Value of pre-operative CTX serum levels in the prediction of medication-related osteonecrosis of the jaw (MRONJ): a retrospective clinical study

Martin Salgueiro¹ · Michael Stribos² · Li Fang Zhang³ · Mark Stevens¹ · Mohamed E. Awad⁴ · Mohammed Elsalanty^{4,5}

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Abstract

Objectives The low incidence yet severe presentation of medication-related osteonecrosis of the jaw (MRONJ) makes it necessary to develop reliable predictive and preventive strategies. This study explored the value of pre-operative carboxy-terminal collagen crosslinks (CTX) serum level in the prediction of osteonecrosis-related complications in patients on bisphosphonate therapy.

Patients and methods We examined patient records over 4 years (a total of 137 patients). Biometric data were extracted, in addition to type of treatment, CTX levels, drug holiday, procedure, complications, and co-morbidities. Non-parametric Wilcoxon two-sample tests were used to test the effect of initial CTX level in IV or PO and whether it was predictive of complications. Two independent proportion tests were used for testing the two different complication incident rates before or after the drug holiday.

Results A total of 93 patients were included in the study, of whom 88.17% were female. A total of 11 patients were receiving IV bisphosphonates at the time of initial presentation, 82 oral bisphosphonates. Out of 64 patients who underwent invasive dental procedure (IDP) before a drug holiday, eight were on IV bisphosphonates. Three patients in this group experienced osteonecrosis-related complications (37.5%). Out of the remaining 56 patients on oral bisphosphonates, four (7.14%) developed complications, significantly lower than the IV bisphosphonate group ($p = 0.0364$). On the other hand, of the 34 patients placed on a drug holiday prior to IDP, only one subject developed complications related to osteonecrosis. Five subjects who had operations both before and after drug holiday did not experience any complications. No statistical difference was detected in complication rates based on initial CTX level (above versus below 150 pg/ml), gender, comorbidities, or total duration of bisphosphonate treatment ($p = 0.2675$). The sensitivity and specificity of CTX cutoff of 150 pg/ml in predicting osteonecrosis were 37.5% and 57.7, respectively.

Conclusions Serum levels of CTX by itself are not reliable as a predictive or preventive measure for such complications. Our data also suggested that a drug holiday of 5 months was not helpful in preventing osteonecrosis-related complications in patients on intravenous bisphosphonates. Further studies are urgently needed to develop adequate predictive and preventive strategies of MRONJ.

Keywords Bisphosphonates · Osteonecrosis · Drug holiday · Osteoporosis treatment · Prediction of complications

✉ Mohammed Elsalanty
melsalanty@augusta.edu

¹ Oral and Maxillofacial Surgery Department, Dental College of Georgia, Augusta University, Augusta, GA, USA

² Medical Student, Medical College of Georgia, Augusta University, Augusta, GA, USA

³ Department of Biostatistics and Epidemiology, Medical College of Georgia, Augusta University, Augusta, GA, USA

⁴ Department of Oral Biology and Diagnostic Sciences, Dental College of Georgia, Augusta University, Augusta, GA, USA

⁵ Department of Oral Biology, Dental College of Dentistry, Augusta University, 1120 15th Street, Room #2404E, Augusta, GA 30809, USA

Introduction

Osteoporosis has been one of the leading public health priorities in the USA. Between 1995 and 2005, the rate for hip fractures among older Americans declined. For people aged 65 years or more, the rate decreased by 24.5% in women and 19.2% in men [1]. Much of this progress has been attributed to the development of potent anti-resorptive medications, including bisphosphonates. However, reports of uncommon side effects, specifically osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF), have caused a 50% decline in the prescription rates of these otherwise useful medications in recent years [2, 3].

Reliable prediction of medication-related osteonecrosis of the jaw (MRONJ) occurrence and its consequences is one of the most challenging tasks for clinicians. Given the low incidence, severe complications, and lack of effective treatment of MRONJ, developing efficient predictive and preventive strategies becomes all the more necessary, although none such strategy has so far gained wide acceptance [4]. Personalized medicine is currently being tested across several clinical fields to predict risks, prevent complications, and optimize outcomes [5]. Most incidences of MRONJ occurred following an invasive dental procedure (IDP). Over the last decade, pre-operative serum level of C-terminal telopeptide cross-link (CTX), a byproduct of bone remodeling, has been presented as a predictor of the risk of developing post-operative MRONJ [6], as well as a prognostic factor [7]. Furthermore, a pre-operative drug holiday of 3–6 months has been recommended for patients with a 3-year or greater history of bisphosphonate use [8, 9].

C-terminal telopeptide cross-link (CTX) is a product of bone remodeling that can be measured in blood. Early reports suggested that serum levels of CTX progressively decline with anti-resorptive treatment and recover after the treatment stops. Therefore, it can be used to predict the occurrence of osteonecrosis following a dental procedure in patients on anti-resorptive medications [6].

The study suggested that the risk of MRONJ following a dental procedure in patients on bisphosphonates was high if the CTX level was below 100 pg/ml, moderate at 100–150 pg/ml, and low above 150 pg/ml [6, 10, 11]. Based on these studies and others, many clinicians all over the world performed CTX routinely before any dental procedure in patients on anti-resorptive treatment. Serum levels of CTX were also used to monitor the condition of bone remodeling during drug holiday and to determine the appropriate duration of such holiday before a procedure can be safely performed. The practice continues despite multiple subsequent studies questioning the practice [12, 13].

In a recent clinical practice statement, The American Academy of Oral Medicine stated that, despite the need for predictive biomarkers, there was not enough evidence to justify dependence on CTX in predicting the risk of MRONJ following a dental procedure, especially in patients on intravenous bisphosphonates or denosumab [14].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) defined MRONJ as “persistent exposure of necrotic bone in the jaw that for at least eight weeks with a history of current or past anti-resorptive [sic] medication treatment with no history of radiation therapy of the head and neck area” [13]. Bisphosphonates remain the most commonly prescribed anti-resorptive medication. Oral bisphosphonates are often prescribed for osteoporosis and osteopenia, as well as less common diseases including Paget’s disease and osteogenesis imperfecta. Intravenous bisphosphonates are often

prescribed for patients with multiple myeloma and other cancers that have metastasized to the bones and/or cause hypercalcemia [15, 16].

Intravenous bisphosphonates have been associated with the highest risk for developing ONJ [13]. There are numerous comorbidities that may increase the likelihood of developing the condition in patients receiving bisphosphonates, such as rheumatoid arthritis, diabetes, vitamin D deficiency, smoking, glucocorticoid therapy, dentures, and chronic obstructive lung disease (COPD) [17]. However, the most important risk factor for the development of MRONJ in patients receiving intravenous bisphosphonate treatment has been the history IDP [13].

On the other hand, it has been recommended to stop bisphosphonate treatment for a few months to a few years (drug holiday) prior to IDP [13, 18]. These clinical recommendations suggested that a drug holiday would decrease the risk of MRONJ following an IDP, especially in patients receiving oral bisphosphonates, with less certainty concerning patients on intravenous bisphosphonates.

Rare dental disorders, such as BRONJ, represent a particular field, where the practical application of predictive, preventive, and personalized medicine (PPPM) principles is strongly recommended [19]. For the risk assessment of BRONJ, an individual patient profiling may be possible, since some predispositions can be detected before the clinical manifestation of the pathology. Developing such predictive strategies can therefore be followed by the most effective measures of the targeted prevention [19].

It is important to develop reliable biomarkers that allow stratification of patients undergoing anti-resorptive treatment according to well-known characteristics and predict which patient sub-types are likely to develop BRONJ. Patient stratification is one step towards truly personalized medicine, which tailors therapy based on individual patient profile in order to maximize the efficacy and minimize complications in that one patient [20].

This study involved retrospective analysis of chart data from 137 patients who presented over 4 years to the department of Oral and Maxillofacial Surgery at Augusta University. The main purpose of this study was to investigate the value of pre-operative CTX level in the prediction of post-operative MRONJ. We hypothesized that low pre-operative serum level of CTX is predictive of post-operative osteonecrosis. We also studied the effect of a short drug holiday (6 months) on the change in CTX level and incidence of osteonecrosis. At the time of initial evaluation, all patients had been on long-term bisphosphonate therapy and required an IDP.

Patients and methods

A retrospective analysis was carried out for patients who presented over the duration of four consecutive years to the

Augusta University's Oral and Maxillofacial Surgery service. A total of 137 patients were included in the study, including 16 males and 121 females. All participants had undergone bisphosphonate treatments and were referred to the OMFS office for an IDP. For this study, an IDP was defined as a procedure that required surgical manipulation of alveolar bone. These procedures ranged from simple debridement to surgical dental extraction. The following information were collected from the patient file: gender, age, type of bisphosphonate administered, indication, co-morbidity, duration of bisphosphonate treatment, type of dental procedure, duration of drug holiday (if any), CTX levels at different time points, and complications. Complications were defined as persistent bone exposure or local infection that may be attributed to osteonecrosis, persisting for several weeks after the dental procedure, fitting the AAOMS definition of MRONJ. The study was reviewed and approved by the Institutional Review Board (IRB) at Augusta University, including a waiver of the informed consent requirement (Pro00001995; 5/3/2014).

Participants had to undergo a series of verifications in order to be included in the statistical calculations. Participants were excluded if met at least one of the following criteria:

- Bone exposure prior to any procedure being performed
- Did not receive the planned dental procedure
- The type of bisphosphonate was not included in the chart
- Patient lost to follow-up
- History of radiation to the head and neck

Furthermore, complications that could not be attributed to osteonecrosis, such as bone exposure lasting less than 4 weeks or located away from the extraction site, paresthesia, and extraoral complications, were excluded from the analysis. The categories of IV, PO, osteoporosis, multiple myeloma, nonmalignant indication, and other cancer were all given a score of 0 or 1 depending on whether the particular patient was positive for each one. A score of 0 means the patient did not have the selected category, while a score of 1 means they did.

Collected treatment data included the type of IDP (e.g., extractions, implants, soft tissue procedures, etc.) duration of drug holidays, initial and follow-up CTX levels, and complications following procedures. The dental extraction section had more specific details on the location and the number of teeth extracted, in order to better classify the procedures.

The surgeon made the decision whether to proceed with the procedure based on the CTX levels as well as the urgency of the condition. Whenever possible, patients with initial CTX levels below the recommended 150 pg/ml were given a drug holiday of 3 months before IDP. This allowed bone remodeling to recover, evident by an increased CTX levels beyond the 150 pg/ml threshold prior to the intended procedure. Patients who underwent the drug holiday prior to the dental procedure were classified by the column "procedures following drug

holiday." If the initial CTX level was equal to or higher than 150 pg/ml, the patient underwent the procedure without the drug holiday. All procedures were followed-up, and any complications with the healing process were noted. The complications from procedures were categorized based on whether or not there was an osteonecrosis-related complication, such as persistent bone exposure, sequestration, suppuration, and fistula formation.

Statistical analysis

All statistical analyses were conducted at a significant level of 0.05 using SAS 9.4. Descriptive statistics were provided for all variables. Frequencies and column percentages were given for categorical variables; mean, standard deviation, minimum, and maximum were provided for continuous variables. Fisher's exact tests were conducted to test for incidence of complication in various risk factors. Non-parametric Wilcoxon two-sample tests were used for age effect for complications and initial CTX level in IV or PO and their interaction with complication group. Two independent proportion tests were used for testing the two different complication incident rates before or after the drug holiday. To describe the difference in CTX values for those who went on a drug holiday, a new variable change in CTX was created to be the difference between the follow-up CTX value and the initial CTX value. The rate of change in CTX per day during the drug holiday was also defined as change in CTX divided by duration of the drug holiday in days [21]. For sensitivity and specificity analysis, we used an online calculation tool for diagnostic tests: https://www.medcalc.org/calc/diagnostic_test.php.

Results

Out of 137 patient records retrieved, 44 were excluded based on the study's exclusion criteria (Table 1). The final data set included 93 participants, of whom 11 were male and 82 were female. The participants' age ranged from 47 to 86. The indications for bisphosphonate therapy included osteoporosis, osteopenia, multiple myeloma, and metastasized form of other cancers. Eleven patients were receiving IV bisphosphonates at the time of admission, while 82 were receiving oral bisphosphonates only. Whenever a patient received both IV and PO bisphosphonates, they were considered in the IV group. Tables 2 and 3 include the descriptive statistics for the categorical and continuous variables.

Sixty-four patients underwent IDP before drug holiday. Seven patients from this population experienced complications (Table 4). On the other hand, 34 patients had the invasive dental procedure following a drug holiday (average length 5 months), with only one subject (ID = 75) showing

Table 1 Causes of patient exclusion from the analysis

Reason for exclusion	Number of patients
No invasive dental procedure done after presentation	29
Bone exposure at the time of presentation	12
History of irradiation	1
Patient lost to follow-up	2
Total	44

complications related to osteonecrosis. There were five subjects who had operations both before and after drug holiday, none of whom had complications. In this group, eight patients had received IV bisphosphonates, of which three (37.50%) experienced complications. On the other hand, 56 patients received PO, of which 4 (7.14%) had complication. The

combined total complication rate in patients who underwent invasive dental procedure before drug holiday was 10.94%. As expected, patients who received IV bisphosphonate therapy were significantly more likely to develop complications than those who received PO bisphosphonates ($p = 0.0364$). No statistical difference was detected in complication rates

Table 2 Descriptive statistics for categorical variables for all cohort (where information was available)

Variable	Level	Total number of patients	Percent
Gender	F	82	88.17
	M	11	11.83
Drug holiday	Yes	34	36.56
	No	59	63.44
IV versus PO	IV	11	11.83
	PO	82	88.17
Osteoporosis	Yes	81	86.96
	No	12	13.04
Multiple myeloma	Yes	2	2.15
	No	90*	97.85
Other cancers	Yes	17	18.89
	No	73	81.11
Comorbidities	0	35*	38.89
	1	34	37.78
	2	15	16.67
	3	6	6.67
	4	11	15.49
Total time taking bisphosphonate	1	45*	63.38
	2	8	11.27
	3	7	9.86
	4	11	15.49
Bone exposed on initial consult	No	93	100.00
Initial CTX	≤ 150	39	41.94
	> 150	54	58.06
Before drug holiday procedure	Yes	64	68.82
	No	29	31.18
Complication before drug holiday	Yes	7	7.53
	No	86	92.47
After drug holiday procedure	Yes	34**	36.56
	No	59	63.44
Complication after drug holiday	Yes	1	1.08
	No	92	98.92

*In the missing patients, no information could be found in the chart about these variables

**Five subjects ID = 22, 54, 58, 88, and 93 have both before and after drug holiday operations

Table 3 Descriptive statistics for continuous variables

Variable	Number	Mean	STD	Min	Max
Age	93	67.71	9.65	47	86
Initial CTX value	93	186.29	118.67	30	618
Holiday period	33	155.52	104.28	60	545
Final CTX value	36	218.08	98.96	73	495

based on gender, comorbidities, initial CTX level ($>$ or $<$ 150 pg/ml), or total duration of bisphosphonates treatment (Table 4). There was no significant difference in age between patients who developed complications (64 ± 8.5 years) and those who did not (68 ± 9.7 years; $p = 0.2675$).

It may be important to note that the pre-operative CTX levels tended to be lower in patients who developed complications, compared to those who did not, although statistical significance was not evident (Table 5). Stratifying the complication group by the route of administration (IV versus PO) showed that patients on IV bisphosphonates who developed complications had lower pre-operative CTX levels, compared to patients who received IV bisphosphonates who did not experience complications, although statistical significance was not quite achieved ($p = 0.0736$). Such difference was not as evident in patients receiving PO bisphosphonates, although the trend still existed (Table 5 and Fig. 1).

On the other hand, 34 patients had a drug holiday before they had invasive dental procedures (26 on PO and 8 IV), including 5 patients who also had operation before drug holiday. Therefore, only 29 patients were included in the calculation of complications from this group, and only one patient

developed complications (3.45%). This patient was a 55-year-old female on oral bisphosphonates, her CTX level on presentation was 100 pg/ml, which went up to 130 pg/ml after a 92-day drug holiday. A two independent proportion test yielded no statistical significance in complication rate before and after drug holiday ($p = 0.2301$), despite the large difference in the percentages (Table 6).

The duration of the patients' drug holiday ranged from 60 to 545 days (average 155.5 days), while the average increase in CTX was 120.9 ± 95.86 pg/ml. The mean increase in CTX after a drug holiday for patients taking bisphosphonates by PO (125.93 pg/mL) was greater than the mean increase of CTX in patients taking IV bisphosphonates (70.67 pg/mL). However, the difference was not statistically significant. Interestingly, the mean daily rate of increase in CTX level (mg/mL) during the drug holidays was approximately 1 pg/ml per day.

Finally, based on the incidence of ONJ in patients with pre-operative CTX levels above versus below 150 pg/ml, the sensitivity and specificity of the test were quite low (37.5% and 57.7, respectively; Table 7).

Discussion

This study involved retrospective analysis of chart data from 137 patients who presented over 4 years to the department of Oral and Maxillofacial Surgery at Augusta University. The main purpose of this study was to investigate the value of pre-operative CTX level in the prediction of post-operative MRONJ. We hypothesized that low pre-operative serum level

Table 4 Incidence of complication in IV versus PO, gender, comorbidities, initial CTX level, and total time of taking bisphosphonates before DH in all 64 subjects

Variable	Complication in patients who underwent procedures before drug holiday <i>N</i> (%)			
	Level	Yes	No	Fisher's <i>P</i> value
IV or PO	IV	3 (37.50)	5 (62.50)	0.0364
	PO	4 (7.14)	52 (92.86)	
Gender	F	6 (11.32)	47 (88.68)	1
	M	1 (9.09)	10 (90.91)	
Comorbidities	0	4 (15.38)	22 (84.62)	0.4721
	1	2 (9.52)	19 (90.48)	
	2	0 (0.00)	11 (100)	
	3	1 (20.00)	4 (80.00)	
Initial CTX level	≤ 150	2 (18.18)	9 (81.82)	0.5935
	> 150	5 (9.43)	48 (90.57)	
Total time taking bisphosphonate	1	4 (12.90)	27 (87.10)	0.6205
	2	0 (0.00)	7 (100.00)	
	3	1 (33.33)	2 (66.67)	
	4	1 (14.29)	6 (85.71)	

These are subjects who have had dental procedures before drug holiday. Numbers are based on patient records where information was available

Table 5 Initial CTX level in IV or PO group and interaction with complication in patients who underwent procedures before DH ($N = 64$)

IV or PO	Complication before drug holiday	Initial CTX level					Wilcoxon two-sample test P value
		Number	Mean	STD	Min	Max	
IV	Yes	8	179.88	110.71	30	390	0.1552
	No	56	235.64	119.97	46	618	
PO	Yes	7	200.43	134.02	30	432	0.3895
	No	57	232.14	118.41	46	618	
IV	Yes	3	93.67	61.17	30	152	0.0736
	No	5	231.60	103.25	121	390	
PO	Yes	4	280.50	116.12	152	432	0.3479
	No	52	232.19	120.66	46	618	

of CTX is predictive of post-operative osteonecrosis. We also studied the effect of a short drug holiday (6 months) on the change in CTX level and incidence of osteonecrosis.

At the time of initial evaluation, all patients had been on long-term bisphosphonate therapy and required an IDP. The majority of the study population received oral bisphosphonates. As expected, osteonecrosis-related complications in this group were less than in the IV bisphosphonate group when the procedure was carried out before drug holiday. After drug holiday, however, only one patient developed osteonecrosis-related complications; she had been receiving oral bisphosphonates. There were five subjects who had operations both before and after drug holiday, none of whom had complications. The lack of statistical significance suggests that short drug holiday was not helpful in reducing the rate of osteonecrosis.

The average gain in CTX was 0.98 pg/ml per day, or the equivalent of 29.4 pg/ml for a standard month, which is comparable to previous reports [6]. Interestingly, the increase in CTX value with drug holiday tended to be higher with oral than intravenous bisphosphonates, although not statistically significant.

No statistical difference was detected in complication rates based on gender, comorbidities, initial CTX level ($>$ versus $<$ 150 pg/ml), the number of co-morbidities, or the total duration of bisphosphonate treatment. Importantly, there were interesting trends that were short of statistical significance. One finding was that the incidence of ONJ increased with the number of co-morbidities the patient had. Another finding was that the pre-operative CTX levels were lower in patients who developed complications, although statistical significance was not evident. Such difference was more evident with IV bisphosphonates. These data can be helpful for future meta-analysis to provide solid evidence for routine use of an exact CTX level as predictor of osteonecrosis-related complications following invasive dental procedures in patients on oral and intravenous bisphosphonate therapy.

The sensitivity and specificity of CTX in predicting ONJ were quite low. This was mainly because most of the patients who developed ONJ had pre-operative CTX levels higher than 150 pg/ml, while many patients with levels lower than 150 pg/ml did not have any complications (some were as low as 30 pg/ml). This dataset proved that CTX by itself is not a

Fig. 1 Shows the bar chart for means of initial CTX levels in complication and no complication group before and after stratify IV and PO group

Table 6 Comparison of the complication rate in before and after the drug holiday (including five patients who underwent procedures both before and after DH)

	Complications		Percent (%)	Two independent proportion test <i>P</i> value
	Yes	Total		
Procedure before drug holiday	7	64	10.9	0.256
Procedure after drug holiday	1	34	2.9	

good predictor of the likelihood of post-operative ONJ. The fact that complication rates were so different between the two groups may be related to other confounding variables, which would be expected to have a larger impact in the smaller size group, which is typically the complication group. The difference, therefore, may not be a real one, a fact outlined by the lack of statistical significance.

The blood level of CTX is considered a good marker of bone remodeling. It can be used to measure the effect of different medications on the systemic rate of bone turnover under experimental conditions [22]. Indeed, the data showed that CTX levels increased steadily during the short drug holiday in this study. However, extensive research has shown that the pathogenesis of ONJ is not unifactorial. The systemic effect of anti-resorptive medications on osteoclasts could not fully explain the susceptibility of alveolar bone to osteonecrosis. Multiple other factors, such as the localized change in vascularity, local immune response, oral microbiome, gingival epithelium, and localized deposition of bisphosphonates, have been implicated in the impaired healing following dental procedures in these patients [23, 24].

Other biomarkers have been suggested for the prediction of MRONJ. Serum levels of bone alkaline phosphatase (BAP), N-terminal telopeptide of type I collagen (NTX), parathyroid hormone (PTH), deoxypyridinoline (DPD), osteocalcin (OCN), and pyridinoline (PYD) have been explored [25, 26], with little predictive correlations. Further studies with adequate sample sizes are required to overcome the limitations of existing studies. So far, however, no single marker reliably predicts MRONJ. CTX remains the most widely used, mainly because of higher consistency of its serum level testing than that of N-telopeptide, bone-specific alkaline phosphate or parathyroid hormone [27, 28].

Table 7 The rate of osteonecrosis versus CTX level (above versus below 150 pg/ml)

		Osteonecrosis		Total
		Yes	No	
CTX <= 150 pg/ml	Yes	3	36	39
	No	5	49	54
	Total	8	85	93

Machine-learning algorithm has been presented recently to predict the occurrence of MRONJ following dental extraction in patients on bisphosphonate therapy [29]. The performance of machine-learning models was compared along with single predictors such as serum CTX level. The results showed that patients aged > 84 years on oral alendronate and ibandronate who received drug holiday for less than 1 month before IDP are at higher risk for developing MRONJ. [29] Studies are underway to measure the risk at different scenarios in an effort to develop personalized prevention strategies based on patient-related parameters.

The drug holiday has been a standard precaution before dental procedures in patients on anti-resorptive medications [13]. The recommended duration of drug holiday varied from 3 months to several years [13]. However, some studies have shown that stopping anti-resorptive treatment may result in a rebound in bone loss and an increase in fracture risk [30–32].

Unfortunately, in our study, a short-duration drug holiday did not have significant effect on reducing the incidence of ONJ. More creative preventive strategies are needed to address the localized negative effects of anti-resorptive medications, specifically on alveolar bone and femoral shaft, while maintaining the systemic therapeutic effect. Recent studies have introduced promising options, including localized substitution [33] or removal [34–36] to eliminate the localized bisphosphonates in alveolar bone following dental procedures, rescue the healing process, and prevent osteonecrosis.

It is important to develop biomarkers that can distinguish patients who will have adverse effects to anti-resorptive therapy. Such “stratification” biomarkers would allow proper classification of patients into therapeutic groups, with predictable outcome in each. Integrating this information allows selection of personalized treatment regimens that produce the highest therapeutic effect and lowest complications. However, due to the lack of specific validation and standardization strategies to characterize such biomarkers, there is remarkable variability in the practical use of such biomarkers [19].

Unfortunately, biomarkers with ideal predictive value are very uncommon. One potential solution is to develop assays that combine a number of biomarkers. Recent technological advances in bioinformatics have made it possible to perform simultaneous analysis of a large number of biomarkers, each

of which may not be sufficient by itself but taken together can provide optimal predictive value [19, 20].

Ageing populations and chronic disease, such as osteoporosis, remain a major problem all over the world. This highlights the need to accelerate the translation of biomedical discoveries to new, innovative, and cost-effective prevention and treatment strategies. [37]. Since 2002, the European Strategy Forum of Research Infrastructure (ESFRI) identified priorities for research infrastructures in Europe, including Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-ERIC), the European Advanced Translational Research Infrastructure in Medicine (EATRIS), and the European Clinical Research Infrastructures Network (ECRIN). For example, BBMRI-ERIC aims to establish a pan-European research infrastructure to facilitate access to biological resources and associated data [38]. Such efforts will make it possible to collect, manage, and analyze large heterogeneous patient data in order to develop stratification, then personalization algorithms for the precise prevention and management of medical conditions.

Conclusions

Serum level of CTX by itself is not reliable to predict the likelihood of osteonecrosis following dental procedures in patients on bisphosphonate treatment. Although the levels of CTX increased after stopping bisphosphonate treatment, our data suggest that a short drug holiday of 5 months was insufficient to prevent osteonecrosis-related complications in patients on bisphosphonates treatment, confirming that factors other than the inhibition of bone remodeling are important for osteonecrosis pathogenesis. This data could be useful for future systematic reviews to achieve more solid statistical evidence for the predictive values of drug holiday and pre-operative CTX level. Further studies are critically needed to develop reliable predictive and preventive strategies for MRONJ.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Consent for publication Not applicable.

Ethical approval All investigations conformed to the principles outlined in the Declaration of Helsinki and were performed with approval by the Institutional Review Board (IRB) at Augusta University (Pro00001995; 5/3/2014).

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