



REPUBLIC OF TURKEY
MARMARA UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

**A THREE-DIMENSIONAL EVALUATION OF SELLA TURCICA
IN UNILATERAL CLEFT LIP AND PALATE PATIENTS
DIAGNOSED WITH SKELETAL CLASS III MALOCCLUSION**

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MASTER OF SCIENCE THESIS

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STATEMENT

Hereby I declare that this thesis study is my own work, I had no unethical behavior in any stage from planning of the thesis until writing it, I have obtained all the information in this thesis within the academic and ethical rules, I have cited all the information and comments that are not obtained with this thesis study, and these sources are also included in the list of references, I hereby declare that I have no infringement of patents and copyrights during the study and writing of this thesis.



Mohammad Khalil

ACKNOWLEDGEMENTS

First and foremost, I want to thank my thesis supervisor, Assoc. Prof. Dr. Nuray Yılmaz, from the bottom of my heart. Her encouragement, guidance, and assistance have always inspired me. She has always welcomed my never-ending questions with a smile, and anytime I had a challenge and required her advice, her office door was always open to me. She served as my mentor and a very kind friend, in addition to being my research supervisor. Her invaluable knowledge and experience allowed me to complete my research. Thus I am incredibly grateful to have had the opportunity to be her student.

I would like to extend my gratitude to all my professors in the Orthodontics department: Prof. Dr. Sibel Biren, Prof. Dr. Fulya Özdemir, Prof. Dr. Zeynep Ahu Acar, Assoc. Prof. Dr. Murat Tozlu, Assoct. Prof. Dr. Yasemin Bahar Acar, Asst. Prof. Dr. Elvan Önem Özbilen, Asst. Prof. Dr. Ece Başal and Asst. Prof. Dr. Kadir Beycan. There aren't enough words to express my gratitude for generously sharing your knowledge with us during our residency years. Your efforts were outstanding.

Additionally, I want to thank all of my friends and colleagues in the department. You were my family away from home. Thanks for every tiny moment we shared together; I will never forget you. And to my dearest ones, Yousef and Mohammad, this journey would have never been the same without you; I will always be grateful as I always counted you as a blessing to have by my side throughout the journey in Istanbul.

Above all, I want to say how deeply grateful I am to my family. My parents, who showed me the way, and whose endless sacrifices allowed me to reach this point. Your endless support and unconditional love allowed me to achieve this and be who I am today. My brother Amjad, and my sisters Lana, Ahlam, Haneen, and Noor, from the depths of my heart, thank you. Also, special thanks to Saif, Amro, and Rania. Even though we were separated by miles, you were always by my side. This work is dedicated to you with all my love

CONTENTS

Page No

STATEMENT.....	i
ACKNOWLEDGEMENTS.....	ii
CONTENTS.....	iii
ABBREVIATIONS and SYMBOLS	vi
FIGURE LIST	vii
TABLE LIST	viii
1. ÖZET.....	1
2. SUMMARY	2
3. INTRODUCTION and AIM	3
4. GENERAL INFORMATION	5
4.1. Evolution of Imaging Techniques in Orthodontics.....	5
4.2. Cone-Beam Computed Tomography	5
4.2.1. CBCT technology in orthodontics	8
4.3. Cleft Lip and Palate.....	9
4.3.1. Definition	9
4.3.2. Incidence	9
4.3.3. Embryology.....	10
4.3.4. Etiology	12
4.3.5. Classification.....	13
4.3.6. Characteristics of CLP	14
4.4. Sella Turcica.....	15
4.4.1. Definition	15
4.4.2. ST anatomy	15
4.4.3. ST development	16

4.4.4. ST morphology	18
4.4.5. Types of ST	18
4.4.6. ST dimensions.....	18
4.4.7. ST imaging.....	20
4.4.8. ST bridging	21
4.4.9. ST pathology	22
4.4.10. ST congenital anomalies	23
4.4.11. ST in cleft patients	24
4.5. Malocclusion.....	26
4.5.1. Definition	26
4.5.2. Development	26
4.5.3. Classification.....	27
4.6. Surgical Considerations	28
5. MATERIALS and METHODS.....	31
5.1. Ethical Approval	31
5.2. Sample Size.....	31
5.3. Sample Selection.....	31
5.4. Data Collection and Assessment.....	32
5.4.1. Segmentation and ST volume measurement on CBCT.....	33
5.4.2. Cephalometric measurements	37
5.5. Statistical Analysis	39
6. RESULTS	41
6.1. Reliability Test.....	41
6.2. Demographic Characteristics of the Patients	42
6.3. Intra-Group ST Volume Comparison and Correlations of ST Volume with Age, Vertical, and Sagittal Cephalometric Measurements:	42

6.3.1. Healthy group results	43
6.3.2. UCLP group results.....	45
6.4. Inter-Group Comparison of Sella Turcica Volume.....	48
7. DISCUSSION and CONCLUSION.....	49
8. REFERENCES.....	59
9. ENCLOSURES.....	77



ABBREVIATIONS and SYMBOLS

ACD: Anterior Clinoid Distance
CBCT: Cone Beam Computed Tomography
CL: Cleft Lip
CLP: Cleft Lip and Palate
CP: Cleft Palate
CT: Computed Tomography
(°): Degree
DS: Dorsum Sella
DST: Diameter of Sella Turcica
FOV: Field of View
ICD: Interclinoid Distance
ICL: Interclinoid Ligament
%: Percent
PCD: Posterior Clinoid Distance
UCLP: Unilateral Cleft Lip and Palate
SL: Sella Length
S-point: Sella Point
SD: Standard Deviation
ST: Sella Turcica
STB: Sella Turcica Bridging
2D: Two-Dimensional
3D: Three-Dimensional
TS: Tuberculum Sella

FIGURE LIST

Page No

Figure 1. The bony landmarks used to define the borders	34
Figure 2. ROI square	34
Figure 3. In the display of the ITK-SNAP workspace	35
Figure 4. Measuring the volume confined between TS and DS.....	36
Figure 5. Different views of the segmented part.	36
Figure 6. Volumes and Statistics table in ITK-SNAP.....	37
Figure 7. The vertical measurements performed on cephalometric radiographs.	38
Figure 8. The sagittal measurements performed on cephalometric radiographs.....	39

TABLE LIST

Page No

Table 1. The vertical measurements performed on cephalometric radiographs.....	38
Table 2. The sagittal measurements performed on cephalometric radiographs.	39
Table 3. Single observer's agreements between repeated measurements	41
Table 4. Demographic characteristics of the patients.....	42
Table 5. The vertical, sagittal and ST volume measurements for healthy group.	43
Table 6. Correlation results in the healthy group (cephalometry).....	44
Table 7. Correlation results in the healthy group (age).....	45
Table 8. The vertical, sagittal and ST volume measurements for UCLP group.....	46
Table 9. Correlation results in the UCLP group (cephalometry)	47
Table 10. Correlation results in the UCLP group (age).	47
Table 11. Comparison of the between the healthy and UCLP groups.	48
Table 12. Difference between volumes of males vs. females in the entire sample...	48

1. ÖZET

İskeletsel Sınıf III Maloklüzyona ve Tek Taraflı Dudak Damak Yarığına Sahip Hastalarda Sella Tursikanın Üç Boyutlu Değerlendirmesi

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Anabilim Dalı: Ortodonti Anabilim Dalı

Amaç: Bu çalışmanın amacı, tek taraflı dudak damak yarığına (TDDY) sahip hastalarda sella tursika'nın (ST) hacmini konik ışınlı bilgisayarlı tomografi (KIBT) görüntüleri kullanarak incelemek ve elde edilen sonuçları iskeletsel Sınıf III maloklüzyonu olan ancak TDDY bulunmayan bireylerin sonuçları ile karşılaştırmaktır.

Gereç ve Yöntem: Bu çalışmada Marmara Üniversitesi Diş Hekimliği Fakültesi Ortodonti ve Radyoloji Anabilim Dalı arşivinden alınan 60 KIBT görüntüsü kullanılmış, sağlıklı ve TDDY grubu olmak üzere iki gruba ayrılmıştır. Sella tursika hacmini hesaplamak için ITK-SNAP (versiyon 3.8.0), lateral sefalometrik değerlendirme için NemoCeph yazılımı (versiyon 16.50.0) yazılımı kullanılmıştır.

Bulgular: ST hacmi açısından iki grupta da cinsiyetler arası fark gözlenmemiştir. Sağlıklı kadın bireylerde ST hacmi ve Wits değeri arasında negatif bir korelasyon gözlenmiştir. TDDY grubunda ST hacmi ile Jarabak değeri arasında olumlu bir ilişki saptanmıştır. İki grupta da ST hacmi ile yaş arasında anlamlı bir ilişki gözlenmiştir. Tüm bireyler TDDY varlığı gözetmeksizin kadın ve erkek olarak gruplandırıldığında, ST hacminin erkeklerde istatistiksel olarak anlamlı derecede daha büyük olduğu görülmüştür.

Sonuç: Yaşın ST hacmi üzerinde pozitif etkili olduğu gözlenmiştir. Sınıf III maloklüzyona sahip bireylerde TDDY varlığı ST hacmi açısından sağlıklı bireylerle arasında bir farklılık göstermemiştir.

Anahtar Kelimeler: Sella Tursika, Yarık Dudak, Yarık Damak, Sınıf III, Konik Işınlı Bilgisayarlı Tomografi.

2. SUMMARY

A Three-Dimensional Evaluation of Sella Turcica in Unilateral Cleft Lip and Palate Patients Diagnosed with Skeletal Class III Malocclusion

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Aim: The present study aims to evaluate the volume of the sella turcica (ST) in unilateral cleft lip and palate (UCLP) patients via CBCT (Cone Beam Computed Tomography) images and compares those results to non-cleft individuals diagnosed with skeletal Class III malocclusion.

Materials and Methods: This study used 60 CBCT images collected from the archive of the Radiology Department at the Faculty of Dentistry, Marmara University. The patients were divided into two groups as healthy and UCLP groups. ITK-SNAP (version 3.8.0) software was used to calculate the volume of ST in the CBCT images and NemoCeph (version 16.50.0) software was used for the lateral cephalometric radiographs.

Results: In terms of ST volume, no gender difference was found in either group. A negative correlation was observed between ST volume and Wits appraisal in female patients. There was a positive relationship between ST volume and Jarabak in UCLP group. A significant correlation was observed between ST volume and age in both groups. When all patients were grouped as male and female regardless of the presence of UCLP, the ST volume was found to be statistically larger in males.

Conclusion: Age has a positive effect on ST volume. In patients with Class III malocclusion, the presence of UCLP did not show significant difference in terms of ST volume.

Keywords: Sella Turcica, Cleft Lip, Cleft Palate, Angle Class III, Cone-Beam Computed Tomography.

3. INTRODUCTION and AIM

The sella turcica (ST) is one of the crucial anatomical landmarks in orthodontics since the Sella point (S-point), centered in the sella, is a stable reference in cephalometric analysis (Kjær, 2015). It is assumed that anatomic variations of ST could be correlated with dental changes. So, many pieces of research have focused on the relationship between sella turcica bridging (STB) and dental abnormalities. (Miletich and Sharpe, 2004; Ali et al., 2014). The anterior wall of the ST is used to evaluate craniofacial development and jaw interrelationships and to compare the treatment outcomes of skeletal malocclusions accomplished by dentofacial orthopedic appliances. (Grippaudo et al., 2013; Kjær, 2015; Yasa et al., 2017). These evaluations aid in predicting the orthodontic treatment outcomes, prescribing appropriate orthodontic plans, and describing craniofacial changes. A literature survey shows minimal information, and little work has been done about the association between ST and all types of dental anomalies (Jankowski et al., 2021; Saokar et al., 2022). A review of the available data reveals that bridging occasionally happens in those with craniofacial abnormalities more than in healthy people. This form can also be greatly associated with severe craniofacial variation, tooth agenesis (Sato et al., 2020), canine impaction (Baidas et al., 2018), and individuals with cleft palate (Sinha et al., 2020). It is also realized that an early look at ST anatomic variations during development should draw the attention of clinicians to possible tooth abnormalities later in life. Most of the previous research on the assessment of ST was conducted on traditional lateral cephalograms and panoramic radiographs, which are two-dimensional (2D) images (Leonardi et al., 2006; Ali et al., 2014). Consequently, the precision of three-dimensional (3D) structures and ST diagnosis using routine tools is restricted by limitations in errors resulting from projection, magnification, as well as superimposition, and overlapping structure images (Becktor et al., 2000; Axelsson et al., 2004; Alkofide et al., 2007; Sathyanarayana et al., 2013; Sundareswaran et al., 2019). Furthermore, the right or left side of ST cannot be easily recognized in lateral cephalometric radiographs, and structural superposition can lead to errors. (Ortiz et al., 2018). In some studies, there were no model casts, and some tooth abnormalities could not be detected. More importantly, in all published related literature, it is still unknown

whether the skeletal pattern in patients with a unilateral cleft lip and palate is associated with ST morphological features.

The conventional techniques have inherent drawbacks, while the more recent cone beam computed tomography (CBCT) technology has several advantages. Compared to classical computed tomography (CT), CBCT technology can offer superior-quality images with more valuable information, a lower cost, and lower radiation exposure (Scarfe and Farman, 2008; Yalcin, 2020). Due to these benefits, it is a substitute imaging method for craniofacial hard tissues and the dental field (Yasa et al., 2017). Evidence of ST anomalies on CBCT is scarce (El Wak et al., 2018; Ortiz et al., 2018; Chou et al., 2021). Few studies have measured ST dimensions and evaluated morphology in cleft lip and palate (CLP) using CBCT technology (Yasa et al., 2017; Akay et al., 2020; Yalsin, 2020; Jankowski et al., 2021). Previous studies did not find a statistically significant association between unilateral/bilateral palatal canine impaction and STB. No data on ST morphology in a control group without any dental pathology can be found in any study (Akay et al., 2020; Jankowski et al., 2021).

It has been proposed that the morphological form and dimensions of the ST may be abnormal in individuals with CLP anomaly (Yasa et al., 2017; Yalcin, 2020). Several investigations have also followed the changed dimensions of the ST in skeletal malocclusion classes (Axelsson et al., 2004; Shah et al., 2011; Luong et al., 2016; Akay et al., 2020; Silveira et al., 2020). Nevertheless, only one study (Akay et al., 2020) has been found in the published literature regarding the evaluation of the morphology and dimensions of the ST between CLP subjects and skeletal malocclusion classes.

This thesis aims to evaluate the interrelationship between ST morphology in unilateral cleft lip and palate (UCLP) in a sample of Turkish patients diagnosed with skeletal Class III malocclusion using the 3D images of CBCT technology. Numerous researchers, including radiologists, orthodontists, maxillofacial surgeons, neurosurgeons, pediatricians, and endocrinologists, are expected to gain from this research in order to understand and plan surgical treatments involving the sellar area.

4. GENERAL INFORMATION

4.1. Evolution of Imaging Techniques in Orthodontics

Imaging is a significant diagnostic asset to clinical assessment. Radiographs are used in almost every dental and medical field. Over the decades, 2D radiography, such as panoramic and lateral cephalometric imaging, provided clinicians and dentists with essential data on jaws and maxillofacial structures. To monitor growth and development, evaluate treatment progress outcomes, and collect the data essential for successful orthodontic diagnosis and treatment programs. However, whether used separately or together, intra- and extra-oral techniques are both subject to the same inherent limitations of planar 2D projections, including magnification, disproportional distortion, projective superimposition of anatomical details, patient positioning, and the resulting misrepresentation of structures (Scarfe et al., 2017). Additive manufacturing, generally known as 3D printing, was innovated in the 1980s (Hull, 1986). However, it has only lately begun to be used in dentistry. Little information was available on the unilateral or transverse aspects of malocclusions or craniofacial anomalies. Many efforts have been dedicated to 3D radiographic imaging, such as stereoscopy and tuned aperture CT. Although CT has been around for a while, its use in dentistry has been constrained because of the high cost, the difficulty in accessing it, and the dose issues. Another major obstacle is the need for dental staff to master new skills (Cousley, 2020; Hegedüs et al., 2022).

4.2. Cone-Beam Computed Tomography

The most significant invention in orthodontic diagnostic radiography occurred in 1998 when Mozzo and colleagues introduced the CBCT to dentistry. The emergence of the CBCT revolutionized imaging for orthodontic diagnosis and treatment planning specifically in the maxillofacial region. The dental and maxillofacial CBCT geometry was introduced as a substitute for traditional CT. The method uses either fan-beam or spiral-scan geometries to offer faster gaining of data set of the whole field of view

(FOV) (Scarfe and Farman, 2008). The transition from 2D to 3D image approach to data acquisition and image reconstruction has expanded the role of imaging from diagnosis to image guidance of operative and surgical procedures. Clinicians should have a clinically-related grasp of the technical factors that impact radiation dosage and picture quality in order to perform or comprehend CBCT imaging for orthodontics. In principle, CBCT imaging uses a rotating scaffold to which an X-ray source and detector are fixed. The median area of interest forms a guide onto which the opposing source of ionizing radiation in the form of a pyramid or cone is directed to an X-ray detector on the opposite edge. The center of the area of interest serves as the rotating axis around which the X-ray source and detector rotate. During this rotation, a large number (150-600) of subsequent planar projection pictures of the FOV are acquired in a full or partial arc. This approach differs from a conventional medical CT, which creates individual image slices of the field of view using an X-ray beam that is fan-shaped and arranged in a helical manner. The slices are then layered to create a 3D image. (Scarfe and Farman, 2008). Since the CBCT exposure integrates the whole FOV, only a single rotational sequence of the gantry is needed to gain enough data to reconstruct an image.

The novel technology lowers image blur brought on by patient translation, reduces image distortion brought on by internal patient movements, and improves X-ray tube efficiency, in addition to using a radiation detector that is relatively less expensive. The fundamental drawback of CBCT, however, is that it restricts image quality in terms of noise and contrast resolution since it detects large amounts of dispersed radiation, particularly with larger FOVs. These problems have been overcome when high-resolution, less complicated, and inexpensive flat-panel detectors have been made available. These flat detectors are composed of hydrogenated amorphous silicon thin-film transistors arranged in a large-area pixel configuration, where X-rays are indirectly detected by a scintillator, such as terbium-activated gadolinium oxysulfide or thallium-doped cesium iodide. As a result, X-rays are transformed into visible light, which is then captured by the photodiode array. This arrangement of detectors decreases peripheral distortion and enables a larger dynamic range, but it also requires a little more radiation exposure. (Scarfe and Farman, 2008).

The majority of CBCT scanners either scan the patient while they are standing (axial) or seated (sagittal) (Mah et al., 2011). There is a few pieces of equipment that allow for supine (coronal) scanning of the patient. The CBCT devices can be grouped into three primary operation divisions: stand-alone, hybrid multi-modal systems, which integrate digital panoramic, and cephalometric radiography with a small to medium-FOV CBCT system. An appropriate option for these parameters is essential to optimize image quality and minimize radiation exposure dose (Qu et al., 2010). The image produced by CBCT consists of four parameters; acquisition configuration, image detection, image reconstruction, and image display (Scarfe and Farman, 2008). The CBCT systems can be divided into five groups based on the field of view (FOV) size (spherical volume diameters or cylinder heights) of the selected scan: localized region, single arch, inter-arch, maxillofacial, and craniofacial with a field of view that is less than 5 cm, 5-7 cm, 7-10 cm, 10-15 cm, and greater than 15 cm, respectively. Examples of the captured tissues can be: dentoalveolar and temporomandibular joint, maxilla or mandible, mandible and the concha superiorly, mandible and extending to the nasion, and from the lower border of the mandible to the vertex of the head, respectively (Ludlow and Ivanovic. 2008; Scarfe and Farman, 2008).

The FOV should be adjusted to include only the region of interest. Extension of the FOV scanning integrating the craniofacial region into a cone-beam design is difficult, but this can be attained by conventional geometric arrangement (Mah et al., 2011). Alternatively, it can be accomplished by shifting the location of the flat panel imager and collimating the X-ray beam laterally. Based on the type of detector, the current CBCT units can be classified into two groups; an image intensifier tube/charge-coupled device (IIT/CCD) combination or a flat-panel detector.

Unlike those in conventional CT, which depend on the thickness of the slice, voxel dimensions in CBCT imaging primarily rely on the pixel size on the area detector. The resolution of the area detector is a fraction of a millimeter (0,09 mm to 0,4 mm), which chiefly controls the size of the voxels. Consequently, CBCT units offer voxel resolutions that are isotropic (i.e., equal in all three dimensions). In contrast to conventional CT, CBCT data reconstruction (data processing to generate the volumetric data set) is achieved by a personal computer rather than workstation

platforms. The elements employed for acquisition (voxel size, field of view, number of projections), hardware (processing speed, data flow from acquisition to workstation computer), and software (reconstruction algorithms) all affect reconstruction time, which varies (Hatcher, 2010). Reconstruction should be achieved in a satisfactory time (estimated to be less than 3 min for typical resolution; scans) to complement the patient flow (Scarfe and Farman, 2008, Coşkun and Kaya, 2018).

4.2.1. CBCT technology in orthodontics

Orthodontists today are aware of the potential uses of printing in orthodontics. (Cousley, 2020). The availability of CBCT technology in orthodontics offers clinicians great unique features and advantages. First, being substantially smaller, the physical footprint of CBCT equipment is substantially smaller, and it costs between a quarter and a fifth less than traditional CT. Second, because CBCT generates images of strongly contrasted structures, it improves the efficiency of clinical imaging. The bone structures in the craniofacial region can be imaged using it remarkably effectively. Third, using CBCT machinery in clinical dental practice gives several advantages for maxillofacial imaging (Ludlow and Ivanovic, 2008; Scarfe and Farman, 2008). In addition, CBCT provides significant (up to 98,5%) dose reductions compared with the patient dose described for maxillofacial imaging by conventional CT. The ability of CBCT to provide distinct images that disclose aspects in 3D that intraoral, panoramic, and cephalometric scans cannot is perhaps its most significant advantage CBCT.

To offer corresponding images in three orthogonal planes, CBCT units also rebuild the projection data (axial, sagittal, and coronal). Two techniques have been developed to visualize adjacent voxels due to the enormous number of component orthogonal pictures in each plane and the difficulties linking adjoining structures. By increasing the number of adjacent voxels in the display, any multiplanar image can be "thickened" in the first method, known as the ray sum or ray casting approach, to produce an undistorted image slab that represents a particular volume of the patient. The second method, known as 3D volume rendering, combines vast volumes of nearby voxels with selective display to enable the visualization of 3D data.

Despite the expansion of undeniable clinical applications of CBCT, the current CBCT technology has a number of drawbacks. These restrictions on projection geometry, detector sensitivity, and contrast resolution result in images that lack the sharpness and utility of standard CT scans. Noise and low soft tissue contrast, as well as various artifacts from x-ray projection and patient placement, as well as cephalometric measurement errors, brought on by the inherent challenges of landmark identification, all affect the clarity of CBCT pictures. (Scarfe et al., 2017; Baldini et al., 2022). Image abnormalities like streaking, shading, ringing, and distortion brought on by high attenuation areas also have an impact on the quality of CBCT images (such as metallic restorations).

4.3. Cleft Lip and Palate

4.3.1. Definition

Orofacial clefts of the lip and palate (CLP) are one of the most common congenital anomalies in the craniofacial region (Fogh-Andersen, 1971), representing a heterogeneous group of disorders affecting the craniofacial region, specifically the lips and the oral cavity.

Generally, these anomalies can present as unilateral or bilateral clefts involving the lip alone (CL), the palate alone (CP), or both (CLP) (Shaye et al., 2015). These defects originate from the facial processes' improper growth or their inability to fuse during the early stages of embryonic development (Deshpande et al., 2019). The exact etiology is unknown and complex but is thought to be associated with environmental and genetic factors and interactions between them (Vieira, 2012).

4.3.2. Incidence

Several epidemiological describe the prevalence of these craniofacial anomalies. The overall incidence of occurrence of CLP is around 1 in 700 live births, ranging from 1 in 500 to 1 in 2500 births in various geographic areas (Canıgür Bavbek et al., 2019).

According to W.H.O. (2004), a cleft lip and/or palate baby in every 600 newborns worldwide is born. Say et al. (1973) reported a rate of about 1 in every 1000 newborn babies in Turkey. However, according to Yilmaz et al. (2019), there is no enough national data showing the prevalence of CLP cases in Turkey.

In the United States, for each cleft lip and palate child, an estimated average of \$100,000 for a lifetime medical cost is approximately \$750 million for all children born within one year. The reasoning behind this is the multidisciplinary approach to treating CLP (Waitzman et al., 1994).

CL and CLP account for 65% of all head and neck anomalies (Shapira et al., 1999). The distribution of the clefts reveals that CLP is the largest group, followed by CP and CL. Males are more likely to have CLP, but females are twice as likely to have isolated CP (Davis and Ritchie, 1922; Hagberg et al., 1998). Moreover, the UCLP group, the study sample of the present thesis, is the most common type of orofacial cleft. More specifically, UCLP on the left side is seen more frequently than that affecting the right side (IPDTC, 2011; Yilmaz et al., 2019).

4.3.3. Embryology

Five prominences emerge and fuse to form the basic morphology of the face between the fourth and twelfth weeks of development. These prominences include two maxillary prominences, two mandibular prominences connected to the first pharyngeal arches, and the frontonasal prominence overlaying the forebrain. The cranial neural crest cells rapidly migrate from the neural placode. The midbrain and hindbrain provide neural crest cells to the maxillary and mandibular prominences. Failure of some of these processes to develop and fuse properly leads to the orofacial clefts (Schoenwolf et al., 2020)

By the end of the fourth week, all five facial prominences are formed. They first encircle the primitive oral cavity (the stomodeum), which is isolated from the gastrointestinal tract by the oropharyngeal membrane. Then, maxillary prominences

grow and develop ventrally and medially throughout the fifth week. At the same time, on either side of the frontonasal prominence, a pair of ectodermal thickenings known as nasal placodes form. The ectoderm in the middle of each nasal placode invades to produce an oval nasal pit in the sixth week. The nasolacrimal groove is the ridge that runs between the lateral nasal process and the nearby maxillary prominence. The ectoderm at the bottom of this groove invades the underlying mesenchyme during the seventh week, forming a tube known as the nasolacrimal duct and lacrimal sac (Schoenwolf et al., 2020).

The primordium of the bridge and septum of the nose is formed during the sixth week when the medial nasal processes move closer and unite. The inferior tips of the medial nasal processes develop laterally and inferiorly at the end of the seventh week, joining the maxillary prominences to form the intermaxillary process. The philtrum, primary palate, and four incisor teeth are all produced through intermaxillary processes (Schoenwolf et al., 2020).

Right and left maxillary prominences and medial nasal prominences fuse to produce the primary palate, whereas medial nasal prominences and lateral nasal prominences fuse along with the maxillary prominences to make the upper lip. The formation of the primary palate divides the nasal cavity from the oral cavity anteriorly (Sadler, 2011; Hiatt and Gartner, 2009).

Between weeks 7 and 12, within the right and left maxillary prominences, cellular proliferation leads to the development of the palatal prominences. Beginning with vertical growth and then horizontal growth with the downward tongue placement, the palatal prominences eventually fuse with the nasal septum around the 10th week to produce the secondary palate. As a result, it divides the nasal cavity from the mouth cavity posteriorly. The soft palate develops after the hard palate during weeks 10 to 11, while the uvula develops at week 12 after the hard palate (Sadler, 2011; Hiatt and Gartner, 2009).

These cellular processes that contribute to face formation are all governed by a specific genetic code and are easily influenced by environmental circumstances. Facial clefts

may occur when facial processes are improperly fused for any reason. When the right-left maxillary prominences, lateral prominences, and medial nasal prominence cannot fuse properly, unilateral or bilateral primary cleft lips result. A cleft occurs at the hard palate, soft palate, and uvula if the maxillary prominences do not properly fuse (Sadler, 2011; Hiatt and Gartner, 2009).

4.3.4. Etiology

As mentioned above, CLP is multifactorial and complex. CLP may result from developmental, genetic, and environmental factors.

The effect of genetics as a factor for orofacial clefts was first shown by Fogh-Andersen (1942). There are numerous instances where CLP is linked to family history; patients who have CLP frequently have a family history of the condition and are more likely to have kids with CLP. In addition, the high incidence of CLP in two newborn babies in monozygotic twins compared to dizygotic twins reveals that genetics has an important role. Moreover, CL or CLP incidence increases with consanguineous marriages; the similarity of the gene structure increases the possibility of encountering some recessive genes responsible for the condition (Fraser, 1940; Mitchel and Risch, 1992; Wyszynski et al., 1996; Lidral et al., 2008; Aquino et al., 2011; Dixon et al., 2011).

The organogenesis period during pregnancy lasts for the first three months. The development of CLP in the infant may be triggered by certain environmental variables active at this time. Some drugs used during pregnancy like anticonvulsants, benzodiazepines, steroids, excess vitamin A, and antihypertensive drugs. Maternal and paternal age (a father of 40 years and older, a mother of 35-39 years and older), infections like toxoplasmosis, rubella. Alcohol or smoking, radiation exposure, and excessive stress have been reported as some of the main factors. Lastly, malnutrition like deficiency of folic acid vitamin A and B has been reported to be one of the factors (Werler et al., 1991; Damm et al., 1993; Carmichael et al., 1999; Carmichael et al., 2007; Herkrath et al., 2012).

4.3.5. Classification

Depending on the risk factors, several different CLP forms may occur during facial development. Since CLP necessitates a multidisciplinary treatment strategy, classification is crucial to accurately diagnose the severity and kind of abnormality during professional communication and establish an effective treatment plan. The severity of deformations, premaxilla protrusion, collapse of alveolar arches, deviation of nasal structures, and velopharyngeal function deficit should all be clearly indicated by the CLP classification.

At the American Medical Association meeting in St. Louis in 1922, a call was made to stop using the harelip term. It was said that the term congenital cleft of the lip should be used instead of “the harelip” term (Davis and Ritchie, 1922). Since that day and until recently, many classification models have been proposed over the years; some were accepted, modified, and widely used, while others were not. However, according to Houkes et al., among all the suggested systems that classify orofacial clefts, an acceptable and generally applicable classification system is required to fully address laterality, completeness, and clefts of the alveolus (Houkes et al., 2021). They reported that the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was the most frequently utilized (35,5%), followed by right lip, right alveolus, right hard palate, midline soft palate, left hard palate, left soft alveolus, left lip (LAHSHAL system) (34,0%) and Veau (32,5%) classification. Their results were obtained from a total of 197 registrants from three international cleft/craniofacial meetings.

Clefts of the soft palate (I), clefts of the soft and hard palate up to the incisive foramen (II), clefts of the soft and hard palate extending unilaterally through alveolus (III), and clefts of the soft and hard palate extending bilaterally through alveolus (IV), were the four types that Veau described in 1932 based on the anatomical structures (Allori et al., 2017).

Allori et al. encouraged a standardized structure for describing CL/P phenotypes (Allori et al., 2017). A thorough description of a CL/P phenotype should acknowledge

the alveolar defect, describe the laterality and severity of the labial defect, and describe the morphology of the palatal defect. Many physicians have used this structured longhand method with effectiveness. When such a system is applied consistently, very little is left up for debate-diagnoses are always obvious, treatment protocols can be predicted based on the diagnosis, and even administrative coding is simpler.

4.3.6. Characteristics of CLP

Walker et al. investigated tooth size and morphology in subjects with UCLP, bilateral CLP, and isolated CP (Walker et al., 2009). They reported a reduced teeth size in all cleft groups in both jaws, with the smallest teeth found in the isolated CP group. Also, the upper central and lateral incisors on the cleft-affected side in the UCLP and BCLP groups were frequently hypoplastic or peg-shaped. Akcam et al. investigated the frequency of various dental anomalies in the upper dental arch in different cleft groups (Akcam et al., 2010). They found that the anterior and premolar regions of the CLP groups had considerably greater impaction rates (2.9–29.2%), with the anterior region on the cleft sides having the highest rates. Additionally, it was shown that a very high percentage of participants (97%) had at least one tooth abnormality. In the UCLP and BCLP groups, the upper central and lateral incisors on the cleft-affected side were typically hypoplastic or peg-shaped.

The maxilla and nasal region's distortion, dislocation, and tissue insufficiency are all affected differently depending on whether there is a unilateral or bilateral deformity (Huffman and Lierle, 1949). The maxilla in patients with a complete UCLP is split into greater and lesser segments. The maxillary alveolar segments exhibit morphological alterations due to the tongue's neuromotor activity and the orbicularis oris muscle's interruption. While the lesser segment exhibits more varied (medial or lateral) morphological abnormalities, it is seen that the greater segment rotates anterolaterally in the transverse plane (Bacher et al., 1998). Additionally, the alar cartilage on the cleft side is concave and depressed, whereas the alar cartilage on the noncleft side is situated closer to the tip of the nose. The nostril base width is wider on the cleft side. The columella and nasal septum are turned toward the non-cleft side,

and the nose is flat. Lips and alveolar segments are not in contact (Grayson et al., 1999).

Complete cleft lip and palate is a complex deformity that includes the lip and palate and other structures in the craniofacial region. Deficient growth of the middle face (Class III skeletal malocclusion), posterior crossbite, asymmetric antegonial notching, mandibular asymmetry, and lower facial asymmetry were all reported in UCLP patients by Kyrkanides and Richter (2002).

Moreover, as mentioned above, CLP may have an effect on different parts of the craniofacial region. One of the manifestations is alterations to ST (See section 4.4.11)

4.4. Sella Turcica

4.4.1. Definition

The term sella turcica is a Latin derived from the Turkish word “saddle” (Tekiner et al., 2015). The term “sella turcica” is associated with the shape and function of a seat or a saddle, with a solid connection to its function as a seat for the pituitary gland. However, for the purpose of this thesis, only the name sella turcica (abbreviated as ST) will be used. The ST is a small fossa in the upper part of the sphenoid. (Bonneville et al., 1989; Tekiner et al., 2015; Ganapathy and Tadi, 2022).

4.4.2. ST anatomy

The ST is best visualized on lateral views of the skull. Structurally, it is a cup-shaped depression that is found in the central basisphenoid bone that houses the two parts of the pituitary gland (hypophysis) along with an inferior portion of the infundibular (pituitary) stalk. The pituitary gland, along with the ST, form the sellar region (Kjaer, 2015).

Matching its analogy to the saddle, the ST consists of three portions (Moore et al., 2014). The first is the saddle pommel (tuberculum sella: TS), which is a small anterior elevation in the sphenoid bone's body. The second is the hypophyseal fossa (pituitary fossa), a saddle-like midline bony depression for the pituitary gland in the center. The third portion is the dorsum sellae (cantle of the saddle), which is found posteriorly and is formed by a square plate of bone on the body of the sphenoid.

The ST is bordered on the back by the dorsum sellae and the basilar artery and by the carotid sulcus laterally. Anteriorly, it is related to the cribriform plate of the ethmoid bone and the tuberculum sella (Ganapathy and Tadi, 2022). The suprasellar cistern is located above the sellar area. The circle of Willis, the optic nerves and optic chiasm, the hypothalamus, the pituitary infundibulum, and the infundibular and suprachiasmatic recesses of the third ventricle intersect this region (Moore et al., 2014).

The floor of the ST is entirely covered by the dura mater. A flat dural fold makes the roof of the ST is known as the diaphragm sellae (or sellar diaphragm). The floor spreads from the dorsum sellae to the tuberculum sellae, and laterally, it is bounded by the carotid sulcus. Laterally, the ST is locked by a vertical dural fold which isolates the pituitary fossa from the cavernous sinus. Therefore, the pituitary gland is bounded, with the exception at the diaphragm sellae, where a central circular opening transmits the pituitary stalk.

4.4.3. ST development

The morphological appearance of ST begins in early embryogenesis (Sathyanarayana et al., 2013). The development of the ST is closely associated with that of the pituitary gland, which must be terminated before the ST can be shaped (Kjaer, 2015). With age and gender, the gland's size varies (Osborn et al., 2004). In infants, it is 6 mm; in men and post-menopausal women, it is 8 mm; in pre-menopausal women, it is 10 mm; and in pregnant lactating women, it may be up to 12 mm.

In terms of orthodontics, the ST has an embryologic origin that is intimately connected with the development of the craniofacial region (Kjaer, 2015; Canıgür et al., 2019). The ST area is the major location for the migration of neural crest cells to the frontonasal and maxillary developing regions during embryonic life. These cells are involved in the formation of ST and teeth. The three structures; the anterior portion of the pituitary gland, ST, and teeth, share development processes in common (Miletich and Sharpe, 2004; Morotomi et al., 2005).

At birth, the dorsum sellae is entirely cartilaginous and starts ossification in the first year of life (Bonneville et al., 1989). During infancy, a slight elongation of the ST may go together with the enlargement of the head size. The deposition of bone on the dorsum sellae is complete at age 4 (Berger et al., 1976). Resorption starts on the distal part of the sella floor and on the posterior wall, where it continues for a more extended period of time. The anterior clinoid processes are existing and are frequently very large. Fusion of the presphenoid with the postsphenoid is incomplete at birth. A pillar of cartilage isolating the pre- and postsphenoid shows up on the lateral projection as a lucent gap, the intersphenoid synchondrosis. This begins at the tuberculum sellae and spreads forward and downward as far as the undersurface of the sphenoid.

As previously stated, ST dimensions grow with age due to bone remodeling in the sella, and dorsum sellae ossification is complete by age 4. The intersphenoid synchondrosis usually disappears by the age of three, and the presellar area has all of its components. The growth of the sphenoid sinus will then influence its shape. The sellar area develops progressively from the age of four to adulthood, with the development of the sphenoid sinus toward the basisphenoid completed around the age of four. The sphenoid sinus grows linearly between the ages of 4 and 15 years. In almost one-third of cases, the sinus is fully developed at 15 and does not continue to grow. However, beyond the age of 15, it is still fairly developed in half of the instances (Hinck and Hopkins, 1965). During this time, the ST grows completely. Only the anterior clinoid processes are visible because they have already reached their maximum size at the age of 5. Between the ages of 12 and 18, the spheno-occipital synchondrosis closes (Irwin, 1960). The rate of growth slows at the age of 20-30 years until a plateau is reached (Kashio et al., 2017).

4.4.4. ST morphology

The morphology and dimensions of the ST are influenced by both genetic and local factors and vary from one individual to another (Paknahad et al., 2017). These factors include age, gender, and skeletal maxillofacial growth pattern (Alkofide, 2007; Yasa et al., 2017). There are three familiar shapes of the ST; the oval, the round, and the flat. The most common types, however, are round and oval (Jones et al., 2005; Sathyanarayana et al., 2013). In the lateral projection, the ST mostly (in about 60% of the observed cases) appears oval. However, it may take a round shape in one-fourth of the examined people. It may be flat in less than 20% of the cases.

Generally, the thickness of the ST floor is around 1,0 mm and less than 0,5 mm in about half of the examined specimens (Renn and Rhoton, 1975). The dimensions of the ST are assessed by linear, area, and volume measurements using 2D- or 3D (Axelsson et al., 2004; Alkofide, 2007; Meyer-Marcotty et al., 2010; Ize-Iyamu, 2014; Silveira et al., 2020). Cephalometric radiographs can be used to determine ST size using either linear or area and volume measurements. Typically, it ranges in size from 4 to 12 mm vertically, from 5 to 16 mm for the anteroposterior dimension (Choi et al., 2001; Sathyanarayana et al., 2013). The sella height anteriorly is bigger in females by 0,5 mm. There is also a significant relation between linear/area dimensions and age (Andredaki et al., 2007).

4.4.5. Types of ST

Axelsson et al. classified ST based on its cephalometric morphological appearance into six categories: (a) normal ST; (b) irregular dorsum sella; (c) oblique anterior wall; (d) sella turcica bridging (STB); (e) double contoured sella; and (f) pyramid-shaped dorsum sella (Axelsson et al., 2004).

They reported that normal ST was the most prevalent with sex differences in the incidence; females 65% and males 71%. In their study, Chauhan et al. found that

normal ST was the most common type, followed by the oblique anterior wall at 28% and 23%, respectively (Chauhan et al., 2014).

4.4.6. ST dimensions

The linear measurements of ST were reported using the methods of Silverman (1957), Di Chiro (1960), and Kisling (1966). A line depicted from the TS to the remotest point on the posterior inner wall of the fossa represents the largest antero-posterior diameter or the width (W). The diameter is calculated by measuring the distance from the farthest point on the fossa's posterior wall to the tuberculum sella. The length (L) of ST is defined as the distance from the TS to the tip of the DS. The depth (D) or height is the longest vertical line from the line above (diaphragm sella) to the deepest point on the floor (fossa).

It should be noted that variations in the ST dimensions in the reported literature exist. The variations are probably attributed to the use of different landmarks, radiographic techniques, and degree of radiographic enlargement. The average length of the ST is about 10,5 mm. The ST ranges from 4 to 12 mm in depth, with an average of 8 mm. Di Chiro (1960) proposed a third parameter of the ST (the width; W) to account for the diversity in pituitary fossa width. That is to say, according to the Di Chiro formula ($V = \frac{1}{2} [L \times D \times W]$), a ST whose area on a lateral view seems small may actually have a large volume. On the contrary, a ST that appears big in lateral view may have an average volume if its floor is narrow. The width ranges between 10 and 15 mm. The maximum and minimum volume or size calculations for ST are 233 and 1092 mm³, with an average of 594 mm³.

Investigation of the relation between the sella area and age demonstrated a positive correlation, meaning pituitary fossa increased in size with age. Beyond 26 years of age, no significant increase in the ST size was seen (Preston, 1979; Choi et al., 2001). Elster et al. (1990) concluded that young adults had marginally but significantly smaller glands than adolescents of the same sex. No statistically significant differences were reported between males and females in all the ST dimensions (Elster et al., 1990;

Alkofide et al., 2007). It has been indicated that measurements of the dimensions of the ST are of no practical value in revealing an increase in the volume of the hypophysis (du Boulay and El Gammal, 1966; Bonneville et al., 1989). Conversely, form alterations and, in particular, localized cortical thinning are much better signs of the existence of a suspected intra-sellar tumor.

In orthodontics, the ST is considered as a cephalometric anatomical landmark (Kjaer, 2015). The structure is used to assess cranial morphology and establish the relationship of the maxilla and mandible with each other or the cranial base (Alkofide, 2007; Meyer-Marcotty et al., 2010).

4.4.7. ST imaging

It is true that conventional plain radiographic examination of the ST is a simple and fast procedure to the pituitary gland itself and its surroundings (Bonneville et al., 1989). However, when there is a clinical basis to suspect hypothalamic-pituitary anomalies, it must be supplemented by a CT scan (Tehiner et al., 2015). CT is helpful in the delineation of the bony margins of the sella. In particular, it is useful in evaluating the osseous alterations due to pathologic processes.

Making distinctive diagnoses can be challenging due to the complexity of the constituents of the sellar and suprasellar region. Knowledge of anatomy differences can help develop distinctive diagnostic information related to clinical symptoms. Dividing this area into the pituitary fossa, cavernous sinuses, and the suprasellar cisterns may prove helpful. Nevertheless, many diseases can include multiple parts of the sellar and parasellar region, and occasionally it is not easy to determine the origin of large tumors and massive disease processes (Schubiger and Haller, 1992). Documentation of normal anatomies, such as the pituitary gland, in relation to the pathology can be beneficial in determining the etiology. Treating pathologic conditions in the parasellar and sellar regions requires perfect neuroanatomy knowledge. The anatomy of the normal state is complicated.

4.4.8. ST bridging

As mentioned before, there are numerous systems for classifying the shape of ST. Among healthy individuals, the prevalence of STB ranged from 3,8% to 13% (Axelsson et al., 2004; Jones et al., 2005). Other research found that approximately 67% of people had a normal appearance and approximately 33% exhibited shape deviations. (Sathyanarayana et al., 2013). Using CBCT images, Bayrak et al. (2019) observed interclinoid ligament calcification in 4,88% of their investigated Turkish patients. However, variations from the usual form of ST might be deceiving because they can be detected in both normal and medically affected patients, such as spina bifida. (Kantor and Norton, 1987). The ligament's ossification between the anterior and posterior clinoid processes is one of the most common ST anatomical alterations (Meyer-Marcotty et al., 2010; Leonardi et al., 2006). That is to say, the anterior and the posterior clinoid processes fuse. According to the Leonardi quantitative scale, calcification of the clinoid processes was categorized into three levels based on sella dimensions:

Level I: No calcification. The length of ST is $\geq 3/4$ of its diameter.

Level II: Partial calcification. The length of ST is $\leq 3/4$ of the diameter.

Level III: Complete calcification. Only the diaphragm sellae is visible radiographically.

Type III alteration is referred to as ST bridging (STB) (Jones et al., 2005). Two types of bridging can be distinguished depending on their radiographic appearance (Saokar et al., 2022); a ribbon-like bridge and a thin bridge anteriorly, posteriorly, or in the middle. STB is the most commonly investigated anomaly of ST. It is a predictor of skeletal and dentofacial abnormalities such as (Dixit et al., 2017) higher angles of incisor inclination and a more retruded mandibular alveolus (Kucia et al., 2014), as well as malocclusion (Motwani et al., 2017; Dasgupta et al., 2018). Hypodontia, tooth transposition, and missing mandibular second premolars are other examples of the syndromes; associated with interclinoidal calcification (Leonardi et al., 2011).

Furthermore, STB occurs among individuals with severe craniofacial disproportion or congenital missing maxillary lateral incisors (Alqahtani, 2020).

4.4.9. ST pathology

Calcification of the clinoid processes, on the one hand, is seen as a normal anatomical variation of the sella if it is not accompanied by symptoms. Therefore, measurements of the sella size and dimensions have been shown to be of no use (Bonneville et al., 1989). On the other hand, this phenomenon is likely linked to numerous disorders. (Kantor and Norton, 1987). Therefore, determining precise dimensions of the ST can be of interest when the development of its pathology is monitored. In these cases, it is preferred to use tomography with constant magnification because it helps directly assess possible alterations and in a reliable comparison of the tomograms (Mahmoud, 1958).

ST varies in the general configuration among individuals. Therefore, it is important to differentiate between these variations and the pathologic abnormalities (Bonneville et al., 1989). Under certain clinical situations, the form and size of the ST are critical. It should be remarked that many variants of the diaphragm sella are possible. These variants play a significant role in pathology. The configuration of ST in a lateral projection relies on the shape of the skull, which can vary from rather a long front to back in persons of the Dolichocephalic and African race to round with a lower anteroposterior diameter in brachycephalic subjects. According to the size of the aditus (the distance between the TS and the tip of the DS), the sella is typically described as "open" or "closed". Typically, when the sella is closed, the dorsum has a distinct forward inclination. Thus, it is vital to differentiate it from the bridged sella, the appearance of which is caused by ossification of the interclinoid ligaments. (See section 4.4.8).

Almost always, any deviation from the typical ST size is attributable to pathology. The most common observation is expansion, which is normally not associated with bone loss. Radiologists have diverse views regarding possible alterations of the ST in

multiparous patients. On the one hand, multiparity does not cause enlargement of the ST, while on the other hand, it frequently produces pituitary fossa expansion (Taveras and Wood, 1976). Nevertheless, others argue that multiparity is a major factor in the formation of an empty ST, where the sella is stretched perpendicularly, and its floor displays a regular and symmetric concavity. Bonneville et al. (1989) draw the conclusion that all viewpoints are valid in the sense that the effects of multiparity on the sella differ significantly. It is interesting to observe that multiparity does not typically alter the radiologic architecture of the ST, although calcification of the carotid siphons alters the general look of the sellar region. In the sellar area of elderly patients, calcified carotid siphons are commonly seen.

It is documented that the most common causes of ST enlargement are intrasellar adenomas (e.g., prolactinoma) (Dostalova et al., 2003) and empty sella syndrome (Weisberg et al., 1976; Ammar et al., 1999). The empty ST is described as an intrasellar displacement of the suprasellar subarachnoid space caused by an incomplete diaphragm sella with compression of the pituitary gland (Bonneville et al., 1989).

4.4.10. ST congenital anomalies

Sellar area anomalies are relatively low. In this context, insufficient pituitary gland maturation may result in an abnormal morphology of the ST (Kjær, 2015). These include poor development of the sphenoid and the sphenoid sinus, resulting in a small ST (Buurman et al., 1978). Also, a small ST is identified in cases of osteopetrosis (Bonneville et al. 1989), where the bones of the sphenoid appear dense and thick. A small ST was seen in patients with severe mental retardation (Bonneville et al., 1989). Compared to healthy subjects, patients with Sheehan syndrome, a case characterized by postpartum pituitary necrosis due to severe hypotension, have significantly lower sella size measured by the Di Chiro formula (Diri et al., 2014).

A short basisphenoid is the result of the genotype altering the morphology of the anterior wall of the ST in people with Down syndrome, which can range from mild depressions in the lower portion of the anterior wall to more severe conditions in which

the anterior wall is completely detached from the posterior wall (Kier, 1971; Kjær, 2015). The dimensions and morphology of the ST can be affected by some conditions, such as Down and Seckel syndromes (Kjær, 2015; Korayem and Alkofide, 2015). Further, according to Kjær (2015), a person with Turner syndrome also has a ST that is larger and more open cranially than average, with or without a cleft in the bottom. The ST has a broad basis in the DS of people with Meckel-Gruber syndrome, together with irregularly shaped notochordal remains (Kjær, 2015).

4.4.11. ST in cleft patients

Morphometric deviations in the ST are connected with severe abnormalities in craniofacial regions (Becktor et al., 2000). Among the common congenital abnormalities of the craniofacial region are the CLP conditions (Nielsen et al., 2005; Alkofide, 2008; Paknahad et al., 2017; Cesur et al., 2018; Yalcin, 2020). Several studies have evaluated the dimensions of the ST in CLP patients using cephalometric images (Alkofide, 2008; Cesur et al., 2018; Sundareswaran et al., 2019; Sinha et al., 2020). These studies have shown that all dimensions of the ST were significantly reduced in cleft patients relative to non-cleft individuals. A few studies have assessed the dimensions of the ST in patients with cleft using CBCT scans. In the CBCT study of Paknahad et al. (2017), all the ST linear measurements were significantly smaller in CLP subjects compared with healthy individuals. Yasa et al. (2017) concluded via CBCT images that the ST length was significantly greater in cleft patients compared with non-cleft individuals. In a more recent study by Yalcin et al. (2020), using CBCTs, they reported that only the ST diameter was significantly lower in the CLP group than in the healthy control group. Contrary to these findings are those reported by Akay et al. (2020), where no statistically significant differences were demonstrated between the cleft and non-cleft groups in the depth, diameter, or length of the ST. The contradictory data could be attributed to differences in age or associated with the imaging technique (2D- or 3D).

Differences were confirmed (Akay et al., 2020) in the ST measurements and morphology between cleft lip and palate patients and skeletal Class I, II, and III

individuals (See section 4.5.3). Although these are in agreement with an earlier investigation (Alkofide, 2007), they are not in line with others (Sinha et al., 2011; Luong et al., 2016; Silveira et al., 2020). These other studies could not confirm a significant correlation in the linear measurement of the ST when classes of skeletal malocclusion were compared. Except for the ST diameter, Canıgür Bavbek et al. (2019) did not find significant differences in ST between unilateral cleft patients and Class I and III individuals. In the literature, no gender influences on ST have been indicated (Alkofide, 2007; Sinha et al., 2011; Paknahad et al., 2017; Yasa et al., 2017; Akay et al., 2020; Yalcin, 2020). However, it was reported that ST was longer in males (Axelson et al., 2007).

As per ST shape, most patients with a cleft exhibited an abnormal appearance of the ST relative to non-cleft subjects (Alkofide, 2008). Sinha et al. (2020) indicated that normal ST morphology was most incidentally observed in non-cleft individuals (56.6%). Sinha group found that the majority of cleft patients showed STB (38%), followed by irregular dorsum sella (17,3%). In two CBCT image studies, the irregular posterior wall ST type was the most spread among cleft-affected individuals (38% to 39,7%) (Akay et al., 2020; Yalcin, 2020). According to the former study, no significant difference was noted in the morphological appearance of the ST between the non-cleft and cleft groups. However, the differences detected between skeletal Class I, II, and III individuals and cleft patients were statistically significant (Akay et al., 2020).

Previously, Becktor et al. (2000) recorded a higher STB rate in individuals with severe craniofacial disfiguration. Double-counteracted sella and bridged ST were not encountered in either the cleft or non-cleft group (Akay et al., 2020). Earlier studies (Abdel-Kader, 2007; Meyer-Marcotty et al., 2010) confirmed a higher ratio of STB in non-cleft Class III individuals. Furthermore, it was indicated that STB significantly occurred more in unilateral cleft patients than in control groups (Sundareswaran et al., 2015).

In reference to the distance between anterior clinoid processes, it was measured in Chinese population by Cheng et al. (2013). The calculated results were 12,16 mm to the right and 12,48 mm to the left of the sagittal midline (Cheng et al., 2013). In healthy

Turkish individuals, it was estimated to be 19,1 mm (Yasa et al., 2017). There were no studies encountered measuring this distance and comparing it between Turkish cleft patients and the corresponding non-cleft individuals (Akay et al., 2020). However, when the interclinoid distance was calculated, they demonstrated a significant difference between cleft patients and non-cleft individuals (Akay et al., 2020).

Moreover, they found a statistically significant difference between the genders; for cleft patients, the distance was longer in females compared to males. Contrary to this, the inter-clinoid distance was higher in the non-cleft control males. The ST length and prevalence of STB, as well as the ponticulus posticus, a bony bridge in the atlas between the lateral mass and the posterior arch, were not influenced by age, sex, and cleft type (Mosavat et al., 2022).

4.5. Malocclusion

4.5.1. Definition

Head and face disorders are very familiar birth defects in all human races. Skeletal malocclusion or “bad bite” is a developmental condition that refers to the distortion of the maxillary and/or mandibular development, where the upper and lower teeth do not align when the mouth is closed. Typically, malocclusion is seen when the teeth are crowded, i.e., the teeth are too large for the mouth- or are crooked. It is one of the most widespread clinical problems (Thilander et al., 2001). The most common cause of skeletal malocclusion is what is known as micrognathia, which means having a small mandible or maxilla (Vettraino et al., 2003). The prevalence of this disorder in the general population is 1 in 1500 live births. This typically occurs alongside other skeletal anomalies such as cleft palates and deformity tongue (glossoptosis).

4.5.2. Development

The probability of birth distortion in orofacial tissues is high because the face structure and development are complicated. Additionally, the formation and growth of this

region of the body are vulnerable to intrinsic and extrinsic perturbations (Rajeshkumar et al., 2016). Skeletal malocclusion results from the deformation of the normal growth and fetal development of the mandible and/or maxilla (Joshi et al., 2014). During fetal development, the forces of the muscles from the stomatognathic system interconnect to change the normal growth forces (Rajeshkumar et al., 2016). As a result of these collaborations, different forms of faces are observed. Particular styles of head and face are also related to specific skeletal and dental occlusion. This might be due to the domination of the germ layer during growth. These normal and/or aberrant alterations in muscle forces form the foundations for the development into various classes of malocclusions (Loudon, 2013). Dental malocclusion, or the misalignment or incorrect relationship between two dental arches while they reach one another when the jaws close, has a number of etiological causes (Thilander et al., 2001). An open bite may develop from long faces, whereas a deep bite may be linked to short faces (Rajeshkumar et al., 2016). It can also be secondary to skeletal asymmetry or transverse skeletal discrepancy.

4.5.3. Classification

The "father of modern orthodontics" is credited with coining the phrase "dental malocclusion"; Edward Angle in 1890 (Gruenbaum, 2010). Angle published the first classification of malocclusion (Riolo and Avery, 2003). The most commonly used method for assessing and differentiating between skeletal and dental malocclusion is the cephalometric technique introduced by Broadbent and Hofrath in 1931 (Broadbent, 1981). Siriwat and Jarabak (1985) searched 500 randomly selected orthodontic children-patients between 8 and 12 years. They found obvious associations between Angle's class of malocclusion and the vertical facial dimensions. A positive correlation between facial morphology and malocclusion was confirmed using the cephalometric technique (Siriwat and Jarabak, 1985; Roy et al., 2012) and clinically measurable morphological parameters (Rajeshkumar et al., 2016).

It has been reported that patients with skeletal malocclusion may experience oral health problems related to dental trauma and mastication troubles as secondary results of

bruxism and teeth crowding (Joshi et al., 2014). Classification of skeletal and dental malocclusions is crucial for diagnosis and treatment planning in practice. The link between the mandibular first molar buccal groove and the maxillary first molar mesiobuccal cusp served as the basis for categorizing malocclusions. The teeth can line up into a proper occlusion when this molar connection is present. A typical overbite, overjet, and congruent maxillary and mandibular midlines characterize the teeth's alignment. The space between the mandibular incisors' labial surfaces and the maxillary incisors' incisal edge is known as the overjet. The term "overbite" describes how much of the maxillary anterior teeth overlap the mandibular anterior teeth when measured vertical to the occlusal plane.

According to Angle's classification, malocclusion falls into three classes based on the location of the upper first molar relative to the lower first molar. The proper molar relation is still there in Class I Malocclusion, but there is crowding, tooth misalignment, and crossbites. The malocclusion is known as a Class II Malocclusion when the molar relationship shows the buccal groove of the mandibular first molar once in occlusion with the mesiobuccal cusp of the maxillary first molar. When the teeth are in occlusion, Class III Malocclusion, where the buccal groove of the mandibular first molar is mesially positioned to the mesiobuccal crossing of the maxillary first molar. The distribution and prevalence of these classes are heterogeneous in different races (Joshi et al., 2014). Importantly, Class III malocclusions are the most problematic to treat, and patients with Class III malocclusion cannot undergo orthognathic surgery for various causes (Pérez Varela et al., 2018; Duarte et al., 2022).

4.6. Surgical Considerations

The possibility of replacing conventional imaging modalities is one of the forces influencing the promotion of CBCT devices to dentists. For instance, replacing cephalometric radiography and panoramic radiography with precisely generated CBCT volumes. Although the concept of replacement appeals to many, concerns have been expressed about the expense to the patient, both financially and in terms of the

dosage change from a "one-size-fits-all" approach to diagnostic imaging (Farman, 2005; Valentin, 2007). Since radiation risk in children is 3 to 5 times higher than in adults for the same dose, the decision to use CBCT imaging in orthodontics should always be cautious and intelligent (Scarfe et al., 2017).

Dental surgeons need full knowledge of some crucial information, such as the complex anatomical relationships and supporting structures of the maxillofacial skeleton. This is especially important for orthodontic planning since it allows you to select the best therapy from a wider range of potential treatment alternatives. For instance, following a septum within a more or less longitudinal track on a tomogram may go lateral to the carotid groove rather than directly to the floor of the sella. Additionally, it's important to consider the possibility of an upright chiasmatic sulcus to avoid confusing the tuberculum sellae with the limbus sphenoidale. A cerebrospinal fluid fistula results from surgically perforating the skull base above the tuberculum (above the diaphragma sellae) (Rothman et al., 1976). The sinus wall around the optic eminence must be strictly respected because it is very fragile.

The incidence rates of STB differ across populations. Anatomical and radiographic research reported that the presence of STB scales from 5,5% to 22% in normal individuals (Kantor and Norton, 1987; Becktor et al., 2000; Axelsson et al., 2004). The incidence of STB was also observed to be influenced by the malocclusion pattern. According to Jones et al. (2005), patients who were treated with a combination of surgical orthodontics experienced bridging 16,7% more frequently than patients receiving orthodontics alone (7,3%). Saudi (Abdel-Kader, 2007) and Turkish (Marsan and Oztas, 2009) participants were monitored for the presence of an STB in connection to the three skeleton classes. Orthognathic-surgical Saudi patients with a skeletal Class III malocclusion (10,71%) and orthodontic patients with a Class III malocclusion (7,14%) both showed a higher prevalence of ST bridges. Bridging affected 18% of Class III courses in the Turkish population, compared to 5% of Class I subjects. These results were quite in line with another study by Meyer-Marcotty et al. (2010), in which bridging was present in 16,8% and 9,4% of individuals with skeletal Class III and Class I malocclusion, respectively. Class III malocclusions and dental anomalies had a high STB rate (Sathyanarayana et al., 2013). Similar to this, Japanese patients with

cleft and tooth agenesis had a higher frequency of bridging (Sinha et al., 2020). There were 159 people in Taiwan, and the total rates of complete and partial bridging were 6,6% and 56,9%, respectively (Chou et al., 2021). In this study, partial bridges were more prevalent in females (62,4% versus 49,2%), whereas complete bridges were more common in males (9,1% against 4,8%). Different craniofacial skeletal patterns did not significantly differ in the rates of STB or the ST dimensions (skeletal Classes I, II, and III).

In a Yemeni population (AL Mohana et al., 2021), STB was highly prevalent (35,9%). The three skeletal patterns, Class I (17,1%), Class II (18,9%), and Class III (20%), had nearly comparable rates of full ST. The incidence of dental abnormalities in Polish patients aged 6–15 years with ST abnormalities was 16,98%, compared to individuals with normal sella, it was 3% (Jankowski et al., 2021). No studies have looked at the worldwide prevalence of STB despite the significant effects of STB during neurosurgery (Mosavat et al., 2022), as it changes regional anatomy. Cuschieri et al. (2022) discovered in a recent review that the worldwide incidence of STB (26,54%) was greater than previously believed. Radiography of people with and without comorbidities, males and females, as well as of partial, complete, unilateral, and bilateral bridging, were all included in the survey. They recommended that "because of its significant occurrence and impact on the regional anatomy, anatomical and embryological textbooks should consider including material on STB in their textbooks".

5. MATERIALS and METHODS

5.1. Ethical Approval

This thesis study was approved by Clinical Research Ethics Committee at the Faculty of Medicine at Marmara University with the protocol number of '09.2022.73' and the project title of 'A Three-Dimensional Evaluation of Sella Turcica in Unilateral Cleft Lip and Palate Patients Diagnosed with Skeletal Class III Malocclusion'.

5.2. Sample Size

G*Power software (version 3.1.9.2, Heinrich-Heine-University Düsseldorf, Germany) was used for sample size calculation based on a previous study (Alkofide et al., 2007). Each group should include 30 patients for 80% power, with a difference of 1,35 mm between the groups in terms of sella width ($\alpha = 0,05$).

5.3. Sample Selection

This retrospective study was performed on CBCT images and cephalograms. The records were derived from patients treated in the Department of Orthodontics, and Oral, Dental, and Maxillofacial Radiology Department, Faculty of Dentistry, Marmara University. The files and records in the archive system were searched to select the sample of this study according to the following inclusion criteria:

- Unilateral CLP patients with skeletal Class III relationship.
- Healthy patients with skeletal Class III relationship.
- Patients' ages between 12 and 21 years old.

Moreover, the exclusion criteria were:

- History of any craniofacial anomalies or systemic disease (except for CLP).

- The presence of pathology in the region of sella turcica and the pituitary gland and a positive history of previous combined surgical-orthodontic treatment.
- Patients using hormonal medications or corticosteroids, suffering from nutritional deficiencies or endocrinal disturbances, and having significant anatomical variations in the sella turcica region.
- CBCT images of patients who did not give a clear reproduction of the sella turcica.

CBCT images were chosen randomly from the records of patients who were evaluated for impacted wisdom teeth or canine, dentoalveolar analyses, possible bone lesions, etc. The 3D images of non-syndromic subjects with CLP and healthy patients were acquired before orthodontic treatment. Skeletal Class III malocclusion was selected based on the A point-nasion-B point (ANB) angle in the cephalometric analysis, where the ANB angle was < 2 . The anteroposterior relationship of the teeth was the foundation for the classification of angles (Riolo and Avery, 2003).

All patients or their guardians had signed informed consent forms as part of the routine process at the Department of Orthodontics. Totally 60 patients were included in the study and divided into 2 groups as UCLP and healthy groups. Both groups consisted of 30 samples including 15 males and 15 females.

5.4. Data Collection and Assessment

CBCT images of high diagnostic quality in which the ST is located within the imaging area (FOV) were used. All CBCT images were obtained using Planmeca® Promax 3D Mid (Planmeca Oy, Helsinki, Finland, 2012) tomography device with a $0,4 \text{ mm}^3$ isotropic voxel and a 0,4 mm section thickness (90 kvp, 10 ma and 36 seconds).

CBCT images saved in Digital Imaging and Communications in Medicine (DICOM) format were visualized using ITK-SNAP (version 3.8.0, University of Pennsylvania, United States).

In addition to CBCT, for each patient, a cephalometric radiograph taken at or around the same period was collected from the archive. The cephalograms were then added to the NemoCeph (version 16.50.0) (Nemotec, Madrid, Spain) cephalometric software and traced by a single examiner to avoid bias.

5.4.1. Segmentation and ST volume measurement on CBCT

With regards to the bony landmarks that were used to identify the borders of region whose volume was measured, they were similar to those described by Silverman (1957), Di Chiro (1960), and Kisling (1966) (see section 4.4.6.). However, the two methods differ in the technique used to measure the volume. Unlike Silverman-Di Chiro-Kisling method that implies linear measurements on a two-dimensional image for a three-dimensional structure, our proposed method measures the volume of the region in all three planes using segmentation technique. The measured region was bounded anteriorly by TS wall that extends from the sella floor and elevates upwards where the diaphragm is fused. The fusion point has a protrusion-like appearance. The superior border therefore, started from this fusion point and extended posteriorly towards the highest point on the anterior wall of DS. This represented the highest border that segmentation reached (Figure 1a). The floor of ST, that anatomically spreads between the TS anteriorly and DS posteriorly, connecting them together, represented the lower border of the segmented region (Figure 1). However, the lateral extensions (right and left sides) of the segmentation were terminated at the first slice where the DS wall separates from the sellar floor (Figure 1b and 1c). Prior to segmenting the region of interest, segmentation of the bony structures surrounding it was completed to ensure accuracy and precision of the results (Figure 3).

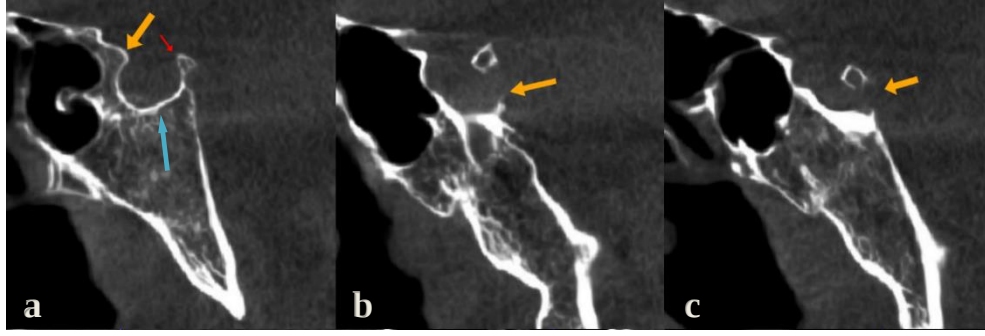


Figure 1. The bony landmarks used to define the borders of the measured volume, shown in sagittal view: a) the orange arrow points at the fusion of the diaphragm with the TS, the red arrow points at the highest point on the anterior wall of DS (which is where diaphragm fuses to the DS), the blue arrow points at the floor of the ST. b) and c) the orange arrows show the lateral extensions of the segmentation on the right and the left sides, respectively (the separation between the floor and the DS).

It is also worth mentioning that ITK-Snap has a ROI (Region of Interest) built-in feature, which basically borders the region of interest by a square (Figure 2). This square, borders the region in all three planes; laterally, antero-posteriorly, and vertically; meaning it functions as a cube. If an adjustment to any of the sides of this square is made, the change also takes place in the other 2 views. Segmentation then takes place in three dimensions only within the borders of a square. Also, if any discrepancy was seen between the previously defined anatomical borders, and the ROI square borders, the manual mode (Paintbrush Mode) was used to either segment any area missed by the software, or remove any extra structures segmented by the software.

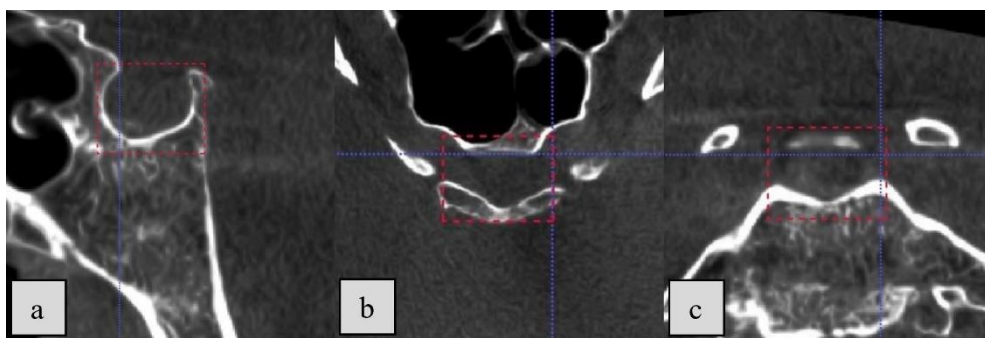


Figure 2. ROI square (in red) shown in a) sagittal, b) axial, and c) coronal views.

Semi-automatic segmentation of the sphenoid bone, including the ST area, was performed by applying the classification pre-segmentation mode, which is the most accurate and reliable method according to the creators of the software (<http://www.itksnap.org/> Accession date: 9 January 2022). Every segmented part was then re-evaluated for accuracy, and if needed, corrections were made using the Paintbrush Mode, which is used to perform manual segmentation (Figure 3).

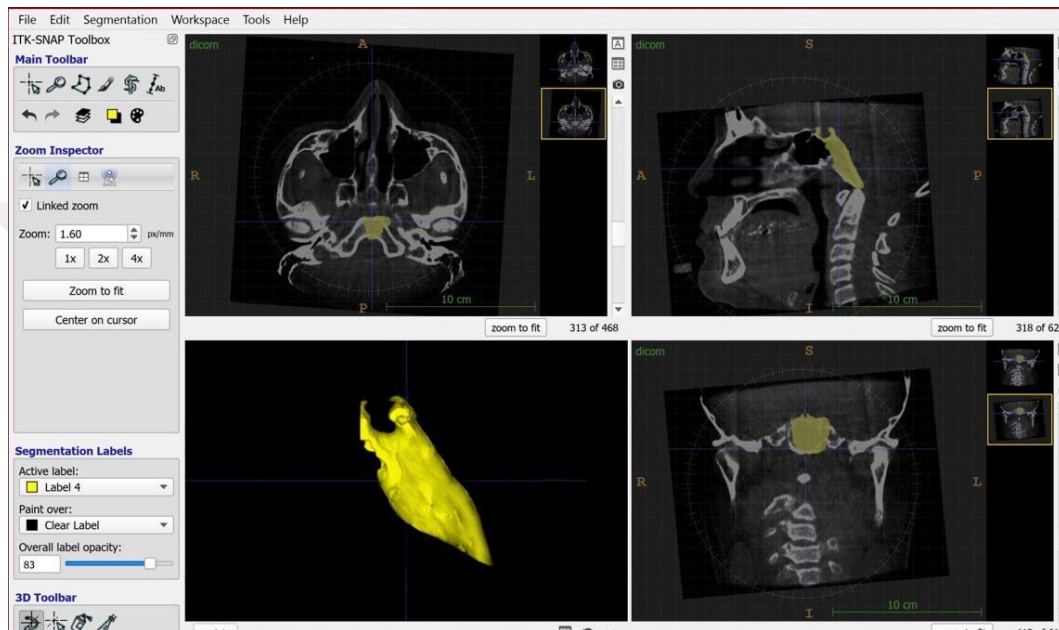


Figure 3. In the display of the ITK-SNAP workspace, three separate views of data (sagittal, coronal, and axial) can be seen, along with a fourth separate 3D view of the segmented structure.

After that, anatomical 3D models were created for the ST (Figure 4), and the resulting-space volume confined between the TS and DS was calculated in cubic millimeters for each sample patient. In order to do that, segmenting the space area using a different label color was done using the classification pre-segmentation mode (Figure 4). Moreover, the Paintbrush Mode was used to assess the segmented parts and make any necessary corrections. The ability to work around and view the segmented structures helped in the re-evaluation process to produce precise 3D models (Figure 5). All segmentations and measurements were done by a single operator to avoid bias.

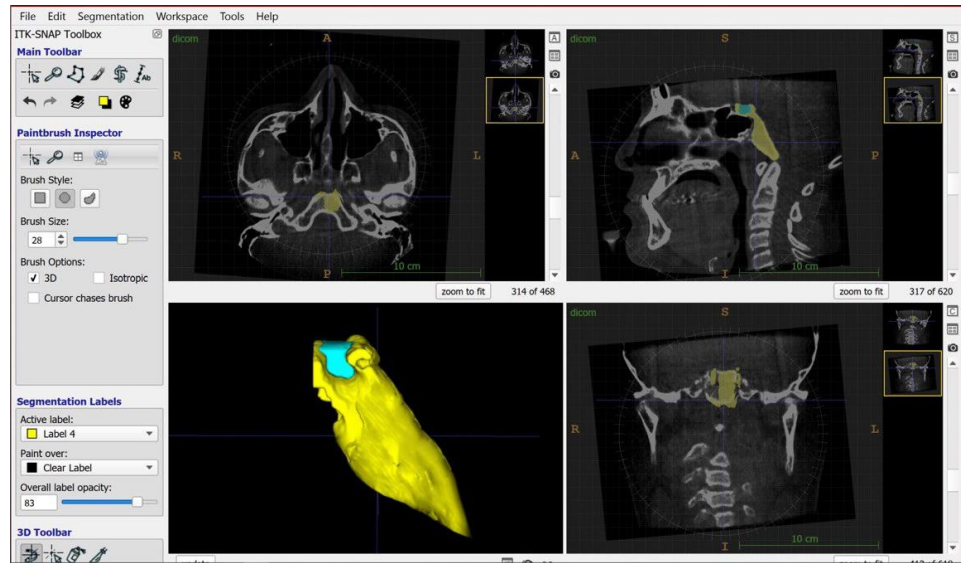


Figure 4. Measuring the volume confined between TS and DS. Segmentation of the sphenoid bone (Yellow) can be seen, while segmentation of the space confined between TS and DS is shown in color Blue.

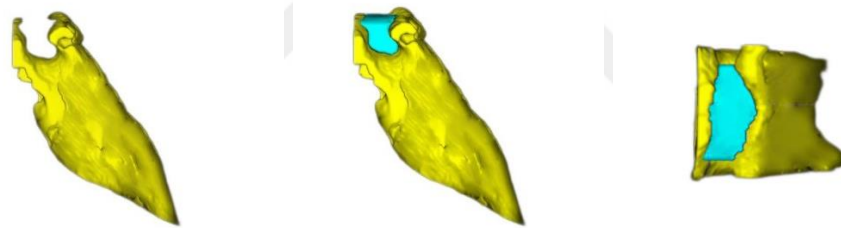
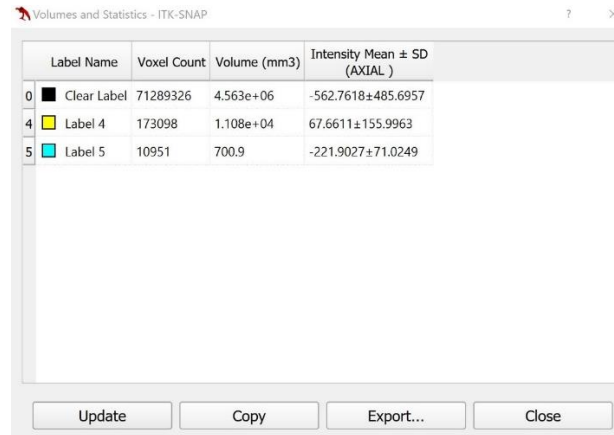


Figure 5. Different views of the segmented part.

Additionally, ITK-SNAP provides the ability to compute volume and other statistics related to segmented structures (Figure 5). In the end, volumes and statistics were saved in a pre-specified text files, then used for this study.



	Label Name	Voxel Count	Volume (mm3)	Intensity Mean $\pm$ SD (AXIAL)
0	Clear Label	71289326	4.563e+06	-562.7618 $\pm$ 485.6957
4	Label 4	173098	1.108e+04	67.6611 $\pm$ 155.9963
5	Label 5	10951	700.9	-221.9027 $\pm$ 71.0249

Figure 6. Volumes and Statistics table in ITK-SNAP.

5.4.2. Cephalometric measurements

Landmarks were identified on the cephalograms using the digital tracing software NemoCeph, which formed reference planes connecting points. The measurement angles and values were then constructed accordingly.

In order to assess the relationship between the ST volume and the vertical skeletal pattern in both groups, five different vertical parameters were selected to be recorded, that includes GoMe-SN, FMA, Facial-axis, Y-axis, and Jarabak (Table 1) (Figure 7).

Table 1. Description of the vertical measurements performed on cephalometric radiographs.

FMA (°)	The angle between Frankfort Horizontal plane and Mandibular plane (Go-Me)
GoMe-SN (°)	The angle between Mandibular plane and Sella-Nasion plane
Facial-axis (°)	The angle formed by Ba-N (Basion-Nasion) plane and the Ptm-Gn (Pterygomaxillary fissure-Gnathion) plane
Jarabak ratio	The ratio of posterior facial height (Sella-Gonion) to anterior facial height (Nasion-Menton)
Y-axis (°)	The angle formed by Frankfort Horizontal plane and SGn (Sella-Gnathion) plane

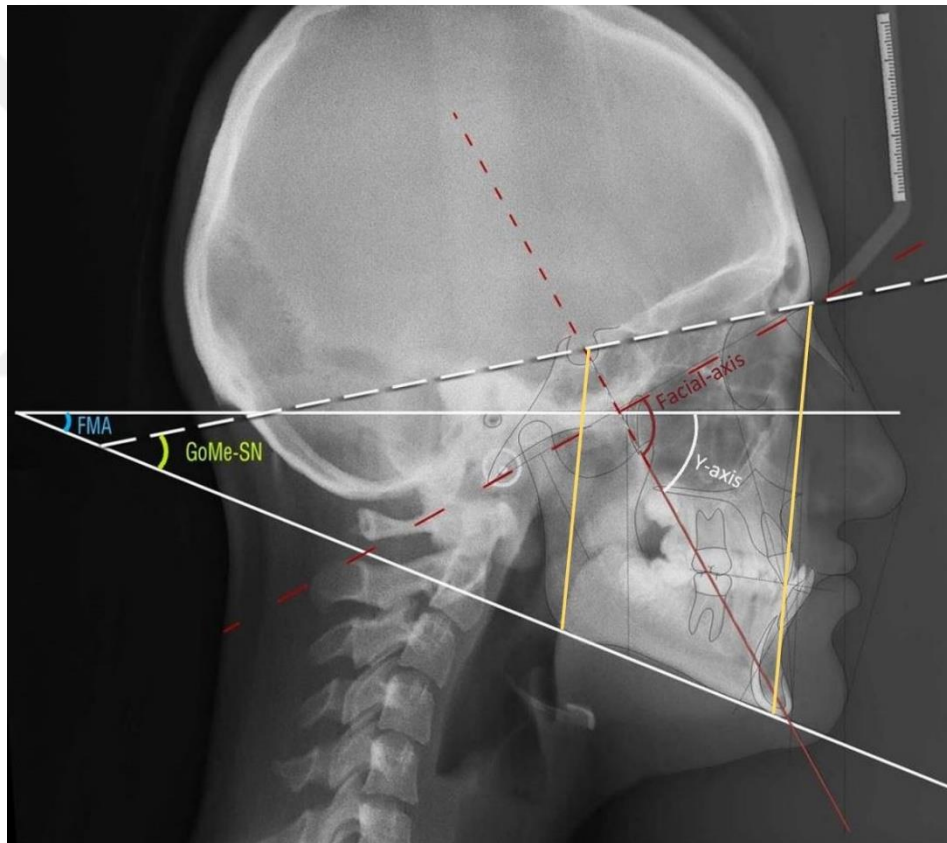


Figure 7. The vertical measurements performed on cephalometric radiographs.

Additionally, four different sagittal relationship indicators were studied in relation to the ST volume, and those are SNA, SNB, ANB, and Wits appraisal (Table 2).

Table 2. Description of the sagittal measurements performed on cephalometric radiographs.

SNA (°)	The angle between points Sella (S), Nasion (N), and (A)
SNB (°)	The angle between points (S), (N), and (B)
ANB (°)	The angle between points (A), (N), and (B)
Wits appraisal (mm)	The distance between perpendiculars dropped from points (A) and (B) to the functional occlusal plane

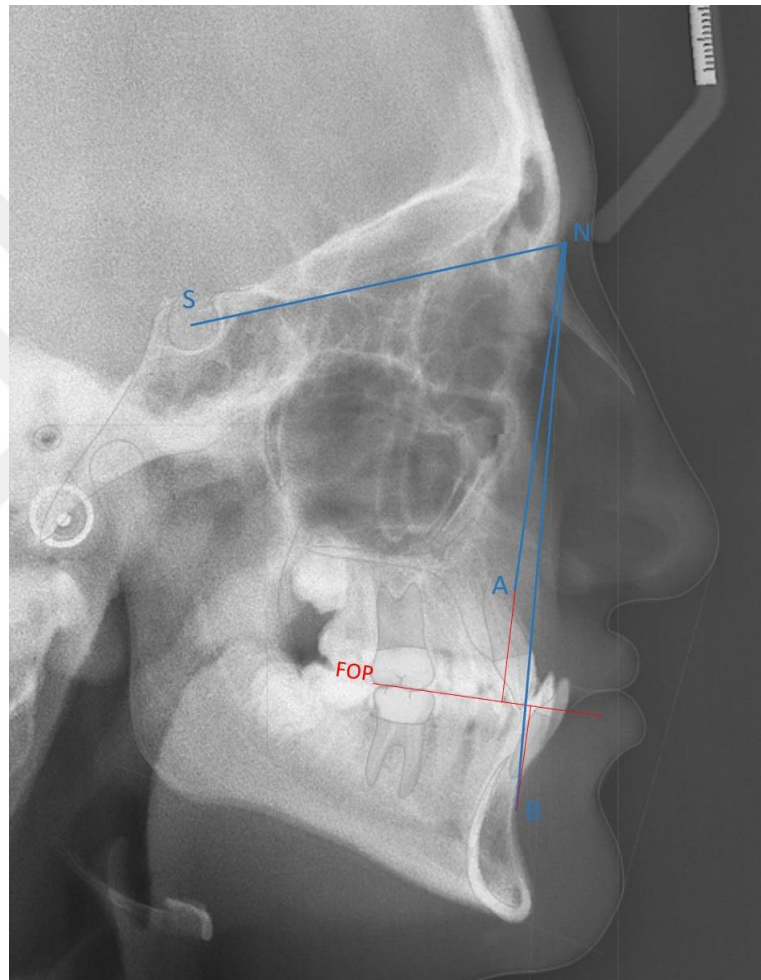


Figure 8. The sagittal measurements performed on cephalometric radiographs.

5.5. Statistical Analysis

Statistical methods were used to analyze the data, including the calculation of descriptive statistics such as the frequency and percentage for categorical variables,

the mean, the median, the standard deviation (SD), frequency, and the minimum and maximum for the continuous variables.

Intra-observer method error was investigated by remeasuring 53% of our sample (32 subjects) under the same conditions three weeks after the initial measuring. For the analysis of reliability regarding parameter measurements, standard error of measurement (SEM) was calculated, as well as paired t-test. Pearson correlation test was performed to evaluate the associations between specific corresponding variables. An independent t-test was done to compare the intra- and inter-group volumes.

An alpha level of 0,05 was used for all statistical tests, and all were two-tailed. All calculations and analyses were done with the IBM SPSS (Statistical Package of Social Sciences) software (version 26.0, Armonk, NY: IBM Corp).

6. RESULTS

6.1. Reliability Test

The method error for the examined variables is displayed in Table 3. Intraclass Correlation Coefficient was found to be close to 1 for all the measurements. All the measurements were found to be reliable. The errors were non-fatal and did not affect the results of our measurements

Table 3. Single observer's agreements between repeated measurements.

	Intraclass Correlation	95% CI		p
		Lower Bound	Upper Bound	
Volume	0,986	0,971	0,993	0,00
FMA	0,962	0,921	0,982	0,00
GoMe-SN	0,993	0,983	0,997	0,00
Facial-axis	0,993	0,984	0,997	0,00
Jarabak ratio	0,999	0,998	0,999	0,00
Y-axis (°)	0,995	0,990	0,998	0,00
SNA	0,962	0,921	0,982	0,00
SNB	0,993	0,983	0,997	0,00
ANB	0,908	0,895	0,921	0,00
Wits appraisal	0,998	0,992	0,999	0,00

6.2. Demographic Characteristics of the Patients

Descriptive statistics were conducted to describe the characteristics of the total study sample and stratified by the presence of UCLP. The total sample recruited for the study was 60 patients. All subjects were Caucasian and from the same geographic area (Turkey). The mean age for the total sample was $14,38 \pm 2,32$ years (between 12-21 years). The mean ages for UCLP and healthy participants were $14,44 \pm 2,22$ and $14,88 \pm 2,61$, respectively (Table 4)

Table 4. Demographic characteristics of the patients.

Groups	UCLP Group mean $\pm$ SD	Healthy Group mean $\pm$ SD	Total mean $\pm$ SD
Age (years)	14,44 $\pm$ 2,22	14,88 $\pm$ 2,61	14,38 $\pm$ 2,32

6.3. Intra-Group ST Volume Comparison and Correlations of ST Volume with Age, Vertical, and Sagittal Cephalometric Measurements:

Pearson's correlation test (r) was used to examine the associations between the volume of ST and the measured cephalometric variables. This correlation coefficient is a single number that measures the strength and the direction of the linear relationship between two continuous variables. Values can range from -1 to +1 and are interpreted in the following manner:

r= 0,8-1,0: A very strong positive relationship.

r= 0,6-0,8: A strong positive relationship.

r= 0,4-0,6: A moderate positive relationship.

r= 0,2-0,4: A weak positive relationship.

r= 0,0-0,2: A very weak positive relationship.

$r = 0,0$: No relationship.

The same is applicable for negative (r) values as for the strength of the relationship, except it indicates a negative relationship in terms of direction between the values.

Also, the pearson correlation test was used to assess the relationship between ST volume and age.

6.3.1. Healthy group results

The values for the measurements performed both on CBCT and cephalometric radiographs are shown in details in Table 5. There were no significant differences between males and females regarding cephalometric and ST volume values.

Table 5. The vertical, sagittal and ST volume measurements for healthy group.

Variables	Female mean $\pm$ SD	Male mean $\pm$ SD	p	Total mean $\pm$ SD
Vertical				
GoMe-SN (°)	40 $\pm$ 4,81	35,87 $\pm$ 7,48	0,083	37,93 $\pm$ 6,53
FMA (°)	30,33 $\pm$ 4,95	27,6 $\pm$ 7,13	0,233	28,97 $\pm$ 6,19
Facial axis (°)	86,73 $\pm$ 4,11	87,87 $\pm$ 6,37	0,567	87,3 $\pm$ 5,3
Y axis (°)	59,33 $\pm$ 4,27	59,27 $\pm$ 4,03	0,965	59,3 $\pm$ 4,08
Jarabak ratio	66,01 $\pm$ 3,77	68,5 $\pm$ 5,85	0,176	67,26 $\pm$ 5
Sagittal				
SNA (°)	77,13 $\pm$ 3,74	79 $\pm$ 5,06	0,260	78,07 $\pm$ 4,47
SNB (°)	79,47 $\pm$ 3,54	81,13 $\pm$ 5,54	0,335	80,3 $\pm$ 4,65
ANB (°)	-2,2 $\pm$ 2,86	-2,66 $\pm$ 2,96	0,606	-2,43 $\pm$ 2,42
Wits (mm)	-8,52 $\pm$ 2,53	-8,22 $\pm$ 2,46	0,745	-8,37 $\pm$ 2,46
ST volume (mm³)	702,03 $\pm$ 180,63	897,99 $\pm$ 335	0,056	800,01 $\pm$ 282,6

Independent Samples t-test. * $p < 0,05$

The yielded analysis findings suggested that the mean volume of ST (800,01 mm³) did not show any statistically significant correlations with the vertical and sagittal parameters except the Wits appraisal (Table 7).

On the other hand, a statically insignificant negative correlation was noted between ST mean volume and Facial axis, SNA, SNB mean values ($p>0,05$), as shown in Table 6.

Table 6. Correlation results between ST volume and corresponding cephalometric parameters in the healthy group.

	N	Volume	
		Pearson Correlation	P
GoMe-SN	Total	0,156	0,411
	Males	0,392	0,148
	Females	0,052	0,854
FMA	Total	0,031	0,869
	Males	0,247	0,374
	Females	-0,213	0,446
Facial-Axis	Total	-0,176	0,352
	Males	-0,392	0,148
	Females	0,231	0,407
Y-Axis	Total	0,09	0,635
	Males	0,414	0,125
	Females	-0,435	0,105
Jarabak	Total	0,083	0,664
	Males	-0,064	0,821
	Females	0,156	0,580
SNA	Total	-0,141	0,457
	Males	-0,225	0,419
	Females	-0,272	0,328
SNB	Total	-0,273	0,145
	Males	-0,491	0,063
	Females	-0,008	0,979
ANB	Total	0,195	0,303
	Males	0,418	0,121
	Females	-0,334	0,224
Wits	Total	0,195	0,978
	Males	0,280	0,313
	Females	-0,556*	0,032

* Correlation is significant at the 0,05 level (2-tailed).

In healthy females, ST volume and Wits showed a negative correlation (moderate), and this correlation was statistically significant ($P \leq 0,05$) as seen in Table 7.

Table 7. Correlation results between volume and age in the healthy group.

	N	Volume	
		Pearson Correlation	P
Age	Total	0,473*	0,008
	Males	0,411	0,128
	Females	0,682**	0,005

* Correlation is significant at the 0,05 level (2-tailed).

** Correlation is significant at the 0,01 level (2-tailed).

In an attempt to find the association between ST volume and age, a moderate positive relationship that is statistically significant was seen ($P \leq 0,05$), as shown in Table 7. Furthermore, ST volume showed a strong significant increase with age in healthy females ($P \leq 0,01$).

6.3.2. UCLP group results

The values for the measurements performed both on CBCT and cephalometric radiographs were shown in details in Table 8. There were no significant differences between males and females regarding cephalometric and ST volume values.

Table 8. The vertical, sagittal and ST volume measurements for UCLP group.

Variables	Female mean±SD	Male mean±SD	p	Total mean±SD
Vertical				
GoMe-SN (°)	39,67±7,83	38,73±6,8	0,730	39,2±7,23
FMA (°)	30,27±6,53	29,47±6,2	0,734	29,87±6,27
Facial axis (°)	85,67±5,86	85,8±5,1	0,947	85,73±5,4
Y axis (°)	62±3,59	60,93±5,49	0,534	61,47±4,59
Jarabak ratio	66,47±3,54	65,59±5,23	0,597	66,03±4,41
Sagittal				
SNA (°)	74,67±4,12	76,2±5,8	0,411	75,43±5
SNB (°)	75,47±4,66	78±6,64	0,237	76,73±5,78
ANB (°)	-0,8±5,06	-1,87±4,94	0,564	-1,33±4,94
Wits (mm)	-2,77±6,34	-4,67±5,85	0,401	-3,72±6,07
ST volume (mm³)	839,37±235,95	983,28±329,83	0,180	911,32±291,12

Independent Samples t-test. *p<0,05

Table 10 showed that there was no statistically significant correlation between the ST mean volume and the vertical and sagittal measurements except the Jarabak value which presented significant correlation with ST mean volume ($P \leq 0,05$) (a strong positive relationship (Table 10).

Table 9. Correlation results between volume and corresponding cephalometric parameters in the UCLP group.

	N	Volume	
		Pearson Correlation	P
GoMe-SN	Total	0,411	-0,257
	Males	-0,240	0,389
	Females	-0,276	0,320
FMA	Total	0,869	-0,275
	Males	-0,246	0,378
	Females	-0,308	0,264
Facial-Axis	Total	0,352	0,16
	Males	0,275	0,321
	Females	0,036	0,899
Y-Axis	Total	0,635	-0,307
	Males	-0,390	0,150
	Females	-0,071	0,802
Jarabak	Total	0,664*	0,034
	Males	0,304	0,271
	Females	-0,064	0,821
SNA	Total	0,457	0,217
	Males	0,504	0,055
	Females	-0,439	0,102
SNB	Total	0,145	0,235
	Males	0,427	0,113
	Females	-0,283	0,307
ANB	Total	0,303	-0,086
	Males	-0,025	0,929
	Females	-0,110	0,695
Wits	Total	0,978	-0,197
	Males	-0,262	0,346
	Females	0,160	0,570

* Correlation is significant at the 0,05 level (2-tailed).

Additionally, when the volume of ST and age were examined for correlation (Table 10), a statistically significant positive relationship was seen ($P \leq 0,05$). Furthermore, ST volume showed a significant increase with age in males who had UCLP ($P \leq 0,05$).

Table 10. Correlation results between volume and age in the UCLP group.

	N	Volume	
		Pearson Correlation	P
Age	Total	0,363*	0,049
	Males	0,551*	0,033
	Females	0,018	0,950

* Correlation is significant at the 0,05 level (2-tailed).

6.4. Inter-Group Comparison of Sella Turcica Volume

A comparison between the ST volume of UCLP and healthy groups was made, and the results showed no significant difference between males, females or total groups (Table 11).

Table 11. Comparison of the ST volumes of the males, females and total between the healthy and UCLP groups.

		Healthy mean±SD	UCLP mean±SD	p
Volume (mm³)	Female	702,03±180,63	839,37±235,95	0,084
	Male	897,99±335	983,28±329,83	0,488
	Total	800,01±282,6	911,32±291,12	0,138

Independent Samples t-test. *p<0,05

Moreover, regardless of being healthy or UCLP groups, the difference between the ST volume of all males included in the study and the ST volume of all females included in the study was statistically significant ($P \leq 0,05$) (Table 12).

Table 12. Difference between the ST mean volumes of males vs. females in the entire sample.

	Female (Healthy+UCLP) n=30 mean±SD	Male (Healthy+UCLP) n=30 mean±SD	p
Volume (mm³)	770,7±217,96	940,63±329,51	0,022*

Independent Samples t-test. *p<0,05

7. DISCUSSION and CONCLUSION

This retrospective study aimed to evaluate the volume of ST in UCLP patients compared to a healthy (non-cleft) control group. Both groups had the same number of male and female participants, and the age was within the same range.

Additionally, in hopes of understanding if there is any relationship between ST volume and skeletal craniofacial growth, one objective of this study was to look at the correlation between ST volume and the corresponding skeletal growth. In other words, it aimed to assess if a change in the volume would affect the skeletal growth in either direction, and if any relation existed, to what extent the volume and corresponding skeletal values were correlated.

Multiple previous studies examined the size and shape of ST using different methods. Its importance comes from the additional information provided to diagnose many of the pathological conditions that affect the pituitary gland, and syndromes that have an effect on the craniofacial area (Ruiz et al., 2008). Various methodologies have been utilized to examine the ST in past studies, including direct observation of dry skulls, conventional radiographs, and CBCTs and MRIs. However, many of those approaches used in the past had limitations, such as superimposition, distortion, and magnification.

The advancement in diagnostic imaging techniques has offered the ability to assess anatomical structures in a better and more detailed manner. We used CBCT imaging technology, which is commonly utilized in dentistry for diagnosis and treatment planning. Intracranial physiological calcifications are widely chance discoveries in CBCT scans. In clinical investigations relative to CT, CBCT provides superior, more accurate, and sensitive anatomical images, especially when physiological calcification of the intracranial space is recognized when intracranial physiological calcification is identified (Yasa et al., 2017; Chou et al., 2021). Up to date, only a few studies (Canıgür et al., 2019; Akay et al., 2020; Gulsun et al., Silveira et al., 2020; Yalcin, 2020; Chou et al., 2021) have measured the ST dimensions and shape using CBCT mainly concentrated at various skeletal relations. Turkish researchers used CBCT images and

demonstrated that the ST's measurements vary significantly with age (Yasa et al., 2017). However, they did not find statistical differences in the ST dimensions between males and females. Another group in Turkey stated that interclinoid distance and dimensions of ST did not deviate significantly in various skeletal relations (Akay et al., 2020). Other researchers investigated Turkish Class I or Class III adult females (Marsan and Öztas, 2009). They found a higher STB incidence rate in the Class III group. However, no significant differences in ST dimensions were found between the classes. The results of a study conducted on Brazilian patients found no statistically significant difference in the size of the anterior cranial base between Classes II and III, confirm this (Silva et al., 2020). Additionally, there were no significant differences in the frequency of STB and ST readings across different craniofacial skeletal types (skeletal Classes I, II, and III). Differences in the study's ethnic groups can also cause discrepancies in the study's results. Additionally, differences between reports could be attributed to the use of different reference landmarks representing the same dimension, superimposition of corresponding anatomic regions, different magnification, and the variation in the composition of study samples (Yasa et al., 2017).

Our study has a sample of 60 patients that was created after the inclusion and exclusion criteria were applied. The patients were assigned into two subgroups depending on the presence of UCLP: A healthy (non-cleft) group including 30 patients with a mean age of 14,88 years (15 male, 15 female) and a UCLP group including 30 patients with a mean age of 14,44 years (15 male, 15 female). The mean age for both groups was almost similar, as well as the gender distribution.

CBCT scans were viewed using ITK-Snap software. ST was segmented as part of the sphenoid bone from the CBCT images inside the same software. The technique used to segment the specified part was the semi-automatic segmentation of the sphenoid bone, including the ST area, by applying the classification mode, which is the most accurate and reliable method according to the creators of the software (<http://www.itksnap.org/> Accession date: 9 January 2022). All segmented parts were then re-evaluated, and corrections were made, if there were any, using the manual segmentation mode (the Paintbrush tool).

ITK-SNAP is a free versatile tool for image visualization, manual segmentation, and semi-automatic segmentation. The tool was designed to be easy for novice computer users to learn, and it was designed to focus almost entirely on the problem of segmentation. However, over time the tool has gradually been acquiring new features and development. Since 2006, ITK-SNAP has been cited by over 1700 articles, indicating its widespread use by the biomedical imaging community (Yushkevich et al., 2017). The software displays three separate data views in a synchronized way (sagittal, coronal, and axial), which allows the user to depict a target structure's contour. A continuous 3D surface can be derived from the output data, which is composed of a series of 2D contours.

The segmentation creates 3D models beginning with 2D images: it characterizes each voxel according to its nature rather than just its intensity; the segmentation of a structure entails labeling its voxels with a specific label (Ferrari et al., 2012). There are different types of segmentation techniques; this includes manual, semi-automatic, and automatic segmentation. The researchers found no statistically significant differences in paranasal sinus volume determination between manual and semi-automatic segmentation approaches (Tingelhoff et al., 2007). Moreover, the construction of the primary 3D model is enabled by the automatic segmentation method, while semi-automatic segmentation enables the precise ability to distinguish the best border between neighboring structures on a virtual surface (Grauer et al., 2009; El H and Palomo, 2010; Almuzian et al., 2018). Thus, in our study, semi-automatic and manual segmentation techniques were used for extra accuracy of the measurements.

To our knowledge, this is the first study to evaluate CBCT images of ST with a combination of volumes and radiodensity measurement by ITK-SNAP. However, the same software was used by multiple researchers to measure the volume of different anatomical parts of the human body. For instance, it was concluded that the ITK-SNAP software package is reliable and cost-effective for segmenting and measuring airway changes on CBCTs (Almuzian et al., 2018). In addition, it was reported that ITK-SNAP made it possible to segment the pelvic anatomy in 30 patients and found the software reliable for 3D patient-specific reconstruction of the female pelvis prior to

surgeries (Albanesi et al., 2019). However, the need to compare our result to a similar method underlines the need for more studies to ascertain the differences and variability of ST volume within CLP individuals.

Regardless of having the limit of being a 2D picture of 3D structures, cephalometry is, as yet, a commonly involved tool in the diagnosis and treatment planning of cases in orthodontics. Being feasible, easily accessed, reasonable, reproducible, and producing an insignificant radiation dose makes it a reliable and helpful tool.

Continuous improvements in computing technology, combined with clinical advances in dental radiography, resulted in the invention of computer software aiming to perform computerized cephalometric tracing and measurements. The benefits of digital tracing over the manual include reducing mistakes that could happen while defining landmarks and estimating points, lines, and angles. In addition, the digital software automatically calculates linear and angular measurements once the required landmarks have been identified (Tsorovas and Karsten, 2010; Erkan et al., 2012), and it does all that in a less-consuming way.

In the present study, NemoCeph software was used to trace the collected cephalograms digitally. The tracing was done by the same examiner. The linear and angular skeletal, dental, and soft tissue measurements were calculated automatically by the software following the tracing.

For the purpose of the study, five different vertical parameters were selected, including GoMe-SN, FMA, Facial-axis, Y-axis, and Jarabak, as well as four different sagittal relationship indicators: SNA, SNB, ANB, and Wits appraisal.

This retrospective study is not the first to use CBCT to examine the ST to determine its volume. However, it is the first to assess and measure the volume using segmentation techniques. Also, it is the first of its kind to relate the ST volume to various cephalometric readings in a specific skeletal class to check how and to what extent the volume of ST affects craniofacial growth. We calculated the volume in an adult population that fulfilled the inclusion criteria while taking into account that it is

an asymmetrical three-dimensional structure. Our three-dimensional assessment method exhibits strong reliability as well as statistically significant differences or correlations between various factors. Although it resulted in an overall larger means of volumes, it reports more precise measurements with a lower standard deviation than the Di Chiro method, which is based on linear dimensions on a 2D image of a 3D structure. Radiographs were one of the standard techniques used to examine and analyze pituitary diseases at the time of their publication.

The linear measurements of ST were reported using the methods of Silverman et al. (1957), Di Chiro et al. (1960), and Kisling et al. (1966); which relied on lateral cephalometric radiographs to measure the volume with three linear dimensions that are width, length, and depth. After that, much research was done to study ST's anatomical shape and dimension. Understanding the embryonic origin of ST (Kjaer, 2015; Canıgür et al., 2019) may be one reason for the raised awareness about the importance of such studies, and since then, ST volume and shape variations have been linked to syndromes affecting the craniofacial region, pituitary gland pathologies, growth changes and orthodontics (Axelsson et al., 2004). As a result, the authors adopted various new methodologies and imaging techniques to study the ST.

The authors used dry skulls to measure hypophyseal fossa with a mathematical strategy (Venieratos et al., 2005). They concluded that the fossa size measurement is too small to be determined and that direct measurement of its dimensions is impossible and may lead to erroneous results. With the Di Chiro method, they did measure the sella's overall volume, yielding measurements that ranged between 460 and 1570 mm³. In our study, the mean volume for both groups lies within the same range; nearly 800 mm³ of ST volume was measured in the healthy group and 911 mm³ in the UCLP group. The means of volumes in both studies are larger than those calculated in older studies; this may be attributed to the methodology used in which measurements are done on different mediums and the different age ranges of the recruited samples. Another reason that might contribute to this variation is that all patients were diagnosed with Class III malocclusion, which will be discussed later in this text.

A study via CBCT scans done on a Turkish population of cleft patients in comparison to non-cleft individuals that a larger diameter, depth, and length of ST is present in the cleft group of patients, meaning an overall greater volume of ST is present in cleft patients (Yasa et al., 2017). The only significant difference in their study was observed for sella length, without reporting the details of the cleft phenotypes included. A similar result is seen in our study, in which the mean volume of ST is larger in the UCLP group than measured in the healthy group. However, the difference between the two means in our study was not statistically significant. An exception was seen when we compared the volume of ST in the healthy (non-cleft) females and found it larger than that of the UCLP female group. However, that amount was not statistically significant either. On the other hand, a more recent study using CBCTs, reported that only the ST diameter was significantly lower in the CLP group than in the healthy control group (Yalcin et al., 2020).

Moreover, contradictory data are seen when comparing our results to other studies. Several studies have evaluated the dimensions of the ST in CLP patients using cephalometric images (Alkofide, 2008; Cesur et al., 2018; Sundareswaran et al., 2019; Sinha et al., 2020; Antonarakis et al., 2020). These studies have shown that all dimensions of the ST were significantly reduced in cleft patients relative to non-cleft individuals. A few studies have assessed the dimensions of the ST in patients with cleft using CBCT scans. In one CBCT study, all the ST linear measurements were significantly smaller in CLP subjects compared with healthy individuals (Paknahad et al., 2017).

Contrary to these findings, other reserahers reported no statistically significant differences between the cleft and non-cleft groups in the depth, diameter, or length of the ST (Akay et al., 2020). The contradictory data could be attributed to differences in age or differences associated with the imaging technique used (2D- or 3D).

Only a few studies have examined the ST's size and shape in CLP. According to the functional matrix theory, the sella turcica acts as a skeletal unit and can be remodeled depending on changes in hypophysis size and function; according to the researchers who were looking at the relationship between sella turcica size and the hypophysis

(Gopalakrishnan et al., 2015). Growth hormone insufficiency was reported in more than a quarter of the cleft sample who were known to be suturally underdeveloped (Abdollahi-Fakhim et al., 2015). They also connected these discoveries with the concurrent embryological growth of fetal oral cavity and hypophysis, without forgetting the malnutrition factor in these patients particularly.

Additionally, in the literature, gender effect on sella turcica size has been evaluated in healthy individuals. Although multiple studies reported insignificant differences between males and females in terms of ST dimensions (Alkofide et al., 2007; Shah et al., 2011; Paknahad et al., 2017; Yasa et al., 2017; Akay et al., 2020; and Yalcin 2020), in our study, we found that the volume of ST is significantly greater in all of the males than that of all of the females when all patients were separated by gender regardless of the presence of the cleft. Similarly, in a recent study which was one of few to utilize CT scans to measure the ST size by adopting a modified Di Chiro (9 measurements) method, they concluded that women had significantly smaller ST volume than men (Ortega-Balderas et al., 2021). However, other researchers stated that males showed a greater length than females (Axelson et al. 2007). Our method to determine the ST volume showed that it was larger in healthy males than in healthy females. However, the difference was not statistically significant. The variation between these studies may be due to the study samples' varying ages and the timing at which pubertal growth spurt occurs in the two genders up to the age of 15.

Another factor that might determine the size of ST is age. Among our findings, it is seen that ST volume increases with age in the healthy group of patients. Furthermore, although the relationship was significant only in females, it was going in the same direction in the males from the same group. On the other hand, males with UCLP presented increased ST volume with age. These findings come in part with Silverman et al. (1957) and Chilton et al. (1983). They calculated the sella turcica from cephalometric radiographs and found an increase with age and larger volumes in males than in females. However, the former reported that the only exception for the sella volume-age trend is during puberty, as it takes place two years earlier in a more pronounced way in females than in males.

The patients in our two groups have been diagnosed with skeletal Class III malocclusion. The first is the healthy control group, and the second is the study group comprised of UCLP patients. A factor that might contribute to the differences between results among the studies is the skeletal class. Although very few studies have correlated ST size with the skeletal pattern, numerous studies have looked at variations in sella size in various skeletal classes or malocclusions in non-cleft populations. Compared to those with Class I and Class II malocclusion, Alkofide et al. and Shrestha et al. reported a larger diameter of the ST in subjects with skeletal Class III (Alkofide et al., 2007; Shrestha et al., 2018). Soakar et al. found the same results in Class III subjects compared to Class I patients (Soakar et al., 2014). Length, on the other hand, has been reported to be larger in Class III skeletal facial types by some researchers (Valizadeh et al., 2015; Neha et al., 2016; Shrestha et al., 2018). Also, people with Class II malocclusion had a shallower sella turcica than people with Class III malocclusion (Filipovic et al., 2011). Finally, Sathyanarayana et al. and Luong et al. found that ST has a larger volume in Class III individuals than in Class I and II individuals (Sathyanarayana et al., 2013; Luong et al., 2016).

It should be mentioned that an age-associated growth of ST in size is predicted since hypophysis, the basic content of ST, has been proven to increase in size with age (Argyropoulou et al., 1991). Sella follows the somatic growth pattern and increases steadily with age, which may be related to the anterior lobe's function (Silverman, 1957). Furthermore, with the assumption that ST growth is related to maxillofacial growth, considering the embryogenic origin of the hypophysis, it may be possible that orofacial clefts affect the hypophyseal formation. Also, knowing that the anterior lobe of the pituitary is created through Rathke's pouch, which later forms the maxilla and the mandible—followed by further cell differentiation and migration to form the hypophysis (Antonarakis et al., 2020). Therefore, in their report, the authors advocated further investigations to find the link between the growth of ST with that of the maxilla and the mandible.

In their most recent study on UCLP individuals, Antonarakis et al. concluded that sella size is associated with maxillary length and height using cephalometric radiographs (Antonarakis et al., 2022). However, using cephalometric landmarks, we tried to find

the relationship between ST volume and maxillofacial growth in both vertical and sagittal directions. In our results, it was seen that there is a significant negative association between ST volume and Wits appraisal in healthy (non-cleft) female individuals. In our study sample of UCLP patients, we found that ST volume and Jarabak are positively associated. Antonarakis et al. reported that ST area was correlated with basal maxillary length and anterior maxillary height (Antonarakis et al., 2022). Furthermore, Neha et al. also found a correlation between ST dimensions and the maxillary base length (ANS-PNS) (Neha et al., 2016). These results suggest that the volume of ST may be related to craniofacial growth, which determines the maxillo-mandibular skeletal relationship in individuals regardless of the presence or absence of UCLP. This warrants further research and investigation to answer the question, which very few studies were done to answer.

There are some key features that set this work distinct. The first is the application of CBCT technology, and the second is that all measurements were carried out by a single examiner. Third, it is one of the few studies in its field. Although measuring the volume of anatomical structures using the segmentation technique is widely used in the medical field, none of the previous studies used the tool to measure the volume of ST. However, the cross-sectional, retrospective nature of the current study, as well as the sample size, are its limitations. A follow-up would have ideally allowed for a more accurate assessment of the impact of the ST dimensions over the long term on maxillary and mandibular growth. However, the fact that patients receive orthodontic treatment, which may also affect growth, presents a potential challenge for a long-term study. A bigger sample size would have allowed for more powerful analysis, but the advantage of the current sample was its homogeneity because it only had patients with the UCLP cleft phenotype. Lastly, because our method has not been examined by other research or compared to other segmentation software techniques, it might have intrinsic imprecision. A thorough three-dimensional analysis of ST may be used in future studies with a larger sample or construct a follow-up study to compare the readings for each patient to assess the changes in ST volume; although it might be difficult, this may provide a more precise understanding of ST volume changes as well as craniofacial growth over time.

In conclusion, UCLP patients have a larger ST volume than healthy (non-cleft) individuals however the results were not statistically significant. Males presented a greater ST volume than females ($p < 0,05$), regardless of the presence or absence of UCLP condition. Age and ST volume are positively correlated. Regardless of the presence or absence of the UCLP condition, as the age increases, ST volume increases as well. In healthy group, there was a negative correlation between Wits appraisal and ST volume for females. In the UCLP group, no correlation was found between ST volume and cephalometric values.



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9. ENCLOSURES

Enc.1 Ethical committee approval



