PREVALENCE OF NON-SYNDROMIC HYPODONTIA AND ITS ASSOCIATION WITH MALOCCLUSION AND SKELETAL MORPHOLOGY

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by

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LIST OF ABBREVIATIONS

AMDI	Advanced Medical and Dental Institute
HH	Hedgehog
IPPT	Institut Perubatan Dan Pergigian Termaju
LAFH	Lower Anterior Facial Height
NSH	Non-Syndromic Hypodontia
OPG	Orthopantomogram
SNP	Single Nucleotide Polymorphisms
SPSS	Statistical Package for the Social Sciences
TA	Tooth Agenesis
TAC	Tooth Agenesis Code

PREVALENS HIPODONTIA BUKAN SINDROMIK DAN KAITANNYA DENGAN MALOKLUSI DAN MORFOLOGI RANGKA

ABSTRAK

Agenesis gigi adalah salah satu anomali gigi yang biasanya dipengaruhi oleh beberapa faktor dalam perkembangan gigi seperti faktor genetik dan persekitaran. Kajian ini bertujuan untuk mengira prevalens dan corak hipodontia bukan sindromik dan kaitan antara hipodontia bukan sindromik dengan maloklusi dan morfologi rangka dalam kalangan pesakit ortodontik di Klinik Pakar Ortodontik, Institut Perubatan dan Pergigian Termaju (IPPT). Seramai 630 pesakit (n = 630) (459 wanita,171 lelaki) yang menerima rawatan di Klinik Pakar Ortodontik, IPPT dari 2011 hingga 2019 dinilai. Data pesakit, radiograf panoramik, dan model gigi digunakan untuk mengenal pasti pesakit dengan agenesis gigi kekal, tidak termasuk gigi bongsu. Kaedah data analisis menggunakan Kod Agenesis Gigi digunakan untuk menentukan prevalens dan corak hipodontia bukan sindromik. Kesemua empat puluh lima model gigi pesakit dengan hipodontia bukan sindromik telah dinilai oleh tiga pakar ortodontik untuk menentukan maloklusi pergigian bagi setiap pesakit dan pengesanan cephalometric sisi pada pesakit hipodontia dilakukan menggunakan Web Ceph, platform ortodontik dan ortognatik berasaskan "artificial intelligence", untuk menentukan maloklusi rangka pesakit. 84 batang agenesis gigi kekal dijumpai daripada sejumlah 630 pesakit. Purata bilangan agenesis gigi bagi setiap pesakit ialah 0.13±0.61. Prevalens hipodontia bukan sindromik pada pesakit ortodontik di IPPT adalah 7.1%, di mana kejadiannya lebih tinggi pada rahang bawah daripada rahang atas. Agenesis gigi yang paling kerap adalah gigi kacip sisi rahang atas (27.5%), diikuti dengan gigi kacip sisi rahang bawah (24.0%), dan premolar kedua rahang atas (12.0%). Agenesis gigi dua belah sisi (53.6%) lebih biasa terjadi daripada agenesis gigi sebelah sisi (46,4%).

40.0% pesakit mempunyai maloklusi pergigian kelas II bahagian 1 diikuti oleh kelas I (33.3%), kelas III (15.6%), dan kelas II bahagian 2 maloklusi (11.1%). Pesakit ini kebanyakannya mempunyai maloklusi rangka kelas I dengan nilai SNA, SNB, ANB dan MMPA yang normal. Walau bagaimanapun, kajian ini menemui nilai LAFH di antara pesakit ini lebih rendah berbanding dengan kumpulan kawalan. Penemuan fenotipik ini seterusnya mengesahkan keperluan untuk memastikan kajian genotipik hipodontia bukan sindromik pada masa hadapan.

PREVALENCE OF NON-SYNDROMIC HYPODONTIA AND ITS ASSOCIATION WITH MALOCCLUSION AND SKELETAL MORPHOLOGY

ABSTRACT

Hypodontia is one of the common dental anomalies influenced by several factors in dental development such as genetic and environmental factors. This study aims to estimate the prevalence and pattern of non-syndromic hypodontia excluding third molars and its association with dental malocclusion and skeletal morphology among orthodontic patients at the AMDI (Advanced Medical and Dental Institute) Orthodontics Specialist Clinic. A total of 630 patients (n = 630) (459 females, 171 males) attending AMDI Orthodontics Specialist Clinic from 2011 to 2019 were assessed. Patients' data, panoramicradiographs, and study casts were used to identify patients with missing permanent teeth, excluding third molars. TAC Data Analysis Tool method was used to determine the prevalence and pattern of non-syndromic hypodontia excluding third molars. All forty-five dental casts of patients with NSH were assessed by three orthodontic specialists to determine the dental malocclusion for each patient and lateral cephalometric tracing on hypodontia patients was done using the Web Ceph, an artificial intelligence web-based orthodontic and orthognathic platform, to determine the patients' skeletal malocclusion. 84 missing teeth excluding third molars were found in a total of 45 patients with a range age from 7 to 34 years old when the pre- treatment OPGs were taken. The average number of missing teeth per patient is 0.13±0.61. The prevalence of non-syndromic hypodontia excluding third molars among orthodontic patients is 7.1%, where the incidence is higher in the mandible than in the maxilla. The most common missing teeth are the maxillary lateral incisors (27.5%), followed by mandibular lateral incisors (24.0%), and maxillary second premolars (12.0%). A bilateral tooth missing

(53.6%) was more common than unilaterally missing teeth (46.4%). 40.0% of patients had Class II division 1 dental malocclusion followed by Class I (33.3%), Class III (15.6%), and Class II division 2 malocclusion (11.1%). These patients presented with skeletal Class I malocclusion with normal SNA, SNB, ANB, and MMPA values. However, in this study, LAFH in these patients was reduced compared to the control group. These phenotypic findings further confirm the need to ascertain the genotypic study of NSH.

CHAPTER 1

INTRODUCTION

1.1 Overview

Hypodontia or commonly described as congenitally missing teeth is one of the most common dental anomalies. Patients with hypodontia are commonly presented with a variety of underlying skeletal and dental issues, necessitating a multidisciplinary approach to the management of the condition. However, there are conflicting viewpoints and a paucity of research regarding the effect of hypodontia on patients' dental and skeletal features. The current literature also portrays a varied prevalence and pattern of hypodontia by populations and countries.

This research thus aims to determine the phenotypic variation of non-syndromic hypodontia (NSH) and its association with dental malocclusion and skeletal pattern among orthodontic patients in Advanced Medical and Dental Institute (AMDI).

1.2 Background of Study

There are several terms to explain congenitally missing teeth which include “hypodontia”, “tooth agenesis”, “anodontia” or “oligodontia”. The prevalence of NSH excluding third molars ranges from 1.0% to 12.9% among populations in various countries. In Malaysia, research by Mani, Mohsin, and John (2014) on Malay children found that the prevalence rate of NSH was 3.2%. Maxillary lateral incisors were found to be the next common missing tooth with a percentage of1.7% followed by maxillary and mandibular second premolars. Another study by Hasyiqin *et al.* (2019) found that the prevalence of tooth agenesis among the Malaysian population was 1.005% excluding third molars.

These two studies showed that the prevalence rate was inconsistent among the different populations studied. The reason for this could be due to variations in the research methods, the sample size of the population studied, race, and any possible

genetic involvement in the studies. Commonly, NSH was identified by examining non-syndromic patients attending dental clinics with missing teeth and no evidence of crown mineralization from the orthopantomogram (OPG). However, patients with Down syndrome, ectodermal dysplasia, and other syndromes related to hypodontia were excluded.

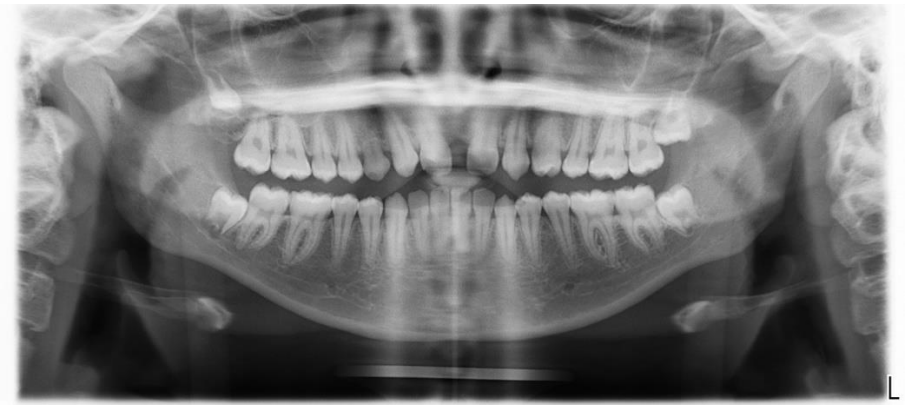

Figure 1.1: An orthopantomogram of hypodontia patient with missing left maxillary lateral incisor.

One of the methods to determine the prevalence and pattern of NSH is by using the Tooth Agenesis Code (TAC) Data Analysis. Using the idea of binary arithmetic, the absence and presence of teeth are represented by 1 and 0 which are then translated into corresponding unique values, making it easier for researchers to conduct studies on hypodontia. Due to a lack of research in this area, it is impossible to ascertain how the prevalence rate of NSH has changed over time in Malaysian populations and none of the hypodontia studies in Malaysia focus on the orthodontic population specifically.

Several studies have reported the association between NSH and malocclusion. Uslu *et al.* (2009) and Hedayati and Dashlibrun (2013) observed that there is no significant difference between non-syndromic tooth agenesis and malocclusion. However, some authors found that NSH is associated with skeletal Class III malocclusion (Acharya *et al.*, 2010; Vahid-Dastjerdi *et al.*, 2010) while Costa *et al.* (2017) suggested that only premolar agenesis is involved with Class III

malocclusion. Ota and Arai (2015) in another study discovered an association between NSH and Class II division 2 malocclusion.

The inconsistency in these findings shows that the association between malocclusionand NSH varied among different populations. Genetic and environmental factors might be the contributing factors to the condition while the mechanism is still in debate. Several studies were done on the genetic implication of NSH and malocclusion. Few mutated genes have been reported to be associated with NSH; MSX1, PAX9, AXIN2, and EDA (Chhabra, Goswami, and Chhabra, 2014). A recent study by Marañón-Vásquez *et al.* (2019) discovered that single nucleotide polymorphisms (SNPs) in the GLI2 and GLI3 genes influence human craniofacial skeletal morphology.

1.3 Research Problem

The prevalence rate of non-syndromic hypodontia is typically lower than that of other types of anomalies according to researchers. Treatments for patients with this condition will be more arduous, especially when it is associated with malocclusion, which complicates treatment. Patients with tooth agenesis usually have distinct craniofacial morphologies than normal patients, mainly as the number of missing teeth increases.

However, concerning the impact of hypodontia on a patient's dental and skeletal features, there are differing viewpoints and a scarcity of research in this area. The existing literature also depicts a wide range of prevalence and pattern of hypodontia by population and country highlighting the need to establish the phenotypic variation focusing on the Malaysian orthodontic populations. It is impossible to discern how the prevalence rate of NSH has changed over time in Malaysian populations due to a lack of research in this area, and none of the hypodontia studies in Malaysia have specifically targeted the orthodontic population.

As a result, researchers are unable to determine whether hypodontia is still one of the most common dental anomalies among Malaysians, or whether the condition requires more attention from all dental practitioners for them to stay up to date on the clinical management of patients with this anomaly. Furthermore, the contradictory findings on the relationship between non-syndromic hypodontia and malocclusion and skeletal pattern suggest that there could be genetic involvement in different populations and races. The focus of this research thus will be on the phenotypic variations of non-syndromic hypodontia in AMDI orthodontic populations.

1.4 Research Aim

Given the limited research on non-syndromic hypodontia and its relationship with malocclusion and skeletal pattern among the orthodontic Malaysian population, the study, therefore, aims to identify the phenotypic variation of non-syndromic hypodontia and its association with dental malocclusion and skeletal pattern among orthodontic patients in Advanced Medical and Dental Institute (AMDI).

1.5 Objectives of Study

1.5.1 Objective 1

To provide the prevalence and pattern of non-syndromic hypodontia in AMDI Orthodontics Specialist Clinic.

1.5.2 Objective 2

To identify the prevalence of skeletal and dental malocclusion among 630 AMDI orthodontic patients.

1.5.3 Objective 3

To ascertain the association between non-syndromic hypodontia and dental malocclusion (Class I, Class II division 1, Class II division 2, and Class III).

1.5.4 Objective 4

To compare the association between non-syndromic hypodontia with skeletal morphology (Class I, Class II, and Class III) and craniofacial morphologies.

1.6 Research Questions

1.6.1 Question 1

What are the prevalence and pattern of non-syndromic hypodontia in AMDI Orthodontics Specialist Clinic?

1.6.2 Question 2

What is the prevalence of skeletal and dental malocclusion among AMDI orthodontic patients with NSH?

1.6.3 Question 3

Is there any association between non-syndromic hypodontia and dental malocclusion (Class I, Class II division 1, Class II division 2, and Class III)?

1.6.4 Question 4

Is there any relationship between NSH with skeletal malocclusion (Class I, Class II, and Class III) and craniofacial features?

1.7 Significance of Study

The study of the prevalence rate and pattern of NSH over time may guide the researchers in determining possible mechanisms or evolutionary trends in the populations. The establishment of frequency and pattern of NSH also would aid in early diagnosis and possible early intervention. It is critical to understand the phenotypic variations of non-syndromic hypodontia and their links to dental

malocclusion and craniofacial morphology in different specific populations.

As a result, practitioners will have a better understanding of their patient's conditions and will be able to treat them appropriately based on the established pattern of hypodontia and its possible relationship with malocclusion. The available data would also help in further understanding the correlation between the phenotype-genotype of this dental abnormality.

CHAPTER 2

LITERATURE REVIEW

2.1 Classification of Hypodontia

Many methods of classifying hypodontia as described by several authors. Some authors found that hypodontia occurs in inherited and isolated forms (Arte *et al.,* 2001; Tan, Wijk, and Prahl-andersen, 2011). Inherited form refers to the occurrence of hypodontia in the type of autosomal-recessive, autosomal-dominant, and X-linked trait (Mostowska *et al.*, 2003).

Hypodontia can also occur in an isolated form where the occurrence is not related to any syndromes while syndromic hypodontia is a form of anomaly that is known to be related to congenitally missing teeth. Other authors classified the congenital absence of teeth by the number of missing teeth. The term "hypodontia" refers to congenitally missing teeth less than six while "oligodontia" is a condition of congenitally missing six or more teeth. Some patients presented with a complete absence of teeth which is commonly defined as "anodontia" (Nunn, Gillgrass, and Meechan, 2003; Gupta *et al.*, 2011).

On the other hand, Dhanrajani (2002) in his paper classified hypodontia according to the severity excluding third molars. Mild hypodontia referred to one to two missing teeth while moderate hypodontia was used to indicate three to five missing teeth. More than six missing teeth are considered severe hypodontia which is rare and often associated with specific syndromes. However, there is no consensus among authors on how to classify hypodontia but commonly it is classified according to the severity of missing teeth (Ide *et al.*, 2011; Hasyiqin *et al.*, 2017; Behr *et al.*, 2011).

2.2 Odontogenesis

The consensus on tooth agenesis is some disturbances or alterations occur during the tooth development process causing failure of tooth formation. A molecular study has found that tooth development necessarily involves a series of epithelial-mesenchymal interactions involving a variety of signaling molecules (Thesleff and Vaahtokari, 1995). Odontogenesis or tooth development is a complex process of tooth formation that involves the cells of oral epithelium and ectomesenchyme.

During the initiation stage which is the first stage of tooth development, an interaction between mesenchymal tissue and ectodermal tissue happens. The embryo's stomodeum which is lined by ectoderm gives rise to the oral epithelium. During the later part, the oral epithelium grows deeper into ectomesenchyme and is induced to form thedental lamina. The lack of initiation within the dental lamina will result in tooth agenesis(Dassule *et al.*, 2000).

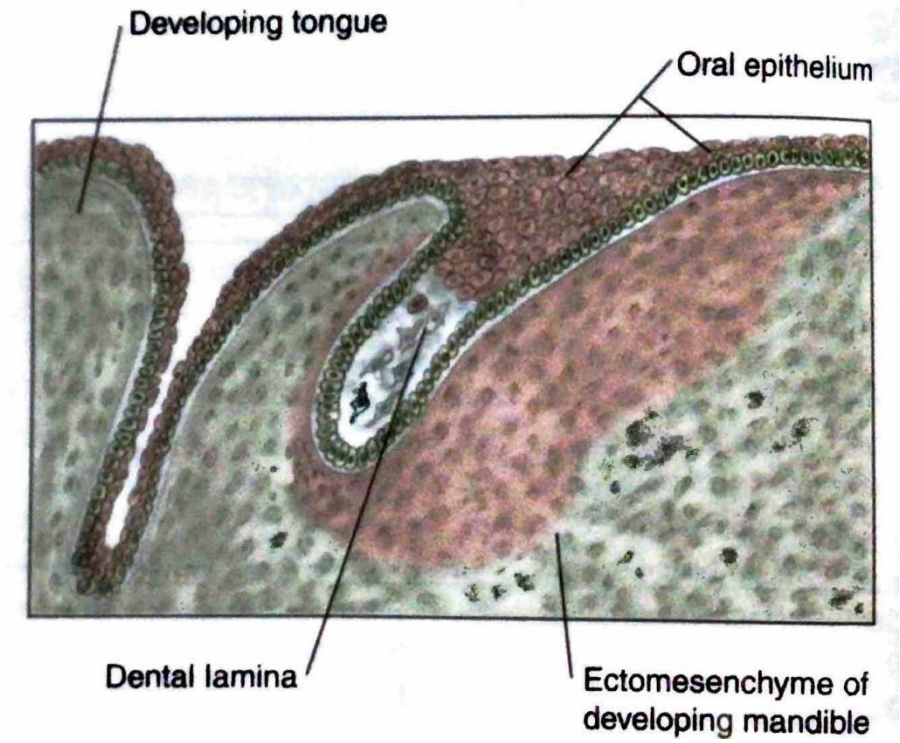

Figure 2.1 Formation of dental lamina surrounded by ectomesenchyme where the primary teeth will later form.

2.3 Aetiology

There are vast concepts explaining the concepts of tooth agenesis in the literature. However, it is agreeable that multifactorial aetiologies are involved in contributing to the developmental defect which includes genetics and environmental factors.

2.3.1 Tooth Agenesis Theories

Several theories have been developed explaining tooth agenesis. These theories can be divided into two; evolutional and anatomical theories. Butler's field theory (Butler, 1956), Sofaer's model (Sofaer *et al.,* 1971) of compensatory tooth size interactions, and other theories have been proposed to explain the developmental defect.

The current trend of eating and chewing soft food somehow reduces the functional activity of the maxillomandibular complex (Galluccio, Castellano, and La, 2012). This condition contributes to the narrowing of the anteroposterior dimension of the maxilla and mandible, thereby reducing the number of teeth that attempt to adapt to the smaller arches which illustrates the theory of evolution (Vastardis, 2000). The concept is supported by a study done by Lavelle, Ashton, and Flinn (1970) where they found that homo sapiens compared to monkeys, apes and great apes tend to have a shrinkage of the maxillomandibular skeleton.

Based on Butler's theory, mammalian dentition can be categorized into 3 groups which are incisors, canines, and premolars/molars. It is presumed that there is one stable "key" tooth within each group and other teeth that are less stable. The less stable teeth might appear to have the most variable in size and shape (Bailit, 1975).

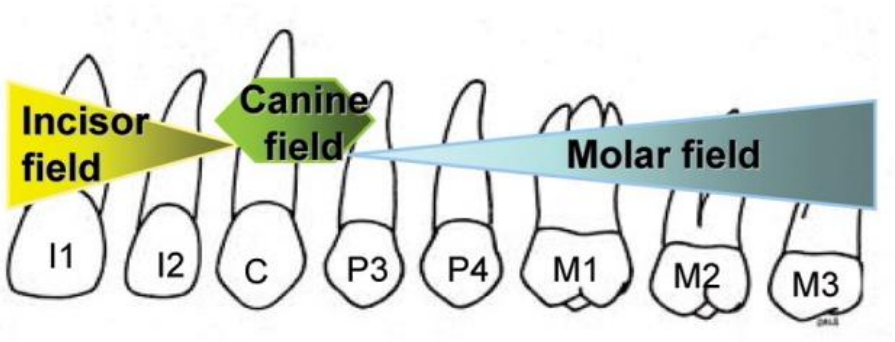

Figure 2.2 The field theory is divided into three fields

This theory was then adapted by Dahlberg who found that each of the tooth classes has a stronger effectof field of influence on the “key” tooth. The more distally the tooth is placed, the more varied the teeth' characteristics will be. Besides, in contrast to Butler’s, he added a premolar field which then was argued by Butler explaining that premolars are modified anterior members of a permanent molar field that cannot be in its field (Hobkirk *et al.,* 2010).

On the other hand, Sofaer’s model explains the relationship between tooth agenesis and tooth size where there is compensatory interaction between tooth germs during odontogenesis. They hypothesized that hypodontia occurs when the primordia are not enough during the initiation stage explaining that the absence or smaller size of the teeth on one side results in a compensatory rise in the size of the contralateral side teeth (Sofaer *et al.,* 1971).

2.3.2 Genetic implications

Advances in genetic and molecular technology and research have aided in identifying the genes responsible for NSH development. The mutated genes that are believed to be related to non-syndromic hypodontia are MSX1, PAX9, AXIN2, and EDA (Chhabra, Goswami, and Chhabra, 2014). Single nucleotide polymorphisms (SNPs) linked to diseases like hypertension, cancer, and diabetes have been the focus of research in recent years. However, research on SNPs linked to tooth agenesis is still

limited. The most common polymorphisms in the human genome are single nucleotide changes, which commonly occur and can affect gene function (Zhang, Qu, and Zhang, 2014).

Other than that, the Hedgehog (HH) family's Sonic Hedgehog (SHH) signaling pathway is crucial and is used repetitively during tooth formation. The three zinc finger transcription factors (GLI1-3), which are encoded by their respective GLI1-3 genes, are the key parts of the mediation of the SHH signaling pathway. GLI2 and GLI3 have already been associated with non-syndromic hypodontia. Interestingly, HH pathways are important during general embryogenesis as well as toothdevelopment and it was discovered that SNPs in the TA-associated GLI2 and GLI3 genes contributed to the development of skeletal malocclusions (Marañón-Vásquez *et al.*, 2019).

In another study, it has been identified that SHH is important in the regulation of craniofacial morphogenesis (Du *et al.*, 2012). In Malaysia, the study of genetic involvement in non-syndromic hypodontia is still lacking. However, research has identified the link between MSX1 and PAX9 with NSH among a few Malaysians where the sample study was very small (Fauzi *et al.*, 2018).

2.4 Prevalence and Pattern of Non-Syndromic Hypodontia

The prevalence of non-syndromic hypodontia excluding third molars varies among different populations across the countries. It was found that the prevalence ranges between 1% to 7.25% hypodontia among general dental populations. The lowest rate was found among patients attending IIUM dental polyclinics which was 1.005%. The study was done by Hasyiqin *et al.* (2019) among 3481 patients attending IIUM dental polyclinics. Tallón-Walton *et al.* (2010) reported that 7.25% of the population studied has non-syndromic hypodontia. The study was done on a total of 1518 patients in an age group ranging from 6 to 83 years old.

Table 2.1 Prevalence of non-syndromic hypodontia among general dental populations

Population	Prevalence (%)	References
IIUM dental polyclinic, Malaysia population	1.005	(Hasyiqin *et al.*, 2019)
Indore, India population	4.19	(Gupta *et al.*, 2011)
ISCSN Dental clinic, Portugal population	6.1	(González-Allo, A. *et al.*, 2013)
Slovenian population	6.9	(Fekonja, 2015)
The Odontological Service of the Primary Health Center of Cassa de la Selva, Spain population	7.25	(Tallón-Walton *et al.*, 2010)

However, the prevalence rate among orthodontic patients was found to be higher than in the general dental populations which supports the finding by Al-Jabaa and Aldrees (2013) who reported that teeth were more likely to be missing in orthodontic patients than in the normal population. The range of prevalence is between 3% and 12.9% in orthodontic patients. The possible explanation for this may be most of the cases were referred by other general dental practitioners to orthodontic specialist clinics. Studies were done on French, Iranian, Brazilian, Eastern Bavaria, Turkish, Japanese, Erbil City, Saudi and Sudanese orthodontic patients showing that the prevalence of hypodontia varies across different populations. Up to the current literature, no study onhypodontia has been done in Malaysian orthodontic patients.

Table 2.2 Prevalence of non-syndromic hypodontia among orthodontic populations

Population	Prevalence(%)	References
Brazilian orthodontic patients	3.0	(Souza-silva *et al.*, 2018)
Sudanese orthodontic patients	5.1	(Hassan, D.A *et al.,* 2014)
French orthodontic patients	5.81	(Baron *et al.*, 2018)
Erbil City orthodontic patients	6.66	(Mohammed Amin, Abduljabbar and Saleh, 2017)

Turkish orthodontic patients	7.0	(Gokkaya, Motro, and Kargul, 2015)
Iranian orthodontic patients	9.1	(Vahid-Dastjerdi *et al.*, 2010)
Japanese orthodontic patients	9.4	(Endo, Ozoe, Kubota, *et al.*, 2006)
Korean orthodontic patients	11.2	(Chung, Han, and Kim, 2008)
Eastern Bavaria orthodontic patients	12.6	(Behr *et al.*, 2011)
Serbian orthodontic patients	12.9	(Marković *et al.*, 2020)

A survey done by Behr *et al.* (2011) on 1353 orthodontic patients in Eastern Bavaria found that 171 patients have congenitally missing teeth. Another study on 3400 Brazilian orthodontic patients with a range of ages between 8 to 30 years old reported that the prevalence of non-syndromic hypodontia was 3.0%. (Souza-silva *et al.*, 2018) The genetic variation among different countries and populations might be the possible explanation for the findings.

Studies reported by Fekonja (2015) and Heuberer S. *et al.,* (2019) found that the most frequent form of tooth missing was mild hypodontia among general dental populations, where a majority of the cases have congenitally missing one or two teeth. Mild hypodontia also was found to be the most common form in Malaysia (Mani, Mohsin, and John, 2014; Hasyiqin *et al.*,2019). The same condition was also recorded among Sudanese and Eastern Bavaria orthodontic populations with cases of two to three missing teeth (Hassan, D.A *et. al.,* 2014; Behr *et al.,* 2011). Most of the studies did not report any anodontia cases.

The pattern of missing teeth, however, is different among populations, ethnicity, and countries. A study among the general dental populations in India found that maxillary lateral incisors were the most frequently missing teeth (Gupta *et al.,* 2011). When comparing the pattern of missing teeth among orthodontic populations, studies

in Iran, Brazil, Sudan, and Erbil City found that the most commonly missing teeth were the maxillary lateral incisors (Vahid-Dastjerdi *et al.*, 2010; Souza-silva *et al.*, 2018; Hassan, D.A *et. al.,* 2014; Mohammed Amin, Abduljabbar and Saleh, 2017). However, other orthodontic population studies reported that mandibular second premolars were the most common tooth missing (Behr *et al.*, 2011; Ide *et al.*, 2011; Bozga, Rp and D, 2014; Gökkaya, Motro and Kargül, 2015; Baron *et al.*, 2018).

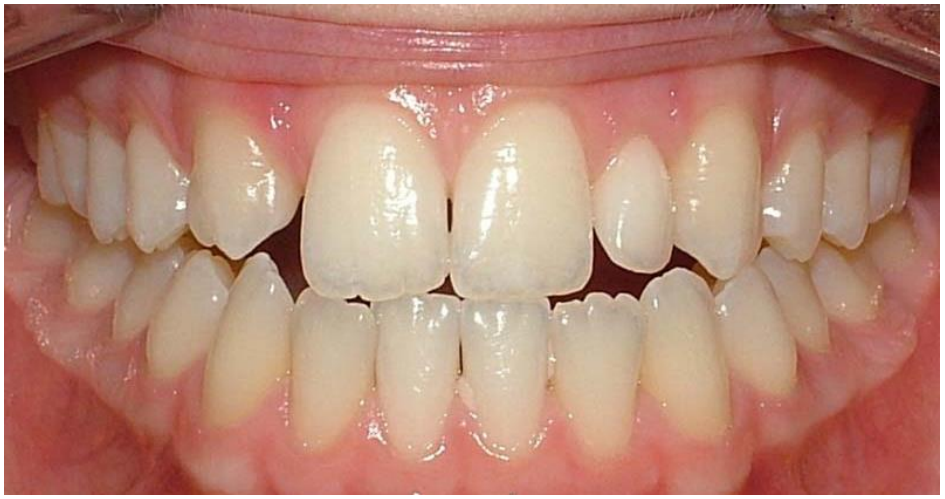

Figure 2.3 A patient with missing right maxillary lateral incisor

Hypodontia of maxillary central incisors seems to be a very rare occurrence in most of the populations studied (Lynham, 1990). It is normally presented with syndromic conditions such as cleft lip/palate, ectodermal dysplasia, and Down syndrome. Congenitally missing maxillary permanent canine also is usually rare (Lombardo, Barbato, and Leonardi, 2007) and only a few cases were reported. The result however is contradictory with research among the Chinese population (Leong and Calache, 1999; Cho, Lee, and Chan, 2004) and IIUM dental polyclinics patients (Hasyiqin *et al.*, 2019). The variation in the number of cases reported could be due to racial differences in the pattern of hypodontia and may be comparatively more common in Asian people (Leong and Calache, 1999).

Studies by Vahid-Dastjerdi *et al.* (2010) and Gomes *et al.* (2010) showed that hypodontia was more likely to occur in the maxilla compared to the mandible, according to the sides and locations of missing permanent teeth. Other studies by Ide *et al.* (2011) among Japanese children and Kim (2011) among Korean orthodontic patients found that the prevalence of hypodontia was significantly higher in the mandible than in the maxilla. Studies among orthodontic populations across the countries reported that most of the missing teeth were found on the left side (Larmour *et al.*, 2005; Amini, Rakhshan, and Babaei, 2012; Hassan D.A *et al.,* 2014). However, other studies among the Korean and Brazilian orthodontic populations reported the opposite (Chung, Han, and Kim, 2008; Gomes *et al.*, 2010).

2.5 Tooth Agenesis Code (TAC) Data Analysis.

There were several methods used by the researchers to determine the prevalence and pattern of NSH including Microsoft Office Excel and SPSS. Few researchers have recently used the newly developed TAC Data Analysis Tool in their studies (Souza-silva *et al.*, 2018; Heuberer *et al.*, 2019). TAC Data Analysis Tool was invented based on the idea of Gottfried Wilhelm Leibniz (1646–1716). The tool allows two types of datasets to be uploaded which are the separate elements and TAC values.

The separate elements will be translated into TAC values by inserting the data as code 0 or 1 to represent the presence and absence of teeth. The tool provides insight into the pattern of hypodontia in our clinic by assigning unique values for each hypodontia condition. In their paper, Van Wijk, A.J. and Tan, S.P. (2006) described the procedure of translating unique values into the pattern of hypodontia. According to the FDI system (Peck S. and Peck L., 1993), the teeth are numbered from 1 to 8 and each of the missing tooth values can be calculated by using this formula $2^{(n-1)}$ where n is the tooth number. They proposed that the total unique value will be from 0

to 255 by quadrants which also can be referred to as Tooth Agenesis Code (TAC).

Table 2.3 A, tooth numbering according to FDI system; B, missing teeth value

	q1								q2							
A	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
B	128	64	32	16	8	4	2	1	1	2	4	8	16	32	64	128
A	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
	q4								q3							

The process of changing a given TAC value into a dental pattern is less obvious and necessitates a script-like method (computer). From the TAC value, the tooth value will be then subtracted, for example, 80 with the highest value, 128. This value is excluded from the TAC value if the remainder is negative. The pattern is established if the remainder is 0 which shows that the tooth is missing but, if the remainder is positive, the tooth is also missing, and proceed with subtracting the next largest tooth, 64.

Findings reported by Souza-silva *et al.* (2018) on the pattern and distribution of non-syndromic tooth agenesis using the TAC Values for each case portraying incredibly detailed symmetric agenesis patterns, single tooth symmetry, and distribution of missing teeth across quadrants and the type of missing teeth. This procedure hence provides an easier data analysis over existing methods and allows researchers to be able to communicate clearly and unambiguously on their phenotypic studies.

2.6 Clinical Implications of Hypodontia

It is rare for mild hypodontia patients with only missing one to two teeth to be presented with generalized spacing. Patients with a more severe case of hypodontia may require more complicated and arduous orthodontic treatments. However, the symmetry of the smile can sometimes be affected by localized spacing

in less severe cases, particularly in patients who have missing maxillary incisors, and this can be easily noticed by other people. In these situations, orthodontic management can be done, nonetheless, it is encouraged to reassure patients with milder cases of spacing to accept the gap or to consider any other restorative approaches to improve the aesthetics.

Researchers and clinicians have suggested a few treatment options to replace missing maxillary incisors, such as fixed orthodontics to close the space and modify the neighboring teeth to resemble lateral incisors or opening the space and replace with a fixed or removable prosthesis. These two choices depend on a few additional factors, so experts' advice should be sought prior to making any decision.

One of the factors for orthodontic treatment options is the skeletal pattern of the patient. In the case of skeletal pattern Class III, the closure of the space will affect the incisor relationship which is less favourable compared to Class II division 1 patients. Besides, the number and the site of missing teeth either unilaterally or bilaterally will also affect the treatment plan. The colour and shape of the adjacent teeth also must be taken into consideration in the space closure option. Last, but not least, after a thorough and in-depth explanation from clinicians, one of the most crucial elements to success in treatment planning is the patient's ability to cooperate and commit to every step of treatment (Mitchell L., 2013)

2.7 Classification of Malocclusion and Skeletal Pattern.

Classification of malocclusion according to The British Standard Institute(BSI) in 1983 is based on the maxillary and mandibular incisors relationship. Class I malocclusion is when the mandibular incisor edges lie or are below the cingulum plateau of the maxillary incisors.

Figure 2.4 Class I incisor classification

Class II malocclusion is observed when the mandibular incisor edges lie posterior to the cingulum plateau of the maxillary incisor. Class II malocclusion can be further divided into Class II division I where the maxillary incisors are proclined with an increase overjet. Class II division II is when maxillary central incisors are retroclined and lateral incisors proclined, or both central and lateral incisors are retroclined.

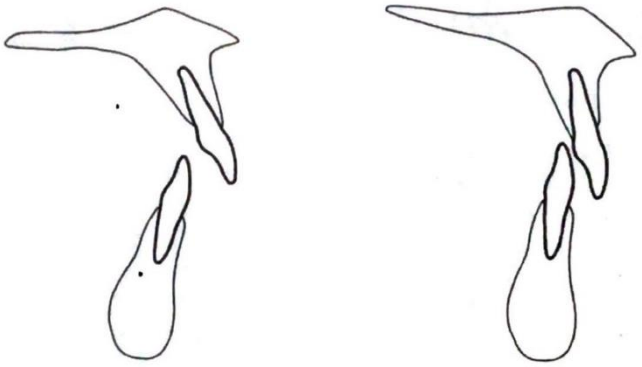

Figure 2.5 Class II division 1 (left) and Class II division 2 (right) incisor classification

Class III malocclusion is where the mandibular incisor edges lie anterior to the cingulum plateau of the maxillary central incisors.

Figure 2.6 Class III incisor classification

The most common used classification method is Angle's classification of malocclusion developed by Edward H. Angle in 1980. The classifications are based on the relationship between the buccal groove of the mandibular first permanent molar and the mesiobuccal cusp of the maxillary first permanent molar.

According to Edward H. Angle, malocclusion was classified under three classes which are Class I, Class II which are further divided into Class I division 1 and Class II division 2, and the last one is Class III malocclusion.

Class I or neutrocclusion: Normal molar relationship but other irregularities such ascrowding, rotations, cross-bites, and misalignment of teeth are present.

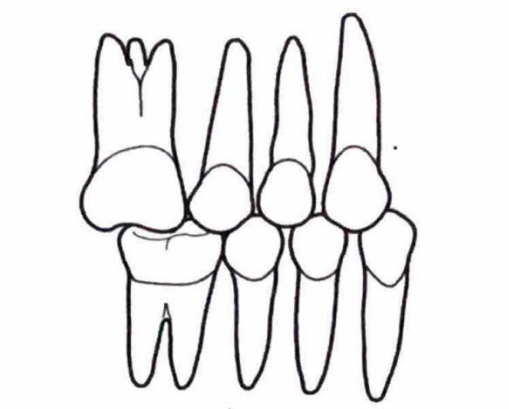

Figure 2.7 Class I

Class II or distocclusion: The mesiobuccal cusp of the maxillary first molar occludes anterior to the buccal groove of the mandibular first molar.

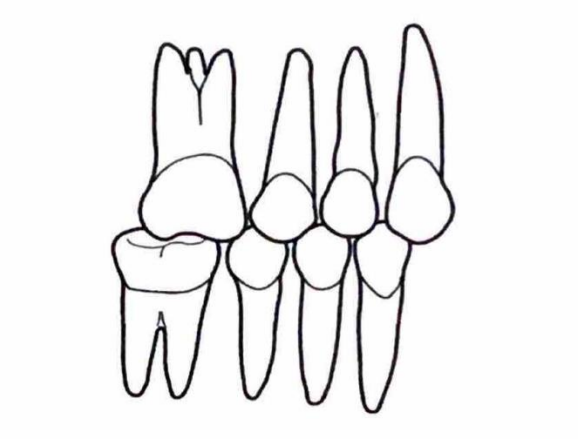

Figure 2.8 Class II

Class III or mesiocclusion: The mesiobuccal cusp of the maxillary first molar occludes posterior to the buccal groove of the mandibular first molar.

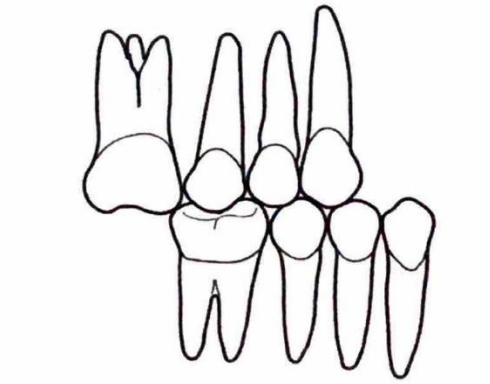

Figure 2.9 Class III

The skeletal pattern can be classified by using the cephalometric standard for skeletal type where the values of the sagittal intermaxillary angle are SNA – SNB = ANB.

- Class I skeletal pattern: ANB angle with values between 0° to 4°
- Class II skeletal pattern: ANB angle with values > 4°
- Class III skeletal pattern: ANB angle with values < 0°

2.8 Association between Non-Syndromic Hypodontia with Malocclusion and Skeletal Pattern

Several studies on the association between non-syndromic hypodontia and dental malocclusion have been conducted across countries and populations. The result varies, and it is influenced by the population's sample size as well as the genetic variation among the populations studied. The link between NSH and dental malocclusion in Malaysians, however, is still debatable.

Haider and Sheeraz (2016) found a significant difference between Angle Class III malocclusion and hypodontia among Pakistani orthodontic clinic patients. Another study among the Turkish population depicted a lower prevalence of NSH among Class II division 2 malocclusion with the highest prevalence in Class III malocclusion patientsimplying a regional difference (Uslu *et al.*, 2009).

However, Ota and Arai (2015) found that the prevalence of non-syndromic hypodontia excluding third molars was significantly higher in patients with Class II division 2 malocclusion. Other authors also reported that congenitally missing teeth are related to retroclination of maxillary incisors (Endo *et al.*, 2004; Kim, 2011). Another study was done among German patients also found that NSH is common among Class II division 2 malocclusion (Basdra, Kiokpasoglou, and Komposch, 2001). According to Øgaard and Krogstad (1995), maxillary incisor retroclination is reflected by a decrease in lip protrusion, and the degree of retroclination increases with the severity of hypodontia.

Ota and Arai (2015) and Basdra, Kiokpasoglou, and Komposch (2001) suggested that missing maxillary lateral incisors was one of the characteristics of ClassII division 2 malocclusion and can be a standard feature of Class II division 2 malocclusion. None of the studies from the literature reported that NSH was more prevalent in Class II division 1 malocclusion patients. Maxillary hypodontia usually

manifests in maxillary retrognathism which further explains why none of the studies reported hypodontia in Class II division 1 malocclusion.

Hamdany, Saleem, and Qasim (2007) in their paper found that there was no significant difference between angle classification of malocclusion and hypodontia even though they found that congenitally missing teeth are frequent among Class I malocclusion patients. However, the reason for the higher prevalence of hypodontia among Class I malocclusion patients is because of higher sample populations with Class I malocclusion.

It is still unclear why congenitally missing teeth are associated with skeletal morphology. Many studies have reported there was an association between hypodontia and skeletal morphology which varied according to the populations studied (Bondarets and McDonald, 2000; Endo, Ozoe, Yoshino, *et al.*, 2006; Chan, Samman, and McMillan, 2009; Costa *et al.*, 2017). However, several other studies reported the opposite where they found no significant difference between hypodontia and malocclusion (Uslu *et al.*,2009; Hedayati and Dashlibrun, 2013; Pedreira *et al.*, 2016; Ota, Hirakata, and Endo, 2019). The variation in the age range of the population studied and the cephalometric analyses standard used for different populations might influence the difference in the result.

Pedreira *et al.* (2016) stated that the prevalence of hypodontia was more frequent in Class I malocclusion patients but the result was not significant. Studies done by Ben-Bassat, and Brin (2009) found that patients with hypodontia tend to exhibit a smaller mandibular plane angle and more retrognathic maxilla which results in skeletal Class III skeletal pattern. Costa *et al.* (2017) also found that tooth agenesis was associated with a smaller ANB angle and a strong relationship was found between premolarteeth agenesis and skeletal Class III skeletal pattern. From these findings, it can be hypothesized that congenitally missing teeth do have an impact on the development of

patients' skeletal features.

Chan, Samman, and McMillan (2009) found that there was a significant difference between hypodontia and Class III skeletal profile. They found that patients with hypodontia were associated with a flatter mandibular plane, a more pronounced chin, and a shorter face. The result was supported by Gungor and Turkkahraman (2013) where they found they found that facial and ramus height was shorter in the hypodontia group compared to the control but they found no significant difference between congenitally missing teeth and SNA, SNB, and ANB angle.

With the increase in severity of hypodontia, the skeletal pattern showed a tendency towards a Class III skeletal profile. Acharya *et al.* (2010) suggested the cause of the condition might be a decrease in maxillary and mandibular prognathism and mandibular length. They found that in the presence of severe hypodontia, the anteroposterior size of the maxilla was more affected than the mandible. The maxillary length decreased significantly in hypodontia groups.

Bajraktarova Miševska *et al.* (2017) found that patients with severe hypodontia related to significantly reduced lower anterior face height. Patients with tooth agenesis may have a unique craniofacial morphology as a result of dental and functional compensations. A decrease in occlusal support and the growth of alveolar bones have been linked to an anti-clockwise rotation of the mandible, resulting in Class III skeletal relationship and hypodivergent pattern.

These studies led us to believe that in some cases both non-syndromic hypodontia and skeletal malocclusion are caused by the same genes as mentioned by Marañón-Vásquez *et al.* (2019) where they suggested that the SNPs in *GLI2 and GLI3* genes may be involved in the development of skeletal malocclusions. Although there is some evidence of the genetic components in the aetiology of NSH and skeletal malocclusion in various populations, there is still lacking in the aetiology of the genetic

involved in this condition and whether the genetics are different or vary in different populations studied.