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Research Article

Classification of Potential Risk Factors for Maxillary Sinus Membrane Perforation Using Cone-Beam Computed Tomography

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ABSTRACT

Objective: To determine the frequency of anatomic variations, pathologies, and physiological alterations in the maxillary sinus, and to identify the most common combinations in which these risk factors coexist and may predispose to perforation of the maxillary sinus membrane. The relationship between the most common potential risk factor and patients' age, gender, and dental status was also evaluated.

Methods: Radiographic examinations of the anatomic variations, pathologies, and physiological alterations in 500 maxillary sinuses from 376 patients were classified under 16 headings using cone beam computed tomography images, and their coexistence was evaluated. For each evaluated sinus, every pathology, physiological alteration, and anatomic variation observed was recorded. A Mann-Whitney U test was conducted to assess the effect of age, sex, and dental status on the most common potential risk factor.

Results: The average mucosal thickening was 3.64 mm. Pathological mucosal thickenning was the most common pathology in the maxillary sinus (67.2%). The rates of mucosal thickening, septa-mucosal thickening, interruption of the medial sinus wall, and pneumatization-septa-mucosal thickening were 30.8%, 29.2%, 7.6%, 6.2%, respectively. Pathological mucosal thickenning was the most common in partially edentulous, males, aged 36-53 years ($P < 0.05$).

Conclusion: The most common anatomic variations, physiological alterations, and pathologies in the maxillary sinus were pathological mucosal thickening, septa, interruption of the medial sinus wall, and pneumatization. The most coexisting combinations were mucosal thickening-septa and pneumatization-septa-mucosal thickening. In addition to these combinations, partially edentulous patients of 36-53 age group may be considered as sinus membrane perforation risk.

Keywords: Anatomy, cone-beam computed tomography, maxillary sinus, membrane perforation, sinus floor augmentation

INTRODUCTION

The maxillary sinus epithelium is ciliated and captures foreign materials, carrying them to the ostium via spiral movements. The drainage ostium of the maxillary sinus is located in the anterior one-third of the ethmoid infundibulum, between the processus uncinatus and the lamina papyracea. When pathology is present, ciliary wave motion is disrupted, and foreign substances cannot be expelled from the ostium. For mucociliary drainage to function normally, ostia and mucociliary transport pathways must remain patent.[1]

Implant placement in the posterior atrophic maxilla can be a challenging surgical procedure because of insufficient bone height due to maxillary sinus expansion. Maxillary sinus floor elevation procedures are often necessary for implant treatment planning in the presence of insufficient bone height.[2] During these procedures, two distinct complications may arise from

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anatomical variations, physiological alterations, or pathologies. The most common of these is maxillary sinus membrane perforation, which occurs in 20-60% of cases; the second most common is bleeding.[3] Generally, inadequate surgical planning or maneuvers are the major cause of membrane perforation.[4] Although maxillary sinus floor elevation procedures cause these complications, the high survival rates of implants placed in grafted sinuses make this method advantageous.[5] Therefore, a thorough knowledge of the anatomy, physiology and possible variations of the maxillary sinus to minimize the risk of potential complications associated with the surgical procedure is important to improve success of the procedures.[6]

Numerous studies have investigated risk factors for maxillary sinus pathologies and sinus membrane perforation. It has been reported that the membrane perforation rate is inversely proportional to maxillary sinus mucosal thickness. In addition, the cortical thickness of the lower border of the maxillary sinus has been inversely associated with membrane perforation. Odontogenic and periodontal infections affect the cortical border. The principal factors related to the maxillary sinus are the presence and height of septa, residual ridge height, thickness of the lateral sinus wall, antrum width, and the extent and condition of mucosal thickening.[7-9] The parameters determined in this study such as pneumatization, septa, exostosis, pathological mucosal thickening, polypoid lesion, interruption of the sinus floor, interruption of the medial sinus, lateral wall bone thickening, antroliths, fluid retention, foreign bodies, interruption of the lateral sinus wall, ectopic tooth in the sinus, root in the sinus may directly or indirectly cause perforation of the sinus membrane or spread of existing infection during or after sinus surgery.

However, no study has evaluated the distribution of multiple pathologies, variations, and physiological alterations in the sinus in relation to their coexistence. Also to our knowledge relationship between the most common potential risk factor and patients's age, gender, and dental status has not been evaluated yet. The hypothesis of our study was that the risk of sinus membrane perforation would increase as the prevalence of coexisting anatomic variations, physiological alterations, and pathologies in a single sinus increased. Morover the importance of maxillofacial surgeons' and radiologists' knowledge on the most common potential risk factor and subsequent coexistence combinations is emphasized.

MAIN POINTS

- Pathological mucosal thickening alone was a strong risk factor for maxillary sinus membrane perforation.
- The presence of multiple coexisting risk factors may further increase the likelihood of maxillary sinus membrane perforation.
- Cone beam computed tomography examination is essential for major surgical procedures.

MATERIAL AND METHODS

Study Samples

This retrospective study included cone-beam computed tomography (CBCT) images of the maxillary posterior regions of 2,500 patients, retrieved from the archives of the Faculty of Dentistry of Ege University, for whom data on sex, age, and indications for scanning were available. The Clinical Research Ethics Committee of the Medical Faculty of Ege University approved this study (approval no: 14-7.1/6, date: 08.09.2014), and informed consent was obtained from all participants. Images with artefacts (e.g., beam hardening, noise, metal artefacts, and ring artefacts), images of individuals younger than 18 years (because the maxillary sinus continues to develop until age 18)[10], images with prosthetic restorations on the teeth, and unclear, low-quality, or incomplete images were excluded. A total of 500 images were included in the study.

To evaluate the age distribution of maxillary sinus pathologies, anatomic variations, and physiological alterations, patients were divided into four age groups: 18-35, 36-53, 54-71, and ≥ 72 years. The patients were further subdivided into three groups according to their dental status: dentate, partially edentulous, and totally edentulous.

CBCT Image Analysis

The CBCT images of all the patients were obtained using a Kodak 9000 3D device (Carestream Health, Rochester, NY, USA), with total filtration > 2.5 mm Al, a 5 × 3.7 cm field of view (FOV), a 76 μm isotropic voxel size, and 14-bit contrast resolution. The CBCT images were taken at 70 kVp (maximum of 10 mA) by positioning the patient perpendicular to the sagittal plane and parallel to the Frankfort horizontal plane. All CBCT images were retrospectively evaluated by a dentomaxillofacial radiologist with 5 years' experience, using Care stream 3D Imaging Software 3.1.9 (Carestream Health, Inc., Rochester, NY, USA). The anatomic variations, physiological alterations and maxillary sinus pathologies were evaluated on the axial, sagittal, and coronal sections of all the CBCT images, and the amounts of mucosal thickening were measured on the sagittal and coronal sections. Measurements were made along a straight line from the deepest point of curvature of the maxillary sinus floor to the point of greatest mucosal thickening (Figures 1 and 2). Measurements of this parameter were made separately in the right and left maxillary sinuses. All data were recorded and correlations between this variable were evaluated. To ensure consistency, the first author selected all images and measured maxillary sinus mucosal thickening. Fifty percent of these images (250 images) were randomly selected, re-marked, and re-measured. Coefficient of variation (CV) analysis was performed to determine the accuracy and reproducibility of the measurements. For this purpose, the first author re-measured the images two weeks after the initial measurements, and the first and second measurements were analyzed for 250 randomly selected dental CT images.

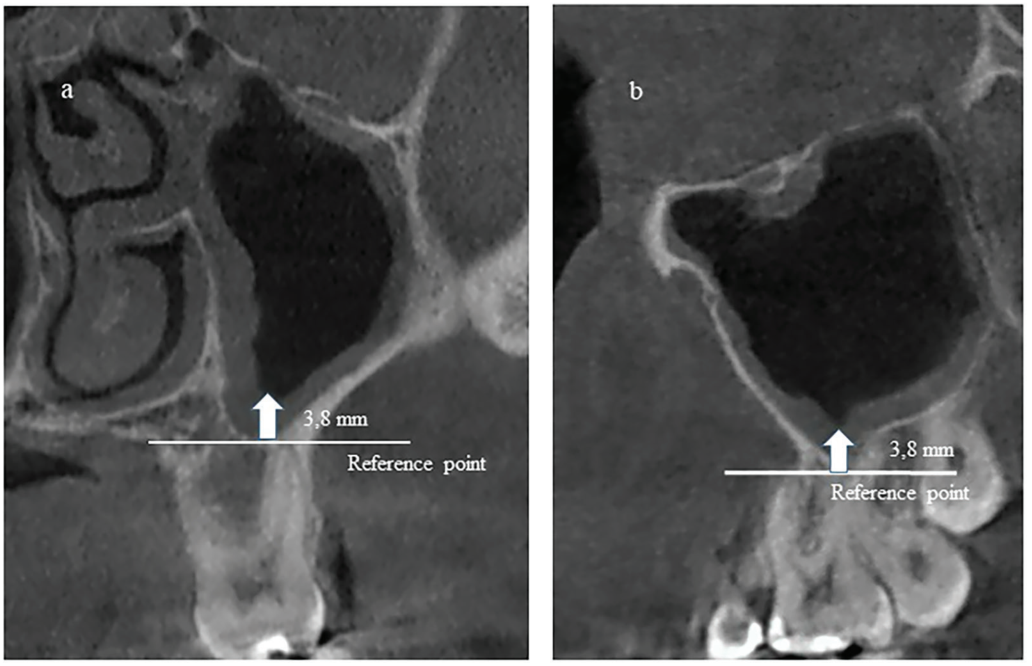

Figure 1. Detailed radiographic demonstration of mucosal thickening measurements. a) Coronal sections b) Sagittal sections.

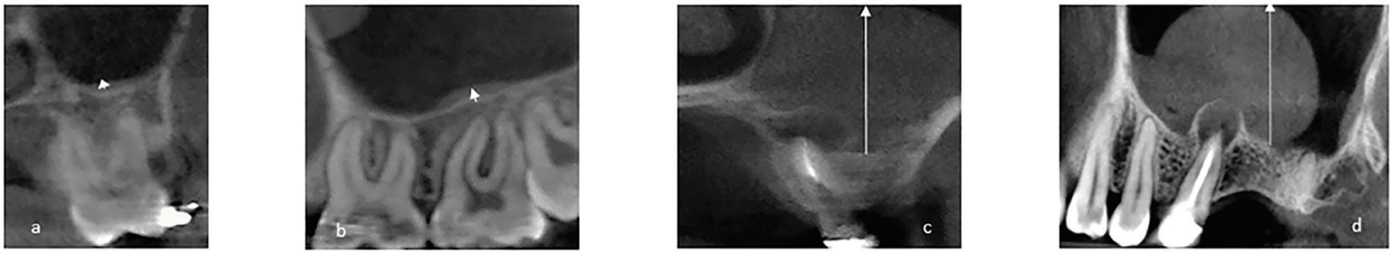

Figure 2. Radiographic demonstration of mucosal thickening measurements. a) Normal mucosal thickenning coronal sections, b) normal mucosal thickenning sagittal sections, c) pathologic mucosal thickenning coronal sections, d) pathologic mucosal thickenning coronal sections.

Study Variables

Assessment of Maxillary Sinus Anatomic Variations, Physiological Alterations and Pathologies

Anatomic variations identified were septa, exostoses, and lateral wall bone thickening. Physiological alterations were categorized as pneumatization and normal mucosal thickening. Pathologies identified included pathological mucosal thickening; polypoid lesions; interruption of the sinus floor and of the medial and lateral sinus walls; antroliths; fluid retention; foreign bodies; ectopic tooth in the sinus; and tooth root in the sinus.

The pathologies, physiological alterations, and anatomic variations in the maxillary sinus found on the coronal, sagittal, and axial sections of the CBCT images were classified as follows: 1) pneumatization (a), 2) septa (b), 3) exostoses (c), and 4) mucosal thickening > 0 mm; the presence of mucosal thickening greater than 0 mm was evaluated as a physiological alteration and a pathology. The presence or absence of mucosal thickening was evaluated.), normal mucosal thickenning (d) 5) pathological mucosal thickenning (e), 6) polypoid lesion (f) 7) interruption of the sinus floor (g), 8) interruption of the medial sinus wall (h-ı), 9) lateral wall bone thickening (i), 10) antroliths (j), 11) fluid retention (k), 12) foreign bodies (greft.etc) (l),13) interruption of the lateral sinus wall (m), 14) ectopic tooth in the sinus (n), 15) root in the sinus (o), (Figure 3). Since the presence of multiple pathologies, physiological alterations, and variations was thought to increase the risk of surgical complications, every pathology, physiological alteration, and variation observed in the sinus was recorded. Thus, only the presence or absence of the specified parameters was evaluated, and measurements were limited to pathological and normal mucosal thickening.

Evaluation of the Images

Measurements of Mucosal Thickenning

Maximum mucosal thickness was measured as the greatest distance from the sinus floor on the coronal and sagittal sections, and values greater than 0 mm were defined as mucosal thickening. Figures 2a, 2b, and 3d show the normal mucosal thickening measurements of the patients. In the

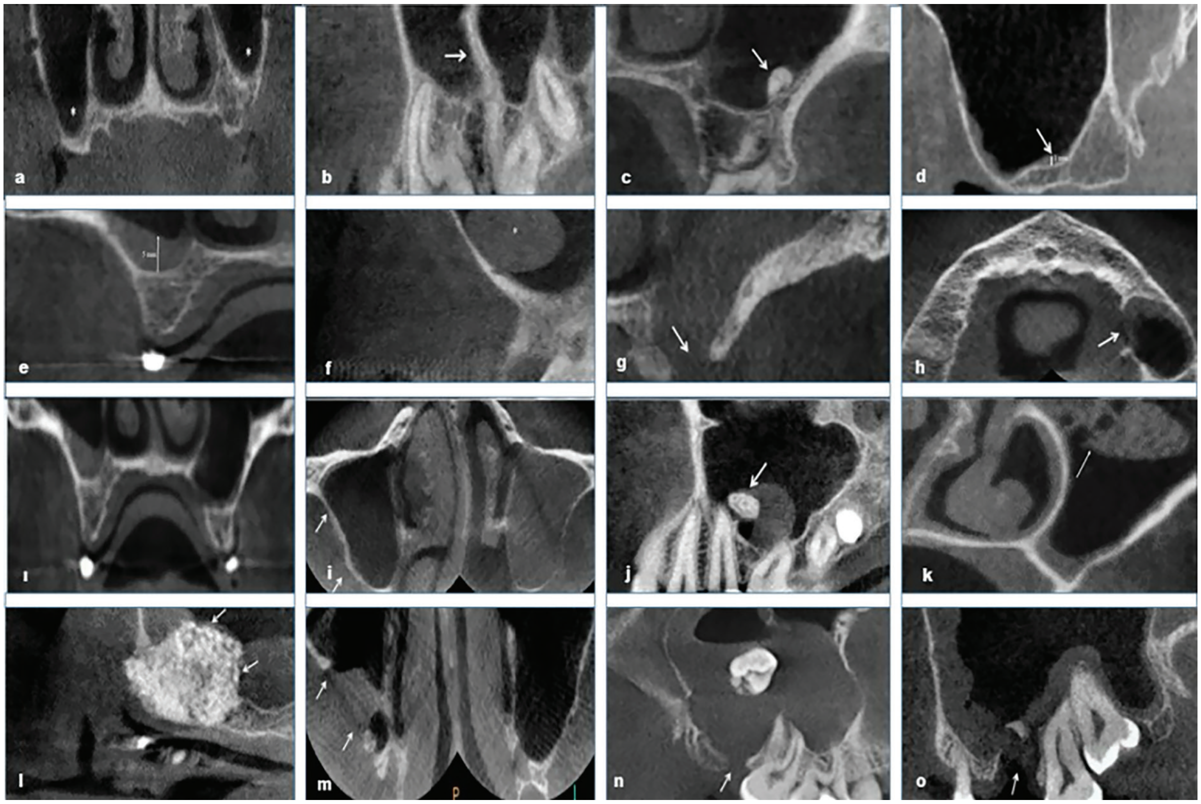

Figure 3. Radiographic demonstration of identified anatomical variations in the maxillary sinuses. a) Pneumatization, b) septa, c) exostoses, d) normal mucosal thickenning, e) pathological mucosal thickenning, f) polypoid lesion, g) interruption of the floor, h-ı) interruption of the medial wall, i) lateral bone wall thickening, j) antrolith, k) fluid retention, l) foreign body, m) interruption of the lateral wall, n) ectopic tooth, o) root.

current study, mucosal thickening of more than 2 mm was considered pathological (Figures 1a, 1b, 2c, 2d, 3e). Thus, the range of 0-2 mm represents physiological variation in mucosal thickness. Also, when a point in mucosal thickenning was measured more than 2 mm, it was evaluated as pathological mucosal thickenning.[7,11-12]

Types of Mucosal Thickenning

In all the patients, the types of mucosal thickenning were determined on the sagittal sections of CBCT images according to the classification criteria of Kocak et al.[13]: 1) normal (less than < 2 mm), 2) flat (flat, limited), 3) semipheric (polypoid), 4) mucocele-like (filling the sinus) or 5) mixed (both flat and polypoid). All types of mucosal thickening ≥ 2 mm were defined as pathological mucosal thickening.[11,12]

Mucosal Thickenning-Related Factors

Among the patients evaluated, mucosal-thickening-related factors were determined on sagittal CBCT sections according to Maillet et al.'s[14] classification criteria: 0) total edentulism; 1) stable, healthy mucosal thickening < 2 mm; 2) odontogenic sinusitis (i.e., mucosal thickening or polypoid pathology limited to a tooth); 3) non-odontogenic sinusitis (i.e., sinusitis occurring in the absence of an odontogenic origin; mucosal thickening not restricted to any one tooth); and 4) unknown origin (i.e., sinusitis for which the origin cannot be determined when more than one odontogenic factor is present; mucosal thickening not limited to any one tooth in the presence of a tooth with a defective restoration, a periapical lesion, any carious tooth, or a disrupted socket). Because mucosal thickening was evaluated with respect to odontogenic factors, totally edentulous patients were excluded from this analysis. Therefore, mucosal thickening in edentulous patients was evaluated to distinguish pathological from normal mucosal thickening.

Statistical Analysis

Descriptive statistics were used to summarize the distribution of maxillary sinus pathologies and anatomical variations. The Mann-Whitney U test was performed to evaluate the effects of age, sex, and dental status on the most common potential risk factor. A value of $P < 0.05$ was considered significant.

RESULTS

Demographic Data

Of the 2,500 CBCT images of the maxillary posterior region, 500 maxillary sinus images from 376 patients met the inclusion criterion. In the population analyzed, of the 376 patients, 177 were women (47%) and 199 were men (53%) with a mean age of 45.24 years (range: 18 to 90 years). Figure 4 presents the CBCT scanning indications among the 500 maxillary sinus cases: 256 (51.2%) sinuses in males and 244 (48.8%) sinuses in females.

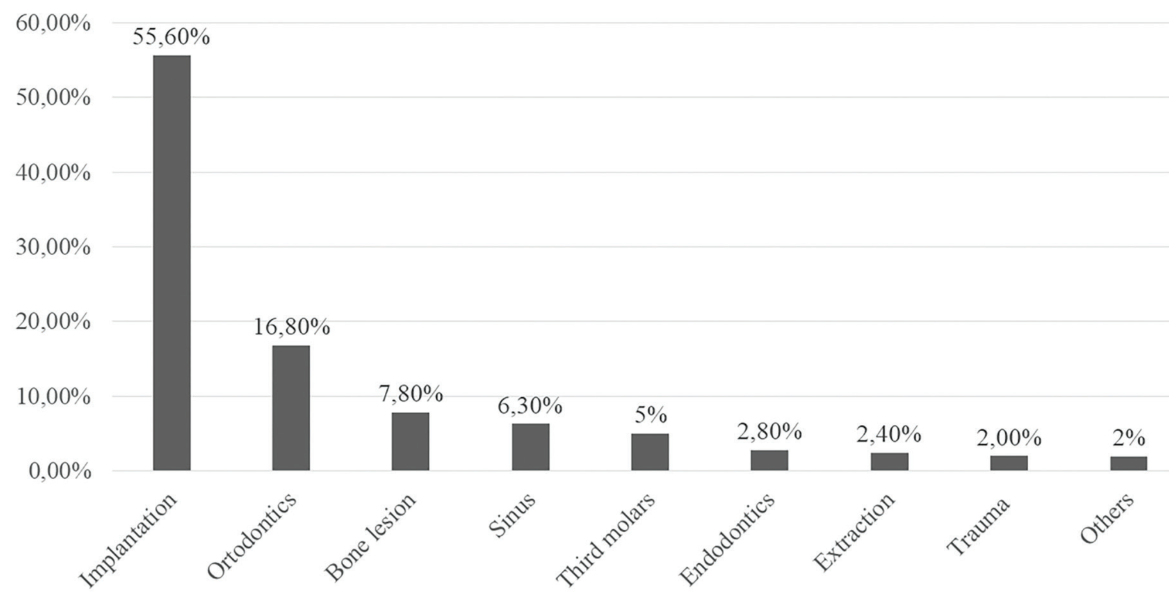

Figure 4. Distributions of the CBCT indications of the participants.

CBCT, cone-beam computed tomography.

The age distribution of the participants was as follows: 18-35 years (34.2%), 36-53 years (30.6%), 54-71 years (33.0%), and ≥ 72 years (2.2%). In the patient population, 45.6%, 33.6%, and 20.8% of cases were partially edentulous, dentate, and totally edentulous, respectively.

Study Variables

Assessment of Maxillary Sinus Anatomic Variations, Physiological Alterations and Pathologies

Interruption of the sinus floor, fluid retention, and both bony thickening and interruption of the lateral wall were conditions observed in association with other pathologies.

The most common potential risk factor was pathological mucosal thickening, with a rate of 67.2%. Then, frequently observed maxillary sinus pathologies, physiological alterations and anatomic variations were found as, mucosal thickenning (30.8%); septa and mucosal thickenning (29.2%); interruption of the medial sinus wall (7.6%); pneumatization, septa and mucosal thickenning (6.2%); sinus opacifying lesions (4.4%); and septa (3%) (Table 1). The CV for measurements of maxillary sinus mucosal thickening was found to be 0.91%.

Evaluation of the Images

Types of Mucosal Thickenning

The most common mucosal thickening type was flat (34.8%), followed by normal (32.8%), semipheric (11.6%), mixed (11.4%), and mucocele-like (9.4%) (Figure 5). The average mucosal thickenning was 3.64 mm.

Table 1. Pathologies and AVs With Distributions Above 1% in MS

AVs and pathological formations	Distribution %
No pathology and/or variation	3.6%
Septa	3%
Mucosal thickening	30.8%
Sinus opacifying lesion (retention cyst, polyp, etc.)	4.4%
Interruptionof the medial sinus wall	7.6%
Mucosal thickening and septa	29.2%
Septa and sinus opacifying lesion	1.8%
Pneumatization, septa, and mucosal thickening	6.2%
Septa, mucosal thickening, and antrolith	1%
Septa, mucosal thickening, and interruption of the medial sinus wall	1%

AVs, anatomic variations; MS, maxillary sinus

Mucosal Thickenning-Related Factors

The percentages of normal mucosal thickening (< 2 mm), non-odontogenic sinusitis, mucosal thickening of unknown origin, and odontogenic sinusitis were 29%, 19.4%, 18.6%, and 12%, respectively; 21% of the total edentulism cases were excluded from mucosal thickening-related factors. Pathological mucosal thickening was most common in partially edentulous individuals (P = 0.001), in males (P = 0.005), and in those aged 36-53 years (P = 0.05) (Table 2).

Table 2. Distributions of Normal and Pathological MT According to Age, Sex and Dental Status

		Normal MT	PMT	Total
Age	18-35	74 14.8%	97 19.4% *P* > 0.05	171 34.2%
	36-53	33 6.6%	120 24% *P* = 0.05	153 30.6%
	54-71	50 10%	115 23% *P* > 0.05	165 33%
	72-90	7 1.4%	4 0.8% *P* > 0.05	11 2.2%
Sex	Female	95 19%	149 29.8% *P* > 0.05	243 48.7%
	Male	69 13.8%	187 37.4% *P* = 0.005	257 51.3%
Dental Status	Dentate	73 14.6%	95 19% *P* > 0.05	168 33.6%
	Partially edentulous	64 12.8%	164 32.8% *P* = 0.001	228 45.6%
	Total edentulous	27 5.4%	77 15.4% *P* > 0.05	104 20.8%

MT, mucosal thickening; PMT, pathological mucosal thickening.

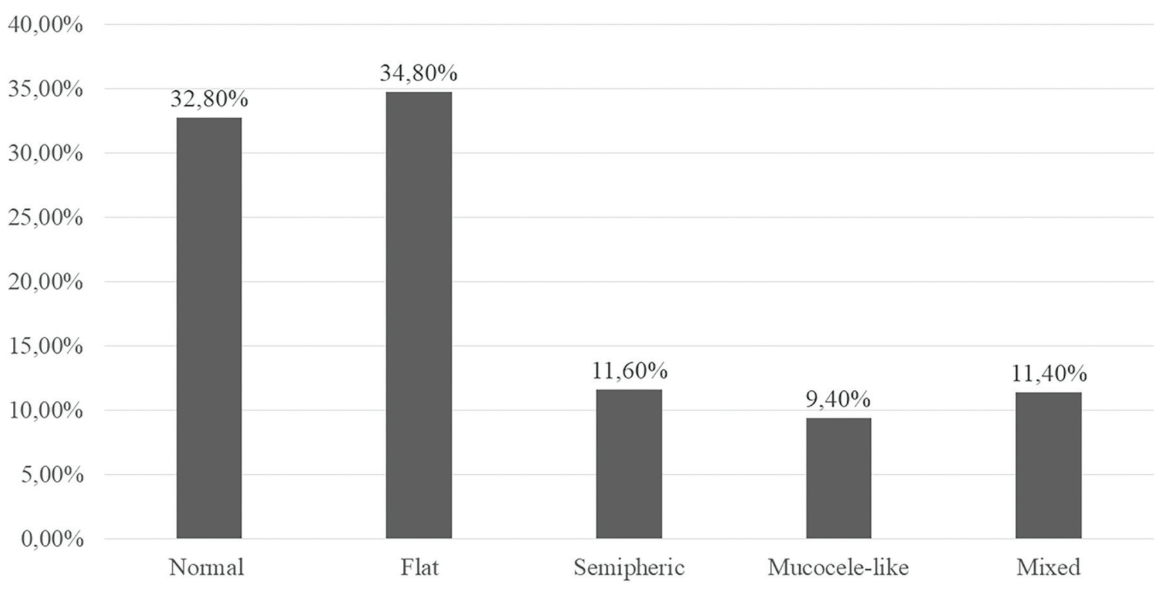

Figure 5. Distribution of the types of mucosal thickening in the maxillary sinuses of participants.

DISCUSSION

In the current study, the most frequently encountered maxillary sinus pathologies, physiological alterations, and anatomic variations are: pathological mucosal thickening, followed by mucosal thickening, septa, interruption of the medial sinus wall, pneumatization, and sinus opacifying lesions. When the maxillary sinus pathologies, physiological alterations and anatomic variations are analysed with respect to their coexistence; mucosal thickening and septa binary combination; interruption of medial wall and a combination of mucosal thickenning, septa and pneumatization was found to be most frequent respectively. Vogiatzi et al.[15] concluded that the most common maxillary sinus pathologies and anatomic variations were mucosal thickenning, septa and pneumatization in their systematic review. However Ata-Ali et al.[16] determined that, the most common pathologies and anatomic variations were mucosal thickening, sinusitis and sinus opacification in their systematic review.

The present study differs from that of previous studies due to the use of CBCT with a limited FOV, the use of different classification criteria based on the coexistence of anatomic variations and maxillary sinus pathologies, and the inclusion of a general population without specific indications (e.g. orthodontic, implant surgery or trauma patients).[17,18]

In the current study, the rate of pathological mucosal thickening was 67.2%, which is consistent with the result reported by Lana et al.[19] Differences in age groups, target populations, sample sizes, and classification probably explain the variation in reported incidence rates of pathological mucosal thickening in the literature (12%-67.2%).[7,17,19,20-23] In our study, the most up-to-date, commonly accepted classification system, pathological mucosal thickening > 2 mm, was used.[7,11,12,14,20,23]

Previous studies that evaluated the maxillary sinus reported mean mucosal thickening values ranging from 2.69 to 3.38 mm.[3,24] The average mucosal thickening was 3.64 mm (maximum: 6.24 mm, minimum: 1.04 mm) in our study. Investigators reported that mucosal thickenning may vary according to age and sex with increased mucosal thickenning found among those older than 40 years, with a male preponderance.[17,21] In the current study, pathological mucosal thickening was significantly higher in men (P = 0.005) and in participants aged 36-53 years (P = 0.05) than in females and other age groups, which is consistent with the literature.[17,21] The preponderance of pathological mucosal thickening in men may be explained by poorer oral hygiene and higher smoking rates compared with women.

A previous study demonstrated that the presence of chronic bacterial inflammation can lead to mucosal thickening of the maxillary sinus.[23] Although some studies have evaluated the relationship between periodontal bone loss and mucosal thickening[23,24], none have examined the relationship between dental status and mucosal thickening. In the current study, pathological mucosal thickening was most common among partially edentulous patients (P = 0.001), demonstrating a correlation between dentition and mucosal thickening.

The maxillary sinus is at risk of bacterial, fungal, viral, or odontogenic infections because of its anatomic position. Untreated odontogenic inflammation may cause sinusitis by extending into the maxillary sinus.[20] Therefore, imaging of the maxillary sinus is important for preventing inflammation-related complications, as well as for diagnosis and treatment planning.[3] A previous study reported that implant therapy and tooth extraction were potential causes of mucosal thickening.[25] Studies on the effects of mucosal thickenning emphasized that mucosal thickenning caused by dental factors contributed to the development of odontogenic sinusitis and that mucosal thickenning was associated with periodontal destruction.[14,23,24] Radiological images alone are not sufficient to confirm maxillary sinus pathology and anatomic variations, and clinical and radiological findings should be evaluated together, especially in the sinusitis diagnosis.[7]

CBCT is considered as an radiologic gold standard for implant planning, prior to implant procedures to determine the coexistence of maxillary sinus pathologies and anatomic variations and to prevent potential complications.[26] In the current study, implant planning (55.6%) was the primary reason for CBCT scanning, similar to the findings of Rege et al.[21]. Various imaging methods, including panoramic radiography, combined with CT and magnetic resonance imaging have been used to evaluate maxillary sinus pathologies.[17,18,27] Studies comparing the effectiveness of various radiographic methods for evaluating anatomic variations and pathologies of the maxillary sinus found that CBCT was the superior method.[17] In a previous study comparing panoramic radiography with CBCT, panoramic radiography failed to detect mucosal thickening < 3 mm.[18] CBCT allows detection of anatomic and pathological structures because it provides high spatial resolution and employs isotropic voxels.[2,17] Decreasing FOV and voxel size, the sensitivity and accuracy of CBCT images increases. Therefore, a smaller FOV provides higher diagnostic accuracy.[28]

Sayar and Aydın[29] conducted their study on a smaller sample comprising approximately 230 sinuses and used a CBCT device with an imaging field of 23 × 17 cm. Contrary to the findings of our study, they reported septal deviation as the most common pathology (13.9%), whereas mucosal thickening was the least common (2.6%). In contrast, Yalcin and Akyol[30] evaluated 650 maxillary sinuses in 2019 using CBCT devices with FOV of 16 × 5 cm, 16 × 9 cm, and 16 × 16 cm and identified mucosal thickening as the most prevalent pathology (53.5%). Similarly, Dogan et al.[31], in a 2024 study analyzing 1.000 maxillary sinuses with a 13 × 16-mm FOV, found a 45.8% prevalence of pathological mucosal thickening. Kawai et al.[32] reported incidental radiodensities in 56.3% of 338 maxillary sinuses examined in 2019 using FOVs of 20 × 10 mm and 20 × 17 mm. In our study, pathological mucosal thickening was observed in 67.2% of cases when a CBCT device with a significantly smaller FOV of 5 × 3.7 cm was used. The variation in findings across these studies may be attributed to differences in pathology-defining criteria, methodological approaches, and, particularly, the size of the FOV used during imaging.

Bone volume/height in the posterior maxilla is affected by a number of different factors; many factors such as age, gender, race, sinus pneumatization, trauma history and extraction of adjacent teeth, periodontitis, osteoporosis, edentulous period, multiple tooth extraction are the causes of atrophic alveolar ridge.[12,33] Risk assessment for maxillary sinus perforation includes factors such as sinus membrane thickness, septal presence and orientation, residual bone height, smoking status, sinusitis, and gingival biotype.[34,35]

Maxillary sinus membrane perforation is the most common complication encountered during lateral maxillary sinus floor elevation procedures and is associated with multiple factors. Prospective clinical studies reported in the literature identify age, presence of edentulous areas, lateral wall thickness, residual bone height, membrane thickness, smoking, presence of septa, and presence of mucous retention cysts as the most commonly reported factors associated with increased risk. Strategies to reduce risk in implant surgery vary depending on the physician's knowledge and skills, the technique applied, the surgical instruments and devices used, and treatment planning. Schneiderian membrane perforation, which is closely related to the anatomical variations of the maxillary sinus, can occur when local stress exceeds the membrane's stretch potential. The choice of surgical approach and the clinical outcomes are affected by the tensile properties of the Schneiderian membrane. In addition to residual bone height, clinicians should consider the stress potential, which is affected by membrane health status, maxillary sinus contours, and the presence of antral septa, when evaluating the choice of surgical approach and clinical outcomes.[36]

The risk of sinus pathologies can be reduced through therapeutic interventions by ear, nose, and throat specialists. A thick Schneiderian membrane is required for a safe sinus-lift procedure; pathology weakens the membrane, making it vulnerable to perforation.[34-39] Although not all of these criteria were included in our study, they were included as predictive factors. The limitations of our study include the small FOV of our CBCT device, its archival design, and the inability to evaluate multiple factors simultaneously. In addition to age, gender, and dental status, factors such as smoking, systemic disease status, and previous sinus surgery should also be included in the sample.

The study design is retrospective, and archival radiographic records were analyzed to derive conclusions and insights.[40] Prospective studies may be considered to confirm the findings and further investigate potential risk factors.[41] Using our study methodology as the basis for clinical prospective studies of membrane-perforation risk, and observing changes in maxillary sinus mucosa thickness and sinusitis risk over time, will provide a more comprehensive understanding of the study.

CONCLUSION

In this study, potential risk factors were identified as pathological mucosal thickening (67.2%), mucosal thickening (30.8%), septa-mucosal thickening (29.2%), non-odontogenic sinusitis (19.4%), mucosal thickening of unknown origin (18.6%), odontogenic sinusitis (12%), interruption of the medial sinus wall (7.6%), pneumatisation–septa–mucosal thickening (6.2). Particular attention should be paid to the presence of these factors. Membrane perforation, which is closely associated with anatomical variations of the maxillary sinus, can occur when local tension exceeds the membrane's stretch potential. In this regard, the presence of more than one pathology during sinus lift procedures may further increase the risk of local, tension-related perforations and susceptibility to infection. Patient-specific factors should be carefully evaluated before surgical procedures, and detailed imaging should be performed using CBCT to minimize potential complications.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the Medical Faculty of Ege University (approval no.: 14-7.1/6, date: 08.09.2014).

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

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Footnotes

Author Contributions

Concept Design – E.A.; Data Collection or Processing – N.K.T., E.A.; Analysis or Interpretation – H.B.; Literature Review - N.K.T.; Writing, Reviewing and Editing – N.K.T.

Declaration of Interests: The authors declared no conflicts of interest.

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