magyar Urológa, 2012, 24: 153-158.

LIST OF PAPERS NOT RELATED TO THE SUBJECT OF THE THESIS

I. Janovszky Á, **Vereb T**, Szabó A, Piffkó J.: Aktuális trendek a gyógyszer indukálta állcsontnecrosis korai felismerése és kezelési stratégiája terén. [Current approaches for early detection and treatment of medication-related osteonecrosis of jaw] Orv Hetil 2014; 155: 1960-1966. [Hungarian]
Q3

II. Lóderer Z, **Vereb T**, Paczona R, Janovszky Á, Piffkó J.: An anterolateral thigh chimeric flap for dynamic facial and esthetic reconstruction after oncological surgery in the maxillofacial region: a case report. Head & Face Med 2018; 14: 7.
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III. Antal M, Szabó RM, Juhász Z, **Vereb T**, Piffkó J.: A COVID–19-vírusfertőzés klinikai felismerését szolgáló új információk és a fej-nyaki régióban dolgozó egészségügyi személyzet védekezésének lehetőségei. [Essential new information for the clinical recognition of COVID-19 infection and the prevention possibilities of healthcare personnel working in the head and neck region] Orv Hetil 2020; 161: 660–666. [Hungarian]
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IV. **Vereb T**, Augusztin LÉ, Seres L, Piffkó J.: Transzplantált betegek fogorvosi-szájsebészeti ellátásának alapelvei [Principles of dental care of transplanted patients] Orv Hetil 2020; 161: 1507-1514. [Hungarian]
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V. Sarvari KP, Santha D, Kovacs R, Kormondi S, Peto Z, **Vereb T,** Sztano B.: Six cases of Solobacterium moorei isolated alone or in mixed culture in Hungary and comparison with previously published cases Anaerobe 2020; 10224 - in press
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List of abbreviations

AAOMS	-	American Association of Oral and Maxillofacial Surgeons
ADR	-	adverse drug reaction
ANOVA	-	analysis of variance
AR	-	antiresorptive
BP	-	bisphosphonate
BRONJ	-	bisphosphonate related osteonecrosis of the jaws
cc.	-	cancer
CI		confidence interval
CTLA4	-	cytotoxic T-lymphocyte-associated antigen-4
EGFR	-	epidermal growth factor receptors
FDA	-	Food and Drug Administration (US)
MRONJ	-	medication related osteonecrosis of the jaws
mTOR	-	mammalian target of rapamycin
ONJ	-	osteonecrosis of the jaws
OPG	-	osteoprotegerin
OPGL	-	osteoprotegerin ligand
PDGFR	-	platelet-derived growth factor receptor
RANK	-	receptor activator of nuclear factor kappa-B
SPSS	-	Statistical Package for the Social Sciences
TKI	-	tyrosine kinase inhibitor
VEGFR	-	vascular endothelial growth factor receptor

Summary of the thesis

Introduction: Bisphosphonate-related osteonecrosis of the jaws is considered to be a rare but severe complication of bisphosphonate therapy. The presumably multifactorial pathomechanisms of medication-related osteonecrosis of the jaws have not been fully elucidated so far. To understand this condition better data collection is essential. Although the number of scientific papers about this subject is large, only a few multicenter reports have been published. Management of this serious side effect is a real challenge and requires a multidisciplinary approach.

Material and methods: We present a novel cloud-based data collection system for the evaluation of the risk factors of bisphosphonate-related osteonecrosis of the jaws. Web-based questionnaire and database have been set up and made available to voluntary researchers and clinicians in oral and maxillofacial surgery in Hungary and Slovakia.

Results: To date, fifteen colleagues from eight maxillofacial units have joined the study. Data of 180 patients have been recorded. Collected data were statistically analysed and evaluated from an epidemiological point of view.

Discussions: Authors consider cloud-based multicenter data collection a useful tool that allows for real-time collaboration between users, facilitates fast data entry and analysis, and thus considerably contributes to widening our knowledge of bisphosphonate-related osteonecrosis of the jaws.

Conclusions: Although several issues are still open regarding the management of the disorder, this study may help to develop evidence-based, individualized, stage-adapted therapeutic strategies that will replace the previous empirical treatment.

I. Introduction

1.1. Definition of MRONJ and its changes

Bisphosphonates (BPs) are considered to be the "gold standard" of the treatment of some osteologic (osteoporosis, rheumatoid arthritis, Paget-disease) and metastatic oncologic diseases. BPs have an antiresorptive effect on bones and they effectively reduce pathological bone pain and the frequency of skeletal related events. They also decrease intraosseous tumor growth and tumor-induced hypercalcaemia; and finally, they improve the patient's quality of life. The first known cases of medication related osteonecrosis of the jaw (MRONJ) were published in the literature in 2003 [Marx 2003][Ruggiero 2004]. These cases have been related to BP treatments, therefore, this adverse drug reaction (ADR) was named bisphosphonate-related osteonecrosis of the jaw (BRONJ) [Migliorati 2005]. The first Position Paper in this topic from the American Association of Oral and Maxillofacial Surgeons (AAOMS) also used this nomenclature [Ruggiero 2009].

Definition of BRONJ (AAOMS 2009)	**Definition of MRONJ (AAOMS 2014)**
1. Current or previous treatment with a bisphosphonate	1. Current or previous treatment with ***antiresorptive or antiangiogenic agents***
2. Exposed bone in the maxillofacial region that has persisted for more than 8 weeks	2. Exposed bone or ***bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region*** that has persisted for more than eight weeks
3. No history of radiation therapy to the jaws	3. No history of radiation therapy to the jaws or ***obvious metastatic disease to the jaws***.

Table 1. Changes in the nomenclature and definition of bisphosphonate/medication related osteonecrosis of the jaws.

Osteonecrosis of the jaw has been observed in connection with several new groups of drugs since 2009, so it became necessary to amend the terminology, definition and description of the disease. This condition has been referred to as medication-related osteonecrosis of the jaws (MRONJ) by the AAOMS since 2014 [Ruggiero 2009]. The changes in definition are illustrated in Table 1 [Vereb 2020].

1.2. Potential pathomechanisms of MRONJ

The pathomechanism of MRONJ has not been completely clarified so far. Several hypotheses were imposed to elucidate the full process of osteonecrosis that develops in the maxilla or in the mandible. It is most likely that the multifactorial disease is a consequence of the interaction of drugs acting at different biochemical points of attack and signaling pathways with trigger factors from the external environment [Aghaloo 2016][Ikebe 2013][Otto 2010][Otto 2015][Ristow 2014][Wat 2016]. Figure 1 shows the several local and systemic factors that are thought to play an important role in the development of the disease. The possible pathophysiological theories of MRONJ development are discussed in more detail in the following subsections.

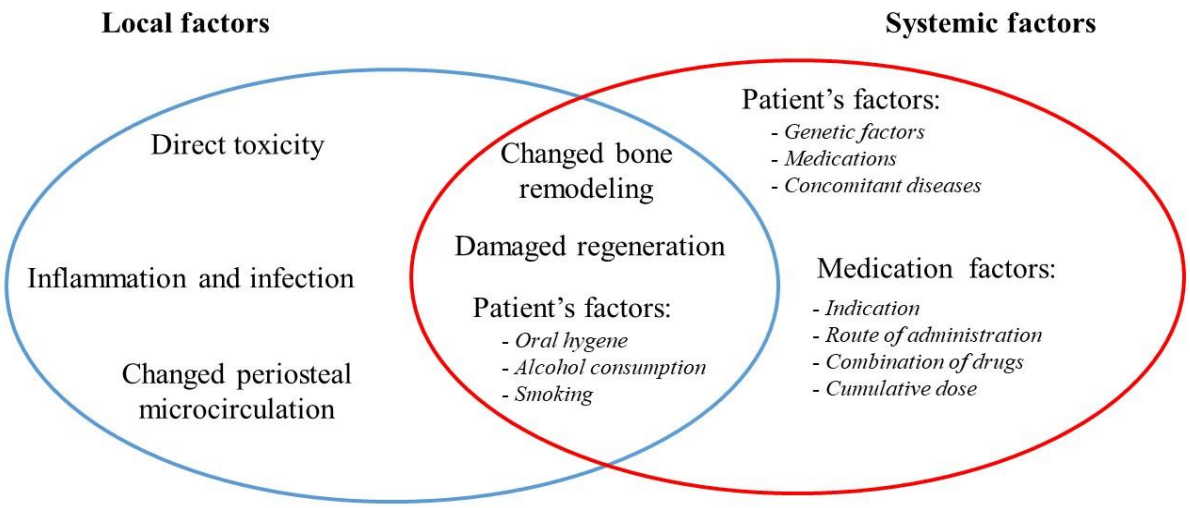

Figure 1. Local and systemic factors of MRONJ

1.2.1. Changes in bone remodelling

Bone remodeling - a balance between bone resorption and bone formation - is a complex mechanism regulated by paracrine, autocrine and endocrine hormones. If this pathway is disturbed, different pathological conditions may develop. Antiresorptive drugs inhibit not only osteoclast activity directly and indirectly, but through this inhibition osteoblast-osteoclast coupling and thus osteoblast functional activity are also injured, as demonstrated by numerous studies [Aguirre 2012][Janovszky 2014][Kobayashi 2010][Yamashita 2011].

1.2.2. Inhibition of angiogenesis

Bone regeneration depends not only on bone remodeling, but also on blood supply and angiogenesis. Tooth extraction related tissue ischemia initiates an inflammatory cascade, which promotes the expression of different hypoxia-induced angiogenic factors [Sharma 2013]. A considerable contribution of VEGF in the pathogenesis of MRONJ can be presumed, since suppression of this protein or its signaling pathway alone can provoke the development of MRONJ. However, antiresorptive treatment in combination with antiangiogenic drugs can significantly increase the incidence of this severe disorder [Aragon-Ching 2009][Mozzati 2012][Pakosch 2012]. This theory is supported by several studies investigating antiangiogenic effects of bisphosphonates [Kobayashi 2010][Pabst 2014] [Wood 2002].

1.2.3. Inflammation and infection

Local contamination and infection after invasive dental procedures in bisphosphonate-treated patients have also been emphasized in the pathogenesis of MRONJ [Mawardi 2011][Wei 2012]. Biofilm formation promoting the effect of BP’s may establish this concept [Kumar 2010] [Sedghizadeh 2008], but clinical experience contradicts this theory, since MRONJ can develop several years after tooth extraction, too.

BP administration can upregulate the expression of pro-inflammatory cytokines (e.g. Il-1 or TNF-alpha), consequently an enhancement of leukocyte–endothelial cell interactions, which is more pronounced in the mandibular periosteum and has not been observed in any other skeletal location yet [Anastasilakis AD 2012][Norton JT 2011][Senel FC 2010][Yu YY 2012].

1.2.4. Soft tissue toxicity

The biological utilization significantly differs depending on the administration way of BPs. Gastrointestinal absorption is approximately 1%, as long as intravenous absorption is about 60%. This is followed by binding to the bone surface [Ezra 2000], where these drugs exert their effect, and periosteal stem cells responsible for bone regeneration can be found [Allen 2004][Chappuis 2012][Xie 2008].
After prolonged use, BPs accumulate in the skeleton, and reach the highest concentration in the mandible. Potentially a toxic level may develop, which may affect cellular mechanism and bone regeneration, leading to the development of MRONJ [Açil 2012][Agis 2010][Kimmel 2007] [Marolt 2012] [Naidu 2008] Reid 2007][Scheper 2009].

1.2.5. Dysfunctions of immune system

Immune system is responsible not only for defensive mechanisms against infective agents, but also for regenerative mechanisms. These signaling pathways can be affected by BPs in different manners. Clinical studies have revealed that some BPs can elevate the level of pro-inflammatory cytokines, such as TNF-alpha [Anastasilakis 2012][Katz 2011][Tzermpos 2013], although interestingly it was not observed in animal studies [Janovszky 2015]. Polymorphonuclear leukocytes activated by inflammatory cascade showed alteration in number and functional activity [Hagelauer 2014] [Kuiper 2012][Salvolini 2009], which were investigated as a biomarker for MRONJ susceptibility [Favot 2013]. After chronic BP treatment, altered chemotaxis and enhanced leukocyte-endothelial interactions can be observed in the mandibular periosteum, presumably mediated by different degrees of endothelium-derived adhesion molecule expression at the different anatomical locations [Janovszky 2015].

1.3. Staging and clinical appearance of MRONJ

Based on the Position Paper of AAOMS 5 stages of MRONJ can be distinguished according to their severity [Ruggiero 2014]:

At risk: no apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates

Stage 0*:* no clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms

Stage 1: exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection

Stage 2: exposed and necrotic bone or fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage

Stage 3: exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor (Figure 2)

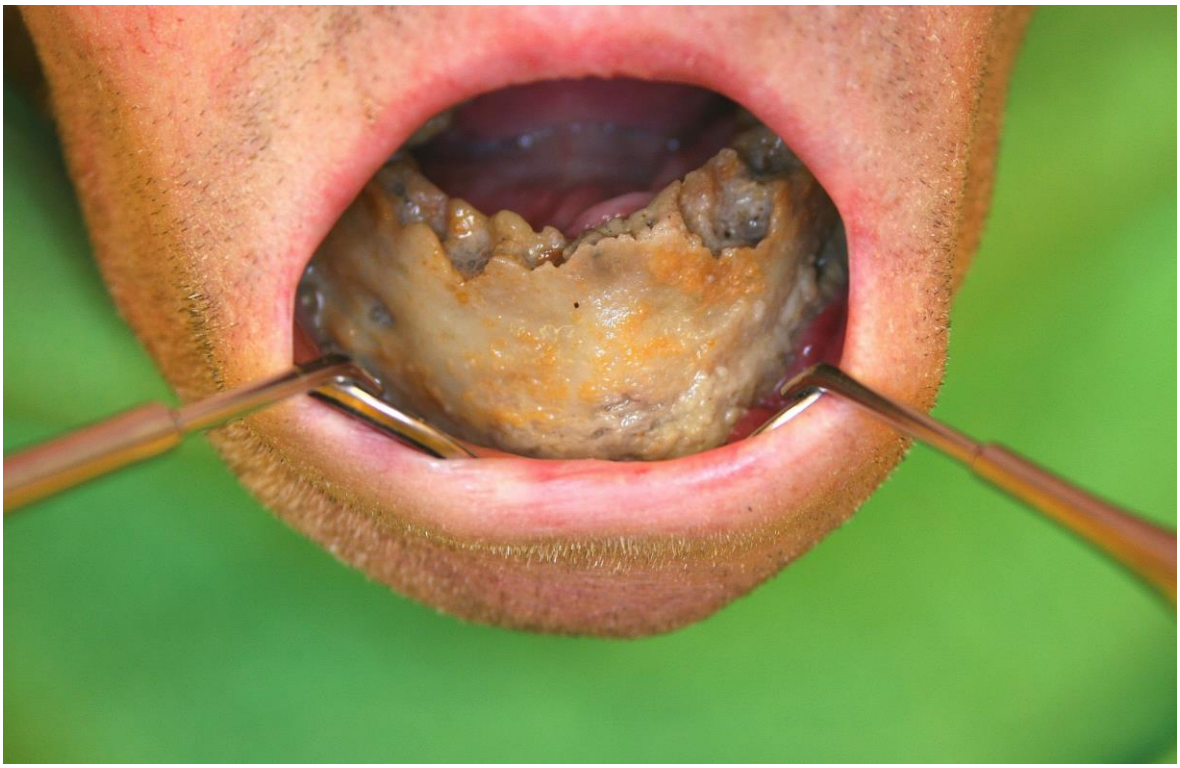

Figure 2. Severe osteonecrosis of the mandible (MRONJ stage 3 caused by intravenous BP)

1.4. Medications causing potentially MRONJ

As a result of modern oncologic treatments, increased life expectancies and significantly improved quality of life have become available to patients. However, studies have reported a decrease in bone density and bone loss as a result of long-term hormone ablation treatments (eg.: breast and prostate cancer) [Brufsky 2008].
In addition to bisphosphonates, other antiresorptive agents with better pharmacokinetics have been developed to treat these side effects [Hellstein 2011][Uyanne 2014][Van den Wyngaert 2011]. Explosive development of biological target therapies have led to the detection of additional MRONJ cases in association with non-antiresorptive medications [Abel Mahedi Mohamed 2018][King 2019][Patel 2015].

1.4.1. Pharmacology of bisphosphonates

Bisphosphonates (BPs) are widely used for the treatment of osteolytic conditions, such as osteoporosis, oncological diseases with bone metastasis or multiplex myeloma [Ruggiero 2014]. These antiresorptive drugs are pyrophosphate analogs, where oxygen is replaced by a carbon atom, resulting in a stable molecule against hydrolytic enzymes. They contain two side-chains (R1 and R2) attaching to the central carbon atom. At position R1 all BPs contain a hydroxyl side-group, which is responsible for the quality of binding to bone. R2 side-chain determines the physicochemical and biological properties of BPs, especially in case of nitrogen-containing BPs, which are generally considered to be the most efficient antiresorptive drugs [Cremers 2011][Ebetino 2011][Rogers 2011].

A distinction is made between BPs, according to the development (first- (e.g. etidronate, clodronate), second- (e.g. alendronate and pamidronate), third-generation (e.g. zoledronate, olpadronate and neridronate) compounds) or nitrogen content. Latter is clinically more relevant as more severe side-effects (i.e. osteonecrosis) have been attributed to BPs containing nitrogen [Marx 2003][Ruggiero 2004]. The therapeutic effect of BPs is linked to the inhibition of functional activity of osteoclasts, leading to the inhibition of bone resorption and a reduction of bone turnover [Brozoski 2012][Rodan 1998].

The mechanism of action shows differences as a function of the nitrogen content [Luckman 1998] [Mönkkönen 2006]. Beside their antiresorptive effect, BPs may inhibit antiangiogenic signaling pathway by the modification of VEGF or VEGF receptor expressions [Smidt-Hansen 2013] [Wood 2002], the migration of different cell types, influencing regeneration [Koch 2011] [Ohba 2014][Ziebart 2013], and also modulate immunological processes [Kalyan 2014][Sasaki 2013] (Figure 3).

The therapeutic indication or the severity of skeletal disorders may determine the route of administration, the dose or the frequencies of BPs. Gastrointestinal absorption by paracellular transport is about 1%, irrespective of nitrogen content, while BPs administered intravenously may show 60% bioavailability [Cremers 2011][Ezra 2000]. It is well-known that BPs can affect bone remodeling for several years, owing to their long half-life (~ 10 years) [Brozoski 2012].

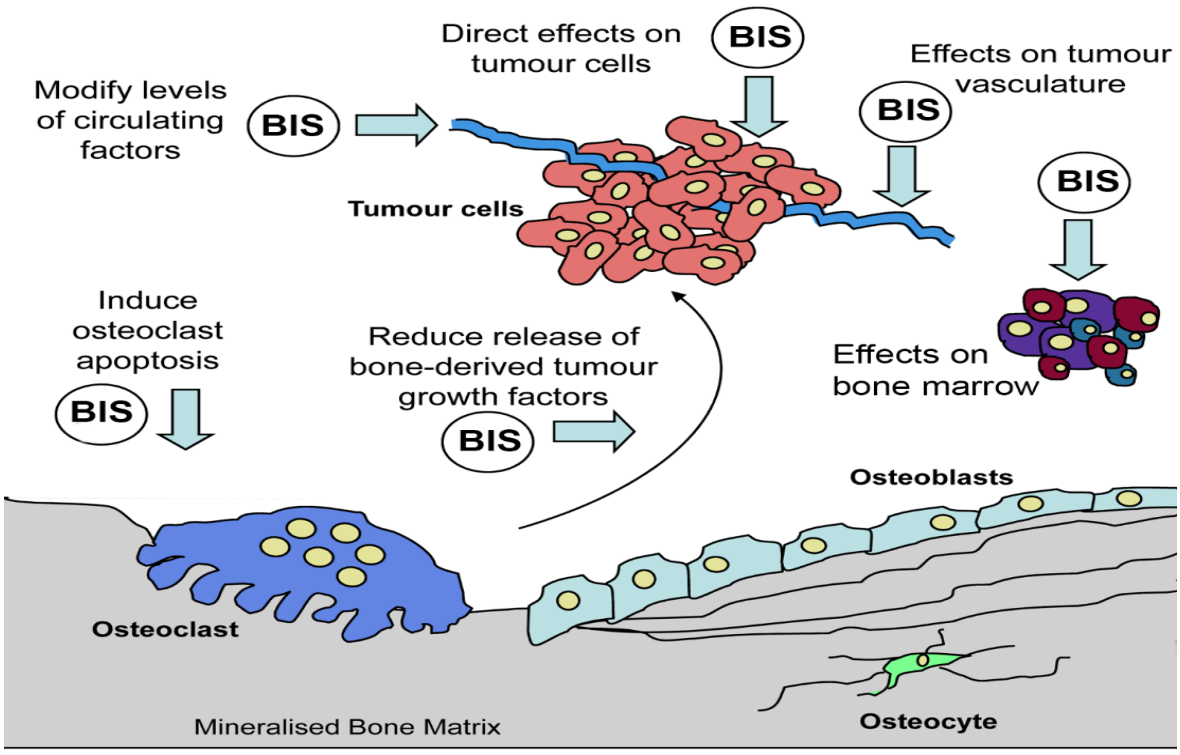

Figure 3. The effects of bisphosphonates [Holen 2010]

1.4.2. Pharmacology of RANKL inhibitors (denosumab)

Receptor activator of nuclear factor kappa-B ligand (RANKL) is one of the most important factors that regulates bone remodeling [Walsh 2014]. Denosumab is a fully human monoclonal antibody that specifically binds and inactivates RANKL. Denosumab has provided a breakthrough in the treatment of osteoporosis, multiple myeloma and solid tumors with bone metastases.

By binding to RANKL, denosumab affects the key signaling pathway involved in bone remodeling and disrupts the cycle of bone destructions stimulated by the metastasized tumor cells [Chiu 2017][Tanaka 2018][Tanaka 2019][Van Dam 2019]. Inhibition of the RANKL inhibits osteoclast maturation and activity, consequently reducing the incidence of skeletal-related events (Figure 4) [Brown 2012].

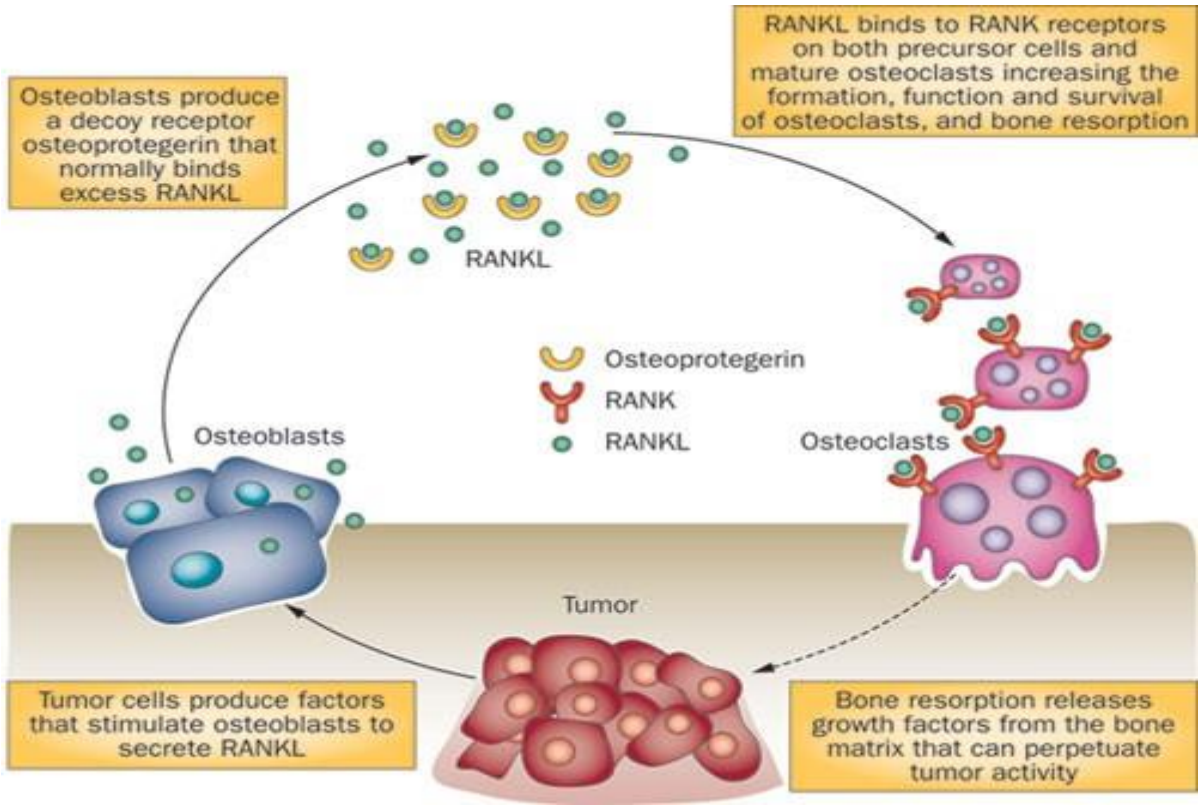

Figure 4. The effects of denosumab [Brown 2012]

In addition to its excellent effect on the underlying disease, denosumab may also result in severe side effects in the mandible or in the maxilla. In the literature, osteonecrosis of the jaws resulting from denosumab treatment is defined as DRONJ (denosumab-related osteonecrosis of the jaw) [Kyrgidis 2011].

Due to the long treatment period of the underlying disease, bisphosphonates and denosumab are often used consecutively or concomitantly in the same patient, which significantly increases the likelihood of developing osteonecrosis [Krestan 2016][Limones 2020]. Osteonecrosis due to the use of bisphosphonates, RANKL inhibitors, or their combined use is called as ARONJ (antiresorptive agent related osteonecrosis of the jaws) [Hellstein 2014][Shibahara 2019].

1.4.3. Pharmacology of tyrosine kinase inhibitors

Tyrosine-kinases (TKs) are enzymes that play an important role in modulating growth factors and signaling molecules. They increase cell growth and proliferation, which promotes the formation of metastases. Tyrosine kinase inhibitors (TKIs) effectively inhibit TK enzyme activity and block the overexpression of excitatory molecules in tumor cells [Hartmann 2009]. Vascular endothelial growth factor receptors (VEGFR), epidermal growth factor receptors (EGFR), platelet-derived growth factor receptors (PDGFR) are the main targets of TKIs. The most widely accepted hypothesis in connection with the TKI-related osteonecrosis is their antiangiogenic effect, which may block the overexpression of VEGF in tumor cells, but alters normal bone remodeling as well [Gharwan 2015]. To date, osteonecrosis of the jaws has been described in association with eight different tyrosine-kinase inhibitors. Increasing number of sunitinib- [Fleissig 2012] [Soós 2015], sorafenib- [Garuti 2016], cabozantinib- [Marino 2015], regorafenib- [Antonuzzo 2016], imatinib- [Viviano 2017], axitinib- [Patel 2017], pazopanib- [Jung 2017] and dasatinib-related [Abel Mahedi Mohamed 2018] osteonecrosis of the jaws were reported in the recent years.

VEGF induces angiogenesis in vivo and plays a key role in bone angiogenesis. Two sets of opposing molecules regulate angiogenesis under homeostatic condition. The balance of the proangiogenic (e.g. VEGF) and antiangiogenic (e.g. thrombospondin-1) factors ensure the normal (neo)vascularisation of the human body. In tumorous lesions, the balance is disrupted

and shifted towards angiogenesis [Rajabi 2017]. VEGF is considered an important factor of angiogenesis in tumor cells, therefore, blocking VEGF may have an anticancer role.

Bevacizumab is a human recombinant monoclonal antibody against VEGF, which binds specifically to VEGF molecules and effectively ceases the angiogenesis [Guarneri 2010]. This drug is usually prescribed in lung, breast, colorectal and ovarian cancer. Wound healing complications occur frequently during treatment [Magremanne 2012]. Several authors reported bevacizumab-related osteonecrosis with or without a concomitant bisphosphonate treatment [Christodoulou 2008][Estilo 2008][Serra 2009].

Aflibercept is composed of extracellular domains of human VEGF receptor and specific portion of human immunoglobulin. These molecules effectively bind to VEGFs and behave like a trap for them. This interaction blocks vascular growth and decreases vascular permeability in the tumor [Siu-Chung Chu 2009]. In recent years, case reports of aflibercept related MRONJ have appeared in the literature [Mawardi 2016][Ponzetti 2016].

1.4.4. Pharmacology of mTOR inhibitors

The mTOR (mammalian target of rapamycin) is a pathway, which plays an important role in the regulation of bone turnover. Different bone cell populations are regulated by mTOR signaling, which results in changes in bone remodeling [Shen 2017]. Inhibiting of mTOR reduces VEGF production and release, thus successfully blocks angiogenesis in malignancies [Dowling 2010]. This process could be responsible for the delayed progression of bone metastases and developing mTOR-associated osteonecrosis of the jaws. [Fusco 2016][Nifosi 2019][Yamamoto 2017].

1.4.5. Pharmacology of CTLA-4 inhibitors

The human monoclonal antibody ipilimumab was developed against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). CTLA-4 molecules are expressed by activated T-lymphocytes and suppressor T-lymphocytes. After binding to antigen presenting target cells these molecules may reduce T-cell dependent immune response [Langer 2007]. According to Kong et al., the systemic activation of T-cells implies the production of OPGL (osteoprotegerin ligand), whose

corresponding receptor (RANK) is expressed on mature osteoclasts. The interaction between OPGL and RANK leads to osteoclastogenesis and resultant bone loss [Kong 1999]. Only a few cases of CTLA-4 induced osteonecrosis are reported in the literature; this is probably explained by the fact that ipilimumab treatment is usually short-term. [Owosho 2015].

1.5. Epidemiology of MRONJ

The incidence and prevalence of MRONJ show an increasing trend due to the broadened indications, the increased number of patients, the unexpected interactions and synergistic effects between different groups of drugs (bisphosphonate - denosumab, bisphosphonate - VEGF inhibitors, denosumab - VEGF inhibitors) [Sivolella 2013][van Cann 2018]. Only a few single- or multicenter, nationwide large cohorts study has been published in this field, but some of these have had methodological limitations, including the lack of standardized case definitions, absence of information on patients characteristics and the scarcity of comparable data [Bamias 2005][Chaurand-Lara 2019][Gliklich 2009][Rogers 2015][Vescovi 2011][Yuh 2014]. Many authors agree that data reported in the literature tend to underestimate the real incidence and prevalence [Fusco 2016][Galis 2017]. The incidence of the disease may vary widely depending on the type of bisphosphonate(s) used, route of administration (iv / orally), cumulative dose, underlying disease and comorbidities, concomitant medication therapies and surgical interventions [Ghidini 2017][Khan 2017][Otto 2012][Park 2012][Ruggiero 2006].

A retrospective observational study analyzed the socioeconomic and medication data of 236 207 Hungarian bisphosphonate users and revealed the estimated incidence of BRONJ in Hungary. Accordingly, the incidence of BRONJ among bisphosphonate users is 0.9% in patients with malignancy and 0.1% in patients with non-malignant diseases, and the odds ratio (OR) to develop BRONJ was 9.7 (95% CI) between them [Veszelyné 2019].

The current literature distinguishes between “low-risk” and “high-risk” patients in terms of the likelihood of developing MRONJ. In general, there is a lower risk of developing osteonecrosis in cases of benign underlying disease, oral administration, low cumulative drug dose, lack of comorbidities, lack of concomitant drug therapy, good oral hygiene, and adequate patient compliance. Factors contributing to the development of MRONJ include underlying malignancy, intravenous drug administration, high cumulative dose, long-term drug use,

concomitant use of drugs with different attack points, poor oral hygiene, poorly fitting dentures, and inadequate compliance [Aghaloo 2015][McGowan 2018][Vereb 2020].

Diagnosis and staging are established based on clinical and radiological findings. Differential diagnostically, MRONJ should be differentiated from osteomyelitis, osteoradionecrosis and metastatic bony lesions. The main purposes of radiological examinations are to assess the extent of osteonecrosis, to facilitate individual surgical treatment planning, to follow up cases and to evaluate prognosis [Tsuchimochi 2019]. The pathogenesis of MRONJ is not fully elucidated yet, effective and reliable therapy is not currently available, consequently. Treatment options include prevention of the disease, delaying or blocking progression, conservative, surgical and complementary therapies of soft and hard tissues [Janovszky 2014] [Ramaglia 2018].

II. Objectives

To the author's best knowledge, no comprehensive nationwide epidemiological study has previously been performed in Hungary among BRONJ patients. The main objectives of the study are detailed below:

1) nationwide retrospective and prospective data collection of symptomatic BRONJ patients in Hungary
2) epidemiological description of the gender and age distribution of the involved patients
3) investigation of underlying and concomitant diseases potentially related to the development of the disease
4) examination of the type, concentration and route and frequency of administration of bisphosphonates causing BRONJ
5) analysis of triggering factors of osteonecrosis of the jaws
6) investigating the relationships between disease severity and the localization and extent of necrosis
7) identification of associations between disease severity and environmental effects

III. Material and methods

3.1. Ethical permission

In 2012, following the approval of the local Scientific and Research Ethics Committee of the Medical Research Council (license number: 17773/2012/EKU 320/PI/12.) an online spreadsheet-based questionnaire and database have been set up and made available for non-profit use to voluntary researchers and clinicians in Hungary and Slovakia.

3.2. Data collection

The questionnaire has been made available to cooperating maxillofacial units. Seven maxillofacial units from Hungary and one from Slovakia joined the study. Altogether 15 colleagues participated in the data collection. Patients were selected and excluded based on well-defined criteria for the study.

Inclusion criteria of the study were determined as follows:

1) Previous or current BP treatment regardless of drug type, dose or route of administration
2) Consecutive or concomitant BP treatment with different bisphosphonate agents
3) Intra- or extraoral lesion following or after bisphosphonate therapy

Exclusion criteria of the study were described below:

1) Asymptomatic patients with previous or current bisphosphonate treatment
2) Symptomatic patients consecutive and/or concomitant combined antiresorptive and antiangiogenic therapies
3) Patients with previous or undergoing radiation therapy of head and neck region

Data have been collected on gender, age on onset of the BRONJ, underlying and concomitant diseases, medical and dental history, smoking and alcohol consumption, type of bisphosphonate taken, treatment duration, frequency and route of administration, presumed trigger factors, clinical stage of disease, location and extent of lesions.

3.3. Data processing

To achieve the purposes of the study a free-accessible Google Sheets (Google LLC, CA, USA) was used. Google Sheets is a spreadsheet program which is available as a web and mobile application for each platform. It has a user's interface which may easily be adapted to the needs of the survey. The web based data collection system enables not only detailed data collection but also the analysis of the data gained.

This system is suitable for controlling access permissions and user restrictions in different levels. These properties allowed easy real-time collaboration between multiple users working on the same document at the same time regardless of distance. Further advantages of the applied data collection system are the following:

1. Easy retrieval and updating of data
2. (Common) database eliminates duplicate information
3. Increase efficiency and data consistency
4. Automatic backup prevents accidental data loss
5. Data entries and edits are tracked by admin(s)
6. Data integrity and portability are assured between platforms
7. Only the bandwidth of the network limits the speed of data transmission
8. Information security

A detailed dental and medical history was recorded with regard to previous and current chronic diseases. Clarification of triggering factors during the development of osteonecrosis has received special attention during retrospective data collection. To determine the location and extent of the osteonecrotic lesions both jaws were divided into 5 regions (right molar, right premolar, frontal, left premolar, left molar). If more than one region were affected by the osteonecrosis, each was taken into consideration.

3.4. Statistical analysis

Statistical analysis was performed with the Statistical Program for Social Sciences version 23.0 for Windows (SPSS, Chicago, IL, USA). A p-value of less than 0.05 was interpreted to imply statistical significance. Means and standard deviations (SD) were calculated. Unpaired student's t-test was used for evaluation of statistical significance. Pearson Chi-square test was performed to examine the relationships between different biological variables.

IV. Results

The data of 180 symptomatic BRONJ cases have been recorded during the data collection period (from 2012-2016). The number of reported cases decreased from year to year; 64 patients, 41 patients, 34 patients, 23 patients, 18 patients respectively. Full data were obtained for 148 (82.2%) patients. In 32 cases (17.8%) data collection was incomplete. The data on age, sex, underlying disease, method of drug administration, staging were complete in all cases. All data were included in the statistical analysis.

4.1. Age and gender distribution

There was a female predominance in the distribution of BRONJ. 122 women (67.8%) and 58 men (32.2%) were affected. Male-to-female ratio was 1:2.1, this correlates well with the results of other authors. (Table 2)

The mean age at the time of the diagnosis was 66.80 years; 66.22 years in women (range 37-85 years; SD 10.29 years) and 68.02 years in men (range 42-89 years; SD 9.33 years). There was no significant difference between the ages of males and females (p=0.246). Patients suffering from non-malignant diseases (osteoporosis, rheumatoid arthritis) were generally older (n=36; mean 68.57 years; range 38-84 years, SD 9.79 years) than patients with malignant disease (n=140; mean 66.32 years; range 37-89 years, SD 9.43 years).

Within the malignant group renal cancer patients were generally younger (n=13; mean 62.92 years; range 51-77 years, SD 8.45 years) than the rest of the group (n=127; mean 66.67 years; range 37-89 years, SD 9.49 years) but the difference was not significant (p=0.153). Breast cancer patients were only slightly younger (n=66; mean 64.68 years; range 37-85 years, SD 10.16 years) but the age difference was statistically significant (p=0.045) when compared with the rest of the group (n=74; mean 67.86 years; range 48-89 years, SD 8.49 years).

The mean age of multiple myeloma and lung cancer patients were 67.62 (n=16; range 57-80 years, SD 6.9 years) and 65.00 (n=7; range 48-81 years, SD 10.77 years), respectively. Prostate cancer patients (n=30; mean 71.57 years; range 61-89 years, SD 7.00 years) were significantly

older (p=0.000075) than the other malignant cases (n=110; mean 64.93 years; range 37-85 years, SD 9.53 years).

	Number	*Female*	*Percent*	*Male*	*Percent*
Vereb 2020	180	122	67.8%	58	32.2%
Otto 2012	126	92	73.0%	34	27.0%
Diniz-Freitas 2012	20	19	95%	1	5%
Schubert 2011	258	175	67.8%	83	32.2%
Kos 2010	34	19	55.9%	15	44.1%
Mavrokokki 2007	114	63	55%	51	45%
Summary	**732**	**490**	**66.9 %**	**242**	**33.1 %**

Table 2**.** Male-female ratio by different authors

4.2. Underlying diseases

*T*he vast majority of BRONJ cases occurred in patients with malignant diseases (n=140; 77.8%). 34 patients (18.9%) received bisphosphonate for osteoporosis; 2 patients (1.1%) were diagnosed with rheumatoid arthritis. In 4 cases (2.2 %) the reasons for treatment remained unknown because of the nature of retrospective studies. (Table 3)

Underlying disease		n	mean	min	max	SD
Malignant	Breast cc.	66	64.68	37	85	10.16
	Prostate cc.	30	71.57	61	89	7.00
	Multiple myeloma	16	67.62	57	80	6.09
	Renal cc.	13	62.92	51	77	8.45
	Lung cc.	7	65.00	48	81	10.77
	Gastrointestinal cc.	5	66.80	54	80	-
	Other cc.	3	62.00	53	75	-
Total malignant		**140**	**62.32**	**37**	**89**	**9.43**
Benign	Osteoporosis	34	70.31	42	84	9.79
	Rheumatoid arthritis	2	39	38	40	-
Total benign		**36**	**68.57**	**38**	**84**	**-**
Summary		**176**	**66.80**	**37**	**89**	**-**

Table 3. Age distribution based on known underlying disease (n=176)

4.3. Comorbidities

Data of comorbidities were complete in 162 (90%) cases. High blood pressure and/or cardiac disease was reported in 75 (46.29%) cases. Nineteen (11.72%) patients suffered from diabetes mellitus. Chronic obstructive pulmonary disease (COPD) and/or asthma were diagnosed in 6 (3.70%) cases. Concomitant renal, hepatic and gastrointestinal diseases were reported in 11 (6.79%), 7 (4.32%) and 9 (5.56%) patients, respectively.

4.4. Types of bisphosphonates and routes of administration

Fifty-two individuals (28.9%) were given oral bisphosphonates alone. In this group ibandronic acid (n=19; 36.6%) and alendronic acid (n=18; 34.6%) were the most frequently used agents, followed by clodronic acid (n=9; 17.3%) and risedronic acid (n=6; 11.5%). (Table 4)

Oral bisphosphonate	Benign diseases	Malignant diseases	Summary
alendronate	**17**	**1**	**18**
ibandronate	**2**	**17**	**19**
clodronate	**4**	**5**	**9**
risedronate	**6**	**-**	**6**
Summary	**29**	**23**	**52**

Table 4. BRONJ cases caused by oral bisphosphonates

Number of bisphosphonate infusions	zoledronate (combined)	zoledronate (single)	ibandronate	pamidronate
1-6 x	**-**	**29**	**-**	**-**
7-12 x	**1**	**17**	**5**	**-**
13-18 x	**-**	**11**	**1**	**-**
19-24 x	**3**	**12**	**3**	**-**
25-30 x	**1**	**6**	**1**	**-**
31-36 x	**-**	**7**	**-**	**-**
37-42 x	**-**	**2**	**-**	**-**
43-48 x	**-**	**6**	**1**	**-**
>48 x	**1**	**20**	**-**	**1**
Summary	**6**	**110**	**11**	**1**

Table 5. Development of osteonecrosis depending on the type of intravenous bisphosphonate and the number of infusions administered

In the vast majority of the cases, bisphosphonates were administered intravenously alone (n=106; 58.9%) or in combination with oral drugs (n=22; 12.2%). A total of 128 patients (71.1%) received intravenous bisphosphonate therapy.

Intravenous zoledronic acid was associated with the highest risk of BRONJ, 110 patients (61.1%) were treated with this drug alone, or in combination with other agents (n=6; 3.3%). Altogether 116 patients (64.4% of all patients; 90.6% in the intravenously treated group) were administered intravenous zoledronic acid. (Table 5)

Results of the Pearson Chi-square test showed a statistically significant relationship (p=0.023) between the severity of stages (Stage 1: mild versus Stage 2+3:serious) and the administration method**.** (Table 6)

	Staging			**Total**
	Stage1	**Stage 2**	**Stage 3**	
Intravenous	14	57	35	106
	13,2%	53,8%	33,0%	100,0%
Both	7	11	4	22
	31,8%	50,0%	18,2%	100,0%
Oral	15	28	9	52
	28,8%	53,8%	17,3%	100,0%
Total	36	96	48	180
	20,0%	53,3%	26,7%	100,0%

Table 6. The correlation between the severity of ONJ and the route of administration.

4.5. Triggering factors

Presumed triggering factors were reported in 167 cases. Dental extraction was the most common predisposing event (n=121; 72.4%). A further 6 patients (3.6%) had previous other dentoalveolar surgery (implant placement, periodontal surgery). Pre-existing inflammatory diseases such as periodontal and/or periapical pathology were present in 19 cases (11.4%). Denture use was thought to be the main trigger factor in 12 cases (7.2%). BRONJ was considered of spontaneous origin in 9 cases (5.4%).

4.6. Staging of BRONJ

At the time of the first clinical examination 36 cases (20.0%) were categorized as stage 1. The majority of the patients (n=96; 53.3%) were diagnosed as stage 2. Forty-eight cases (26.7%) were classified as stage 3 with extraoral fistula, pathological fracture, involvement of the maxillary sinus or the inferior border or the ramus of the mandible. The underlying disease and its malignant or benign nature were determined in 176 cases. There were 36 benign cases, the distributions of stages were as follows: stage 1: 36.1% (n = 13), stage 2: 47.2% (n = 17), stage 3 16.7% (n = 6) respectively. From the 140 underlying malignancies, 23 (16.4%) were classified in stage 1, 77 cases (55.0%) ranked as stage 2 and 40 cases (28.6%) belonged to stage 3.

At the time of the first visit, more severe stages (2-3) occured in a higher proportion of patients with malignancies compared to patients with benign conditions (stage 1: 36.1 % vs. 16.4 %, stage 2 : 47.2 % vs 55.0 %, stage 3: 16.7 % vs 28.6%) As stage worsened, the proportion of malignant cases increased significantly compared to the number of benign cases (stage 1 - 1:1.77, stage 2 - 1:4.53, stage 3 - 1:6.66) A significant difference was found between the benign and malignant groups (Pearson Chi-Square test p=0.026). Although much more women than men are affected by BRONJ; in stage 3 the number of female and male patients were almost equal, 26 (54.2%) and 22 (45.8%) respectively.

4.7. Localization of osteonecrosis

194 jaws were affected by bisphosphonate-related osteonecrosis of the jaws altogether. In 124 patients (68.9%) only the mandible, in 42 patients (23.3%) only the maxilla; in 14 cases (7.8%)

both jaws were affected. Altogether 304 regions were affected by BRONJ in 180 patients; 213 regions (70.1%) in the mandible and 91 regions (29.9%) in the maxilla. The most common sites of osteonecrosis were the molar (n=98; 32.2%) and the premolar regions of the mandible (n=82; 27%), followed by the upper molar (n=36; 11.8%) and premolar regions (n=35; 11.5%). The lower and upper front regions were affected in 33 (10.9%) and 20 (6.6%) cases, respectively. (Figure 5.) In terms of localization, the results correlate well with the results published by Otto et al [Otto 2012].

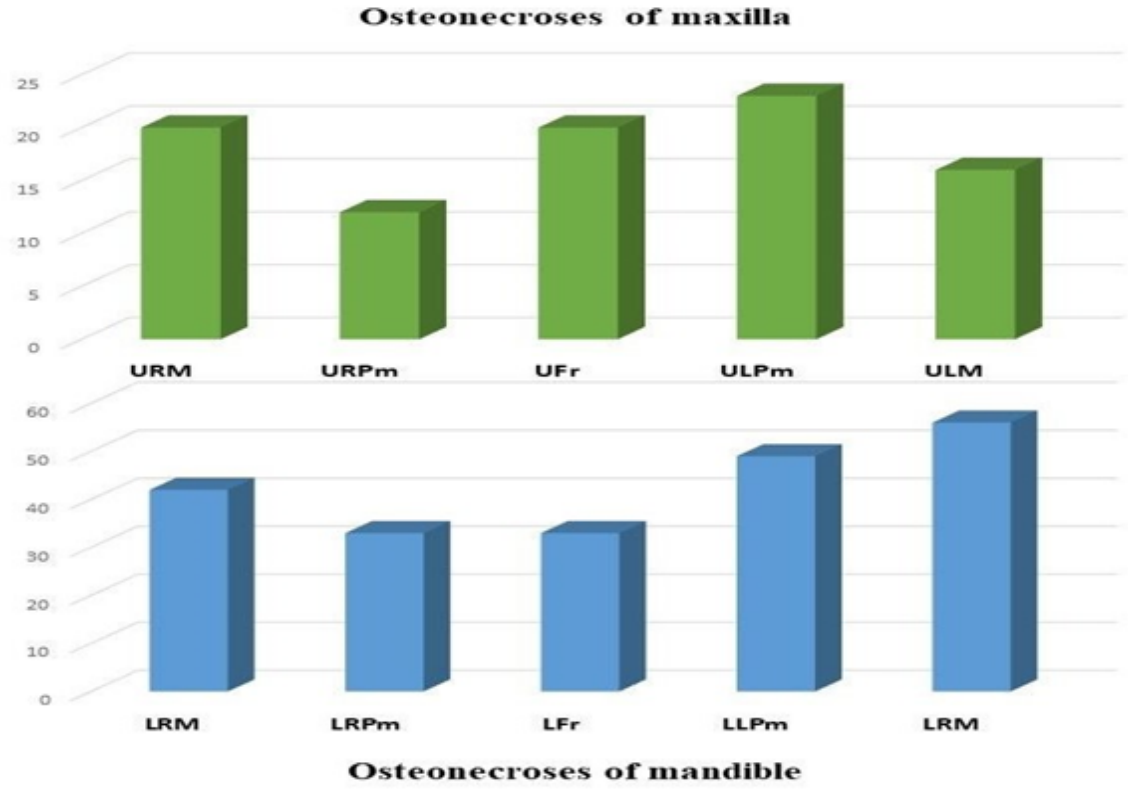

Figure 5**. Localizations of BRONJ by regions** (Abbreviations: URM-upper right molar, URPm-upper right premolar, UFr-upper frontal, ULPm-upper left premolar, ULM-upper left molar, LRM-lower right molar, LRPm-lower right premolar, LFr-lower frontal, LLPm-lower left premolar, LLM-lower left molar).

V. Discussion

BRONJ is a relatively newly recognized condition that has generated great interest not only amongst oral and maxillofacial surgeons but also in other medical and research communities.

Our study found female predominance among BRONJ patients (female 67,8 %, male: 32,2 %; male to female ratio 1 : 2.1) which is in line with the results of Otto and Schubert [Otto 2012][Schubert 2012], but slightly higher than in Kos' and Mavrokokki's publications [Kos 2010][Mavrokokki 2007]. Female-to-male ratio of 8:1 were published by Pazianas [Pazianas 2007].

77.8% of the patients suffered from an underlying malignant disease, this proportion closely correlates with Mavrokokki's result, who referred to 72% of bone malignancies among their patients [Mavrokokki 2007]. The mean age of the benign group (68.57 years) is not significantly higher than the age of the malignant group (66.32 years). Within the malignant group, BRONJ developed at a significantly higher age in prostate cancer patients compared to the remainder of the group. BRONJ was diagnosed at a significantly younger age in breast cancer patients compared to the rest of the malignant group. Although in our investigation there were only two rheumatoid arthritis patients (mean: 39.0 years SD: 1 years); there is still a surprisingly huge age difference when it is compared to the results of Di Fede (n=18 mean: 68 years SD: 8 years) [Di Fede 2016].

Gabbert's examination pointed out that osteonecrosis free survival in single bisphosphonate users was significantly longer in pamidronate-treated patients than in zoledronate or ibandronate users [Gabbert 2015]. In our study, from the intravenous group 127 of 128 patients (99.2%) were administered zoledronate and/or ibandronate and only one patient (0,8%) was diagnosed with BRONJ following pamidronate treatment. Our results also prove that the route of administration has a significant ($p=0.023$) association with the severity of the osteonecrosis.

According to Thumbigere-Math et al. increased cumulative doses and long-term bisphosphonate treatment are the most important risk factors for osteonecrosis, but the type of bisphosphonate may also play a role in the incidence of osteonecrosis; our results confirm these findings [Thumbigere-Math 2012].

According to the literature, the mandible is affected in 64 to 70.6%; the maxilla is involved in 18.3 to 27%. BRONJ was present in both jaws in 9 to 11.1%. Our findings (mandible 70.1%, maxilla 23.3%, both jaws 7.8%) correlate well with these results. There is a characteristic distribution of osteonecrosis with a predilection for the molar and premolar region in both jaws, just as it was pointed out by Otto et al [Mavrokokki 2007][Otto 2012].

At the time of the diagnosis the majority of the patients (53.3%) were categorized as stage 2; 20.0% and 26.7% were classified as stage 1 and stage 3, respectively. These findings are similar to those of Schiodt et al (stage 1: 26%; stage 2: 58%; stage 3: 10%; unknown: 3%; resolved: 2%) [Schiodt 2018]. Although much more women than men are affected by BRONJ, their number in stage 3 is nearly the same (26 and 22, respectively). The ratio of malignant cases to benign cases increased significantly (p=0,026) as the stage worsened (stage 1 - 1:1.77, stage 2 - 1:4.53, stage 3 - 1:6.66).

The evolution of cloud-based information technology has dramatically changed data collection and analysis for scientific purposes. To the best of our knowledge our study is the first one that has collected data on BRONJ patients from multiple centers with this method.

Despite the many advantages offered by cloud-based technology our study also has some pitfalls. The participation has been voluntary and this has probably resulted in under-reporting; therefore our data are not informative about the incidence of BRONJ. The relatively high number of incomplete reports is surprising but this can be explained by the fact that the online questionnaire was not filled out at the time of the patient's examination and later data were not found in the documents.

The number of patients reported in this study is high compared to other single-center or even multicenter studies but the average number of patients reported per center per year is less than 6 in the 4-year study period.

The decreasing trend of the number of new patients reported per year probably reflects that voluntary researchers have lost their initial enthusiasm, but better patient management, early diagnosis and state-of-the-art prevention techniques might also played an important role. A sample size of 180 BRONJ cases is considered statistically significant but data were not always

sufficient to reach statistically reliable conclusions when the patients were classified into groups. More patients are needed to improve the power of the study. A multicenter registry that collects systematic information on epidemiological data is essential to increase our knowledge of BRONJ. Cloud-based information collection is an ideal tool for this purpose. The online and voluntary nature of the current study may slightly diminish the accuracy of the results but the increasing number of patients involved will improve statistical conclusions.

VI. Summary of new findings

1) We have successfully introduced a cloud-based multicentric real-time data collection method to obtain population-wide epidemiological data on a rare but serious side effect.
2) According to our best knowledge, this examination was the first descriptive epidemiological analysis on a Central European population in terms of BRONJ.
3) Prostate cancer patients (n=30; mean 71.57 years; range 61-89 years, SD 7.00 years) were significantly older (p=0.000075) than the other malignant cases (n=110; mean 64.93 years; range 37-85 years, SD 9.53 years)
4) Breast cancer patients were only slightly younger (n=66; mean 64.68 years; range 37-85 years, SD 10.16 years) but the age difference was statistically significant (p=0.045) when compared with the rest of the group (n=74; mean 67.86 years; range 48-89 years, SD 8.49 years).
5) We have demonstrated that if the stage worsened, the proportion of malignant cases increased significantly compared to the number of benign cases (stage 1 - 1:1.77, stage 2 - 1:4.53, stage 3 - 1:6.66) A significant difference has been found between the benign and malignant groups (p=0.026).
6) We have found statistically significant (p=0.023) correlation between the severity of stages (Stage 1: mild cases versus Stage 2+3: serious cases) and the administration method (oral versus intravenous).

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IX. Annex

LIST OF PAPERS RELATED TO THE SUBJECT OF THE THESIS

I.

II.

III.