A review of hypodontia: the possible etiologies and orthodontic, surgical and restorative treatment options—conventional and futuristic

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ABSTRACT  This review covers the etiology and prevalence of hypodontia and its associated conditions, dental anomalies and skeletal patterns. Different treatment modalities specified for hypodontia patients are outlined to provide clinicians with a panoramic appreciation of different treatment approaches.

Key words: Anodontia/etiology; Tooth abnormalities; Review literature

Introduction

The term ‘hypodontia’ refers to the developmental absence of one or more teeth, either in primary or permanent dentition, excluding the third molars. It is the most common craniofacial malformation. If six or more permanent teeth are missing, the term ‘oligodontia’ is used.

Hypodontia creates significant challenges to the clinicians in both diagnosis and management. Comprehensive management often requires a multidisciplinary approach. Counseling from a geneticist might be essential to determine whether the specific type of hypodontia is a stand-alone condition or one associated with other anomalies. The advances in the understanding of tooth development and genetic control of tooth morphology not only allows clinical research to broaden its understanding of tooth agenesis but also provides a basis for the clinicians to provide optimum clinical care.

The ability to address this condition during the early stages of the dentition maximizes the potential for a treatment with functional, esthetic, and stable results. This review attempts to aid the clinicians in the early and appropriate diagnosis and management for patients with hypodontia.

Etiology

Environmental factors

The differences found between monozygotic twins suggest an environmental influence in hypodontia. The failure of tooth bud cell proliferation from the dental lamina may be due to infection (e.g. rubella, osteomyelitis), trauma, drugs (e.g. thalidomide), chemotherapy or radiotherapy at a young age. In addition, Kjaer et al. suggested that the pathogenesis of mandibular tooth agenesis was related to disturbances in nerve tissue, oral mucosa and supporting tissues, all of which interact during odontogenesis.

Genetic factors

A strong genetic component is suggested from monozygotic twin studies. Segregation analyses in many family studies have indicated that hypodontia is a single-gene defect, often transmitted as an autosomal dominant trait with incomplete penetrance and variable expressivity. Mutation of MSX1 and PAX9 genes are known to cause missing permanent teeth. Mice lacking Msx1 function manifest cleft palate, deficient mandibular and maxillary alveolar bones, and failure of tooth development. Hypodontia is also often
seen in syndromes, particularly those involving ectodermal anomalies, and in non-syndromic conditions such as cleft lip/alveolus with or without cleft palate. Tooth agenesis is probably caused by several independent defective genes, acting alone or in combination with others, which eventually lead to specific phenotypes.

Associated conditions

Ectodermal dysplasia

Ectodermal dysplasia (ED) refers to a group of inherited disorders involving the ectodermally derived structures. These conditions are usually X-linked or autosomal dominant. The clinical presentations of the hypohydrotic X-linked form include multiple congenitally missing teeth, fine sparse hair, dry skin, and frontal bossing with hypoplastic maxilla. Rather than shape and enamel anomalies, dental agenesis is the primary abnormality in EDs. Many reports have emphasized the range of abnormalities (from hypodontia to anodontia of the primary or permanent teeth) in the diagnosis of ED. Till and Marques reported that approximately 25% of ED children present with anodontia, whereas 75% present with oligodontia. Crawford et al. noted that in permanent tooth hypodontia, affected boys had an average of 24 missing permanent teeth, in contrast to affected girls who had an average of four. The consequences of dental ageneses are retarded maxillary and mandibular growth in sagittal and transverse direction, and also a decreased alveolar height in case of severe hypodontia.

Cleft lip and palate

Disruption of the dental lamina in cleft palate patients may cause abnormal induction or proliferation of the oral mesenchyme, which leads to the formation of supernumerary teeth and hypodontia at the same time. The congenital absence of permanent teeth is significantly more common in children with cleft lip (CL) and or cleft palate (CP), both inside and outside the cleft region than in the normal population. The prevalence of hypodontia (excluding third molars) ranged from 5 to 21% in patients with CL with or without cleft alveolus; it ranged from 28 to 49% in persons with unilateral cleft lip and palate (CLP), 18 to 29% in those with bilateral CLP, and 23 to 27% in isolated CP sufferers. The prevalence of hypodontia increases with the extension and severity of CP (e.g. submucous 27%, partial 30%, and complete CP 41%) in patients with cleft deformities, the teeth that are most frequently missing (excluding third molars) are the maxillary permanent lateral incisors in the cleft area. Outside the cleft region, the most frequently missing teeth are the maxillary second premolars (8-32%), followed by the mandibular second premolars (0.4-11%) and the maxillary lateral incisors (3-10%). These rates are much higher than the corresponding rates in children without cleft defects. In all cleft defect groups, hypodontia also involves other teeth that more often are less sensitive to disturbances than in controls without cleft defects. More teeth are congenitally missing from the upper than from the lower jaw. In unilateral defects, hypodontia is more frequent on the affected side of the upper jaw than in those without cleft defects.

Down syndrome

The prevalence of hypodontia in Down syndrome patients ranged from 40 to 60%, about half of whom had absence of one or two teeth, and only 7% were missing 6 or more. In the Caucasian Down syndrome population, the most frequently absent teeth were the maxillary lateral incisors followed by the mandibular second premolars and maxillary second premolars. A different sequence was reported in the Japanese Down syndrome population, where the mandibular lateral incisors (23%) were the most affected teeth, followed by the maxillary second premolars (18%), the maxillary lateral incisors (16%), and the mandibular second premolars (15%). As compared to the normal population, mandibular second premolars and maxillary lateral incisors were the most commonly missing teeth in the Caucasian population, while the mandibular incisors were the most commonly missing teeth in the Japanese population.

Hemifacial microsomia

Hemifacial microsomia (HFM) patients are 5 times more likely to have missing teeth than the general population. This may be attributed to a disturbance in the development of neural crest cells in the dorsolateral aspect of the developing neural tube, where mandibular tissues and dentine originate. The prevalence of hypodontia among HFM patients ranged from 18 to 27%, however third molars were included in some of the studies. The prevalence was found to increase with increasing severity of mandibular deformity. Type III HFM cases had the highest prevalence of hypodontia (69%), in which there is complete absence of the ramus, glenoid fossa, and temporomandibular joint. Whilst in type I cases, in which
the sizes of the mandible, ramus and glenoid fossa are reduced, the prevalence was reported to be only 23%  

The pattern of hypodontia in HFM patients was described as follows: 17% had bilateral absence of teeth, 13% had missing teeth on the side ipsilateral to the mandibular deformity, and 3% had missing teeth contralateral to the side of the mandibular deformity  

No difference in prevalence was found between maxillary and mandibular missing teeth. The most commonly missing were mandibular second premolars, followed by maxillary second molars, mandibular second molars, and mandibular lateral incisors; while both maxillary and mandibular first premolars and first permanent molars were missing least commonly  

Prevalence
Primary dentition
The prevalence of hypodontia in primary dentition is generally low (about 0.5%)  

A strong correlation was found between missing primary teeth and their permanent successors: it was reported that about 60 to 100% of those who had missing primary teeth also had missing permanent successors  

About half of the children with hypodontia in the primary dentition involved only one primary tooth, and 8% had more than two missing primary teeth  

The most frequently affected primary teeth are the maxillary and mandibular lateral incisors, and hypodontia of maxillary lateral incisors occurred twice as frequently as that of mandibular lateral incisors  

Permanent dentition
Ethnic difference
The prevalence of hypodontia in permanent teeth has been reported to vary from 2.2 to 10.1%, while most studies indicate a range of 6 to 8%  

A recent meta-analysis showed that Australian Caucasians have the highest prevalence (6.3%) of hypodontia, followed by European Caucasians (5.5%) and North American Caucasians (3.9%). Prevalence in African Americans (3.8%), Saudi Arabs (2.5%), and Chinese (6.9%) were not included in the meta-analysis, as the tooth samples were considered too small.

It is important to critically appraise each study before pooling its data with others, lest the results mislead. In early studies, radiographs were either not taken or only taken when hypodontia was suspected, and some even ignored a previous history of extraction and trauma. Moreover, in some studies, children were examined at the age of 6 years, in whom late development of permanent teeth would be misinterpreted as absent, particularly for second premolars. Therefore the reported differences in prevalence between various, mostly retrospective studies may not be due to true ethnic differences, but caused by variations in data collection, recall bias, timing, and sampling methodology.

Sex difference
Most studies showed a higher prevalence of hypodontia in females as was evident in the meta-analysis, which demonstrated a male to female prevalence ratio of 1:1.4  

The case is exceptional in ED as it is transmitted with an X-linked mode of inheritance and the presentation would be more severe in male patients.

Distribution of hypodontia teeth
The third molar is the most commonly missing tooth in the permanent dentition, being absent in about one fifth of the population  

Among the remaining 28 teeth, in the Caucasian population the most frequently affected were mandibular second premolars (41%), maxillary lateral incisors (23%), maxillary second premolars (21%), and the mandibular incisors (6%)  

Unilateral occurrence of dental agenesis is more common than bilateral occurrence, except for maxillary lateral incisors  

However the Asian population has a different distribution, with mandibular incisors being the most commonly missing teeth in the Chinese and Japanese populations  

In the Chinese population, 60% of all missing teeth were the mandibular permanent incisors, followed by maxillary second premolars (10%) and maxillary lateral incisors (8%)  

Severity
Most (83%) patients with hypodontia have absence of one or two permanent teeth only. Congenital absence of four or more permanent teeth (excluding third molars) was found to be as low as 0.3% in the Swedish population  

and the absence of six permanent teeth is encountered in only 0.1% , usually in association with other conditions.

Associated dental anomalies
Microdontia
The association between hypodontia and microdontia is well established. The presence of peg-shaped maxillary lateral incisors was frequently associated with absence
of the contralateral incisor. Peg-shaped maxillary lateral incisors were observed in 8.9% of hypodontia patients, while this anomaly only affected 1.6% of the general population. Permanent tooth dimensions are reported to be significantly smaller in severe cases (with six or more congenitally missing teeth).

Transposition of permanent teeth

In patients with maxillary canine–first premolar transposition, agenesis of third molars occurred at a near-normal rate (19%), while the prevalence of maxillary lateral incisor agenesis (26%) was 16-fold higher than that in the normal population (1.6%).

Ectopic permanent canine teeth

A higher prevalence of palatal displacement of both maxillary and mandibular canines was found in patients with hypodontia. In such cases the prevalence of palatally displaced canines was reported to be 5% in patients with one third of patients with palatally displaced canines had congenitally missing permanent teeth. The close association between impacted canines and hypodontia may suggest a common underlying genetic mechanism.

Taurodontism

A higher prevalence of taurodontism was reported in hypodontia patients, the mandibular first permanent molar being affected in one third of them, which is much higher than in the normal population (7%).

Infraocclusion of primary molar teeth

Two thirds of hypodontia patients were reported to have infraocclusion of primary molars, which was much higher than that in 6- to 11-year-old children (8-14%) in the general population reported by Kurol.

Skeletal pattern in hypodontia case

The maxillary or mandibular lengths were not reduced or affected in mild types of hypodontia. Only in severe hypodontia (with the absence of six teeth) or in oligodontia, associated findings (flat or concave facial profile, obtuse nasolabial angle, retrognathic maxilla, reduced anterior face height and mandibular plane angle) were reported.

A significant retroclination of incisors and an increased interincisal angle were also observed with increasing severity of hypodontia.

On the whole, the typical dentofacial structure in persons with untreated hypodontia was due to dental and functional compensation (e.g. the over-eruption of unopposed teeth, the axial inclination of teeth adjacent to edentulous spaces, the retention of primary teeth, etc.) On the contrary, it seemed that different growth patterns of hypodontia had little effect on general growth.

Treatment modalities for hypodontia patients

Space closure

Spontaneous space closure

The mandibular second premolar was the most commonly missing tooth in the Caucasian populations. Correct timing of the extraction for the early loss of the primary second molars was advocated to facilitate bodily movement of the permanent first molars. Lindqvist reported that there was a residual space of 2 mm in the mandible and less than 1 mm in the maxilla 4 years after extraction of the primary second molars. Mamopoulou et al also showed a similar finding and reported that most of the extraction space closed during the first year and unilateral extractions caused midline shift to the same side in the mandible. It is suggested that 8 to 9 years old is the ideal age for extraction of primary second molars to facilitate spontaneous space closure, by that age the first premolars have already achieved good occlusion. However, possible delayed development of the second premolar should also be considered. For example, a mandibular second premolar, diagnosed as agenetic in a 7-year-old, eventually developed after the patient was 10 years old. Therefore diagnosis of mandibular second premolar agenesis before the age of 7 years is probably not reliable.

Conventional orthodontic space closure

In conventional orthodontics, anchorage is reinforced by grouping teeth as a block, adding palatal root torque to the anchor teeth and the use of Class II or Class III elastic to facilitate forward movement of posterior teeth to close the edentulous space. However unwanted tooth movement still occurs, therefore in hypodontia patients with retrusive or flat facial profiles, orthodontic space closure is not always a good option with the conventional techniques.
Orthodontics and reverse headgear
In the presence of hypodontia, reverse headgear has been recommended to provide anchorage, so as to move maxillary posterior teeth forward to close the edentulous space or advance the hypoplastic maxilla. However, this procedure requires a high level of patient cooperation.

Orthodontics and the ‘absolute’ anchorage system
The introduction of ‘absolute’ anchorage systems helps reduce the anchorage control problem for orthodontic tooth movement.

Micro/miniscrew system
The miniscrews used in orthodontics are not osseointegrated implants; their small dimensions make them more versatile in the sites that they can be placed. In hypodontia patients, they were placed in the mandibular retromolar area to push molars and close the void due to congenital missing premolars, without affecting the incisal angulation. Moreover there was no imperative for patient compliance, once they had been fitted. They could also be placed in the alveolar process, buccal to the premolars, so as to provide anchorage for vertical and sagittal movement of both molars and premolars.

Osseointegrated implant system
Owing to the reduced bone height available in the palate, implantation of small endosseous palatal implants (4-6 mm in length, 3.3 mm in diameter) in the anterior middle region was suggested with a view to prevent perforation into the nasal cavity. This would also provide absolute anchorage control for orthodontic movement of the anterior teeth and for mesialization of the posterior teeth. In cases where posterior teeth are missing, this technique can also be used to reinforce anchorage during protraction of the nasomaxillary complex.

Onplant system
Onplant was first described by Block and Hoffman in 1995. It is a type of subperiosteal implant comprising an 8-10 mm subperiosteal disc with a textured hydroxyapatite coating for integration with palatal bone. The onplant does not sit in a bony cavity; it only rests on the surface of the palatal bone. Once the onplant is uncovered, transpalatal bars can be used to gain anchorage reinforcement.

Mini-plate system
Use of titanium mini-plates secured with screws have been reported to act as absolute orthodontic anchorage units. The anchor plates can be placed at the piriform opening rim, the zygomatic buttresses, and any regions of the mandibular cortical bone. As all portions of the anchor plates and screws are placed outside the teeth, they do not interfere with tooth movement.

Orthodontics and orthognathic surgery
Where hypodontia patients present with skeletal discrepancies, orthognathic surgery can be used to reduce the space surgically and simultaneously harmonize the skeletal pattern. For example, in patients with a prognathic maxilla and missing maxillary teeth, Le Fort I osteotomy with segmentation can be used to set back the anterior segment and reduce the space surgically. On the other hand, provided the facial profile is good, the edentulous space could also be reduced by recourse to Le Fort I osteotomy, which involves advancing the posterior segments surgically.

If the absent teeth are in the lower arch, anterior subapical osteotomy or body osteotomy could be used to reduce edentulous spaces.

Other surgical techniques to treat the atrophic alveolar ridge
Absence of teeth is associated with alveolar bone atrophy (Wolff’s law). An atrophic alveolar ridge is common in patients with hypodontia and creates problems for dental implantation or orthodontic tooth movement. Ridge augmentation could be carried out by autogenous bone graft, distraction osteogenesis, and the following bone induction techniques.

Bone graft for alveolar ridge augmentation
Autogenous cancellous bone grafting has been considered the gold standard for bone induction. However its associated disadvantages are morbidity of the donor bed, infection and unpredictable absorption, particularly during the months prior to implant placement (due to contraction of adjacent soft tissues).

Distraction osteogenesis of the alveolar ridge
The use of distraction osteogenesis for alveolar ridge augmentation was first reported by Chin and Toth. Standardized protocols are not yet established, but in general a latency period of 5-7 days is recommended with a distraction rate of 0.5-1 mm/day and a consolidation period of 8-12 weeks.

Since there is no need to obtain bone from elsewhere, surgery time and postoperative morbidity are evidently reduced, such that it has now become...
a popular means of alveolar ridge augmentation. Problems that may arise during alveolar distraction ensue during distractor placement; they include incorrect direction of distraction and associated soft-tissue complications \(^{60}\).

Transport distraction osteogenesis

In transport distraction, bone is distracted in the direction of the defect by osteotomy of bone adjacent to the affected bone. It has been applied to close alveolar cleft defects \(^{61}\) and those created after tumor excision \(^{62}\).

The advantages of transport distraction are: simultaneous distraction of the surrounding soft tissue with new bone formation, e.g. to be used for dental implants. Also there is no requirement for donor-site sacrifice and the possibility of performing all procedures on an outpatient basis. Its disadvantages are the need for relatively complex procedures and the requirement of precise micro-adjustment.

Dentoalveolar distraction

Application of dentoalveolar distraction for rapid orthodontic tooth movement into fresh extraction sockets was first reported by Liou and Huang in 1998 \(^{63}\). Full retraction of the canines could be achieved in around 10 days, with minimal anchorage loss and the overall treatment time reduced by nearly 50\% \(^{64}\). No root fracture, root resorption, ankylosis, periodontal problems, and soft tissue dehiscence was observed with this technique \(^{65}\).

Orthodontic space redistribution

For prosthetic replacement

In some hypodontia cases, orthodontic space redistribution is needed to facilitate prosthetic replacement. To make a more favorable abutment for a prosthesis, orthodontic uprighting of a mesially tilted molar is quite common.

For implants for oral rehabilitation

Since Branemark et al. \(^{66}\) introduced the possibility of direct alveolar anchorage for the replacement of missing teeth, osseointegrated implants have been used successfully in dentistry for more than 30 years. Implants are a predictable and successful means of replacing missing teeth by supporting crowns, bridges, overdentures and other maxillofacial prostheses. In longitudinal studies, conventional implant treatment has a success rate of 91 to 99\% in the mandible and 84 to 92\% in the maxilla \(^{67,68}\).

Patients with congenitally missing teeth usually present in childhood, but implant placement usually has to be postponed till the completion of skeletal growth. During the interim period, preservation of alveolar bone volume is important. However, in severe hypodontia with large edentulous spaces and no expected development of alveolar processes, exceptionally implants can be placed at an earlier age.

For autotransplantation

Autotransplantation was developed in the 1970s for the replacement of missing incisors due to adolescent trauma \(^{69}\). It was reported to be as successful as dental implants, so long as an appropriate protocol was used \(^{70}\). Transplanted teeth need to have an open apex to allow revascularization of the pulp and sufficient root length to allow continued development of the root \(^{71}\). The prognosis for complete periodontal healing was better than 90\% if the donor teeth reached 2/3 to 3/4 of their final root length \(^{72}\); an atraumatic surgical procedure is essential to avoid damaging the follicle, disturbing Hertwigs epithelial root sheath and compromising further root development \(^{73}\). Therefore autotransplantation is a very operator-dependent technique, and its success rate varies from 50 to 100\%. Ensuring an adequate mesio-distal and labiopalatal space, bone support and keratinized gingiva in the recipient site are also important. During the first 2 months, it is also necessary to avoid jiggling contacts between the transplanted and opposing tooth, though physiological mobility should be allowed during the period of splinting.

A long-term survival rate of 90\% and success rate of 79\% (two out of 33 transplants had ankylosed) for autotransplanted premolar teeth were reported after a mean observation period of more than 25 years (range, 17-41 years) \(^{74}\). These patients generally responded very favorably with regard to how they perceived their treatment; their only reservation was related to discomfort during surgery \(^{74}\).

Bone induction

Bone induction (involving synthetic or allogeneic materials) was developed to assist in bone repair, to overcome the major limitations of autogenous bone graft. Three general approaches: matrix-based, factor-based, and cell-based techniques have been developed to facilitate this process \(^{75}\).
Both in vivo and ex vivo gene therapies used in bone induction have achieved promising and effective results. Gene transfer in vivo using non-viral vectors 76 and viral vector constructs 77 have been developed. Their improved safety widens the fields in which they can be applied. Ex vivo gene therapy by genetically transfected cells that express osteogenic growth factor 78 to promote bone regeneration in bony defects is also a promising strategy.

Conventional restorative procedures

Restorative reshaping treatment
Hypodontia with a tooth-size discrepancy has considerable impact on the final occlusion. To achieve a good interdigitated occlusion, reshaping of teeth and a composite build-up or veneers have to be considered. Zachrisson and Mjör 79 showed that extensive cuspal, labial, lingual, and interproximal contouring of the canine to mimic lateral incisors did not create any patient discomfort and resulted in only minor short-term clinical and radiographic reactions.

Fixed and removable partial dentures
Fixed partial dentures like conventional and resin-bonded bridges are the preferred definitive restorative interventions for the majority of hypodontia patients, if only a few teeth are missing. At a young age, a resin-bonded bridge is preferable to a conventional bridging due to the size of the immature pulp; it may also be used as an interim prosthesis before placement of an implant. Two-unit cantilevered resin-bonded bridges were found to have a mean service life of 4 years and 4 months (standard deviation, 20 months) with a range of 13 to 142 months 80. For conventional bridges, a survival rate of about 84% after 10 years was reported; long bridges had lower survival rates 81.

The use of overdentures and removable partial dentures were reported to be a more economic option to restore appearance and function in severe oligodontia 82. They can also serve as space maintainers before definitive restorative work and as a bite plane that increases the vertical dimension in cases of overclosure. However, their prolonged use may increase the risk of caries and periodontal disease, unless there is excellent oral hygiene and daily use of topical fluoride.

Conclusions and future perspectives

The future—organ engineering
The generation of biological tooth substitutes from autologous human tissues might be a future alternative to replacement of missing teeth in hypodontia patients. Tissue engineering shows promise in this area 83. In the fields of maxillofacial surgery, it has been used to generate mandibular condyles 84. Cultured human dental pulp and gingival fibroblasts adhering to biodegradable scaffolds have been shown to proliferate and differentiate in vitro 85 and in vivo 86.

More recently, the successful bioengineering of a whole tooth crown composing of accurately formed enamel, dentin, and pulp tissues was reported in pigs 87. Furthermore, tooth structures generated from non-dental mesenchymal cells placed in contact with embryonic oral epithelium and transplanted to an ectopic site 88 was able to bioengineer tooth tissues. These observations offer very exciting opportunities for replacement of natural teeth damaged through disease, trauma, or missing due to hypodontia. However many practical obstacles need to be overcome before such techniques become available as routine clinical treatment.

Conclusions
Successful outcomes in the management of patients with hypodontia depend on careful diagnosis and treatment planning, which requires cohesive cooperation between specialists in different disciplines. With the development of new materials and techniques, the education of those who provide clinical care for hypodontia patients needs to be updated. In addition, excellent communication with patients and parents (including informed consent) is necessary, as the treatment duration for patients with hypodontia may extend over many years.

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