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Accuracy of Schneiderian membrane thickness: a cone-beam computed tomography analysis with histological validation

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Abstract

Objectives: Cone-beam computed tomography (CBCT) has been used in the literature to evaluate Schneiderian membrane thickness (SMT), but its accuracy has never been validated. The primary aim of this study was to compare the SMT measured by CBCT to the gold standard histological assessment. The correlations between SMT and anatomical structures of the maxillary sinus and alveolar bone were also tested.

Materials and Methods: Fourteen fresh cadaver heads were used for the study, and 28 sinus lift augmentation procedures were performed to obtain the membrane samples. Samples were fixed in formalin and stained with hematoxylin–eosine and Masson trichrome. Specimens were measured by optic microscope at three points, and a mean was obtained. Anatomical landmarks were used to accurately position the CBCT slice, so the SMT could be measured in predetermined locations. Wilcoxon signed-rank test was used to compare values of histological and CBCT measurements, and Spearman's correlation coefficient was calculated to examine the relationship between thickness and anatomical parameters.

Results: A total of 597 histological measurements were performed, and the mean SMT thickness was 0.30 ± 0.17 mm. The mean CBCT membrane thickness was 0.79 ± 0.52 mm. A statistically significant difference from histological and radiological readings was observed ($P = 0.000$). Interestingly, 87.77% histological measurements had membrane less than 0.5 mm in thickness compared to 26.66% in CBCT assessment.

Conclusions: Within the limitation of this study, the median histological Schneiderian membrane thickness was 0.30 mm. Cone-beam computed tomography assessment was 2.6 times higher than the histological examination.

Sinus augmentation has become a widely used and predictable procedure in augmenting vertical deficient ridge in the posterior maxillary area (Wallace & Froum 2003; Bornstein et al. 2008; Pjetursson et al. 2008; Tetsch et al. 2010). Nevertheless, complications still occur, mainly associated with membrane perforation that is often triggered by inadequate surgical planning or maneuvers (von Arx et al. 2014).

As such, the Schneiderian membrane perforation or damage has been reported in an average of 19.5% (up to 58.3%) (Pjetursson et al. 2008). However, the influence of membrane perforation over graft and implant survival rate remains to be controversy. Some authors have observed no difference in vital bone formation and implant survival after sinus membrane perforation (Ardekian et al. 2006; Testori et al. 2012; Karabuda et al. 2006; Froum et al. 2013). Others, on the contrary, have shown more postoperative complications such as sinusitis, graft failure (Nolan et al. 2014) and less implant survival rate (Cho-Lee et al. 2010). Barone et al. noted that membrane perforation might lead to graft migration and sinus infection. Thus, an intact Schneiderian membrane is desirable to have better vascularity, graft stability and environment for the maturation of the inserted bone graft materials. (Barone et al. 2008; Pikos 1999). In addition, it has been reported that Schneiderian membrane contains osteoprogenitor cells which might

speed up bone formation (Srouji et al. 2009). Based upon the above observations, it is generally agreed that membrane integration often associated with a better clinical outcome.

It has been reported that the risk of membrane perforations is highly correlated to sinus membrane thickness (SMT) (Lin et al. 2015; Aimetti et al. 2008; Berengo et al. 2004; van der Bergh et al. 2000; Torres Garcia-Denche et al. 2013).

Cone-beam computed tomography (CBCT) technique was developed in the late 1970s (Robb et al. 1979; Ritman et al. 1980), but dento-maxillofacial CBCT was introduced in 1998 (Mozzo et al. 1998; Schulze 2015); nowadays, it becomes a desired tool for better diagnosis as it offers cross-sectional images and 3-dimensional (3D) reconstruction with much lower radiation when compared to medical CT (Chan et al. 2010; Harris et al. 2012). However, CBCT is not without its limitations especially when studying fine details that are beyond the spatial resolution of the machine (Brullmann & Schulze 2015). In other words, during clinical application, higher accuracy than 0.5 mm (500 μm) cannot be clearly identified. A recent study demonstrated that for detection of bone tissue structures of less than 1 mm, CBCT tended to underestimate their dimensions (Gonzalez-Martín et al. 2015). Others have also pointed out that CBCT is not accurate when examining soft tissue thickness (Adibi et al. 2012). Nonetheless, many studies/clinicians are still using CBCT for soft tissue thickness assessment.

Data on Schneiderian membrane characteristics (e.g., thickness, structure and mechanical properties) and their clinical significance remain scarce (Aimetti et al. 2008; Schneider et al. 2013; Lin et al. 2015). There is a great disagreement among the mean SMT determination methods (i.e., CBCT and histological analysis) (Yoo et al. 2011; Pommer et al. 2012; Anduze-Acher et al. 2013; Yilmaz & Tozum 2012; Pazera et al. 2011; Yoo et al. 2011; Bornstein et al. 2012; Janner et al. 2011; Dagassan-Berndt et al. 2013; Schneider et al. 2013; Cakur et al. 2013; Shanbhag et al. 2014; Quirynen et al. 2014; Wen et al. 2015; von Arx et al. 2014; Guo et al. 2015; Makary et al. 2015; Tos & Mogensen 1979; Aimetti et al. 2008; Pommer et al. 2009; López-Niño et al. 2012). At this moment, histological "gold standard" for anatomical dimensional assessment is lacking.

To the best of our knowledge, no study has evaluated the SMT by histological and radiological CBCT analyses in human fresh heads.

Therefore, the aims of this study were as follows: (i) to determine the Schneiderian membrane in fresh cadaver heads using histological as well as CBCT approaches; (ii) to correlate both measurements; and (iii) to study the influence of anatomical factors (i.e., lateral wall thickness – LWT; or residual ridge height – RH) upon SMT.

Material and methods

Totally, 14 fresh cadaver heads with 28 lateral wall sinus augmentation procedures were performed for the study. Briefly, a round diamond bur, inserted in a low-speed (3.35 g) handpiece with external irrigation, was used to perform an ostectomy in the lateral wall of the maxillary sinus with 10×5 mm mesio-distal/apico-coronal dimension. The window was opening in the center of the region of interest that is located at 3 mm above the sinus floor regardless (Wang and Katranji, 2008).

Clinical data acquisition
The position of the lateral window was reproduced utilizing anatomical landmarks to obtain a correct radiological measurement in the CBCT slices described as following: (i) residual ridge height (RH), (ii) window dimension, (iii) distance from the crest to the upper window border, (iv) lower border of the window and (v) buccal to the medial wall distance. Also, (vi) the mesio-distal distance from the mesial side of the window to the proximal tooth and (vii) from the distal side to the distal tooth was determined. If neither mesial nor distal teeth were present, the distance was determined by measuring from the mesial side of window to the anterior wall and from the distal side to the posterior wall of the maxillary sinus.

Sample acquisition
The sinus membrane was lifted with conventional sinus curettes, and a biopsy of the Schneiderian membrane (10×10 mm) was obtained using a 15c-blade scalpel. During the procedure, the lateral bony window was detached from the membrane by gentle luxation but if a strong adherence was observed, membrane and bony wall (lateral wall) were processed together to avoid perforation/tearing.

Histological analysis
The membrane samples were positioned on a thin cardboard where the mesial and distal sides were marked to determine their orientation. All the specimens were fixed in 10% neutral-buffered formalin for 24 h and

paraffin-embedded following standard procedures. Several sections were obtained for each specimen and mounted on microslides for hematoxylin–eosine and Masson trichrome stainings. Specimens were coded and studied by a pathologist by optic microscope with a micrometer at 4×, 10× and 40×. Only areas with perpendicular orientation were selected, and each section was measured at three points (center, left and right aspects). The captured images were imported and analyzed using NIS Elements Ar (Nikon Instruments, Melville, NY, USA) and ImageJ (National Institutes of Health, Bethesda, MD, USA). Mean, minimum and maximum thicknesses of each specimen were recorded.

Image acquisition and assessment
Cone-beam computed tomography images were obtained with a 3D Accuitomo 170 Tomograph (J Morita, Kyoto, Japan) with a voxel size 0.08–0.16 mm. Operating parameters were set at 5.0–7.0 mA and 90 kV. Exposure time was 17.5 s. Limited FOV was selected for all images. The CBCT scans of each head were reconstructed with built-in software and analyzed on a desktop computer with an implant planning software program (Invivo5, InvivoDent, Anatomage, San Jose, CA, USA).

Cone-beam computed tomography images were evaluated by an experienced oral surgeon (AI) on a desktop monitor (28-inch Dell 2407, resolution 1920 × 1200 pixels, refresh rate 59 Hz; Dell Inc., Round Rock, TX, USA) under room lightening and keeping approximately 30 cm to the monitor. CBCT images were reoriented to get the nasal spine and midline aligned in the center of the image in axial slice, the posterior maxillary segment in vertical position in the coronal slices and the hard palate and the floor of the nose in horizontal position parallel to the ground in the sagittal slices.

For the evaluation of intra-examiner reliability, five cases were randomly selected to perform two measurements on different days. The mean difference between the two measurements in membrane parameters was 0.11 mm (range 0.02–0.23 mm). The mean difference between the two measurements in bone parameters was 0.18 mm (range 0.08–0.26). For image assessment, each sample was conducted twice and a mean value was obtained (Janner et al. 2011). If more than 0.2 mm of difference was measured in the same point, a third assessment was performed (Bornstein et al. 2011). Likewise, a second examiner (AM) randomly selected five cases to evaluate inter-examiner reliability.

A Cohen's kappa value of 0.81 was obtained, showing almost perfect agreement.

CBCT data acquisition

Anatomical landmarks and the position of the lateral window were used to properly position the CBCT slice. Membrane thickness measurements were conducted in the sagittal and in the cross-sectional images (Fig. 1) and were conducted by a built-in digital caliper in millimeters perpendicularly from the underlying bone plate of the sinus to the mucosal surface. Three measurements of sinus membrane thickness were recorded in the center, mesial and distal points of the region of interest in the CBCT mid-sagittal axis.

Additionally, measurements of membrane thickness were carried out in standardized landmarks in the proper cross-sectional slices: TLS – thickness in the lowest point of the maxillary sinus; TLW – thickness in the lowest point of the bony window; TUW – thickness in the uppermost point of the bony window; TFN – thickness in the ipsilateral nasal floor; and TOZ – thickness in the onset of the zygomatic process.

In the same cross-sectional slice, measurements of the lateral bone wall thickness (LWT) and sinus width (SW) distance were obtained at 3, 5, 7,10,13 and 15 mm from the level of the alveolar crest as described elsewhere (Chan et al. 2014; Monje et al. 2014). The 15-mm level was chosen due to be the level where the lateral window augmentation usually ends (Wang and Katranji, 2008). Residual bone height (RH) was measured from the top of the alveolar crest to the sinus floor as described previously (Monje et al. 2015).

Statistical analysis

Statistical analysis was expressed using mean, median, minimum and maximum values, standard deviations (SD), 95% confidence interval and range for each item. 95% confidence interval was obtained by bootstrap method due to the reduced sample size. Wilcoxon signed-rank test was used to compare values of histological and radiological measurements. The significance level chosen for all statistical tests was $P \leq 0.05$. Spearman's correlation coefficients were calculated to examine the relationship between the histological SMT and radiological SMT, LTW, SW and RH. The analyses were performed using software packages (IBM SPSS Statistics 23, Armonk, NY, USA and Microsoft Excel 2010, Seattle, WA, USA).

Results

Histological Schneiderian membrane thickness

A total of 14 unfixed fresh heads (13 men and one woman (aged 65–85), 13 Caucasian ethnicity and one African American ethnicity) were analyzed. Twenty-seven Schneiderian membrane samples were harvested and immediately fixated and processed. One of the samples did not meet the requirements for processing, and thus, it was discarded. A total of 597 measurements (Table 1) were performed in total, and the overall mean membrane thickness was 0.30 ± 0.17 mm (min. 0.04 mm–max. 1.09 mm). The median of the samples was 0.26 ± 0.03 mm (range 0.21–0.34 mm) (Fig. 2).

CBCT Schneiderian membrane thickness

Fourteen CBCT and 28 maxillary sinuses were radiographically analyzed. Eight of 28 sinuses were discarded for the measurement of SMT in the region of interest due to the presence of liquid/artifacts that filled the sinus and avoided accurate assessment. Overall, 180 measurements (sagittal and coronal) were completed in the 28 sinus. Overall, mean membrane thickness was 0.79 ± 0.52 mm (min. 0.19 mm–max. 2.27 mm). The median of the samples was 0.63 ± 0.10 (range 0.52–0.95 mm).

CBCT anatomical data

The mean of all the measurements from LWT, SW and RH was, respectively, 1.23 ± 0.88 mm (min. 0.13–max. 3.92 mm), 12.36 ± 6.32 mm (min. 2.12–max. 29.12 mm) and 5.14 ± 3.13 (min. 0–max. 12.98 mm).

The median of the samples from LTW, SW and RH was, respectively, 0.97 ± 0.12 mm (range 0.72–1.28), 11.99 ± 0.66 mm (range 10.78–13.31 mm) and 5.04 ± 1.17 mm (range 2.46–6.67 mm).

Accuracy of radiographic and histological data

Wilcoxon signed-rank test determined that there was a statistically significant difference comparing the median values of thickness obtained by histological and radiological methods, $Z = -3.659$; $P = 0.000$ (Fig. 3). Spearman's correlation between histological and CBCT sample measurements was $r = 0.105$, $P = 0.659$, showing a positive but weak and nonsignificant correlation (Fig. 4).
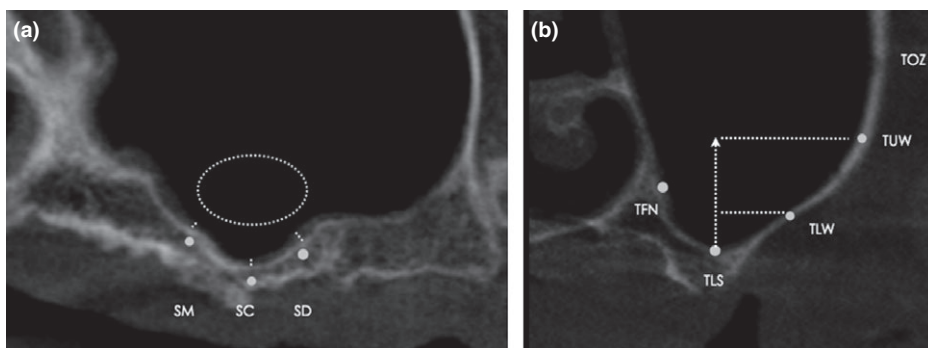

Fig. 1. Cone-beam computed tomography assessment landmarks in the sagittal and in the cross-sectional view.

Table 1. Demographics of histological Schneiderian membrane thickness, CBCT thickness, total CBCT thickness, lateral wall thickness (LWT) and sinus width (SW)

	Histology	CBCT total	LWT	SW	RH
N	26 (597)[*]	21 (180)[*]	28 (123)	28	28
Mean	0.32 (0.30)[*]	0.76 (0.79)[*]	1.25 (1.23)[*]	13.91 (12.36)[*]	5.14
Median	0.26 (0.26)[*]	0.63 (0.63)[*]	0.97 (0.97)[*]	12.10 (11.99)[*]	5.04
Max	0.67 (1.09)[*]	1.64 (2.27)[*]	2.74 (3.92)[*]	23.85 (29.12)[*]	12.98
Min	0.12 (0.04)[*]	0.26 (0.19)[*]	0.20 (0.13)[*]	5.25 (2.12)[*]	0.6
SD	0.03	0.10	0.12	0.66	1.17
Range	(0.21–0.34)	(0.52–0.95)	(0.725–1.28)	(10.78–13.31)	(2.46–6.67)

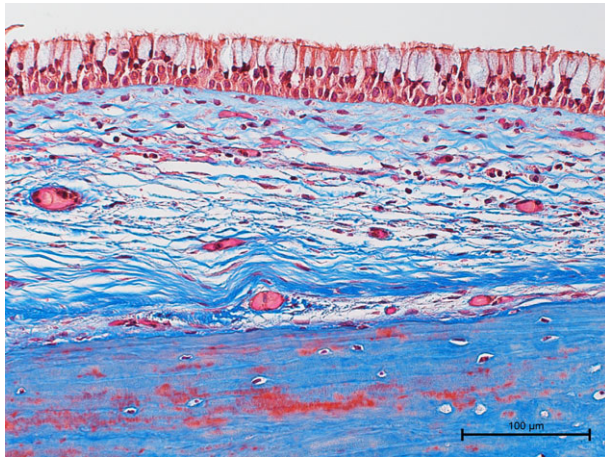[*]Values obtained from overall number of observations.

Fig. 2. Histological slice image of the Schneiderian membrane (20× optical microscope).
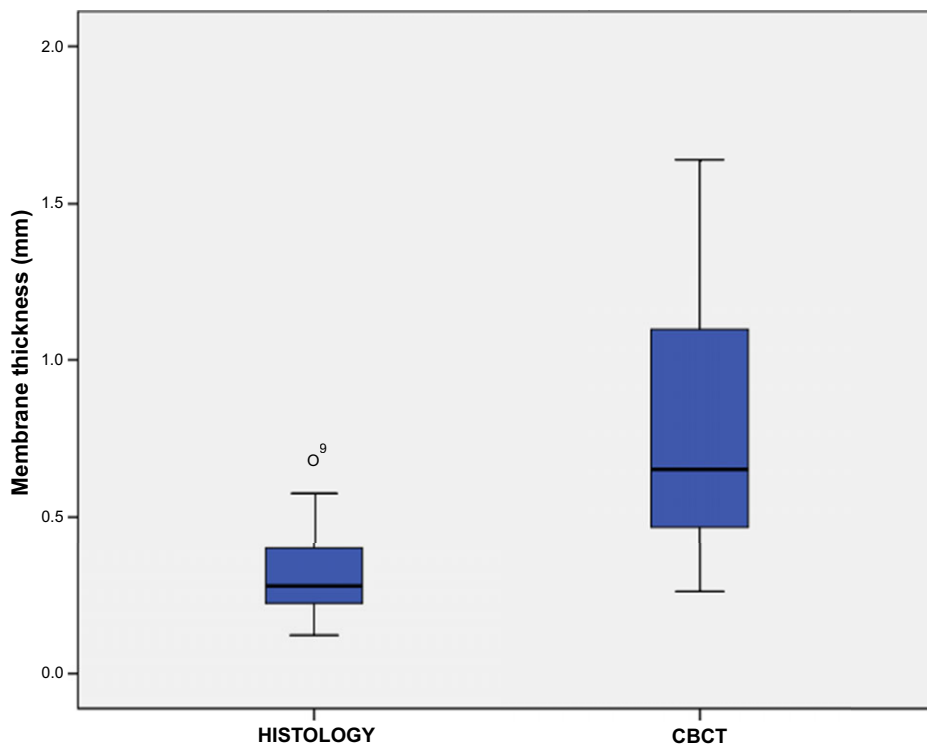

Fig. 3. Plot distribution based on the median values of Schneiderian membrane thickness examined by histological and radiological methods.

Overall, 87.77% histological measurements had membrane less than 0.5 mm in thickness compared to 26.66% in CBCT assessment (Table 2 and Fig. 5). Alike, only 0.16% histological sample displayed membrane thickness of more than 1 mm compared to 77.23% in the CBCT assessment. Hence, albeit a positive statistical correlation was found, SMT – as evaluated in CBCT – might be potentially overestimated.

Correlation between SMT and anatomical structures

The bivariate correlation between histological membrane thickness medians (Fig. 6) and LWT means (HISTO-LWT) showed a statistical insignificant but positive weak correlation ($r = 0.351$, $P = 0.079$). Spearman's correlation between histological SMT and SW (HISTO-SW) was $r = 0.104$, $P = 0.612$, without a clear linear correlation. Correlation between histological SMT and residual height (RH) showed a weak negative correlation ($r = -0.197$, $P = 0.336$).

Discussion

Schneiderian membrane thickness (SMT) is not a frequent data reported in the literature.

In addition, there is a big variation in terms of membrane thickness due to various techniques that have been used to record the amount (Lin et al. 2015). To the best of our knowledge, only four histological studies have been published so far (Tos & Mogensen 1979; Aimetti et al. 2008; Pommer et al. 2009; López-Niño et al. 2012). For example, Tos & Mogensen (1979) reported 0.3 and 0.8 mm mean membrane thickness from 10 unfixed cadavers. Pommer et al. (2009) recorded 0.09 mm (range 0.024–0.35 mm) mean membrane thickness and also discussed the mechanical properties of the Schneiderian membrane. These cases did not differentiate between health and disease sinus membrane thickness. Nonetheless, it has been reported that chronic maxillary sinusitis or allergic conditions might lead to membrane thickening (van der Bergh et al. 2000; Pommer et al. 2009; Chan & Wang 2011). Even though, it seems that even healthy membrane had a great variation in the membrane thickness (up to 800 µm) in the same sample Tos & Mogensen (1979). Aimetti et al. (2008) harvested the samples during ENT procedures and reported a mean thickness of 0.97 mm. Surprisingly, they demonstrated a positive correlation between the gingival phenotype and the membrane thickness. As such, subjects presenting thicker gingival phenotype also presented a thicker mucosal membrane (mean membrane thickness: 1.26 mm) than thin biotype individuals (mean membrane thickness: 0.61 mm). Moreover, López-Niño et al. (2012) conducted a biopsy in formalin-fixed human heads, obtaining a SMT of 0.40 ± 0.15 mm.

Data from this study showed histologically the mean SMT of 0.30 ± 0.17 mm which is in agreement with most of the above reports [Tos & Mogensen (1979); Pommer et al. (2009); López-Niño et al. (2012)]. However, it was slightly lower when compared to Aimetti et al. (2008). The differences were attributed to: differences in the location of the biopsy, amount of inflammatory infiltrate, population assessed, lack of documentation on the influence of gingival biotype and the limited sample size of both studies.

Recently, CBCT was used in the determination of the SMT: Janner et al. (2011) found out values of 0.9 and 1.84 mm in the lateral and medial aspects of the wall, respectively, and 2.16–3.11 mm in the mid-sagittal areas. This is similar to our data where we observed a thicker SMT in mid-sagittal position (1.12 mm) than in the lateral wall. However, this is slightly lower than the Janner et al. (2011) reported mean. The difference probably
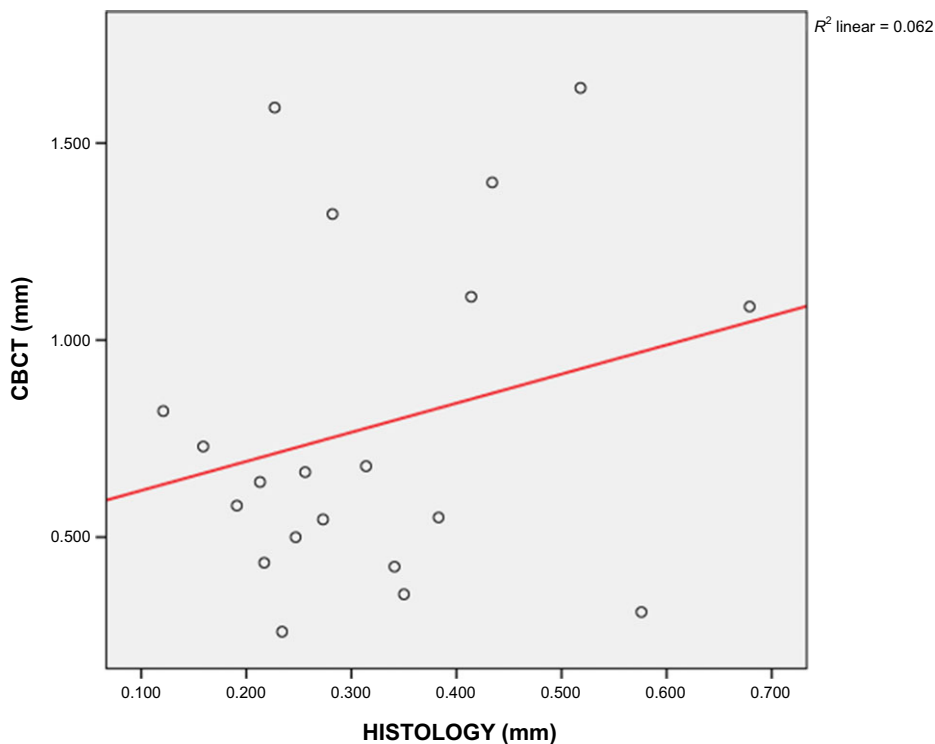
R^2 linear = 0.062

Fig. 4. Spearman's correlation between histological and radiological median values.

Table 2. **Distribution of mean SMT values in histological and radiographic assessments**

	Histology	CBCT
$N < 0.5$ mm	524 (87.77%)	48 (26.66%)
$N > 0.5$ mm	73 (12.22%)	132 (73.33%)
$N < 1$ mm	596 (99.83%)	139 (77.23%)
$N > 1$ mm	1 (0.16%)	41 (22.77%)
$N > 2$ mm	0	8 (4.44%)

CBCT, cone-beam computed tomography; SMT, Schneiderian membrane thickness.

is due to CBCT inability to differentiate between liquid and soft tissue. This inability makes clinician unable to properly differentiate between real membrane thickness and mucous accumulation.

Again, data from our study showed membrane thickness of (0.19–2.27 mm) with a mean of 0.79 mm when measured by the CBCT. This is in agreement with many previous published reports (Quyrinen et al. 2014; Cakur et al. 2013; Guo et al. 2015; Rancitelli et al. 2015). For example, Quirynen et al. 2014 compared the thickness of the membrane before and after the sinus augmentation. They showed that membrane thickness of 1.3 mm in the mid-sagittal area; 0.7 mm in the medial wall; and 0.5 in the lateral wall before the sinus augmentation (Quyrinen et al. 2014). Pazera et al. in 2011 also reported a mean of 1.58 mm membrane thickness in young healthy orthodontic

patients. Furthermore, Bornstein et al. (2012) examined SMT in patients with and without apical pathology. They noted a coronal mean thickness of 2.74 mm in the pathology group, whereas 1.21 mm in the healthy group. It has also been demonstrated that males had thicker membrane thickness (0.74 mm) when compared to females (0.34 mm) (Cakur et al. 2013). Additionally, Shanbhag et al. (2014) reported 53.6% of samples examined had >2 mm membrane thickness. Later on, von Arx et al. (2014) reported a mean sinus membrane thickness of 2.1 mm in 77 patients. They also observed that the mean membrane thickness was higher in the cases without perforations (2.4 mm) than in the cases with perforations (1.3 mm) during the sinus augmentation. (von Arx et al. 2014). Guo et al. further reported a value of normal Schneiderian membrane of 0.94 mm (vs. 5.03 mm in sinus showing flat thickening) (Guo et al. 2015). Area with sinus septa showed higher membrane thickness (1.87 mm) than in the no septa sinus membrane (0.85 mm) Rancitelli et al. (2015).

Even though a weak correlation was obtained, a statistically significant difference was reached when compared the mean SMT obtained under histological and CBCT methods. Interestingly, 87.77% of the histological samples had <0.5 mm membrane thickness. On the contrary, only 26.66% of the CBCT recorded data showed the same. Likewise, only 0.16% histological sample displayed a SMT > 1 mm vs. 77.23% in CBCT. Irrespective of the location where the membrane was measured, the histological mean thickness (0.30 mm) was significantly lower than the mean CBCT thickness (0.79 mm). Alike, our histological thickness (0.3 mm) almost doubled the spatial resolution of the CBCT (0.5 mm) and that might explain of why the membrane was not visible in some slices. Accumulation of mucous secretion (Janner et al. 2011), low resolution, scatter and the limitations of the CBCT (Brullmann & Schulze 2015) could illustrate the differences between the measurements of these two methods. Taking this value of 0.5 mm as a lower limit reference, it should be stand out that only 12.2% of the histological samples in our study presented SMT above this level. Therefore, albeit a positive statistical correlation was found, SMT – as evaluated in CBCT – might be potentially overestimated. This might be of particular relevance in SMT <1 mm and >1.5 mm for sinus augmentation via lateral window approach (Lin et al. 2015) and <1.5 and
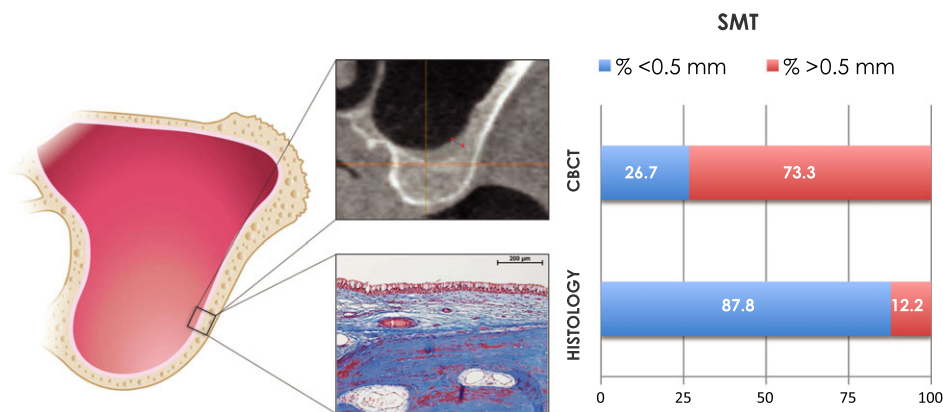

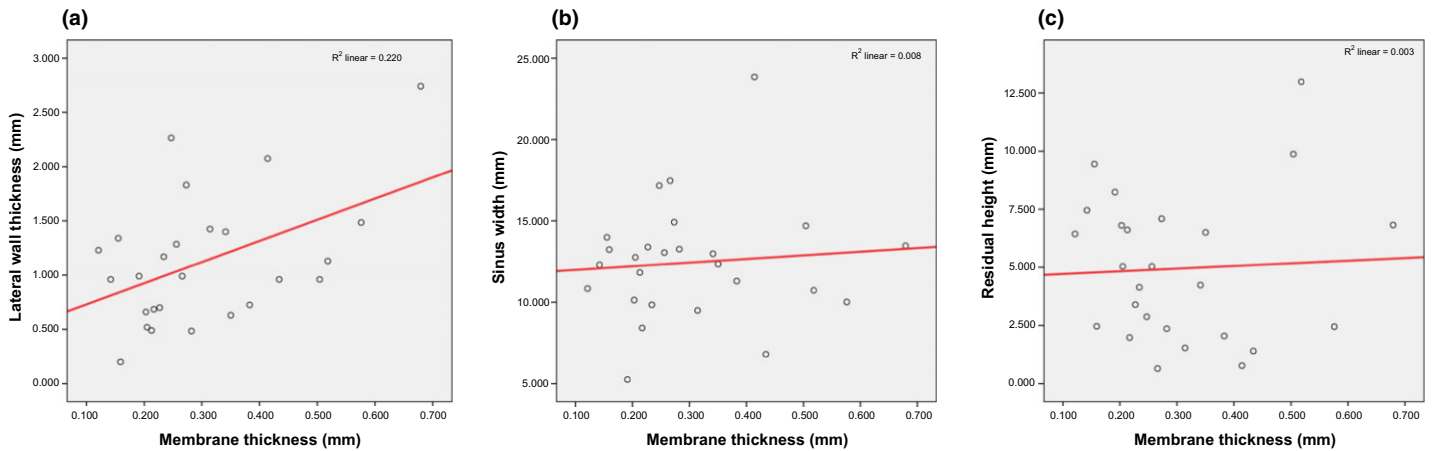*Fig. 5.* Demographics of the Schneiderian membrane thickness in histological and radiographic assessments.

Fig. 6. Spearman's correlation between the median values of the histological thickness and (a) lateral wall thickness (LWT); (b) sinus width (SW) and (c) residual height (RH).

>2 mm for transcrestal sinus lift procedures (Wen et al. 2015), where higher membrane perforation was often found.

In addition, in this study, a positive but not statistically significant ($P = 0.079$) correlation between histological thickness and LWT was observed. This means that a thin LWT caused by long-term bone resorption could be associated with a thinner SMT. This is in agreement with Lin et al. 2015; where they showed no significant correlation between residual bone height and membrane thickness (Lin et al. 2015).

Limitations and recommendations for future research

In our study, the SMT was calculated on formalin-fixed sections but previous studies have reported that the tissue shrinkage after fixation has a minimal impact upon SMT (Aimetti et al. 2008). Tran et al. (2015) reported shrinkage of 4.6% in renal tumors after formalin fixation. Jonmarker et al. (2006) demonstrated a 4.5% reduction. Chen et al. (2012) described a decrease in length (4.40%), width (6.18%) and depth (4.10%) after formalin fixation of head and neck samples of tumors. Vent et al. (2014) concluded that formalin fixation does not significantly influence the tissue dimensions of palatal tonsils. Based on these studies, we can speculate a 4–5% of shrinkage of membrane thickness, and hence, the formalin fixation had a very limited influence on the membrane thickness measurement (Jonmarker et al. 2006; Aimetti et al. 2008; Chen et al. 2012; Vent et al. 2014; Tran et al. 2015).

Cone-beam computed tomography also presents some limitations when the anatomical structures have a dimension similar or inferior to the spatial resolution of the machine.

Brullmann & Schulze (2015) reported that during a routinely CBCT clinical application, higher accuracy than 0.5 mm cannot be expected and so, some structures could be seen with difficulties. Pixel/voxel size does not equal the spatial resolution, inasmuch as this is affected by the size of the sensor, gray-level resolution, exposure parameters, rotation arc and the patient motion (Brullmann & Schulze 2015). Interestingly, a study reported amplitudes of 80 μm measured at the teeth of the patient only due to the heartbeat (de Kinkelder et al. 2011).

All in all, further research is needed to increase the knowledge on the relationship between the SMT and some anatomical configurations in the maxillary sinus, such as the influence of the lateral wall thickness and the level of bone atrophy. In the future, a more precise CBCT machine with better spatial resolution will help clinicians to detect and measure maxillary soft tissues accurately.

Conclusion

Within the limitation of this study, the median histological Schneiderian membrane thickness was 0.30 mm. Radiographic cone-beam computed tomography assessment was 2.6 times higher than the histological examination.

Author contributions

A. Insua contributed to conception, design, clinical and radiological data collection, data interpretation, drafted and critically revised the manuscript; A. Monje and H. Chan contributed to design, radiological data collection, data interpretation, drafted and critically revised the manuscript. N. Zimmo and L. Shaikh contributed to clinical data collection; H-L. Wang contributed to design, data interpretation and critically revised the manuscript.

Conflict of interest

The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the manuscript. This article was partially supported by the University of Michigan Periodontal Graduate Student Research Fund.

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