Awareness of medical doctor on medication-related osteonecrosis of the jaw in osteoporosis patients

Mr. Nachapol Supanumpar

A Thesis Submitted in Partial Fulfillment of the Requirements
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ความตระหนักของแพทย์ต่อภาวะกระดูกขากรรไกรตายจากการใช้ยาในผู้ป่วยโรคกระดูกพรุน

นายณัชพล ศุภนำพา

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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By	Mr. Nachapol Supanumpar
Field of Study	Oral and Maxillofacial Surgery
Thesis Advisor	Associate Professor KESKANYA SUBBALEKHA, D.D.S., Ph.D.

Accepted by the FACULTY OF DENTISTRY, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master of Science

..... Dean of the FACULTY OF DENTISTRY

(Professor Pornchai Jansisyanont, D.S., M.S., Ph.D.)

THESIS COMMITTEE

..... Chairman

(Associate Professor ATIPHAN PIMKHAOKHAM, D.D.S., M.P.A., Ph.D.)

..... Thesis Advisor

(Associate Professor KESKANYA SUBBALEKHA, D.D.S., Ph.D.)

..... External Examiner

(Assistant Professor Chakorn Vorakulpipat, M.D., D.D.S., Ph.D.)

ณัชพล ศุภนำพา : ความตระหนักของแพทย์ต่อภาวะกระดูกขากรรไกรตายจากการใช้ยาในผู้ป่วยโรคกระดูกพรุน. (Awareness of medical doctor on medication-related osteonecrosis of the jaw in osteoporosis patients) อ.ที่ปรึกษาหลัก : รศ. ทพญ. ดร.เกศกัญญา สัพพะเลข

บทคัดย่อ

ยาต้านการสลายของกระดูกได้ถูกใช้กันอย่างแพร่หลายในการรักษาโรคกระดูกพรุน ผลข้างเคียงที่รุนแรงจากยากลุ่มนี้คือภาวะกระดูกขากรรไกรตายจากการใช้ยา (MRONJ) ซึ่งการให้ข้อมูลและให้ความรู้กับผู้ป่วยเกี่ยวกับ MRONJ การส่งต่อหาทันตแพทย์ และ การติดตามสุขภาพช่องปากของผู้ป่วยที่ได้รับยาต้านการสลายของกระดูก แพทย์นั้นสามารถลดความเสี่ยงในการเกิด MRONJ ได้ เราจึงทำการศึกษาความตระหนักและการปฏิบัติทางคลินิกของแพทย์ในประเทศไทยที่เกี่ยวกับ MRONJ โดยให้แพทย์ผู้ที่จ่ายยาต้านการสลายของกระดูกเพื่อรักษาโรคกระดูกพรุนตอบแบบสอบถามออนไลน์ เรื่อง ข้อมูลทั่วไปของแพทย์, ความตระหนักและการปฏิบัติเกี่ยวกับ MRONJ ผลออกมาว่าผู้ตอบแบบสอบถามส่วนใหญ่เห็นด้วยว่ายาต้านการสลายของกระดูกอาจเป็นสาเหตุที่ทำให้เกิด MRONJ ร้อยละ 92, เห็นด้วยว่าสุขภาพช่องปากที่ไม่ดีจะเพิ่มความเสี่ยงในการเกิด MRONJ ร้อยละ 84 และเห็นด้วยว่า MRONJ เป็นสิ่งคำสัญที่ต้องคำนึงถึงในผู้ป่วยโรคกระดูกพรุน ร้อยละ 48.1 และ 15.5 ของผู้ตอบแบบสอบถามส่งต่อผู้ป่วยหาทันตแพทย์ก่อนและระหว่างได้รับการรักษาโรคกระดูกพรุนตามลำดับ โดยผู้ตอบแบบสอบถามส่วนใหญ่จะส่งต่อในกรณีที่ผู้ป่วยมีความเสี่ยงในการเกิดMRONJ ประมาณร้อยละ 60 แจ้งรายละเอียดเกี่ยวกับความเสี่ยง MRONJ ให้กับผู้ป่วยก่อนเริ่มรักษาโรคกระดูกพรุน และร้อยละ 30 สอบถามอาการเกี่ยวกับสุขภาพช่องปากของผู้ป่วยในวันที่นัดติดตามอาการหลังเริ่มให้การรักษาโรคกระดูกพรุน ร้อยละ 44 แนะนำผู้ป่วยเกี่ยวกับการดูแลสุขภาพช่องปาก โดยเหตุผลที่พบได้บ่อยที่สุดที่ไม่ได้แนะนำคือผู้ตอบแบบสอบถามไม่คิดว่าตัวเองมีความรู้เพียงพอที่จะตรวจหาปัญหาของสุขภาพช่องปากได้ สรุปว่าผู้ตอบแบบสอบถามส่วนใหญ่มีความตระหนักเกี่ยวกับ MRONJ และ มีเหตุผลของตัวเองในการปฏิบัติ อย่างไรก็ตามหลายคนปฏิบัติเพียงเล็กน้อยเพื่อป้องกัน MRONJ แพทย์ผู้ที่จ่ายยาต้านการสลายของกระดูกควรปฏิบัติตามแนวทางการปฏิบัติทางคลินิกเพื่อลดความเสี่ยงในการเกิด MRONJ

สาขาวิชา	ศัลยศาสตร์ช่องปากและแม็กซิลโลเฟเชียล	ลายมือชื่อนิสิต .....
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Nachapol Supanumpar : Awareness of medical doctor on medication-related osteonecrosis of the jaw in osteoporosis patients. Advisor: Assoc. Prof. KESKANYA SUBBALEKHA, D.D.S., Ph.D.

Abstract

Antiresorptive drugs are widely used to treat osteoporosis. A serious adverse effect of these drugs is medication-related osteonecrosis of the jaw (MRONJ). By informing and educating patients about MRONJ, providing proper dental referral, and monitoring the oral health of patients who receive antiresorptive agents, physicians can reduce the risk of MRONJ. We investigated the awareness and clinical practices of physicians in Thailand with regard to MRONJ. Physicians who prescribed antiresorptive drugs for osteoporosis filled out an online self-administered questionnaire about demographic characteristics, awareness, and practices related to MRONJ. Most respondents agreed that antiresorptive drugs may cause MRONJ (92.3%), that poor oral health increased the risk of MRONJ (84%), and that MRONJ is an important consideration in patients with osteoporosis (85%). Of the respondents, 48.1% and 15.5% always referred patients to dentists before and during antiresorptive therapy, respectively; the majority, however, referred only patients considered at risk for MRONJ. Approximately 60% informed patients of the risk for MRONJ before antiresorptive therapy began, and 30% inquired about patients' oral symptoms at the follow-up visit after antiresorptive therapy began. Forty-four percent advised patients to receive oral health care; the most common reason for not advising this was that respondents did not consider themselves knowledgeable enough to detect oral health problems. Most respondents were aware of MRONJ and accounted for it in their practice; many, however, did little to prevent MRONJ. Physicians prescribing antiresorptive drugs should adhere to clinical practice guidelines for reducing the risk of MRONJ.

Field of Study:	Oral and Maxillofacial Surgery	Student's Signature .....
Academic Year:	2022	Advisor's Signature .....

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Conflict of Interest

All of the authors declare that they have no conflict of interest.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethical committee of the Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand (approval no. HREC-DCU 2022-079).

Informed Consent

Informed consent was obtained from all individual participants included in the study

Nachapol Supanumpar

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Chapter I

Background and rationale

In 2016, 11 million Thais, or 16.5 percent of the entire population, were 60 years or older. The elderly population (age 60 and over) is growing at an annual rate of 5% per year. The population of the oldest cohort (age 80 and over) is growing at an even greater rate (6% per year). Thailand will have met the condition of a "complete-aged society" in around five years (whereby at least one in five members of the population is age 60 years or older) (1). Aging affect to all organ systems, one of the physiological change is the declination of bone mass (2). Osteoporosis is one of the most common metabolic bone diseases that have been affecting more than 200 million people around the world. Surveys on the prevalence of osteoporosis in Thai females hospitalized in Thai governmental hospitals and random surveys of females in communities around Thailand estimated 11-21 percent. This disease is caused by the reduction of bone mass and change of bone structure which results in increased bone fragility and fracture risk as well (3, 4). This disease is more common in postmenopausal women and elder men (5-7). It is expected that Osteoporosis will increase considerably in the future due to an aging society (8, 9)

The main purpose of Osteoporosis therapy is to minimize the risk of bone fracture (10). Treatments and prevention have both non-pharmacological and

pharmacological methods (11-13). For the pharmacological method, this method can prevent risk of fracture from osteoporosis by internal/family doctors, rheumatologists orthopedists, endocrinologists, or gynecologist who prescribe antiresorptive drugs to decrease bone resorption.

Antiresorptive drugs such as bisphosphonates (BPs) and denosumab decrease bone resorption by reducing the rate of bone resorption and formation, therefore, it increases the overall Bone Mineral Density (BMD) (14). Despite the fact that antiresorptive drugs have benefits to treat metabolic bone diseases but one of the most serious adverse drug effects of antiresorptive that called medication-related osteonecrosis of the jaw (MRONJ) is concern (15, 16).

MRONJ is defined as necrotic bone exposure in the maxillofacial region for more than 8 weeks in patients with previous or current treatment with antiresorptive drug and no history of radiation therapy (15). MRONJ usually has unpredictable treatment because it affects many aspects on patients's quality of life Including physical, mental and psychosocial aspect moreover, MRONJ demands long-term treatment and follow up if it occurred (17). The risk factors that relate MRONJ are drug-related factor, systemic condition, local factors, patient's attitude, dentist's attitude and physician's attitude.

To decrease risk of MRONJ, prevention is the best strategy for MRONJ by reducing dental risk factors. Its goal is to maintain good oral hygiene and to

decrease the risk of the development of pathological conditions. Awareness of medical doctor on MRONJ is one of factors that can reduce risk of MRONJ because If they aware about adverse drug effect of antiresorptive drugs before they prescribe drug to osteoporosis patients, they will explain risk of MRONJ from antiresorptive therapy and refer their patients to dentists for oral examination to remove possible sources of infection to reduce risk of MRONJ from local factors in oral cavity (17-20).

Considering the worldwide trend of increasing BP therapy and high BP dependence, the incidence is expected to continuously grow (21). Awareness of physicians who prescribe antiresortive agents toward MRONJ is still low in many countries. There have no studies on medical doctors' awareness of MRONJ and how well dental referrals are being carried out in Thailand.

Research question

How many percentage of medical doctor who aware of MRONJ in Thailand?

Research objective

To investigate the experience and practices of medical doctors in Thailand on MRONJ

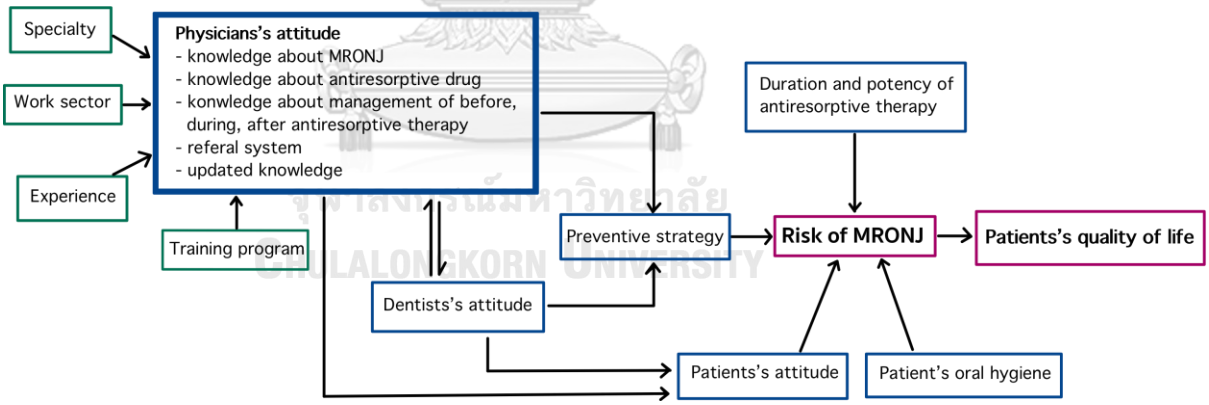
Hypothesis

More than 50% of medical doctor in Thailand are aware on MRONJ.

Expected benefits of the study

Awareness of MRONJ among medical doctors in Thailand that shows in this study will encourage medical doctor to emphasize regarding MRONJ. If awareness level of MRONJ is low, we recommend to promote knowledge about MRONJ to medical doctors in order to increase awareness of MRONJ that lead to cooperation between medical doctors and dentists or changing for appropriate training strategies to reduce risk and incidence of MRONJ. If awareness level of MRONJ is high, we suggest to update knowledge about MRONJ and maintain dental referral in hospital.

Conceptual framework



Chapter II

Review of literature

Normal bone and Osteoporotic bone

Normally, homeostasis of normal bone consists of two cells which are osteoclasts

and osteoblasts. Osteoclast is responsible for bone resorption while Osteoblast is

responsible for bone formation (22). In general, the age of 25-30 in women is the period when peak bone mass is reached. The accelerated loss of bone mass occurs during the perimenopausal period, and it gets slower after a few years of menopause. There is a slow decline of bone mineral density (BMD) in men. However, by the age of 60, both males and females would eventually have equal rates of bone loss (6).

Definition of osteoporosis by The world Health Organization is based on BMD measurements that obtained on dual energy x-ray absorptiometry (DEXA) as a T-score of greater than 2.5 standard deviations below the mean for normals (23). Characteristic of osteoporosis is low bone mass. Microarchitectural degeneration of bone tissue including accelerated osteocyte death, increased bone turnover, thinned trabeculae, decreased cortical width, and increased cortical porosity are caused by increased bone resorption, decreased bone formation and insufficient forming

response which enhances bone fragility and fracture risk. The strength of the bone is associated with bone mass, mass distribution, and bone quality. For that reason, a low BMD is associated with increased fracture risk in osteoporosis patients (24).

It is important to know the process of bone remodeling in order to fully understand how excessive bone resorption and insufficient formation result in skeletal fragility (25).

Bone remodeling process

Bone is an active tissue that keeps reforming in every individual by the process of bone remodeling (26). This physiological process occurs at a specific location of the bone architecture to enable bones to adapt to mechanical stresses, to repair its microstructure to remove old or damaged bone and followed by the deposition of new bone. Moreover, this process protects the structural integrity of the skeletal system and metabolically contributes to the homeostasis of calcium and phosphorus. Bone remodelling depends on function of osteoclast and osteoblast. An optimal balance between bone resorption and osteogenic functions is necessary to maintain bone mass at constant (27).

The process of bone remodeling is completed by the following phases:

Activation Phase

The first stage of bone remodeling relates to the detection of input signal such as microdamage. Microdamage or mechanical stress are sensed by osteocytes and some cytokine such as insulin growth factor-I (IGFI), tumour necrosis factor-**α** (TNF-**α**), interleukin-6 (IL-6) that are released in the bone environment and stimulate the lining cells which are inactive osteoblasts. After that the surface of lining cells is stimulated to express Receptor Activator of Nuclear **K**B Ligand (RANKL), which interacts with Receptor Activator of Nuclear **K**B (RANK) that is expressed on surface pre-osteoclasts. Triggered pre-osteoclasts are differentiated toward osteoclasts, multinucleated cells that destroy the bone matrix (28).

Resorption Phase

Osteoclasts attach to bone surface and dissolve bone. This phase requires 2 steps: 1.Resorption of inorganic component by acidification of bone matrix

2.Degradation of organic component by releasing of lysosomal enzymes such as cathepsin K, and of Matrix Metalloproteinase 9 (MMP9) when osteoclast accomplished their function, it will be apoptosis. This consequence is necessary to prevent an excessive bone resorption

Reverse Phase

This phase is a transition from osteoclastic activity to osteoblastic activity. While osteoclast undergo apoptosis, osteoblasts are recruited and differentiated. The debris that is produced during matrix degradation is removed by macrophage-like cells (28).

Formation Phase

Resorption of bone matrix leads to release bone morphogenic protein (BMPs), several growth factors such as fibroblast growth factors (FGFs) and transforming growth factor β (TGF

β) which recruit osteoblasts to the reabsorbed area. Osteoblast produces the new bone matrix that is called osteoid. Osteoid is an unmineralized organic tissue, it promotes its mineralization and is deposited as lamellae or layers in the bone matrix that completes the remodeling process. Therefore, imbalance of resorption phase and formation phase affects bone mass that lead to pathological condition such as osteoporosis (28).

Osteoporosis treatment

The main purpose of Osteoporosis therapy is to minimize the risk of bone fracture (10). Treatments and prevention have both non-pharmacological and pharmacological methods (11-13). Non-pharmacological method that use to prevent osteoporosis and osteoporotic fractures includes fall avoidance which have several strategies such as reducing consumption of medication that alters alertness and

balance, practicing physical activity to improve muscle strength, balance, and maintaining bone mass, reducing consumption of cigarette and alcohol, and adequate dietary intake of protein, calcium, and vitamin D (5). On the other hand, pharmacological method is one way to prevent risk of fracture from osteoporosis by using pharmacological agents to treat osteoporosis disease. Osteoporosis drugs are classified into 2 groups: 1. Antiresorptive drug 2. Anabolic drug (14). Antiresorptive drugs such as bisphosphonates (BPs), denosumab and, romosozumab decrease bone resorption by reducing the rate of bone resorption and formation, therefore, it increases the overall Bone Mineral Density (BMD) (23). Anabolic drugs such as teriparatide, romosozumab increase bone formation and partially bone resorption (5)

Bisphophonate

Bisphosphonates are the first choice for the treatment of osteoporosis. These drugs inhibit bone resorption and increase the BMD of trabecular bones, for example, alendronate, risedronate, ibandronate, etidronate, clodronate, and zoledronic acid (29).

Bisphosphonates are widely used to treat osteoporosis in both women and men since the 1990s. Their ability of inhibition of bone resorption has the benefit of treating osteoporosis and other conditions as well (30-32). Bisphosphonates are indicated to use for treatment of osteoporosis in postmenopausal women, osteoporosis in men, glucocorticoid-induced osteoporosis, hypercalcemia of

malignancy, Paget disease of the bone, and malignancies with metastasis to the bone by FDA-approved (33).

Bisphosphonates are derivatives of inorganic pyrophosphate (PPi) which occurs from esterification of 2 phosphate groups. Both bisphosphonates and pyrophosphate are similar. The P-C-P bonds of bisphosphonates are stable. They are resistant to heat, most chemical

reagents and enzymatic hydrolysis. They have a strong affinity for the skeleton. Their abilities are a key pharmacological feature. The P–C–P structure can change the two side chains on the carbon so it creates a number of possible variations (34).

Modification of chemical structure of bisphosphonates can change the potency of drug and specificity for bone to inhibit bone resorption. The structure of bisphosphonates in current clinical use is different from the core structure of bisphosphonates where the central carbon is attached by a hydroxyl group. bisphosphonates have a strong affinity for hydroxyapatite in the bone by the flanking phosphate groups. Moreover, a hydroxyl group increases the ability of bisphosphonates to bind calcium. The tertiary interaction between bisphosphonates and bone matrix that is created by phosphate and hydroxyl groups has more affinity than the binary interaction that is created by only phosphate groups. The last moiety that bond to the central carbon is the primary determinant of potency of bisphosphonates for antiresorptive activity. The presence of a nitrogen or amino

group increases the antiresorptive potency of bisphosphonates 10 to 10,000 times, compared with non- nitrogen containing bisphosphonates, such as etidronate (35).

Pharmacokinetic

Bisphosphonates have high affinity for hydroxyapatite binding sites on the bone and poor internal absorption because the properties of oral bisphosphonates are low lipophilicity and high negative charge. Hence, they have low oral bioavailability that ranges less than 1% to 10% of an oral dose (36, 37). Absorption mainly occurs via passive diffusion in the small intestine and possibly via a paracellular pathway. Meals, the presence of calcium will interfere drug absorption when take them at the same time (38). Bone absorb bisphosphonates aprroximately between 30%-70%. The main route that eliminates bisphosphonates is through the kidney. The remainder are rapidly excreted in the urine because the renal clearance of bisphosphonates is high (39). The renal clearance can exceed glomerular filtration rate of bisphosphonates due to bisphosphonates are only partially ultrafiltrable and renal secretion can occur (40). However, renal transporters for bisphosphonates have not been clarified. Renal function, rate of bone turnover and the affinity for bone mineral are factors that affect the skeleton to take up an amount of bisphosphonates. The skeleton has a high capacity to keep bisphosphonates in bone.

The half-life of circulating busphosphonate is approximately 0.5 to 2 hours in humans (41). In constant amounts of different bisphosphonates are ultrafiltrable

during in the circulation. The values are depend on species. The remnant of bisphosphonates is either bound to proteins such as albumin, or very small aggregates (42).

Bisphosphonates in the circulation are rapidly uptaken by skeleton (41). Skeletal uptake might be included bone vascularization. Soft tissue are exposed to bisphosphonates for short time only. For this reason, it explains their bone-specific effects. When humans take bisphosphonates at clinic doses, the total skeletal uptake seem to be no saturation even periods as long as years or decades. Conversely, the antiresorptive activity rapidly reaches to the maximum level, both in animals and in humans (43). Even though bisphosphonates accumulate in the skeleton, it seems to be buried because it is not accessible to the osteoclasts on the bone surface. Bisphosphonates are probably released from the skeleton by physicochemical mechanisms such as desorption, diffusion, and ion exchange, but that processes are release bisphosphonates less than when the bone that are deposited is resorbed (44). Skeletal retention depends on bone turnover rate that is influenced by bisphosphonates themselves. The drugs can prolong their own lifetime in the skeleton. Retention times and terminal half-lifes have been estimated to be up to 1 year in mice (45), and even longer up to 10 years, in humans (44). There is a possibility that some bisphosphonates can stay buried in the skeleton for life like other “bone-seeking” substances such as tetracyclines, heavy metals, and fluoride, even though they are in inactive form.

Bisphosphonates can be classified into 2 groups. Both 2 groups are metabolized differently. The first class is non-nitrogen which contains bisphosphonates including etidronate, clodronate, and tiludronate that are metabolized to cytotoxic and non-hydrolysable of ATP (46). The increase of these byproducts affects mitochondrial function that leads to apoptosis of osteoclasts. Another group of bisphosphonates is nitrogen- containing bisphosphonates including alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid that is more potent than non-nitrogen containing bisphosphonates. This group is not metabolized and is excreted through the kidney. Oral bisphosphonates should be taken when fasting because food interfere drug absorption (47).

Pharmacodynamic

All bisphosphonates inhibit bone resorption by attaching to hydroxyapatite binding sites on the bone, particularly in areas where remodeling occurs. Bisphosphonates have a high affinity to bind the surface of bone. At that point, they come to be part of osteoclasts through endocytosis (48). Bisphosphonates in the bone will be released and interfere ability of osteoclasts. The 2 different mechanisms of action have been unveiled (31).

For non-nitrogen containing bisphosphonates which metabolized within the cell to the substrates that substitute some terminal pyrophosphate of ATP which forms a cytotoxic analogs of ATP that competes with ATP in cell metabolism.

Therefore, cytotoxic analogs of ATP that interfere with mitochondrial function and induce apoptosis of osteoclasts is a mechanism to inhibit bone resorption (46).

For nitrogen-containing bisphosphonates, it inhibits enzymes of the mevalonate pathway. Consequently, prenylation and activation of small GTases are inhibited that affect to the bone resorption activity and survival of osteoclasts. The mevalonate pathway is an intracellular pathway that is responsible for isoprenoid lipids, cholesterol and other sterols (49). Some isoprenoid lipids such as farnesyl pyrophosphate and geranyl-geranyl pyrophosphate, are necessary for the prenylation and activation of the small GTPases. The small GTPases play an important role in regulating osteoclast morphology, cytoskeleton arrangement, membrane ruffling, trafficking, and cell survival (50). Inhibition of enzymes that are responsible for the mevalonate pathway may deteriorate the prenylation process and be the cause of malfunction of the small GTPases. Many enzymes in the mevalonate pathway have been studied as targets for nitrogen containing bisphosphonates.

According to Amin et al., 1996 study, only incadronate and ibandronate are role inhibitors for squalene synthase (FDFT1). The mevalonate pathway needs squalene synthase (FDT1) for cholesterol biosynthesis. Even though squalene synthase (FDT1) is inhibited, it does not affect the loss of protein prenylation (51). Presently, the major target protein of the Nitrogen containing bisphosphonates is considered to be farnesyl pyrophosphate synthase (FDPS) that is a key regulatory

enzyme which produces isoprenoid lipids. Several studies showed that farnesyl pyrophosphate synthase (FDPS) is inhibited by all the nitrogen containing bisphosphonates and the antiresorptive potency of different nitrogen-containing bisphosphonates correlates with their capacity of farnesyl pyrophosphate synthase (FDPS) inhibition (49). When farnesyl pyrophosphate synthase (FDPS) is inhibited by nitrogen-containing bisphosphonates, it inhibits the synthesis of farnesyl pyrophosphate and geranyl- geranyl pyrophosphate that affects to stop prenylation of small GTPases and interrupts normal osteoclast function.

To summarize, the central mechanism of nitrogen-containing bisphosphonates that inhibits bone resorption is inhibition of farnesyl pyrophosphate synthase (FDPS). When compare both classes of bisphophonate, non-nitrogen-containing bisphosphonates are less potent antiresorptive agents than the nitrogen-containing bisphosphonates. In addition, non-nitrogen-containing bisphosphonates are found to have higher potential to inhibit bone mineralization and can increase risk of osteomalacia. However, they are not widely used at the present time.

Denosumab

Denosumab is a total human IgG2 monoclonal antibody that binds to and competitively inhibits the binding of receptor activator of NF kappa B ligand (RANKL) to receptor activator of NF kappa B (RANK). Soluble RANKL is a trimer that relates to the tumor necrosis factor (TNF) ligand family. Each RANKL trimer has the ability to

bind and oligomerize up to three receptors. When coupled to RANK, RANKL promotes osteoclast differentiation from hematopoietic stem cells, and also activates and prolongs lifespan of mature osteoclasts. The primary function of osteoclasts is to stimulate bone resorption. Denosumab has a high affinity to bind RANKL and block it from binding to and oligomerizing its receptor RANK, resulting in inhibiting osteoclast maturation and bone resorption (52).

Denosumab's pharmacokinetics are non-linear and dose-dependent. After a single subcutaneous dose of 60 mg, the maximum serum concentration (Cmax) is reached in a median of 10 days and Denosumab does not accumulate when treated at the recommended subcutaneous dosage (i.e. 60mg q6m). Denosumab, as an immunoglobulin, is expected to be degraded into peptides and amino acids independent of hepatic metabolism. Denosumab serum concentrations gradually fall over 3–5 months after achieving Cmax. Denosumab has a half-life of approximately a month (26 or 25 days) and is undetectable 6 months after administration in more than half of the patients (53 %) (52).

Romosozumab

Romosozumab is a humanized monoclonal antibody against sclerostin (sclerostin inhibitor) that inhibits sclerostin, causing the Wnt signaling pathway to be activated and RANK-RANKL binding to be inhibited. Since April 2019, the US Food and Drug Administration has authorized romozosumab as an anti-osteoporosis agent. To

maximize the best benefit, it is advised to treat osteoporosis in postmenopausal women, anybody at high risk of fracture, and anyone with a history of failed osteopenic therapy, with a monthly dose of 210 mg subcutaneously administered method (53).

In differentiated osteoblasts, the Wnt signaling pathway stabilizes intracellular β-catenin via Wnt ligand bind the Frizzled co-receptor, lipoprotein-related protein 5 and 6 (LRP5/6). Glycogen synthase kinase-3 (GSK-3) is inhibited, which prevents β-catenin breakdown and leads to nuclear translocation. β-catenin which is a nuclear transcriptional regulator induces transcription of bone-related genes is increased, resulting in increase bone mass. It also increases the expression of osteoprotegerin (OPG), which binds to the receptor activator of nuclear factor kappa-B ligand (RANKL), preventing RANK from binding to RANKL. As a result, bone resorption and osteoclastogenesis are inhibited (54, 55).

Wnt, LRP5/6, and the Frizzled family cannot bind together because Sclerostin antagonizes the Wnt signaling pathway by attaching to LRP5/6. As a result of this activity, GSK-3 is inhibited, leading β-catenin to be phosphorylated and subsequently degraded. Bone formation is then inhibited. It also increases RANKL, which promotes bone resorption. This mechanism emphasizes the importance of sclerostin inhibition as a therapy option for osteoporosis (55, 56).

Rromosozumab is absorbed through lymphatic vessel and Hepatic and renal function are less involved in the clearance of romosozumab. It peaked around the first month, then steadily declined to the baseline between months 9 and 12. As a result, following the 12th month, the effect of bone formation begins to fade (57, 58).

Despite the fact that antiresorptive drugs have been shown to be effective in treating osteoporosis, there has been a serious side effect of jaw necrosis associated with their administration in recent years (59, 60). Although the mechanism of drug-induced jaw necrosis is yet unclear, considerable suppression of bone remodeling based on the drug's pharmacological effects is expected to be the main cause.

Medical-related osteonecrosis of jaws

Medical-related osteonecrosis of the jaw (MRONJ) is one of the most severe adverse effects of bisphosphonates. After the first report of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in 2003 Most cases of MRONJ have occurred in patients who took high doses of intravenous bisphosphonates for multiple myeloma and breast cancer treatment. Incidence of MRONJ that has been reported in patients taking bisphosphonates for osteoporosis is around 1 in 10,000 to 1 in 100,000 (61).

To diagnose MRONJ, clinical practice must meet all the following criterias:

- History of treatment with a antiresorptive drug either intravenous form or oral form

- Patient who has persisted exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region for more than 8 weeks
- No radiation therapy to the jaw

Pathogenesis of medical-related of osteonecrosis of jaws

Over a decade since the first MRONJ case has been reported, the pathophysiology of disease has not been fully clarified (59, 60). Many hypotheses were proposed to explain the localization of MRONJ to the jaws comprise bone remodeling alteration, angiogenesis inhibition, inflammation or infection and others (62).

Inhibition of osteoclastic bone resorption and bone remodeling

bisphosphonates inhibit osteoclast function and lead to apoptosis that result to decreased bone resorption and remodeling (63). In all skeletal sites, osteoclast function plays role in bone healing and remodeling but ONJ only occurs in the maxillofacial region (64). An increasing of remodeling rate in the maxillofacial region may explain the tendency of pathophysiology of ONJ compared with bones in others area. A similar incidence of ONJ that observed with other antiresorptive medications, such as denosumab can confirm the central role of bone remodeling inhibition (65).

Inflammation and infection

Systemic and local risk factors have been associated with ONJ pathogenesis, in which have related to dental disease or bacterial infection (66). Most case reports of ONJ show teeth that were performed for extraction and had existing periodontal or periapical disease (67). Inflammation or infection are the important factors of ONJ. Actinomyces species are identified from biopsied specimens of necrotic bone removed from patients with ONJ (68). The persistence of bacteria has been studied to estimate the possibility of a complex biofilm on exposed bone (69). Complex biofilm have been identified that consist of bacteria, fungi and viruses, which may require combination therapies against the multi-organism ONJ- associated biofilm (64).

Inhibition of angiogenesis

Angiogenesis is a development of new blood vessels which engages with growth, migration and differentiation of endothelial cells. It favorably influences tumor growth and tumor invasion of vessles, which results in tumor metastasis. The binding of signaling molecules are required for Angiogenesis, such as vascular endothelial growth factor (VEGF), to receptors on the endothelial cells; as a consequence, the new blood vessel growth is promoted by this signaling. Osteonecrosis is considered as a disturbance in vascular supply or avascular necrosis; thus, it is not surprised that angiogenesis inhibitor is a main hypothesis in ONJ

pathophysiology (70, 71). In the laboratory experiments, it has shown a consistent decrease in angiogenesis when use of zoledronic acid (72). Plenty of studies that focused on patients with cancer who were treated with zoledronic have reported the decrease in circulating VEGF levels (73). Additionally, there is literature about growing bodies that links ONJ and osteonecrosis of other bones in patients receiving novel antiangiogenic drugs (tyrosine kinase inhibitors [TKIs] and monoclonal antibodies–targeting VEGF).

Stages of MRONJ have been defined by The American Association of Oral and Maxillofacial Surgeons as follows:

- Stage 0: Indicated by no exposed bone but nonspecific clinical finding and symptoms. - Stage 1: Indicated by exposed, inflamed necrotic bone without symptoms.

- Stage 2: Indicated by exposed, necrotic bone with local signs or symptoms of infection.

- Stage 3: Indicated by exposed, necrotic bone with pain and infection, pathologic fracture, extraoral fistula, and extensive osteolysis.

Risk factors

Medical related risk for MRONJ

The risk of MRONJ in osteoporosis patients using BPs varies from 0.02 % to 0.05 %, which is similar to the risk of MRONJ in patients taking placebos (0 % to 0.02 %). However, the risk of MRONJ in patients who are treated with denosumab is higher, ranging from 0.04 % to 0.3 %. The risk of MRONJ in patients who treated with romosozumab (0.03 % to 0.05 %) is more similar to the risk of BPs (17, 74).

According to present review, the risk of MRONJ in osteoporotic patients treated with BPs, DMB, or romosozumab is minimal. The incidence of cases found is best explained by a rare occurrence among a large number of patients exposed to these drugs, 5.1 million over the age of 55 (15).

Based on retrospective study, the prevalence of MRONJ was found to have increased over time from near 0 % at baseline to 0.21 % after four or more years of BP exposure. More recent findings from a large prospective, randomized placebo-controlled study show that patients treated for up to 9 years have no significant increase in MRONJ. As a result, while duration may be a risk factor, the risk level is low (75, 76).

Local factors

MRONJ is more likely to occur in the mandible (75%) than the maxilla (25%), however it can occur in both jaws (4.5 %) (18). One of the main local risk factors for MRONJ is infections at the dental-periodontal and peri-implant sites. These infections are usually the major factor for surgical procedures such as dental extraction or implant removal during or after therapy. The most frequent recognized predisposing factor for MRONJ is dentoalveolar surgeries. Tooth extraction is cited as a predisposing event in 62 % to 82 % of patients with MRONJ, by several studies (18, 68). The risk of MRONJ in osteoporotic patients exposed to BPs after tooth extraction is currently estimated at between 0 % and 0.15 %. The risk of MRONJ after tooth extraction was 1% in osteoporotic patients exposed to DMB (77, 78).

The risk of MRONJ in patients who have been prescribed antiresorptive drugs for other dentoalveolar procedures including dental implant placement, endodontic or periodontal treatments is unclear. AAOMS recommends that osteoporosis patients be advised of possible risks, which include the development of MRONJ and early and late implant failure (15, 79).

Demographic, systemic factors and other medication

MRONJ is related to risk factors such as age and gender. MRONJ is more common in women than in men, which is most likely due to the underlying disease for which the drugs are administered (eg, osteoporosis, breast cancer). Corticosteroids have been associated with a higher risk of MRONJ. When used in combination with

antiresporptive drugs, corticosteroids were related to increase the risk of MRONJ (18, 79, 80).

In the current literature, Compared to patients taking antiresorptive drug for osteoporosis, the risk of MRONJ is much lower than patients taking antiresorptive drug for cancer. Furthermore, type of medication (BPs, DMB, romoszumab) or dose schedule, the incidence of MRONJ in osteoporosis patients who undergoing antiresorptive treatment remains very low (15).

Risk reduce strategies

Primary prevention for MRONJ is removing or reducing oral and dental risk factors. Its goal is to restore and maintain good oral hygiene while decreasing the risk of the development of pathological conditions or any other unfavorable event. This strategy has the best impact when it is focused at maintaining the oral health of patients at risk of MRONJ on a regular recall. Secondary prevention or early diagnosis is the second pillar in the MRONJ approach, since we know that MRONJ detected early is more likely to be effectively treated (17-20).

In order to control MRONJ infective outbreaks, primary preventive should be performed not only prior to using MRONJ-related drugs, but also during and after treatment with antiresorptive agents (AR). It is the responsibility between dentist and doctor to consult and assess the risk factors leading to the development of MRONJ each other and advice a strategy to reduce the risk factor. Both are necessary to

maintain oral health, reducing the outbreak of MRONJ and/or detecting possible signs of the early symptoms of this disease (20).

Awareness of MRONJ in medical doctors

Awareness meaning is knowledge, understanding or perception of situation or something at the present time base on information or experience.

In 2016, a study of 192 medical physicians in Korea, 21.9 percent had never heard of the disease. Only 8.9 percent correctly answered all five MRONJ knowledge-testing questions. Dental referrals from medical doctors were used by lower than 30% of the total patients. Given medical doctors' poor MRONJ perception and implementation level of dental referrals, it is critical to improve MRONJ information and establish a highly accessible educational program recognizing the necessity for dental referrals (81).

A study in Japan 2021, Neither physicians nor dentists were kept up to date on the latest developments in the diagnosis and treatment of MRONJ. Physicians have less MRONJ experience than dentists. It is reported that dentists did not mention the development of jaw osteonecrosis in their patients to their physicians. For physicians part, 67% of them did not give their patients with the essential information on MRONJ and did not refer their patients for dental treatment prior to starting antiresorptive therapy. As a result, there is a lack of collaboration between physicians and dentists during osteoporosis therapy (82).

A questionnaire-based survey was administered to general surgeons, urologists, orthopedics, rheumatologists, and oncologists in Iraq. The questionnaire contained four questions about drug prescription, patient preparation before drug administration, and MRONJ knowledge and awareness. Only 15.8% of respondents know how to prepare their patients before drug administration. 26.3% of respondents aware about the side effects of drugs that was prescribed to their patients. There was a significant difference between groups in levels of dental referral, MRONJ awareness and knowledge. The oncologist group had the highest rates (83).

A total of 1370 health professionals in Brazil took part in the research. The awareness of MRONJ among dentists, doctors, and nurses was examined using questionnaires. The surveys described the health professionals' characteristics, training time, and specialties, as well as their knowledge of antiresorptive drugs and MRONJ. 84.59% of physicians believe the importance of referral to the dentist before starting antiresorptive therapy but this awareness considerably decreased when the staging of MRONJ was considered, 13.8% of physicians were aware of the importance of referral to the dentist. The data revealed a significant lack of knowledge of MRONJ among dental surgeons and physicians (84).

An observational cross-sectional study in Lebanon, A total of 136 self-administered questionnaire responses showed 37.5% of physicians who involved in prescribing antiresorptive drugs and managing the ONJ were unaware of MRONJ.

Moreover the level of knowledge was poor because participants answered incorrectly more than 60%. 55.9% of physicians considered that prevention of MRONJ is important. However, physicians still require appropriate training program to improve their knowledge and awareness (85).

All above mentioned, it can see that the percentage of dental referral among medical doctors in many country are few. So It can imply that awareness of medical doctors still low.

In conclusion, Regarding the adverse effect on patients' quality of life, the specialists who prescribe and those who follow up (dentists, nurses, and other multidisciplinary team participants) must communicate in order to optimize patient care and proper treat these patients at risk of developing MRONJ. This communication between professionals is important, but good communication between professionals and patients is essential in their adherence to treatment and follow-up. It is also important in guiding patients regarding the therapeutic indications, the benefits of treatment with these drugs, the potential side effects, and the available preventive practices. Improvements in MRONJ awareness and knowledge among medical specialists, as well as dental referral implementation, are important in the prevention, diagnosis, and treatment of MRONJ.

Chapter III

Research Methodology

Sample size population

This descriptive cross sectional study will survey medical specialists and residents who prescribe antiresorptive drug from December 2022 to February 2023 .

Inclusion criteria

- Medical specialists and residents of internal medicine who are involved in prescribing antiresorptive drugs or in managing the ONJ (eg, endocrinology, ear nose and throat (ENT) specialty, family medicine, gynecology, internal medicine, nephrology, oncology, orthopedics, and rheumatology departments)
- Medical doctors who work at public hospitals in Thailand

Exclusion criteria

- Physicians who incomplete response
- Physicians who cannot read Thai
- Physicians who does not accept the consent form

Sample size calculation

The sample size is calculated by using formula:

$$n = \frac{Z^2 p(1-p)}{d^2}$$

N = population size

Z = Z score of alpha (1.96)

p = expected prevalence or population (in this study, use prevalence from Lee,2016, p = 0.089)

d = the acceptable sampling error (In this study, e = 0.05)

$125 = ((1.96)^2(0.089)(0.911))/(0.05)^2$

A total sample size 150 = 125 x 1.2 is required including 20% incomplete questionnaire

Study design

This descriptive cross-sectional study was performed using a web-based structured questionnaire among medical doctors in Thailand. The online self administered questionnaire including a cover letter explaining the purpose of study was sent out electronically.

The questionnaire survey consisted of two parts:

1. part I: All participants will be informed about the study's details and asked to sign in consent form before answer the questionnaire.
2. Part II: Evaluated the demographic and professional data including age, years of experience, specialization and a type of working sector.
3. part III: Assessed awareness and practice about MRONJ.

Validity and reliability test

- The content validity of the questionnaire was evaluated by 3 experts, separately.
- The recommended modifications were done and the questionnaire was ready for the main research.
- Reliability is tested by 5 physicians took part in a pilot study.

Data analysis

SPSS Statistics 28 (IBM Corporation, Armonk, NY, USA) was used for data analysis. The chi-square test and multivariable logistic regression were employed for bivariable and multivariable analyses. A p value of <0.05 was considered statistically significant.

Ethical Consideration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethical committee of the Faculty of

Dentistry, Chulalongkorn University, Bangkok, Thailand (approval no. HREC-DCU 2022-079).

Timeline

	2022											2023				
	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5
Review literature																
Research proposal preparation and presentation																
Ethic approval																
Data collection																
Data analysis and disscussion																
Report preparation																
Research presentation																

Budget

1. Participation souvenir 10,000 baht
2. Documentary 2,000 baht

Chapter IV

Results

Table 1 Demographic characteristics of the respondents (*N* = 195)

Characteristic	**Group**	***n* (%)**
Gender	Male	103 (52.8)
	Female	92 (47.2)
Age	25–30 years	57 (29.2)
	31–40 years	86 (44.1)
	41–50 years	27 (13.8)
	>50 years	25 (12.8)
Work sector	Medical school	102 (52.3)
	Quaternary care center	37 (19)
	Tertiary care center	35 (17.9)
	Private hospital	21 (10.8)
Position at medical school (*n* = 102)	Instructor	56 (54.9)
	Resident	25 (24.5)
	Fellow	21 (20.6)
Specialty	Internal medicine	66 (33.8)
	Orthopedics	65 (33.3)
	Family medicine	20 (10.3)

	Gynecology and obstetrics	18 (9.2)
	Physical therapy and rehabilitation	26 (13.3)
Length of antiresorptive drug prescription	<5 years	110 (56.4)
	5–10 years	44 (22.6)
	>10 years	41 (21)
Frequency of drug prescription	<10 cases/month	129 (66.2)
	10–30 cases/month	50 (25.6)
	>30 cases/month	16 (8.2)
Recognition of MRONJ	Yes	181 (92.8)
	No	14 (7.2)
Practice includes patients with MRONJ	Yes	38 (19.5)
	Never	157 (80.5)
Source of knowledge about MRONJ	Textbook	42 (21.5)
	Instructor	41 (21)
	Academic meeting	51 (26.2)
	Journal/paper/article	47 (24.1)
	Never known	14 (7.2)
Have read articles about MRONJ in the past 3 years	Yes	124 (63.6)

	No	57 (29.2)

MRONJ medication-related osteonecrosis of the jaw

Demographic data

Of the questionnaires returned by 205 respondents, those from 195 were used in the analysis; the other 10 respondents did not prescribe antiresorptive drugs. The numbers of male and female respondents were nearly equal. Many respondents (44.1%) were in the age range of 30–34; approximately half the respondents were instructors in medical schools. The majority of respondents were in the fields of internal medicine and orthopedics. Most respondents (56.4%) had prescribed antiresorptive drugs for less than 5 years, and 66.2% prescribed these drugs for fewer than 10 patients per month. Of the 195 respondents, 181 (92.9%) were aware of MRONJ, but only 38 (19.5%) had patients who had MRONJ. Sources of knowledge about MRONJ were textbooks, instructors, academic meetings, and media (journals, papers, and articles; Table 1).

Table 2 Assessment of physicians' awareness of MRONJ and related practices (*N* = 181)

Question	*n* (%)		
	Agree	**Disagree**	**Not sure**
Awareness			
1: Do antiresorptive drugs cause the risk of developing MRONJ?	167 (92.3)	1 (0.6)	13 (7.2)
2: Are patients with poor oral health conditions at greater risk for developing MRONJ than are people with good oral	152 (84)	11 (6.1)	18 (9.9)

health conditions?			
3: Is MRONJ an important consideration in patients with osteoporosis?	172 (95)	2 (1.1)	7 (3.9)
	Always	**Never**	**Sometimes**
Practice			
4: Did you inform patients about the risks associated with MRONJ before antiresorptive therapy?	113 (62.4)	15 (8.3)	53 (29.3)
5: Did you refer patients to a dentist for an oral examination and preparation before antiresorptive therapy?	87 (48.1)	30 (16.6)	64 (35.4)
6: Did you refer patients to a dentist for oral health care during antiresorptive therapy?	28 (15.5)	55 (30.4)	98 (54.1)
7: Did you inquire about patients' oral symptoms while monitoring them?	59 (32.6)	29 (16)	93 (51.4)
8: When you suspected that one of your patients has MRONJ, did you refer the patient to a dentist?	175 (96.7)	3 (1.7)	3 (1.7)
9: Did you recommend oral health care to patients who receive antiresorptive drugs?	80 (44.2)	45 (24.9)	56 (30.9)

MRONJ medication-related osteonecrosis of the jaw

Awareness of MRONJ

Most respondents agreed that antiresorptive drugs may cause MRONJ (92.3%), that poor oral health increased the risk of MRONJ (84%), and that MRONJ is an important consideration in patients with osteoporosis (85%; Table 2).

Table 3 Reasons why physicians did not always refer patients to dentists

Reason	Number of responses
Why did you not inform patients of the details of the risks associated with MRONJ before antiresorptive therapy began?	
- The risk of developing MRONJ is very low in patients with osteoporosis.	60
- I do not think antiresorptive drugs cause MRONJ.	5
- I think it is a detail that is not important to patients.	2
- Other.	6
Why did you not refer patients to a dentist for an oral examination and preparation before antiresorptive therapy began?	
- I refer only patients who are considered at risk.	64
- I think it unnecessarily burdens dentists.	14
- I do not think dentists are involved in osteoporosis treatment.	10
- Osteoporosis needs to be treated urgently, before the patient sees the dentist.	13
- The referral system is difficult to navigate.	18
- Patients are uncooperative.	7
- Patients have difficulty paying for dental treatment.	8
- Other.	3
Why did you not refer patients to a dentist for oral health care during antiresorptive therapy?	

- I refer only patients who are considered at risk.	80
- Patients already have a dentist whom they visit regularly.	37
- I think it unnecessarily burdens dentists.	27
- The referral system is difficult to navigate.	20
- I do not think dentists are involved in osteoporosis treatment.	16
- Patients have difficulty paying for dental treatment.	13
- Patients are uncooperative.	5
- Other.	13
Why did you not inquire about patients' oral symptoms while monitoring them?	
- The patients did not mention oral symptoms at all and did not inquire further.	101
- I think that oral health is not related to osteoporosis treatment.	8
- I think that patients are already taking good care of their oral health.	22
- Other.	7
Why will you not refer patients to a dentist if you suspect that they have MRONJ?	
- I will refer such patients to another specialist.	4
- I do not think dentists are helpful in MRONJ management.	2
- I can manage MRONJ myself.	1
- I think the symptoms are still unclear and monitor patients' symptoms first.	1
Why did you not recommend oral health care to patients who receiving antiresorptive drugs?	
- I do not consider myself knowledgeable enough to detect oral health problems.	55
- I think that patients are already taking good care of their oral health.	30
- I think that oral health is not related to osteoporosis	14

treatment.	
- I think it is not my duty to give advice about oral health.	6
- Other.	9

MRONJ medication-related osteonecrosis of the jaw

These answers were from respondents who answered “never” or “sometimes” in questions 4–9. Participants could select multiple answers

Practice

MRONJ-related practices of the 181 respondents who were aware of MRONJ are listed in Table 2, and reasons for answering practice items negatively are listed in Table 3. Approximately 60% of respondents informed patients of the risks associated with MRONJ before antiresorptive therapy began (question 4). The main reason why physicians did not inform patients of these risks before antiresorptive therapy was that the incidence of MRONJ is very low among patients with osteoporosis. Approximately 30% of physicians inquired about patients’ oral symptoms during antiresorptive therapy (question 7). The most common reason for not inquiring was that patients did not mention oral symptoms (n = 101). Patients taking antiresorptive drugs received advice about oral health care from 80 physicians (question 9). The reason why 101 physicians did not give such advice was that they did not consider themselves knowledgeable enough to detect oral health problems.

Most respondents agreed that oral health is related to the risk of MRONJ; the proportions of physicians who always and those who did not always refer the

patients to a dentist for an oral examination and preparation before antiresorptive therapy were similar (question 5). Only 15.5% of physicians always referred patients to a dentist for oral health care during antiresorptive therapy (question 6). The main reason why physicians did not refer the patients to a dentist before and during antiresorptive therapy (questions 5 and 6) was that they referred only patients considered to be at risk for MRONJ. If patients were suspected of having MRONJ, 96.7% of physicians would refer them to a dentist (question 8). Only 4.9% reported that they always practiced all the activities mentioned in questions 4–9.

Table 4 Multivariable analysis of factors associated with practice

Q4			Q5			Q6			Q7			Q8		
AOR	95% CI	*p* value	AOR	95% CI	*p* value	AOR	95% CI	*p* value	AOR	95% CI	*p* value	AOR	95% CI	*p* value
		0.033*			0.450			0.302			0.287			0.987
0.450	0.180-1.125	0.088	0.803	0.314-2.052	0.646	0.492	0.152-1.587	0.235	0.971	0.376-2.520	0.952	1.109	0.103-11.892	0.932
2.889	0.499-16.714	0.236	2.786	0.380-20.411	0.313	1.436	0.098-21.035	0.791	4.958	0.639-38.485	0.126	0	0	0.997
1.272	0.220-7.351	0.788	3.858	0.459-32.417	0.214	5.589	0.216-144.327	0.300	5.544	0.679-45.299	0.110	0	0	0.996
		0.772			0.713			0.192			0.136			0.893
0.721	0.236-2.202	0.566	0.638	0.216- 1.886	0.416	0.683	0.147-3.167	0.627	0.394	0.130-1.194	0.1	0.411	0.011-15.910	0.634

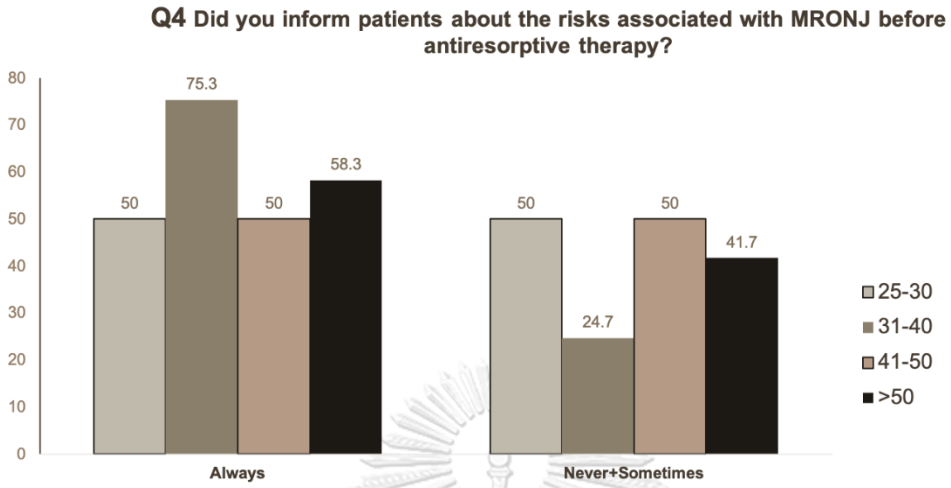
		0.167			0.002*			0.033*			0.606			0.879
0.554	0.154-1.994	0.366	0.166	0.042-0.648	0.01*	0.145	0.016-1.334	0.088	0.609	0.151-2.463	0.487	0	0	0.995
1.242	0.351-4.394	0.737	0.447	0.115-1.731	0.244	0.544	0.053-5.533	0.607	0.925	0.225-3.808	0.914	0.305	0.10-9.702	0.501
0.327	0.068-1.563	0.161	0.05	0.008-0.301	0.001*	0.162	0.15-1.774	0.136	0.622	0.114-3.407	0.584	0.555	0.025-12.362	0.710
0.547	0.128-2.349	0.418	0.265	0.058-1.207	0.086	1.730	0.091-33.033	0.716	0.362	0.072-1.816	0.217	0.095	0.001-6.821	0.280
		0.852			0.019*			0.075			0.974			0.930
0.749	0.262-2.139	0.589	3.498	1.312- 9.327	0.012*	4.311	1.096-16.950	0.036*	0.893	0.341-2.336	0.817	1.795	0.089-36.191	0.703

0.696	0.131-3.701	0.671	0.692	0.98- 4.882	0.711	0.677	0.47-9.675	0.773	0.904	0.129-6.313	0.919	14128675	0	0.996
		0.360			0.244			0.622			0.286			0.920
0.640	0.274-1.498	0.304	1.054	0.464- 2.396	0.9	1.226	0.396-3.789	0.724	0.647	0.275-1.519	0.317	0.521	0.023-11.866	0.683
0.402	0.100-1.614	0199	3.748	0.759- 18.508	0.105	3.374	0.290-39.310	0.332	0.319	0.072-1.402	0.130	0	0	0.998
0.766	0.310-1.895	0.564	0.638	0.263-1.550	0.321	0.545	0.171-1.735	0.304	0.566	0.234-1.365	0.205	50.921	1.793-1446.275	0.021*

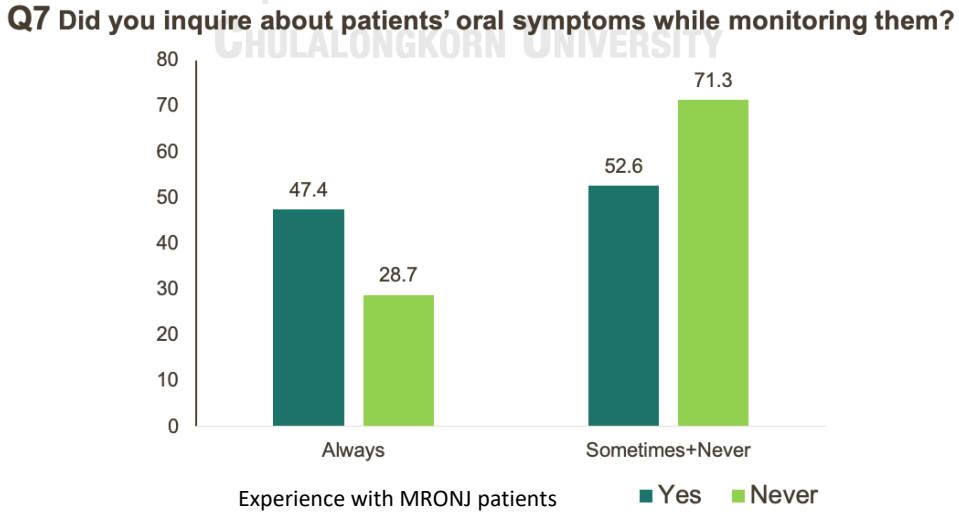
0.597	0.278-1.283	0.187	0.714	0.320-1.595	0.412	0.809	0.264-2.474	0.710	0.464	0.194-1.111	0.085	0.058	0.002-1.443	0.083

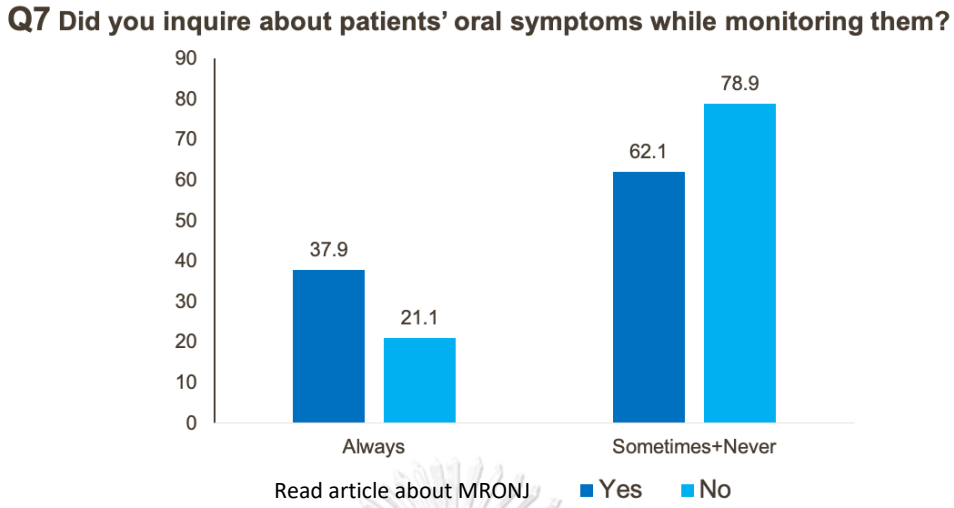
MRONJ medication-related osteonecrosis of the jaw, *AOR* adjusted odd ratio, *ref* reference, *Q* question, *CI* confident interval, * *p* value < 0.05

Factors associated with practices

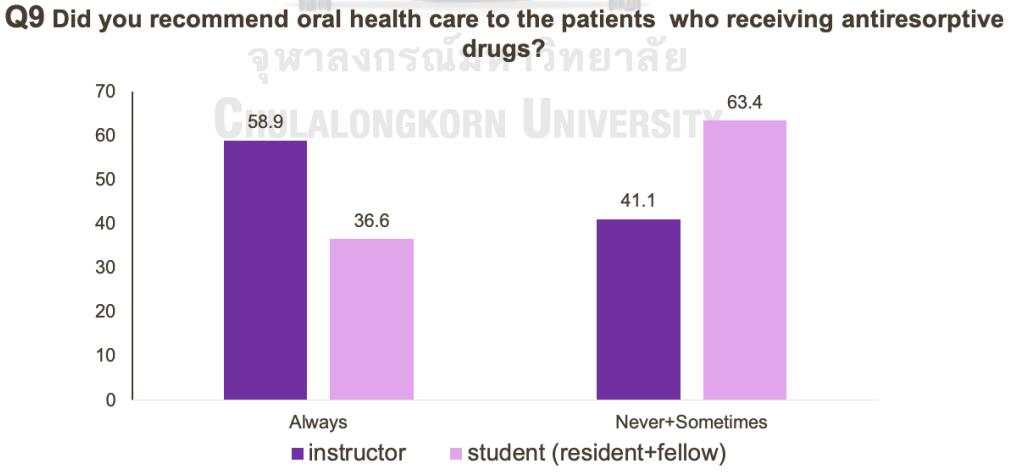


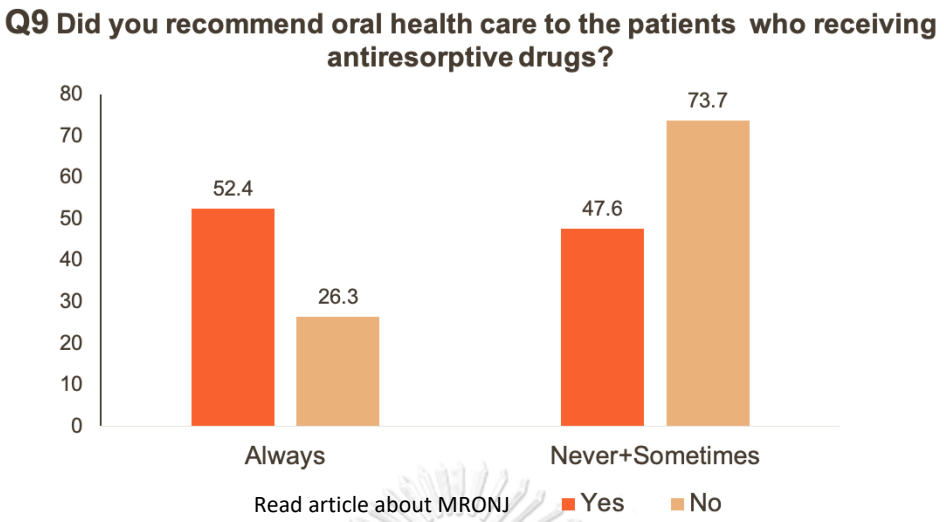
The multivariable analysis revealed that age of the physician was a factor associated with providing information about the risks of MRONJ to patients before antiresorptive therapy (question 4; p = 0.033). However, when we compared the reference group (aged 25–30 years; who had the least experience in treating patients with osteoporosis) with every other age group, we found no difference.



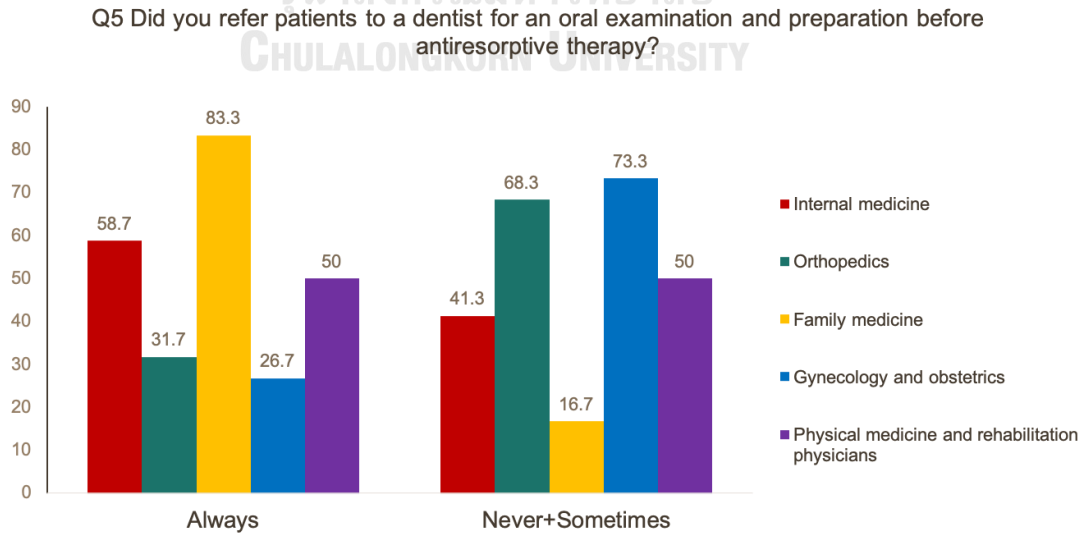


Univariable analysis of responses to question 7 revealed that physicians' experience with patients who had MRONJ (p = 0.029) and reading articles about MRONJ (p = 0.025) were associated with inquiry about patients' oral symptoms while patients were monitored (question 7), whereas multivariable analysis did not reveal the effect of independent variables.

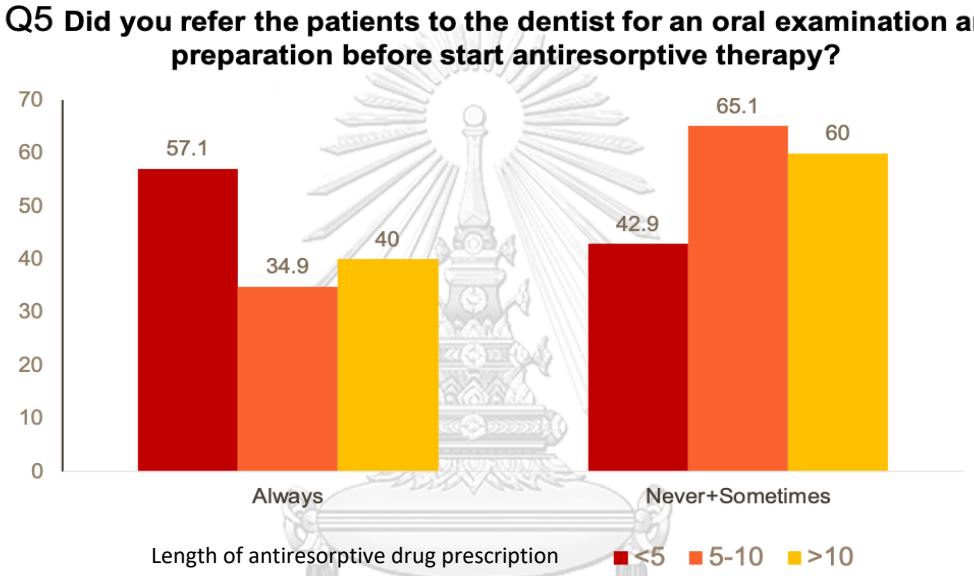




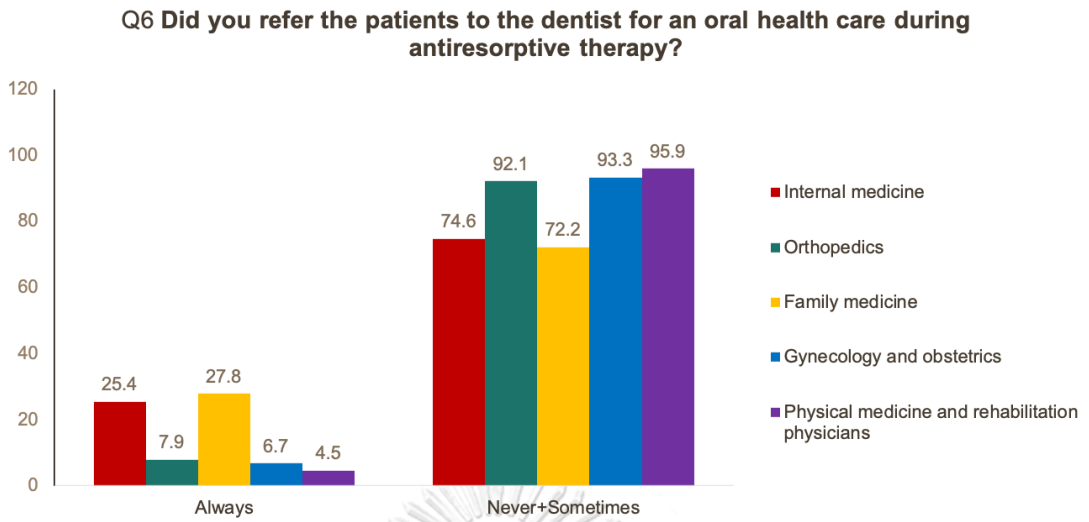
Multivariable analysis revealed that position in medical school was associated with advising patients about oral health care (question 9): instructors tended to give this advice 3.13 times more often than residents and fellows (p = 0.028). Moreover, physicians who read articles about MRONJ (question 9) tended to advise patients about oral health care 3.17 times more often than did those who did not read such articles (p = 0.005).



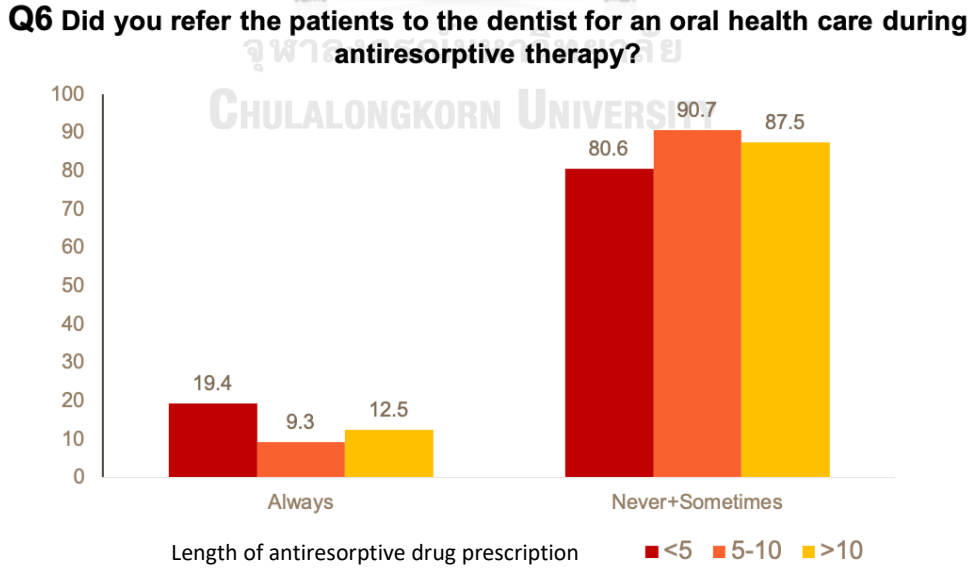
Factors that affected the decision to refer patients to the dentist before antiresorptive therapy (question 5) were the physician's specialty (p = 0.002) and period of antiresorptive drug prescription (p = 0.019). Physicians in the fields of internal medicine and family medicine tended to refer patients to dentists 6.02 times and 20 times more than those in the field of gynecologists and obstetricians.



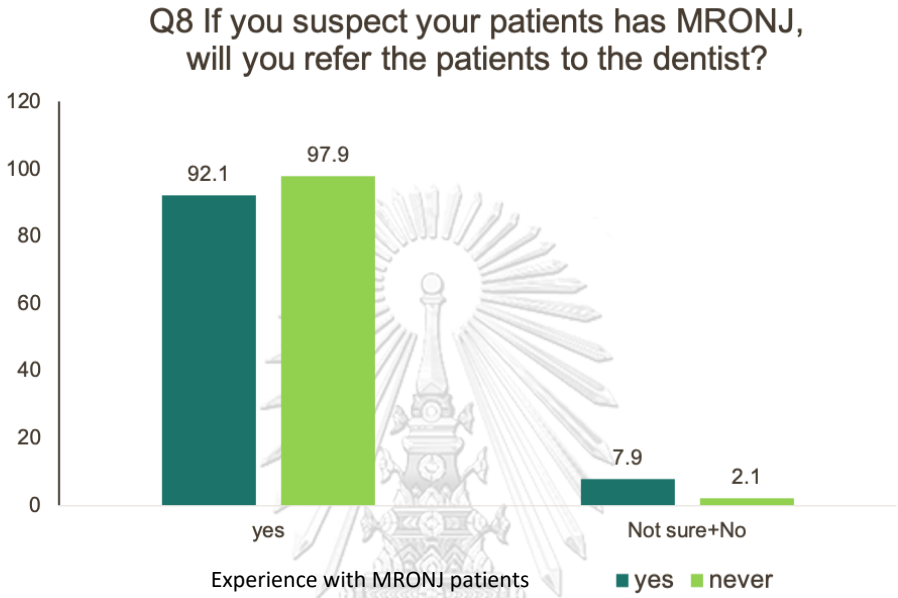
Physicians who had been prescribing antiresorptive drugs for less than 5 years were 3.5 times more likely to refer patients to dentists before antiresorptive therapy than were those who had been prescribing for 5–10 years (p = 0.012).



Referral of patients to dentists after antiresorptive therapy began was associated with physicians' specialties (question 6; p = 0.03); however, comparisons of individual specialties with the reference specialty (gynecology and obstetrics; who were less involved in treating patients with osteoporosis compared to other specialties) revealed no differences.

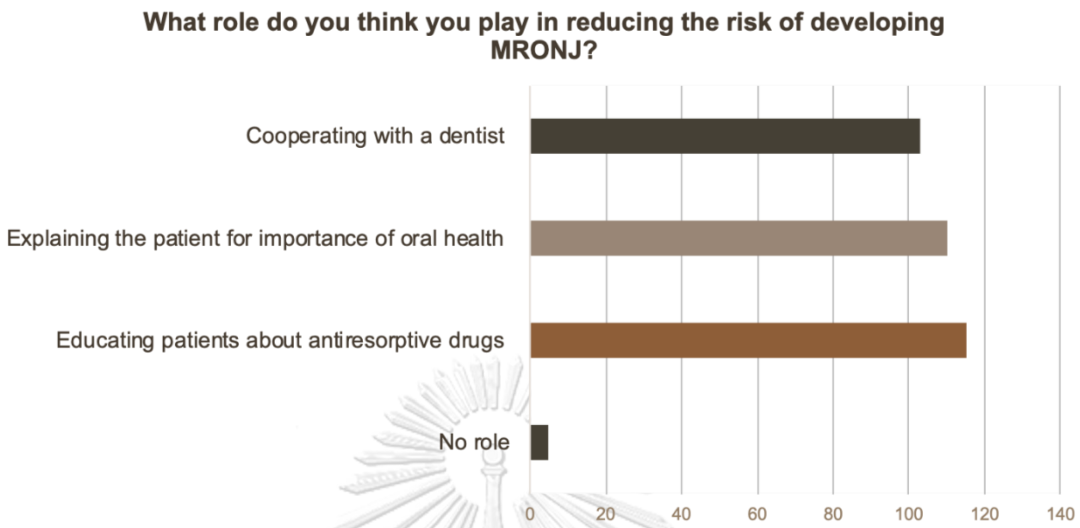


Physicians who had prescribed antiresorptive drugs less than 5 years were 4.31 times more likely to refer patients to the dentist after antiresorptive therapy began than were those who had been prescribing for 5-10 years (p = 0.036).



Physicians who had experience with patients who had MRONJ were 50.92 times less likely to refer a patient with suspected MRONJ to a dentist (question 8) than were those who had no experience with such patients (p = 0.021; Table 4).

Role in MRONJ prevention



To the question "What role do you think you play in reducing the risk of developing MRONJ?" 115 physicians replied that they educated patients about, and enhanced their understanding of, antiresorptive drugs; for 110 physicians, education included explanations of the importance of oral health. In addition, 103 physicians thought that collaborating with a dentist played a part in reducing the risk of MRONJ.

Chapter V

Discussion

We investigated the knowledge and awareness of Thai physicians about MRONJ and their related practices. In this survey, almost all the physicians were aware of MRONJ (92.8%) and knew that MRONJ could occur in patients with osteoporosis (95%). This finding is the same as in Japan (94%) (82) and higher than those in Brazil (78.66%) (84). On the other hand, only 31.5% of physicians in Saudi Arabia (86) and 26.3% of those in Iraq (83) were aware of MRONJ. However, fewer than 5% of the physicians in this study always informed their patients about MRONJ, referred patients to dentists, and considered patients' oral health. These findings implied that most of physicians know the adverse effects of the medications that they prescribe to their patients, they agree that oral health is related to the risk of MRONJ, and they agree that MRONJ is a serious condition of concern in patients with osteoporosis. In practice, however, it may not be possible to follow the 2022 clinical practice guidelines recommended by the American Association of Oral and Maxillofacial Surgeons (AAOMS) (15), which emphasize the importance of a multidisciplinary approach to the treatment of patients who are receiving antiresorptive therapy, informing patients of the risk of MRONJ from antiresorptive therapy, and referring patients to dentists to remove possible sources of infection in the oral cavity and thereby reduce the risk of MRONJ.

The previous studies demonstrated that maintenance of good oral hygiene is most important in patients who require treatment with antiresorptive drugs; therefore, informing them of the dental risk of MRONJ and obtaining dental treatment before and after drug administration are of utmost importance (87, 88). Several authors have recommended the extraction of teeth with poor prognoses before antiresorptive therapy to prevent MRONJ (17, 61). Also, if all dental procedures are performed before antiresorptive therapy, future dentoalveolar surgery can be unnecessary. A preventive strategy for proper oral health can reduce the incidence of MRONJ (17). However, according to this study, the proportion of patients who received dental referrals before and during the administration of antiresorptive drugs was less than 50%. This finding is consistent with data in many countries, such as Korea (<30%) (81), Japan (30%) (82), Brazil (17.99%) (84), India (49.2%) (89), and Iraq (15.8%) (83).

In our study, some physicians did not provide dental referrals except for patients considered to be at risk for MRONJ. This may lead to misdiagnosis or undertreatment in some cases; in a few patients with MRONJ, signs and symptoms can be subclinical disease. Hence, before antiresorptive therapy begins, physicians should schedule dental consultations and dental follow-up for oral hygiene maintenance after patients begin therapy. Also, as a result of physicians' belief that referring a patient to a dentist is too burdensome for dentists, a patient's oral health may be unprepared for antiresorptive medication, which in turn increases the

likelihood that future surgery will be necessary and may increase the risk of MRONJ. Because MRONJ is an unpredictable, long-term condition, and the incidence of MRONJ is increasing, the resulting burden on both physicians and dentists will compromise patient care.

Many physicians did not inquire about patients' oral symptoms during follow-up because the patients did not mention oral symptoms, and many physicians did not advise their patients about oral health care because they were not knowledgeable about it. Dental referral is important because oral health care education, oral examination for early detection, and oral hygiene maintenance are important for reducing the risk of MRONJ. Physicians should at least mention the importance of oral health to patients and should inquire about patients' oral health, using questions specifically about symptoms in the oral cavity.

The referral system should be improved for easy communication between physicians and dentists. Moreover, the oral care of patients with osteoporosis should be prioritized before antiresorptive therapy because some patients are at high risk for fracture or because fracture has already occurred. The importance of dental examination and a well-coordinated referral system should be emphasized as described in the clinical practice guidelines of the AAOMS (15) and of Thai Osteoporosis Foundation (90); physicians should be encouraged to adhere to those standards through open communication, collaboration with dentists, and routine

provision of dental referrals to patients before and during antiresorptive therapy. Therefore, to decrease the risk, and incidence of MRONJ, educational programs for physicians should include an emphasis on oral health and on collaboration between professional health care providers.

A limitation of this study is that there were only 195 physicians responded to a questionnaire through a Google Form link and QR code; therefore, the probability of response bias should be considered. Since there is no official registry regarding physicians who treat osteoporosis, the actual number of physicians who treat osteoporosis in Thailand is unknown, and the sample in this study might not represent all physicians who prescribe antiresorptive drugs. Although we sent the questionnaire to medical associations, some physicians may not reach the questionnaire; therefore, we could not calculate the response rate. In further studies of the incidence of MRONJ, investigators should compare antiresorptive-treated patients who routinely maintain oral health with those who do not.

Conclusion

Most physicians who prescribe antiresorptive drugs are aware of and knowledgeable about MRONJ. In practice, however, it may not be possible to follow clinical practice guidelines strictly in certain circumstances. To improve the rate of dental referral, physicians should adhere to clinical practice guidelines and establish a routine of dental referral of patients before and during antiresorptive therapy. To

decrease the risk and incidence of MRONJ, educational programs for physicians should increase the awareness of oral health in patients with osteoporosis and emphasize collaboration between physicians and dentists.

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ภาคผนวก

<u>ส่วนที่ 2: ข้อมูลทั่วไปและประสบการณ์ทำงานของผู้เข้าร่วมวิจัย</u>

Definition

ภาวะกระดูกขากรรไกรตายจากการใช้ยา = osteonecrosis of the jaw (ONJ), bisphosphonate-related osteonecrosis of the jaw (BRONJ), medication-related osteonecrosis of the jaw (MRONJ), antiresorptive-related osteonecrosis of the jaw (ARONJ)

1. เพศ
   คำตอบ ชาย/หญิง
2. อายุ
   คำตอบ (มีช่วงอายุให้เลือก)
3. สถานที่ทำงาน
   คำตอบ โรงเรียนแพทย์/ รพศ./ รพท./ รพช./ รพ.เอกชน/ คลินิกเอกชน
4. ท่านทำงานในตำแหน่งใดในโรงเรียนแพทย์
   คำตอบ อาจารย์/ resident/ fellow/ แพทย์ fulltime/ อื่นๆ
5. สาขาเฉพาะทางที่จบ (สาขาที่มีประสบการณ์มากที่สุด)
   คำตอบ Internal medicine (Endocrinology/ Oncology/ Rheumatology) / Orthopedics/ Family medicine/ Gynecology and obstetrics/ Physical Medicine and Rehabilitation physicians/ Geriatric/ อื่นๆ
6. ท่านมีประสบการณ์จ่าย antiresorptive drug มาแล้วกี่ปี
   คำตอบ <5 ปี/ 5-10 ปี/ 10-20 ปี/ >20 ปี
7. โดยเฉลี่ย ท่านจ่าย antiresorptive drug สำหรับรักษา/ป้องกันโรคกระดูกพรุนกี่เคสต่อเดือน
   คำตอบ <10/ 10-30/ 31-50/ >50 เคส
8. Antiresorptive drug ที่ท่านจ่ายยาบ่อยที่สุด 3 ลำดับแรก
   คำตอบ Zoledronate/ Alendronate/ Risedronate/ Ibandronate IV form/ Ibandronate oral form/ Denosumab/ อื่นๆ
   ท่านเคยได้ยินภาวะ MRONJ หรือไม่

คำตอบ ใช่/ไม่

9. ท่านได้ทราบข้อมูลเกี่ยวกับภาวะ MRONJ ผ่านช่องทางใด
   คำตอบ เพื่อนร่วมงาน/ อาจารย์/ ผู้ป่วย/ text/ journal/ social media/ ไม่เคยทราบข้อมูลเกี่ยวกับ MRONJ มาก่อน/ อื่นๆ
10. ท่านเคยพบผู้ป่วยที่มีภาวะ MRONJ หรือไม่
    คำตอบ เคย/ไม่เคย

<u>ส่วนที่ 3: ทัศนคติและการปฏิบัติต่อภาวะกระดูกขากรรไกรตายจากการใช้ยา (MRONJ)</u>

1. ข้อใดคือยาต้านการละลายของกระดูก (antiresorptive drug)
   คำตอบ methotrexate/ bisphosphonate/ clopidogrel/ etoricoxib
2. Antiresorptive drug ทำให้มีความเสี่ยงในการเกิด MRONJ
   คำตอบ เห็นด้วย/ไม่เห็นด้วย/ไม่แน่ใจ
3. ผู้ที่มีสภาวะสุขภาพช่องปากที่ไม่ดีจะมีผลให้เกิดความเสี่ยงต่อการเกิด MRONJ มากกว่าผู้ที่มีสภาวะสุขภาพช่องปากที่ดี
   คำตอบ เห็นด้วย/ไม่เห็นด้วย/ไม่แน่ใจ
4. ภาวะ MRONJ เป็นสิ่งสำคัญที่ต้องคำนึงในผู้ป่วยโรคกระดูกพรุน
   คำตอบ เห็นด้วย/ไม่เห็นด้วย/ไม่แน่ใจ
5. ท่านได้แจ้งรายละเอียดถึงความเสี่ยงเกี่ยวกับ MRONJ ให้ผู้ป่วยได้รับทราบก่อนจ่ายยาให้ผู้ป่วยหรือไม่
   คำตอบ แจ้งทุกเคส/ไม่เคยแจ้งเลย/เป็นบางกรณี

a. สาเหตุที่ท่านไม่ได้แจ้งรายละเอียดความเสี่ยงเกี่ยวกับ MRONJ ก่อนที่ผู้ป่วยจะได้รับยาคือ
   คำตอบ - คิดว่าความเสี่ยงในการเกิด MRONJ มีน้อยมากในผู้ป่วยโรคกระดูกพรุน
   - คิดว่าเป็นรายละเอียดที่ไม่ได้สำคัญสำหรับผู้ป่วย
   - ไม่คิดว่ายาที่จ่าย มีผลทำให้เกิด MRONJ
   - อื่นๆ

6. ก่อนเริ่มให้ยาต้านการละลายของกระดูก ท่านได้ส่งผู้ป่วยให้ทันตแพทย์ตรวจสุขภาพช่องปากหรือไม่

คำตอบ ส่งต่อทุกเคส/ไม่เคยส่งต่อ/ส่งต่อบางเคส

a. สาเหตุที่ท่านไม่ส่งผู้ป่วยให้ทันตแพทย์ตรวจช่องปากก่อนเริ่มรับยาต้านการละลายของกระดูกคือ

คำตอบ - ไม่คิดว่าทันตแพทย์มีความเกี่ยวข้องกับการรักษาโรคกระดูกพรุน
- คิดว่าเป็นการเพิ่มภาระกับทันตแพทย์มากเกินความจำเป็น
- ส่งเฉพาะเคสที่คิดว่ามีความเสี่ยงเท่านั้น
- มีความเร่งด่วนในการรักษาโรคกระดูกพรุน ไม่สามารถรอพบทันตแพทย์ได้
- ผู้ป่วยไม่ให้ความร่วมมือ
- ผู้ป่วยมีปัญหาค่ารักษาทางทันตกรรม
- มีความยุ่งยากในการส่งต่อ
- อื่นๆ

7. หลังจากเริ่มให้ยาต้านการละลายกระดูกแก่ผู้ป่วย ท่านได้ส่งผู้ป่วยให้ทันตแพทย์ดูแลสุขภาพช่องปากหรือไม่

คำตอบ ส่งต่อทุกเคส/ไม่เคยส่งต่อ/ส่งต่อบางเคส

7.1 สาเหตุที่ท่านไม่ส่งผู้ป่วยให้ทันตแพทย์ตรวจช่องปากหลังจากจ่ายยาต้านการละลายของกระดูกไปแล้วคือ

คำตอบ - ไม่คิดว่าทันตแพทย์มีส่วนช่วยในการดูแลผู้ป่วย
- ผู้ป่วยมีทันตแพทย์ที่ไปหาเป็นประจำอยู่แล้ว
- ส่งเฉพาะเคสที่คิดว่ามีความเสี่ยงเท่านั้น
- คิดว่าเป็นการเพิ่มภาระกับทันตแพทย์มากเกินความจำเป็น
- ผู้ป่วยไม่ให้ความร่วมมือ
- ผู้ป่วยมีปัญหาค่ารักษาทางทันตกรรม
- มีความยุ่งยากในการส่งต่อ
- อื่นๆ

8. ท่านได้สอบถามอาการที่เกี่ยวกับช่องปากของผู้ป่วยขณะ follow up ผู้ป่วยหรือไม่

   คำตอบ สอบถามทุกเคส/ไม่เคยสอบถาม/สอบถามบางเคส

a. เหตุผลที่ท่านไม่ได้ถามอาการที่เกี่ยวกับช่องปากของผู้ป่วยขณะ follow up คือ

   คำตอบ - คิดว่าสุขภาพช่องปากไม่ได้มีความเกี่ยวข้องกับการรักษาโรคกระดูกพรุน

   - ผู้ป่วยไม่ได้พูดถึงอาการในช่องปากเลยไม่ได้สอบถามต่อ
   - คิดว่าผู้ป่วยดูแลสุขภาพช่องปากได้ดีอยู่แล้ว
   - อื่นๆ

9. หากท่านสงสัยว่าผู้ป่วยของท่านมีภาวะ MRONJ ท่านจะส่งต่อผู้ป่วยให้ทันตแพทย์ดูแลต่อหรือไม่

   คำตอบ ส่งต่อทุกเคส/ไม่เคยส่งต่อ/ส่งต่อบางเคส

a. สาเหตุที่ท่านจะไม่ส่งให้ทันตแพทย์ดูแลผู้ป่วยต่อ เมื่อสงสัยว่ามีภาวะ MRONJ คือ

   คำตอบ - ไม่คิดว่าทันตแพทย์มีส่วนช่วยในการรักษาภาวะ MRONJ

   - ท่านสามารถจัดการภาวะ MRONJ ได้ด้วยตัวท่านเอง
   - ท่านจะส่งผู้ป่วยไปหาแพทย์เฉพาะทางอีกสาขา (เช่น plastic surgery, ENT)
   - คิดว่าอาการยังไม่ชัดเจน จะติดตามอาการก่อน เลยยังไม่ส่งต่อ
   - มีความยุ่งยากในการส่งต่อ
   - อื่นๆ

10. ท่านได้แนะนำการดูแลรักษาสุขภาพช่องปากแก่ผู้ป่วยที่ได้รับยาต้านการละลายของกระดูกหรือไม่

    คำตอบ แนะนำทุกเคส/ไม่เคยแนะนำ/แนะนำเป็นบางเคส

10.1 สาเหตุที่ท่านไม่ได้แนะนำเรื่องการดูแลสุขภาพช่องปากให้แก่ผู้ป่วยคือ

คำตอบ - คิดว่าเรื่องสุขภาพช่องปากไม่มีความเกี่ยวข้องกับผู้ป่วยที่ได้รับยาต้านการละลายของกระดูก

- คิดว่าไม่ใช่หน้าที่ของตัวเองที่ต้องไปแนะนำเกี่ยวกับเรื่องของสุขภาพช่องปาก
- คิดว่าผู้ป่วยสามารถดูแลสุขภาพช่องปากได้ดีอยู่แล้ว
- คิดว่าตัวเองไม่ใช่ผู้เชี่ยวชาญเรื่องการดูแลสุขภาพช่องปาก
- อื่นๆ

11. ท่านคิดว่า ท่านมีบทบาทในการลดความเสี่ยงในการเกิดภาวะ MRONJ อย่างไร

คำตอบ - ช่วยให้ผู้ป่วยมีความตระหนักถึงความสำคัญของการดูแลสุขภาพช่องปากมากขึ้น

- ช่วยให้ผู้ป่วยมีความรู้ ความเข้าใจเกี่ยวกับยาที่ตัวเองได้รับมากขึ้น
- ทำงานร่วมกับทันตแพทย์ ทำให้การวินิจฉัยและการจัดการภาวะ MRONJ เหมาะสมมากขึ้น
- ไม่มีบทบาท

12. ช่วง 3 ปีที่ผ่านมาท่านได้อ่านบทความที่เกี่ยวกับ MRONJ หรือไม่ (บทความรูปแบบใดก็ได้)

คำตอบ อ่าน/ไม่ได้อ่าน

13. ท่านต้องการทราบรายละเอียดเกี่ยวกับภาวะ MRONJ มากขึ้นหรือไม่

คำตอบ สนใจ/ไม่สนใจ

VITA

NAME	ณัชพล ศุภนำพา
DATE OF BIRTH	14 เมษายน 2539
PLACE OF BIRTH	กรุงเทพมหานคร
INSTITUTIONS ATTENDED	จุฬาลงกรณ์มหาวิทยาลัย
HOME ADDRESS	251/266 หมู่บ้านสัมมากร ซอย 48/3 ถนนรามคำแหง 112 เขตสะพานสูง แขวงสะพานสูง 10240 กทม