

# **Evaluation of Anatomical and Volumetric Characteristics of the Nasopalatine Canal** in Anterior Dentate and Edentulous **Individuals: A CBCT Study**

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he nasopalatine canal (NPC) is a long, narrow, varyingly shaped duct, present at the palatal midline, that links a bony connection between the nasal and oral cavities and involves the nasopalatine nerve and the terminal ramification of the nasopalatine artery, as well as connective tissue, fat, and small salivary glands.<sup>1,2</sup> At the inferior end of the NPC, located under the incisive papilla posterior to the central incisors, is a circular opening called the incisive foramen.<sup>3</sup>

It is important that morphological characteristics, dimensions, and the volume of the NPC, which is the most significant anatomical structure in the anterior maxilla region, should be well known for the purpose of differentiating between normal NPC and NPC pathology

Objective: To examine the nasopalatine canal (NPC) anatomical and volumetric measurements in anterior edentulous (AE) and anterior dentate (AD) individuals and to compare these findings according to sex, age, shape, and severity of resorption in the premaxilla.

Methods: Two hundred cone beam computed tomography images were divided into 2 groups: AE and AD. The diameter, the length of the NPC and the width, the length of the buccal bone anterior to the NPC were measured and recorded. Linear and volumetric measurement results were evaluated in terms of age, sex, dental status, shape, and severity of resorption.

Results: No significant differences were observed between the AE and AD groups in terms of the NPC volume (P = 0.289). In the AE group, the spindle shape had the highest volume, and in the same group, with aging, the volume significantly increased (P = 0.00). The mean NPC volume was found to be statistically significantly larger in males than females (P = 0.02). A statistically significant relation was observed between NPC volume and resorption status.

Conclusion: Severe bone resorption due to sustained edentation complicated implant surgery because of the increase in incisive and nasal foramen diameters and decrease in buccal residual bone dimensions. The NPC volume was found fewer in edentulous patients, and by the resorption, the volume decreased. (Implant Dent 2018;27:474-479)

Key Words: dental implant surgery, bone resorption, incisive foramen

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and of taking protective measures before surgery. Despite there being numerous publications related to the pathology of the NPC region, there are only a limited number of studies dealing with its anatomical variations, size, and morphology.4 At present, to the best of our knowledge, there is only 1 study that has been published on the volume of NPC.<sup>5</sup>

NPC dimensions were found to be highly variable and influenced by age, sex, and the presence or absence of maxillary anterior teeth. Given the tooth extraction results in bone resorption and remodeling of surrounding anatomical structures, it is not surprising that maxillary anterior dental status was found to have an effect on measurements.<sup>5</sup>

Atrophic edentulous anterior maxilla rehabilitation has always been a difficult task for the clinician because of the insufficient quality and quantity of

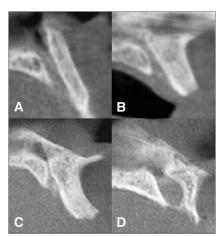


Fig. 1. Four shapes of the NPC observed in cone beam computed tomography images. A, Cylindrical shape (parallel labial and palatal walls). B, Funnel shape (from the hard palate to the nasal fossa increasing anteroposterior dimension). C, Hourglass shape (the narrowest anteroposterior dimension at the midlevel compared with the nasal fossa and hard palate). D, Spindle shape (the widest anteroposterior dimension at the midlevel compared with the nasal fossa and hard palate).

residual bone and the substantial aesthetic and functional demands.<sup>6</sup> One of the more complex issues related to implant planning involves the shortening of the NPC length and the widening of the diameter, which are required as a result of the high resorption rates after tooth extraction in the anterior region.<sup>7</sup>

Before placement of an implant in the anterior maxilla region, it is necessary that a detailed radiographic preoperative examination be conducted to obtain a precise measure of the amount of bone present, to preserve the anatomical structures, and to avoid intraoperative complications, such as perforation of the NPC and buccal bone plate.<sup>8</sup>

Although periapical and panoramic radiographs are regularly used for preimplant treatment planning in clinical practice, the projection geometry of the x-ray beam can lead to magnification and distortion of these 2D images.9 Innovations in imaging systems and the increased use of cone beam computed tomography (CBCT) in dentistry have afforded a more accurate and closer look at anatomical structures, such as the NPC, mandibular canal, and mental foramen.4 In recent years, the use of CBCT in providing three-dimensional imaging has been accepted as an invaluable imaging technique by many dentomaxillofacial researchers because of its lower radiation doses and lower costs compared with computed tomography  $(CT)^{10}$ 

The aim of this retrospective study was to examine the NPC anatomical and volumetric measurements in anterior edentulous (AE) and anterior dentate (AD) individuals and to compare these findings according to sex, age, NPC shape, and severity of resorption in the premaxilla.

#### MATERIALS AND METHODS

The study protocol was carried out according to the principles described in the Declaration of Helsinki, including all amendments and revisions. The ethical approval was granted by the Abant İzzet Baysal University Ethical Committee (institutional review board number: 2017/54).

In the present retrospective study, 200 subjects who presented to the Dentomaxillofacial Radiology Department of Abant Izzet Baysal University Faculty of Dentistry to undergo a required CBCT examination as part of their routine examination and implant treatment planning were enrolled in the study. Patients who had the NPC with evidence of pathology, jaw diseases caused by metabolic, developmental, or inflammatory factors or jaw fractures; had undergone orthognathic surgery; and had poor-quality CBCT images or technical problems related to CBCT were excluded from the study. Images were divided into 2 groups by dental status before conducting evaluations and measurements—group 1: AE patients (between canine regions) and group 2: AD patients (as a control group). Both of the AE (45 men and 55 women) and AD (51 men and 49 women) groups consisted of 100 patients. The CBCT images were obtained with the I-CAT 3D Imaging System (Imaging Sciences International, Hatfield, PA) using the following parameters: 5 mA, 120 kVp,  $16 \times 7$  to 13 cm field of view, voxel size 0.3 mm.

The volume and shape of each canal were identified in both groups. The volume estimates were obtained by stereological analysis according to the

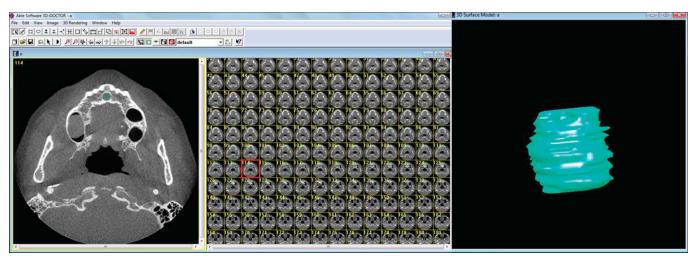


Fig. 2. Representative images from 3D-DOCTOR analysis software.

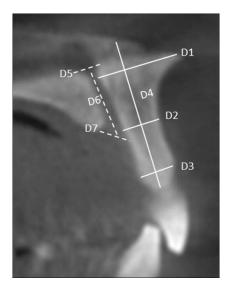


Fig. 3. Measurements of anatomical structures in sagittal sections from the cone beam computed tomography image. Ridge width anterior to the canal; (D1) apical, (D2) middle, (D3) crestal, (D4) the length of buccal residual bone, (D5) the diameter of the nasopalatine foramen, (D6) the length of the nasopalatine canal, and (D7) the diameter of the incisive foramen.

Cavalieri principle. Each canal was separated into consecutive axial section thicknesses of 0.1 mm using 3D-DOC-TOR software (3D-DOCTOR Able Software Corp., Lexington, KY). There were no intervals between sections. The NPC images were outlined manually with the mouse by using a tool called "Free" to mark the region of interest.

The planimetry method was used to calculate the surface area of these sectional images, and the software automatically gave the total volume by multiplying the total surface area and the section thickness. This procedure was followed for all NPCs in every section thickness of 0.1 mm. (Fig. 1). The canal shapes were classified under 4 categories according to their shape on the sagittal sections: cylindrical, funnel, spindle, or hourglass (Fig. 2).

The following standardized measurements were recorded in millimeters on sagittal images for the AD and AE groups: D1, apical ridge width anterior to the canal; D2, middle ridge width anterior to the canal; D3, crestal ridge width anterior to the canal; D4, the length of buccal residual bone; D5, the diameter of the nasopalatine foramen; D6, the canal length from its nasal base to the palatal opening (a horizontal line parallel to the nasal base from the palatal crest); and D7, the diameter of the incisive foramen (Fig. 3).

In the AE group, the NPC was examined in terms of the severity of resorption, and the available residual edentulous ridge was classified under the following 5-point classification system proposed by Lekholm and Zarb: (A) intact ridge form, (B) minor resorption at the alveolar ridge, (C) advanced resorption of the alveolar

**Table 1.** Number and Mean Volume of the NPC According to Sex in the AD and AE Groups

Sex	AE (n)	Mean Volume (mm <sup>3</sup> )	AD (n)	Mean Volume (mm <sup>3</sup> )
Male	45	104.50	51	140.04
Female	55	102.30	49	86.25
Total	100	103.29	100	113.68

Looking at the groups separately, the volume of the canal was larger in the males of the AD group than in the females of the same group (P = 0.001), whereas in the AE group, the canal volume was not statistically correlated with sex (P = 0.774).

**Table 2.** Number and Mean Volume of the NPC According to the Canal Shape in the AD and AE Groups

Canal Shape	AE (n)	Mean Volume (mm <sup>3</sup> )	AD (n)	Mean Volume (mm <sup>3</sup> )
Carrar Criapo	/ \L (II)	TVICATI VOIAITIC (ITIITI )	/ (II)	Weart Velame (mm)
Cylindrical	51	99.16	43	116.92
Funnel	16	69.96	24	105.9
Hourglass	21	108.55	27	118.22
Spindle	12	156.11	6	101.16
Total	100	103.29	100	113.68

In the AE group, statistically significant results were obtained in reference to the relationship between canal volume and canal shape types. Specifically, in this group, a cylindrical-shaped canal was the most common (P > 0.05), whereas the spindle-shaped canal had the largest volume (P = 0.009). In the AD group, there was no relation detected between the canal volume and shape.

**Table 3.** Number and Mean Volume of the NPC According to the Resorption Group in the AE Group

Resorption Groups	Mean Volume n (mm <sup>3</sup> )		
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Α	30	123.62	
В	22	93.87	
С	23	111.65	
D	8	76.04	
Е	17	81.13	
Total	100	103.29	

The highest volume (123.62 mm $^3$ ) was determined to be in the intact ridge form (A), whereas the lowest volume (76.04 mm $^3$ ) was determined in the base of the dental arch initial resorption group (D) with statistical significance (P < 0.05).

# **Table 4.** Statistical Relations of Resorption Groups

Resorption	Р	
А	В	0.006*
Α	С	0.209
А	D	0.038*
А	E	0.004*
В	С	0.229
В	D	0.696
В	Е	0.566
С	D	0.275
С	Е	0.087
D	Е	0.887

Although group C, advanced resorption group, showed no statistically significant difference with the other groups, group A, intact ridge form, exhibited statistically significant difference with the other resorption groups.

\*Statistical differences between groups.

ridge to the base of dental arch, (D) initial resorption of the base of the dental arch, and (E) extreme resorption of the base of the dental arch. For both groups, NPC was compared according to age, sex, canal shape, and dental status.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 20.0, for Windows. Independent samples t test and one-way ANOVA were performed to compare the groups. The post hoc test was used to determine differences between variables. The significance level was set at P > 0.05.

#### RESULTS

The mean age of the AE and AD groups was  $58.3 \pm 8.3$  and  $51.7 \pm 9.2$  years, respectively. There was no

of the Canal D4 (mm) D2 (mm) D5 (mm) D1 (mm) D3 (mm) D6 (mm) D7 (mm) Sex  $5.11 \pm 1.98 \ \ 3.95 \pm 2.06 \ \ 15.57 \pm 3.21$  $11.19 \pm 2.33 \quad 3.37 \pm 1.43$ Female  $10.09 \pm 2.32$  $3.32 \pm 1.17$ Male  $5.3 \pm 1.99 \ \ 3.87 \pm 2.16$  $15.96 \pm 4.65$  $11.77 \pm 2.54$  $3.56 \pm 1.6$  $10.77 \pm 3.18$  $3.9 \pm 1.08$  $5.2 \pm 1.98 \ \ 3.91 \pm 2.1$  $11.47 \pm 2.4$  $11.47 \pm 2.4$  $3.46 \pm 1.51$  $10.42 \pm 2.78$  $3.6 \pm 1.71$ Total Anterior dental status AD  $6.09 \pm 1.2$  $5.4 \pm 1.42$  $18.2 \pm 2.4$  $11.89 \pm 2.21$  $2.92 \pm 1.28$  $11.29 \pm 2.64$  $3.36 \pm 1.17$ ΑE  $4.3 \pm 2.12$  $2.3 \pm 1.47$  $13.32 \pm 3.72$  $11.04 \pm 2.51$  $4.0 \pm 1.54$  $9.5 \pm 2.65$  $3.84 \pm 1.12$ Total  $5.11 \pm 1.98 \ \ 3.91 \pm 2.1$  $15.76 \pm 3.96$  $11.47 \pm 2.4$  $3.46 \pm 1.51$  $10.42 \pm 2.78$  $3.6 \pm 1.71$ Resorption groups  $14.58 \pm 2.1$ Α  $4.04 \pm 2.01 \quad 2.53 \pm 1.56$  $3.77 \pm 1.56$  $3.21 \pm 1.72 \quad 10.18 \pm 2.1$  $4.06 \pm 1.14$ В  $4.87 \pm 3.13 \ \ 2.54 \pm 1.79$  $4.32 \pm 1.92$  $10.82 \pm 2.10$  $9.86 \pm 2.71$  $3.77 \pm 1.47$  $4.77 \pm 1.38$ C  $4.38 \pm 1.81 \quad 2.33 \pm 1.39$  $2.03 \pm 1.70$  $11.26 \pm 2.12$  $3.9 \pm 1.53$  $8.88 \pm 2.71$  $4.63 \pm 1.114$ D  $5.05 \pm 2.11 \ \ 2.10 \pm 1.0$  $3.32 \pm 1.37$  $10.7 \pm 3.83$  $3.36 \pm 1.57$  $9.3 \pm 3.61$  $4.58 \pm 0.78$ Ε  $3.63 \pm 1.48 \quad 2.14 \pm 1.23$  $2.99 \pm 1.76$  $8.61 \pm 2.17$  $3.98 \pm 1.26$  $9.5 \pm 2.6$  $4.96 \pm 0.83$  $11.046 \pm 2.51$  $9.54 \pm 2.65$  $4.31 \pm 2.12 \ \ 2.38 \pm 1.47$  $3.28 \pm 1.72$  $3.6 \pm 1.54$  $4.60 \pm 1.12$ Total Shape of the NPC Cylindrical  $5.35 \pm 2.21$   $3.87 \pm 2.14$  $15.48 \pm 4.5$  $11.54 \pm 2.41$  $3.73 \pm 1.52$  $10.39 \pm 2.78 \ \ 3.51 \pm 1.34$ Funnel  $5.14 \pm 1.62 \ 4.21 \pm 1.92$ 16 + 11 $11.51 \pm 2.69$  $2.73 \pm 1.16$  $10.54 \pm 2.95$   $3.54 \pm 0.7$ Hourglass  $5.22 \pm 1.84 \quad 3.98 \pm 2.24 \quad 16.10 \pm 4.42$  $11.24 \pm 2.33 \quad 3.59 \pm 1.56$  $10.45 \pm 2.76 \quad 3.72 \pm 1.12$ Spindle  $4.54 \pm 1.85 \quad 3.32 \pm 1.96 \quad 15.52 \pm 52$  $11.59 \pm 1.94 \quad 3.34 \pm 1.61$  $10.2 \pm 2.66$  $3.9 \pm 1.17$ Total  $5.2 \pm 1.98 \quad 3.91 \pm 2.1$  $15.76 \pm 3.96$  $11.47 \pm 2.4$  $3.46 \pm 1.51$  $10.42 \pm 2.78$ 3.6 + 1.71

Table 5. Mean Values With SD of Linear Measurements According to Sex, Anterior Dental Status, Resorption Groups, and Shape

Although the mean of D1, D2, D3, D4, and D6 was statistically significantly higher in the AD group; the mean of D5 and D7 was found lower in the AD group compared with the AE group (P  $\leq$  0.05). The incisive foramen mean diameter was statistically higher in the male group ( $P \le 0.05$ ) as the resorption increased (from groups A–E) in the AE group, NPC nasal and incisive diameters increased, and all the other linear measurements decreased. No statistically significant difference was observed between canal shapes according to measurements ( $P \ge 0.05$ ).

statistically significant difference between the AE and AD groups with regard to the canal volume (P =0.289). Age was determined to be unrelated to the canal volume for the AD group (P = 0.149), whereas for the AE group, the mean volume significantly increased with age (P = 0.009). Among the participants constituting both groups, the mean canal volume was statistically significantly larger in males  $mm^3$ ) than in (123.38)females  $(94.74 \text{ mm}^3)$  (P = 0.004) (Table 1).

The observed canal shapes and the mean volumes in the sagittal plane are given for both groups in Table 2. In the AE group, statistically significant results were obtained in reference to the relationship between canal volume and canal shape types ( $P \le 0.05$ ). In the AE group, there was a statistically significant relation between NPC volume and resorption status (P < 0.05). As the resorption increased, NPC volume was gradually decreased in AE patient group (Tables 3 and 4).

Mean linear measurements of the NPC and buccal residual bone were statistically different between the AE and AD groups ( $P \le 0.05$ ), and there was a statistically significant difference between sex groups only in the mean diameter of the incisive foramen (D7)  $(P \le 0.05)$ . NPC volume measurements did not vary statistically by buccal residual bone measurements, but significant correlations were found between volume and nasal and incisive foramen diameters (P = 0.00). The buccal residual bone lost 40.9% of its mean length; it decreased from 15.58 (Class A) to 8.61 mm (Class E) with the resorption increased (P = 0.01). As the resorption increased from Class A to E, the decrease in the width of apical, middle. and crestal regions of buccal residual bone was found as 10.1%, 15.1%, and 20.6%, respectively.

The mean NPC length decreased from 10.18 (Class A) to 9.5 mm (Class E) without statistical significance ( $P \ge$ 0.05). Contrary to these findings, the NPC diameter increased with the degree of ridge resorption both in nasopalatine and incisive foramen regions. The mean diameter enlargement (Classes A-E) was 0.9 mm (22.1%) in the incisive foramen area and 0.77 mm (23.9%) in the nasal foramen part of the canal (Table 5).

### DISCUSSION

In the maxillary anterior region, it is necessary that a detailed radiographic assessment be conducted to confirm the precise location and dimensions of the anatomical structures before dental implant surgery and other surgical procedures. The literature features many studies on the use of various imaging methods for the morphological evaluation of NPC. To cite some examples, Tözüm et al11 and Mardinger et al<sup>12</sup> investigated NPC with CT; Mraiwa et al9 and Liang et al<sup>13</sup> used spiral CT; Song et al<sup>2</sup> used micro-CT; and Jacobs et al14 performed endoscopic evaluations of the NPC in their cadaver study. In these studies, because morphological measurements were usually made on a single plane and between 2 points, the distances in the other planes were ignored. In the present study, however, this problem was avoided for the channel volume because it does not change according to the plane on which the structure is made. Sagittal CBCT images were also used to evaluate morphologic measurements.

Numerous studies have also been conducted on the topic of volume estimation on CBCT images under a wide range of subjects, such as extraction sockets, 15 pulp-to-tooth volume, 16 oropharynx volume, 17 and maxillary sinus volume<sup>18</sup> to name several. A high correlation has been reported between physical and volume measurements performed with 3D-DOCTOR software, which is capable of measuring vector-based segmentation.<sup>19</sup> In the present study, we applied the Cavalieri principle, a stereological method, in the quantitative assessment of NPC volumes using 3D-DOCTOR software. Kayipmaz et al<sup>20</sup> indicated that the Cavalieri principle used on CBCT images was a valid method for the volumetric analysis of sheep mandible defects, supporting this validity on the basis of its effective use in performing a volumetric analysis of the artificial defects that they had created in their study.

Acar and Kamburoğlu<sup>5</sup> reported that the NPC volume was higher when one central incisor was present (73.10 mm<sup>3</sup>) than when both central incisors were absent (61.28 mm<sup>3</sup>). In line with these results reported by Acar and Kamburoğlu, we calculated there to be a higher volume (113.6 mm<sup>3</sup>) in the dentate group than in the edentulous group (103.2 mm<sup>3</sup>).

The absence or presence of anterior incisors also influenced some dimensions. Bornstein et al4 reported an increase in the buccal bone width in dentate patients compared with edentulous patients, and anterior maxillary bone resorption was shown to result in a reduction of canal length. Similarly, Güncü et al<sup>21</sup> stated that the dimensions of the buccal bone plate and NPC length were decreased in the absence of maxillary anterior teeth. In the current study, although edentulous patients exhibited higher measurements in the incisive and nasal foramen diameter, they showed lower results in the buccal bone and NPC length. In line with Bornstein et al,4 we observed that there was a decrease in the length of the buccal bone, NPC, and ridge width anterior to the canal by an increase in the resorption.

In the literature, NPC shape or morphology is classified according to several criteria, including number of canals, direction, course, or appearance of the image on CT. These criteria are specified on either cross-sectional or axial slices or determined on 3D images. For instance, Mardinger et al<sup>12</sup> and Güncü et al<sup>21</sup> classified the forms of the NPC under 4 groups (banana, funnel, hourglass, and cylindrical) in sagittal sections, whereas Liang et al<sup>13</sup> categorized only 2 groups (cylindrical and conical). In the present study, the canal shape was classified under 4 groups according to sagittal images: hourglass, funnel, spindle, and cylindrical. Acar and Kamburoğlu<sup>5</sup> determined there to be no relation between the canal shape and volume. On their evaluation of axial views, the largest volume was seen in the heart shape (without separation) and the lowest in the oval shape (without separation). In the dentate patient group, we found no relation between the canal shape and volume, whereas in the edentulous group, the highest volume was observed in the spindle-shaped canals. The most and the least common canal shapes were observed to be cylindrical and spindle, respectively. These results are consistent with those obtained from previously published studies. 12,21

In the research conducted by Liang et al,13 the NPC length and diameter were found to be larger in males compared with females. Similar results were obtained in the study by Bornstein et al,4 which compared sex and dental status on buccal bone dimensions and the length and width of the NPC. Their results showed there to be statistically higher buccal bone dimensions and longer canal lengths in the male group. Acar and Kamburoğlu<sup>5</sup> reported that NPC volume was statistically smaller in females than in males. In the present study, in line with Acar and Kamburoğlu, the NPC volumetric measurements were found to be higher in the males than in the females of the dentate group. But among the anatomical measurements, statistically higher dimension was observed only in the incisive foramen region of the male group, and the remaining measurements showed similar results.

Age is another parameter that has been analyzed in several studies in terms of its impact on the NPC dimensions and morphology. A review of the literature showed different results with regard to age and NPC. Tözüm et al<sup>11</sup> found no significant correlations between age and canal length and diameter. Likewise, Mraiwa et al<sup>9</sup> reported an independent association between age and canal characteristics in their study. Acar and Kamburoğlu<sup>5</sup> found that volume measurements did not vary statistically by age. Contrary to the above findings, Bornstein et al4 reported that the age of the patients had an important effect on the length of the NPC, with the mean values generally decreasing as age increased. According to our results, volume was found to increase with age in edentulous patients, whereas in the dentate group, no relation was observed.

Mardinger et al<sup>12</sup> examined the radiological changes of the NPC in different resorption phases of the premaxilla alveolus according to the Lekholm and Zarb classification and stated that the mean canal length decreased from 10.7 (Class A) to 9 mm (Class E). They also reported that the canal diameter was wider along the degree of ridge resorption from Classes A to E in all dimensions, with the most pronounced widths seen in the palatal opening, middle area, and nasal area. According to the results of our study, as the bone resorption increased, the volume and length of the canal decreased, whereas nasal and incisive diameters increased, similar to the study by Mardinger et al.<sup>12</sup>

The NPC is not a static structure but rather tends to enlarge with age and especially after tooth extraction. The present study showed NPC volumes to be highly variable and to be influenced by age and sex; dental status, on the other hand, did not have a definitive effect on volume. To the best of our knowledge, only 1 study, outside of ours, has investigated the NPC volume and its possible affecting factors, such as bone resorption in the premaxilla.

# Conclusion

Although conventional morphometric techniques have been used in most of the studies that have evaluated NPC morphometry, in the present study, also the volume of the NPC was

measured, as opposed to more typical linear measurements, as this was considered to be the most rigorous and most accurate, although timeconsuming, way of quantifying the NPC size. The results of this study have shown that the NPC volume was affected by the age and sex of patients, shape of the NPC, and severity of resorption. Severe bone resorption due to sustained edentation complicates implant surgery because of the increase in the incisive and nasopalatine foramen diameters and decrease in the ridge width anterior to the canal dimensions. To verify the study results and further specify the effect found in this setting, additional studies with larger sample sizes should be conducted.

#### DISCLOSURE

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

## APPROVAL

The study protocol was carried out according to the principles described in the Declaration of Helsinki, including all amendments and revisions. The ethical approval was granted by the Abant İzzet Baysal University Ethical Committee (institutional review board number: 2017/54).

# ROLES/CONTRIBUTIONS BY AUTHORS

All authors have made substantive contribution in all stages (concept/design; data interpretation and analysis; and drafting of the manuscript), and all have reviewed and approved the final manuscript before its submission. Coauthors' individual contribution—K. Ö. Demiralp: performed the interpretation of the data and writing of the manuscript. E. Ş. Kurşun-Çakmak: performed study design; interpretation of the data, and writing of the manuscript. S. Bayrak: performed study design; interpretation of the data; and writing of the manuscript. O. Sahin: performed study

design; interpretation of the data, and writing of the manuscript. C. Atakan: performed statistical data analysis. K. Orhan: performed study design and interpretation of the data.

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