

Preliminary Insights into Association of Growth Factors with Hypodontia: A Clinical Study

Rana H Alenzi¹⁻³, Abdullah F Alshammari⁴, Mashan L Abdullah¹⁻³, Sultan M Aldukhyeel¹, Mohammed N Aldosari¹, Yousef I Aljameel¹

¹King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia; ²King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; ³King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; ⁴Department of Basic Dental and Medical Science, College of Dentistry, University of Ha'il, Ha'il, Saudi Arabia

Correspondence: Mashan L Abdullah, Email Aldlamyme@mngha.med.sa

Purpose: Hypodontia, defined as the congenital absence of teeth, may reflect underlying disturbances in molecular pathways regulating odontogenesis. This pilot cross-sectional study aimed to investigate whether systemic levels of insulin-like growth factors (IGFs), IGF-binding proteins (IGFBPs), and human growth hormone (HGH) differ between individuals with congenital bilateral absence of mandibular second premolars and individuals with normal dentition.

Methods: Twenty-two participants aged 12–31 years were included and allocated into two groups: individuals with congenital bilateral absence of mandibular second premolars (n = 11) and age- and sex-matched controls (n = 11). Hypodontia was confirmed using panoramic radiographs. Plasma concentrations of IGF-I, IGF-II, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-6, and HGH were measured via multiplex magnetic bead assays. Between-group comparisons were performed using the Mann–Whitney *U*-test.

Results: No statistically significant differences in the IGF-I (p = 0.897), IGF-II (p = 0.519), IGFBP-2 (p = 0.573), IGFBP-3 (p = 0.189), IGFBP-4 (p = 0.380), IGFBP-6 (p = 0.193), or HGH levels (p = 0.747) were observed between the hypodontia and control groups. Exploratory analyses suggested age- and body mass index-related variability in the IGF-I levels, indicating potential metabolic influences on circulating growth factor profiles.

Conclusion: In this small exploratory cohort, the systemic IGF, IGFBP, and HGH levels did not differ significantly between the individuals with and without hypodontia. These findings suggest that circulating growth factor alterations are unlikely to play a dominant role in nonsyndromic mandibular second premolar agenesis. Larger, well-controlled studies incorporating tissue-specific or genetic analyses are required to clarify the biological mechanisms underlying hypodontia.

Keywords: congenital abnormalities, growth factors, hypodontia, insulin-like growth factor-binding proteins, odontogenesis

Introduction

Hypodontia, defined as the congenital absence or agenesis of up to six teeth (excluding third molars), is the most prevalent dental developmental anomaly in humans.¹ Studies have identified genetic regulation and environmental influences as key factors contributing to its aetiology.² During early odontogenesis, disruptions in signalling pathways between epithelial and mesenchymal tissues derived from neural crest cells can occur.³ These disruptions may alter tooth morphogenesis, resulting in conditions such as hypodontia.² Environmental factors, such as viral infections (eg rubella), pharmaceutical agents (eg thalidomide), dental trauma, radiation therapy, and jaw surgeries, have also been implicated.⁴ A study involving schoolchildren in Saudi Arabia revealed a hypodontia prevalence rate of 4%.⁵ Notably, mandibular second premolars were the most affected (1.6%), followed by maxillary lateral incisors and maxillary second premolars.⁶ The congenital absence of teeth has been linked to sociopsychological challenges, particularly during puberty, as well as functional complications such as mastication difficulties, speech impairments, and alveolar bone atrophy.³

Insulin-like growth factors (IGFs) including IGF-I and IGF-II are key regulators of postnatal growth and tissue development. Their activity is modulated by specific high-affinity IGF-binding proteins (IGFBPs), which control bioavailability and half-life in circulation.⁷

Among the six high-affinity IGFbps, several (eg IGFbp-2, -3, -4, and -6) modulate IGF action and have been implicated in cellular proliferation and differentiation relevant to craniofacial development. Growth hormones (GHs) stimulate the production of IGF-I and IGFbp-3, and individuals with GH deficiencies (GHDs) exhibit reduced levels of these substances in their serum.⁸ Tooth anomalies associated with GHD include smaller crowns and delayed eruption of permanent teeth.⁹ Conversely, individuals with acromegaly exhibit elevated serum levels of IGF-I and IGFbp-3.¹⁰ These findings highlight the complex interplay between hormonal regulation and dental development.

During tooth development, growth factors, such as fibroblast growth factors, transforming growth factors, bone morphogenetic proteins, and IGFs, regulate intercellular interactions between epithelial and mesenchymal tissues.¹¹ The binding of IGF-I to its receptor in dental tissues triggers a cascade of biological processes, including cell proliferation and differentiation as well as apoptosis inhibition. Each IGFbp exhibits unique tissue expression patterns and mechanisms of action, either enhancing or inhibiting IGF activity depending on cell type and specific physiological conditions.¹²

One notable case study involved a patient with leprechaunism, a rare congenital syndrome characterized by severe insulin resistance and cognitive impairment.¹³ Long-term treatment with recombinant human IGF-I resulted in abnormal enlargement and malformation of multiple teeth, including the upper and lower canines and lower premolars.

The dental lamina is essential for enamel organ formation in both deciduous and permanent teeth, with tightly regulated epithelial extensions guiding tooth development during prenatal and early postnatal stages.¹⁴ Although tooth agenesis is primarily linked to genetic and local developmental mechanisms, systemic endocrine factors may influence odontogenesis during critical developmental windows. Circulating IGFs and their binding proteins represent accessible biomarkers of growth-related signalling and have been implicated in other craniofacial growth conditions. However, whether subtle variations in systemic growth factor profiles are detectable in individuals with isolated, nonsyndromic mandibular second premolar agenesis remains unclear. Addressing this gap may help clarify whether systemic hormonal alterations contribute to or reflect developmental susceptibility to hypodontia.¹⁴

Accordingly, this pilot study aimed to explore whether circulating levels of IGFs, their binding proteins, and human growth hormone (HGH) differ between individuals with isolated bilateral mandibular second premolar agenesis and matched controls. Given the limited existing evidence, this investigation was designed as an exploratory, hypothesis-generating analysis rather than a confirmatory assessment. To test this, we compared the levels of these proteins between affected individuals and matched controls to identify any significant systemic differences.

Despite growing evidence supporting the role of genetic mutations and local signalling pathways in tooth agenesis, the contribution of systemic growth factor profiles to isolated nonsyndromic hypodontia remains poorly understood. Most existing studies have focused on local expression patterns within dental tissues or on syndromic conditions associated with overt endocrine abnormalities. In contrast, limited data are available regarding whether subtle variations in the levels of circulating IGFs, their binding proteins, or GH are detectable in individuals with isolated mandibular second premolar agenesis. Recent reviews have emphasized the multifactorial nature of hypodontia and highlighted the need for integrative approaches that consider both systemic and local biological influences on odontogenesis.^{15,16}

Patients and Methods

Study Duration

This cross-sectional study was conducted from June 2021 to October 2023.

Participants

Twenty-six participants, aged 12–31 years, were initially enrolled in this pilot study and categorized into two groups. The patient group comprised 11 patients with congenital bilateral absence of the lower second premolars (hypodontia), confirmed through routine dental examinations and panoramic radiographs. The control group included 11 volunteers with no history of missing teeth, carefully matched to the patient group in terms of number, age, medical history, and place of residence. Participants were recruited from individuals receiving routine dental care and attending orthodontic clinics at King Abdul-Aziz Medical City in Riyadh, Saudi Arabia, and its primary healthcare centre in Ha'il City. Given the exploratory nature of this pilot study, no a priori power calculation was performed. The sample size was determined

pragmatically based on feasibility, recruitment availability, and resource constraints, with the primary aim of estimating variability and generating preliminary data to inform the design of future adequately powered studies.

The inclusion criteria for the patient group were 1) congenital bilateral absence of mandibular second premolars confirmed by panoramic radiography, 2) age of 12–31 years, and 3) absence of known syndromic conditions. The control group was required to have a complete permanent dentition excluding third molars and no history of tooth agenesis or extraction. The exclusion criteria for both groups included a history of systemic endocrine disorders (eg GHD or diabetes mellitus), previous orthodontic extractions, craniofacial syndromes, systemic inflammatory disease, or current use of medications known to affect growth factor levels.

Body mass index (BMI) was calculated using the standard formula: weight in kilograms divided by the square of height in metres (kg/m^2). No statistical adjustments were made for age or sex due to the limited sample size, but these variables were recorded and considered during the interpretation of results.

Four individuals were excluded due to unilateral absence of lower second premolars, tooth extraction due to dental issues, or medical conditions such as diabetes mellitus or GHD. The final groups consisted of 11 participants each, with the patient group having three male participants and eight female participants.

This study was approved by the Institutional Review Board of King Abdullah International Medical Research Center (Protocol No. NRC21R/141/04). Written informed consent was obtained from all participants or their legal guardians prior to inclusion in the study. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Blood Collection

Blood samples were collected in a non-fasting state to reflect baseline systemic hormone levels under typical physiological conditions. Although fasting can influence certain metabolic parameters, IGFs, IGFBPs, and HGH are relatively stable and not acutely affected by food intake, making non-fasting collection appropriate in this exploratory setting. Approximately 4 mL of venous blood was drawn from each participant and collected into purple-capped tubes containing ethylene diamine tetra-acetic acid as an anticoagulant. Samples were centrifuged at 4000–5000 rpm for 5 min to separate plasma, which was then aliquoted into three equal-volume tubes and stored at -18°C or below until analysis.

Laboratory Analysis

Blood parameters, including IGF-I, IGF-II, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-6, and HGH levels, were measured using commercially available magnetic bead panels from Merck KGaA (Darmstadt, Germany). Plasma samples (25 μL per assay) were analyzed in duplicate following overnight incubation, as per the manufacturer's instructions. Hormone levels were quantified based on mean fluorescent intensity using the Luminex FLEXMAP 3D system and xPONENT software v4.2 (Luminex Corporation, Austin, USA). The results were calculated via a five-parameter logistic regression of the standard curve, processed using the Belysa software v1.1.0 (Merck KGaA). Details of the standard curve data are provided in the supplementary section.

All laboratory measurements were performed in duplicate. Data quality was assessed using the coefficient of variation between duplicate measurements. Samples with unacceptably high variability were excluded from the final analysis for the affected parameter only and were not imputed. No other missing data were present.

Statistical Analysis

The Mann–Whitney *U*-test, a nonparametric method for comparing two independent samples, was used to analyze and compare the levels of IGF-I, IGF-II, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-6, and HGH between the control and patient groups. A *p*-value of >0.05 indicated no statistically significant difference between the medians of the two groups, supporting the null hypothesis of equal medians. Conversely, a *p*-value of ≤ 0.05 indicated a statistically significant difference, leading to the rejection of the null hypothesis and confirming that the medians of the two groups were unequal. Due to the exploratory design and small sample size, statistical adjustments for BMI, age, and sex were not feasible. These confounders should be rigorously controlled in future studies.

The Mann–Whitney *U*-test was selected due to the small sample size and the non-normal distribution of several biomarker variables, as assessed through visual inspection and summary statistics. Effect size estimation and

multivariable analyses were not performed because of limited statistical power. Accordingly, all statistical analyses were interpreted descriptively and considered exploratory.

Results

The study included 22 participants divided into two groups: individuals with congenital bilateral absence of mandibular second premolars (hypodontia group, $n = 11$) and controls with complete permanent dentition excluding third molars (control group, $n = 11$). The demographic and clinical characteristics of the participants are summarized in [Supplementary Table 1](#). The mean plasma concentrations of IGFs, IGFBPs, and HGH for both groups are presented in [Supplementary Table 2](#) and [Figure 1](#).

No statistically significant differences were observed between the hypodontia and control groups for any of the analyzed biomarkers. The mean plasma IGF-I levels were comparable between the hypodontia (mean $\pm$ SD: 72.3 ± 19.6 ng/mL) and

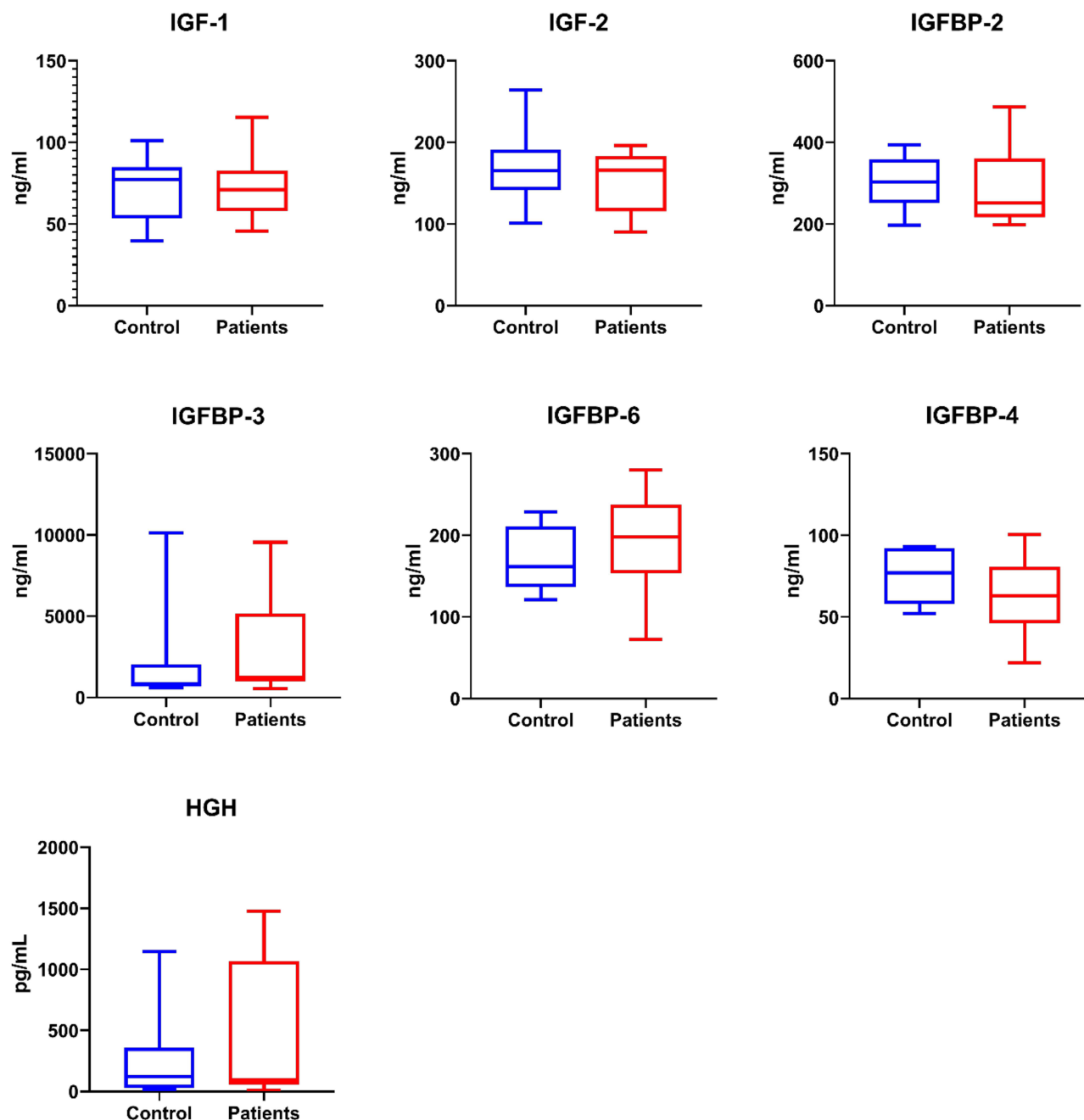


Figure 1 Hormone Level Comparison between the Control and Patient Groups.

control groups (71.5 ± 19.6 ng/mL), with no significant difference detected ($p = 0.897$). Similarly, the IGF-II concentrations did not differ significantly between the groups ($p = 0.519$).

The analysis of IGFBPs also demonstrated no significant between-group differences. The plasma IGFBP-2 levels were similar in the hypodontia and control groups ($p = 0.573$). No statistically significant differences were observed in the IGFBP-3 ($p = 0.189$), IGFBP-4 ($p = 0.380$), or IGFBP-6 levels ($p = 0.193$). The HGH concentrations were likewise comparable between the groups, with mean levels of 471.9 ± 559 pg/mL in the hypodontia group and 281 ± 372 pg/mL in the control group ($p = 0.747$).

Exploratory descriptive observations were made within the subgroup of participants aged 12–14 years. Among these individuals, variability in the IGF-I concentrations was observed across both groups. Two participants, one from the hypodontia group and one from the control group, exhibited the lowest IGF-I levels (48.4 ng/mL and 39.6 ng/mL, respectively). These participants also differed in BMI classification, with one categorized as underweight (BMI: 15.8 kg/m²) and the other as obese (BMI: 42.3 kg/m²). In addition, lower plasma IGFBP-4 levels were observed in two participants within the hypodontia group. These findings are reported descriptively, and no formal statistical comparisons were conducted for subgroup analyses.

Discussion

This pilot study explored whether systemic levels of IGFs, their binding proteins, and HGH differ between individuals with isolated bilateral mandibular second premolar agenesis and matched controls. Contrary to the initial hypothesis, no statistically significant differences were identified between the groups for any of the analyzed biomarkers. These findings suggest that circulating growth factor profiles, as measured in plasma, may not reflect mechanisms underlying isolated nonsyndromic hypodontia. This study involved 22 participants categorized into two groups: patient group ($n = 11$), with congenital absence of lower premolars, and control group ($n = 11$), without tooth loss, as presented in [Supplementary Table 1](#). We aimed to examine the relationship between hypodontia, specific growth factors, and binding proteins. The results showed no significant differences in the levels of IGF-I, IGF-II, IGFBP-2, IGFBP-4, IGFBP-6, or IGFBP-3 between the two groups, challenging the hypothesized association between altered levels of these factors and hypodontia in the studied population.

Although widely suggested, the impact of IGF-I and IGF-II on tooth agenesis lacks substantial supporting evidence.¹⁷ One study demonstrated the role of IGF-I in promoting cell proliferation and mineralization in dental pulp cells, wherein immunohistochemistry and in situ hybridization studies confirmed the paracrine and autocrine functions of IGF-I during tooth morphogenesis, highlighting its dynamic role.¹⁷ Moreover, local synthesis of IGF-I and IGF-II by odontogenic cells has been observed.¹¹ These findings should be interpreted cautiously and do not demonstrate a statistically significant association between systemic IGF levels and tooth agenesis. Predominant IGF-I expression has been noted in epithelial tissues, particularly within the dental lamina and adjacent oral epithelium, underscoring its importance up to the early bell stage, followed by a decline primarily within the dental lamina.¹⁸

Our analysis of the IGF-I and IGF-II levels showed no statistically significant differences between the control and patient groups, suggesting that systemic IGF concentrations may not reflect mechanisms underlying isolated hypodontia ([Supplementary Table 1](#)). These findings highlight the complex interplay between local dental conditions, systemic factors, and the regulatory mechanisms underlying these growth factors. A deeper understanding of dental anomalies may necessitate investigating a broader spectrum of factors beyond IGF-I and IGF-II alone.

IGFBP-3, the most abundant circulating IGFBP, plays a multifaceted role in plasma by regulating IGF transport and its interaction with receptors.¹⁹ In addition to its IGF-dependent functions, IGFBP-3, along with IGFBP-5, exhibits IGF-independent activities, influencing essential cellular processes such as proliferation, migration, survival, and apoptosis.²⁰ In dental biology, IGFBP-2 and IGFBP-3 regulate the effects of IGF-I on dental pulp cells.²¹ Studies on mouse incisors have confirmed widespread IGF-I and IGF-IR expression in dental pulp, wherein IGF-I facilitates cell proliferation and migration as well as apoptosis suppression.²² Furthermore, a recent study showed that IGFBP-3 was transiently expressed during odontoblast differentiation, suggesting its involvement in restraining excessive proliferative actions while promoting cellular differentiation.²³

Although the mean IGFBP-3 levels were numerically higher in the hypodontia group, no statistically significant association was identified. However, this observation lacks statistical significance, as indicated in [Supplementary Table 1](#), making definitive conclusions premature. Further investigation using a larger sample size and rigorous statistical analyses

is essential to clarify this potential correlation. Similarly, the IGFBP-2 levels showed no significant differences between the groups. These findings underscore the need for a deeper understanding of IGF and IGFBP regulation in dental tissues, emphasizing the complex interplay of systemic factors and local dental conditions. Further research is required to elucidate the underlying mechanisms underpinning these relationships and to determine their clinical relevance.

The role of IGFBP-6 in odontogenesis, particularly its involvement within the IGF axis and the periodontal ligament, aligns with previous reports of a temporal increase in IGF-II and IGFBP-6 expression in periodontal ligament cells *in vivo*.²⁴ Although the present study did not reveal significant differences ($p = 0.193$), an intriguing observation was made: one participant in the patient group (P24) exhibited the lowest IGFBP-6 levels as well as reduced IGF-I and IGF-II levels. Although the overall statistical results lack significance, this isolated observation should be interpreted cautiously and may warrant further investigation in larger cohorts, emphasizing the importance of a larger sample size and a detailed medical history for a more nuanced understanding.

IGFBP-4, a member of the IGFBP family, exerts an inhibitory effect on IGF activity.²⁵ In this study, two patients with congenital absence of lower second premolars demonstrated a significant reduction in their plasma IGFBP-4 concentrations compared with age-matched participants ([Supplementary Table 2](#)). This observation did not reach statistical significance and should be interpreted cautiously, pending confirmation in future studies.

HGH plays a critical role in dental development, influencing preameloblast and odontoblast differentiation, enamel formation, and the complex processes involved in dentinogenesis.²⁶ Studies such as that by Smid et al, conducted on an animal model, highlight the impact of GH status on hard tooth tissues, revealing changes in crown size, root dimension, and mesiodistal width at the cemento-enamel junction in dwarf animals.²⁷ Their findings demonstrated that GH influences both pre-dentinogenesis and the appositional growth of dentin.²⁷ Despite these insights, limited attention has been paid to the prevalence of hypodontia in children with GHD. Sarnat et al reported a 30% incidence of hypodontia in cases of isolated GHD and Laron-type dwarfism.²⁸ Additionally, Torlińska-Walkowiak et al recently found that 33% of patients with GHD exhibited dental anomalies, including hypodontia, microdontia, or macrodontia.²⁹

While no statistically significant differences in the HGH levels were observed between the patient (471.9 pg/mL) and control groups (281 pg/mL) ($p = 0.747$), the numerical difference did not reach statistical significance and should not be interpreted as evidence of a biological association. In the context of a pilot study, such findings are informative in refining hypotheses for future research. Notably, the absence of statistical significance does not negate potential biological relevance, particularly in small, exploratory samples with high interindividual variability. More broadly, the absence of systemic hormone differences should not preclude a role for IGFs and GH in dental development. Odontogenesis is governed by tightly regulated epithelial–mesenchymal interactions involving paracrine and autocrine growth factor signalling. These localized tissue-level events may not be accurately captured by systemic biomarker profiles alone. Future research should consider incorporating salivary biomarkers, dental tissue-specific analyses, or gene expression profiling to more directly assess pathway activity at the site of tooth development.

Finally, the demographic heterogeneity within the cohort including wide age ranges (12–31 years), BMI extremes, and sex imbalance may have introduced residual confounding. These factors likely influence hormone profiles and further complicate the detection of associations with hypodontia. As such, this pilot study should be viewed as hypothesis-generating, with future studies requiring larger, matched cohorts and integrative methods to explore growth factor dynamics in dental anomalies. In summary, the analysis of the IGFBP-2, IGFBP-4, IGFBP-6, IGFBP-3, and HGH levels in the patients with hypodontia revealed unexpected results, challenging traditional assumptions in dental endocrinology.

Complex Interplay Between BMI, Age, and IGF-I Levels

The variations in the IGF-I levels among the individuals aged 12–14 years, particularly those with notably low IGF-I levels and contrasting BMI classifications, underscore a potentially complex relationship. A previous study showed strong associations between metabolic health, nutritional status, and IGF-I levels, with energy and protein intake playing crucial roles in restoring serum IGF-I levels after fasting.³⁰ Additionally, nutrient intake modulates plasma IGFBP levels: IGFBP-3 levels remain stable to support consistent IGF-I levels, whereas IGFBP-1 levels are rapidly suppressed by nutrient intake (31). IGF-I deficiencies have been linked to metabolic disorders, and imbalances in IGF-I/GH levels are

associated with obesity (32). In this study, among the six individuals aged 12–14 years, two – one from the patient group and one from the control group – had the lowest IGF-I levels, measured at 48.4 ng/mL and 39.6 ng/mL, respectively. These participants displayed striking differences in their BMI, with one classified as underweight (BMI: 15.8 kg/m²) and the other as extremely obese (BMI: 42.3 kg/m²). These findings highlight the need for further research to investigate the interplay between IGF-I levels, BMI, and age in the context of dental and metabolic health.

Integrating age and BMI considerations into future research may offer critical insights into differential risk patterns for hypodontia. For example, stratifying participants by metabolic status or developmental stage could help uncover whether systemic growth factor levels exert a more pronounced effect during specific periods of tooth development. Such subgroup analyses may also clarify whether metabolic health acts as a modifier rather than a primary cause in the aetiology of dental anomalies such as hypodontia.

Methodological Reflections and Limitations

This pilot study provides preliminary insights into the systemic hormonal profiles associated with isolated nonsyndromic hypodontia; however, several methodological limitations should be considered when interpreting the findings. The small sample size and cross-sectional design limited the statistical power and precluded multivariable analyses to adjust for potential confounders such as age, sex, and BMI. In addition, the wide age range, interindividual variability in hormone levels, BMI extremes, and sex imbalance may have further reduced the ability to detect subtle systemic differences.

Another important consideration is that circulating plasma biomarkers may not accurately reflect local growth factor activity within developing dental tissues. Odontogenesis is governed by tightly regulated epithelial–mesenchymal interactions and tissue-specific signalling events, which may not be captured through systemic measurements alone. Furthermore, the focus on a specific dental phenotype and the potential influence of unmeasured confounding factors may limit the generalizability of the results.

Despite the absence of statistically significant differences in the systemic IGF, IGFBP, and HGH levels between the individuals with and without hypodontia, the findings remain informative in an underexplored area of dental research. Negative or null results in early exploratory studies are valuable, as they help refine hypotheses, delineate the boundaries of biological relevance, and guide future research design. In this context, the present findings suggest that systemic variations in growth factor profiles are unlikely to play a dominant role in the aetiology of isolated nonsyndromic hypodontia.

Future studies should incorporate larger, demographically matched cohorts and apply longitudinal or mechanistic designs to better delineate the role of growth factor signalling in tooth development. Integrating systemic measurements with tissue-specific analyses, salivary biomarkers, or genetic profiling may provide more direct insights into the molecular pathways underlying hypodontia and clarify whether growth factor dysregulation contributes to dental agenesis at critical developmental stages rather than being detectable at the systemic level.

Conclusion

This pilot cross-sectional study explored systemic levels of IGFs, their binding proteins, and HGH in individuals with isolated bilateral mandibular second premolar agenesis compared with matched controls. No statistically significant differences were identified between the groups for any of the analyzed biomarkers.

The findings suggest that circulating growth factor profiles, as measured in plasma, are unlikely to reflect the biological mechanisms underlying isolated nonsyndromic hypodontia. However, given the small sample size, cross-sectional design, and interindividual variability, the results should be interpreted cautiously and regarded as hypothesis-generating rather than definitive.

Future investigations incorporating larger, well-matched cohorts and integrative approaches combining systemic, tissue-specific, and genetic analyses may provide more comprehensive insights into the molecular pathways involved in tooth agenesis.

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Disclosure

The authors report no conflicts of interest in this work.

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