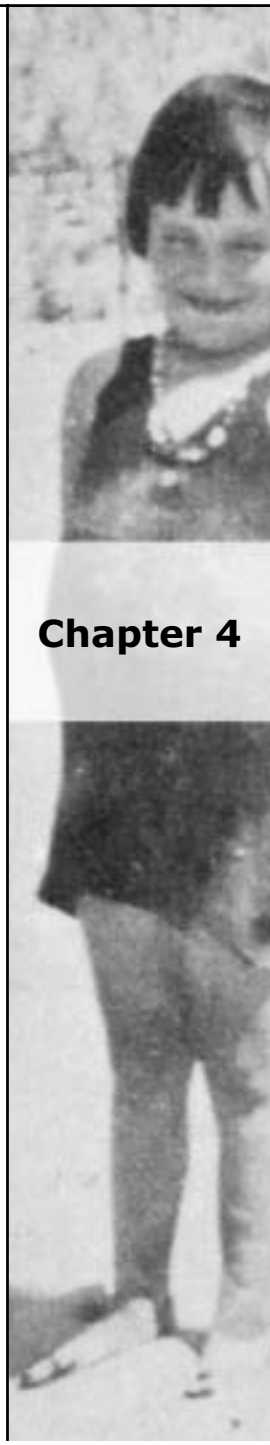
Osteopenia in Glycogen Storage Disease type I

4 Bone mineral density in children, adolescents and adults with glycogen storage disease type Ia: a cross-sectional and longitudinal study.



Chapter 4

4 Bone mineral density in children, adolescents and adults with glycogen storage disease type Ia: a cross-sectional and longitudinal study.

Jan Peter Rake
Gepke Visser
Dieuwke Huismans
Sietske Huitema
Eveline van der Veer
D. Albertus Piers
G. Peter A. Smit

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Summary

The occurrence of (symptoms related to) osteopenia is a known complication in glycogen storage disease type Ia (GSD Ia) patients. However, only limited information is available about bone mineral density (BMD).

Using dual energy X-ray absorptiometry, we studied, both cross-sectional and longitudinal, lumbar spine areal BMD (BMD_{areal} in g/cm^2), areal BMD corrected for delayed bone maturation ($BMD_{bone\ age}$ in g/cm^2) and volumetric BMD (BMD_{vol} in g/cm^3). Prepubertal GSD Ia patients (n=8) had normal BMD (median z-scores BMD_{areal} -0.6, $BMD_{bone\ age}$ -0.5 and BMD_{vol} -0.5), whereas adolescent patients (n=12) and adult patients (n=9) had significantly reduced BMD (BMD_{areal} -2.3, $BMD_{bone\ age}$ -1.6, BMD_{vol} - 2.0, and BMD_{areal} -1.9, BMD_{vol} -1.5, respectively). Our longitudinal study, showing a stable BMD_{areal} but a trend to a decrease in BMD_{vol} in prepubertal patients during follow-up, did not clarify whether the difference in BMD between prepubertal and adolescent and adult patients reflects a diminished accretion of BMD during childhood or that it reflects historical differences in treatment. In adolescent and adult GSD Ia patients, BMD_{areal} and BMD_{vol} were reduced but stable during follow-up. Especially patients with delayed bone maturation were at risk for reduced BMD. No correlation between parameters of metabolic control and BMD could be detected. Daily calcium intake was within recommended allowances ranges. Abnormal biochemical results included hypomagnesaemia (29%), hypercalciuria (34%) and reduced tubular resorption of phosphate (21%).

Although the underlying pathophysiology of reduced BMD in GSD Ia remains unsolved, metabolic control should be optimized to correct as much as possible metabolic and endocrine abnormalities that may influence both bone matrix formation and bone mineral accretion.

Introduction

Glycogen storage disease type Ia (GSD Ia, McKusick 232200) is caused by an inherited defect of glucose-6-phosphatase (G6Pase, E.C.3.1.3.9) in liver, kidney and intestine. G6Pase plays a central role in both glycogenolysis and gluconeogenesis, hydrolysing glucose-6-phosphate to glucose. As a result of inadequate glucose production, patients suffer from severe fasting hypoglycaemia. Other features are a protruding abdomen because of marked hepatomegaly, short stature, truncal obesity, rounded doll face, hypotrophic muscles, hyperlactacidaemia, hyperuricaemia, hyperlipidaemia and bleeding tendency[6].

The aim of dietary treatment (frequent meals, continuous nocturnal gastric drip feeding and the oral administration of uncooked cornstarch) is to prevent hypoglycaemia and suppress secondary metabolic derangements. As a consequence of intensive dietary treatment, life expectancy in GSD Ia has improved considerably. However, adult patients may develop numerous complications, such as liver adenomas and progressive renal disease[8,32].

Bone mineralisation in GSD Ia has received relatively little attention, although the risk developing osteoporosis was shown by assessment of cortical thickness more than 30 years ago[29]. Thereafter, one histo-pathologic study showed pure osteoporosis (reduction in mass of bone matrix) with no evidences of significant osteomalacia (reduced mineralisation of bone matrix)[38] and two radiographic studies showed osteopenia, retarded bone maturation, multiple fractures and various associated non-specific skeletal abnormalities[26,27]. Although the occurrence of symptoms related to osteopenia is a known complication in ageing GSD Ia patients nowadays[32,40], so far only one study concerning bone mineralisation in GSD Ia has been published: a reduced bone mineral content (BMC) was demonstrated in five prepubertal GSD Ia patients[24].

The aim of the present study was to obtain insight in bone mineralisation in GSD Ia by answering the following questions. First, is bone mineral density (BMD) reduced in GSD Ia patients compared to healthy controls? Second, does a difference in z-score BMD exists between prepubertal, adolescent and adult patients? And if so, does this difference reflect natural course or is it historically based? Finally, is BMD related to metabolic control? Both cross-sectional and longitudinal data of lumbar spine BMD measured by dual energy X-ray absorptiometry (DXA) of paediatric and adult GSD Ia patients are presented to answer these questions. The endocrine and metabolic abnormalities in GSD Ia that may influence normal bone mineralisation are discussed.

Patients and methods

In the period 1991 - 2000, 29 (14 males) GSD Ia patients (all caucasian) attending the metabolic clinic at the Beatrix Children's Hospital were studied cross-sectionally. Median age was 15.7 years (3.3 - 27.4). Three groups of patients were distinguished on the basis of age: prepubertal patients (< 10.0 years), adolescents (10.1 - 19.9 years) and adults (> 20.0 years). Longitudinally, 18 GSD Ia patients were studied for at least two years. Median follow-up was 5.1 years (2.1 - 6.8).

All patients shared the clinical as well as the biochemical characteristics that are associated with GSD Ia. The diagnosis was established by enzyme studies in liver tissue according to Narisawa et al[28] and/or by mutation analysis[31].

All patients were being treated with intensive dietary treatment, which was started at least one year preceding the first DXA measurement. Intensive dietary treatment consisted of frequent meals during daytime and continuous gastric drip feeding overnight (4 patients), frequent meals and uncooked cornstarch during daytime and continuous gastric drip feeding overnight (19) or frequent meals and uncooked cornstarch during daytime and uncooked cornstarch overnight (6). Galactose and fructose intake was restricted in all patients (maximum 15 g/day).

Areal BMD (BMD_{areal}, grams hydroxyapatite/cm^2) was measured by DXA (Hologic QDR 1000, Hologic, Inc., Waltham, MA, USA). Measurements were taken at the L1-L4 vertebrae. z-Scores (observed value minus mean for matched controls divided by standard deviation for matched controls) were calculated by comparing BMD_{areal} with age-matched (3 to 16 years) or age- and sex-matched (above 16 years) reference values according to the manufacturer's internal reference database. z-Scores were also calculated using bone age-matched instead of chronological age-matched reference values ($BMD_{bone\ age}$). In addition, a volumetric lumbar spine BMD (BMD_{vol}, grams hydroxyapetite /cm^3) was calculated (as BMD_{vol} = BMD × [4/(π × width of measurement area in lumbar spine)] based on a method described by Kröger et al[21]. z-Scores of BMD_{vol} were calculated by comparing BMD_{vol} with age- and sex matched reference values adapted for the Hologic QDR 1000[3,22].

Height was measured with a stadiometer by a trained antropometry nurse. Height results were compared to age-, sex- and geographical descent matched reference values and expressed as z-score.

Bone age was assessed using an X-ray of the left hand according to the Tanner-Whitehouse (TW-2) method. Delayed bone maturation was defined as bone age < 10^{th} centile of chronological age[41].

Serum concentrations of calcium (total), phosphorus, magnesium, alkaline phosphatase (AP), parathyroid hormone (PTH), calcitonin (CT), 25 hydroxyvitamin D (25OHvitD) and 1,25 dihydroxyvitamin D (1,25diOHvitD) were measured. Urinary excretion of calcium was assessed in first morning urine. Hypercalciuria was defined as calcium/creatinine ratio (mmol/mmol) > 1.1 in patients aged 3 - 5 years, > 0.8 in patients aged 5 - 10 years, and > 0.7 in patients aged above 10 years. Tubular resorption of phosphorus (TRP) was calculated on the basis of concentrations of phosphorus and creatinine in serum and first morning urine. Reduced TRP was defined as a TRP < 85%.

Plasma concentrations of cholesterol and triglycerides along with urinary excretion of lactate were measured as parameters of metabolic control. Urinary excretion of lactate was measured in three urine collections during the daytime and three urine collections overnight. Optimal metabolic control was defined as urinary lactate < 0.6 mmol/l in at least 5 out of 6 collections, intermediate control as urinary lactate < 0.6 mmol/l in 2, 3, or 4 out of 6 collections and non-optimal control as urinary lactate < 0.6 mmol/l in 0 or 1 out of 6 collections[8].

Mean daily dietary calcium-intake was assessed by a dietician (S.H.) using the patient's recommended dietary schedules of the year before the BMD measurement.

Descriptive data are presented as medians and ranges (between brackets) in view of the small number of patients. Data were analysed using one sample two tailed t-tests to compare variables with a normal distribution to normal population data, unpaired two tailed t-tests to compare variables with a normal distribution between two groups, and paired two tailed t-tests to compare variables with a normal distribution obtained by repeated measurements. One-way analyses of variance (ANOVA) were used to compare variables with a normal distribution between three groups. Pearson's parametric correlations were used to test for linearly relation between two compared sets of paired data.

Results

cross-sectional study

Height, lumbar spine BMD_{areal}, lumbar spine $BMD_{bone\ age}$ and lumbar spine BMD_{vol} (z-scores and percentages of patients with z-score ≤ -2.0) among prepubertal, adolescent and adult GSD Ia patients are shown in Table 4.1.1, along with plasma cholesterol and triglycerides concentrations and numbers of patients with optimal, intermediate and non-optimal metabolic control, based on urinary excretion of lactate.

Table 4.1.1 Height and lumbar spine BMD_{areal}, $BMD_{bone\ age}$ and BMD_{vol} (median z-scores with ranges, percentages (%) of patients with z-score ≤ -2.0) among prepubertal, adolescent and adult GSD Ia patients along with parameters of metabolic control (median and ranges; numbers)

	height	BMD_{areal}	$BMD_{bone\ age}$	BMD_{vol}	cholesterol (mmol/l)	triglycerides (mmol/l)	urine lactate (O / I / N-O)[$]
prepubertals (n = 8)	**-0.2**	**-0.6**	**-0.5**	**-0.5**	**5.55**	**6.74**	**1 / 4 / 3**
age 6.4 y (3.3 - 8.4)	(-2.3 - 0.9)	(-2.0 - 1.3)	(-1.3 - 1.3)	(-0.8 - 0.4)	(2.14 - 8.50)	(1.18 - 17.90)	
	13%	13%	0%	0%			
adolescents (n = 12)	**-0.7**[*]	**-2.3**[*** ##]	**-1.6**[*** #]	**-2.0**[*** ##]	**5.76**	**3.63**	**4 / 6 / 2**
age 15.7 y (10.4 - 19.7)	(-3.9 - 1.6)	(-4.5 - -0.1)	(-3.4 - -0.5)	(-3.8 - -1.4)	(3.26 - 7.23)	(1.27 - 10.10)	
	33%	67%	42%	67%			
adults (n = 9)	**-0.6**	**-1.9**[** #]		**-1.5**[** #]	**7.08**	**7.98**	**2 / 4 / 3**
age 23.1 y (21.8 - 27.4)	(-3.4 - 2.1)	(-2.8 - 0.3)		(-2.9 - 0.1)	(3.89 - 13.43)	(2.54 - 14.95)	
	11%	44%		33%			

[*] differences between GSD Ia patients and healthy controls in height and BMD:[*] $p < 0.05$, [**] $p < 0.01$, [***] $p < 0.001$;
[#] differences between pre-pubertal and adolescent / adults GSD Ia patients in height and BMD: [#] $p < 0.05$, [##] $p < 0.01$;
[$] urinary excretion of lactate: number of patients with *O* optimal metabolic control, *I* intermediate metabolic control, *N-O* non-optimal metabolic control (see Patients and methods)

Plasma cholesterol concentration correlated with z-scores for BMD_{areal} ($r = -0.38$, $p < 0.05$), but not with $BMD_{bone\ age}$ ($r = -0.38$, $p = 0.09$) or BMD_{vol} ($r= -0.33$, $p = 0.10$). Plasma triglycerides concentration did not correlate with z-scores for BMD_{areal} ($r = -0.33$, $p = 0.07$), $BMD_{bone\ age}$ ($r = -0.39$, $p = 0.08$) or BMD_{vol} ($r = -0.18$, $p = 0.38$). Furthermore, no differences in BMD_{areal}, $BMD_{bone\ age}$ or BMD_{vol} could be demonstrated between patients with optimal metabolic control (n = 7; age 14.7 years (5.7 - 27.4); z-score for height 0.1 (-2.9 - 1.6)), intermediate metabolic control (n = 14; age 16.1 years (3.6 - 23.1); z-score for height -0.4 (-3.4 - 2.1)), and non-optimal metabolic control (n = 8; age 17.9 years (6.8 - 26.8); z-score height -1.4 (-3.9 - 0.2). BMD_{areal} was -0.6 (-3.1 - 0.3), -1.8 (-3.0 - 1.3) and -2.0 (-4.5 - -0.1) respectively ($p = 0.37$), $BMD_{bone\ age}$ -0.9 (-2.6 - -0.4), -1.2 (-2.6 - 1.3) and -1.3 (-3.4 - -0.1) respectively ($p = 0.84$), and BMD_{vol} -2.0 (-3.8 - 0.1), -1.7 (-2.9 - 0.4) and -1.5 (-3.8 - 0.4) respectively ($p = 0.90$).

No pathological fractures were reported. Physical activity was reported to be normal in all patients. Delayed bone maturation was observed in 45% (9/20) of the patients. Daily calcium-intake the year preceding the BMD-measurement was 1000 mg (700 - 1150) in prepubertal patients, 1000 mg (600-1500) in adolescent patients, and 925 mg (600 - 1400) in adult GSD Ia patients.

The biochemical results for calcium, phosphorus, magnesium, AP, PTH, CT, 25OHvitD, 1,25diOHvitD, urinary calcium/creatinine ratio and TRP are shown in Table 4.1.2.

Longitudinal study

During follow-up, z-scores for BMD_{areal} and BMD_{vol} did not change significantly (Figure 4.1.1). However, in the four prepubertal patients, BMD_{vol} showed a tendency to decrease ($p = 0.10$). No differences in plasma cholesterol concentration, plasma triglycerides concentration or urinary lactate excretion could be demonstrated during follow-up (data not shown).

Two groups of GSD Ia patients were distinguished on the basis of bone maturation: patients with normal bone maturation and patients with delayed bone maturation (Figure 4.1.1). At latest BMD measurement, patients with normal bone maturation (n = 12) had significantly less reduced BMD_{areal} (z-scores -1.2 vs. -3.1, $p < 0.01$) and BMD_{vol} (z-scores -1.7 vs. -2.6, $p < 0.05$) compared to those with delayed bone maturation (n = 6).

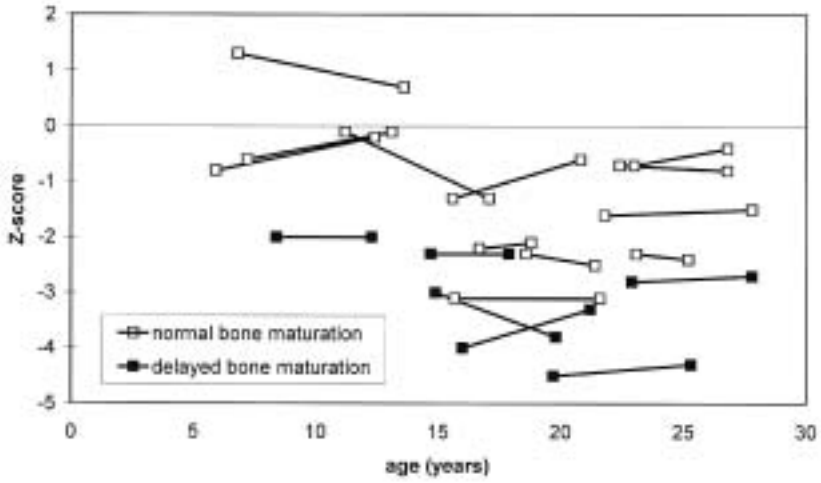
Table 4.1.2 Biochemical data in GSD Ia

		age group	median (ranges)	reference range	remarks
blood					
calcium (total)	mM/l		2.52 (2.30 - 2.75)	2.20 - 2.70	
phosphorus	mM/l	3 - 15 yrs	1.55 (1.36 - 1.94)	1.20 - 1.80	
		> 15 yrs	1.48 (0.95 - 1.68)	0.90 - 1.50	
magnesium	mM/l		0.71 (0.48 - 0.90)***	0.65 - 1.05	6 / 21 < 0.65
AP	IU/l	prepubertals	267 (153 - 320)	150 - 420	
		10 - 15 yrs	225 (171 - 282)	100 - 500	
		15 - 20 yrs	248 (139 - 622)	50 - 260	2 / 7 > 260
		adults	70 (40 - 181)	30 - 120	2 / 9 > 120
PTH	pM/l		1.79 (0.1 - 5.0)	0.1 - 4.5	
CT	pM/l	children	14.3 (0.4 - 37.8)	7 - 20	4 / 11 > 20
		adults	15.0 (8.4 - 26.1)	7 - 42	
25OhvitD	nM/l		89.5 (41 - 151)	35 - 150	
1.25diOHvitD	pM/l		120 (52 - 198)	40 - 140	
urine					
calcium/creatinine	ratio	3 - 5 yrs	0.53 and 1.23	0.05 - 1.1	1 / 2 > 1.1
(mmol/mmol)		5 - 10 yrs	0.73 (0.33 - 1.72)	0.04 - 0.8	2 / 6 > 0.8
		adolescents	0.44 (0.05 - 1.62)	0.04 - 0.7	3 / 12 > 0.7
		adults	0.63 (0.13 - 1.48)*	0.04 - 0.7	4 / 9 > 0.7
TRP	%		89.3 (78.9 - 99.3)	> 85	6 / 29 < 85

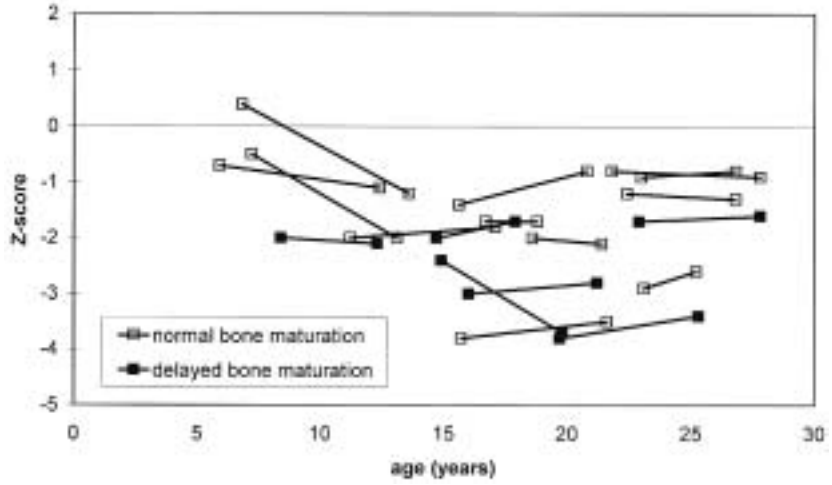
differences between GSD Ia patients and healthy controls: * p <0.05, *** p < 0.001

Figure 4.1.1 BMD_{areal} (A) and BMD_{vol} (B) in patients with GSD Ia during follof-up

A



B



Discussion

Using DXA, prepubertal GSD Ia patients had normal lumbar spine BMD, whereas adolescent and adult GSD Ia patients had reduced BMD in this study. Using single photon absorptiometry, Lee et al[24] found radial BMC z-score ≤ -2.0 in 3 out of 5 prepubertal GSD Ia patients. No previous studies of BMD in adolescent GSD Ia patients have been published. Using DXA, Goans et al[12] found that BMD in five adult GSD Ia patients averaged approximately -4.5, -3.8, and -3.0 SDS for L2-L4, the femoral neck, and Ward's triangle, respectively.

The assessment of BMD using DXA has some pitfalls, especially in paediatric patients and in patients with stunted height. In paediatric patients, application of different sets of reference data may result in differences in calculated z-scores[25]. We used the sex-non-specific reference data set provided by Hologic Inc., which is approved by the Food and Drug Administration and based on data of Southard et al[39]. Mean values of this data set are 2 to 10% higher compared to other reference data sets[25]. However, using other reference data sets, BMD was still normal in prepubertal and significantly reduced in adolescent GSD Ia patients (data not shown)[2,9,13,15]. Furthermore, using a sex-non-specific reference data set, the prevalence of osteopenia in boys 9 to 15 years may be overestimated[25] since BMD in adolescent girls is greater because of earlier onset of puberty, which is associated with a marked increase in bone accretion[2,9]. In our study, in this age range, 7 patients were included, of whom 5 were boys. This may explain why in our study z-scores BMD are more reduced in adolescent patients compared to adult patients. Another pitfall is that, calculating z-scores using chronological age matched reference values, BMD will be underestimated in GSD Ia patients, since many GSD Ia patients have delayed bone maturation (in this study 45%). To correct for delayed bone maturation, z-scores ($BMD_{bone\ age}$) were also calculated by comparing BMD results with bone age-matched controls. A final pitfall is that BMD is expressed as g/cm^2. For a constant bone density, a larger vertebra (tall stature) will typically yield higher areal BMD than a smaller one (short stature)[1,35]. To minimize this effect of vertebrae size, we also calculated a volumetric BMD (BMD_{vol}) using the formula postulated by Kröger et al[21], in which they assumed that the geometry of the vertebra approximates a cylinder. BMD_{vol} has been shown to be independent for height[23]. The observed reduced $BMD_{bone\ age}$ and BMD_{vol} in both adolescent and adult GSD Ia patients indicates that bone mineralisation in these patients is genuinely reduced, and that this is not a misjudgement because of delayed bone maturation or stunted height.

Our cross-sectional study showed that lumbar spine BMD_{areal}, $BMD_{bone\ age}$ and BMD_{vol} are reduced in adolescent and adult GSD Ia patients and not in prepubertal GSD Ia patients. In these prepubertal patients, z-scores for BMD_{vol} tended to decrease during follow-up; in contrast z-scores for BMD_{areal} were stable. Part of the difference in BMD between prepubertal patients and adolescent/adult patients may therefore reflect the natural course of bone mineralisation in GSD Ia with a diminished bone mass accretion during childhood. On the other hand, it may also be based on historical differences in dietary and/or pharmacological treatment. Improvement of metabolic control during more recent years may have positively influenced bone mineralisation in prepubertal GSD Ia patients. In adolescent and adult GSD Ia patients BMD_{areal} and BMD_{vol} are reduced but stable during follow-up.

Theoretically, a number of metabolic and endocrine disturbances in GSD Ia may explain reduced lumbar spine BMD. Both bone matrix formation and bone mineralisation may be at risk. The only histo-morphometric study available showed a 'pure osteoporosis' (reduction in mass of bone matrix) with no evidence for reduced mineralisation[38]. Hypoglycaemia causing a reduced non-enzymatic glycosylation of bone matrix protein(s) or metabolic sequelal of hypoglycaemia, such as insulinopenia, were suggested to be causative factors. Bone matrix formation in GSD Ia may also be influenced by other metabolic or endocrine sequelal such as hyperlactacidaemia, endogenous glucocorticoid excess, altered growth hormone levels and altered insulin like growth factors levels[6,7,8,44], which have all been demonstrated to reduce bone collagen and matrix synthesis[4,16,20]. Furthermore, many GSD Ia patients have an abnormal pubertal growth spurt[32,34], which is associated with sex hormone secretory dysfunction[17]. Sex steroids play an important role in bone formation, especially during puberty. Pubertal growth spurt seems to be of critical importance in forming an adequate peak bone mass and delayed puberty is a risk factor for osteoporosis[1]. In our study, a difference in BMD between GSD I patients with normal and delayed puberty is indeed observed.

According to the Utah paradigm control of bone strength and mass depends strongly on muscle strength[11]. GSD I patients may have somewhat hypotrophic muscles and decreased muscle function as a result of reduced whole body protein synthesis and of increased proteinolysis due to increased gluconeogenesis, especially if dietary treatment is less optimal[8]. Therefore, in GSD I the adaptation mechanism of bones to respond with an increase in cortical thickness and cross-sectional area in response to biomechanical loads[36], especially muscular strength, may well be understimulated. Another factor that may negatively influence bone strength is decreased physical

activity. It is well known that physical activity is decreased in many patients with chronic disease. However, physical activity was reported to be normal in all investigated GSD Ia patients. Physical activity was defined as normal if normal school/job activities and no hospitalisation longer than 2 weeks were reported during the year preceding the DXA measurement. Unfortunately, no studies to determine muscular strength were performed and no specific questionnaires about physical activity were completed to investigate these two factors in more detail.

Many factors in GSD Ia may influence normal mineralisation of bone. Low calcium intake or decreased intestinal calcium absorption disturbs normal bone mineral formation. In our study, calcium intake the year before the first BMD measurement was in the majority of patients within recommended ranges. However, less attention to optimal calcium intake in earlier years may be part of the explanation of a historical difference in BMD observed between prepubertal and adolescent and adult patients. In the prepubertal patients studied by Lee et al[24] calcium intake was generally low, the median being 59% of national average intakes. The effects of intestinal dysfunction in GSD Ia[42] on calcium absorption are unclear. An increased calcium absorption in adult GSD Ia patients was even demonstrated by Goans et al[12] suggesting a compensatory physiological adjustment in an attempt to maintain normal bone mineralisation.

Decreased bone mineralisation in GSD Ia could be a consequence of chronic lactacidaemia. Bone tissue plays an important role in buffering long-term acid loading, because it contains a large reservoir of potentially mobilisable alkaline salts[14,18,19]. The consequence of this mechanism may well be the loss of mineral content from bone. Acidosis inhibits osteoblastic and stimulate osteoclastic activity resulting in a calcium flux from bone[20]. The theory of long-term acid loading negatively influencing normal bone mineralisation is supported by the fact that in three out of five prepubertal GSD Ia patients from the U.K.[24] a BMC z-score < -2.0 was found, whereas in our study only one out of eight prepubertal GSD Ia patients had a BMD z-score < -2.0. In contrast to our patients, galactose and fructose intake was not restricted in these patients from the U.K., enhancing the production of lactate.

The tubular resorption of calcium, phosphorus and magnesium causing increased urinary loss of calcium, phosphorus and magnesium is also negatively influenced by (lact)acidaemia[10,30,43]. In our study, one-third of the patients had hypercalciuria and one-fifth of the patients had reduced TRP. Lee et al[24] demonstrated hypercalciuria in 36% of prepubertal GSD patients, whereas Goans et al[12] demonstrated reduced urinary calcium excretion in adolescent GSD Ia patients. Hypercalciuria in GSD Ia may also be a result of

an incomplete form of distal renal tubular acidosis[33], whereas reduced TRP may be the consequence of proximal tubular dysfunction as is observed in poorly controlled GSD I patients[5]. In all patients, blood concentration of calcium and phosphorus were within normal ranges. Hypomagnesaemia was observed in one-fourth of the patients. As far as we know, no previous reports about hypomagnesaemia in GSD I are available. Unfortunately we did not measure urinary magnesium excretion. Serum concentrations of PTH, 25OHvitD and 1,25diOHvitD were generally within normal ranges. To maintain normal bone mineralisation one would expect compensatory mechanisms causing increases in serum concentrations of CT and AP, since CT inhibits the motility and the ability of bone resorption of the osteoclast and increased AP may reflect compensatory increased osteoblast activity[1]. CT was increased in 36% of the prepubertal and adolescent patients, but normal in all adult patients. AP was normal in all prepubertal patients and increased in 25% of the postpubertal adolescent and adult patients. However, increased AP may also reflects liver cell damage due to glycogen and fat storage, since we measured total serum AP rather than skeletal AP iso-enzyme. Using a stable calcium isotope as label, Goans et al[12] observed less active bone mineralisation in adolescent GSD I patients and increased bone mineral turnover in adult GSD I patients compared with healthy controls.

We could not demonstrate a correlation between parameters of metabolic control and BMD, and neither did Lee et al[25]. However, parameters such as plasma cholesterol and triglycerides, and urinary excretion of lactate reflect short-term metabolic control. No useable parameters of long-term metabolic control in GSD I are yet available.

In conclusion, in this study we have demonstrated normal BMD in prepubertal GSD Ia patients along with reduced BMD in adolescent and adult patients, even when a correction for delayed bone maturation or stunted height is made. Our longitudinal study does not clarify whether the difference in BMD between prepubertal and adolescents and adults reflects the natural course of BMD in GSD Ia, with a diminished accretion of BMD during childhood, or that it is based on improvement of dietary and pharmacological treatment during more recent years. No correlation between BMD and parameters of short-term metabolic control could be demonstrated. The precise patho-physiology of reduced BMD in GSD Ia remains unsolved. However, it is hoped that meticulous dietary treatment started at early age, hereby preventing as much as possible metabolic and endocrine abnormalities - including hyperlactacidaemia (lactose and fructose restriction) - may positively influence bone mass formation. Furthermore, optimal dietary treatment will improve physical strength and vitality hereby creating the possibility for patients to

participate in physical activities comparable with healthy peers which may also influence bone mass formation positively. It is our opinion that there is no place for pharmacological intervention (e.g. biphosphonates), at this moment. Further follow-up studies of BMD in GSD Ia are warranted, however.

Addendum

In the period between submission and acceptance of this paper, Schwahn et al[37] published the results of a cross-sectional study on muscle force and distal radius bone mass and density in patients with GSD I using peripheral quantitative computed tomography. In 15 prepubertal and adolescent patients with GSD Ia, average BMC was moderately low with a mean SDS -0.9 (range -2.9 - 1.6), mainly as a result of low values in a poorly metabolic controlled subgroup, whereas volumetric trabecular BMD was normal with a mean SDS -0.6 (range -2.3 - 2.3). Muscle force (maximal isometric grip force quantified using a dynamometer) was moderately low with a mean SDS -0.9 (range -2.9 - 2.0). In 12 out of 15 patients, bone mass was adequately adapted to the mechanical requirements imposed by muscle contraction. In these 12 patients reduced bone mass seems therefore a direct effect of reduced muscle strength. In the others, a direct disease effect, possibly chronic lactacidaemia, may contribute to low bone mass. In an accompanying editorial, Wolfsdorf[45] underlines the importance of avoiding lactate production in GSD I by providing a continuous supply of glucose throughout the day and night, and avoiding foods that contain galactose (dairy products), which in patients with GSD I is converted into lactate instead of glucose. Consequently, the provision of adequate amounts of supplemental calcium and vitamin D should be ensured. Furthermore, the importance of normal physical activity of patients with GSD Ia for normal bone mass formation is underlined.

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