The Relation between Bone Mineral Density, Insulin-Like Growth Factor I, Lipoprotein (a), Body Composition, and Muscle Strength in Adolescent Males

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ABSTRACT

Osteoporosis is the most common metabolic bone disease. A low peak bone mass is regarded a risk factor for osteoporosis. Heredity, physical activity, and nutrition are regarded important measures for increasing bone mass. Lp(a) lipoprotein is a well-known risk factor for atherosclerosis. Serum insulin-like growth factor I (IGF-I) has been found to be increased in males with early cardiovascular disease. In this study, we evaluated the association between bone mass, body constitution, muscle strength, Lp(a), and IGF-I in 47 Caucasian male adolescents (mean age, 16.9 yr). Bone mineral density (BMD) and body composition were measured by dual x-ray absorptiometry, muscle strength of thigh using an isokinetic dynamometer, IGF-I by RIA, and Lp(a) by enzyme-linked immunosorbent assay. IGF-I was only associated with Lp(a) (r = 0.38, P < 0.01). Lp(a) was related to total body (r = 0.40, P < 0.01), skull (r = 0.45, P < 0.01), and femoral neck BMD (r = 0.44, P < 0.01). Lp(a) was also related to fat mass (r = 0.34, P < 0.05) and muscle strength (r = 0.30–0.42, P < 0.05). After multiple regression and principal component (PC) analysis, the so-called PC body size (weight, fat mass, lean body mass, and muscle strength) was the most significant predictor of BMD (β = 0.28–0.51, P < 0.05–0.01), followed by the so-called PC physical activity (β = 0.28–0.38, P < 0.05–0.01, weight-bearing locations). However, the PC analysis confirmed that Lp(a) was an independent predictor of total body, skull, and femoral neck BMD (β = 0.33–0.36, P < 0.01).

The present investigation confirms that BMD, body size, and muscle strength are closely related and that the level of physical activity is a major determinant of BMD. However, the positive relation of Lp(a), a major risk factor for cardiovascular disease, to BMD has not previously been described. The importance of this observation has to be further investigated. (J Clin Endocrinol Metab 84: 3025–3029, 1999)

OSTEOPOROSIS is the most common metabolic bone disease, and the incidence of osteoporotic fractures is increasing in most Western societies (1). Peak bone mass is considered a major determinant of risk for future fracture (2). Heredity is the major determinant of the variance in bone mineral density (BMD) in younger adults (3); but life-style factors, such as physical activity (4), are also important determinants of peak bone mass.

Insulin-like growth factors have important effects on multiple organ systems, including bone. The insulin-like growth factor I (IGF-I) in serum is mainly synthesized by the liver, and serum levels peak during puberty (5). In bone, IGF-I is produced by osteoblasts and regulated by different factors known to affect bone metabolism, e.g., GH, estrogen, PG E2, PTH, and calcitriol, exerting autocrine and/or paracrine effects on bone cells (6–8). Higher levels of serum IGF-I have been found in Swedish males with early cardiovascular disease than in male controls (9).

Lipoprotein (a), [Lp(a)], is regarded an important risk factor for atherosclerosis and probably thrombogenesis (10). White children with parental cardiovascular disease have higher plasma levels of Lp(a) than children without parental cardiovascular disease (11–13). Lp(a) is synthesized solely by the liver and differs from low-density lipoprotein by an additional large protein, apoa (a), disulfide linked to an apo B-100 apoprotein. The Lp(a) level in plasma peaks during early childhood (14, 15), and approximately 90% of the variability of the Lp(a) in plasma is genetically determined, primarily by sequence polymorphisms in the apo(a) gene (16).

The association between BMD, IGF-I, and Lp(a) has not been investigated. The purpose of this study was to examine the relation between BMD, IGF-I, and Lp(a), and their relation to anthropometric data, muscle strength, and pubertal status in adolescent males.

Subjects and Methods

From advertisement and information in schools and local sports clubs, 47 nonsmoking Caucasian boys (age, 16.9 ± 0.3 yr) volunteered to participate in the present study and were investigated at the Sports Medicine Unit. None of the subjects had any disease or medication known to affect bone metabolism except one boy suffering from diabetes mellitus. This boy did not differ in physical characteristics or bone mass from the rest of the boys. Weight and height were measured using standardized equipment. The boys were divided into different pubertal stages according to Tanner, using clinical interviews, inspection of axillary hair growth, and growth of beard. Growth spurt data were derived by self-report of height in all cases and from measurements of the boys’ height and weight two times during 1 yr or more. All the participants and their parents gave informed consent, and the Ethical Committee of the Medical Faculty, Umeå University, approved the study protocol.
Anthropometry

The subject's height in stockings was recorded, to the nearest centimeter, on a wall-mounted stadiometer. The subject's weight was measured, to the nearest 0.1 kg, in underwears and stockings. BMI was calculated as (weight (kg)/height (m²)).

Assessment of BMD and body composition

Fat mass, lean body mass, and BMD of the head were derived from a total body scan and the autoanalysis program, using a DFX-L dual energy X-ray absorptiometer (Lunar Corp., Madison, WI), software version 1.3y. The skull was then defined as the whole head including the first four cervical vertebrae. The right femoral neck BMD was obtained using the femur software, and BMD of the lumbar spine (L2-L4) was obtained using the spine software. To minimize the interobserver variation, all analyses were made by the same investigator. In our laboratory, the coefficient of variation (CV-value, sd/mean) is 0.7% for the total body scan, 1.7% for femur, 2.5% for spine, 0.9% for lean body mass, and 2.6% for fat mass (4).

Measurement of isokinetic muscle strength

Isokinetic muscle strength of the left quadriceps femoris and hamstring muscles was measured in Newton-meters (Nm) using an isokinetic dynamometer (Biodex Co., Shirley, NY). The subject was sitting with a 60-degree flexion of the hip, with the lever attached just above the ankle. The dynamometer's axis of rotation was aligned with the knee joint, and the angular movement of the knee joint was 90 degrees. Each subject made 5 maximal consecutive repetitions at 90 degrees per sec (°/sec) and 10 at 225°/sec. The rest between change of velocities was approximately 30 seconds. The highest peak torque for each velocity was used in the correlation analysis.

Serum IGF-I and Lp(a)

Blood samples were collected from a cubital vein, in a half-sitting position, after an overnight fasting. IGF-I was determined using an RIA kit for quantification of IGF-I in human serum from INCSTAR Corp., Corporacion, Stillwater, MN. The interassay CV was less than 10%. Lp(a) was determined by an enzyme-linked immunosorbent assay. The detection limit was 10 mg/L, and the day-to-day CV was less than 5.4%.

Statistical analysis

Bivariate correlations were calculated using Pearson's correlation coefficient and confirmed by Spearman's rank correlation test. The relationship between bone density and Lp(a) was also evaluated using a multiple regression analysis. It was then assumed that bone density could be explained from the regression equation: BMD = Lp(a) + bc + height + pubertal development + sex + error term, where bc = body constitution (fat mass and lean body mass), ms = muscle strength of the quadriceps and hamstring muscles measured at 90 and 225°/sec, pub = pubertal development, and phys = physical activity (h/week). The error term consists of measurement errors, genetic effects on BMD, and the environmental factors not investigated in the present study. Because many of the explanatory variables were found to be highly intercorrelated (r > 0.8, P < 0.001), a principal component (PC) analysis (PCA) was conducted to avoid the consequences of multicollinearity, i.e., imprecise regression parameter estimates. The PCs formed from the original variables were then used in a multiple regression model to evaluate the independent relationship between BMD at different sites and the explanatory variables above. PCA is a statistical technique that linearly transforms an original set of variables into a substantially smaller set of uncorrelated variables. PCA searches for a few linear combinations of the original variables that capture most of the information (variance) of the original variables. Geometrically, the first PC is the line of closest fit to n observations in the multidimensional variable space. The second PC is the line of closest fit to the residuals from the first PC, and so on. The PCs are sometimes rotated if the unrotated PCs are difficult to interpret. The most frequently used orthogonal rotation is Varimax (17). In short, the Varimax rotation results in new perpendicular coordinate axes, where the original variables have either small or large rotated component loading, resulting in PCs that are easier to interpret. The rotated component loadings are the original variables' correlation with the PC that they form. The SPSS statistical package for PC was used for the analysis. A P-value less than 0.05 was considered significant.

Results

Physical characteristics, results of BMD measurements, IGF-I, and Lp(a) levels for the 47 boys are presented in Table 1. The distribution of Lp(a) was highly skewed with many low values. Therefore, the median value for Lp(a) is also shown.

Bivariate correlations were tested between IGF-I, Lp(a), and BMD of the different sites and also height, weight, fat mass, lean body mass, muscle strength of the thigh, physical activity, and pubertal stage. IGF-I was only associated with Lp(a) (r = 0.38, P < 0.01). Lp(a) was significantly associated with BMD of the total body (r = 0.40, P < 0.01), skull (r = 0.45, P < 0.01), and femoral neck (r = 0.44, P < 0.01). Lp(a) was also significantly correlated with fat mass (r = 0.34, P < 0.05), quadriceps strength at 90 and 225°/sec (r = 0.39–0.42, P < 0.05), hamstrings strength at 90 and 225°/sec (r = 0.30–0.34, P < 0.05), and BW (r = 0.34, P < 0.05). No association between Lp(a) and physical activity was noticed (r = 0.14, P > 0.05).

The independent contributors of BMD of the different sites were investigated by means of a multiple regression analysis. Because IGF-I did not predict BMD of any site, this factor was not included. Thus, the explanatory variables Lp(a), lean body mass, fat mass, weight, muscle strength of the quadriceps and hamstrings muscles, pubertal development, and physical activity (h/week) were first transformed into four PCs (Table 2). The first PC consisted of weight, fat mass, lean body mass, and muscle strength of the thigh and was interpreted as body size. The second, third, and fourth PC consisted of physical activity, Lp(a), and pubertal development, respectively (Table 2). Lp(a) was found to independently predict total body BMD, skull BMD, and femoral neck BMD (all P < 0.01).

TABLE 1. Anthropometric data, levels of IGF-I and Lp(a) lipoprotein, muscle strength, and BMD in 47 healthy Caucasian boys. Mean values, SD, and the range are presented.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>16.9 ± 0.3</td>
<td>16.2–17.3</td>
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<tr>
<td>Pubertal stage</td>
<td></td>
<td></td>
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<tr>
<td>Tanner stage 5</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Tanner stage 4</td>
<td>11</td>
<td></td>
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<tr>
<td>Weight (kg)</td>
<td>73.1 ± 11.5</td>
<td>57.0–104.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179 ± 7</td>
<td>165–192</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>56.7 ± 6.5</td>
<td>45.0–72.8</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>13.2 ± 6.7</td>
<td>6.0–35.1</td>
</tr>
<tr>
<td>Physical activity (h/week)</td>
<td>5.2 ± 3.9</td>
<td>0–15</td>
</tr>
<tr>
<td>Quadriceps strength 90°/sec (Nm)</td>
<td>206 ± 36</td>
<td>125–279</td>
</tr>
<tr>
<td>Quadriceps strength 225°/sec (Nm)</td>
<td>140 ± 26</td>
<td>69–220</td>
</tr>
<tr>
<td>Hamstrings strength 90°/sec (Nm)</td>
<td>110 ± 17</td>
<td>71–158</td>
</tr>
<tr>
<td>Hamstrings strength 225°/sec (Nm)</td>
<td>85 ± 15</td>
<td>52–122</td>
</tr>
<tr>
<td>IGF-I (nmol/L)</td>
<td>40.3 ± 12.6</td>
<td>23.0–85.5</td>
</tr>
<tr>
<td>Lp(a) lipoprotein (mg/L)</td>
<td>191 ± 219</td>
<td>10–804 (median 94)</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>1.22 ± 0.10</td>
<td>0.97–1.42</td>
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<tr>
<td>Total body</td>
<td></td>
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<tr>
<td>Skull</td>
<td>1.99 ± 0.18</td>
<td>1.51–2.38</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>1.24 ± 0.12</td>
<td>0.99–1.46</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>1.22 ± 0.16</td>
<td>0.77–1.56</td>
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The association between Lp(a) and BMD of the femoral neck is illustrated in Fig. 1, and Lp(a) and quadriceps strength at 90°/sec are shown in Fig. 2.

Discussion

The precise physiological role of Lp(a) in the human organism has not yet been elucidated. Increased levels of Lp(a) have been found in athletes with extreme levels of physical activity, suggesting that Lp(a) may be involved in tissue synthesis and repair (18). Acute endurance exercise for 8 days in cold climate decreases plasma levels of Lp(a) (19). In a large cross-sectional study, physical activity was associated with favorable Lp(a) levels, although the association was rather weak (15). Other studies, however, have shown that a moderate level of physical activity has no (or only minor) influence on plasma levels of Lp(a) (20–24). These observations were confirmed by the present study, during which we found no relation between physical activity (h/week) and plasma concentrations of Lp(a).

Lp(a) may play a role in immunological processes, given that high plasma levels of Lp(a) have been found in subjects with a lower insulin increase after oral glucose load (25), patients with rheumatoid arthritis (26), and in children with chronic renal diseases (27). An elevated plasma level (>200–300 mg/L) of Lp(a) is regarded as a strong predictor for atherosclerosis and thrombosis, especially in subjects with high levels of low-density lipoprotein (10). Supporting the role of Lp(a) as a thrombogenic factor, higher plasma levels of Lp(a) have been found in patients with aortic aneurysms subjected to operation than in a comparable group of normal subjects (28). Besides this, a higher level of Lp(a) was noticed in the aneurysmic thrombus than in the aortic wall (28). After operation, plasma levels of Lp(a) increased and continued to be elevated at the end of the study period of 8 weeks. The latter observation may support the theory that Lp(a) is a factor involved in tissue reinforcement or repair (18, 28). The strong association between plasma levels of Lp(a) and body weight, fat mass, and muscle strength observed in the present investigation may support the role of Lp(a) as a factor involved in tissue synthesis during growth. In adults, however, generally no association has been found between Lp(a) and body weight or body mass index (29, 30).

Body size (PC 1) was the strongest predictor of BMD in the adolescent boys and explained 8–26% of the variance in BMD. These results may support the hypothesis that fat mass, lean mass, muscle strength, and BMD are developed simultaneously and equivalent during puberty (31). However, besides this, the level of physical activity was an independent predictor of BMD. The association of the level of physical activity was most pronounced at the location supposed to be subjected to the highest load during activity, i.e. the femoral neck, and it explained 15% of the variance in BMD at this location. On the other hand, virtually no association was registered between physical activity and the unloaded skull. This observation is in accordance with a previous report (4).

The major and novel finding of the present study was the positive association between plasma levels of Lp(a) and BMD. Lp(a) was found to be an independent predictor of BMD of the total body, skull, and femoral neck; and it accounted for 4–13% of the variance in BMD at the different locations. It is intriguing to speculate about the biological

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<th>Dominant content of each PC</th>
<th>BMD site</th>
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<tr>
<td></td>
<td>Total body</td>
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<tr>
<td>1. Body weight</td>
<td>0.51&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Fat mass</td>
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<td>Lean mass</td>
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<td>Quadriceps strength</td>
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<td>Hamstrings strength</td>
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<tr>
<td>2. Physical activity</td>
<td>0.30&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3. Lp(a)</td>
<td>0.36&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>4. Pubertal stage</td>
<td>0.43&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>R&lt;sup&gt;2&lt;/sup&gt; values</td>
<td>0.66&lt;sup&gt;a&lt;/sup&gt;</td>
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The explanatory variables were transformed into four principal components (PC). The first PC consisted of body weight, fat mass, lean body mass, and muscle strength of the thigh. The second, third, and fourth PC consisted of physical activity, Lp(a), and pubertal development, respectively. Beta values, R<sup>2</sup> values, and <i>P</i> values are presented.

<sup>a</sup> <i>P</i> < 0.01.
<sup>b</sup> <i>P</i> < 0.05.
explanation of the observed association between Lp(a) and bone in these adolescent boys. The relation of Lp(a) to BMD in our study does indicate a connection between adipose tissue metabolism and bone tissue metabolism. Leptin, a recently discovered hormone, synthesized mostly by adipocytes, has been suggested to mediate the effect of obesity on bone mass in young girls (32). Stem cells in bone marrow give rise to adipocytes as well as osteogenic cells and adipocytes producing Lp(a) and osteoblasts responsible for bone formation might be influenced by the expression of common genetic factors during childhood and puberty. However, this may not be true, because maximal levels of Lp(a) in plasma are exhibited during early childhood, whereas BMD does not peak until late puberty or early adulthood (14, 33). The observations from the present study support the idea that Lp(a) is independent of pubertal development, because no association between plasma levels of Lp(a) and pubertal stage was observed. On the other hand, pubertal stage was an independent predictor of BMD at all measured locations.

In an experimental study, heavy physical activity, but not low or moderate activity, has been shown to increase GH in adolescent boys (34) and induce a slight (but significant) increase in IGF-I (35). Physical status has been found to be related to serum levels of IGF-I, especially in younger men (36). However, this finding could not be confirmed in the present study because we observed no relation between IGF-I and the level of physical activity. Serum levels of IGF-I show a weak relationship to BMD in healthy children (37). We found no significant association between IGF-I and BMD. However, a significant positive correlation was observed between IGF-I and Lp(a). The synthesis rate of IGF-I in serum is closely related to the total amount of secreted GH (38). Treatment with GH in normal short children (39), as well as in adults with GH-deficiency (40) (predominantly males) results in a marked increase in Lp(a). Other studies have shown no change in Lp(a) (41, 42). On the other hand, therapy with recombinant human IGF-I seems to decrease serum Lp(a) in normal adult men (43). So, the serum levels of IGF-I and Lp(a) in the present study might reflect the synthesis rate of GH in the adolescent boys. However, the relation between GH, IGF-I, and Lp(a) during childhood and adolescents in healthy youths has not been subject to examinations.

In conclusion, the Lp(a) lipoprotein was found to be a predictor of BMD in adolescent boys, independent of factors such as body size, level of physical activity, and pubertal development. The cellular mechanisms responsible for this connection between adipose tissue metabolism and bone metabolism have to be subjected to further investigations.

References

12. 1994 Bone mineral density of total body, spine, and hip as an independent predictor of BMD at all measured locations.
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