Dental and skeletal development in various endocrine and metabolic diseases

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To define the role of various intrinsic hormonal factors and their relative importance in normal dental development, a study was made of dental growth in patients with known endocrine or metabolic dysfunction. Skeletal and dental ages were determined radiographically and compared with chronologic age to learn the effect of the disease on the rate of development.

Because of variations in development among individuals of the same chronologic age, the concept of physiologic or biologic age has been developed to describe progress toward completeness of development. Physiologic age is based on the growth and maturation of one or more tissue systems and is measured by the occurrence of one or a sequence of irreversible events. Developmental indicators most commonly used are bone maturation, secondary sex characteristics, height, and weight. More recently, the dental maturation indicator system has been described as another useful index for comparison.

Genetic, functional, nutritional, endocrine, and metabolic factors all have some influence on dental development; however, the quantitative and qualitative effects of each factor have not been completely elucidated.

Where endocrinopathy is known or suspected, a precise evaluation of the dental development may be worthwhile. In addition, a study of dental growth in patients with known endocrine or metabolic dysfunction may help to define the role of various intrinsic hormonal factors and their relative importance in normal dental development.

Materials and methods

During a two-year period, 179 patients with various endocrine and metabolic diseases were selected for study from among the pediatric patients at the Mayo Clinic. The radiographic technic and normal values of Moorrees and co-workers were used to evaluate dental development. Sklar established the validity of these data for our use by comparing dental development in our population of patients with dental development among children at the Forsyth Dental Infirmary.

Anterior periapical and extraoral panoramic radiographs were used to score all teeth except the canine and posterior teeth in the maxillary arch. We found the panoramic radiograph superior to the standard oblique mandibular body radiograph for scoring the mandibular posterior teeth, especially in the younger age groups. Teeth that demonstrated complete development, as indicated by closure of the apical foramen, were not used for scoring because the exact time of closure was not known. In addition, teeth of patients were not evaluated if dental development had progressed to the point where only a few teeth in a given patient could be scored.

In each patient, the stage of calcification of each tooth that could be scored was determined by inspection of the radiographs, and a dental age score and a standard deviation score were assigned each tooth. For each patient an average dental age (DA) and average standard deviation score (S) were calculated. The absolute difference (DCA) between DA and the patient's chronologic age (CA) and the absolute difference (DSA) between
the skeletal age (SA) and DA were calculated. The statistical significance of an acceleration or delay in dental development in each patient was determined by calculating a relative deviate score (K) as follows:

$$K = DA - CA$$

In the various pathologic groups in which a consistent trend toward advancement or delay in dental development was apparent, an average DCA, DSA, and K were calculated.

Repeated determinations of the calcification stages in a large group of patients by two independent observers established the reproducibility of the scoring. In addition, the diagnosis in each case was not known at the time the radiographs were evaluated.

The skeletal age was determined for each patient from radiographs of the wrist and hand (by Dr. James R. Stewart, selection of diagnostic radiology, Mayo Clinic) according to the standards of Greulich and Pyle; the clinical status of the patient was not known at the time this evaluation was made.

### Table: Summary of calculated values in 179 patients with endocrine and metabolic diseases.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>Mean</th>
<th>Range</th>
<th>Mean</th>
<th>Range</th>
<th>Mean</th>
<th>Range</th>
<th>Mean</th>
<th>Range</th>
<th>Mean</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>22</td>
<td>-0.17</td>
<td>-1.38</td>
<td>-0.10</td>
<td>-1.18</td>
<td>-0.37</td>
<td>-0.27</td>
<td>-0.18</td>
<td>-1.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional precocious puberty with treatment</td>
<td>6</td>
<td>-1.57</td>
<td>+2.45</td>
<td>+1.50</td>
<td>+2.75</td>
<td>+3.25</td>
<td>+3.45</td>
<td>+1.32</td>
<td>+3.20</td>
<td></td>
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<tr>
<td>Without treatment</td>
<td>16</td>
<td>-0.20</td>
<td>+1.23</td>
<td>-0.20</td>
<td>+1.63</td>
<td>+2.95</td>
<td>+3.33</td>
<td>+1.14</td>
<td>+7.35</td>
<td></td>
<td></td>
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<tr>
<td>Adrenogenital syndrome</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Early adequate treatment</td>
<td>9</td>
<td>-0.38</td>
<td>-1.11</td>
<td>-0.65</td>
<td>-1.20</td>
<td>-0.74</td>
<td>-1.54</td>
<td>-0.59</td>
<td>+0.90</td>
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<tr>
<td>Late or inadequate treatment</td>
<td>15</td>
<td>+0.02</td>
<td>+1.72</td>
<td>+0.05</td>
<td>+2.26</td>
<td>+5.15</td>
<td>+10.09</td>
<td>+5.84</td>
<td>+8.25</td>
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<td></td>
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<tr>
<td>Short stature</td>
<td>20</td>
<td>-1.57</td>
<td>-5.77</td>
<td>-1.76</td>
<td>-5.50</td>
<td>-1.50</td>
<td>-4.09</td>
<td>-0.07</td>
<td>+9.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>19</td>
<td>-2.27</td>
<td>-3.05</td>
<td>-1.90</td>
<td>-3.33</td>
<td>-2.48</td>
<td>-5.08</td>
<td>+0.20</td>
<td>+2.08</td>
<td></td>
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<tr>
<td>Thyroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hyperthyroidism</td>
<td>15</td>
<td>-0.12</td>
<td>-2.25</td>
<td>-0.20</td>
<td>+1.92</td>
<td>+2.42</td>
<td>+2.73</td>
<td>+3.73</td>
<td>+2.99</td>
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<td></td>
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<tr>
<td>Cretinism</td>
<td>14</td>
<td>-0.85</td>
<td>-2.85</td>
<td>-1.25</td>
<td>-3.70</td>
<td>-0.77</td>
<td>-2.75</td>
<td>-0.26</td>
<td>+2.87</td>
<td></td>
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<tr>
<td>Juvenile myxedema</td>
<td>15</td>
<td>-1.26</td>
<td>-4.76</td>
<td>-0.80</td>
<td>-6.60</td>
<td>-3.31</td>
<td>-10.00</td>
<td>+0.02</td>
<td>+4.75</td>
<td></td>
<td></td>
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<tr>
<td>Lymphocytic thyroiditis</td>
<td>9</td>
<td>-1.22</td>
<td>-3.35</td>
<td>-1.10</td>
<td>-3.20</td>
<td>-1.28</td>
<td>-5.17</td>
<td>0.00</td>
<td>-4.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior pituitary insufficiency (idiopathic)</td>
<td>22</td>
<td>-3.79</td>
<td>-6.95</td>
<td>-4.03</td>
<td>-7.70</td>
<td>-6.03</td>
<td>-15.00</td>
<td>-2.00</td>
<td>+1.15</td>
<td></td>
<td></td>
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<tr>
<td>Secondary to chromopharyngitis</td>
<td>7</td>
<td>-2.53</td>
<td>-4.80</td>
<td>-2.33</td>
<td>-3.87</td>
<td>-3.93</td>
<td>-5.76</td>
<td>-1.27</td>
<td>+4.65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(DCA = \) absolute difference between dental age and chronologic age in years; \(K = \) relative deviate; \(DSA = \) absolute difference between dental age and skeletal age in years; \(SCA = \) absolute difference between skeletal age and chronologic age in years.

### Results

The means of the various calculated values are shown in the table. Figures 1 and 2 illustrate the differences between dental age and chronologic age (DCA) and between skeletal age and chronologic age (SCA), plotted to show the amount of retardation or acceleration of each of these measures and how they relate to each other.

- **Diabetes mellitus:** Dental and skeletal age corresponded well with chronologic age in all 12 patients, regardless of the duration of the disease.

- **Constitutional precocious puberty:** The treated group consisted of six girls who had received serial injections of medroxyprogesterone acetate, and were evaluated separately. The skeletal age was advanced significantly over the chronologic age in a majority of the nontreated patients; in contrast, dental age was consistently close to the chronologic age. Skeletal age was consistently advanced in all six treated girls, and there was a
trend toward advanced dental development. A 9-year-old girl who had been treated for seven years had a skeletal age of 15 years and a dental age of 12 years.

- **Adrenogenital syndrome**: In the group of nine girls who had received early and adequate treatment, dental and skeletal ages consistently agreed with the chronologic age. In contrast, among the inadequately treated patients, the skeletal age was advanced in all, but the dental age was consistently within normal limits. In one 5½-year-old boy with a skeletal age of 12½ years, the dental age was five years.

- **Delayed puberty**: Significant delay of dental and skeletal development was present in a majority of this group. Dental age was retarded by more than 1.50 standard deviations in 14 of the 18 patients and by less than 1.00 standard deviation in only 1 patient. The relationship between skeletal delay and dental delay was inconsistent; however, there was a tendency for the dental delay to be equal to or greater than the skeletal delay.

- **Short stature**: Six of the 20 patients with idiopathic short stature had a familial history of short stature. A mild but consistent dental delay was observed but, in contrast, the skeletal delay was highly variable and its relationship to dental and chronologic age was inconsistent.

- **Hyperthyroidism**: In ten patients the radiographs were made before or shortly after surgical treatment; the five other patients were receiving medical treatment at the time of evaluation. In a majority of the patients, dental and skeletal development did not vary significantly from normal; however, one patient with exophthalmos, goiter, and Down’s syndrome demonstrated a significant increase in dental age (DCA, +3.58 years; K, +1.92). In contrast, three patients who had not received treatment exhibited a significant delay in dental development (DCA, −1.95, −1.67, and −2.25 years; K, −1.60, −1.87, and −1.77).

- **Cretinism**: The 14 patients who were studied had received early and adequate replacement therapy. Dental and skeletal development was consistently within normal variation.

- **Juvenile myxedema**: The 15 patients were evaluated in three separate groups: four nontreated patients; four receiving long-term (five to ten years) thyroid replacement therapy; and seven receiving short-term (two to three years) thyroid replacement therapy. In two patients who were not treated the dental delay was approximately equal to the skeletal delay; in the other two, the skeletal delay was considerably more than the dental delay. When the treated and nontreated groups were compared, the dental development tended to be retarded to the same degree regardless of treatment duration. In contrast, skeletal age tended to vary with treatment duration, being ahead of the dental age in a majority of the treated patients.

- **Lymphocytic thyroiditis**: All nine patients were euthyroid or mildly hypothyroid at the time of evaluation; five had received thyroid replacement therapy for a short period. Dental development was not consistently or significantly delayed in this group. Skeletal development was highly variable and no definite trend was present in this small group of patients.

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Anterior pituitary insufficiency: Serum growth hormone assays after insulin-induced hypoglycemia were used to establish the diagnosis of anterior pituitary insufficiency of all 29 patients in this group. The patients were divided into two groups, those in whom the cause was unknown and those who were evaluated after removal of a craniopharyngioma. Five patients (four were in the first group) were followed serially for a limited time before and during growth hormone replacement therapy. An occasional patient in both groups was receiving thyroid treatment or cortisone or both. Dental and skeletal developments were consistently and significantly retarded in all patients in both groups; however, those in the first group exhibited more delay (a reflection of the longer duration of their pituitary insufficiency). Skeletal development was consistently more retarded than dental development in all patients except three older ones (14, 18, and 18.5 years); the average DCA was 63% of the average SCA in the first group and 64% in the second group. Dental development was not noticeably altered in the five patients who were followed serially before and during (six months to one year) human growth hormone replacement therapy.

Discussion

The literature on dental development in children with sexual precocity is controversial. Normal dental development in patients with constitutional sexual precocity has been reported by some and is confirmed by our results. In a small group of these patients who had received serial injections of medroxyprogesterone acetate, the advance in dental development was small compared to the advance in facial and skeletal development. Normal dental development in patients with incomplete sexual precocity has been reported and is confirmed by our analysis of non-treated or inadequately treated patients with adrenogenital syndrome. This finding contrasts with observations of others who reported slight to moderate advancement of dental development. Patients who were diagnosed in infancy and adequately treated also had normal dental development. Thus, our findings support those who believe that the dental system is not noticeably affected by factors which greatly accelerate general osseous and sexual maturation.

A general lack of pubertal growth acceleration in our patients with delayed puberty was reflected by a consistent and significant delay in dental development. The dental delay in this group tended to be similar to, but in general not as pronounced as, that found in patients with proved anterior pituitary insufficiency. In addition, the delayed puberty group was the only group in which dental delay tended to be equal to or greater than skeletal delay.

Extreme short stature without recognized endocrine dysfunction characterized our group of patients with familial or unclassified short stature. A highly variable but consistently significant delay in skeletal maturation was present in this group but, in general, dental delay was only moderate. However, a number of these patients exhibited retarded dental development to the same extent as that seen in patients with anterior pituitary deficiency, juvenile myxedema, or delayed puberty. This finding suggests that factors other than known hormonal deficiencies may retard dental development.

All but four juvenile patients with myxedema had received replacement therapy for various lengths of time. The consistent dental delay present in all these patients did not vary, and it could not be correlated with treatment duration. In contrast, the skeletal delay correlated well with treatment duration and was generally less than the dental delay in the long-term treatment patients. These results contrast with Sklar's statement that dental and skeletal systems respond equally to thyroid replacement therapy. Also, our results do not support Garn and co-workers' statement that dental delay is 33% that of skeletal delay, or Sklar's contention that dental and skeletal delays are equal in children with hypothyroidism. All cretinism was diagnosed and treated early in life. The normal rates of skeletal and dental maturation reflect the effect of the treatment these patients received from infancy. A longitudinal study of this relatively young group of patients will be necessary before final conclusions can be reached. For instance, a tendency for dental development to lag behind the chronologic age was observed in the older patients in this group.

Hyperthyroidism in children is uncommon and accurate reports of dental development in this condition are rare. In spite of meager evidence, most textbook authors say that dental development is accelerated in this condition. Our results do not support this opinion and coincide with Sklar's observation that a majority of these patients exhibit normal dental development. The theory...
that an occasional patient will have significant dental advancement\textsuperscript{10,11} is supported by our findings in one case. In contrast, according to our findings, one is more likely to encounter an untreated patient whose dental development is significantly delayed. Even though eruption and calcification of teeth have been shown to correlate closely, our method of evaluation does not permit us to dispute claims that eruption rate is increased. Generalized demineralization of bone, as observed by Stafne\textsuperscript{11} on dental radiographs of patients with hyperthyroidism, was evident in a number of our patients.

Retardation of dental development in patients with anterior pituitary insufficiency is amply documented in the literature\textsuperscript{12-15} and is demonstrated by the results of this study; however, the degree of delay in relation to the skeletal delay is controversial.\textsuperscript{16,18} Our results are in agreement with those of Sklar\textsuperscript{9} who found dental delay to be 66% that of skeletal delay; however, there was considerable variability, and a definite pattern could not be established.

Summary

Skeletal and dental ages were determined radiographically in 179 children with various endocrine and metabolic diseases. These ages were compared with chronologic age to determine the effect of the disease on the rate of development. Children and adolescents with diabetes mellitus exhibited normal dental and skeletal development. Patients with complete or incomplete precocious puberty with advanced skeletal maturation exhibited normal dental development. (The dental system was not noticeably affected by factors which greatly accelerated osseous and sexual maturation.) Serial injections of medroxyprogesterone acetate advanced dental development moderately in female patients with complete precocious puberty. Most patients with hyperthyroidism exhibited normal dental and skeletal development. The dental system did not respond as well as the skeletal system to thyroid replacement therapy in patients with hyperthyroidism; however, skeletal maturation still remained significantly retarded in a majority of treated patients with hyperthyroidism, perhaps a reflection of inadequate treatment. Dental development was moderately delayed in patients with delayed puberty or with familial or unclassified short stature. This dental development delay was consistent in relation to chronologic age but skeletal delay was highly variable in relation to chronologic age. Patients with anterior pituitary insufficiency or juvenile myxedema exhibited similar degrees of delay in dental development. In patients with anterior pituitary insufficiency, the dental developmental delay was somewhat variable but on the average was 65% of the skeletal delay.

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