Anthropometry of patients with osteogenesis imperfecta

Allan M Lund, Jørn Müller, Flemming Skovby

Abstract
Standing height, sitting height, armspan, subischial leg length, head circumference, and growth hormone-insulin-like growth factor I (IGF-I) axis were determined in 86 patients with osteogenesis imperfecta. The aim of this study was to determine standing height and body proportions and their variability among osteogenesis imperfecta types and collagen defects. Mean standing height was reduced in all groups of patients, to the greatest extent and variability in osteogenesis imperfecta type III/IV and in those with qualitative collagen defects. The mean standing height of patients with osteogenesis imperfecta was lower than that of their unaffected first degree family members. Truncal height of patients with osteogenesis imperfecta was reduced; head size was increased, and this was more pronounced in patients with osteogenesis imperfecta type III/IV and qualitative collagen defects than in patients with osteogenesis imperfecta type I and quantitative collagen defects. Mean concentrations of IGF-I and IGF binding protein 3 (IGFBP-3) were low, but most values were within age specific reference values. The reduction of standing height appears to correlate with osteogenesis imperfecta type and the type of collagen defect. A relatively short trunk is typical and head circumference and body length are disproportionate. 

Keywords: osteogenesis imperfecta; anthropometry; collagen; body constitution

Osteogenesis imperfecta is a heritable disorder of collagen I metabolism with generalised involvement of connective tissue. The spectrum of clinical features is wide, ranging from perinatal death to lifelong mild osseous fragility. On the basis of clinical and radiographic features, the disease can be divided into four types, and molecular and protein-chemical studies have shown that at least 95% of cases are caused by heterozygosity for dominant mutations in COL1A1 or COL1A2, the genes encoding the α1(I) and the α2(I) chains of collagen I. In protein-chemical studies using collagen gel electrophoresis (sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE)), two kinds of defects of collagen

Table 1 Characteristics of patients with osteogenesis imperfecta

<table>
<thead>
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<th>Children</th>
<th>Adults</th>
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<tr>
<td><strong>Silence type</strong></td>
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<tr>
<td>I</td>
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<td>36</td>
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<tr>
<td>II</td>
<td>10</td>
<td>5</td>
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<td>IV</td>
<td>8</td>
<td>14</td>
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<td>1:3/4</td>
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**Collagen defect**
Quantitative
-6.2
-3.2

Qualitative
-1.3
-3.4

Table 2 Standing height and endocrine findings in osteogenesis imperfecta (OI)

<table>
<thead>
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<td><strong>Silence type</strong></td>
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<tr>
<td>I</td>
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<tr>
<td>III</td>
<td>-6.2</td>
<td>-10.6</td>
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<tr>
<td>IV</td>
<td>-3.2</td>
<td>-3.4</td>
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<tr>
<td></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
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</table>

**Collagen defect**
Quantitative
-1.9
-6.4

Qualitative
-0.7
-5.2

The Student’s t test was performed between OI type I and type III/IV (1:3/4), as well as between quantitative and qualitative collagen defects. NS, not significant; NA, not available.

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I metabolism are recognised: patients with mild osteogenesis imperfecta, notably type I, have a quantitative defect of collagen I associated with haploinsufficiency of one allele of COL1A1, whereas patients with moderate or severe osteogenesis imperfecta produce qualitatively or structurally defective collagen I molecules. Sillence and colleagues (5th international conference on osteogenesis imperfecta, 1993) and Vetter and colleagues have measured standing height in well characterised patients with osteogenesis imperfecta, but a systematic anthropometric study of patients has not been reported, and no study has correlated height and body proportions to collagen defects. We measured standing height, weight, sitting height, armspan, subischial leg length, and head circumference in adults and children with osteogenesis imperfecta. Our aim was to determine the standing height and body proportions of patients with different osteogenesis imperfecta types and to elucidate whether growth retardation in this disease is symmetrical and whether body proportions vary between osteogenesis imperfecta types and collagen defects.

Patients
We studied 86 patients with osteogenesis imperfecta (44 girls/women and 42 boys/men; table 1), referred to the department of clinical genetics, Rigshospitalet, for diagnostic evaluation and follow up care. All patients were evaluated clinically, and patients with osteogenesis imperfecta bone disorders, liver diseases, or endocrine disorders were excluded. All patients were characterised clinically according to the Sillence classification (types I, III, and IV). Our study was reviewed by the local ethics committee and found to be in accordance with the Helsinki declaration (approval number KF 01–144/94). Written informed consent was obtained from all participants or their parents.

Methods
ANTHROPOMETRIC MEASUREMENTS
Anthropometry was carried out in 86 patients. Each measurement was done three times and the mean was calculated. Standing height was measured as the height from the fifth metatarsal head (subischial leg length) to the top of the head. Table 3 and figure 1 show the anthropometric measurements in osteogenesis imperfecta (OI).

Table 3 Anthropometric measurements in osteogenesis imperfecta (OI)

<table>
<thead>
<tr>
<th></th>
<th>Armspan (SDS)</th>
<th>Armspan/standing height Student’s t test</th>
<th>(SILL SDS) − (sitting height SDS) Student’s t test</th>
<th>Head circumference (SDS) − (standing height SDS) Student’s t test</th>
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<tbody>
<tr>
<td>Children</td>
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<td>Sillence type</td>
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<tr>
<td>I</td>
<td>−1.0</td>
<td>1.0</td>
<td>+1.0</td>
<td>+2.0</td>
</tr>
<tr>
<td>III</td>
<td>−3.7</td>
<td>1:3/4</td>
<td>+2.1</td>
<td>+3.0</td>
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<tr>
<td>IV</td>
<td>−2.0</td>
<td>1:3/4</td>
<td>+3.0</td>
<td>+2.0</td>
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<tr>
<td>Collagen defect</td>
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<tr>
<td>Quantitative</td>
<td>−1.4</td>
<td>1.0</td>
<td>+0.3</td>
<td>+6.0</td>
</tr>
<tr>
<td>Qualitative</td>
<td>−3.1</td>
<td>1:3/4</td>
<td>−2.0</td>
<td>+4.0</td>
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<tr>
<td>Adults</td>
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<tr>
<td>Sillence type</td>
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<tr>
<td>I</td>
<td>−2.1</td>
<td>1.0</td>
<td>+2.2</td>
<td>+3.8</td>
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<tr>
<td>III</td>
<td>−3.1</td>
<td>1:3/4</td>
<td>+2.2</td>
<td>+2.0</td>
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<tr>
<td>IV</td>
<td>−2.6</td>
<td>1:3/4</td>
<td>+2.9</td>
<td>+5.0</td>
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<td>−2.9</td>
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The Student’s t test was performed between OI type I and type III/IV (1:3/4), as well as between quantitative and qualitative collagen defects. SILL, subischial leg length.
measured using a Harpenden stadiometer (Harpenden Ltd, Crymych, UK) to the nearest 0.1 cm. Sitting height was measured using the same stadiometer with the subject sitting on a chair of known height. Armspan was measured as the distance between the tips of the third (or longest) fingers with the arms stretched out horizontally. The subischial leg length was calculated as the difference between standing height and sitting height. Body proportion was expressed as sitting height standard deviation score (SDS) subtracted from subischial leg length SDS. Weight was measured using a digital scale with a precision of 0.1 kg (SECA® model 707). Head circumference was measured using a tape measure. The anthropometric standards used have been published previously.11–13 Height and weight were measured in available first degree relatives (parents or siblings), or the family was asked to provide measurements of these relatives.

ENDOCRINE MEASUREMENTS
We measured insulin-like growth factor I (IGF-I) and IGF binding protein 3 (IGFBP-3) in sera from 31 children. Serum IGF-I and IGFBP-3 concentrations were determined by radioimmunoassay (RIA).14 15 Reference values were those generated with the same assays in the department of growth and reproduction.

SDS-PAGE OF COLLAGEN
We studied collagen in 58 patients. SDS-PAGE of radiolabelled (pro)collagen I has been described in our previous publications.1 7 14 17 We estimated the amount of collagen I produced from the relative amounts of procollagen III and procollagen I. We only considered two kinds of abnormalities on SDS-PAGE: a quantitative (reduced amount of collagen I) or a qualitative abnormality (presence of structurally abnormal collagen I).

STATISTICAL ANALYSIS
All anthropometric values were expressed as SDS from the normal mean or as ratios. We used the Student’s t test to calculate p values for differences in endocrine data and anthropometric values between different osteogenesis imperfecta types and collagen defects.

Results
ANTHROPOMETRIC MEASUREMENTS
The average standing height was reduced in all groups of patients (table 2; fig 1A and 1B). During childhood there was no difference between the standing heights of girls and boys, but women had lower SD scores (−2.6 SDS) than men (−1.6 SDS), and standing height declined more rapidly in female patients than in males patient (p < 0.05) (data not shown). Patients with osteogenesis imperfecta type III/IV and/or those with a qualitative collagen defect were more growth retarded than those with osteogenesis imperfecta type I and/or a quantitative collagen defect (p < 0.01) (fig 1A and 1B). Many patients with osteogenesis imperfecta type I and/or a quantitative collagen defect had a standing height within the
reference interval. In contrast, only two patients with a qualitative collagen defect had a normal standing height. Table 2 shows the final mean adult standing height for each osteogenesis imperfecta type. The mean standing height of patients with osteogenesis imperfecta was significantly different from the heights of their unaffected first degree family members (p < 0.01) (fig 1C; table 2). The difference between patients’ standing height and that of their unaffected family members was significantly greater in patients with osteogenesis imperfecta type III/IV and in those with a qualitative collagen defect than in patients with type I and in those with a quantitative collagen defect. Analysis using target height instead of mean height of unaffected family members gave comparable results (table 2).

The reduction in armspan SDS generally followed the same pattern as for height. Thus, patients with osteogenesis imperfecta type III/IV and those patients with a qualitative collagen defect had lower SD scores than type I patients and those with a quantitative defect. The ratio between armspan and height was increased in children with osteogenesis imperfecta type III and IV (p < 0.01), and in both children and adults with a qualitative collagen defect (p < 0.05), but not in those with osteogenesis imperfecta type I and/or a quantitative collagen defect (table 3; fig 2).

Subtraction of sitting height SDS from subischial leg length SDS should theoretically result in a value of zero, but it gave positive values in most patients, averaging 2.5 in different osteogenesis imperfecta groups, with no significant differences between any of the groups (table 3; fig 3).

Mean head circumference SDS was increased, but above ±2 SD in only one third of patients (table 3; fig 4). There were no significant differences between any of the osteogenesis imperfecta groups. However, subtraction of standing height SDS from head circumference SDS gave positive values in all patients, and patients with osteogenesis imperfecta type III/IV and/or with a qualitative collagen abnormality had more positive scores than did patients with osteogenesis imperfecta type I (p < 0.05) and/or a quantitative collagen abnormality (p < 0.01).

ENDOCRINE MEASUREMENTS

Serum concentrations of IGF-I and IGFBP-3 were within the age specific reference intervals in all but three patients: two patients with osteogenesis imperfecta type III and IV had IGF-I values below −2 SDS and normal IGFBP-3, and one patient with type I had IGFBP-3 below −2 SDS and normal IGF-I. Mean IGF-I and IGFBP-3 concentrations were low/normal, and half of the patients had concentrations below −1 SDS. Concentrations of IGF-I were significantly lower in osteogenesis imperfecta type III/IV than in type I (p < 0.05) (table 2; fig 3).

Discussion

Short stature is frequent in osteogenesis imperfecta type I and often severe in types III and IV. Although growth deficiency is thus a hallmark of osteogenesis imperfecta, neither the cause nor the type of short stature is clear.

Osteogenesis imperfecta is caused by an abnormal metabolism of collagen I, which is the major protein constituent of bone matrix. Collagen II predominates in cartilage at the growth plate of long bones and so linear growth should be normal. Morphological changes in the growth plate have been observed in osteogenesis imperfecta, but the cause of short stature is more likely to be found at the osteoblast level. Unresponsiveness of osteoblasts to normal growth factors or defective osteoblastic/bone matrix feedback on the growth hormone–IGF-I axis have been suggested. The former possibility has not been explored. However, in light of the reduced concentration and defective structure of collagen I in osteogenesis imperfecta bone matrix, it may be important that collagen I is necessary for the expression of the osteoblast phenotype and thus its ability to respond to various growth factors. The different degrees of short stature in patients with quantitative and qualitative collagen defects found in our study could reflect the different consequences of each collagen defect on the osteoblast phenotype. To evaluate whether the IGF-I axis is involved in osteogenesis imperfecta, we measured IGF-I and IGFBP-3 and found that the axis was normal in children with osteogenesis imperfecta. The low/normal values of IGF-I and IGFBP-3 probably reflect short stature—as seen from the significant correlation of IGF-I with height (r = 0.41; p < 0.05). However, even though the growth hormone–IGF-I axis was normal, recent studies suggest that treatment with growth hormone may increase linear growth velocity, in addition to bone mineral content, in children with osteogenesis imperfecta. (Sillence, 6th international congress on osteogenesis imperfecta, 1996) probably as a result of the stimulation of collagen I synthesis exerted by growth hormone.

Using anthropometry we detailed various aspects of the type of short stature in osteogenesis imperfecta, and we were able to obtain final standing heights for each osteogenesis imperfecta type and collagen defect. Each patient with osteogenesis imperfecta had a lower standing height than that of unaffected first degree relatives; the differences between standing height of the patients and mean height of unaffected family members (or target height in other calculations) followed the distribution of heights in each osteogenesis imperfecta type (table 2), pointing to the collagen defect as a primary cause of short stature. Many patients with osteogenesis imperfecta type I and a few with type IV had a standing height within the reference interval, and most of these patients had a quantitative defect of collagen. In contrast, all but two patients whose fibroblasts produced structurally abnormal collagen I were severely growth retarded, pointing to a greater impact on growth of structural collagen defects than of quantitative defects. The extreme variation of standing height in patients...
with qualitative collagen defects (fig 1B) under- 
scores the molecular and protein-chemical 
heterogeneity of the disease in these patients, 
whereas a standing height in patients with a quan-
titative collagen defect varies less, reflecting the 
more uniform biochemical background (non-
functioning COL1A1 alleles) in these patients.22

The armspan:standing height ratio was 
increased in patients with severe osteogenesis 
imperfecta and in those with a qualitative 
defect of collagen I (table 3; fig 2), and sitting 
height SDS subtracted from subischial leg 
length SDS gave positive values in almost all 
children and adults with osteogenesis imper-
fecta. Taken together, these data indicate that 
truncal height is relatively more reduced than is 
the length of bones in the peripheral skeleton. 
Our observation of a reduction of truncal 
height corresponds to the platspondyly seen 
on radiological examination of a number of 
patients with osteogenesis imperfecta. Our 
study cannot resolve whether platspondyly is 
caused by biomechanical (a reduced bone 
mineral content (BMC)) or by biosynthetic 
abnormalities (a reduced growth potential of 
the spine). Biomechanical abnormalities are 
without doubt important for the development of 
platspondyly in osteogenesis imperfecta (AM Lund et al, unpublished data, 1990), but 
patients with severe osteogenesis imperfecta 
types III and IV (who also have low BMC 
scores (AM Lund et al, unpublished data, 1999) 
would be expected to have a shorter 
trunk than those with mild type I (who have 
higher BMC scores (AM Lund et al, un-
published data, 1999)). However, no difference 
between osteogenesis imperfecta types could be 
found regarding truncal height, arguing that 
in patients with mild type I, the development of 
a reduced truncal height might also involve 
biosynthetic abnormalities.

Head circumference often seems dispropor-
tionately increased in patients with osteogen-
esis imperfecta. Mean head circumference SDS 
was positive in all groups of patients, but 
most children and about two thirds of adults 
had SDS within the reference interval. To 
evaluate the degree of disproportion between 
head circumference and height, we subtracted 
standing height SDS from head circumference SDS, 
the mean of which should be zero in 
the case of no disproportion. The mean difference 
was +2 SD or above in all groups, indicating a 
disproportionately large head circumference, 
especially in patients with osteogenesis imper-
fecta type III/IV and/or those with a qualitative 
collagen defect. The probable cause is the 
soft immaturity calvarial bone in these patients, 
as opposed to those with a quantitative defect. 
Impaired cerebrospinal fluid circulation with 
subsequent hydrocephalus has been proposed as 
a causative factor of macrocephaly in osteo-
genesis imperfecta, but few such patients have 
signs of increased intracranial pressure,23 24 and 
the ventriculomegaly seen on imaging studies 
is caused by a disproportion between brain 
volume and intracranial space.

This work was supported in part by grants from the Novo Nor-
disk Foundation, the Foundation of the Queen Louise’s Child-
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Vanførelserne.

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