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ORIGINAL ARTICLE

Third-molar mineralization as a function of available retromolar space

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ABSTRACT

Objective: To test in the maxilla and mandible for an association between stage of third-molar (M3) mineralization and space in the jaws for M3 eruption. Mineralization is hypothesized to be delayed not only for impacted M3s but also for M3s with eruption space less than their mesiodistal crown diameter.
Material and methods: Retrospective cone beam computed tomography (CBCT) scans of 37 females and 32 males aged 17–24 years, for a total sample of 197 upper and lower M3s, were used to assess the status of M3 eruption and measure the M3 crown diameter (CD) relative to the length of the retromolar space (RS). Stage of M3 mineralization was then compared between impacted and erupting M3s as well as between two conditions of relative eruption space ($RS/CD \geq 1$ versus $RS/CD < 1$) using Mann–Whitney *U* tests.
Results: Impacted M3s were at significantly earlier (delayed) stages of mineralization compared to erupting M3s. Mineralization was also delayed for M3s with eruption space less than their mesiodistal crown diameter (e.g. $RS/CD < 1$). A moderate positive correlation between stage of M3 mineralization and space was seen in both jaws, and was stronger in the mandible.
Conclusion: Our study shows for the first time that stage of M3 mineralization is associated not only with impaction but also with amount of retromolar space, and that these associations are consistent in upper and lower jaws. Present findings underscore that M3 mineralization stage may be a clinically useful predictor of M3 impaction that thus merits further investigation.

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Impacted teeth; tooth eruption; teeth calcification; maxillofacial development; cone-beam computed tomography

Introduction

Compared to other teeth, third molars (M3s) show greater variation in the ages at which they reach a given stage of mineralization or eruption.[1,2] Although M3 eruption is widely accepted to depend on adequate space in the jaw, eruption is a complex process that in a number of cases cannot be guaranteed even when sufficient space is available distal to the M2.[3] Thus, although space is important it is likely not the only variable underlying M3 impaction, and the aetiology of this widespread dental condition is more complex than lack of space. Also, highly variable individual patterns of skeletal growth [4,5] limit the usefulness of retromolar space as a parameter for assessing at early ages (e.g. 9–12 years) the likelihood of M3 eruption. Thus identifying earlier and more reliable predictors of M3 impaction has a fundamental clinical value: it could allow, for instance, not only earlier clinical (e.g. orthodontic) interventions to prevent future impaction-related problems but also earlier, safer and potentially less invasive surgical removal of M3s that are deemed at higher risk of becoming problematic.

While much more is now known about the mechanisms that regulate tooth mineralization and eruption, these processes are still not yet fully understood at developmental-genetic or biomechanical levels.[4] It is known that for M3s to erupt into proper occlusion, space distal to the second molar (M2) [5,6] must exceed the mesiodistal diameter of the M3 crown.[7] Since M3s are the last teeth to form, and to erupt, the space distal to already-erupted M2s is not always sufficient to accommodate M3 eruption. As a result, these last-forming molars are often obstructed against adjacent structures (e.g. M2). For this and other as yet unclear reasons, M3s account for about 98% of all impacted teeth,[8] and about ¼ to ½ of the population is estimated to have impacted M3s.[9]

Rate and amount of maxillofacial skeletal growth, and corresponding creation of retromolar space, significantly decrease as a patient becomes physically mature.[10–13] For that reason, late M3 development – especially if coincident with early physical maturation [10] – is also thought to increase the risk of M3 impaction.[14,15] Past work alludes to a mechanistic link between retromolar space and timing of M3 formation, as clinical extraction of first molars (M1s) done to create space in the dental arch not only promotes M3 eruption [16] but also accelerates M3 mineralization.[17,18] Because multiple factors appear to influence eruption, despite that several predictive measures have been suggested,[5,14,19–21] accurately predicting impaction remains challenging.[1,3,22] Yet, this goal continues to merit pursuit towards identifying new predictors and developing new M3 clinical management guidelines that further minimize patient harm and discomfort.

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Another obstacle to progress, and potential research opportunity, is that no data are available in the literature that we are aware of that clarify how M3 mineralization advances relative to available jaw space.[4] This lack of information is likely due to the limitations of conventional 2D radiographs, traditionally used in dental research, to accurately measure oral tissues. Conversely, cone-beam computed tomography (CBCT), a 3D imaging technology that allows a highly accurate analysis of M3 development, M3 crown size and jaw dimensions,[23–25] has been underused to explore the putative relationship between M3 mineralization and retromolar space. With the increasing use of CBCT in dental practice, some institutions have accrued large 3D image databases that can now be leveraged to gain traction on research questions that could not previously be fully addressed using conventional 2D radiographic data. By assessing the space distal to the M2, here we seek to determine, using a retrospective patient dataset captured with CBCT, if delays in M3 mineralization associate not only with impaction but also with an insufficient space for eruption. To test for a link between jaw space and M3 mineralization status, we hypothesize that mineralization will be delayed for: (i) impacted M3s versus erupting M3s and (ii) M3s with eruption space less than their mesiodistal crown diameter.

Materials and methods

Imaging resources and inclusion criteria

Ethics permission (BIO#11-202) was obtained to use retrospective CBCT image datasets of subjects aged 17–24 years generated from 2008 to 2012 and secured at the College of Dentistry (COD), University of Saskatchewan. The subjects scanned and studied in this investigation were residents of the provinces of Saskatchewan and Alberta, Canada, and represent several ethnic groups, with the majority of European descent. All data were collected from de-identified, already-existing (retrospective) CBCT images of patients referred by their respective dentists to the COD for diagnostic CBCT scans. Therefore, none of the CBCT images used here were taken for the purposes of this study. All the images used were selected according to the following criteria:

1. Individuals aged 17–24 years with at least one M3 present: This is the age range within which M3s are expected to erupt.[26,27] In addition, space for M3 eruption is not expected to increase significantly after age 17 years,[11,28] minimizing jaw growth as a variable.
2. Normal craniofacial development: Subjects with congenital malformations, diagnosed pathological lesions (e.g. cysts, tumours), record(s) of dentofacial trauma or disturbances affecting the dental development were excluded.
3. Presence of a developing M3: Because mineralization in mature M3s is by definition complete, tooth maturation was measured up to the penultimate stage.[2] Thus, only M3s with mineralization in-progress were included in the study.
4. No previous extraction(s): Artificial creation of space in the dental arch may affect M3 eruption [16,29] and mineralization.[17,18] Extracted permanent teeth in the same oral quadrant as a given M3 were therefore a disqualifying factor.
5. No dental crowding and dental arch asymmetries: This criterion aimed to reduce the influence of malocclusions in the study.
6. No metallic dental restorations: These restorations often obscure images by producing ‘beam hardening’ or ‘metal scatter’ artifacts that prevent accurate measurements from being made.
7. CBCT image quality: Scan images with noticeable blurring due to motion artifacts were excluded.

Sixty-nine subjects (37 females and 32 males) were selected based on inclusion criteria 1 and 2. Of a possible total of 276 M3s in these subjects, 79 were excluded based on criteria 3–7. The final sample thus comprised 197 M3s (99 upper M3s and 98 lower M3s).

Imaging software package

The proprietary software package Xoran i-CAT (Imaging Sciences International, Philadelphia, U.S.A.), version 3.1.62, was used to visualize and collect measurements from the CBCT images. This software allows 3D multi-planar (e.g. coronal, sagittal, axial and selected custom plane) viewing and linear measurements of scan data, permitting anatomical structures to be assessed with higher accuracy and precision compared to conventional 2D dental radiographs.[25] Xoran i-CAT was the software of choice in this study because it was the default software of the i-CAT imaging unit used to scan patient data.

Measurement design

The region here referred to as the retromolar space (RS) was linearly measured from the distal-most point of the M2 crown to the maxillary tuberosity, or the mandibular ascending ramus (Figure 1(A,B)). The maximum mesiodistal crown diameter (CD) of the M3 was also measured (Figure 1(C)), and a ratio of retromolar space/crown diameter (RS/CD) was calculated for each M3 sampled. Stage of M3 mineralization was then assessed in the following two ratio groups:

(1) RS/CD ≥ 1 = Retromolar space/crown diameter ≥ 1: The length of the space available to accommodate eruption is equal to or exceeds the M3 crown diameter. Sufficient space exists for M3 eruption. (2) RS/CD < 1 = Retromolar space/crown diameter < 1: The length of the space available to accommodate eruption does not exceed the M3 crown diameter. M3s lack minimum required space for eruption. For reproducibility, all measurements were taken on the axial plane rather than on the 3D surface rendering itself. Measurement repeatability was evaluated with intra- and inter-examiner pilot tests as follows: after all authors designed the measurements, they were piloted by DM. Next, a dental student (UK) with similar background to DM and with no investment in this study was asked to replicate all measurements. Because measurements taken by UK and DM were highly correlated ($R \geq 0.98$, $p < 0.01$), we concluded that two examiners was sufficient to ensure the method’s repeatability.

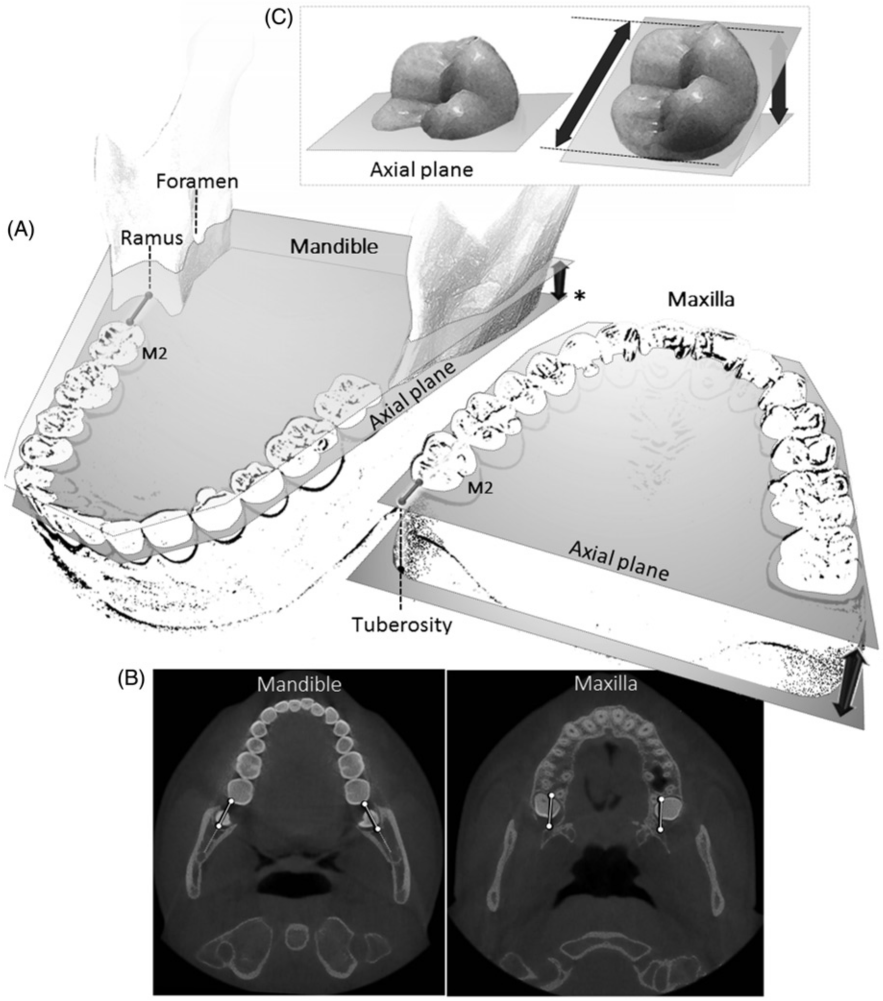

Figure 1. Measurement design using CBCT imaging. (A) Measurements were taken on the axial view, with the axial plane positioned parallel to the occlusal plane and at the level of the interproximal contact points of the permanent molars and premolars(*). From that level, the axial plane can be moved upwards or downwards in order to allow the distance between structures that are located in distinct levels to be linearly measured. The space M2-ramus was measured from the distal-most point of the M2 crown to the ascending ramus of the mandible, at the level where the axial plane touches the ascending mandibular ramus. This measurement was taken parallel and adjacent to a straight line created from the M2 to the mandibular foramen. In the maxilla, the space M2-tuberosity was calculated by linearly measuring the distance between the distal-most point of the M2 crown to the distal-most point of the maxillary tuberosity. (B) CBCT images of the maxilla and mandible showcasing the measurement procedure. (C) The mesiodistal diameter of the M3 crown was also measured. Because M3s are very often inclined (left image), a compensatory inclination of the axial plane allowed their maximum mesiodistal crown diameter to be measured with greater accuracy (right image).

Molar eruption and impaction

Impaction is most frequently defined as arrested tooth eruption due to malposition or physical barrier.[30,31] While most definitions do not account for changes in M3 position that occur with time,[32] severely inclined M3s (e.g. angulations $\geq$45°) are unlikely to erupt into a fully functional position, especially if jaw growth has already ceased.[33,34] For that reason, inclination of the long axis of the M3 during its eruption period, from 17 to 24 years, as well as signs of M3 obstruction against the M2, the mandibular ramus or the pterygoid process, were used to categorize M3s into two groups: (1) VU = Vertical-Unobstructed eruption: vertically erupting M3s, with or without mild deviations. No obstruction against the M2 or other adjacent structures was observed. For the purpose of this study, M3s allocated to this group are referred to as erupting M3s. (2) IO = Inclined-Obstructed eruption: unerupted M3s with severe mesiodistal inclinations ($\geq$45°), accompanied or not by buccolingual inclinations. Obstruction of the M3 eruption path by adjacent structures was commonly observed in this group. For the purpose of this study, M3s allocated to this group are referred to as impacted M3s. The distribution of M3s within space groups (RS/CD $\geq$1, RS/CD $<$1) and impaction groups (VU, and IO) is shown in Figure 2.

Molar development

M3 mineralization was scored according to Demirjian's stages A–G.[35] Stage H was not included because it indicates a tooth that has completed mineralization (see inclusion criteria above). Because of the low probability of catching in our patient sample the relatively fleeting initiation of individual molar cusps (Demirjian's Stage A), Demirjian's Stage A and B were combined into a new Stage 1 to capture the mineralization of the first-third of the M3 crown. Thus we used stages that defined six equally sized portions of the crown (i.e. three thirds) and root(s) (i.e. three thirds) (Figure 3). Our numeric scale was then used to assess the median mineralization

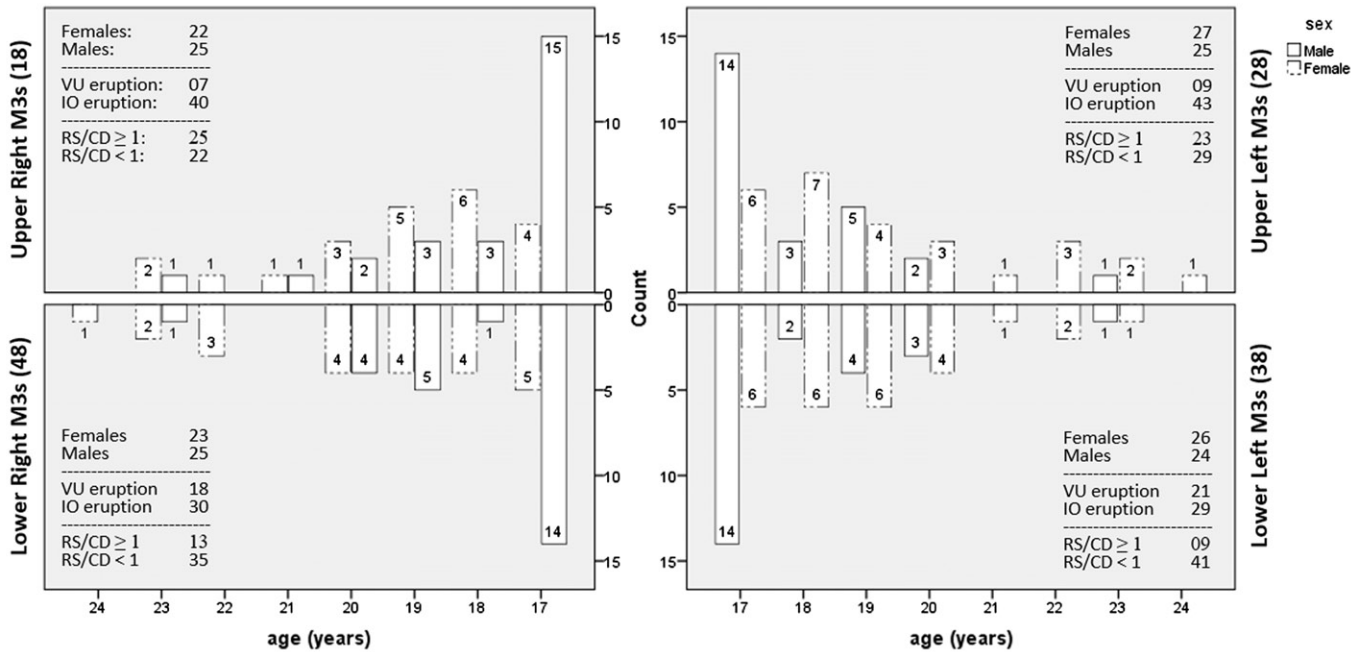

Figure 2. Distribution of M3s per dental arch quadrant and category groups. Eruption (IO, VU), space (RS/CD <1, RS/CD1 ≥ 1) and sex (females, males) groups were assessed within each quadrant. Data from opposite quadrants in each jaw were not combined or tested statistically. The number of females and males in the quadrants was similar.

stage in the following groups: VU versus IO, RS/CD ≥1 versus RS/CD <1, females versus males. The distributions of mineralization stages within these groups are shown in Figure 4.

Statistical analysis of data

Analyses were performed separately for right and left dental arch quadrants of each jaw (i.e. upper and lower). To assure independence of the data, M3s from opposite quadrants were not grouped or compared statistically. Statistical tests were done using SPSS version 21 (IBM), and PAST version 2.18.[36] The level of significance adopted was 5% ($p < 0.05$). Mann–Whitney U-tests were used to identify whether distributions of mineralization stages differed significantly between the M3 groups: VO (Erupting) versus IO (Impacted); RS/CD ≥1 (sufficient space) versus RS/CD <1 (insufficient space) ratio groups; females versus males. To measure the strength of correlation between retromolar space length (mm) and stages of M3 mineralization, the Spearman's correlation coefficient (ρ) was employed.

Results

Impacted M3s were at earlier stages of mineralization compared to erupting M3s (Table 1). This delay was most evident in upper impacted M3s, which were up to two stages (median =4 to 5) behind in root mineralization relative to erupting M3s for which the median stage was 6 ($p < 0.01$). In contrast, a delay of only one stage in root mineralization was found for lower impacted M3s relative to erupting M3s for which the median stage was also 6 ($p < 0.05$). Because the

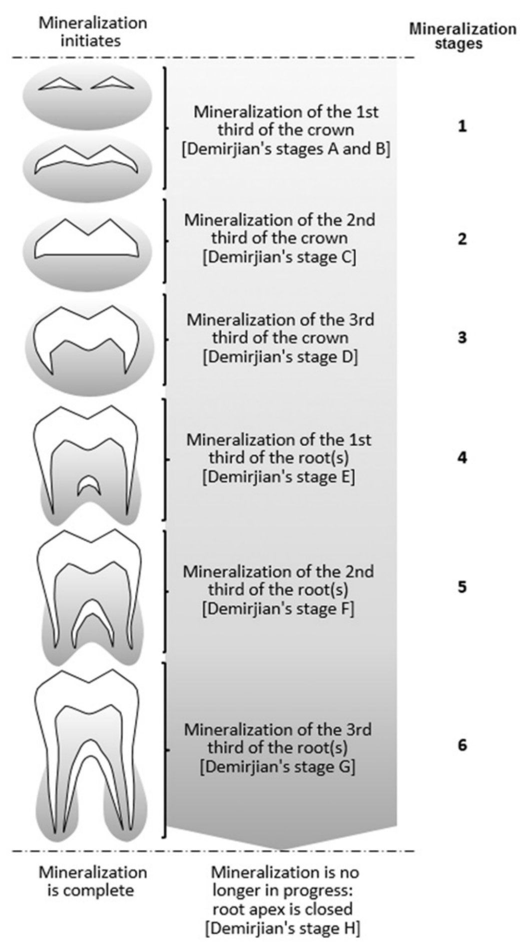

Figure 3. Demirjian's mineralization stages revised as a numerical scale of six mineralization stages.

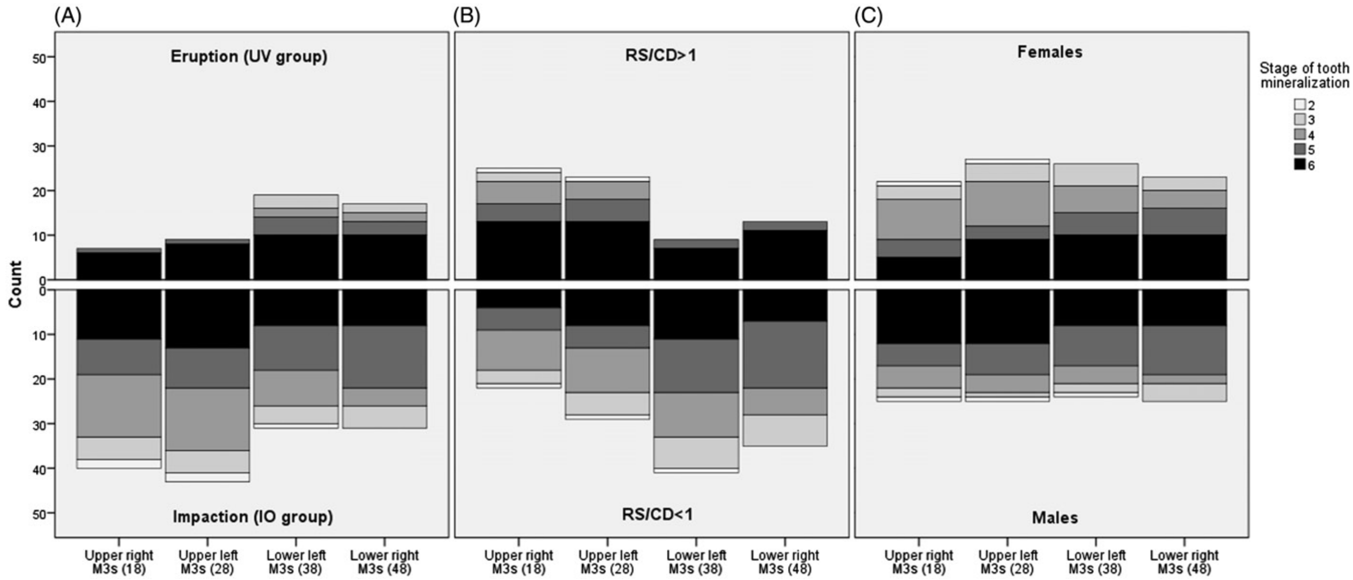

Figure 4. Prevalence patterns of tooth mineralization stages in distinct M3 groups. Each section of the bars represents individual stages of tooth mineralization. The darker the color the more advanced is the stage of tooth mineralization (see scale above). While less advanced stages of tooth mineralization (e.g. lighter colors) were more prevalent within the IO (e.g. impacted) and RS/CD <1 (e.g. insufficient space) groups, no discernable prevalence patterns were seen between females and males. RS: retromolar space; CD: crown diameter of the M3.

median stage of M3 mineralization did not differ significantly between sexes ($p > 0.05$) (Table 2), data from females and males were pooled in our analyses.

M3s developing in retromolar spaces shorter than their mesiodistal crown diameters (RS/CD <1) were at earlier (i.e. delayed) stages of mineralization compared to M3s for which space was sufficient to accommodate their eruption (RS/CD ≥1) (Table 3). Upper M3s lacking the minimum required space for eruption (median stage =4) were delayed by two stages compared to M3s for which this minimum space was available (median stage =6) ($p < 0.05$). This delay was also seen for lower M3s in the group RS/CD <1 (median stage =5), which were one stage delayed relative to group RS/CD ≥1 (median stage =6) ($p < 0.001$, right lower M3s; $p < 0.01$, left lower M3s). Further, M3 mineralization stage was positively and moderately correlated with space available for M3 eruption. This correlation was slightly stronger in the mandible ($\rho = 0.463$ and $\rho = 0.539$ for right and left lower M3s, respectively. $p < 0.01$) than in the maxilla ($\rho = 0.421$ and $\rho = 0.392$ for right and left upper M3s respectively. $p < 0.01$) (Figure 5).

Table 1. Median tooth mineralization stage for erupting and impacted M3s.

	VU group (eruption)			IO group (impaction)			
Third molar	*N*	Md	SR	*N*	Md	SR	*Z*-value
Right upper (18)	07	6.00	260	40	4.00	868	−2.869**
Left upper (28)	09	6.00	363	43	5.00	1016	−3.149**
Left lower (38)	21	6.00	642	29	5.00	633	−2.181*
Right lower (48)	18	6.00	530	30	5.00	647	−1.989*

N: Number of observations in the sample; Md: sample median (tooth mineralization stage); SR: sum of ranks.
**$p \leq 0.01$, *$p \leq 0.05$.

Table 2. Median tooth mineralization stage for females and males' M3s.

	Females			Males			
Third molar	*N*	Md	SR	*N*	Md	SR	*Z*-value
Right upper (18)	22	4.00	446	25	5.00	682	-1.824^{NS}
Left upper (28)	27	4.00	624	25	5.00	754	-1.760^{NS}
Left lower (38)	26	5.00	649	24	5.00	627	-0.293^{NS}
Right lower (48)	23	5.00	581	25	5.00	595	-0.381^{NS}

N: Number of observations in the sample; Md: sample median (tooth mineralization stage); SR: sum of ranks.
NS: non-significant.

Table 3. Median tooth mineralization stage for M3s in distinct jaw space conditions.

	RS/CD ≥1			RS/CD <1			
Third molar	*N*	Md	SR	*N*	Md	SR	*Z*-value
Right upper (18)	25	6.00	695	22	4.00	433	−2.114*
Left upper (28)	23	6.00	738	29	4.00	640	−2.486*
Left lower (38)	09	6.00	342	41	5.00	934	−2.947**
Right lower (48)	13	6.00	479	35	5.00	698	−3.917***

N: Number of observations in the sample; Md: sample median (tooth mineralization stage); SR: sum of ranks.
***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$.

Discussion

Delayed M3 mineralization correlates with impaction and reduced space

This study aimed to test for a significant correlation between M3 mineralization and space for M3 eruption, which we did indeed observe: root mineralization was delayed for M3s without a minimum required space for eruption. Previously, a link between M3 mineralization and jaw space was demonstrated with the use of lateral cephalograms, although solely for lower M3s.[7] The present study is the first to assess upper and lower M3s, based on metrics collected from 3D CBCT image data, which clearly identified stages of tooth mineralization alongside highly accurate linear measurements of the space for M3 eruption and the dimensions of the M3 itself. The data presented here are therefore the first to empirically show different stages and thus tempos of

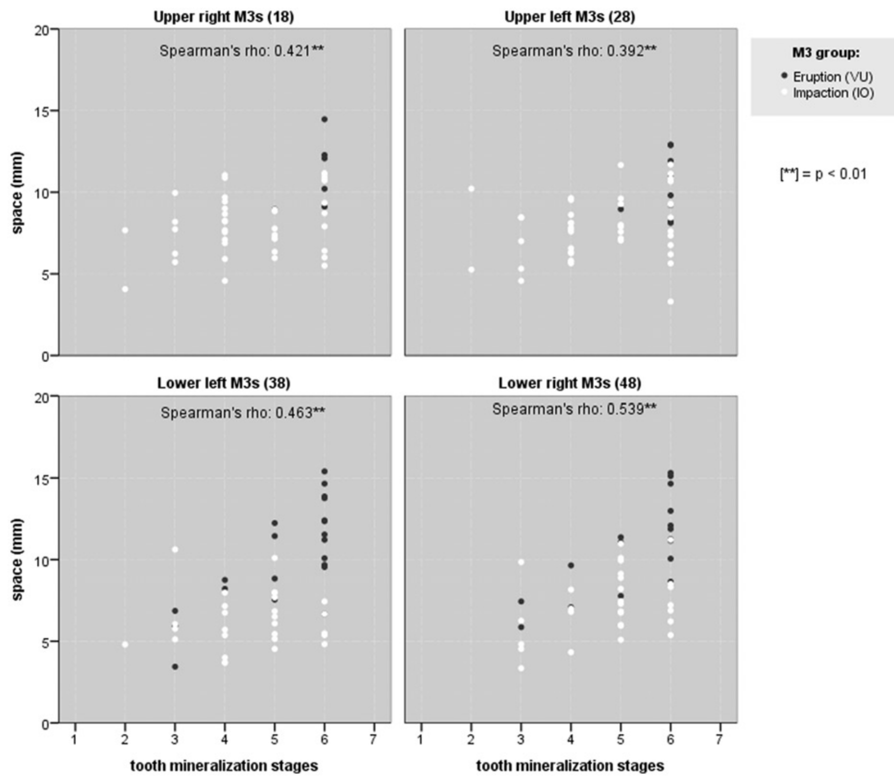

Figure 5. Level of correlation between stages of M3 mineralization and length of retromolar space. Note that the occurrence of M3s in the VU group (eruption) increases with progression of M3 mineralization to more advanced stages (X-axis) and with increased availability of space distal to the M2 (Y-axis).

mineralization for human M3s developing under distinct space conditions in upper and lower jaws. Our results suggest that jaw space and M3 mineralization either influence each other or are affected by some common, additional factor.

To broadly explain delayed mineralization of impacted M3s, we propose two scenarios. First, the tempos of dental and skeletal development are 'mismatched' above a threshold that increases risk of M3 impaction. For example, late M3 formation coupled with early skeletal maturation is more likely to lead to M3 impaction because the jaws will stop growing before the M3 is mature enough to erupt. In this scenario, dental and skeletal growth are decoupled, and are not interdependent.

In the second scenario, delayed M3 mineralization is directly due to late, or less, jaw growth and space creation. The exact mechanism via which reduced space may disrupt tooth mineralization and eruption remains speculative but compressive force on the tooth organ appears to constrain onset and rate of crown and root formation.[37,38] One hypothesis that we suggest here is that jaw growth below a critical threshold alters biomechanical stimulus: specifically, compressive forces remain high (or tensile forces remain low) in the extracellular matrix of the dental and adjacent jaw mesenchyme. The extracellular matrix (ECM) helps to regulate early tooth organogenesis (i.e. mesenchymal cell condensation and epithelial morphogenesis),[39,40] and a large suite of ECM macromolecules in tooth are already well characterized.[41] Changing force distribution may delay, or otherwise perturb, macromolecular signalling in the ECM. As a result, the M3 placode may condense later, delaying M3 onset if not also rate of mineralization, in a jawbone with less growth and thus less space for M3 eruption. It would be interesting to screen the murine dental lamina for local variation in ECM molecules corresponding to onset of M1, M2 and M3, and to perturb *in vitro* ECM signalling with the aim of altering M3 onset time.

Another, related hypothesis is that the extension of the dental lamina is contingent on jaw growth: shorter and/or slower-growing jawbones have shorter and/or slower-growing dental laminas that manifest as slower creation of space distal to M2, later M3 mineralization and higher risk of M3 impaction. This hypothesis is based on the inhibitory cascade model, derived from experimental work that removed the anterior, or M1, part of the dental lamina and found that M2 and M3 initiated earlier and developed faster.[42] In this model, the tail of the dental lamina must grow beyond the inhibitory influence of M1 and, later, M2, in order for M2 and M3 to initiate, respectively. Thus earlier-forming molars appear to constrain later-forming molars, and removing constraint may trigger via mesenchymal activators molar onset and placode formation.[42]

Both our biomechanical hypothesis and the inhibitory cascade model are supported by experimental studies of later stages of molar development and the tooth–bone interface: when the M1 was cultured *in vitro* and apart from jaw mesenchyme and alveolar bone, initial growth of the M1 was accelerated coincident with increased osteoclast activity regulated by RANK-RANKL signalling.[37] Together these results imply that the tooth–bone interface and tissues adjacent to the molar organ constrain M3 development affecting its crown size, if not also timing of onset and rate of mineralization.[37]

These results echo earlier experiments showing that a higher prevalence of osteoclasts in adjacent alveolar bone correlated with accelerated molar root formation and earlier eruption.[38] In the patients we studied, lower osteoclast activity (as a result of a shorter and/or slow-growing jawbones and thus increased physical constraint) may help explain the observed delays in root mineralization for impacted M3s.

In sum, during odontogenesis, molecular signals expressed early from the dental lamina, as well as later from the alveolar bone (itself is a derivative of the tooth organ [43]) appear to regulate the tempo and proportion of developing molars and are thus implicated as mechanisms precipitating M3 impaction. Whether development of M3s lacking space for eruption is indeed slower, or simply starts later (e.g. uncorrelated with skeletal growth), our findings demonstrate that delayed M3 mineralization is a reliable associate of insufficient space in the jaws to accommodate M3 eruption.

M3 mineralization as an independent portent of M3 impaction

The positive correlation between M3 mineralization and retromolar space in the maxilla and the mandible ($\rho \cong 0.40$ for upper M3s, $\rho \cong 0.50$ for lower M3s) not only reiterates tooth mineralization as a potentially useful predictor of impaction but also – since this correlation was moderate – underscores that space is not a singular factor affecting (or, being affected by) M3 mineralization. In fact, the M3 itself seems to be an important stimulus for the growth of the bony region through which these teeth erupt.[2] Because M3 impaction appears to be multifactorial in nature, M3 mineralization status is more likely to inform the developmental aetiology of M3 impaction if considered with a cohort of variables (e.g. available space, tooth crown size and position in the jaws).

In addition, stronger correlation between M3 mineralization stage and retromolar space was seen in the mandible compared to the maxilla, a finding supported by earlier work suggesting that space is more critical for lower M3s than for upper M3s.[7] This finding also receives support from a recent, well-designed meta-analysis of 49 studies involving 83,484 individuals that demonstrated that the odds of impaction in the mandible were 57.6% higher than in the maxilla and did not differ between females and males.[44] It appears, therefore, that space conditions affect: 1) not only M3 eruption but also M3 mineralization; and 2) M3 mineralization differently in the maxilla versus the mandible. These new findings highlight the value of designing distinct clinical management guidelines for upper and lower M3s, another subject that merits investigation in future studies.

The present findings underscore the importance of understanding how M3 mineralization occurs under distinct jaw space conditions, especially in the context of using M3 mineralization stage to reliably anticipate M3 eruption versus impaction. More accurate predictive methods may allow oral health clinicians not only to anticipate and prevent the effects of problematic M3s but also to perform earlier and safer surgical removal of M3s at undeniable high risk of generating impaction-related problems. The results and conclusions presented here are limited to a pooled evaluation of females and males aged 17–24 years. While sex differences, if present, are likely to be small and controversial (much as is the case for odds of impaction),[44] they merit a separate study. Malocclusions and ethnicity may also manifest as variation in the 'M3 mineralization-jaw space' association. Considerably larger sample sizes are needed to conclusively test such questions.

Studies of younger individuals, particularly longitudinal datasets, are also needed to determine if the findings presented here could be used to reliably assess the likelihood of M3 impaction by assessing multiple variables (e.g. M3 mineralization stage, crown size and position) relative not only to availability of space in the jaws but also to individual phases of skeletal maturation. Only by deepening our understanding of the multiple and possibly interacting causes of M3 development, eruption and impaction, will we gain deeper insights towards more effectively managing this condition so commonly encountered in the dental practice.

Conclusions

- Compared to erupting M3s, mineralization of impacted M3s was significantly delayed in young adults aged 17–24 years, underscoring the need to investigate tooth mineralization status as a potential new and additional predictor of M3 impaction.
- Further, M3 mineralization was delayed when space in the jaws was insufficient to accommodate M3 eruption. Based on past work including experimental studies, retromolar space may both affect, and be affected by, timing of tooth mineralization.
- Although important, space is one of multiple variables strongly correlated with M3 mineralization and impaction. Thus, efficiently predicting impaction will likely be improved if a group of key variables is considered (e.g., M3 mineralization status, crown size, position within the jaws, availability of space, individual phases of skeletal maturation).

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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