Height, muscle, fat and bone response to growth hormone in short children with very low birth weight (VLBW) born appropriate for gestational age (AGA) and small for gestational age (SGA)

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Für meinen geliebten Ehemann Johannes
und unsere geliebte Tochter Christina

The fear of the Lord is the beginning of wisdom,
and knowledge of the Holy One is understanding.
Proverbs 9:10, The Bible, New International Version

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1 Abbreviations

χ^2	Pearson's Chi-Square
Δ	delta
µg	microgramme
µSv	Microsievert
AGA	appropriate (weight and height) for gestational age (at birth)
BA	bone age (years)
BIA	bioelectrical impedance analysis
BMC	bone mineral content
BMI	body mass index
CA	chronological age (years)
cm^2	square centimetre
cm^3	cubic centimetre
CSA	cross-sectional area
d	day
DXA-scan	dual-energy X-ray absorptiometry scan
ELBW	extremely low birth weight
EMEA	European Agency for the Evaluation of Medicinal Products
EPH-gestosis	edema-proteinuria-hypertension-gestosis
et al.	et alii
FDA	Food and Drug Administration
g	gramme
GH	growth hormone
GHD	growth hormone deficiency
HOMA2-IR	homeostatic model assessment for insulin resistance index, version 2
IGF-1	Insulin-like growth factor-1
IGFBP-3	Insulin-like growth factor binding protein-3
Inc.	incorporation
J.	Jahre (German for years)
keV	kiloelectrovolt

kg	Kilogramme
L	Litre
MA	muscle area
mg	Milligramme
MI	Michigan
MIGF	maximal isometric grip force
mL	Millilitre
mm	Millimetre
mm^2	square millimetre
mm^4	millimetre to the fourth
mo.	Months
N	Newton
n	Number
NC	North Carolina
ng	Nanogramme
p	level of significance
P3	third percentile
PGR	preterm growth restraint
pQCT	peripheral quantitative computer tomography
R	Resistance
R^2	coefficient of determination of a linear regression
RIA	radio immuno assay
SDS	standard deviation score
SD	standard deviation
SGA	small (weight or height) for gestational age (at birth)
SSI	Strength-Strain-Index
SRS	Silver-Russel-Syndrome
Std Err.	standard error
vBMD	volumetric bone mineral density
vBMDmax	maximum volumetric bone mineral density
vBMDvox	volumetric bone mineral density in the voxel

VLBW	very low birth weight (weight below 1500 g at birth)
vs.	Versus
Xc	Reactance

2 Introduction

2.1 Prematurity

Preterm birth has been defined by the World Health Organization (WHO) as a birth before 37 weeks of gestation and extremely preterm birth before 28 weeks of gestation with a further distinction between three subgroups (preterm: < 37 weeks of gestation; very preterm: < 32 weeks of gestation and extremely preterm: < 28 weeks of gestation [1]. The term small for gestational age (SGA) has been used to describe a lack of fetal growth in relation to duration of pregnancy and has been defined by the WHO as having weight and length below the 10th percentile for gestational age [2]. It has been recommended to express birth length and weight in terms of standard deviation scores (SDS) and a birth weight and/or birth length of -2 SDS or lower for gestational age has been proposed as the criterion for SGA [3].

Low birth weight (LBW) has been defined by the WHO as a birth weight below 2500 g, very low birth weight (VLBW) below 1500 g and extremely low birth weight (ELBW) below 1000 g [4].

Children born very low birth weight (VLBW, defined here as having a birth weight < 1500 g) are differentiated into AGA or SGA according to whether they were born with a weight and/or height above (AGA) or below (SGA) -2 SDS according to a defined reference.

2.2 Growth retardation and catch-up growth

Preterm AGA children born VLBW may suffer extra-uterine growth restraint (EUGR) in their early neonatal life comparable to the situation of a fetus in utero with placental insufficiency [5,6]. Children born VLBW show a similar growth pattern during childhood, irrespective of whether they were appropriate (AGA) or small for gestational age (SGA) at birth [7]. Most of these children show catch-up growth up to or above the third percentile (P3) of height within the first two years of age. It has been shown that birth weight SDS is a significant predictor for catch-up growth in SGA children irrespective of their gestational age [8].

Preterm born children show a substantial growth failure in their early postnatal period. The majority shows catch-up growth until 2-3 years of age and in some cases until adolescence. Preterm growth restraint leads in one out of five children to long-term impairments independent of the perinatal stage at which the growth restraint happened [7]. SGA children tend to be short at the age of 5 or 6 years if their height and/or weight gain in the first year of life was poor, especially if their parents were also short. The same applies to VLBW children born AGA with poor height and/or weight gain in the first two years of life [9]. On average most preterm born infants remain shorter and lighter than term-born infants during their growth period. An altered body composition in adulthood may be the result of disproportionate catch-up growth, though early catch-up growth is beneficial for neurodevelopmental outcome [10].

Those lacking catch-up growth after reaching two years of age with a current length below -2.5 SD need further investigation [3]. Growth hormone (GH) treatment can be prescribed for SGA children who remain very short while no indication has been established for AGA children [3], [11].

Small preterm born children lacking catch-up growth appear to have reduced adult height, strength and motor capacity [7], [12], [10], [13], [14]. An altered body composition with reduced muscle tissue and increased fat tissue implicating an increased risk for cardiovascular diseases has been reported for preterm born children [10], [15], [16], [17], [18].

2.3 Aim

The aim of this study is to examine body composition and growth at start and after one year of GH treatment of short children born with a birth weight under 1500 g (VLBW). GH therapy appears to be an effective therapy to reduce adult height deficit in short SGA children who do not show satisfying catch-up growth [11]. We hypothesize that the effect of GH on height gain, muscle mass and strength as well as bone density and geometry would be similar in the AGA and SGA groups.

3 Patients and Methods

3.1 Patients

The patient group with a total of 50 short prepubertal children born VLBW comprised 19 short children born SGA (6 girls) and 31 short children born AGA (15 girls), classified according to the reference values of Niklasson et al. [19]. Six children had to be excluded from the study because they were unable to take part in the starting examination and after 12 months of GH therapy, leaving a study group of 44 children with complete data of pQCT measurements at start and after twelve months of GH therapy. Due to movement artefacts, the pQCT data of arm measurements was only usable in 41 children (arm pQCT) and the pQCT data of leg measurements in 37 children (leg pQCT), respectively (see TABLE 1). In the interest of better readability TABLE 1 to 3 are placed in the text, all further tables are given in the appendix.

TABLE 1: Study group

	SGA	**AGA**	**Total**
N (girls)	19 (6)	31 (15)	50 (21)
Complete data pQCT arm or leg 0+12 months	17 (6)	27 (12)	44 (18)
Complete data pQCT arm and leg 0+12 months	14 (4)	20 (8)	34 (12)
Complete data pQCT arm 0+12 months	16 (6)	25 (10)	41 (16)
Complete data pQCT leg 0+12 months	15 (4)	22 (10)	37 (14)

This longitudinal follow-up study was performed in the Department of Pediatric Endocrinology and Diabetology of Tübingen University Children's Hospital. All children followed clinical investigations and anthropometrical measurements during the course of the study. Perinatal parameters were gathered from the patient's medical charts. Inclusion criteria were a birth weight below 1500 g and an insufficient catch-up growth (height velocity < 0 SDS) with height at start of treatment being -2 SDS or lower and at least 1 SDS below target height SDS. GH deficiency (GHD) was excluded by a GH peak above 8 µg/L in an arginine test or an overnight GH secretion profile.

Mean GH dose did not differ significantly between groups: 54 µg/kg/d (SD 12 µg/kg/d) in the AGA group and 51 µg/kg/d (SD 11 µg/kg/d) in the SGA group (p = 0.44).

Six children suspected with Silver-Russell-Syndrome were included in the study group with one boy and two girls in each group. Their values at start and during treatment did not differ from the rest of the respective groups. Data on genetic tests were complete in one SGA girl, one AGA girl and the AGA boy. The SGA girl was diagnosed with a maternal UPD 7 (uniparental disomy of chromosome 7). The second SGA girl presented with a triangular face, a clinodactyly at both hands and an asymmetric growth with shortening of the left hand and foot. The SGA boy was born as a second twin and showed a massive teeth misalignment, asymmetric growth with shortened left arm and leg, a big head with a slim mandible, clinodactyly and a discrete left-sided spasm.

A maternal UPD 7 was excluded in the first AGA girl. She presented with a typical face for Silver-Russel-Syndrome, an implied funnel chest, thin hair, purulent rhinitis, visual impairment, adenoids and overall retarded dystrophic development with reduced concentration. The second AGA girl suspected with SRS showed a triangular face, an inverse hairline, a relatively big head with a broad nose bridge, a pectus excavatum, frequent tonsillitis and a high frequency sensorineural hearing loss. The AGA boy showed no maternal UPD 7 and no epimutation in ICR1 (imprinted control region 1) in 11p15 (chromosome 11, allele 15). Phenotypically he presented with a hunchback, clinodactyly of the fifth finger on both hands, a small mouth with hanging mouth angles, a high voice, tooth misalignment, mandibular rethrognathism, thin hair and syndactyly of second and third toe at both feet.

We thus cannot be sure that all six of these children diagnosed with SRS actually had SRS, especially since the known mutations for SRS only account for 70% of the known cases. TABLE 2 shows prenatal and perinatal data as well as further medical conditions of the examined children.

There was significant difference between the groups with regard to respiratory distress syndrome, duration of assisted ventilation and bronchopulmonary dysplasia.

Pregnancy risks such as multiple pregnancy, placental insufficiency and hydramniosis occurred in both groups likewise, whereas amniotic infection syndrome occurred more often in the AGA group and EPH-gestosis in the SGA group. Maternal smoking may be underreported with only one reported case in the SGA group. Respiratory distress syndrome and subsequent bronchopulmonary dysplasia occurred more often in the AGA group. There was a high prevalence of assisted ventilation in the AGA group. Perinatal infections occurred more often among the SGA children, whereas cases of necrotizing enterocolitis and enteropathic acrodermatitis have only been reported in the AGA group. Cerebral malformations, further dysplasias and minor anomalies occurred more often in the AGA group. One case of intracranial hemorrhage and one of internal hydrocephalus were reported among the SGA children. Pearson's Chi-square analysis shows a significant difference between the groups with regard to the parameters: duration of assisted ventilation (> 7 days on assisted ventilation), respiratory distress syndrome (both with $p = 0.00040$) and bronchopulmonary dysplasia with $p = 0.040$. On the other hand results with $p > 0.05$ do not necessarily assure that there is no difference between groups.

TABLE 2: Prenatal and perinatal characteristics and clinical conditions: number of children with the respective condition with Pearson's χ^2 and p

Characteristic	SGA	AGA	Total	Pearson χ^2	Prob > χ^2
N	17	27	44		
Before birth (%)					
Maternal smoking	1	0	1	1.6	0.20
Parity > 0	3	8	11	0.80	0.37
Multiple pregnancy	5	6	11	0.29	0.59
Amniotic infection syndrome	1	5	6	1.4	0.23
Placental insufficiency/Hydramniosis	7	8	15	0.62	0.43
Preterm abruption of placenta	2	6	8	0.77	0.38
EPH-gestosis	4	3	7	1.2	0.27
At or after birth					
Respiratory distress syndrome	1	16	17	12.5	0.00040
> 7 days on assisted	2	18	20	12.7	0.00040

ventilation					
Bronchopulmonary dysplasia	2	11	13	4.2	0.040
Pneumothorax	0	2	2	1.3	0.25
Sepsis/Infection	8	7	15	2.1	0.15
Necrotizing enterocolitis	0	3	3	2.0	0.15
Enteropathic acrodermatitis	0	1	1	0.64	0.42
Hyperbilirubinemia	2	3	5	0.0040	0.95
Cholestasis	1	1	2	0.11	0.74
Transfusion-dependent anemia	9	11	20	0.63	0.43
Intracranial hemorrhage	1	0	1	1.6	0.20
Internal hydrocephalus	1	0	1	1.6	0.20
Cerebral palsy	1	2	3	0.038	0.85
Cerebral malformation	0	3	3	2.03	0.15
Hypoplastic adenohypophysis	1	2	3	0.038	0.85
Convulsions	0	1	1	0.64	0.42
Dysplasias/minor anomalies	5	14	19	2.1	0.14
Hernias	10	8	18	3.7	0.055
Heart malformations	3	3	6	0.38	0.54
Silver-Russell syndrome	3	3	6	0.38	0.54

The study was approved by the independent ethics committee of the medical faculty of the University of Tubingen and informed written consent was given by the parents.

3.2 Methods

At start of GH treatment and at intervals of 6 and 12 months measurements of height, weight and body composition were done for all 44 children (with further measurements at 24, 36, and 48 months in some children). SDS values for height and weight were calculated according to the standards of Prader et al. [20]. Birthweight SDS calculations were done according to given standards by Niklasson et al. [19]. Bone age was estimated according to the method of Greulich and Pyle [21]. Muscle strength was measured by the use of maximal isometric grip force (MIGF) of the non-dominant hand (Newton; N) using an adjustable Jamar dynamometer (Preston, Jackson, MI).

Body composition data on fat-, muscle-, bone-mass and body-water were measured using a DXA body scan. Skinfold thickness was measured at the lower arm, calf, hip and scapula using a Holtain/Tanner-Whitehouse Skinfold Caliper. Measurements of Resistance R (Ohm) and Reactance Xc (Ohm) were obtained by Bioelectrical Impedance Analysis (BIA).

IGF-1 values were measured at start, 3, and 6 months and every 6 months thereafter. The children in this cohort were receiving a relatively high GH dose of 55 µg/kg/d. This dose was thought to be appropriate because it was between the low and high dose used by de Zegher et al. [11] and because the first years of treatment were thought to offer the highest chance of catch-up: one did not want to waste time titrating upwards. This GH dose was reached in increments 4 weeks after starting treatment and then titrated according to IGF-1 levels and reduced if IGF-1 was above +2 SDS (this was necessary in 4 children born SGA and 1 child born AGA). TABLE 3 shows the mean adjusted GH dose given from six months on for the following six months. (SGA children are now usually started at 33 µg/kg/d and titrated to a maximum of 50 µg/kg/d in our institution if they are not responding.)

Fasting glucose, insulin and C-peptide were determined from venous blood samples in the basal fasting state between 8-10 a.m. in the morning. Homeostatic model assessment of insulin resistance (HOMA-IR) is an index of the steady state beta cell function and insulin sensitivity from basal fasting glucose and insulin or C-peptide measurements. Using C-peptide instead of insulin makes the calculations more stable to momentary changes in fasting blood insulin results. HOMA2-IR was calculated using the computerized HOMA2 calculator, as described by Wallace et al. [22].

3.2.1 pQCT measurement

The cross-sectional areas of muscle and fat were measured by pQCT (XCT 2000 (Stratec, Inc., Pforzheim, Germany) on the proximal non-dominant lower arm and leg. The position was exactly 65% of the ulna length (55 % of the tibia length for leg) away from the radius growth plate (tibia growth plate for leg). A scout-view scan enabled a precise location of the radius/tibia growth plate. A

2 mm thick single tomographic slice was taken at a voxel size of 0.4 x 0,4 x 2 mm³. The outer and inner cortical bone contours were detected at a threshold of 710 mg/cm³. The threshold of 30-70 mg/cm³ was used to measure muscle cross-section area and the remaining subcutaneous tissue constituted the fat area. The software package of Stratec, Inc. (version 6.0) was used for performing all image processing and calculations of numerical values. A single scan uses a radiation dose of approximately 0.3 µSv. The effective dose for the forearm is about 0.1 µSv, which is less than 2% of the effective natural background radiation dose acquired within one day (6.6 µSv). The calibration of the pQCT device was done once per week with a standard phantom and once per month with a cone phantom provided by the manufacturer. The low energy X-ray tube of the scanner is of 28 keV. A relative length of the arm was chosen (and the lengths of the radius and tibia were measured anew each time) to ensure exact corresponding measurements regardless of individual and interindividual changing arm lengths. Age- and height-dependent reference values for healthy German children have been established for the 65% site of the ulna length using the same pQCT device by Rauch and Schoenau [23]. Corresponding reference values for the 65% site of the tibia length in healthy children have not yet been established. pQCT measurements of the leg were only done for a subset of 15 SGA children (4 girls) and 22 AGA children (10 girls).

The following offers a brief description of the main parameters measured:

Muscle CSA [mm²] is used as a surrogate marker for muscle force and can be used to study the relationship between muscle and bone tissue [23].

Total CSA [mm²] is the area of the entire bone cross-section which consists of cortical bone and marrow cavity. It is a measure of the outer bone size. Assuming a circular bone size it is also possible to calculate total CSA by using the periosteal perimeter, whereas the direct measurement of total CSA is more precise.

Total CSA is a key determinant of diaphyseal bending strength and is therefore one of the most important parameters of pQCT analysis. It is only influenced by periosteal apposition [23].

Cortical CSA [mm²] is the surface area of cortical bone cross-section and is equivalent to total CSA minus marrow CSA. Cortical CSA changes under periosteal apposition and endocortical resorption [23].

Cortical thickness [mm] is the width of the bone cortex and it changes under periosteal apposition and endocortical resorption.

Total vBMD [mg/cm³] is the ratio of Bone mineral content (**BMC**) [mg/mm] and total CSA [mm²] of a bone. Bone mineral content is the mass of mineral per 1 mm of axial bone length. BMC in pQCT measurements is influenced by periosteal, intracortical and endocortical changes. The bone mineral of diaphyseal bone is only situated in the cortex and therefore total vBMD is the product of cortical vBMD and the ratio between cortical CSA and total CSA [23].

Cortical content [mg/mm] is the mass of mineral in the cortex per 1 mm of axial bone length.

Cortical volumetric bone mineral density [mg/cm³] (**Cortical vBMD**) represents the density of the solid cortex. It is influenced by intracortical remodeling where old material with higher density is replaced by new bone material with lower density. Cortical vBMD can be used as a parameter of cortical porosity. The interpretation of cortical vBMD is limited by the partial volume effect in pQCT measurements. On the outer and inner surface the voxels are not completely filled, which leads to an underestimation of cortical vBMD in thinner cortices. The age-dependent reference values for cortical vBMD are only useful in normal parameters for cortical thickness [23].

The polar moment of inertia [mm^4] is the sum of all bone-filled voxel areas multiplied by the respective voxel's distance from the center [23].

The Strength-Strain-Index [mm³] is the polar moment of inertia divided by the maximal distance of a bone-filled voxel from the center (Section modulus) multiplied by the ratio of volumetric bone mineral density in the voxel (vBMDvox) [mg/cm³] and maximum mineral density under physiological

conditions (vBMDmax: 1200 mg/cm³). It is influenced by changes of bone mineralization and is a parameter of bone strength [23].

Fat area [mm²] measured in pQCT is the subtraction of total area [mm²] minus muscle area [mm²] and total bone area [mm²].

Muscle density [mg/mL] measured in pQCT is expressed in mg per measured volume.

3.2.2 DXA measurement

Basic theory and methodology of DXA for measuring body composition

The method of DXA (dual x-ray absorptiometry) is based on the degrees of attenuation of two different beam energies (6.4 and 11.2 fJ) that pass through the body. The degree of attenuation is dependent on the mass and type of tissue the energy beams pass through. For bone minerals the mass attenuation coefficients for both beam energies are known constants. For soft tissue the ratio of the mass attenuation coefficients varies linearly according to the fat fraction. In a region of interest the ratio for soft tissue is calculated in all pixels which contain only soft tissue and is then averaged. In a second step the ratio for soft tissue is extrapolated to the pixels containing both soft and bone tissue, based on the assumption that the soft-tissue composition in these pixels is similar. Total body bone mineral (TBBM) and soft tissue mass (STM) are then calculated. TBBM divided by the summarized area of bone containing pixels gives the total body bone mineral density (TBBD). Fat tissue mass (FTM) and lean tissue mass (LTM) are calculated from the STM and the fat percentage of the soft tissue deduced from the ratio of soft tissue. Lean body mass (LBM) is the sum of LTM and TBBM. Fat percentage of the body (FAT%) is FTM divided by the sum of LBM and FTM [24].

In DXA bone mineral content (BMC) is calculated in a different way than in pQCT. In DXA BMC refers to the amount of mineral in the bone regions studied (mg/mm^2). This is influenced by bone length or the size of the analyzed region. In pQCT BMC is the mass of mineral per axial bone length and area (mg/mm^3): The calculations of pQCT BMC are therefore not prone to biases caused by the size of the bones [23].

3.2.3 Assays

An in-house RIA was used for measuring GH in serum [25], the variation of the intraassay and interassay coefficients were less than 10%. Serum levels of IGF-I and IGF-binding protein (IGFBP)-3 were measured by RIA as described by Blum et al. [26]. The mean interassay and intraassay coefficients of the IGF-I and the IGFBP-3 assays were lower than 10%. Data were transformed into age-related SDS values on the basis of a reference population of healthy German and Danish children with normal height [26].

3.2.4 Statistics

Statistical analyses were done by Dipl. med. Cornelia Berndt and Prof. Dr. David Martin using the computed statistics program JMP version 8.0.1 (SAS Institute, Cary, NC). Results are expressed in means and SD, unless otherwise specified. Significance of differences was tested with a two-tailed paired t test. A comparative study of both patient groups AGA and SGA was done by a two-tailed unpaired t test. Differences were considered significant below the 5% level. Due to the explorative-descriptive nature of the statistics with a total of 212 t-tests (136 two-tailed paired t tests and 76 two-tailed unpaired t tests), a Bonferroni-correction was not performed. Regression analyses were done using Pearson's coefficient of correlation. Chi-square analyses to test differences between birth-parameters were done using contingency tables and results are given in Pearson's Chi-square. The standard deviation scores (SDS) refer to the age- and sex-matched references, unless otherwise specified and were calculated as subject-value minus mean of age- and sex-matched reference divided by the standard deviation (SD) of age- and sex-matched reference. Calculations for height-dependent SDS for the given pQCT measurements were done according to the standards of Rauch and Schoenau [23] and for height-age SDS according to Schweizer et al. [27].

4 Results

4.1 Baseline characteristics

There were, by definition, significant differences between the AGA and SGA children with regard to gestational age ($p < 0.0001$), birth weight SDS ($p < 0.0001$) and birth length SDS ($p < 0.0001$). No significant differences between groups were found in the auxological characteristics at start of GH and in the GH dose (see TABLE 3, TABLE 4, TABLE 5 and TABLE 6).

TABLE 3: Perinatal and auxological parameters at start of therapy (see TABLE 4, TABLE 5 and TABLE 6 for the remaining parameters) with an unpaired t-test analysis between AGA and SGA.

Perinatal and auxological parameters at GH start	AGA (n = 27)		SGA (n = 17)		AGA vs. SGA
	Mean	SD	Mean	SD	p Value
Gestational age (weeks)	29	2.2	33	2.4	<0.0001
Birth weight (g)	1003	258	948	304	0.54
Birth weight (SDS)	-0.96	0.63	-3.2	0.89	<0.0001
Birth length (SDS)	-0.38	3.3	-3.5	1.1	<0.0001
Height (SDS)	-3.3	0.84	-3.3	0.73	1
Max. GH in test (µg/L)	10	5.9	11	5.4	0.51
GH dose (µg/kg/d) (6 mo)	54	12	51	11	0.44
Height SDS (0 mo) – Target height SDS	-2.7	0.80	-2.8	1.1	0.75

TABLE 2 shows the pre- and perinatal conditions of most of the children, where the medical chart was available. Comparison of pre- and perinatal conditions showed differences between the groups with 16 cases of respiratory distress syndrome being reported in the AGA group and only one case in the SGA group. Two cases of more than seven days on assisted ventilation after birth are reported in the SGA group, compared to 18 cases among the AGA group. Eleven cases of bronchopulmonary dysplasia are reported among the AGA group with only two cases in the SGA group respectively. Unfortunately medical charts of pre- and perinatal conditions were incomplete in two SGA girls and one AGA boy. One SGA girl was born in gestational week 31 as a third triplet at a birth weight of 600 g (-3.8 SDS). The second SGA girl was born in gestational

week 36 at a birth weight of 1480 g (-3.24 SDS). The AGA boy was born at a gestational age of 30 weeks at a birth weight of 1290 g (-0.41 SDS). He developed a postnatal sepsis and suffers from cerebral palsy.

4.2 Changes in auxology during GH treatment

The changes in auxological and endocrinological characteristics during the first year of GH therapy in AGA and SGA in a paired t-test analysis and a comparison between groups in an unpaired t-test are given in TABLE 4, TABLE 5 and TABLE 6.

The increase in height, height SDS, height velocity and height velocity SDS in both groups were all highly significant with $p < 0.001$. The increase in weight was highly significant in both groups and increase in weight SDS in SGA with $p < 0.001$, increase in weight SDS in AGA was significant with $p < 0.001$. Decrease in skinfold thickness measured at the triceps was significant in AGA with $p = 0.0029$, highly significant in SGA with $p < 0.001$. MIGF of the non-dominant hand increased significantly in AGA with $p < 0.001$, in SGA with $p = 0.0018$. MIGF SDS of the non-dominant hand did not show any significant changes in both groups. Resistance R (BIA) decreased significantly in both groups with $p < 0.001$. Bone age changed significantly only in AGA with $p < 0.001$. Reactance Xc decreased significantly only in AGA with $p = 0.048$.
No significant differences between both groups at start, in the changes of the first year of GH and after twelve months of treatment were found in the auxological characteristics (TABLE 6).

4.3 Changes in endocrinology during GH treatment

Increase in IGF-1, IGF-1 SDS and IGFBP-3 were all highly significant in both groups with $p < 0.001$. IGFBP-3 SDS increased highly significant in AGA with $p < 0.001$, in SGA with $p < 0.001$.
Changes in insulin, C-peptide, glucose, plasma glucose and HOMA2-IR did not show any significance in both groups (see TABLE 4, TABLE 5 and TABLE 6).

4.4 Changes in pQCT parameters during GH treatment

TABLE 7, TABLE 8 and TABLE 9 show changes from baseline after twelve months of GH treatment in different arm pQCT parameters for both groups and they show a comparison between these groups.

In arm pQCT measurements muscle area increased significantly in AGA with $p = 0.046$ (TABLE 7), in SGA with $p = 0.043$ (TABLE 8).

Muscle area SDS increased significantly in AGA with $p = 0.001$ (TABLE 7), but not significantly in SGA with $p = 0.060$ (TABLE 8).

Comparison of deltas between both groups were not significant ($p = 0.61$) (TABLE 9).

All other pQCT parameters – fat area, fat area SDS, muscle density and various bone parameters – did not show significant changes in either of the groups.

TABLE 10, TABLE 11 and TABLE 12 show different leg pQCT parameters and their changes from baseline after twelve months of GH treatment.

In pQCT measurements of the leg muscle area increased significantly in SGA with $p = 0.015$ (TABLE 11), increase in AGA was not significant (TABLE 10). Fat area and muscle density did not change significantly in either of the groups (TABLE 10, TABLE 11). Cortical vBMD decreased significantly in AGA with $p = 0.037$ (TABLE 10), but not in SGA (TABLE 11). Significant increases in SGA were found in cortical CSA with $p = 0.030$, cortical thickness with $p = 0.027$ and cortical content with $p = 0.039$ (TABLE 11). These parameters did not show significant increase in AGA (TABLE 10).

No significant difference in the changes of the first year of GH and after twelve months of treatment was found between groups in arm or leg pQCT measurements (TABLE 9 and TABLE 12).

5 Discussion

5.1 Discussion of results

5.1.1 Initial position

Children were selected at early childhood when seen by a pediatrician because of growth retardation. Inclusion criteria were a birth weight below 1500 g for term born and preterm born children and an insufficient catch-up growth with a height at start of treatment being -2 SDS or lower. Further distinctions between the AGA children (e.g. whether growth restraint was experienced before term or afterwards) was not possible since data were not available for all children. It would be good if all preterm born children had been examined by a pediatrician at their calculated term date. We divided the study group by birth criteria AGA and SGA and included only those children with pQCT data from start and after twelve months of GH-treatment.

5.1.2 No significant differences between AGA and SGA

Results of this study show no significant differences between AGA and SGA children in their auxological parameters at start of GH treatment. This has already been described in recent studies [5], [7], [6], [12]. Ranke et al. investigated growth and development in 97 preschool children born AGA or SGA at a birth weight < 1500 g. Short AGA and SGA children at follow-up had smaller head circumferences and a higher rate of bronchopulmonary dysplasia [5]. In a Dutch study on long-term height gain of very preterm born children, Finken et al. demonstrates a 20% prevalence of persistent short stature. Very preterm children with what Wit et al. called the ‘preterm growth restraint’ (PGR) with a height below -2 SDS at the age of 5 years both result in a median adult height of -2,5 SDS, irrespective of whether they were born SGA or AGA. The study states that preterm growth restraint prefigures long-term sequelae independent of the perinatal phase when the growth restraint happened, whether in utero, ex utero or both [7]. Wit et al. thus recommend the usage of the term ‘preterm growth restraint’ (PGR) to indicate poor growth in the third trimester since this appears to be a more appropriate term for either preterm born AGA or term

born SGA with a low weight and/or length at term age [6]. Saigal et al. examined 154 ELBW survivors being born at a birth weight between 501-1000 g. No significant difference in mean heights and weights was found between ELBW adolescents who were born SGA or AGA [12].

5.1.3 Growth restraint in AGA and SGA

Data of this study on AGA and SGA children show low SDS for height, weight, height velocity and muscle mass and higher fat proportions before GH treatment in comparison to age- and sex-matched references. Fat area was lower than normal, but muscle SDS and weight SDS were much lower than fat SDS, leaving relatively more fat on the extremities of the children. This corresponds to clinical experience: the examiner is often astonished to feel more fatty tissue than expected on these very thin extremities.

Euser et al. state in their review that preterm born children show a substantial growth failure in their early postnatal period. The majority shows catch-up growth until 2-3 years of age and in some cases until adolescence. In spite of this, most preterm born infants remain shorter and lighter than term-born infants during their growth period. An altered, often disadvantageous, body composition in adulthood with an increased fat-to-muscle ratio may be the result of disproportionate catch-up growth, though early catch-up growth is beneficial for neurodevelopmental outcome [10].

Saigal et al. report on ELBW adolescents being 5.8 cm shorter and 5.8 kg lighter than term control participants in their study. ELBW children show a significantly greater catch-up in weight than in height with a higher increase in BMI over time in ELBW girls [12].

5.1.4 GH treatment criteria and dosage

The children in this cohort were receiving a relatively high GH dose up to 55 µg/kg/d with similar doses in both groups. There are differing recommendations as to the optimal dosage as described below. The given dose was thought to be appropriate because it was between the low and high dose used by de Zegher et al. [11] and because the first years of treatment were thought to offer the highest chance of catch-up without wasting time titrating

upwards. This GH dose was reached in increments 4 weeks after starting treatment and then titrated according to IGF-1 levels and reduced if IGF-1 was above + 2 SDS. Reduction of the given GH dose was necessary in five children, four of the SGA group and one in the AGA group. In our institution SGA children are now usually started at 33 µg/kg/d and titrated to a maximum of 50 µg/kg/d if they are not responding.

GH treatment of children with short stature who were born SGA is approved by the FDA (Food and Drug Administration) and EMEA (European Agency for the Evaluation of Medicinal Products). The FDA-approved indication (2001) for GH treatment in short SGA children is absent catch-up growth with a starting age of two years; the starting dose is 70 µg/kg/d. No references to height SDS at start nor to midparental height are given. The EMEA-approved indication (2003) for treating short SGA children with GH is for children at the age of four years with height SDS of -2.5, growth velocity for age below 0 SD and height SDS being more than 1 SD below their midparental height SDS. The allocated starting dose is 35 µg/kg/d [3].

In Europe, a daily GH dose of 33 µg/kg has been recommended for short SGA children up to adult height starting at age 4-6 years. If height is below -3 SDS an initial higher dose of approximately 50 µg/kg/d has been recommended with a decrease to 33 µg/kg/d when short-term catch-up growth has been achieved and long-term growth to a normal adult height is likely [11], [28]. A final dosage recommendation can still not be made today since we are lacking long-term follow-up of both SGA and AGA children into adulthood with regard to their health risk profile. The SGA and AGA children of this study show a similar increase in height SDS in the first year of GH treatment with little acceleration of bone maturation under GH treatment in either groups, as already described by Sas et al. in a 5-year randomized, double-blind, dose-response GH study on SGA children (0.033 vs. 0.067 mg/kg per day). The process of bone maturation seemed to be independent of the individually given dose and a lower dose was sufficient for reaching normal height. The increment in height SDS for chronological age was not related to GH secretion levels or baseline IGF-I levels. Only children who remained prepubertal during the study period showed

a significantly higher increase in height SDS for chronological age in the study group receiving 0.067 mg/kg per day vs. 0.033 mg/kg per day [29].

Van Pareren et al. later reported about the same study group as Sas et al. [29] on the achievement of adult height in a randomized, double-blind dose-response trial on long-term GH therapy in children born SGA without persistent catch-up growth: normalization of adult height was independent of GH dose (0.033 vs. 0.067 mg/kg per day). Adult height SDS was significantly higher in the treatment group than in untreated control subjects [28].

Dahlgren et al. showed in a study on short SGA children treated with GH that the highest benefit was achieved when treatment started early before the pubertal growth spurt begins. A normalization of height before puberty is essential and this gain is maintained during puberty to final height. Starting age and the duration of GH treatment were found to be the most indicative predictors for height gain. Height velocity at start has no influence on GH response. Prepubertal height gain through GH treatment seems to be dose-dependent, whereas no dose effect was found during puberty [30]. These results agree with the results of Sas et al. [29].

Jung et al. have shown in the OPTIMA study on prepubertal short children born SGA that an individualized GH dose treatment with 0.035 mg/kg/day is not inferior to a treatment with a fixed high dose of 0.067 mg/kg/day in twelve months of GH-treatment. Treatment dose was increased to the higher dose of 0.067 mg/kg/day after three months in the individually adjusted GH dose group if the predicted change in height SDS was below 0.75, using the Cologne growth-prediction model. Height SDS difference of -0.24 (fixed high dose group – individually adjusted dose group) resulting in a height difference of only 1 cm between the groups after one year was statistically significant but not considered to be clinically meaningful. The chosen non-inferiority margin for height SDS difference between both groups was to be -0.5. Adjustment of GH dosage reduces costs and increases safety by reducing the potential risk of over-stimulating of the IGF-I system with the possible results of impaired glucose tolerance [31].

In a retrospective study on skeletal maturation under GH treatment Darendeliler et al. have shown a normal progression of delayed bone age with a mean progression of one year during the first year of treatment with considerable interindividual variation. Pre-pubertal children from the KIGS database (Pfizer International Growth Database) with idiopathic growth hormone deficiency, Turner syndrome, idiopathic short stature and short children born SGA were included in the study. Bone age was assessed according to the method of Greulich and Pyle at baseline and after one year of therapy. No consistent effect of the dosage of GH on the progression of bone age was found [32].

Arends et al. reported in a Dutch study on pre-pubertal short children born SGA on the effects of GH treatment (0.033 mg/kg/d) vs. no treatment on bone maturation and its relation to changes in height during three years of treatment. Spontaneous catch-up of bone age without GH treatment was about one year, whereas under GH mean catch-up of BA was up to 1.6 years. Under GH treatment a normalization of height with a proportionally increase in bone maturation to height gain can be shown. The reduced BMD and bone maturation in short SGA children normalizes under GH treatment with a significantly increase during the first two years of GH-treatment. A good predictor for 3-year height gain seems to be the ratio of Δ BA (bone age)/Δ CA (chronological age). Height gain of severely short children with height SDS at or below -3 at start of GH treatment was not dependent on the given GH dose (0.033 vs. 0.067 mg/kg per day) and an early start of GH treatment is recommended [33].

Martin et al. found a catch-up of bone age in SGA children of 1.4 years after one year of GH treatment with a treatment dose of 49.8±13.04 µg/kg/d (mean ± SD) [34].

Labarta et al. reported in a retrospective study on untreated children born SGA that the onset of puberty occurs at a normal age but relatively early for body height. Untreated children born SGA appear to generally have a lower pubertal growth spurt than controls whilst the tempo of puberty is similar [35].

Ranke et al. found the levels of IGF-1 and IGFBP-3 to be a useful indicator for GH sensitivity during initial GH dosage step-up in GH-treated short SGA

children and GH-deficient children [36]. These parameters were measured throughout this study; they were low at start of treatment and showed a similar increase in both groups (see TABLE 4).

5.1.5 Changes in body composition under growth hormone treatment

Muscle area changed significantly in both groups in the first year under GH. Only in leg pQCT measurements of the AGA group was no significant change of muscle area found after the first year.

No significant change of muscle density under GH treatment was found in this study, which is the first study to look at this parameter. This, together with the fact that the increase in muscle tissue is accompanied by an increase in muscle strength, indicates that the increase in muscle strength and the increase in muscle area are due to an increase in functional muscle tissue [27]. The increase in muscle strength under GH suggests that the increase in muscle area is mainly functional muscle and not just the water accumulation that GH is also known to induce. The fact that the muscle density does not change also supports this – although this cannot be stated for sure since it is not known how sensitive pQCT is to muscle density changes through water accumulation.

Best correlations to changes in muscle area under GH treatment were observed with changes in Strength Strain Index (SSI), polar moment of inertia, cortical cross-sectional area and cortical content in arm and leg pQCT-measurements, as well as in changes in bone mass in DXA-measurements and maximal isometric grip force of the non-dominant hand.

SSI is a pQCT parameter for bone strength and sensitive to changes of bone mineralization. SSI is derived from the polar moment of inertia and the section modulus, which are mechanical parameters for describing the strength of elongated structures [23]. The pQCT findings in this study with regard to the correlations between bone strength parameters and muscle area are similar to those of Schweizer et al. in a pQCT study on GH-deficient and SGA children [37].

The data of this study display a non-significant decrease of cortical vBMD during the first year of GH therapy in both groups for arm pQCT measurements, being significant for the leg pQCT measurements in the AGA group with $p < 0.05$. Schweizer et al. described an initial decrease of cortical vBMD in GH-

deficient children under GH replacement therapy caused by early bone remodeling [27].

5.1.6 Body composition in preterm born children with growth restraint and further risks

Leger et al. state that long-term GH treatment in short SGA children improves growth velocity and increases muscle cross-sectional area. Adipose tissue decreases during the first year of treatment followed by a slight increase during the second and third year. The effects of the three years of GH treatment can still be demonstrated one year after stopping treatment [38].

Schweizer et al. show in a pQCT study on body composition of short SGA children that a subgroup of children born SGA has deficiencies in muscle-mass, muscle-strength and bone development [39].

Untreated VLBW boys (birth weight < 1500 g) have been studied by Ericson et al. at the age of 19 years with regard to body composition and further sequelae. The young men were shorter and lighter, had a lower BMI than controls and showed a reduction in muscular strength and physical working capacity. A higher rate of visual and hearing impairments, an increased risk for cerebral palsy and other mental impairments, lower intelligent test scores and shorter schooling were also found [13].

Saigal et al. studied ELBW children (birth weight between 501 to 1000 g) at adolescence. They showed significantly lower growth attainment on height, weight and head circumference; a higher prevalence of functional limitations and more use of health care and educational resources than term controls [12].

Rogers et al. compared unimpaired ELBW adolescents being born at a birth weight below 800 g with term-born adolescents at the age of 17 years. ELBW adolescents showed significant differences in motor performance, flexibility and aerobic capacity than term-born controls. These differences can be related to effects of premature birth on the motor system and to a rather inactive lifestyle of ELBW survivors with potential implications for later health problems [14].

A study on preterm birth and later insulin resistance by Finken et al. showed a weak association of rapid infancy weight gain of preterm born children until three months post-term with higher insulin levels at 19 years of age. Adult

obesity is a strong predictor for higher insulin and C-peptide levels, as well as higher HOMA-IR (homeostatic model assessment for insulin resistance index) with a larger effect on these parameters shown in obese adults being born at a lower birth weight [15].

Rapid weight gain in small babies may lead to an imbalance in body composition with high fat mass but low muscle mass, whereas an increase in body weight within the first year is associated with a reduced risk of coronary events as adults. An increase in the SDS for BMI after two years of age has been found by Barker et al. to be a stronger predictor of later coronary events than BMI obtained at any other age [16].

Hack et al. display in a prospective study on growth of VLBW infants up to 20 years of age that VLBW females catch-up more in weight than in height, whereas VLBW males remain shorter and lighter than control subjects. There is concern about children, esp. VLBW females, who catch-up rapidly to have a higher risk for developing metabolic syndrome in adulthood [17].

Singhal et al. showed in a study on body composition of adolescents an association of a higher birth weight with greater fat-free mass, but not with greater fat mass. Poor fetal growth, which is measured in a low birth weight, is suggested to lead to a programming of a smaller proportion of lean mass in further life. The association of birth weight with lean body mass is independent of height. Low birth weight may program a smaller proportion of lean mass and adversely affect later metabolic status with impaired insulin sensitivity and thereby increase the risk for developing cardiovascular diseases [18].

Some untreated preterm born children with growth retardation are thus at risk of developing metabolic disorders such as deranged glucose-tolerance and diabetes and furthermore coronary insufficiency [15], [16], [17], [18]. Whether the GH-induced increase in muscle mass and decrease in fat mass in our study later leads to a better metabolic status is as yet unknown. In the children of this study a clear increase of insulin levels within the normal range was observed (TABLE 4). Martin et al. have shown that in the short term increase in muscle mass and decrease in fat mass was inversely related to increase in insulin resistance in short children born SGA undergoing GH treatment [40]. Long-term monitoring is

necessary to assess whether the effects of growth hormone on fat, muscle and bone of preterm SGA and AGA children has long-term benefits (or risks) for their metabolic health.

5.1.7 Adverse effects of GH treatment

None of the known side effects of GH were observed in the children of this study. Possible long-term adverse effects of GH therapy are not yet fully known. A known effect of GH therapy is the above-mentioned reversible decrease of insulin sensitivity [40]. In our patients we saw a clear increase of insulin levels, within the normal range (see TABLE 4).

5.1.8 Height velocity

The inclusion criteria dictate that height velocity was < 0 SDS at the time the decision to start treatment was taken (which was about 2-5 months before GH start). Yet TABLE 4 shows that some children had normal height velocity at the time of GH start. The height velocity given in TABLE 4 represents the height velocity between the last measurement before GH start and the measurement at GH start. This seeming acceleration of growth after the decision to start GH in some children could either be due to imprecision (short time span between the measurements, too low measurement at the time of making the decision and/or too high measurement at the time of GH start) – or perhaps even because the children experience a psychological boost due to either them or their parents, or both, feeling relieved that something is going to be done about the short stature. This phenomenon would perhaps deserve further study in a metaanalysis of a large number of growth hormone studies. From our previous studies we would expect slightly lower height velocities of about 5.5±1 cm/year (-0.55±1 SDS) at GH start in short children born SGA [40].

5.2 Weaknesses of this study

The weaknesses of this study can be seen in small study groups without randomized control groups receiving placebo or no treatment. The latter would have been an ethically difficult issue in these children. Using no treatment may offer a psychological advantage (no injection stress – which can be very high in

VLBW children) or disadvantage (“no one is doing anything about my short stature”), and giving placebo injections was not acceptable for many parents, whose VLBW children often have had more or less traumatic hospital experiences in the past. This is why we decided to compare the VLBW children with the already well-described SGA children. It would have been useful to have two measurements at different times before GH start to be able to quantify the effect of GH more precisely in each group, but again, this would have been an extra burden on the children and their families. However, these potential drawbacks do not affect the main outcome of this study i.e. the difference between the groups.

Unfortunately an initially planned intraindividual comparison of leg pQCT measurements to jumping performances on a Leonardo Jumping Platform was not possible, because the PC with the database of jumping examinations resetted the actual date of examinations to the basic set date of the PC and this error was not noticed before the examinations were completed.

5.3 Recommendation

On the basis of this study we can make some methodical recommendations for further pQCT studies. pQCT measurements in this study show better results in leg measurements than in arm measurements. Even slight movements during the measuring process reduce the quality. The courses of total area (leg), muscle area (leg), total cross-sectional area (tibia) and cortical cross-sectional area (tibia) to age (y) show smoother increments than the equivalent measurements of the arm, whereas the courses in fat area measurements in arms and legs do not show any uniformity (see appendix).

Unfortunately, 40 pQCT measurements of the arm and 12 pQCT measurements of the calf showed poor quality due to minor movements, with examples in the appendix. Two pQCT measurements of the arm at the beginning of GH treatment had to be excluded (see appendix).

In order to achieve better results it is recommendable to perform pQCT measurements in children of the calf rather than of the arm because the calf

measurements are much less prone to movement artifacts. However, reference data for pQCT measurements of the calf in children have yet to be published.

6 Conclusion

In conclusion, this study did not show significant differences of prepubertal auxological parameters in preterm short VLBW children born AGA and SGA. The AGA group showed a similar or stronger response to GH treatment compared to the SGA group in terms of growth, muscle and fat changes. The positive response and tolerability of growth hormone warrants a discussion about the benefits and risks of growth hormone treatment in both groups instead of excluding a-priori those who experienced the preterm growth restraint outside the uterus i.e. the preterm VLBW AGA. These results reveal the arbitrary nature of using the criterion “SGA” for eligibility to growth hormone treatment in children born with a birth weight below 1500 g.

7 Appendix

Tables

Figures

7.1 Tables

TABLE 4: Baseline values and changes after 12 months of GH treatment for auxology, height velocity (HV), maximum isometric grip force (MIFG), BIA impedance and resistance, IGFs and skinfolds for group AGA

	AGA (N=27, 12 females)						
Time of GH (mo)	**0**	**0**	**12**	**12**	**Δ 0 to 12**	**Δ 0 to 12**	**0 vs. 12 mo**
					Paired t-test analysis		
Auxological characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**Std Err**	**p Value**
Height (cm)	**106**	12	**116**	12	**9.8**	0.32	<.0001
Height (SDS)	**-3.3**	0.84	**-2.4**	0.80	**0.92**	0.070	<.0001
Weight (kg)	**16**	5.82	**20**	7.8	**3.7**	0.43	<.0001
Weight (SDS)	**-2.6**	0.82	**-2.04**	0.72	**0.52**	0.13	0.0003
HV (cm/year)	**6.2**	1.1	**9.6**	1.3	**3.4**	0.32	<.0001
HV (SDS)	**-0.0015**	1.03	**4.2**	1.7	**4.2**	0.44	<.0001
Age (years)	**6.9**	2.3	**8.0**	2.3	**1.0**	0.016	<.0001
Bone age (years)	**5.8**	2.5	**6.8**	2.4	**1.1**	0.19	0.0001
MIGF (N) non-dominant	**62**	37	**81**	43	**23**	4.9	0.0002
MIGF (SDS) non-dominant	**-0.59**	1.2	**-0.31**	1.4	**0.26**	0.21	0.23
Resistance R (Ohm)	**810**	88	**695**	86	**-105**	20	<.0001
Reactance Xc (Ohm)	**71**	8.5	**66**	5.8	**-3.4**	1.6	0.048
IGF-1 (ng/mL)	**95**	41	**214**	112	**122**	19	<.0001
IGF-1 (SDS)	**-1.9**	1.1	**0.43**	1.3	**2.3**	0.27	<.0001
IGFBP-3 (ng/mL)	**2461**	590	**3740**	870	**1313**	150	<.0001
IGFBP-3 (SDS)	**-1.7**	0.98	**-0.08**	0.91	**1.6**	0.19	<.0001
Skinfold triceps (mm)	**7.4**	2.5	**6.1**	4.0	**-1.5**	0.43	0.0029
Insulin (pmol/L)	**28**	31	**42**	56	**-3.7**	9.4	0.70
C-peptide (pmol/L)	**271**	301	**263**	163	**-72**	93	0.45
Glucose (mg/dL)	**80**	12	**75**	10.0	**-6.5**	4.9	0.20
Plasma glucose (mmol/L)	**4.5**	0.68	**4.2**	0.55	**-0.3595**	0.27	0.20
HOMA2-IR	**0.6**	0.56	**0.56**	0.32	**-0.11**	0.16	0.50

TABLE 5: Baseline values and changes after 12 months of GH treatment for auxology, height velocity (HV), maximum isometric grip force (MIFG), BIA impedance and resistance, IGFs and skinfolds for group SGA

	SGA (N=17, 6 females)						
Time of GH (mo)	**0**	**0**	**12**	**12**	**Δ 0 to 12**	**Δ 0 to 12**	**0 vs. 12 mo**
					Paired t-test analysis		
Auxological characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**Std Err**	**p Value**
Height (cm)	**106**	14	**115**	13	**9.3**	0.59	<.0001
Height (SDS)	**-3.3**	0.73	**-2.6**	0.87	**0.71**	0.14	<.0001
Weight (kg)	**15**	4.1	**18**	4.6	**3.2**	0.22	<.0001
Weight (SDS)	**-2.9**	0.55	**-2.3**	0.63	**0.53**	0.091	<.0001
HV (cm/year)	**5.7**	1.7	**8.8**	1.8	**3.1**	0.44	<.0001
HV (SDS)	**-0.18**	1.7	**3.3**	1.9	**3.5**	0.57	<.0001
Age (years)	**7.1**	3.1	**8.2**	3.1	**1.1**	0.035	<.0001
Bone age (years)	**4.3**	3.8	**5.3**	3.5	**0.97**	0.45	0.098
MIGF (N) non-dominant	**49**	32	**82**	47	**39**	9.8	0.0018
MIGF (SDS) non-dominant	**-1.1**	1.6	**-0.56**	1.1	**0.59**	0.56	0.31
Resistance R (Ohm)	**829**	88	**714**	75	**-92**	16	0.0001
Reactance Xc (Ohm)	**75**	11	**70**	8.9	**-4.3**	2.8	0.16
IGF-1 (ng/mL)	**106**	60	**233**	130	**133**	21	<.0001
IGF-1 (SDS)	**-1.9**	1.6	**0.47**	1.4	**2.5**	0.35	<.0001
IGFBP-3 (ng/mL)	**2903**	880	**3957**	884	**1137**	185	<.0001
IGFBP-3 (SDS)	**-1.02**	1.2	**0.14**	0.69	**1.3**	0.27	0.0002
Skinfold triceps (mm)	**7.5**	2.1	**5.9**	2.1	**-2.2**	0.35	<.0001
Insulin (pmol/L)	**22**	11	**41**	24	**13**	8.8	0.18
C-peptide (pmol/L)	**169**	116	**345**	159	**151**	94	0.16
Glucose (mg/dL)	**80**	7.7	**79**	10	**-3.4**	4.7	0.49
Plasma glucose (mmol/L)	**4.4**	0.43	**4.4**	0.53	**-0.19**	0.26	0.49
HOMA2-IR	**0.48**	0.15	**0.75**	0.42	**0.18**	0.16	0.31

TABLE 6: Comparison of p values in unpaired two tailed t-test of group AGA and SGA for baseline values and changes after 12 months of GH treatment for auxology, height velocity (HV), maximum isometric grip force (MIFG), BIA impedance and resistance, IGFs and skinfolds

	AGA vs. SGA		
Time of GH (mo)	**0**	**12**	**∆ 0 to 12**
	Unpaired two tailed t-test		
Auxological characteristics	**p Value**	**p Value**	**p Value**
Height (cm)	0.96	0.85	0.43
Height (SDS)	1.0	0.43	0.19
Weight (kg)	0.60	0.52	0.39
Weight (SDS)	0.14	0.15	0.98
HV (cm/year)	0.33	0.14	0.55
HV (SDS)	0.70	0.13	0.36
Age (years)	0.82	0.79	0.34
Bone age (years)	0.47	0.41	0.83
MIGF (N) non-dominant	0.25	0.95	0.15
MIGF (SDS) non-dominant	0.28	0.54	0.59
Resistance R (Ohm)	0.54	0.52	0.60
Reactance Xc (Ohm)	0.18	0.22	0.81
IGF-1 (ng/mL)	0.50	0.62	0.70
IGF-1 (SDS)	0.92	0.93	0.67
IGFBP-3 (ng/mL)	0.09	0.44	0.46
IGFBP-3 (SDS)	0.081	0.38	0.37
Skinfold triceps (mm)	0.86	0.84	0.21
Insulin (pmol/L)	0.38	0.97	0.20
C-peptide (pmol/L)	0.16	0.16	0.11
Glucose (mg/dL)	0.86	0.22	0.65
Plasma glucose (mmol/L)	0.86	0.22	0.65
HOMA2-IR	0.35	0.18	0.22

TABLE 7: Changes from baseline in arm pQCT after 12 months of GH treatment for group AGA

	AGA (N=25, 10 females)						
Time of GH (mo)	**0**	**0**	**12**	**12**	**Δ 0 to 12**	**Δ 0 to 12**	**0 vs. 12 mo**
					Paired t-test analysis		
Arm pQCT	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**Std Err**	**p Value**
Muscle area (mm²)	**1177**	323	**1400**	316	**223**	105	0.046
Muscle area (SDS, formula)	**-2.2**	0.91	**-0.73**	1.1	**1.5**	0.35	0.0010
Muscle area (height-SDS, formula)	**-2.2**	0.91	**-0.81**	1.3	**1.5**	0.48	0.011
Muscle area (height-age-SDS, formula)	**-1.1**	1.2	**0.17**	1.5	**1.5**	0.50	0.012
Fat area (mm²)	**527**	201	**440**	357	**-87**	75	0.26
Fat area (SDS, formula)	**-1.1**	0.94	**-1.8**	1.1	**-0.77**	0.37	0.054
Fat area (height-SDS, formula)	**-1.4**	1.5	**-2.6**	2.03	**-1.4**	0.71	0.082
Fat area (height-age-SDS, formula)	**-1.10**	1.4	**-1.9**	1.5	**-1.3**	0.51	0.030
Total vBMD (mg/cm³)	**319**	142	**345**	107	**26**	41	0.53
Cortical vBMD (mg/cm³)	**944**	63	**937**	49	**-6.8**	18	0.71
Total CSA (mm²)	**75**	21	**80**	24	**4.9**	6.1	0.42
Total CSA (SDS, formula)	**-0.24**	1.3	**0.13**	1.6	**0.37**	0.61	0.56
Total CSA (height-SDS, table)	**0.19**	2.6	**0.69**	1.8	**0.47**	1.0	0.65
Total CSA (height-age-SDS, formula)	**0.11**	1.4	**0.54**	1.5	**0.52**	0.72	0.48
Cortical CSA (mm²)	**25**	11	**29**	9	**4**	3	0.22
Cortical CSA (SDS, formula)	**-1.3**	0.56	**-1.0**	1.0	**0.31**	0.28	0.29
Cortical CSA (height-SDS, table)	**0.51**	1.5	**0.21**	1.2	**-0.052**	0.55	0.93
Cortical CSA (height-age SDS, formula)	**-0.36**	0.84	**-0.28**	0.74	**0.14**	0.38	0.71
Cortical thickness (mm)	**0.90**	0.39	**1.0**	0.29	**0.12**	0.12	0.32
Cortical thickness (SDS, formula)	**-1.5**	0.90	**-1.2**	1.2	**0.24**	0.39	0.56
Cortical thickness (height-age-SDS, formula)	**-0.73**	1.0	**-0.71**	0.81	**0.062**	0.44	0.89
Cortical content (mg/mm)	**24**	12	**27**	9.1	**3.6**	3.5	0.32
Cortical content (SDS, formula)	**-0.91**	1.0	**-0.92**	1.3	**-0.015**	0.38	0.97
Cortical content (height-age-SDS, formula)	**0.89**	0.97	**0.35**	1.2	**-0.46**	0.46	0.34

Muscle density (mg/mL)	**74**	7.2	**77**	4.0	**2.9**	1.7	0.099
Bone mineral content (SDS, table)	**-2.3**	0.97	**-1.7**	1.4	**0.59**	0.47	0.24
Bone mineral content (height-SDS, table)	**-0.82**	0.99	**-0.41**	0.84	**0.49**	0.39	0.23
Total density (SDS, table)	**0.17**	1.7	**-0.10**	1.1	**-0.42**	0.64	0.53
Total density (height-SDS, table)	**1.8**	1.3	**1.2**	1.3	**-0.73**	0.47	0.15
Cortical density (SDS, formula)	**-0.18**	1.1	**-0.55**	0.95	**-0.26**	0.31	0.41
Cortical density (height-SDS, table)	**2.1**	1.2	**0.42**	0.80	**-1.7**	0.46	0.0028
Cortical density (height-age-SDS, formula)	**0.60**	1.1	**-0.13**	0.72	**-0.63**	0.29	0.0555
SSI (mm^3)	**73**	32	**84**	33	**11**	10	0.28
SSI (SDS, formula)	**-1.1**	0.45	**-1.0**	1.0	**0.11**	0.29	0.71
SSI (height-SDS, table)	**0.31**	1.5	**-0.070**	1.6	**-0.17**	0.47	0.72
SSI (height-age-SDS, formula)	**-0.087**	0.66	**-0.20**	0.95	**0.062**	0.38	0.87

TABLE 8: Changes from baseline in arm pQCT after 12 months of GH treatment for group SGA

	SGA (N=16, 6 females)						
Time of GH (mo)	**0**	**0**	**12**	**12**	**Δ 0 to 12**	**Δ 0 to 12**	**0 vs. 12 mo**
					Paired t-test analysis		
Arm pQCT	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**Std Err**	**p Value**
Muscle area (mm²)	**1067**	261	**1311**	365	**243**	108	0.043
Muscle area (SDS, formula)	**-3.2**	1.9	**-1.2**	1.5	**2.0**	0.92	0.060
Muscle area (height-SDS, formula)	**-3.1**	1.9	**-1.2**	1.6	**0.97**	0.87	0.30
Muscle area (height-age-SDS, formula)	**-2.3**	2.2	**-0.58**	1.9	**1.9**	1.04	0.10
Fat area (mm²)	**525**	195	**408**	210	**-117**	65	0.093
Fat area (SDS, formula)	**-0.62**	1.8	**-1.7**	0.74	**-1.1**	0.66	0.12
Fat area (height-SDS, formula)	**-1.1**	2.1	**-2.4**	1.3	**-1.5**	1.00	0.18
Fat area (height-age-SDS, formula)	**-1.2**	1.7	**-1.7**	0.66	**-0.69**	0.58	0.28
Total vBMD (mg/cm³)	**342**	132	**358**	142	**16**	62	0.80
Cortical vBMD (mg/cm³)	**968**	68	**954**	54	**-14**	21	0.52
Total CSA (mm²)	**71**	16	**86**	16	**16**	7.6	0.061
Total CSA (SDS, formula)	**-0.64**	0.75	**0.70**	1.3	**1.3**	0.72	0.099
Total CSA (height-SDS, table)	**0.59**	2.1	**1.59**	1.9	**0.88**	1.2	0.47
Total CSA (height-age-SDS, formula)	**-0.16**	1.0	**0.95**	1.8	**1.3**	0.70	0.10
Cortical CSA (mm²)	**24**	9	**30**	11	**5.3**	3.0	0.10
Cortical CSA (SDS, formula)	**-1.4**	0.83	**-0.92**	1.3	**0.50**	0.52	0.36
Cortical CSA (height-SDS, table)	**-0.025**	2.7	**-0.023**	1.4	**0.050**	1.2	0.97
Cortical CSA (height-age SDS, formula)	**-0.79**	0.75	**-0.29**	0.85	**0.54**	0.31	0.12
Cortical thickness (mm)	**0.91**	0.33	**1.1**	0.40	**0.14**	0.15	0.37
Cortical thickness (SDS, formula)	**-1.6**	1.0	**-1.5**	1.5	**0.093**	0.66	0.89
Cortical thickness (height-age-SDS, formula)	**-1.1**	0.95	**-0.90**	1.03	**0.26**	0.54	0.65
Cortical content (mg/mm)	**24**	10	**29**	11	**4.7**	3.2	0.17
Cortical content (SDS, formula)	**-0.57**	1.2	**-0.55**	1.7	**0.019**	0.77	0.98

Cortical content (height-age-SDS, formula)	**0.47**	1.13	**0.65**	1.3	**0.032**	0.62	0.96
Muscle density (mg/mL)	**76**	3.7	**78**	4.1	**2.1**	1.3	0.13
Bone mineral content (SDS, table)	**-2.0**	2.1	**-0.83**	1.2	**0.92**	1.03	0.40
Bone mineral content (height-SDS, table)	**-0.82**	0.96	**-0.13**	0.66	**0.72**	0.38	0.10
Total density (SDS, table)	**0.74**	2.0	**0.23**	1.8	**-0.68**	0.88	0.46
Total density (height-SDS, table)	**2.0**	2.1	**1.5**	2.2	**-0.76**	0.97	0.46
Cortical density (SDS, formula)	**0.17**	1.4	**-0.31**	1.3	**-0.52**	0.69	0.47
Cortical density (height-SDS, table)	**4.6**	5.5	**1.7**	2.4	**-3.9**	2.1	0.11
Cortical density (height-age-SDS, formula)	**1.02**	1.4	**0.30**	1.00	**-0.65**	0.59	0.31
SSI (mm^3)	**69**	29	**86**	30	**17**	7.9	0.057
SSI (SDS, formula)	**-1.2**	0.83	**-0.69**	1.3	**0.48**	0.44	0.30
SSI (height-SDS, table)	**-0.38**	2.2	**-0.26**	0.95	**0.18**	0.72	0.81
SSI (height-age-SDS, formula)	**-0.46**	0.67	**-0.033**	0.79	**0.44**	0.32	0.21

TABLE 9: Comparison of p values for changes from baseline in arm pQCT after 12 months of GH treatment

	AGA vs. SGA		
Time of GH (mo)	**0**	**12**	**∆ 0 to 12**
	Unpaired two tailed t-test		
Arm pQCT	**p Value**	**p Value**	**p Value**
Muscle area (mm²)	0.20	0.48	0.89
Muscle area (SDS, formula)	0.13	0.48	0.61
Muscle area (height-SDS, formula)	0.13	0.48	0.60
Muscle area (height-age-SDS, formula)	0.084	0.31	0.71
Fat area (mm²)	1.00	0.74	0.76
Fat area (SDS, formula)	0.44	0.84	0.65
Fat area (height-SDS, formula)	0.61	0.66	0.92
Fat area (height-age-SDS, formula)	0.87	0.56	0.44
Total vBMD (mg/cm³)	0.71	0.88	0.90
Cortical vBMD (mg/cm³)	0.46	0.31	0.79
Total CSA (mm²)	0.48	0.53	0.28
Total CSA (SDS, formula)	0.30	0.41	0.32
Total CSA (height-SDS, table)	0.66	0.23	0.79
Total CSA (height-age-SDS, formula)	0.54	0.53	0.45
Cortical CSA (mm²)	0.80	0.87	0.79
Cortical CSA (SDS, formula)	0.21	0.80	0.76
Cortical CSA (height-SDS, table)	0.52	0.65	0.94
Cortical CSA (height-age SDS, formula)	0.15	0.98	0.43
Cortical thickness (mm)	0.99	0.87	0.92
Cortical thickness (SDS, formula)	0.36	0.59	0.86
Cortical thickness (height-age-SDS, formula)	0.31	0.62	0.78
Cortical content (mg/mm)	0.91	0.78	0.82
Cortical content (SDS, formula)	0.77	0.59	0.97
Cortical content (height-age-SDS, formula)	0.30	0.56	0.53
Muscle density (mg/mL)	0.19	0.32	0.70
Bone mineral content (SDS, table)	0.59	0.083	0.78
Bone mineral content (height-SDS, table)	0.98	0.34	0.67
Total density (SDS, table)	0.42	0.60	0.81
Total density (height-SDS, table)	0.74	0.66	0.98
Cortical density (SDS, formula)	0.45	0.60	0.74
Cortical density (height-SDS, table)	0.12	0.10	0.35
Cortical density (height-age-SDS, formula)	0.38	0.23	0.97
SSI (mm³)	0.62	0.93	0.68

SSI (SDS, formula)	0.45	0.35	0.49
SSI (height-SDS, table)	0.33	0.69	0.68
SSI (height-age-SDS, formula)	0.15	0.62	0.46

TABLE 10: Changes from baseline in leg pQCT after 12 months of GH treatment for group AGA

	AGA (n = 22, 10 females)						
Time of GH (mo)	**0**	**0**	**12**	**12**	**Δ 0 to 12**	**Δ 0 to 12**	**0 vs. 12 mo**
					Paired t-test analysis		
Leg pQCT	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**Std Err**	**p Value**
Muscle area (mm²)	**2435**	623	**2846**	926	**411**	207	0.065
Fat area (mm²)	**894**	414	**666**	475	**-619**	588	0.10
Total vBMD (mg/cm³)	**507**	146	**501**	96	**-6.0**	39	0.88
Cortical vBMD (mg/cm³)	**1030**	56	**999**	35	**-31**	13	0.037
Total CSA (mm²)	**213**	71	**235**	66	**22**	15	0.17
Cortical CSA (mm²)	**102**	33	**118**	41	**16**	11	0.16
Cortical thickness (mm)	**2.3**	0.65	**2.5**	0.64	**0.23**	0.22	0.33
Cortical content (mg/mm)	**105**	43	**119**	51	**14**	12	0.27
Muscle density (mg/mL)	**78**	4.0	**78**	2.9	**0.41**	1.3	0.76
SSI (mm³)	**463**	198	**547**	250	**83**	53	0.14

TABLE 11: Changes from baseline in leg pQCT after 12 months of GH treatment for group SGA

	SGA (n = 15, 4 females)						
Time of GH (mo)	**0**	**0**	**12**	**12**	**Δ 0 to 12**	**Δ 0 to 12**	**0 vs. 12 mo**
					Paired t-test analysis		
Leg pQCT	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**Std Err**	**p Value**
Muscle area (mm²)	**2005**	467	**2526**	583	**521**	188	0.015
Fat area (mm²)	**832**	249	**700**	403	**-132**	87	0.15
Total vBMD (mg/cm³)	**449**	147	**522**	119	**73**	44	0.12
Cortical vBMD (mg/cm³)	**997**	60	**1001**	38	**3.6**	15	0.81
Total CSA (mm²)	**204**	54	**209**	47	**5.2**	18	0.78
Cortical CSA (mm²)	**89**	33	**108**	36	**19**	7.8	0.030
Cortical thickness (mm)	**2.1**	0.71	**2.5**	0.70	**0.45**	0.18	0.027
Cortical content (mg/mm)	**90**	46	**109**	46	**19**	8.1	0.039
Muscle density (mg/mL)	**79**	1.7	**79**	2.2	**-0.21**	0.86	0.81
SSI (mm³)	**398**	192	**463**	195	**64**	46	0.19

TABLE 12: Comparison of p values for changes from baseline in leg pQCT after 12 months of GH treatment

	AGA vs. SGA		
Time of GH (mo)	**0**	**12**	**∆ 0 to 12**
	Unpaired two tailed t-test		
Leg pQCT	**p Value**	**p Value**	**p Value**
Muscle area (mm²)	0.93	0.26	0.70
Fat area (mm²)	0.59	0.83	0.95
Total vBMD (mg/cm³)	0.44	0.49	0.19
Cortical vBMD (mg/cm³)	0.26	0.84	0.10
Total CSA (mm²)	0.79	0.16	0.48
Cortical CSA (mm²)	0.65	0.43	0.84
Cortical thickness (mm)	0.56	0.85	0.45
Cortical content (mg/mm)	0.58	0.46	0.75
Muscle density (mg/mL)	0.23	0.65	0.70
SSI (mm³)	0.67	0.24	0.79

TABLE 13: Correlation to pQCT muscle area (arm/leg) of various pQCT parameters, MIGF and DXA bone mass with R^2, N, p by time from GH start; 0 months

Time from GH start (mo)	0		
Correlation to muscle area (mm^2) of	R^2	N	p Value MA
Total CSA (mm^2) to MA (mm^2) (arm)	0.54	40	<0.0001
Cortical CSA radius (mm^2) to MA (mm^2) (arm)	0.61	38	<0.0001
Cortical thickness (mm) to MA (mm^2) (arm)	0.36	38	<0.0001
Total vBMD (mg/cm^3) to MA (mm^2) (arm)	0.15	38	0.018
Cortical content radius (mg/mm) to MA (mm^2) (arm)	0.59	38	<0.0001
Cortical vBMD (mg/cm^3) to MA (mm^2) (arm)	0.24	38	0.0017
Polar moment of inertia radius (mm^4) to MA (mm^2) (arm)	0.76	38	<0.0001
SSI radius (mm^3) to MA (mm^2) (arm)	0.78	38	<0.0001
Fat area (mm^2) to MA (mm^2) (arm)	0.0058	41	0.64
Muscle density (mg/mL) to MA (mm^2) (arm)	0.0048	41	0.67
DXA bone mass (g) to MA (mm^2) (arm)	0.66	13	0.00070
DXA: Bone mineral density (g/cm^2) to MA (mm^2) (arm)	0.0041	13	0.84
MIGF of non-dominant hand (N) to MA (mm^2) (arm)	0.56	36	<0.0001
Leg: Total CSA tibia (mm^2) to MA (mm^2) (leg)	0.49	32	<0.0001
Leg: Cortical CSA tibia (mm^2) to MA (mm^2) (leg)	0.67	35	<0.0001
Leg: Cortical thickness tibia (mm) to MA (mm^2) (leg)	0.33	35	0.00030
Leg: Total vBMD (mg/cm^3) to MA (mm^2) (leg)	0.064	32	0.16
Leg: Cortical content tibia (mg/mm) to MA (mm^2) (leg)	0.64	35	<0.0001
Leg: Cortical vBMD tibia (mg/cm^3) to MA (mm^2) (leg)	0.10	32	0.072
Leg: Polar moment of inertia tibia (mm^4) to MA (mm^2) (leg)	0.64	35	<0.0001
Leg: SSI tibia (mm^3) to MA (mm^2) (leg)	0.73	35	<0.0001
Leg: Fat area (mm^2) to MA (mm^2) (leg)	0.15	37	0.018
Leg: Muscle density (mg/mL) to MA (mm^2) (leg)	0.000027	36	0.98
MIGF of non-dominant hand (N) to MA (mm^2) (leg)	0.50	31	<0.0001

TABLE 14: Correlation to pQCT muscle area (arm/leg) of various pQCT parameters, MIGF and DXA bone mass with R^2, N, p by time from GH start; 6 months

Time from GH start (mo)	6		
Correlation to muscle area (mm^2) of	R^2	N	p Value MA
Total CSA (mm^2) to MA (mm^2) (arm)	0.44	32	<0.0001
Cortical CSA radius (mm^2) to MA (mm^2) (arm)	0.76	32	<0.0001
Cortical thickness (mm) to MA (mm^2) (arm)	0.56	32	<0.0001
Total vBMD (mg/cm^3) to MA (mm^2) (arm)	0.36	32	0.00030
Cortical content radius (mg/mm) to MA (mm^2) (arm)	0.74	32	<0.0001
Cortical vBMD (mg/cm^3) to MA (mm^2) (arm)	0.39	32	0.00010
Polar moment of inertia radius (mm^4) to MA (mm^2) (arm)	0.67	32	<0.0001
SSI radius (mm^3) to MA (mm^2) (arm)	0.77	32	<0.0001
Fat area (mm^2) to MA (mm^2) (arm)	0.0032	32	0.76
Muscle density (mg/mL) to MA (mm^2) (arm)	0.043	32	0.26
DXA bone mass (g) to MA (mm^2) (arm)	0.53	8	0.041
DXA: Bone mineral density (g/cm^2) to MA (mm^2) (arm)	0.36	8	0.11
MIGF of non-dominant hand (N) to MA (mm^2) (arm)	0.65	29	<0.0001
Leg: Total CSA tibia (mm^2) to MA (mm^2) (leg)	0.53	30	<0.0001
Leg: Cortical CSA tibia (mm^2) to MA (mm^2) (leg)	0.57	28	<0.0001
Leg: Cortical thickness tibia (mm) to MA (mm^2) (leg)	0.48	28	<0.0001
Leg: Total vBMD (mg/cm^3) to MA (mm^2) (leg)	0.216	30	0.0097
Leg: Cortical content tibia (mg/mm) to MA (mm^2) (leg)	0.57	28	<0.0001
Leg: Cortical vBMD tibia (mg/cm^3) to MA (mm^2) (leg)	0.31	30	0.0014
Leg: Polar moment of inertia tibia (mm^4) to MA (mm^2) (leg)	0.47	27	<0.0001
Leg: SSI tibia (mm^3) to MA (mm^2) (leg)	0.52	27	<0.0001
Leg: Fat area (mm^2) to MA (mm^2) (leg)	0.022	28	0.45
Leg: Muscle density (mg/mL) to MA (mm^2) (leg)	0.0015	27	0.85
MIGF of non-dominant hand (N) to MA (mm^2) (leg)	0.36	26	0.00030

TABLE 15: Correlation to pQCT muscle area (arm/leg) of various pQCT parameters, MIGF and DXA bone mass with R^2, N, p by time from GH start; 12 months

Time from GH start (mo)	12		
Correlation to muscle area (mm^2) of	R^2	N	p Value MA
Total CSA (mm^2) to MA (mm^2) (arm)	0.28	41	0.00040
Cortical CSA radius (mm^2) to MA (mm^2) (arm)	0.60	41	<0.0001
Cortical thickness (mm) to MA (mm^2) (arm)	0.31	41	0.00010
Total vBMD (mg/cm^3) to MA (mm^2) (arm)	0.11	41	0.031
Cortical content radius (mg/mm) to MA (mm^2) (arm)	0.57	41	<0.0001
Cortical vBMD (mg/cm^3) to MA (mm^2) (arm)	0.20	41	0.0034
Polar moment of inertia radius (mm^4) to MA (mm^2) (arm)	0.57	41	<0.0001
SSI radius (mm^3) to MA (mm^2) (arm)	0.79	41	<0.0001
Fat area (mm^2) to MA (mm^2) (arm)	0.00057	41	0.88
Muscle density (mg/mL) to MA (mm^2) (arm)	0.011	41	0.51
DXA bone mass (g) to MA (mm^2) (arm)	0.35	11	0.054
DXA: Bone mineral density (g/cm^2) to MA (mm^2) (arm)	0.00045	11	0.95
MIGF of non-dominant hand (N) to MA (mm^2) (arm)	0.71	34	<0.0001
Leg: Total CSA tibia (mm^2) to MA (mm^2) (leg)	0.711	40	<0.0001
Leg: Cortical CSA tibia (mm^2) to MA (mm^2) (leg)	0.76	37	<0.0001
Leg: Cortical thickness tibia (mm) to MA (mm^2) (leg)	0.44	37	<0.0001
Leg: Total vBMD (mg/cm^3) to MA (mm^2) (leg)	0.099	40	0.048
Leg: Cortical content tibia (mg/mm) to MA (mm^2) (leg)	0.73	37	<0.0001
Leg: Cortical vBMD tibia (mg/cm^3) to MA (mm^2) (leg)	0.078	40	0.081
Leg: Polar moment of inertia tibia (mm^4) to MA (mm^2) (leg)	0.79	37	<0.0001
Leg: SSI tibia (mm^3) to MA (mm^2) (leg)	0.79	37	<0.0001
Leg: Fat area (mm^2) to MA (mm^2) (leg)	0.23	37	0.0024
Leg: Muscle density (mg/mL) to MA (mm^2) (leg)	0.0071	35	0.63
MIGF of non-dominant hand (N) to MA (mm^2) (leg)	0.55	32	<0.0001

TABLE 16: Correlation to pQCT muscle area (arm/leg) of various pQCT parameters, MIGF and DXA bone mass with R^2, N, p by time from GH start; 24 months

Time from GH start (mo)	24		
Correlation to muscle area (mm^2) of	R^2	N	p Value MA
Total CSA (mm^2) to MA (mm^2) (arm)	0.30	21	0.010
Cortical CSA radius (mm^2) to MA (mm^2) (arm)	0.36	21	0.0040
Cortical thickness (mm) to MA (mm^2) (arm)	0.11	21	0.15
Total vBMD (mg/cm^3) to MA (mm^2) (arm)	0.011	21	0.64
Cortical content radius (mg/mm) to MA (mm^2) (arm)	0.33	21	0.0069
Cortical vBMD (mg/cm^3) to MA (mm^2) (arm)	0.0090	21	0.68
Polar moment of inertia radius (mm^4) to MA (mm^2) (arm)	0.43	21	0.0012
SSI radius (mm^3) to MA (mm^2) (arm)	0.67	21	<0.0001
Fat area (mm^2) to MA (mm^2) (arm)	0.25	23	0.015
Muscle density (mg/mL) to MA (mm^2) (arm)	0.078	22	0.21
DXA bone mass (g) to MA (mm^2) (arm)	0.97	5	0.0027
DXA: Bone mineral density (g/cm^2) to MA (mm^2) (arm)	0.22	5	0.42
MIGF of non-dominant hand (N) to MA (mm^2) (arm)	0.40	19	0.0034
Leg: Total CSA tibia (mm^2) to MA (mm^2) (leg)	0.72	21	<0.0001
Leg: Cortical CSA tibia (mm^2) to MA (mm^2) (leg)	0.74	20	<0.0001
Leg: Cortical thickness tibia (mm) to MA (mm^2) (leg)	0.16	20	0.076
Leg: Total vBMD (mg/cm^3) to MA (mm^2) (leg)	0.034	21	0.43
Leg: Cortical content tibia (mg/mm) to MA (mm^2) (leg)	0.70	20	<0.0001
Leg: Cortical vBMD tibia (mg/cm^3) to MA (mm^2) (leg)	0.034	21	0.42
Leg: Polar moment of inertia tibia (mm^4) to MA (mm^2) (leg)	0.80	20	<0.0001
Leg: SSI tibia (mm^3) to MA (mm^2) (leg)	0.70	20	<0.0001
Leg: Fat area (mm^2) to MA (mm^2) (leg)	0.00037	21	0.93
Leg: Muscle density (mg/mL) to MA (mm^2) (leg)	0.0094	21	0.68
MIGF of non-dominant hand (N) to MA (mm^2) (leg)	0.48	19	0.00050

TABLE 17: Correlation to pQCT muscle area (arm/leg) of various pQCT parameters, MIGF and DXA bone mass with R^2, N, p by time from GH start; 36 months

Time from GH start (mo)	36		
Correlation to muscle area (mm^2) of	R^2	N	p Value MA
Total CSA (mm^2) to MA (mm^2) (arm)	0.73	17	<0.0001
Cortical CSA radius (mm^2) to MA (mm^2) (arm)	0.75	17	<0.0001
Cortical thickness (mm) to MA (mm^2) (arm)	0.48	17	0.0021
Total vBMD (mg/cm^3) to MA (mm^2) (arm)	0.015	17	0.64
Cortical content radius (mg/mm) to MA (mm^2) (arm)	0.70	17	<0.0001
Cortical vBMD (mg/cm^3) to MA (mm^2) (arm)	0.14	17	0.14
Polar moment of inertia radius (mm^4) to MA (mm^2) (arm)	0.78	17	<0.0001
SSI radius (mm^3) to MA (mm^2) (arm)	0.75	17	<0.0001
Fat area (mm^2) to MA (mm^2) (arm)	0.11	17	0.19
Muscle density (mg/mL) to MA (mm^2) (arm)	0.11	17	0.19
DXA bone mass (g) to MA (mm^2) (arm)	0.91	4	0.047
DXA: Bone mineral density (g/cm^2) to MA (mm^2) (arm)	0.77	4	0.12
MIGF of non-dominant hand (N) to MA (mm^2) (arm)	0.92	9	<0.0001
Leg: Total CSA tibia (mm^2) to MA (mm^2) (leg)	0.84	15	<0.0001
Leg: Cortical CSA tibia (mm^2) to MA (mm^2) (leg)	0.50	15	0.0031
Leg: Cortical thickness tibia (mm) to MA (mm^2) (leg)	0.061	15	0.38
Leg: Total vBMD (mg/cm^3) to MA (mm^2) (leg)	0.084	15	0.29
Leg: Cortical content tibia (mg/mm) to MA (mm^2) (leg)	0.42	15	0.0083
Leg: Cortical vBMD tibia (mg/cm^3) to MA (mm^2) (leg)	0.011	15	0.71
Leg: Polar moment of inertia tibia (mm^4) to MA (mm^2) (leg)	0.93	15	<0.0001
Leg: SSI tibia (mm^3) to MA (mm^2) (leg)	0.76	15	<0.0001
Leg: Fat area (mm^2) to MA (mm^2) (leg)	0.12	15	0.21
Leg: Muscle density (mg/mL) to MA (mm^2) (leg)	0.00073	13	0.93
MIGF of non-dominant hand (N) to MA (mm^2) (leg)	0.83	9	0.0005

TABLE 18: Correlation to pQCT muscle area (arm/leg) of various pQCT parameters, MIGF and DXA bone mass with R^2, N, p by time from GH start; 48 months

Time from GH start (mo)	48		
Correlation to muscle area (mm^2) of	R^2	N	p Value MA
Total CSA (mm^2) to MA (mm^2) (arm)	0.75	9	0.0025
Cortical CSA radius (mm^2) to MA (mm^2) (arm)	0.92	9	<0.0001
Cortical thickness (mm) to MA (mm^2) (arm)	0.58	9	0.018
Total vBMD (mg/cm^3) to MA (mm^2) (arm)	0.096	9	0.42
Cortical content radius (mg/mm) to MA (mm^2) (arm)	0.91	9	<0.0001
Cortical vBMD (mg/cm^3) to MA (mm^2) (arm)	0.25	9	0.17
Polar moment of inertia radius (mm^4) to MA (mm^2) (arm)	0.70	9	0.0047
SSI radius (mm^3) to MA (mm^2) (arm)	0.84	9	0.00050
Fat area (mm^2) to MA (mm^2) (arm)	0.10	10	0.37
Muscle density (mg/mL) to MA (mm^2) (arm)	0.10	10	0.37
DXA bone mass (g) to MA (mm^2) (arm)	0.99	3	0.058
DXA: Bone mineral density (g/cm^2) to MA (mm^2) (arm)	0.30	3	0.63
MIGF of non-dominant hand (N) to MA (mm^2) (arm)	0.85	5	0.027
Leg: Total CSA tibia (mm^2) to MA (mm^2) (leg)	0.82	8	0.0021
Leg: Cortical CSA tibia (mm^2) to MA (mm^2) (leg)	0.92	7	0.00020
Leg: Cortical thickness tibia (mm) to MA (mm^2) (leg)	0.59	7	0.045
Leg: Total vBMD (mg/cm^3) to MA (mm^2) (leg)	0.19	8	0.29
Leg: Cortical content tibia (mg/mm) to MA (mm^2) (leg)	0.88	7	0.00050
Leg: Cortical vBMD tibia (mg/cm^3) to MA (mm^2) (leg)	0.35	8	0.12
Leg: Polar moment of inertia tibia (mm^4) to MA (mm^2) (leg)	0.93	7	0.00010
Leg: SSI tibia (mm^3) to MA (mm^2) (leg)	0.97	7	<0.0001
Leg: Fat area (mm^2) to MA (mm^2) (leg)	0.31	5	0.33
Leg: Muscle density (mg/mL) to MA (mm^2) (leg)	0.61	3	0.43
MIGF of non-dominant hand (N) to MA (mm^2) (leg)	0.36	4	0.19

7.2 Figures

7.2.1 Course of pQCT measurements (arm and leg) from start to 48 months of GH-treatment in SGA boy

The following figures (FIGURE 1 to FIGURE 12) show the course of pQCT measurements in arm and leg in a SGA boy under GH-treatment with good response to growth hormone starting at the age of six up to ten years.

One can see the subcutaneous fat (dark grey) decrease and the muscle area (lighter grey) and bone surface area (white) increase with time under GH treatment. See progression from FIGURE 1 to FIGURE 6 for pQCT measurements of the arm and FIGURE 7 to FIGURE 12 for pQCT measurements of the leg from start to 48 months of GH treatment. These measurements show a good quality in all examinations during the 48 months of GH treatment with only few artifacts due to minor movements.

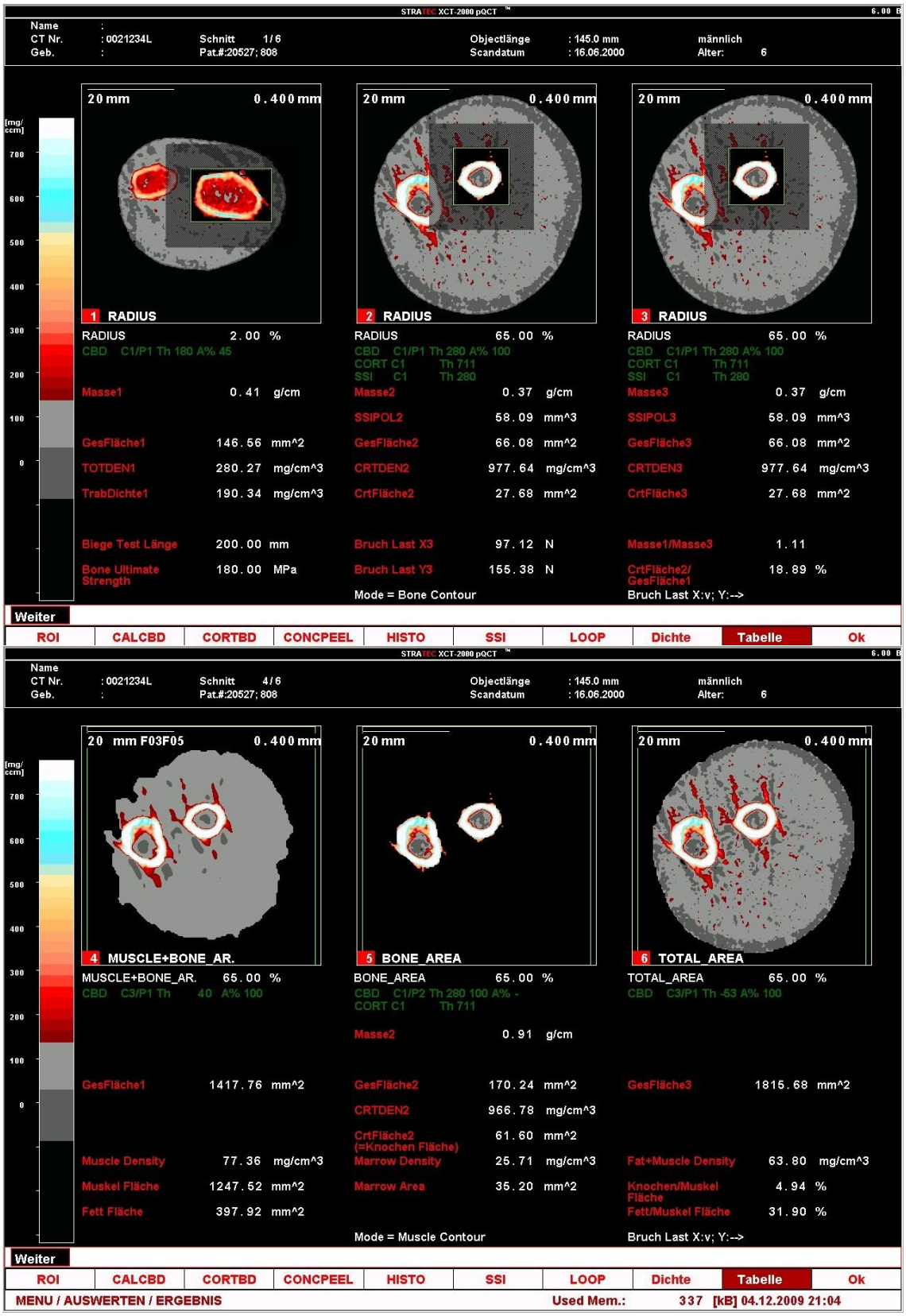


FIGURE 1: Child A: SGA, male; arm pQCT at start of GH-treatment

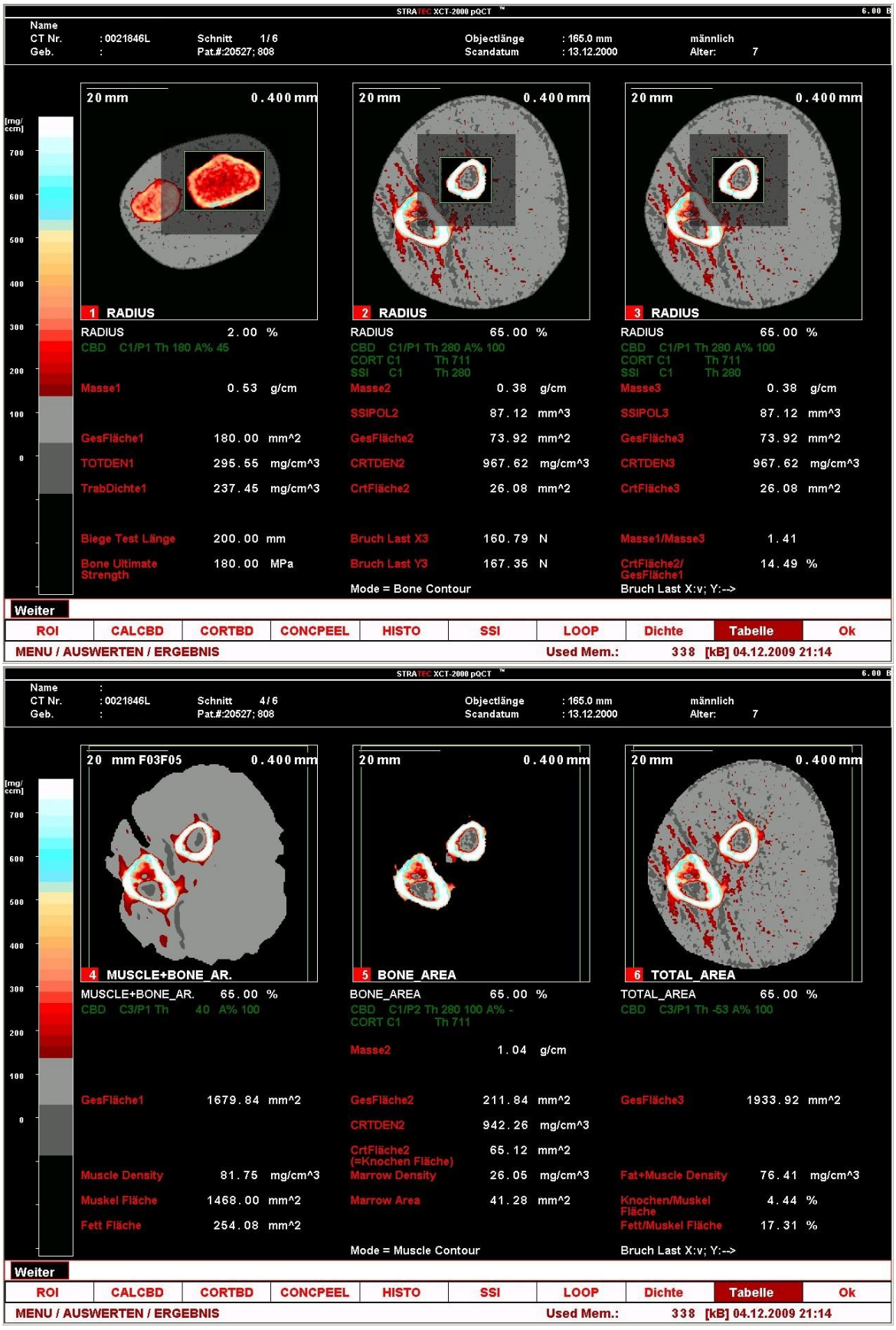


FIGURE 2: Child A: SGA, male; arm pQCT after 6 months on GH-treatment

FIGURE 3: Child A: SGA, male; arm pQCT after 12 months on GH-treatment

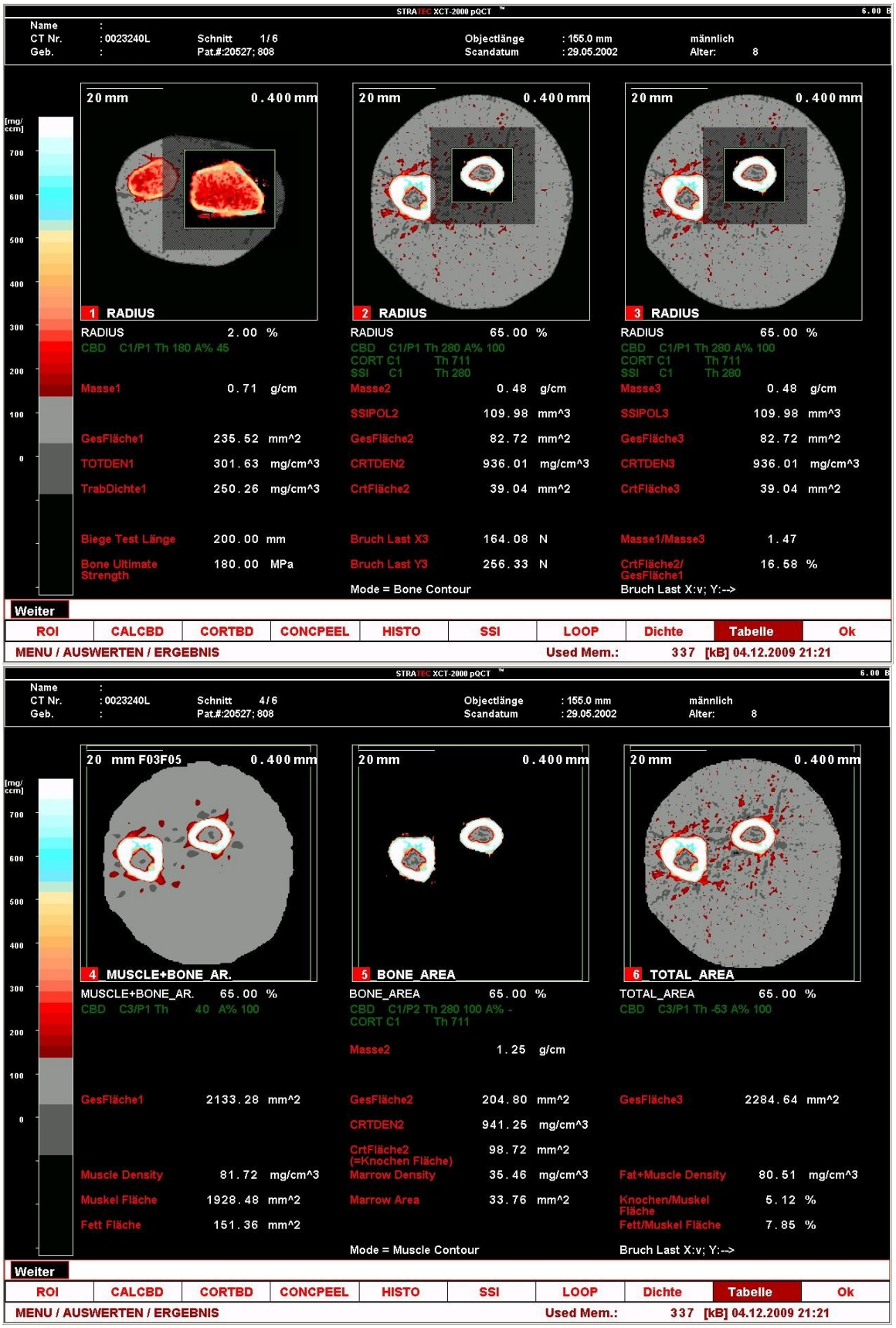


FIGURE 4: Child A: SGA, male; arm pQCT after 24 months on GH-treatment

FIGURE 5: Child A: SGA, male; arm pQCT after 36 months on GH-treatment

FIGURE 6: Child A: SGA, male; arm pQCT after 48 months on GH-treatment

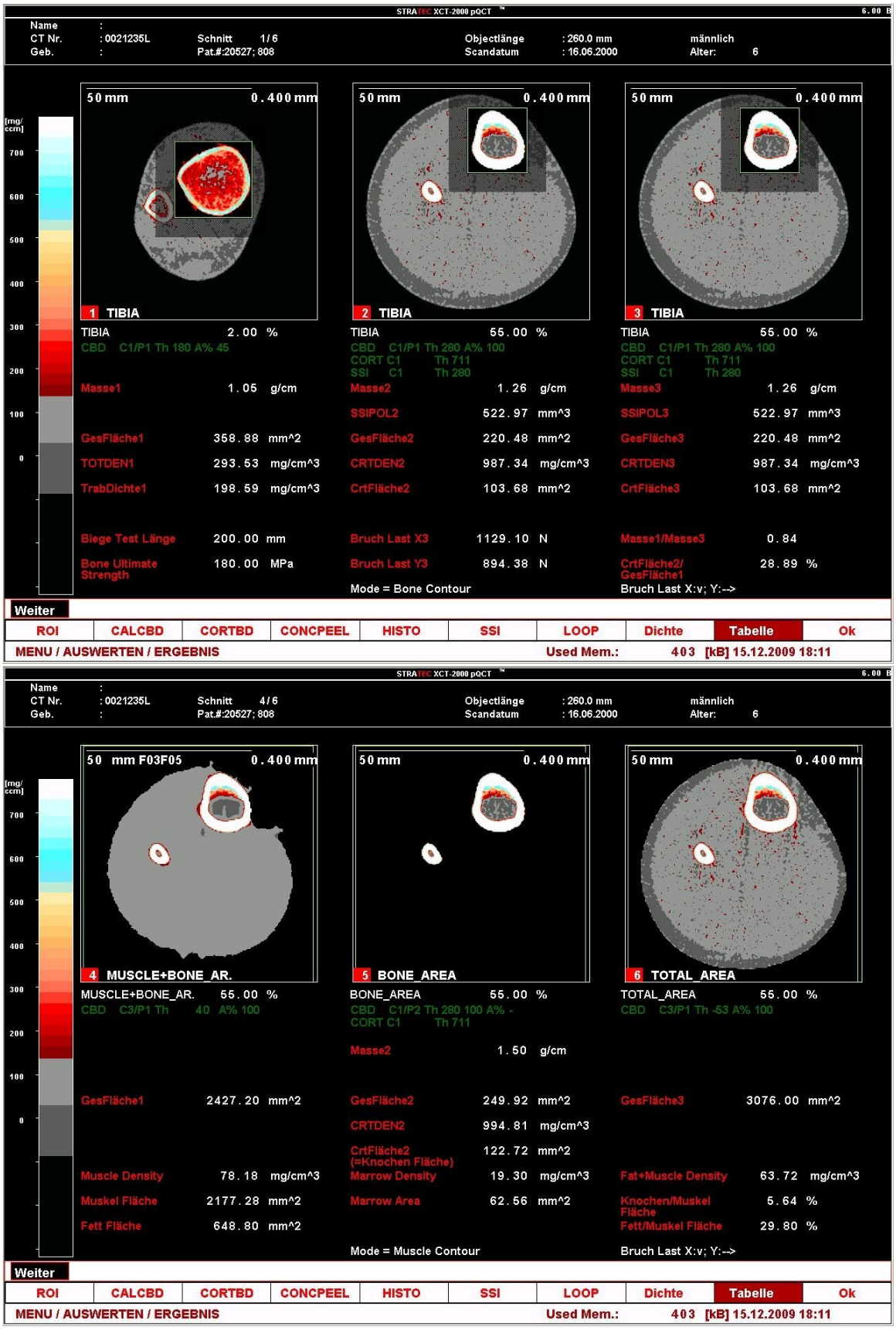


FIGURE 7: Child A: SGA, male; leg pQCT at start of GH-treatment

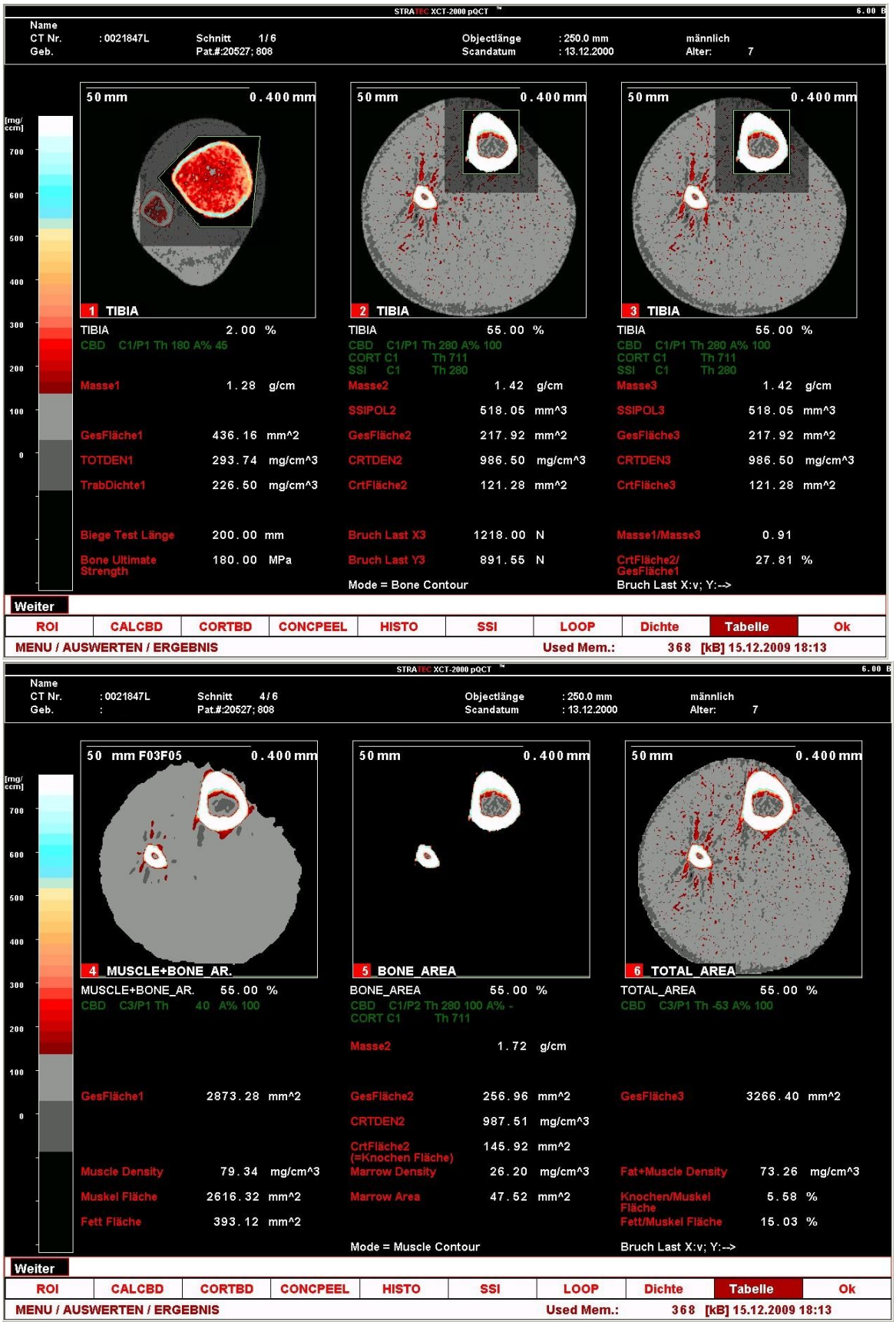


FIGURE 8: Child A: SGA, male; leg pQCT after 6 months on GH-treatment

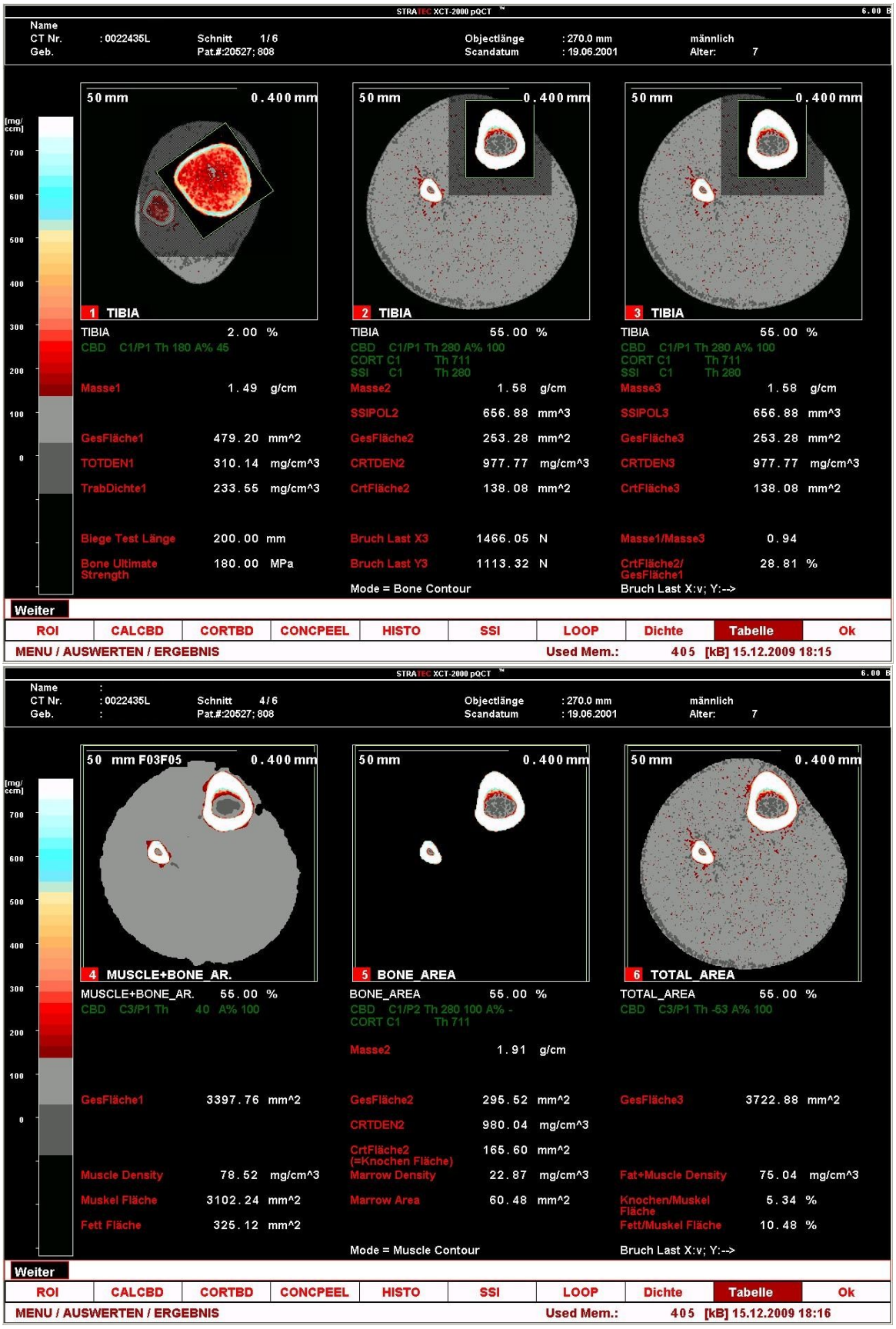


FIGURE 9: Child A: SGA, male; leg pQCT after 12 months on GH-treatment

FIGURE 10: Child A: SGA, male; leg pQCT after 24 months on GH-treatment

FIGURE 11: Child A: SGA, male; leg pQCT after 36 months on GH-treatment

FIGURE 12: Child A: SGA, male; leg pQCT after 48 months on GH-treatment

7.2.2 Excluded pQCT images

The following FIGURE 13 shows pQCT measurements of an AGA girl (child B) aged five years, which had to be excluded, because the quality was too poor for further analysis. Fat, muscle and bone area could not be correctly distinguished by the software of Stratec for pQCT analysis. In the result the calculated value for muscle area was negative and the values for fat area and total area were almost the same. Unfortunately, this child had to be excluded from the study, because without useful data of the starting point of GH-treatment the including criteria could not be met. FIGURE 14 shows the courses of pQCT parameters (total area, fat area, muscle area and percentage of muscle area) during GH treatment. Spikes are for muscle area and fat area at start.

A similar situation occurred in the measurements at start of an SGA boy (child C) aged five years as shown in FIGURE 15 and FIGURE 16. FIGURE 16 shows spikes in muscle area, fat area and muscle area (%) at start. He also had to be excluded from the study.

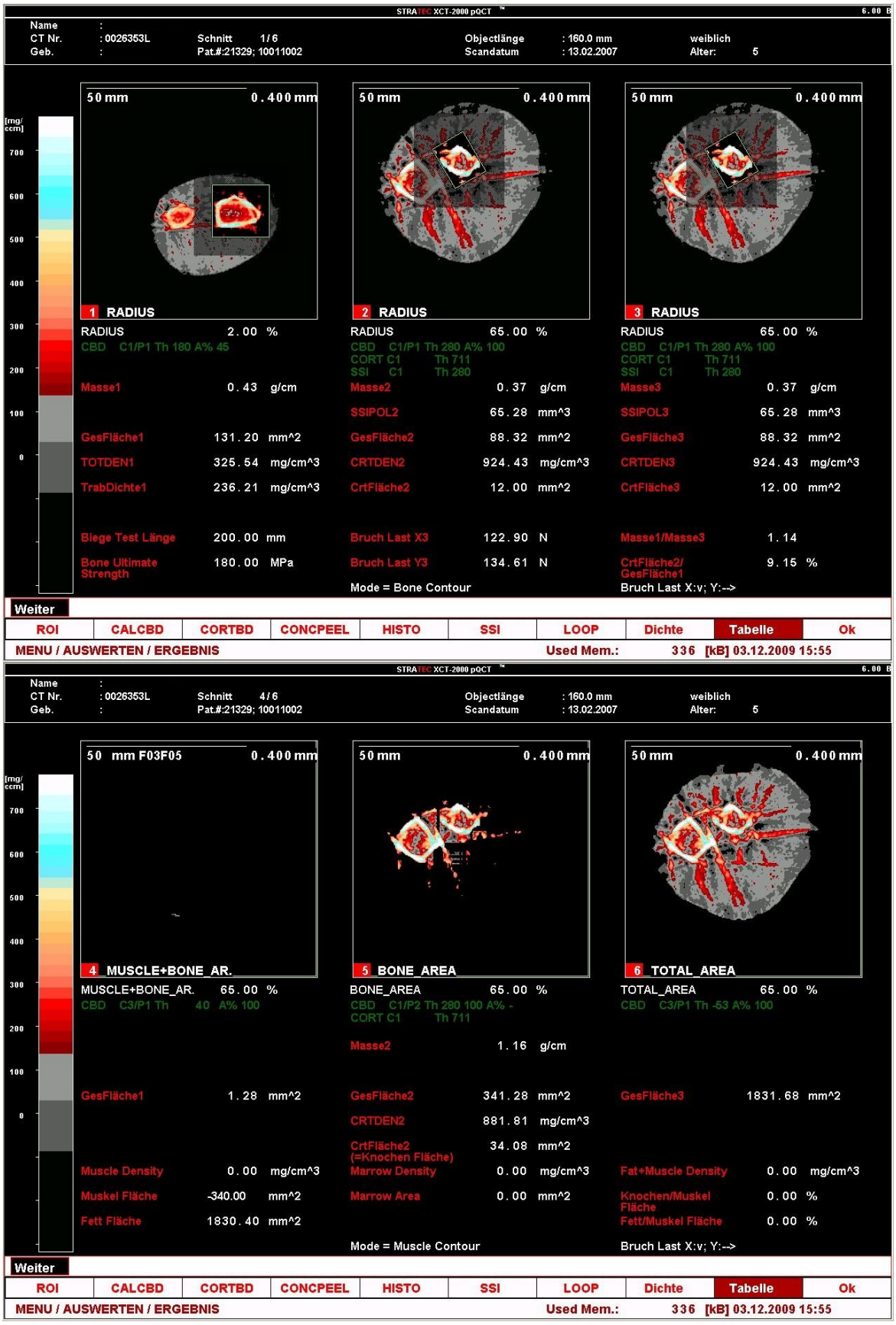


FIGURE 13: Child B: AGA, female; arm pQCT at start of GH-treatment

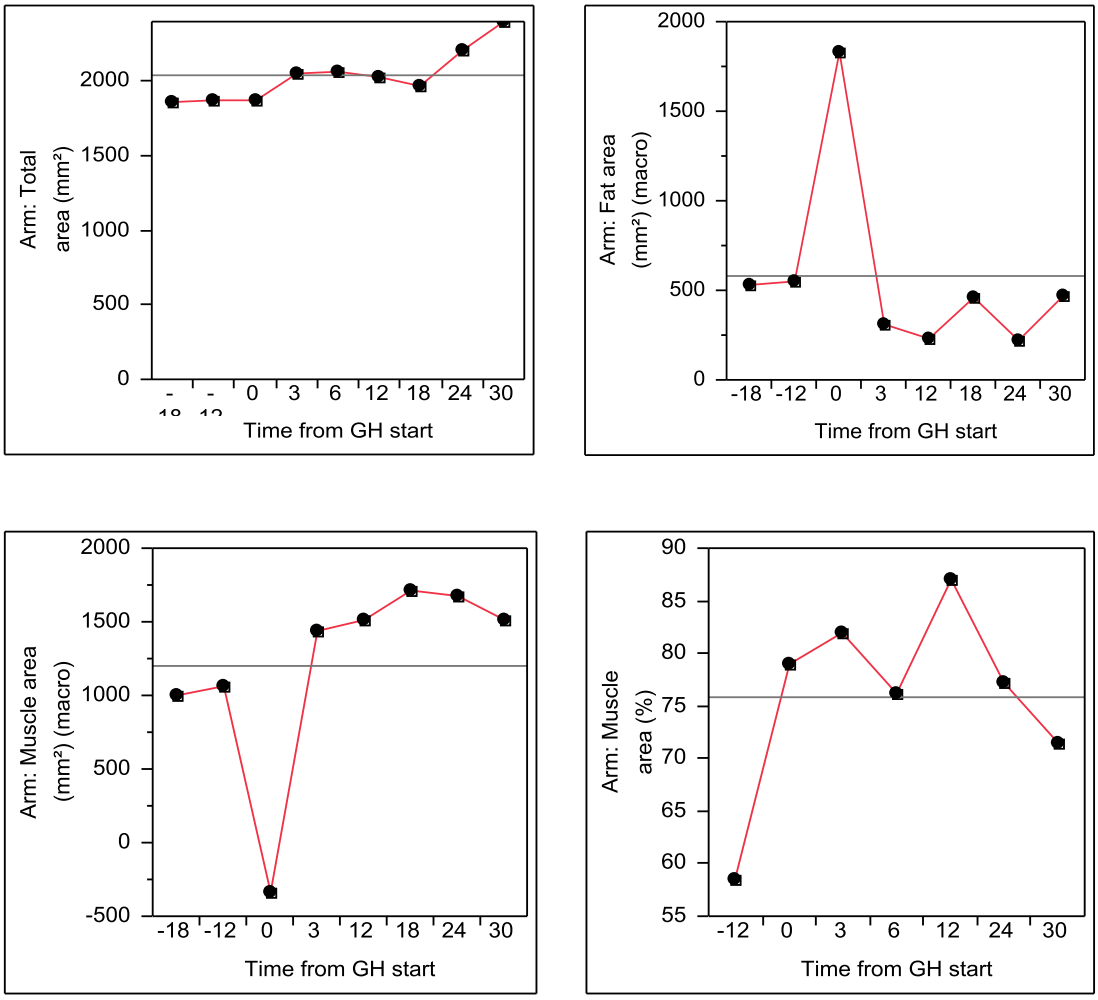


FIGURE 14: Child B: AGA, female; courses of pQCT measurements during GH treatment (x-axis: time from GH start in months; y-axis: various pQCT parameters)

FIGURE 15: Child C: SGA, male; arm pQCT at start of GH-treatment

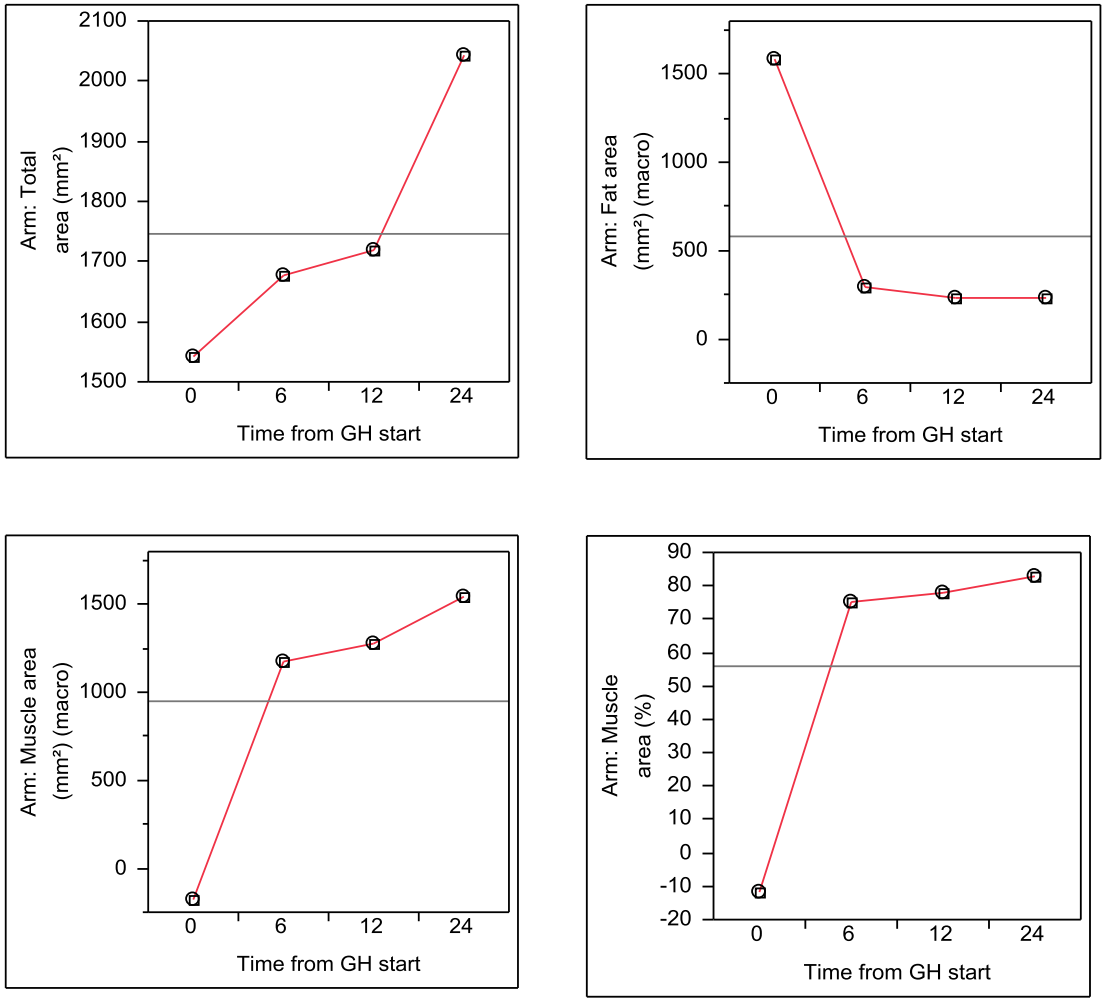


FIGURE 16: Child C: SGA, male; courses of pQCT measurements during GH treatment (x-axis: time from GH start in months; y-axis: various pQCT parameters)

7.2.3 Examples of pQCT images with poor quality

The following figures show examples of pQCT measurements in arm and leg with poor quality due to minor movements during investigation. Results of the calculations for muscle, fat and bone area were still acceptable with no negative results as shown in the example above (FIGURE 13 to FIGURE 16). These measurements were not excluded from the study, because otherwise the study group would have been too small to allow any statistical conclusions.

FIGURE 17: Child D: SGA, male; arm pQCT at start of GH-treatment

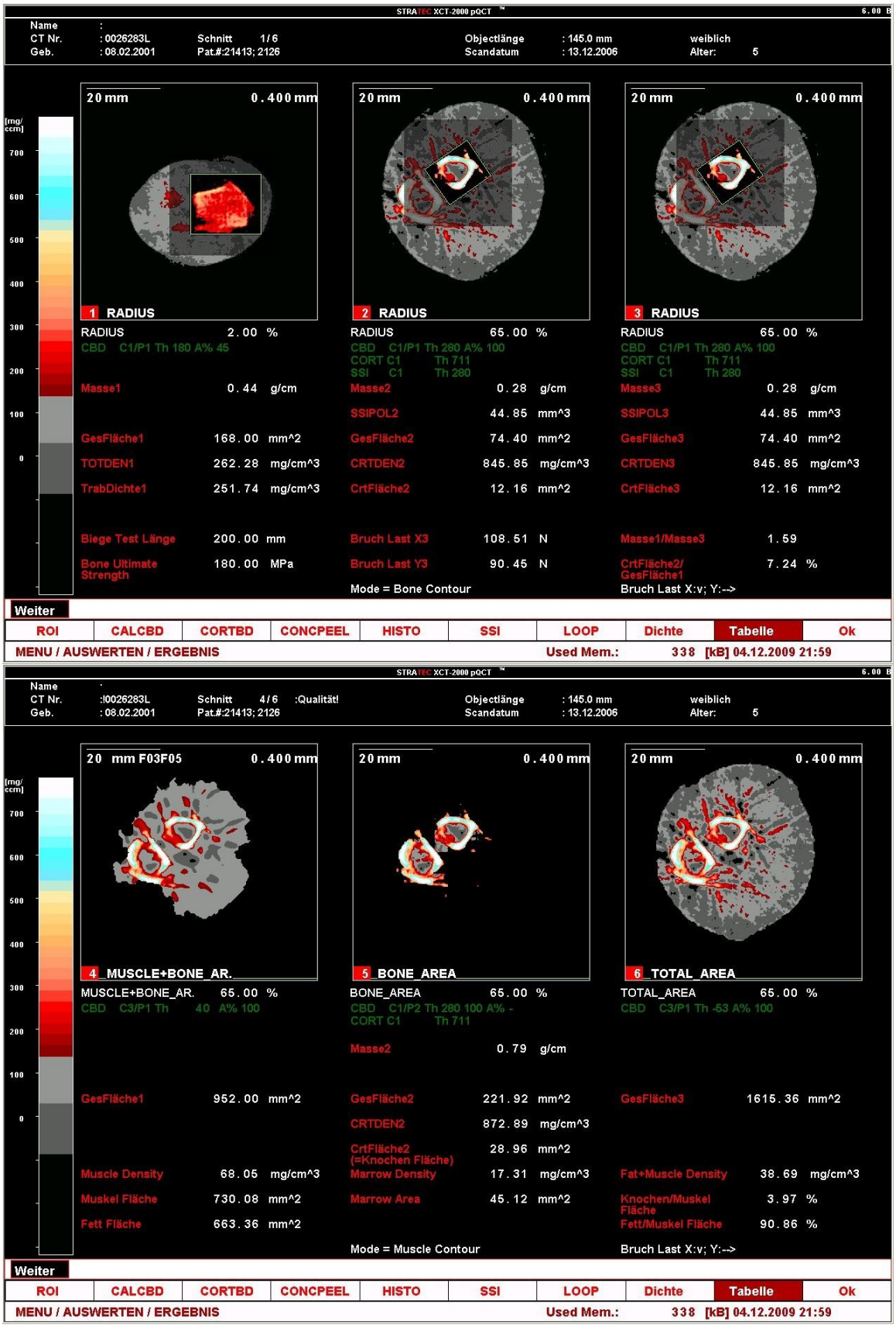


FIGURE 18: Child E: SGA, female; arm pQCT at start of GH-treatment

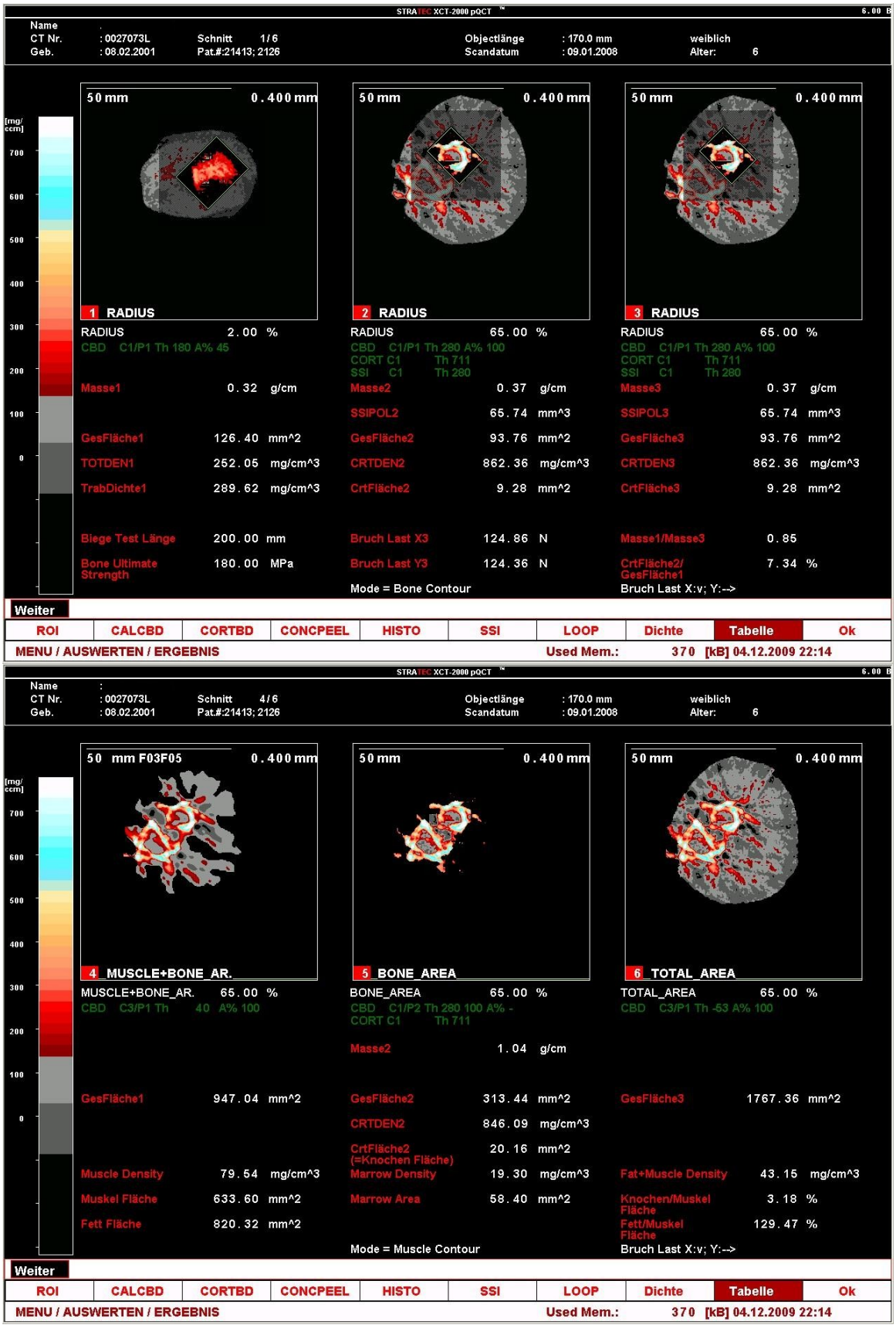


FIGURE 19: Child E: SGA, female; arm pQCT after 12 months on GH-treatment

FIGURE 20: Child F: AGA, male; arm pQCT at start of GH-treatment

FIGURE 21: Child F: AGA, male; leg pQCT at start of GH-treatment

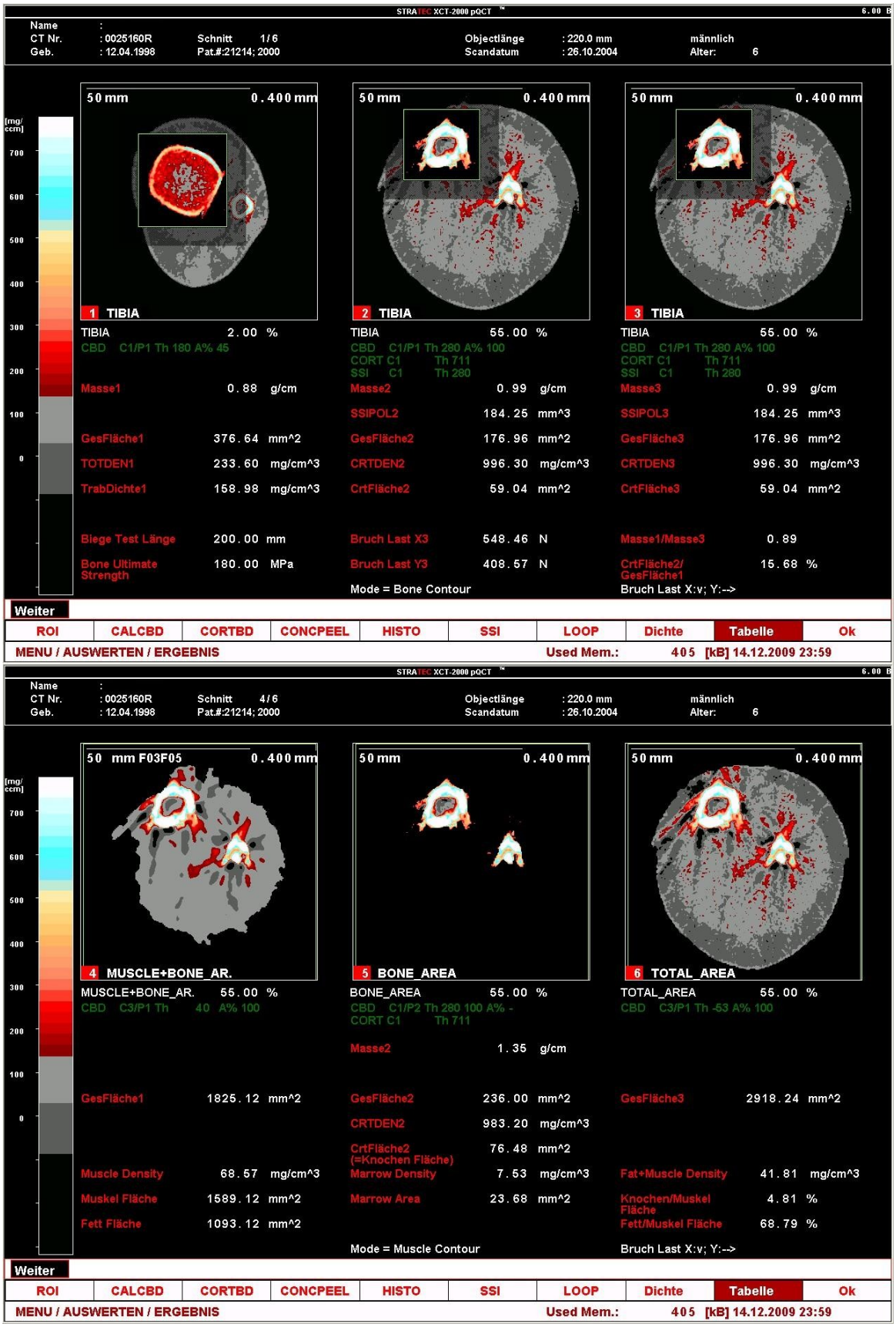


FIGURE 22: Child G: AGA, male; leg pQCT at start of GH-treatment

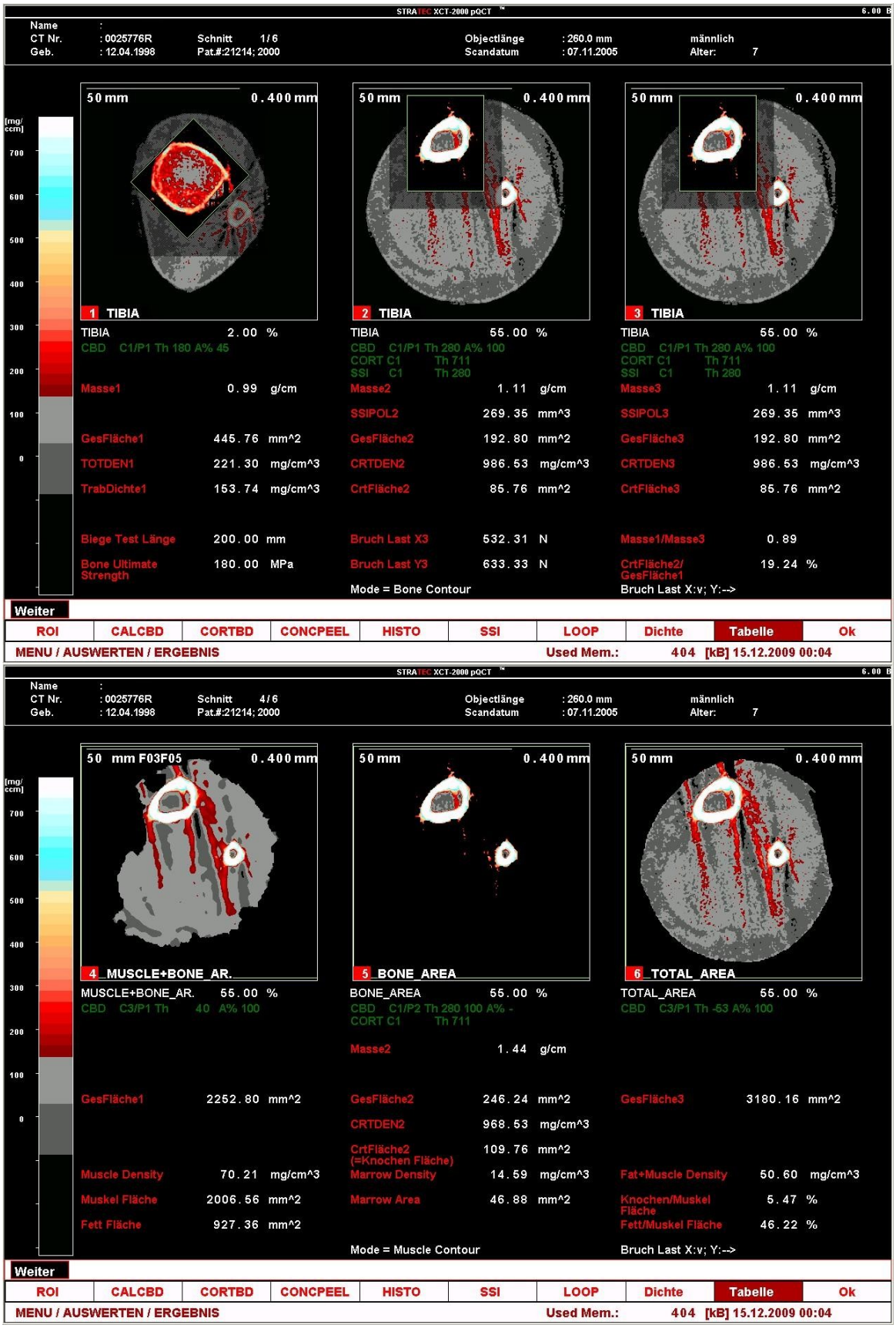


FIGURE 23: Child G: AGA, male; leg pQCT after 12 months on GH-treatment

7.2.4 The correlation of various parameters to muscle cross-sectional area of the arm

The comparison of different bone parameters as well as maximal isometric grip force [N], fat area [mm²] and muscle density [mg/mL] according to their dependency on muscle area [mm²] in arms and legs respectively by a regression analysis at start of GH therapy is given in the diagrams below. Their longitudinal progressions are shown in separate diagrams and with the results listed in TABLE 13-18 (see appendix).

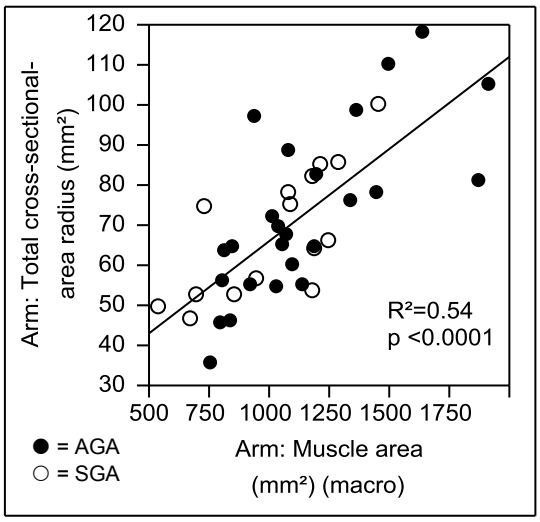


FIGURE 24: Total CSA by pQCT to MA (arm) by pQCT at GH start

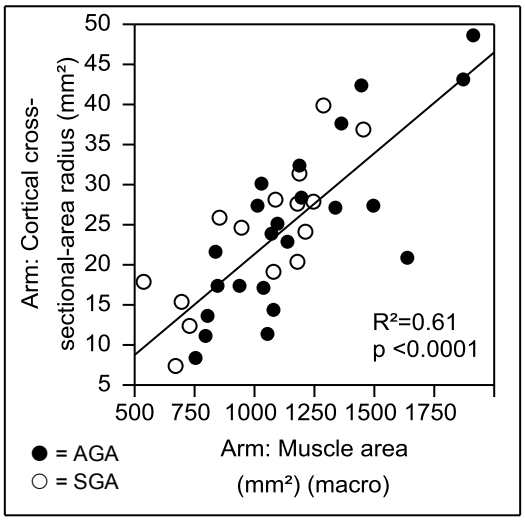


FIGURE 25: Cortical CSA by pQCT to MA (arm) by pQCT at GH start

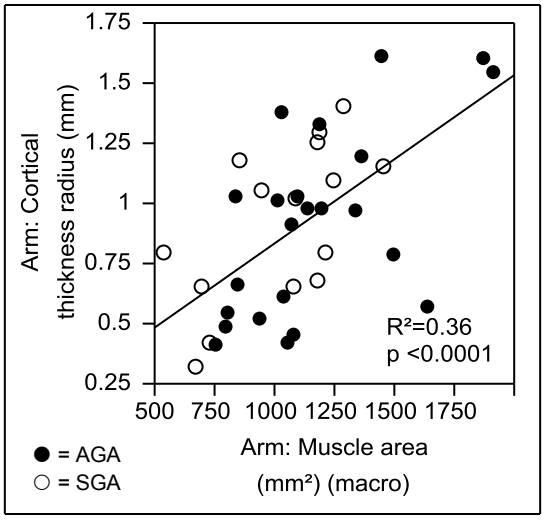


FIGURE 26: Cortical thickness by pQCT to MA (arm) by pQCT at GH start

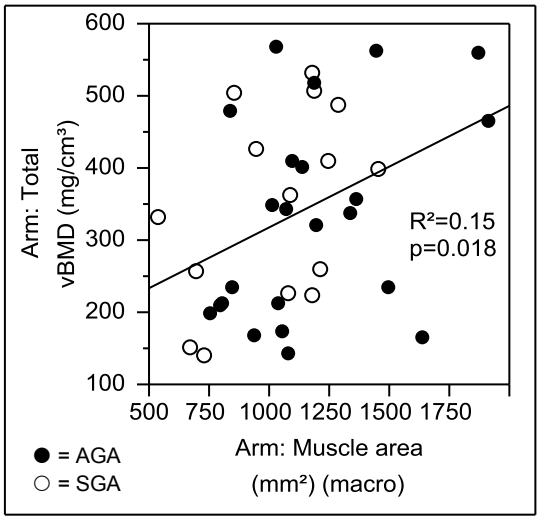


FIGURE 27: Total vBMD by pQCT to MA (arm) by pQCT at GH start

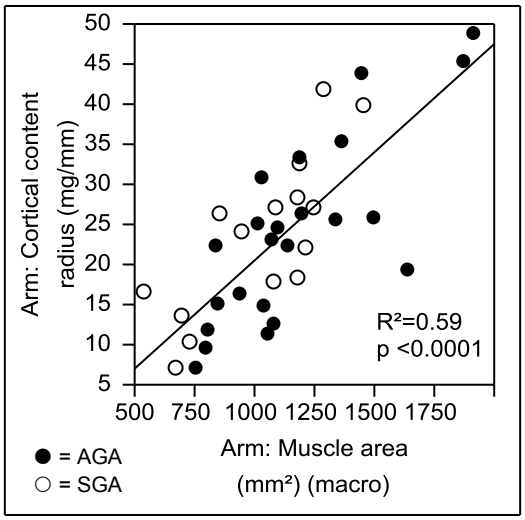


FIGURE 28: Cortical content by pQCT to MA (arm) by pQCT at GH start

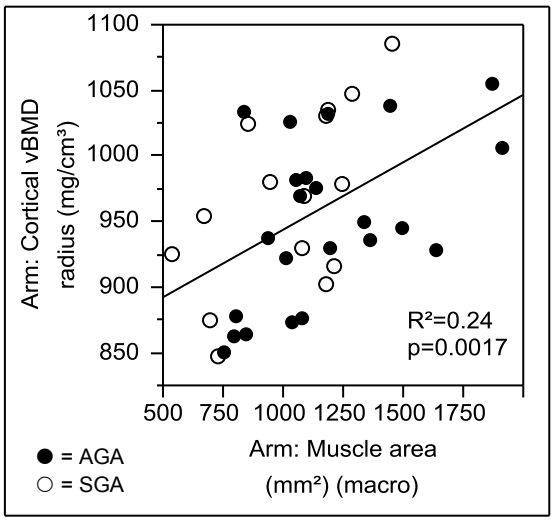


FIGURE 29: Cortical vBMD by pQCT to MA (arm) by pQCT at GH start

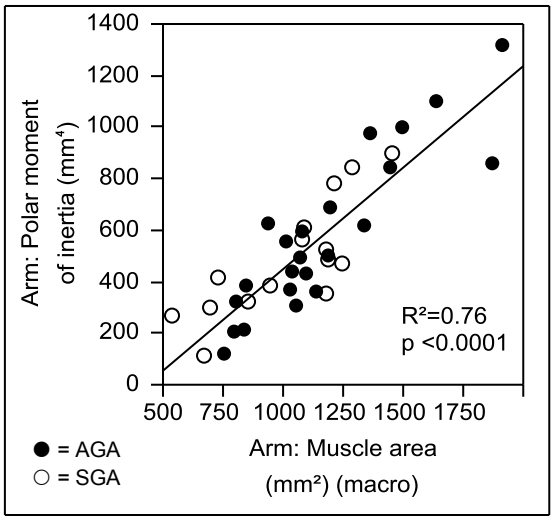


FIGURE 30: Polar moment of inertia by pQCT to MA (arm) by pQCT at GH start

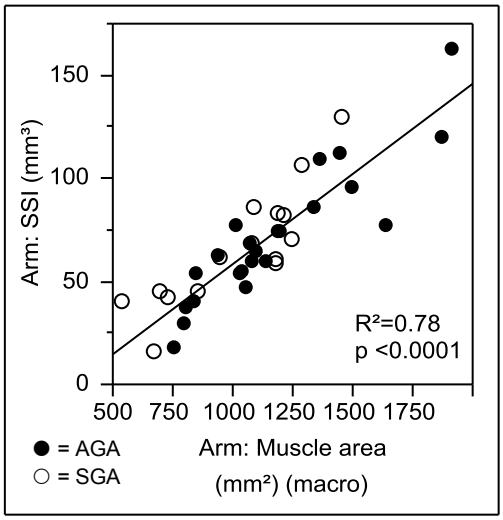


FIGURE 31: SSI by pQCT to MA (arm) by pQCT at GH start

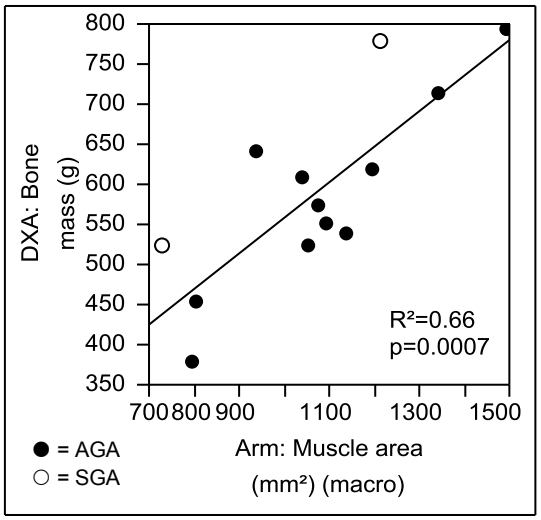


FIGURE 32: DXA Bone mass to MA (arm) by pQCT at GH start

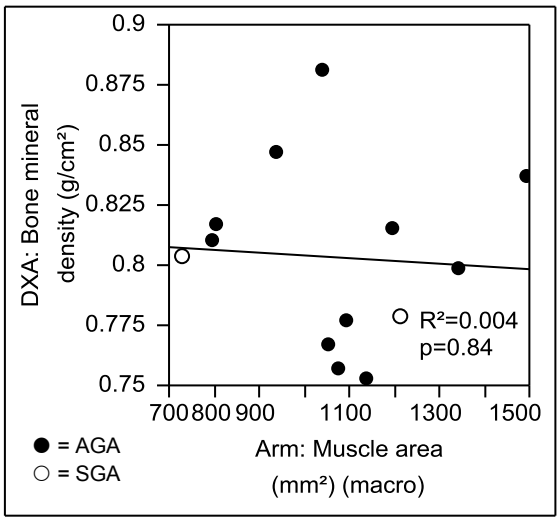


FIGURE 33: DXA Bone mineral density to MA (arm) by pQCT at GH start

Bone mineral density [g/cm²] measured by DXA (complete body scan) refers to the amount of mineral in the entire bone regions studied and is dependent of the measured bone size as described above for bone mineral content by DXA.
In DXA bone mineral content (BMC) is used in a different way than in pQCT. In DXA BMC refers to the amount of mineral in the entire bone regions studied.

This is influenced by bone length or the size of the analyzed region. In pQCT BMC is the mass of mineral per axial bone length (mg/mm) [23].

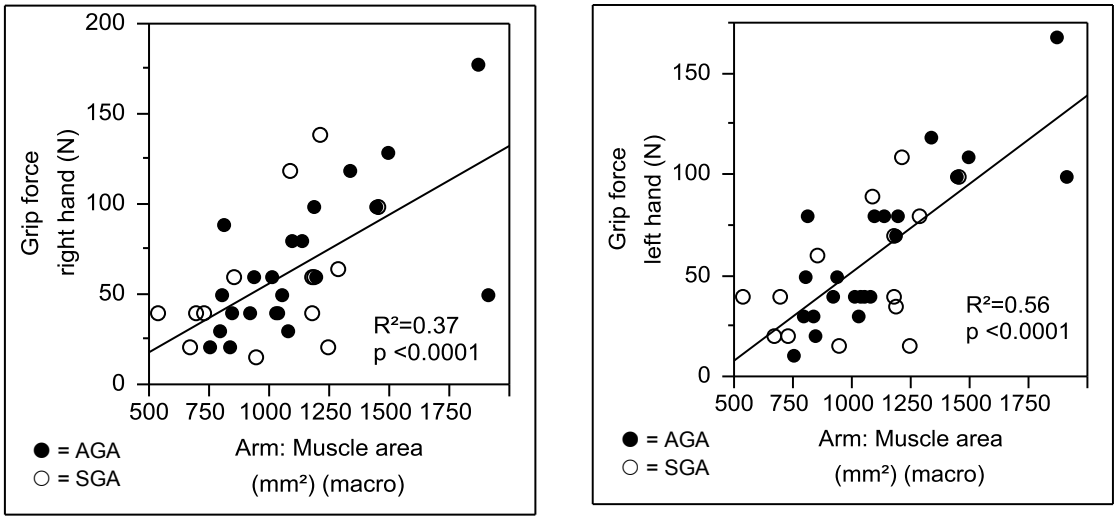


FIGURE 34: MIGF by Jamar dynamometer to MA (arm) by pQCT in the right and left hand at GH start

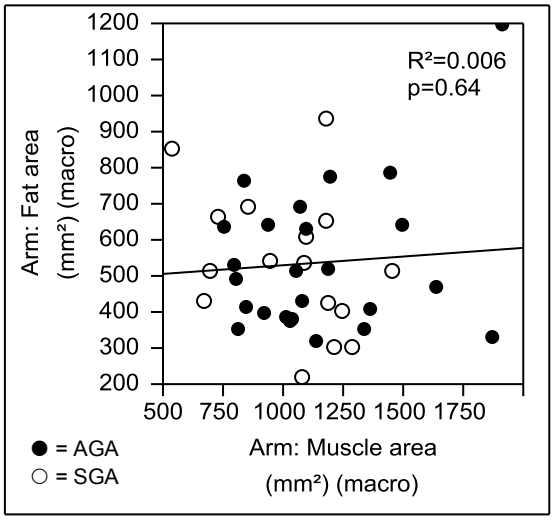


FIGURE 35: Fat area by pQCT to MA (arm) by pQCT at GH start

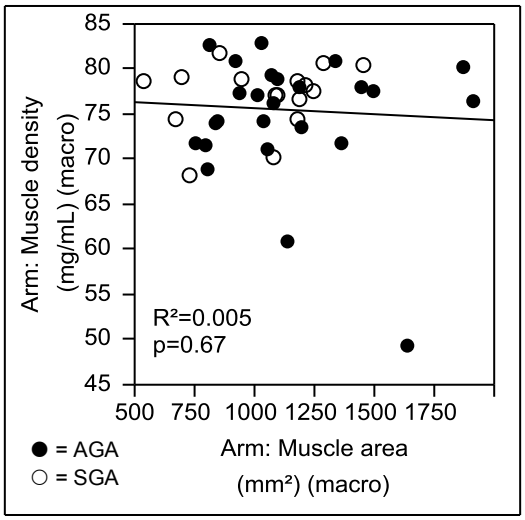
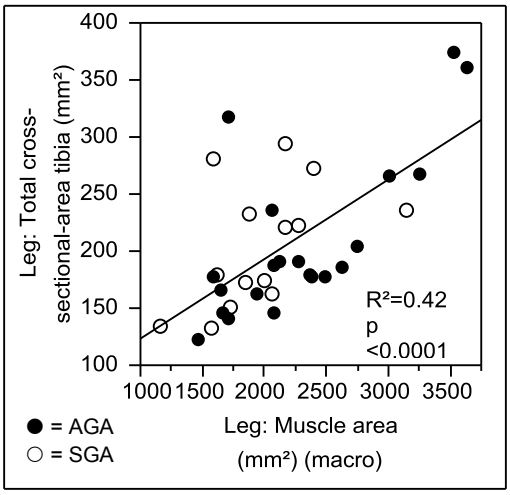


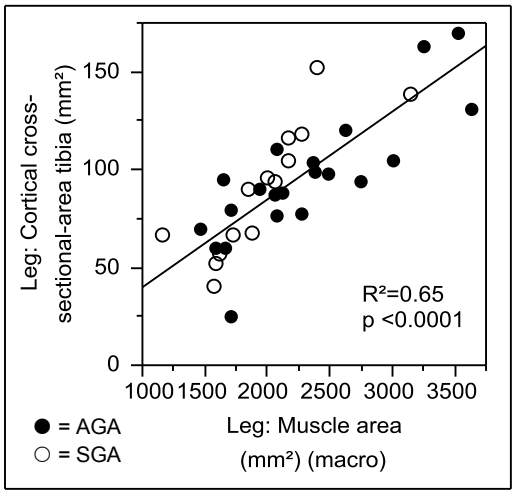
FIGURE 36: Muscle density by pQCT to MA (arm) by pQCT at GH start

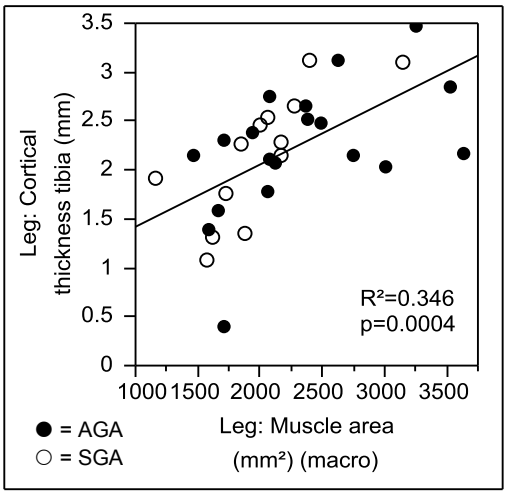
FIGURE 37 shows the correlation of muscle area in leg to different leg pQCT parameters corresponding to the above shown figures of correlations to arm pQCT parameters.
TABLE 13-18 list the longitudinal progression of the correlation to muscle area in arm and leg of the best correlating parameters of pQCT, DXA bone mass and MIGF with the coefficient R^2, N and the level of significance p.

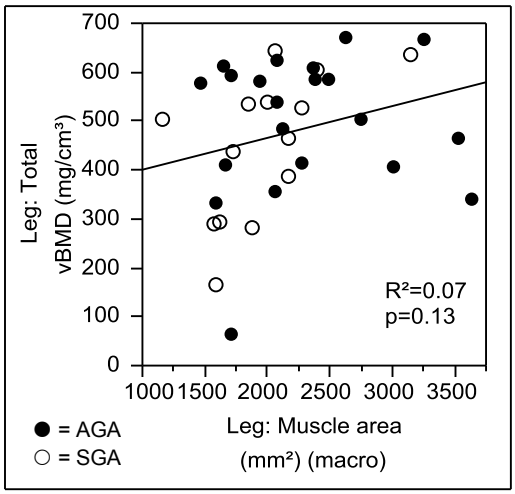
The parameters that correlate best with muscle area of the arm are SSI with $R^2 = 0.78$ and polar moment of inertia with $R^2 = 0.76$ followed by cortical CSA with $R^2 = 0.61$, cortical content with $R^2 = 0.59$, total CSA with $R^2 = 0.54$ and cortical thickness with $R^2 = 0.36$ (all with $p < 0.0001$). MIGF of the non-dominant hand correlates to muscle area with $R^2 = 0.56$ ($p < 0.0001$). Total vBMD correlates to muscle area of the arm with $R^2 = 0.15$ ($p = 0.018$) and cortical vBMD with $R^2 = 0.24$ ($p = 0.0017$). DXA bone mass correlates to muscle area of the arm with $R^2 = 0.66$ with $p = 0.00070$. Fat area, muscle density and DXA bone mineral density do not show significance when correlated to muscle area of the arm.
Best correlating parameters to muscle area of the leg are SSI with $R^2 = 0.73$, cortical CSA with $R^2 = 0.67$, followed by cortical content and polar moment of inertia both with $R^2 = 0.64$ and total CSA with $R^2 = 0.49$ (all with $p < 0.0001$). MIGF of the non-dominant hand shows a poorer correlation to muscle area of the leg than to arm with $R^2 = 0.50$ ($p < 0.001$). Cortical thickness of the tibia correlates to muscle area of the leg with $R^2 = 0.33$ ($p = 0.00030$) and fat area with $R^2 = 0.15$ ($p = 0.018$). No significance is found in the correlation of total vBMD, cortical vBMD and muscle density to muscle area of the leg.

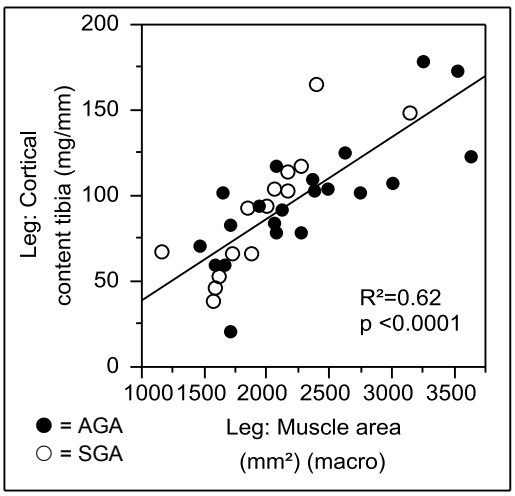
7.2.5 Correlation of various parameters to muscle cross-sectional area of the leg.

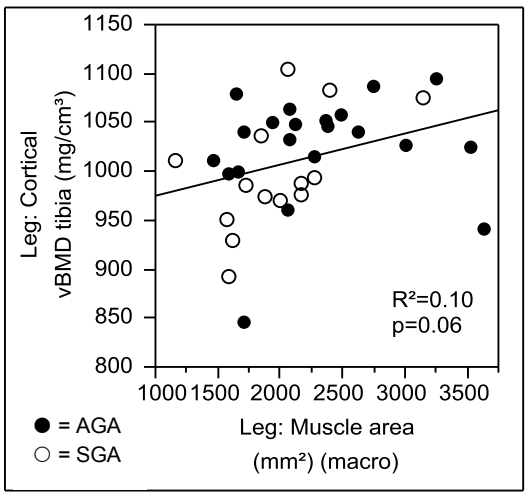












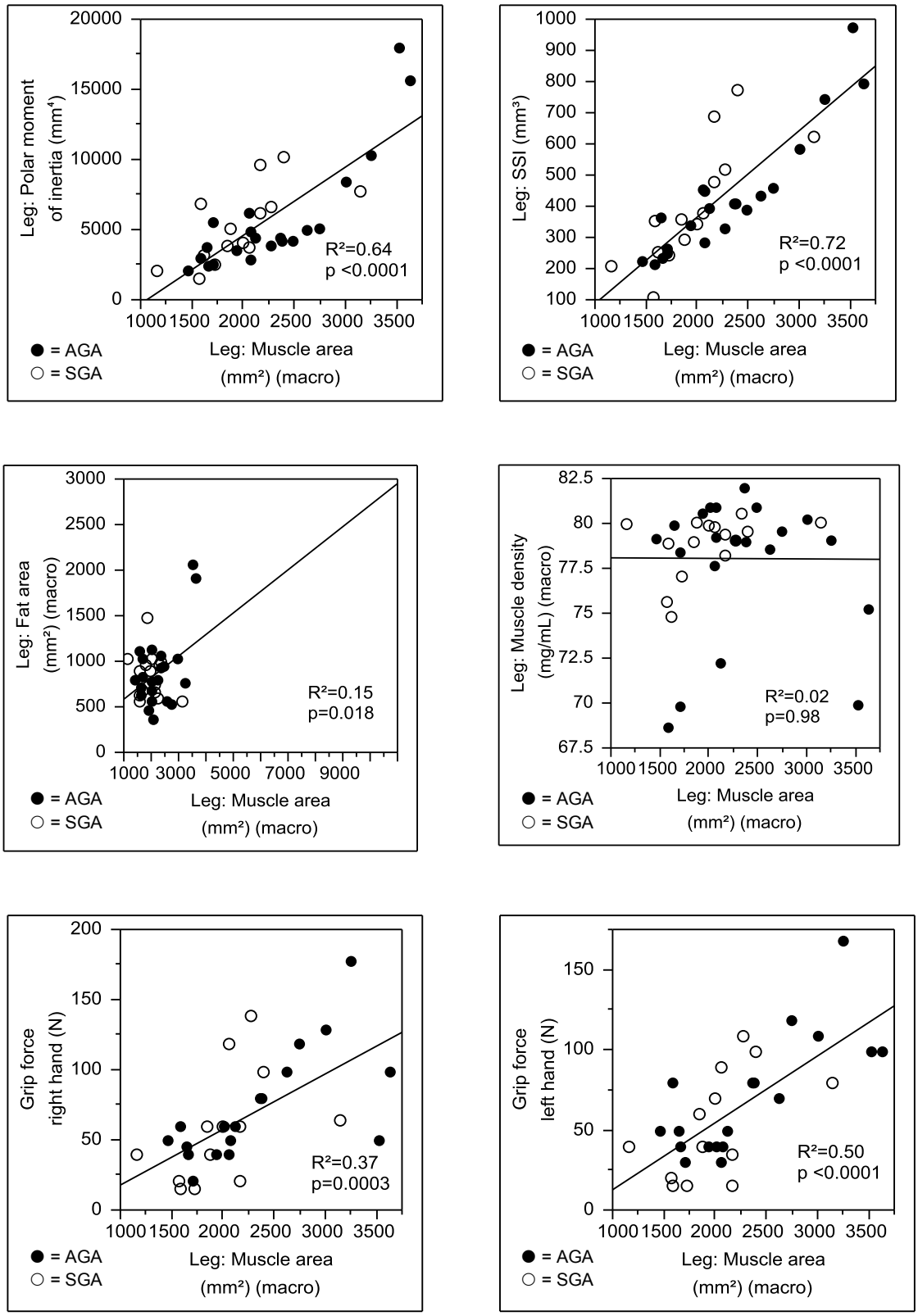
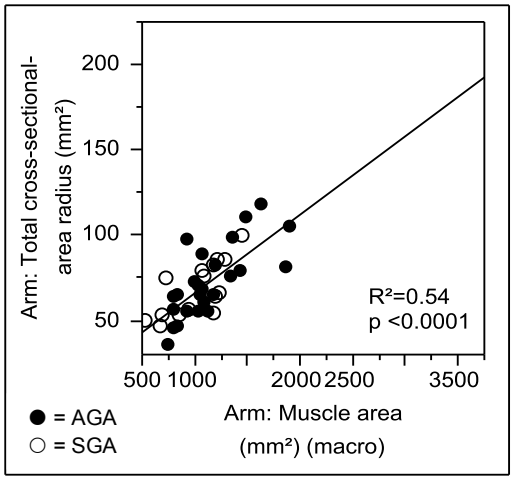
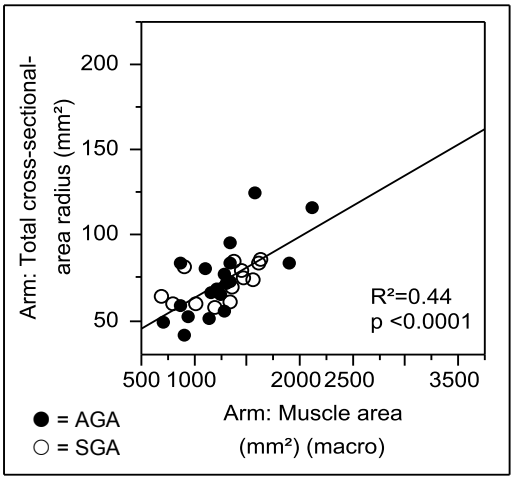


FIGURE 37: Correlation of leg pQCT parameters to leg muscle area

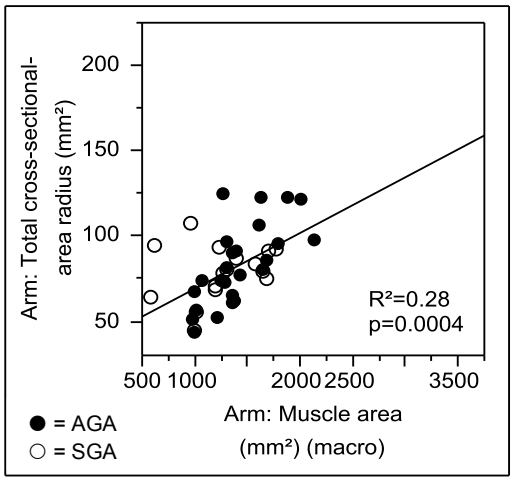
7.2.6 Courses of best correlations to muscle area in arm and leg



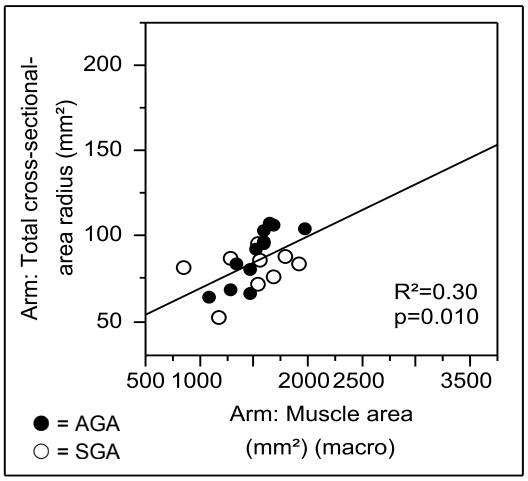
Time from GH start (mo.): 0



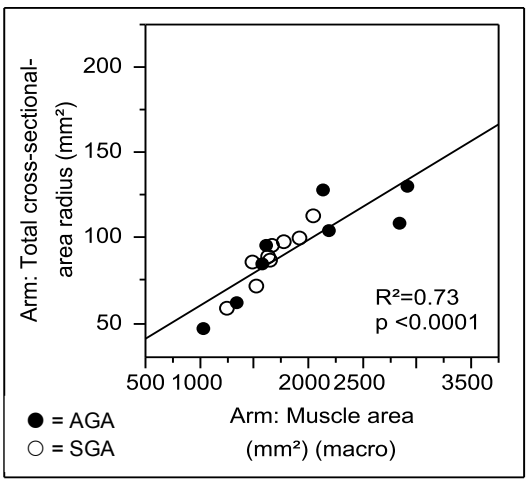
Time from GH start (mo.): 6



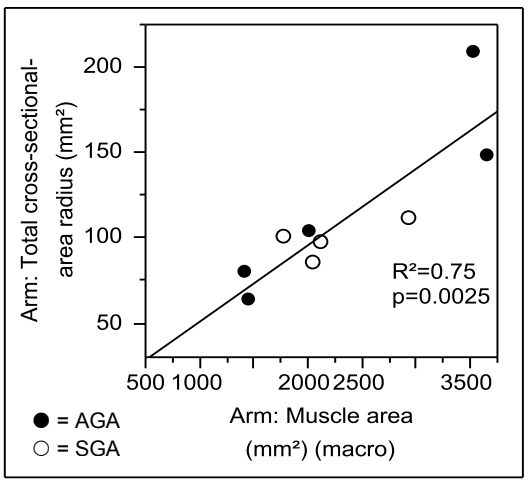
Time from GH start (mo.): 12



Time from GH start (mo.): 24

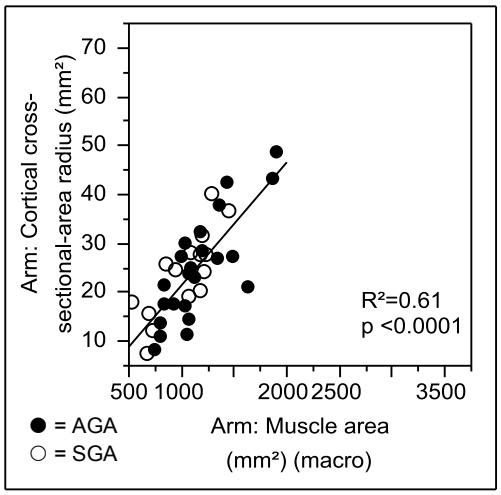


Time from GH start (mo.): 36

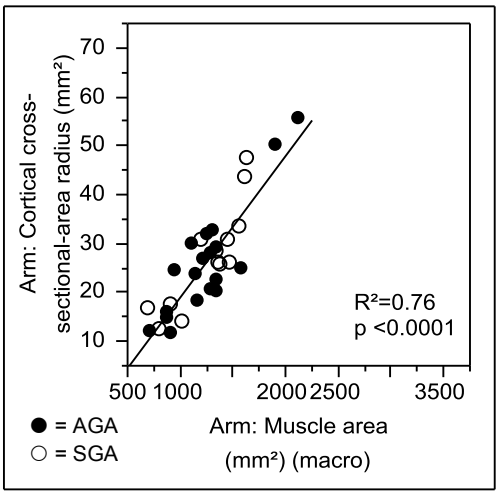


Time from GH start (mo.): 48

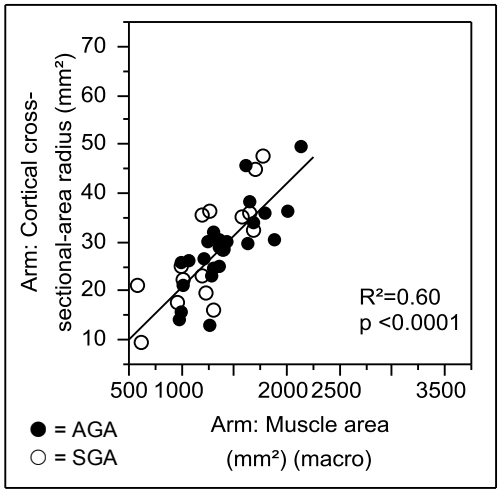
FIGURE 38: Total CSA (radius) [mm²] to MA (arm) [mm²]



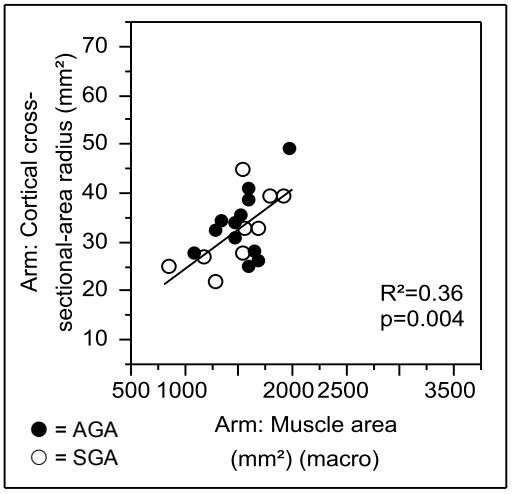
Time from GH start (mo): 0



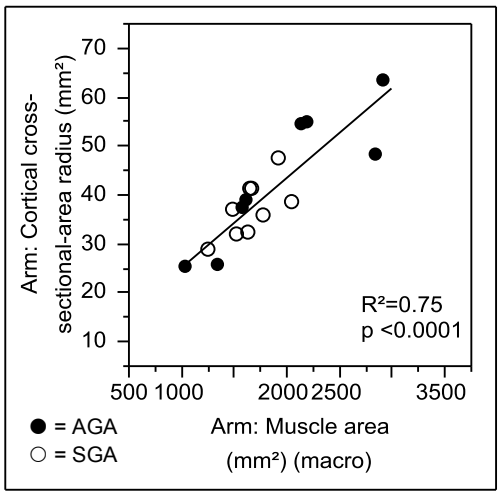
Time from GH start (mo): 6



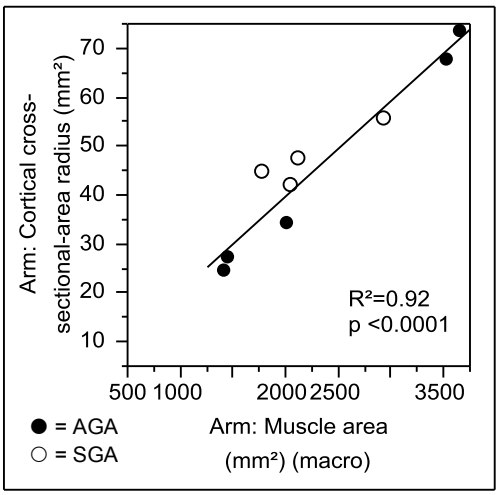
Time from GH start (mo): 12



Time from GH start (mo): 24

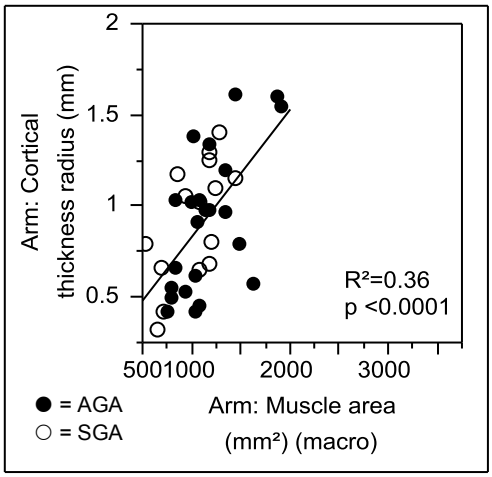


Time from GH start (mo): 36



Time from GH start (mo): 48

FIGURE 39: Cortical CSA (radius) [mm²] to MA (arm) [mm²]



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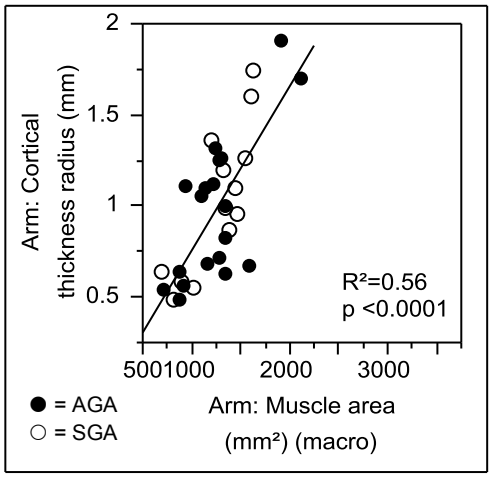
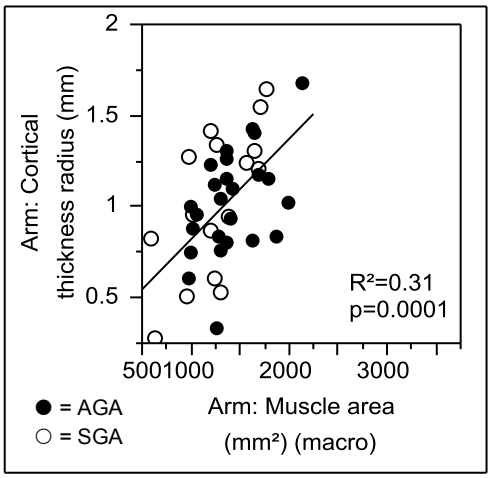
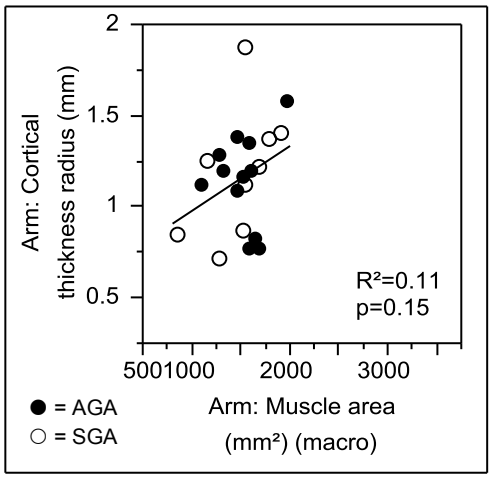


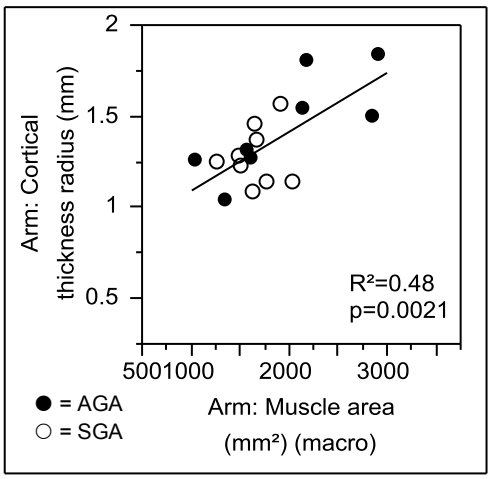
Time from GH start (mo.): 6



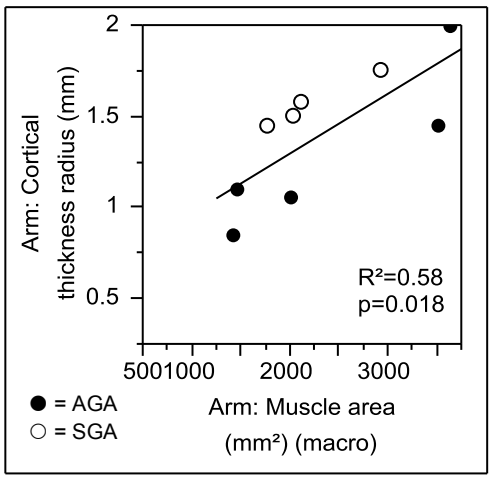
Time from GH start (mo.): 12



Time from GH start (mo.): 24

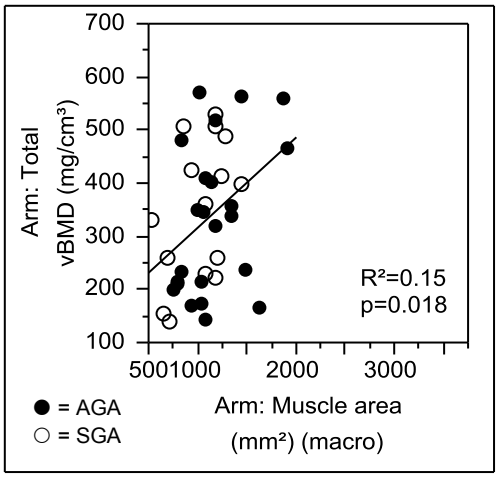


Time from GH start (mo.): 36

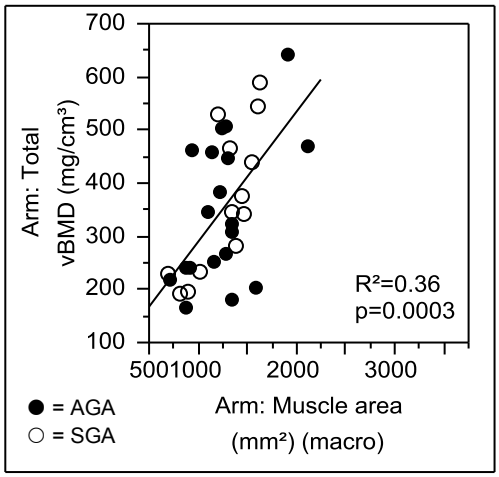


Time from GH start (mo.): 48

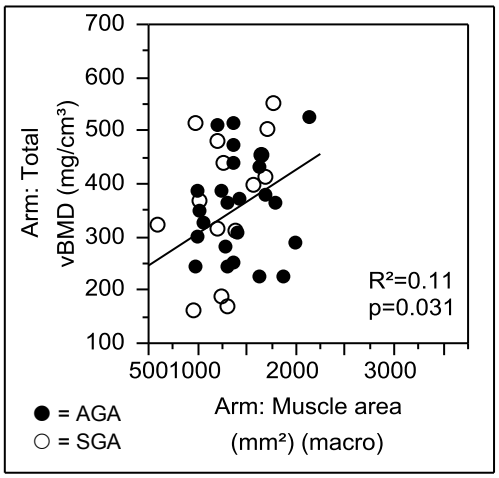
FIGURE 40: Cortical thickness (radius) [mm] to MA (arm) [mm²]



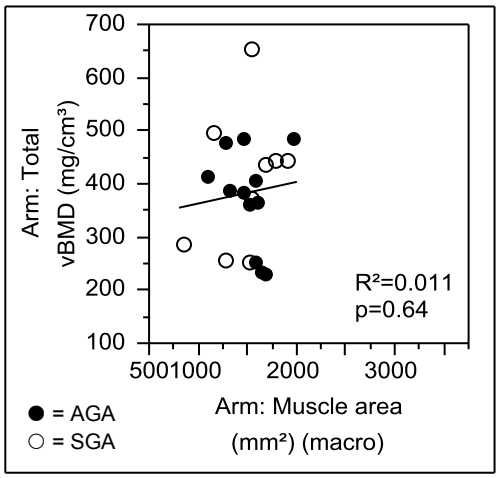
Time from GH start (mo.): 0



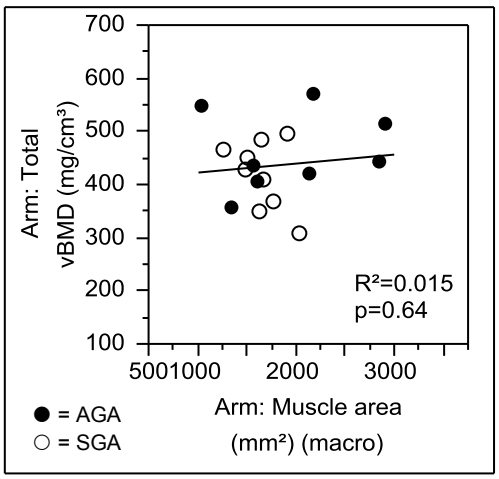
Time from GH start (mo.): 6



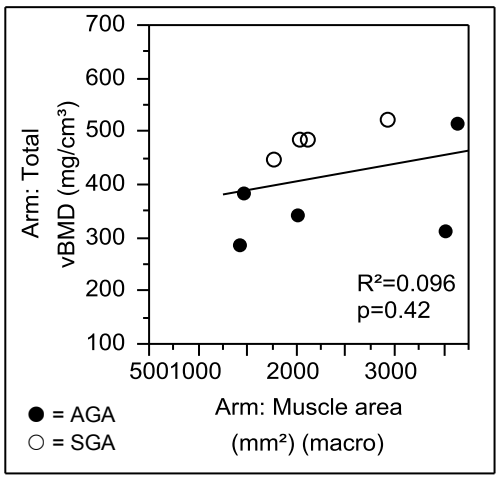
Time from GH start (mo.): 12



Time from GH start (mo.): 24

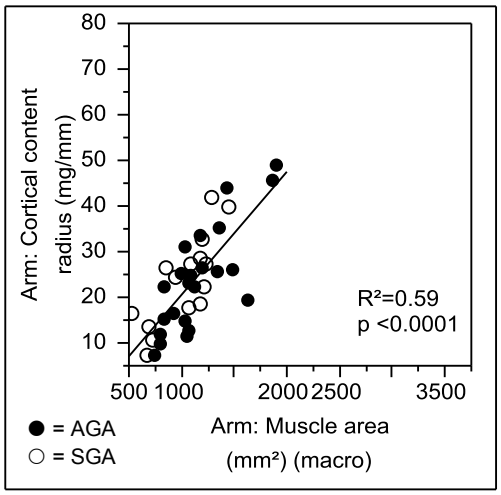


Time from GH start (mo.): 36

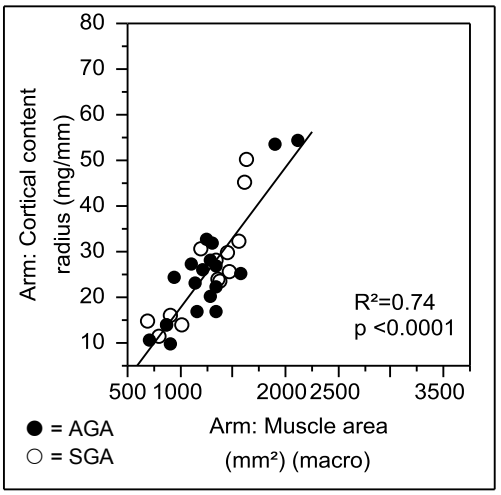


Time from GH start (mo.): 48

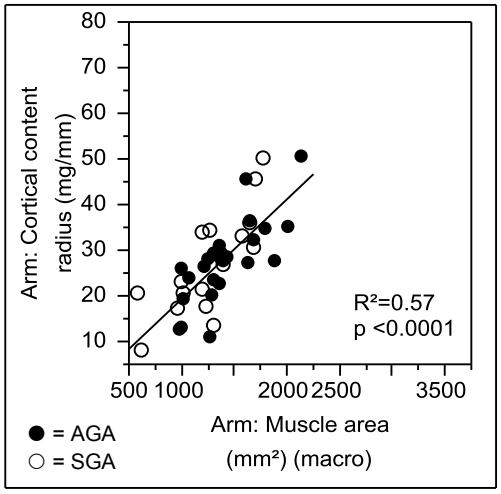
FIGURE 41: Total vBMD (radius) [mg/cm³] to MA (arm) [mm²]



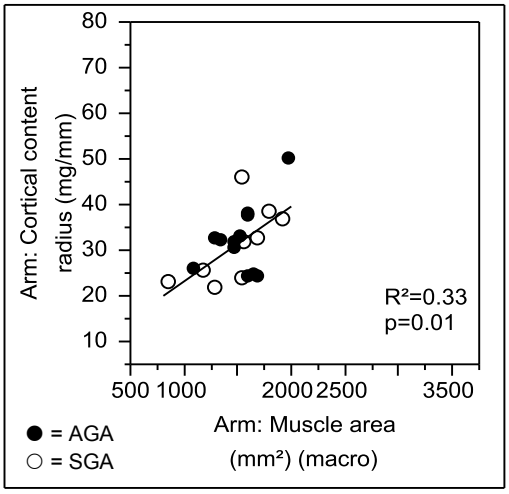
Time from GH start (mo): 0



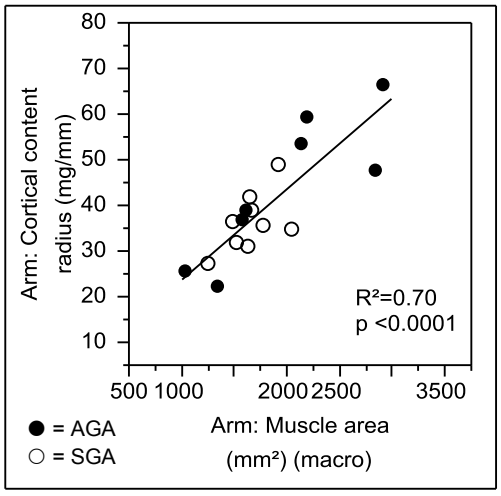
Time from GH start (mo): 6



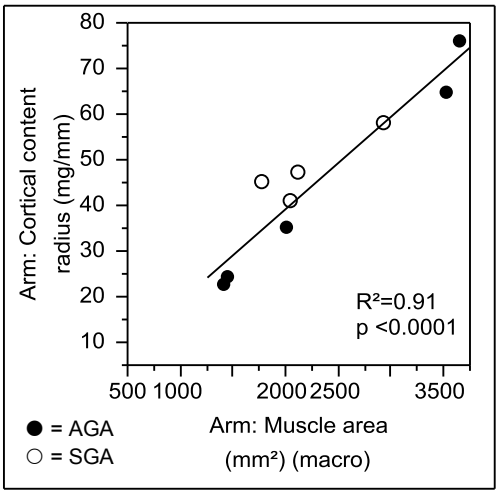
Time from GH start (mo): 12



Time from GH start (mo): 24

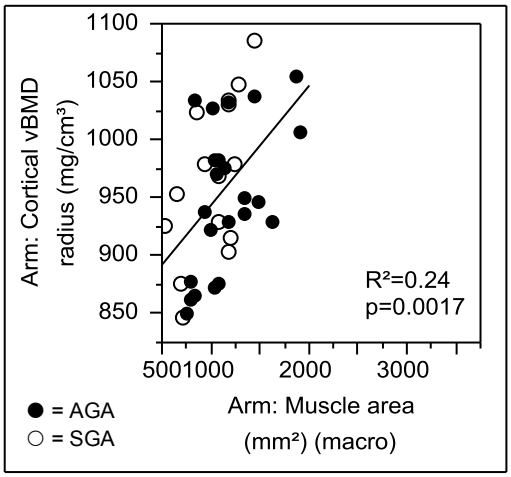


Time from GH start (mo): 36

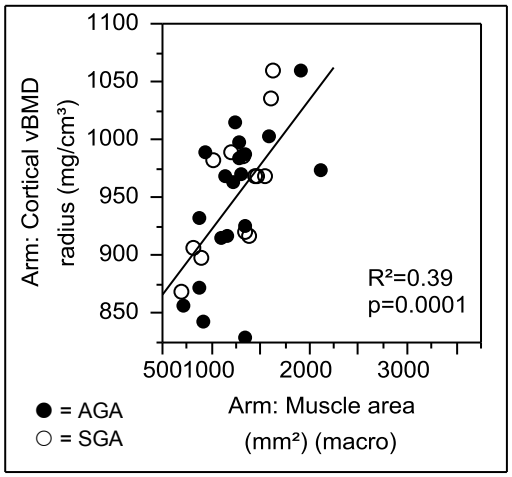


Time from GH start (mo): 48

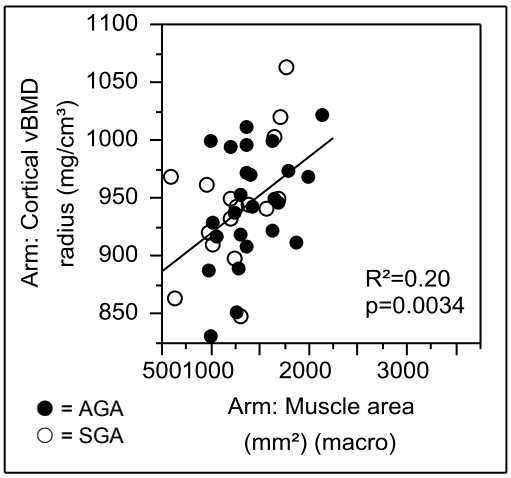
FIGURE 42: Cortical content (radius) [mg/mm] to MA (arm) [mm²]



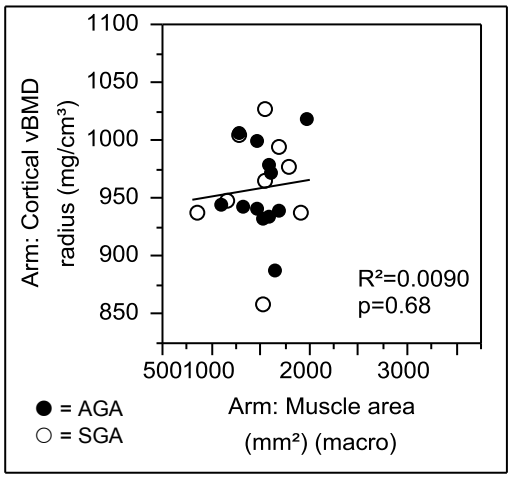
Time from GH start (mo): 0



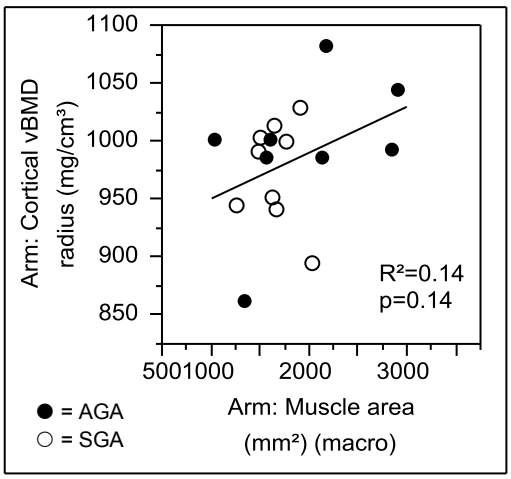
Time from GH start (mo): 6



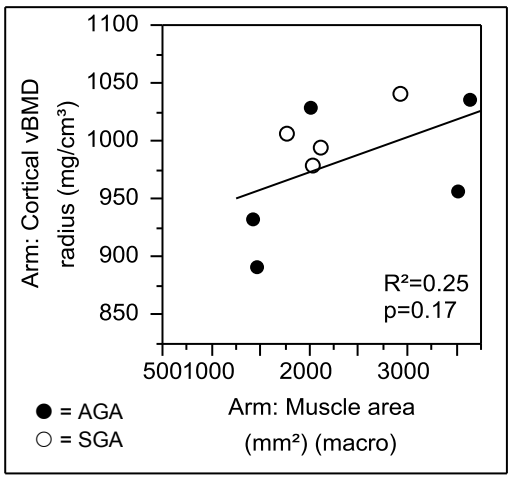
Time from GH start (mo): 12



Time from GH start (mo): 24

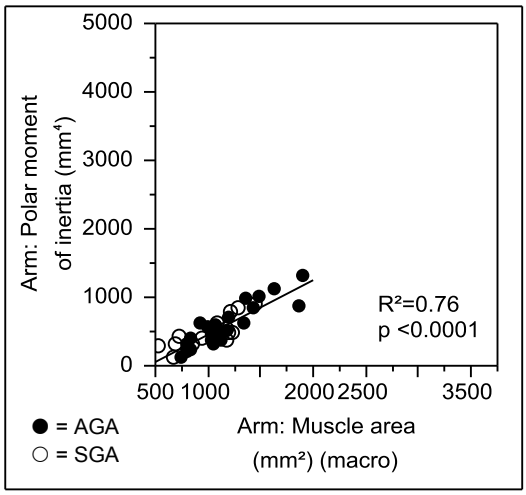


Time from GH start (mo): 36

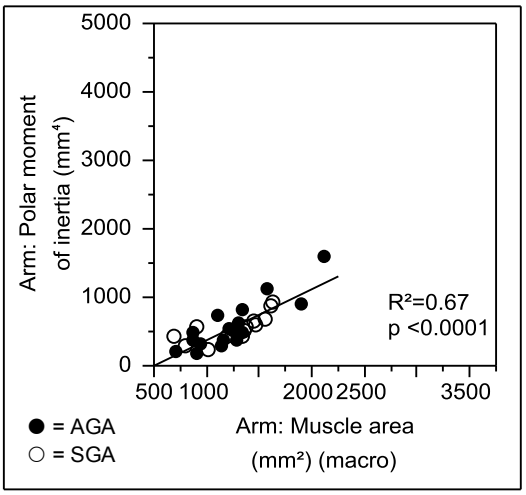


Time from GH start (mo): 48

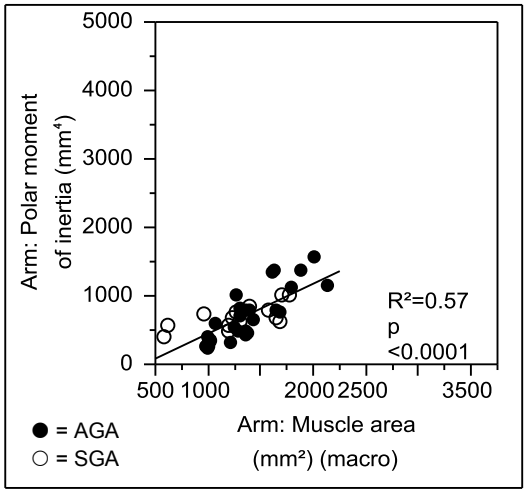
FIGURE 43: Cortical vBMD (radius) [mg/cm³] to MA (arm) [mm²]



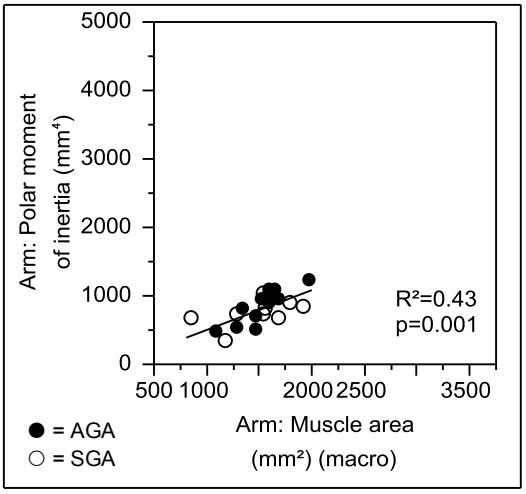
Time from GH start (mo): 0



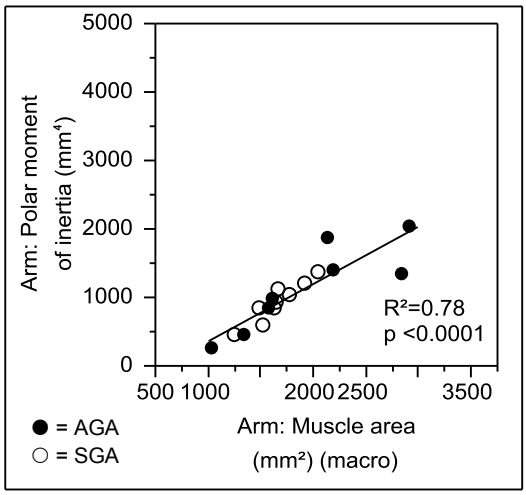
Time from GH start (mo): 6



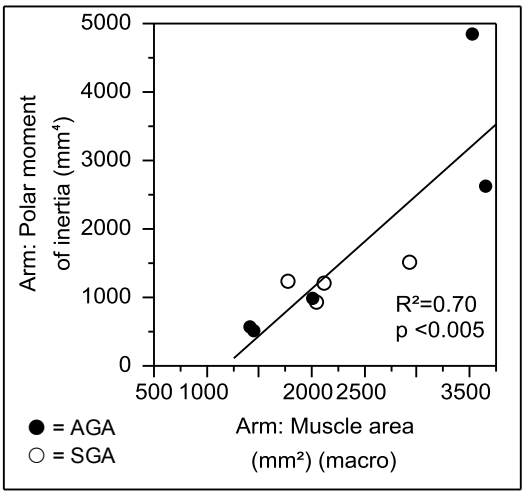
Time from GH start (mo): 12



Time from GH start (mo): 24

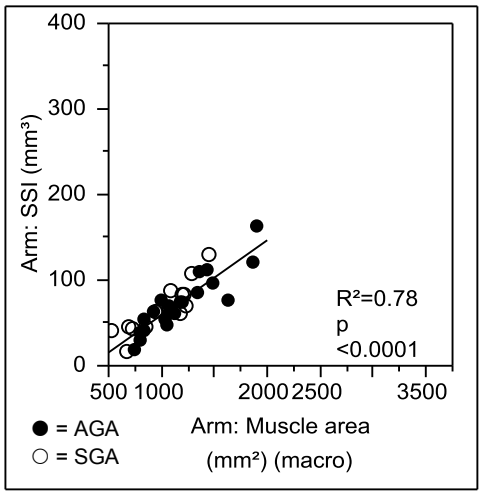


Time from GH start (mo): 36

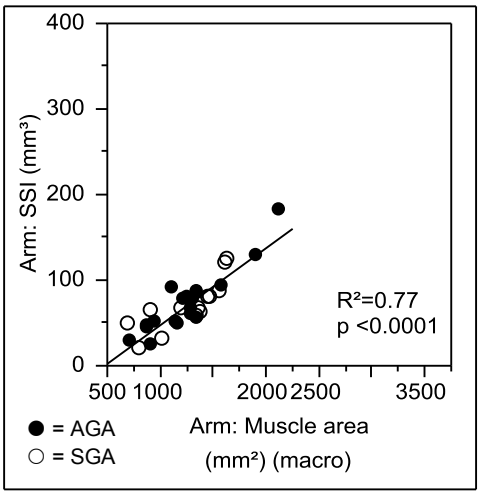


Time from GH start (mo): 48

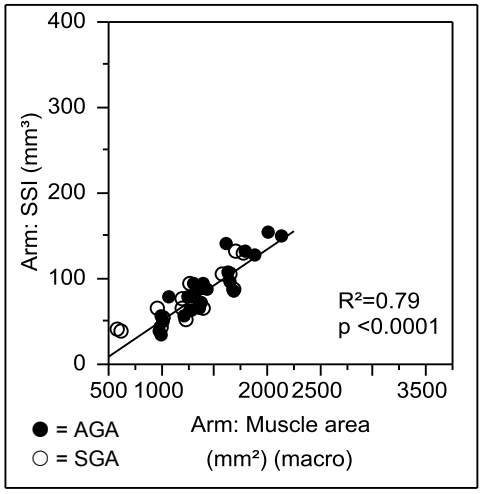
FIGURE 44: Polar moment of inertia (arm) [mm⁴] to MA (arm) [mm²]



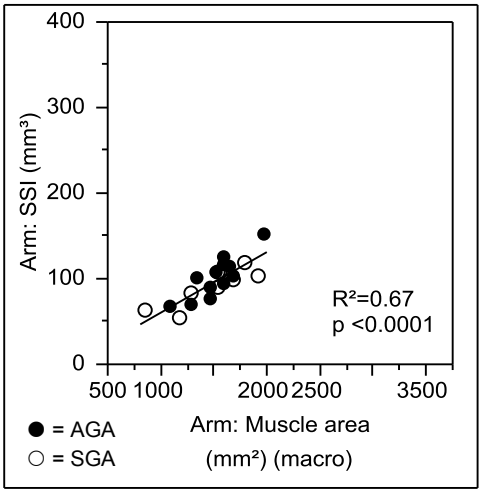
Time from GH start (mo): 0



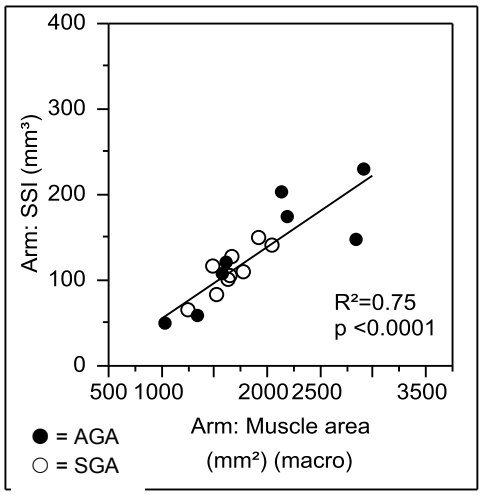
Time from GH start (mo): 6



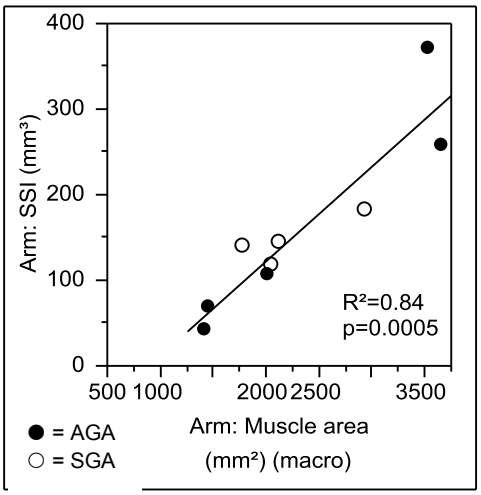
Time from GH start (mo): 12



Time from GH start (mo): 24

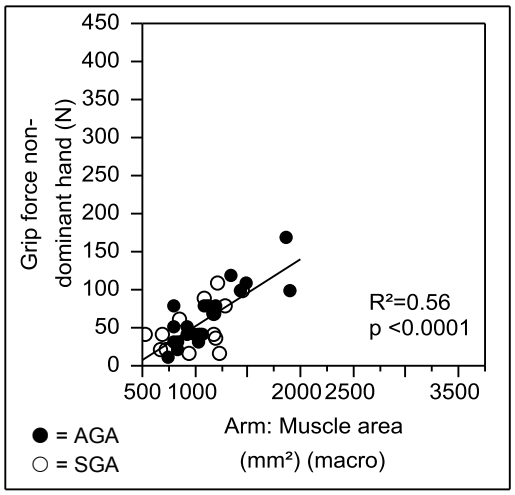


Time from GH start (mo): 36

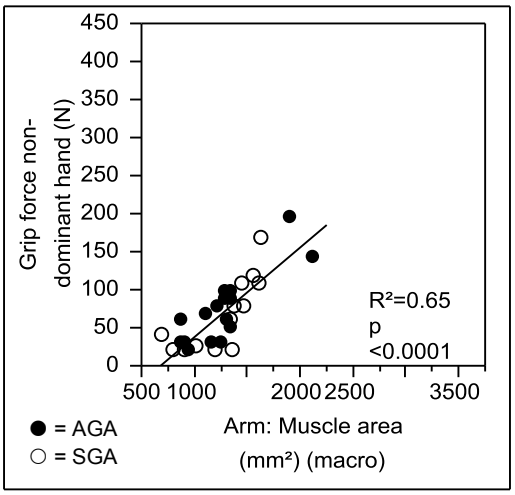


Time from GH start (mo): 48

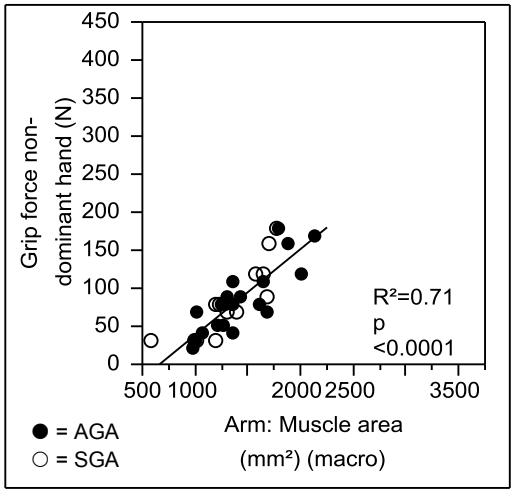
FIGURE 45: SSI (arm) [mm³] to MA (arm) [mm²]



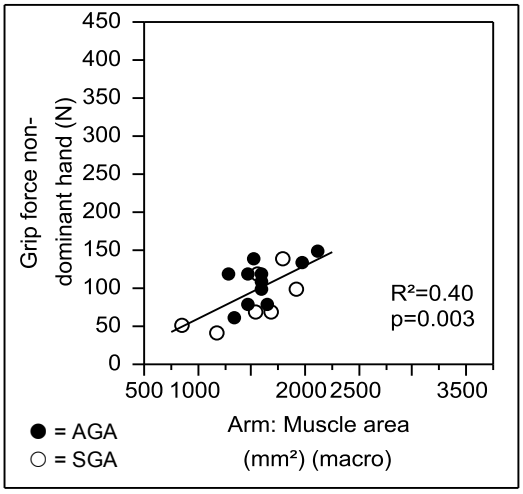
Time from GH start (mo): 0



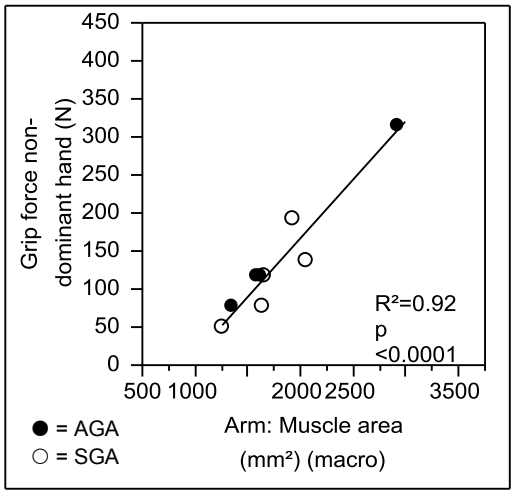
Time from GH start (mo): 6



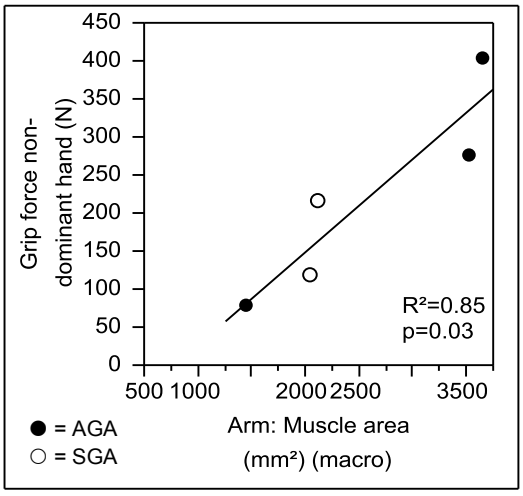
Time from GH start (mo): 12



Time from GH start (mo): 24

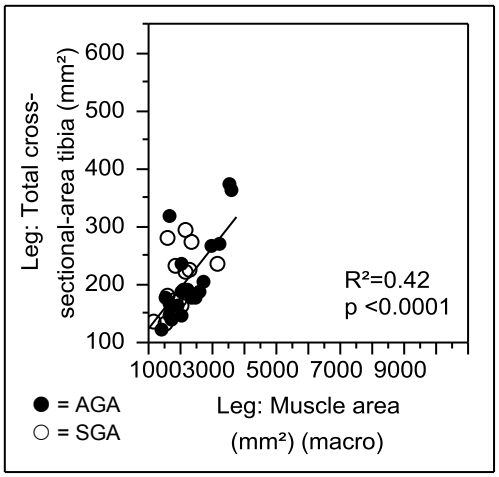


Time from GH start (mo): 36

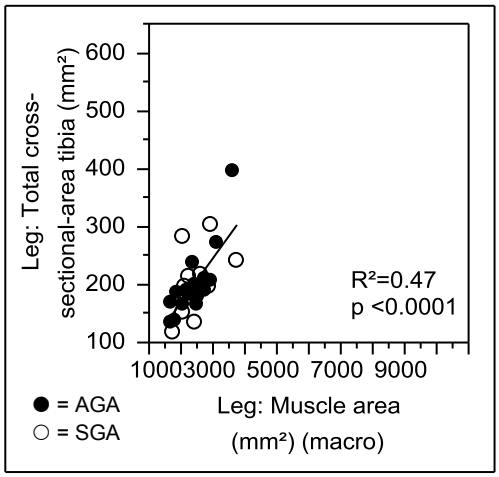


Time from GH start (mo): 48

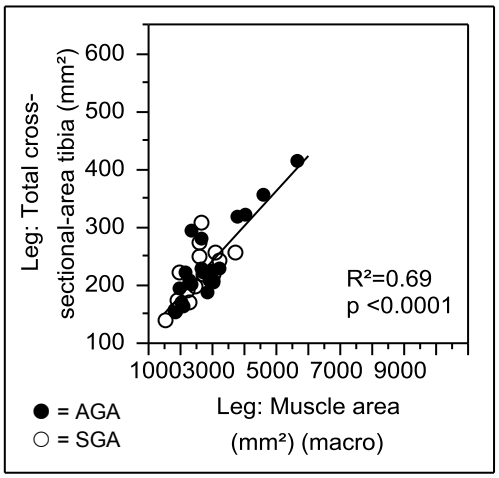
FIGURE 46: Maximal isometric grip force of the non-dominant hand [N] to MA (arm) [mm²]



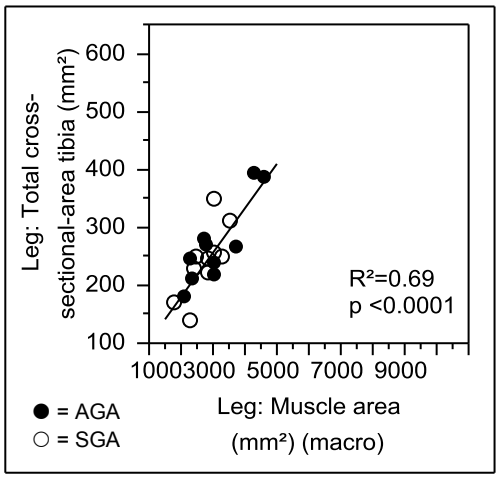
Time from GH start (mo): 0



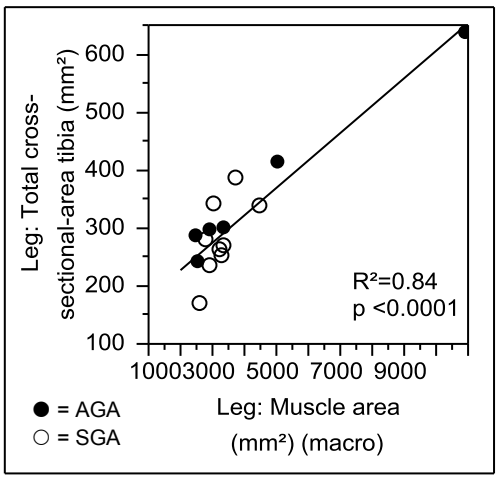
Time from GH start (mo): 6



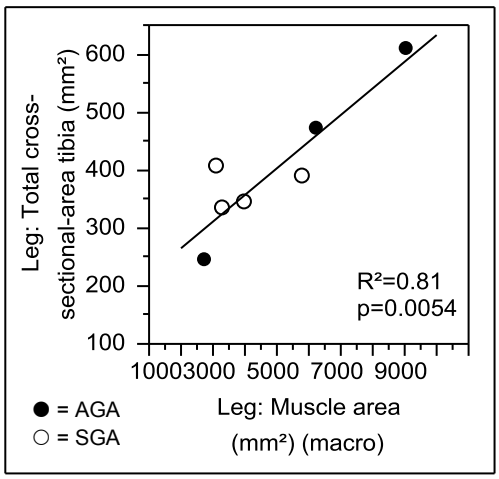
Time from GH start (mo): 12



Time from GH start (mo): 24

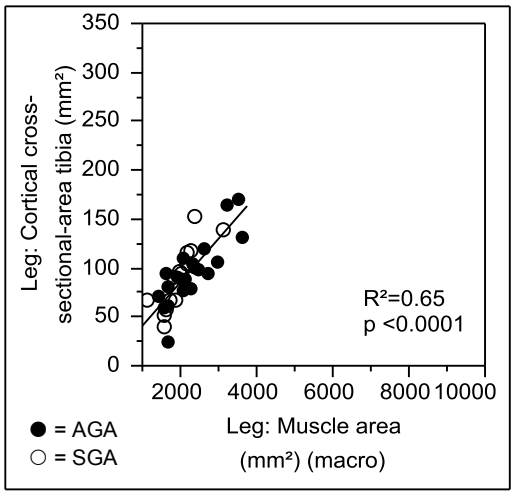


Time from GH start (mo): 36

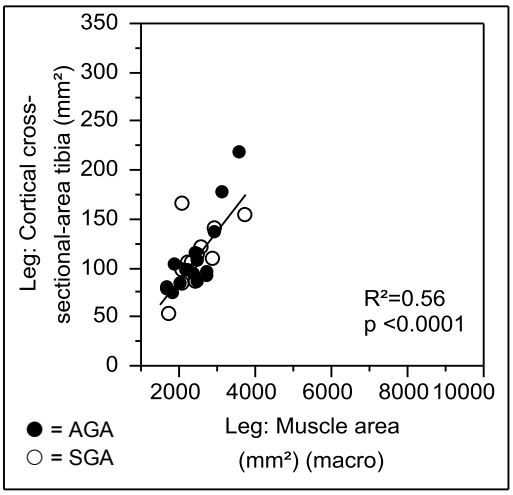


Time from GH start (mo): 48

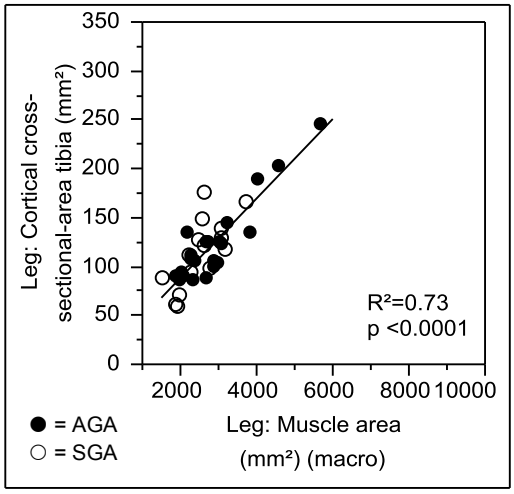
FIGURE 47: Total cross-sectional area (tibia) [mm²] to MA (leg) [mm²]



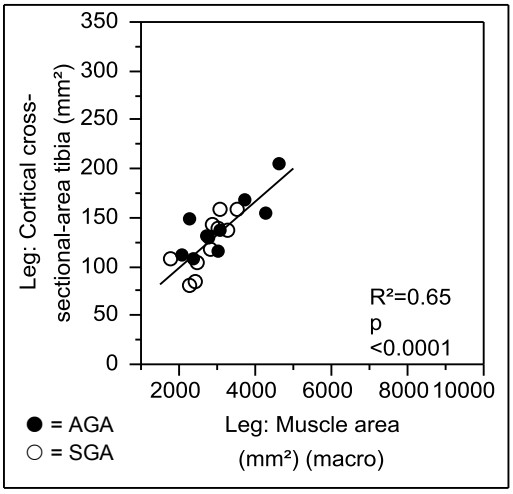
Time from GH start (mo): 0



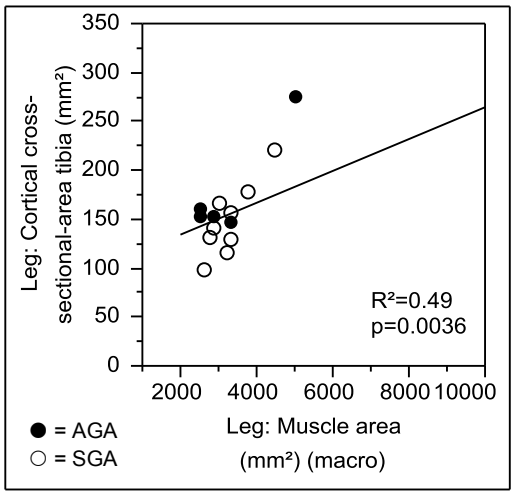
Time from GH start (mo): 6



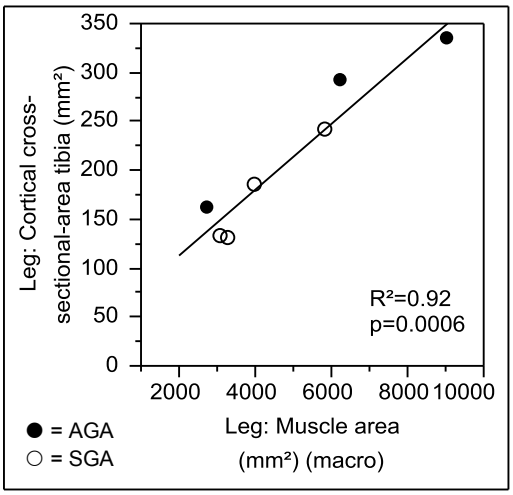
Time from GH start (mo): 12



Time from GH start (mo): 24

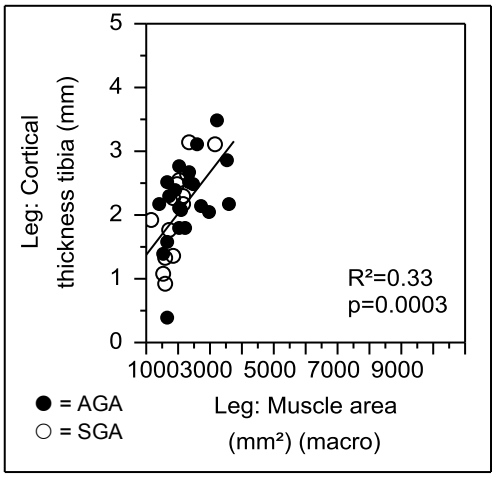


Time from GH start (mo): 36

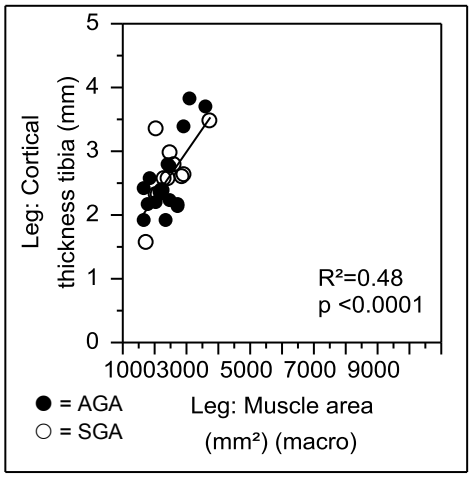


Time from GH start (mo): 48

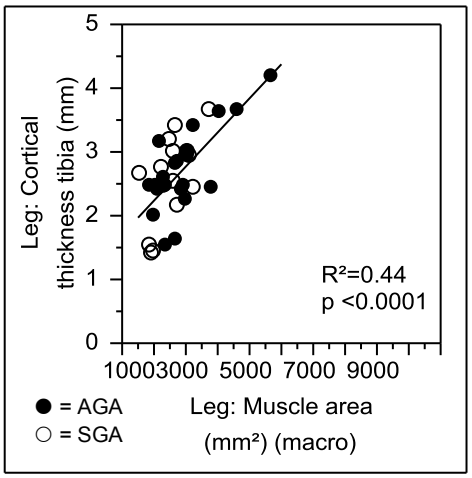
FIGURE 48: Cortical cross-sectional area (tibia) [mm²] to MA (leg) [mm²]



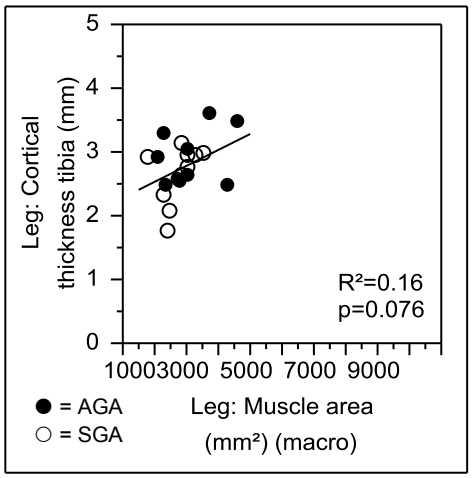
Time from GH start (mo): 0



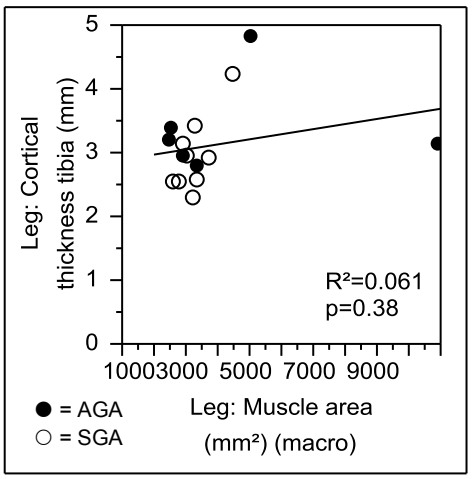
Time from GH start (mo): 6



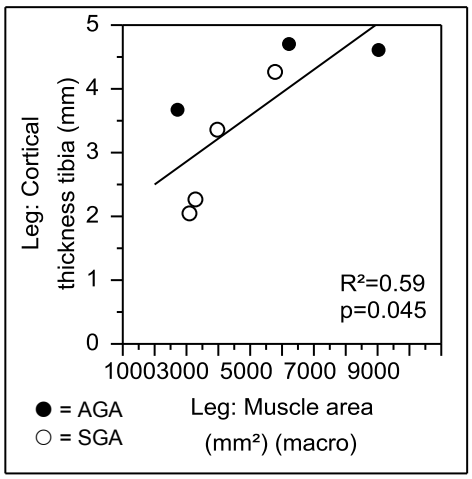
Time from GH start (mo): 12



Time from GH start (mo): 24

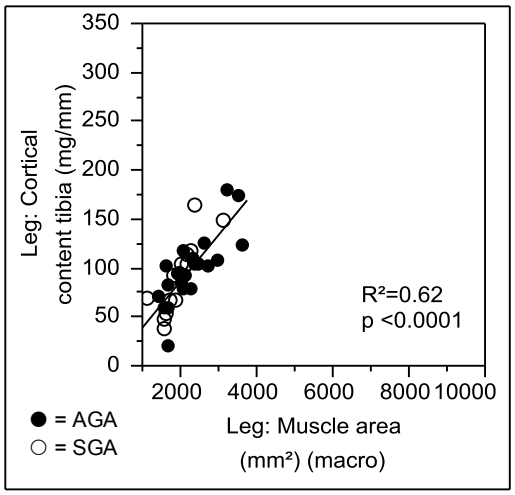


Time from GH start (mo): 36

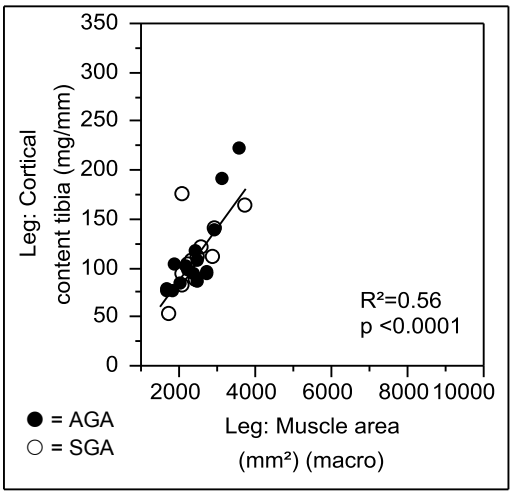


Time from GH start (mo): 48

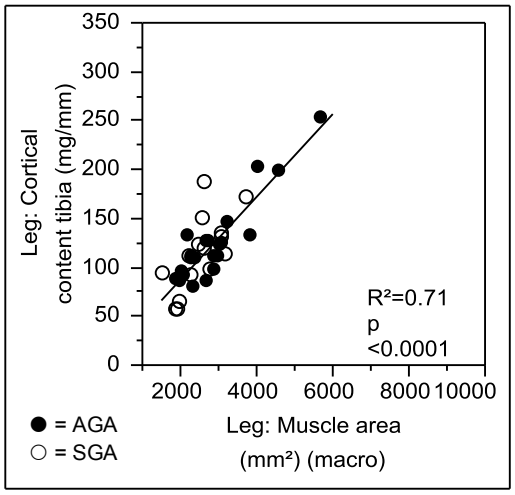
FIGURE 49: Cortical thickness (tibia) [mm] to MA (leg) [mm²]



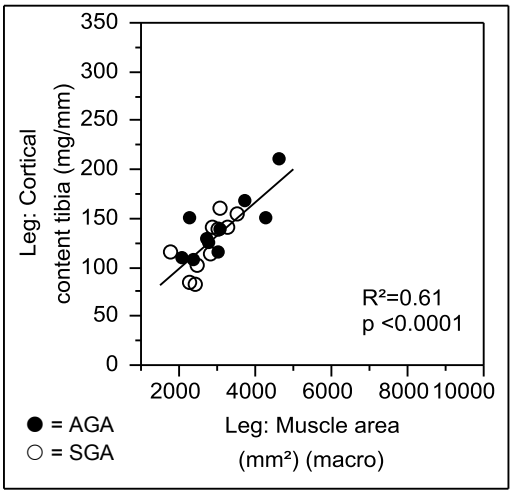
Time from GH start (mo): 0



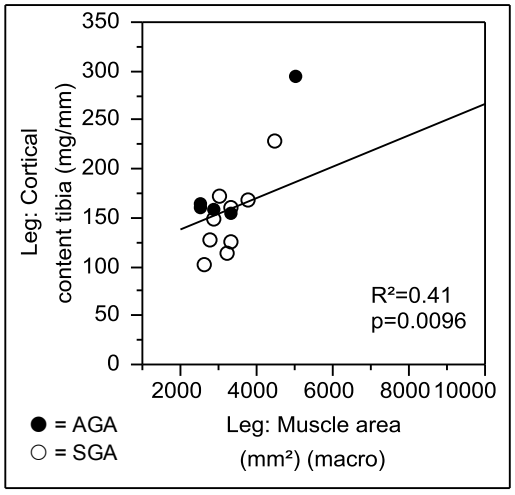
Time from GH start (mo): 6



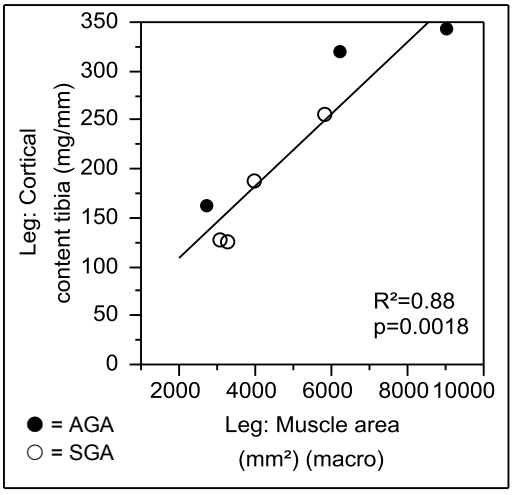
Time from GH start (mo): 12



Time from GH start (mo): 24

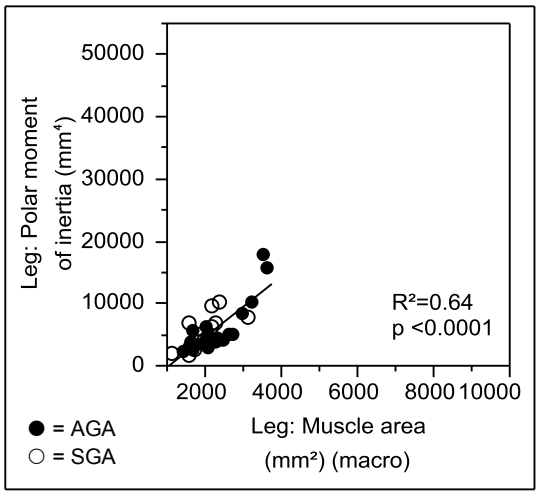


Time from GH start (mo): 36

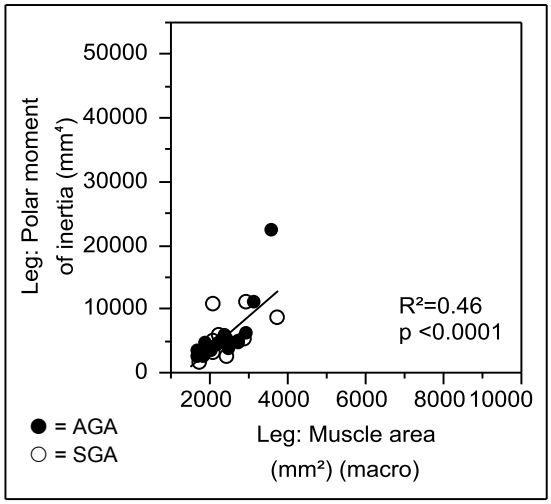


Time from GH start (mo): 48

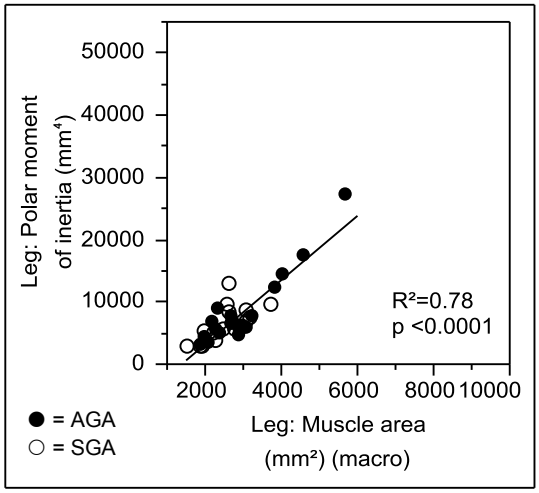
FIGURE 50: Cortical content (tibia) [mg/mm] to MA(leg) [mm²]



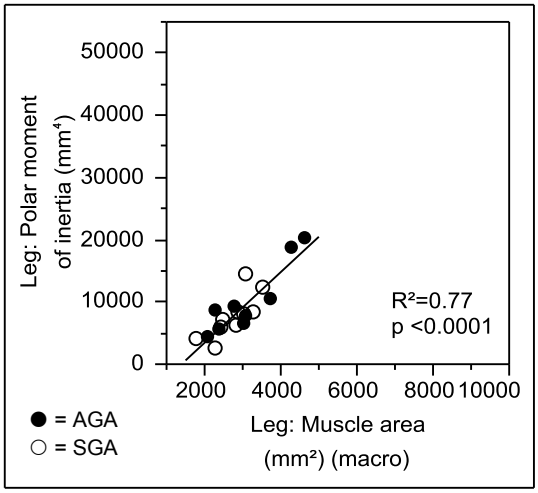
Time from GH start (mo): 0



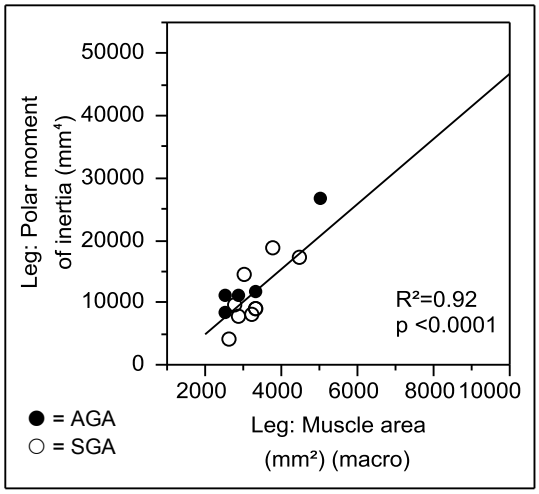
Time from GH start (mo): 6



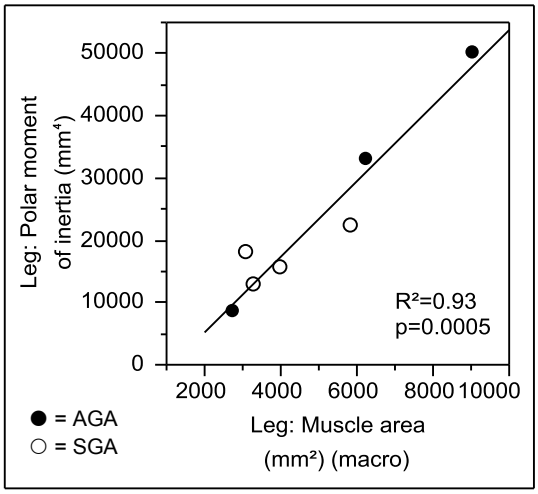
Time from GH start (mo): 12



Time from GH start (mo): 24

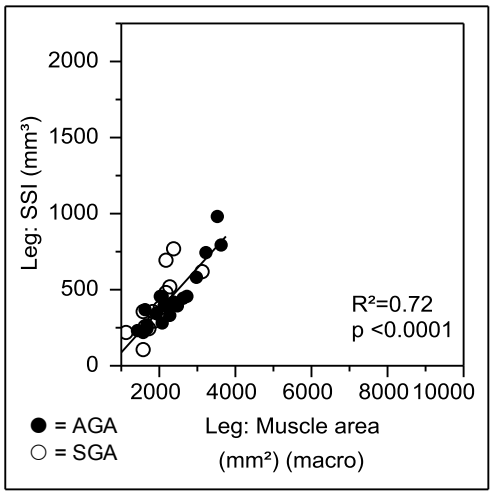


Time from GH start (mo): 36

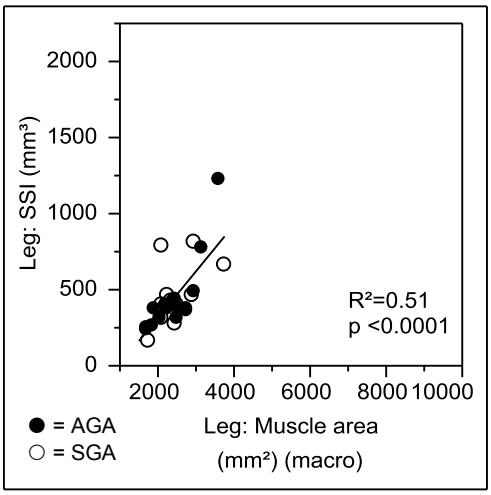


Time from GH start (mo): 48

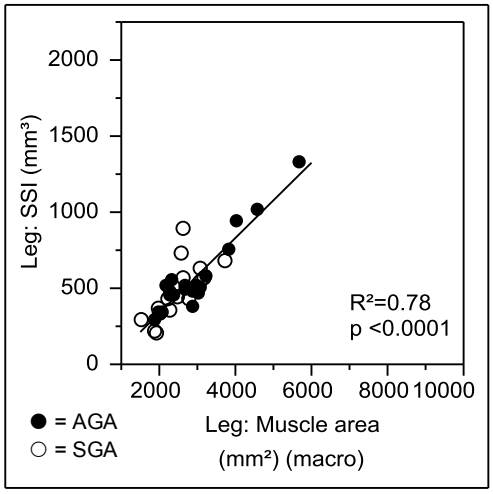
FIGURE 51: Polar moment of inertia (leg) [mm⁴] to MA (leg) [mm²]



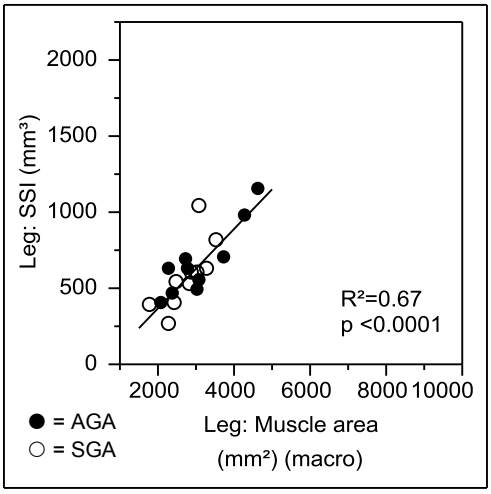
Time from GH start (mo): 0



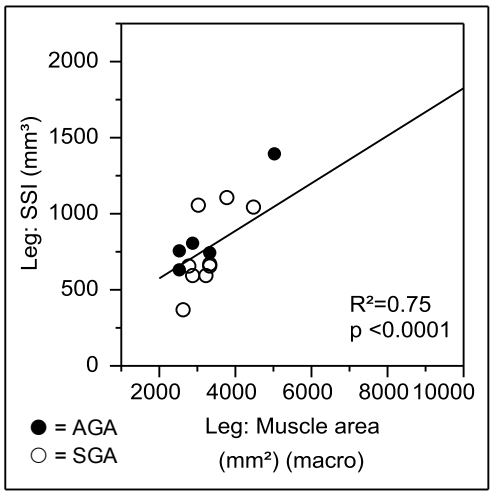
Time from GH start (mo): 6



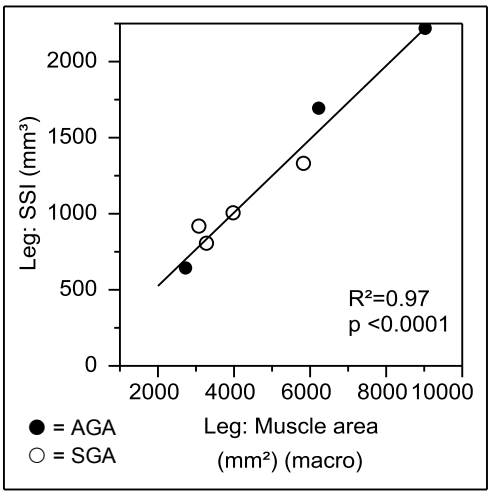
Time from GH start (mo): 12



Time from GH start (mo): 24

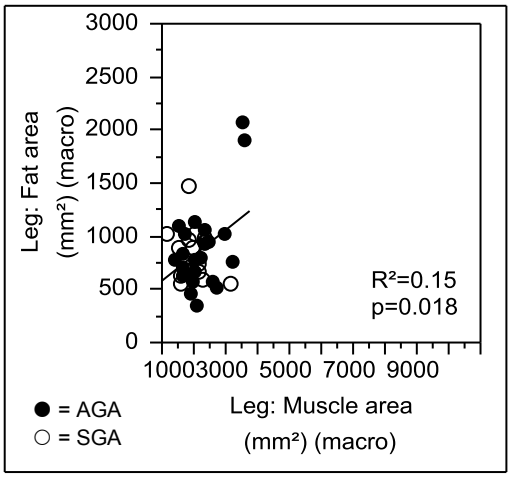


Time from GH start (mo): 36

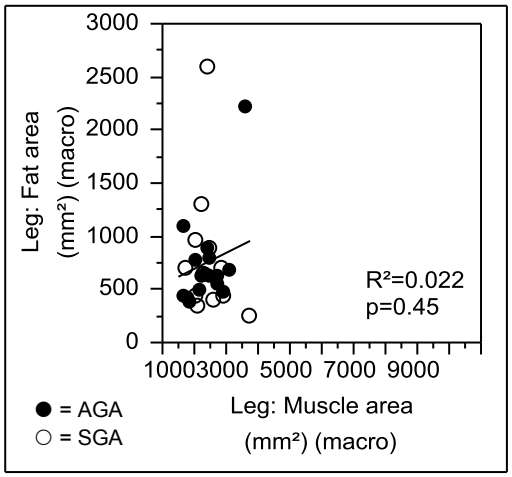


Time from GH start (mo): 48

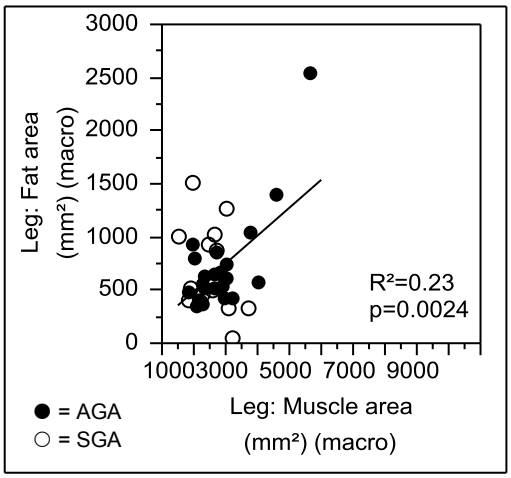
FIGURE 52: SSI (leg) [mm³] to MA (leg) [mm²]



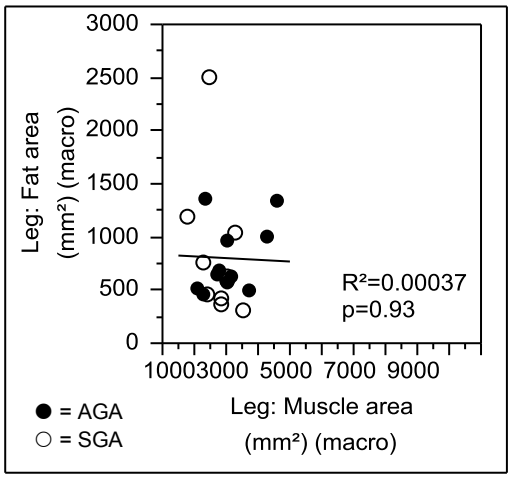
Time from GH start (mo): 0



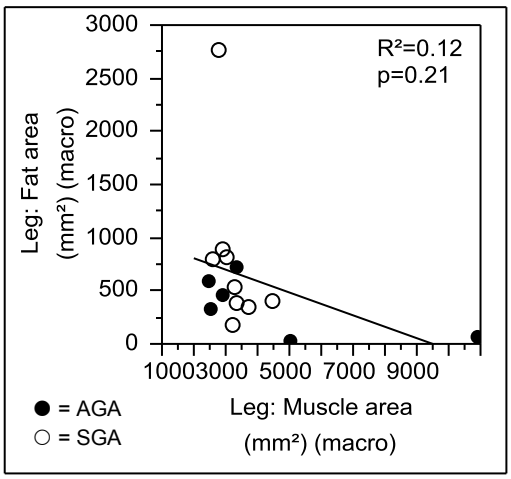
Time from GH start (mo): 6



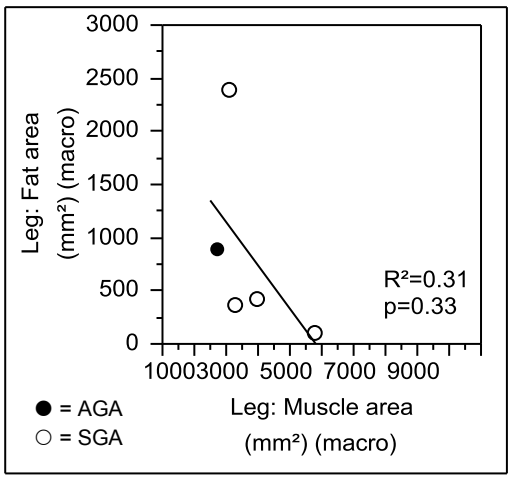
Time from GH start (mo): 12



Time from GH start (mo): 24

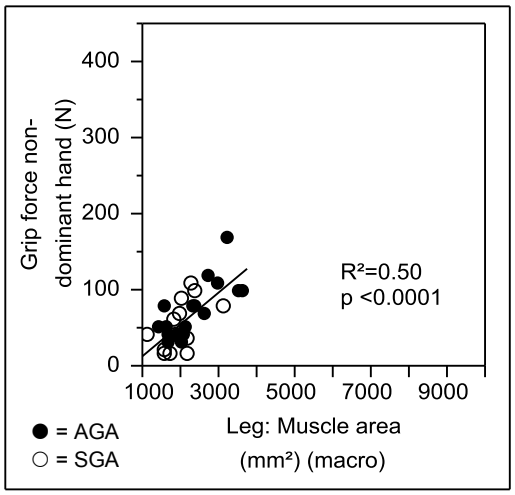


Time from GH start (mo): 36

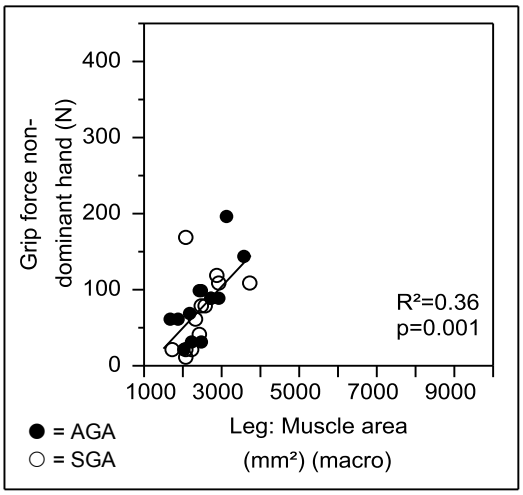


Time from GH start (mo): 48

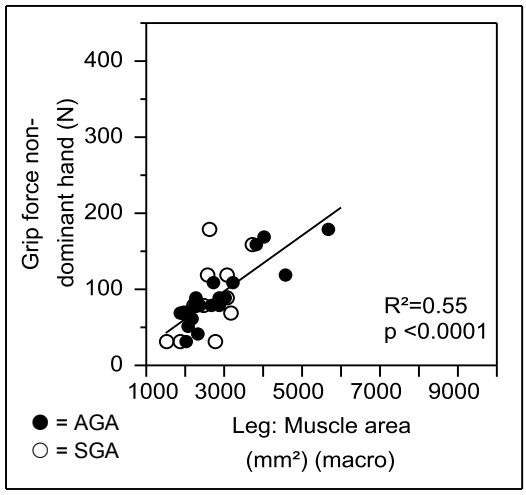
FIGURE 53: Fat area (leg) [mm²] to MA (leg) [mm²]



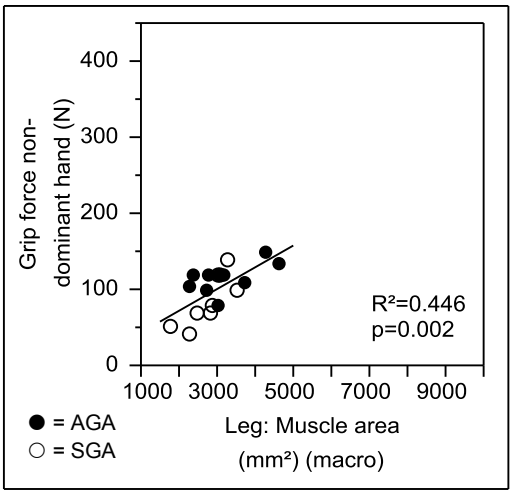
Time from GH start (mo): 0



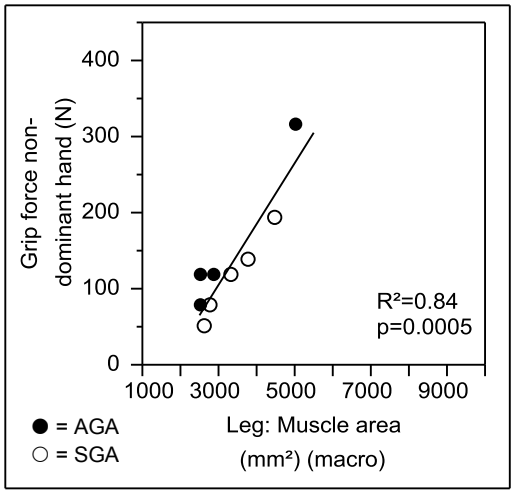
Time from GH start (mo): 6



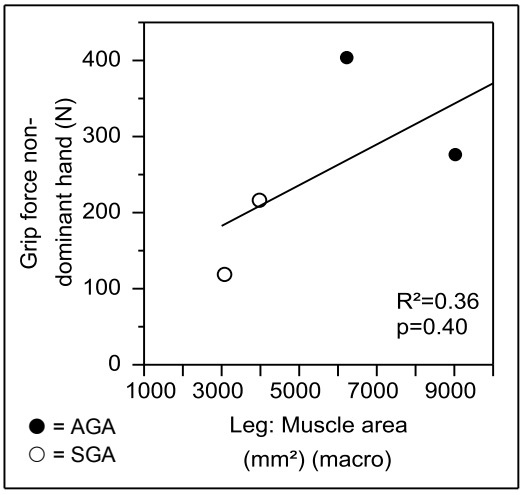
Time from GH start (mo): 12



Time from GH start (mo): 24

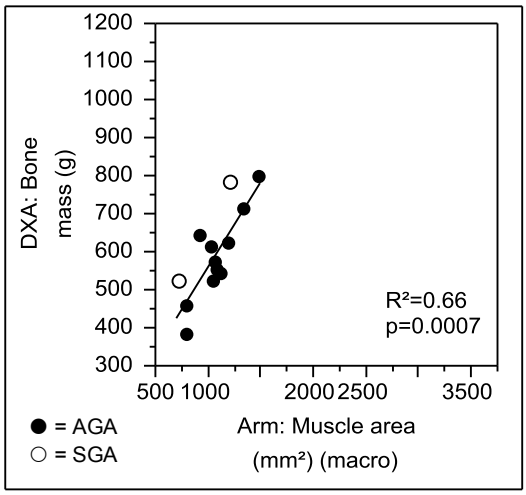


Time from GH start (mo): 36

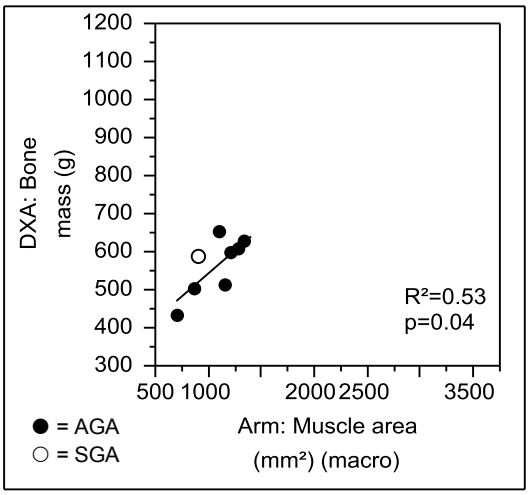


Time from GH start (mo): 48

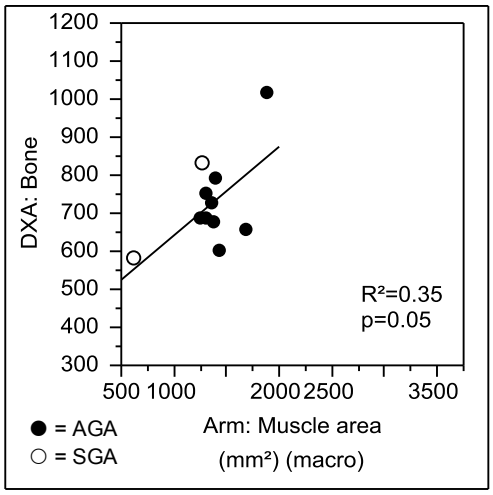
FIGURE 54: Maximal isometric grip force of the non-dominant hand [N] to MA (leg) [mm²]



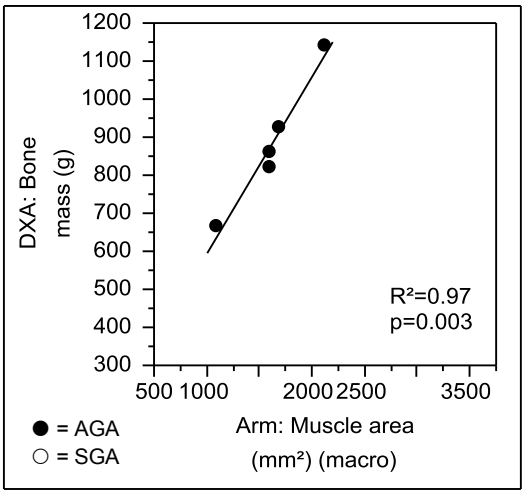
Time from GH start (mo): 0



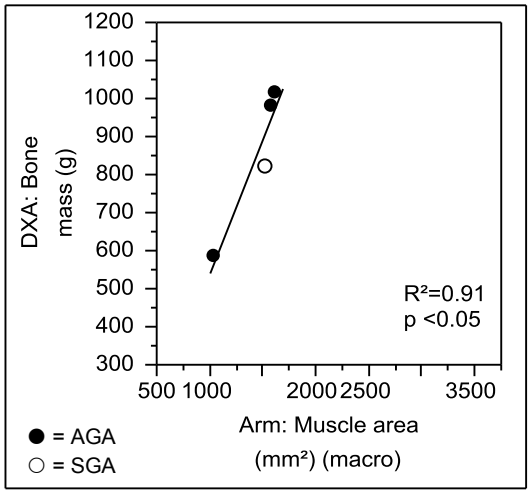
Time from GH start (mo): 6



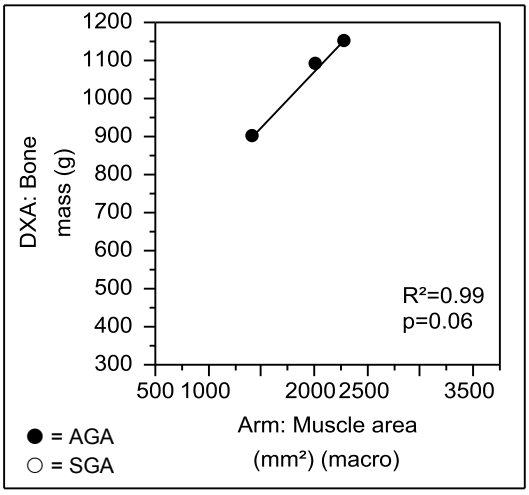
Time from GH start (mo): 12



Time from GH start (mo): 24



Time from GH start (mo): 36



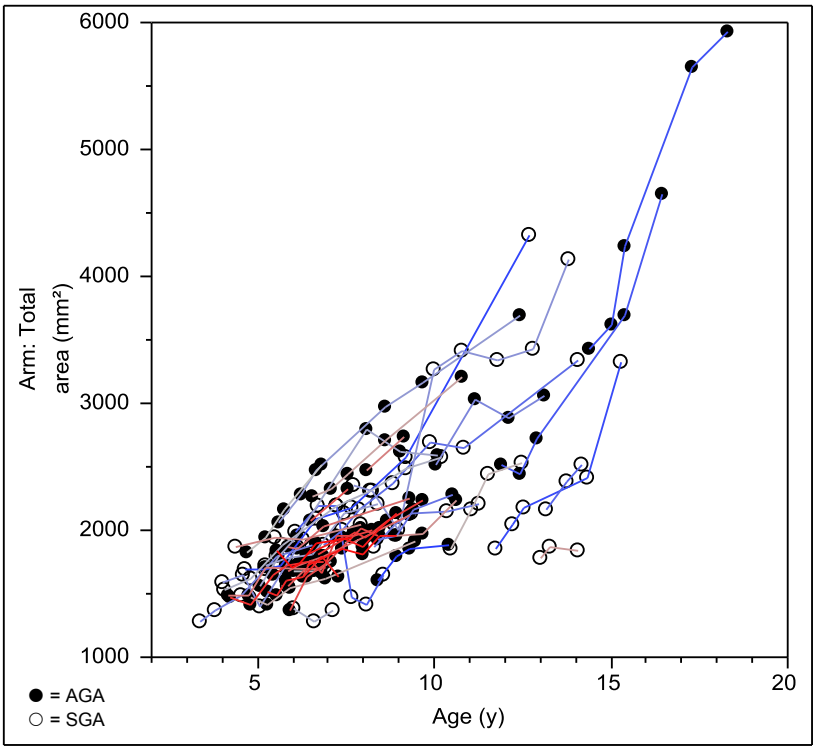
Time from GH start (mo): 48

FIGURE 55: DXA Bone mass [g] to MA (arm) [mm²]

7.2.7 Courses of bone and tissue values in arm and leg pQCT to age

Changes of various pQCT parameters to age (y) under GH treatment are shown in the following figures for arm and leg measurements separately. Total area, muscle area, fat area, total cross-sectional area and cortical cross-sectional area of radius and tibia respectively are correlated to age. Courses of fat area do not show any uniformity in arm and leg measurements. Fat area is not a useful parameter to examine changes under GH treatment when not set in relation to whole body composition. On the one hand changes in fat area are subjected to a decrease under GH treatment and on the other hand to an increase over time with increasing total weight.

pQCT measurements in this study show better results in leg measurements than in arm measurements. Even slight movements during the measuring process reduce the quality, which occurs more often in arm than in leg measurements. The courses of total area (leg), muscle area (leg), total cross-sectional area (tibia) and cortical cross-sectional area (tibia) to age show smoother increments than the equivalent measurements of the arm. Differences are especially clear in bone parameters having the smallest surface values.



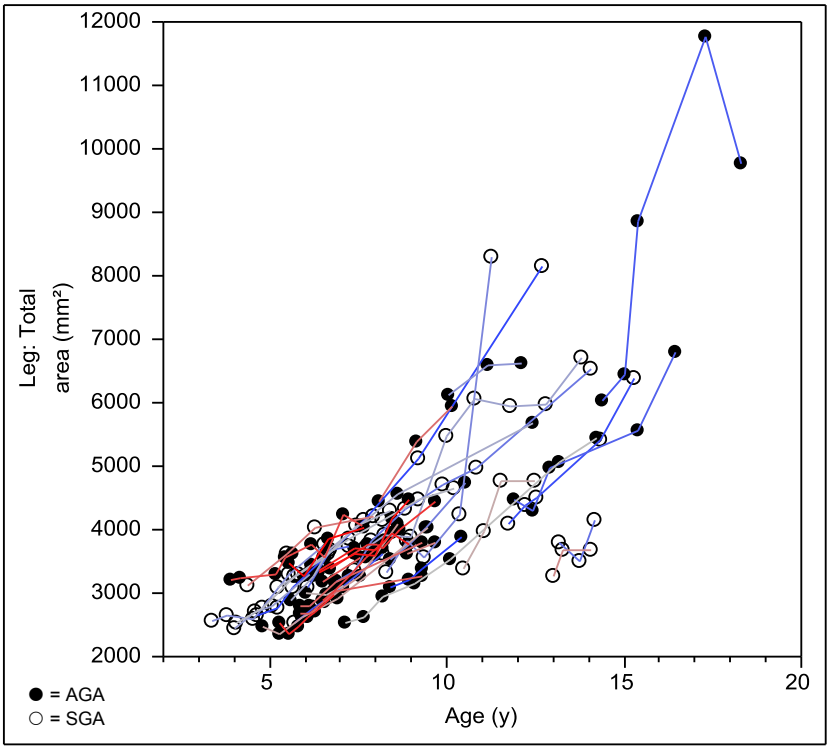
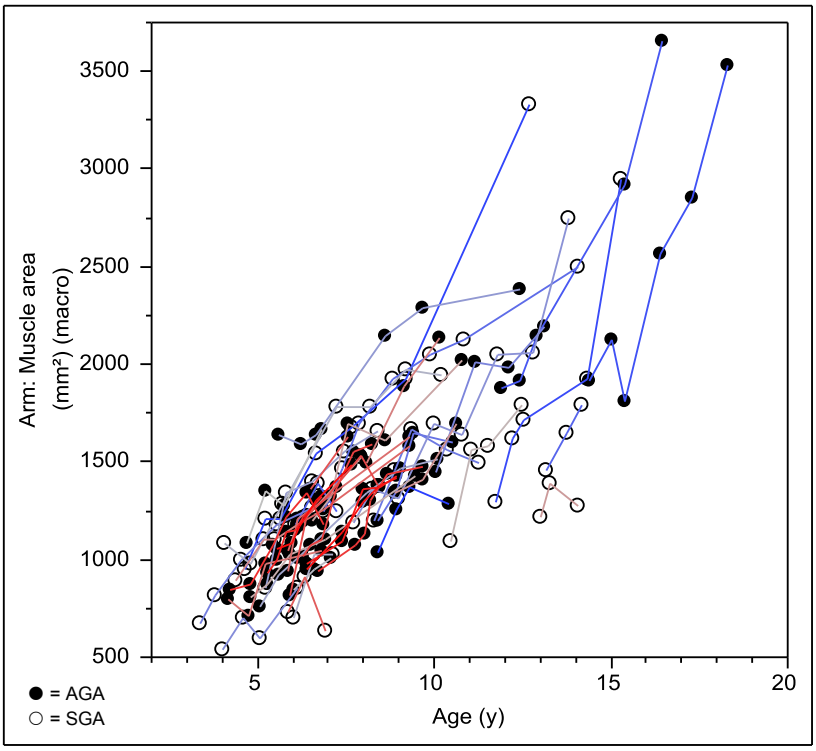


FIGURE 56: Total area (mm²) to age (y) (arm and leg pQCT)



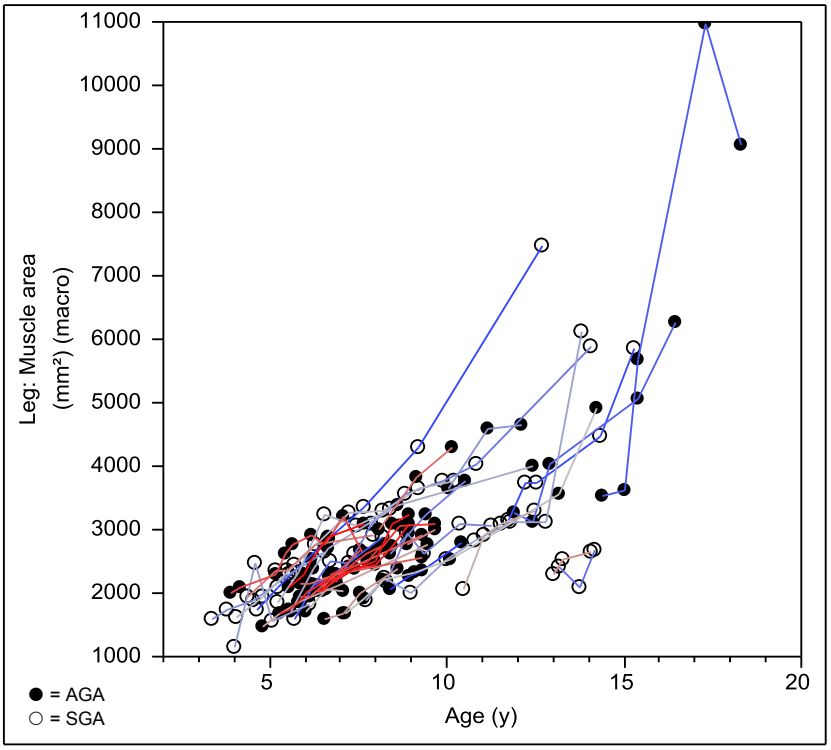
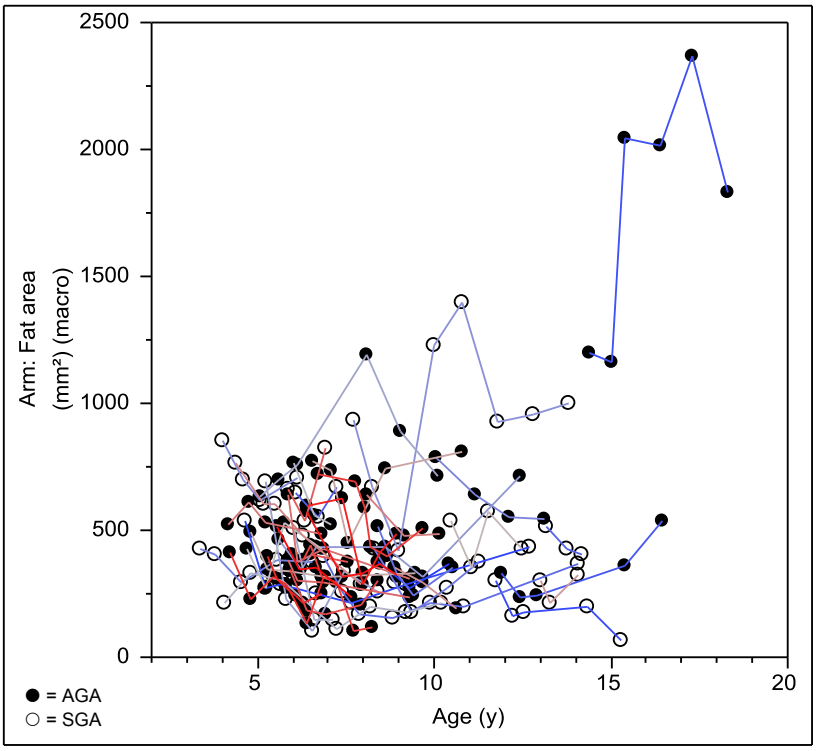


FIGURE 57: Muscle area (mm²) to age (y) (arm and leg pQCT)



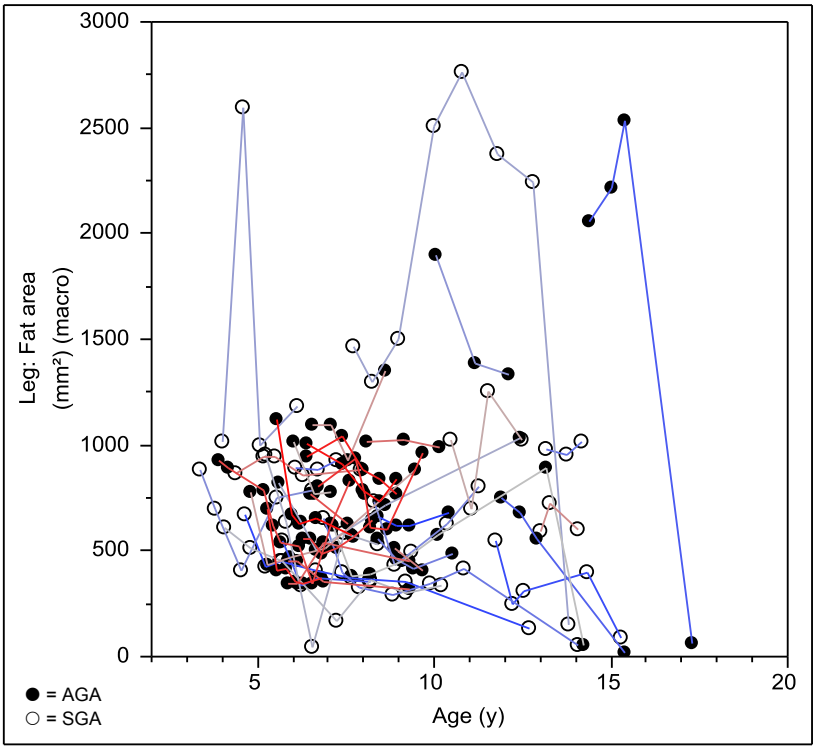
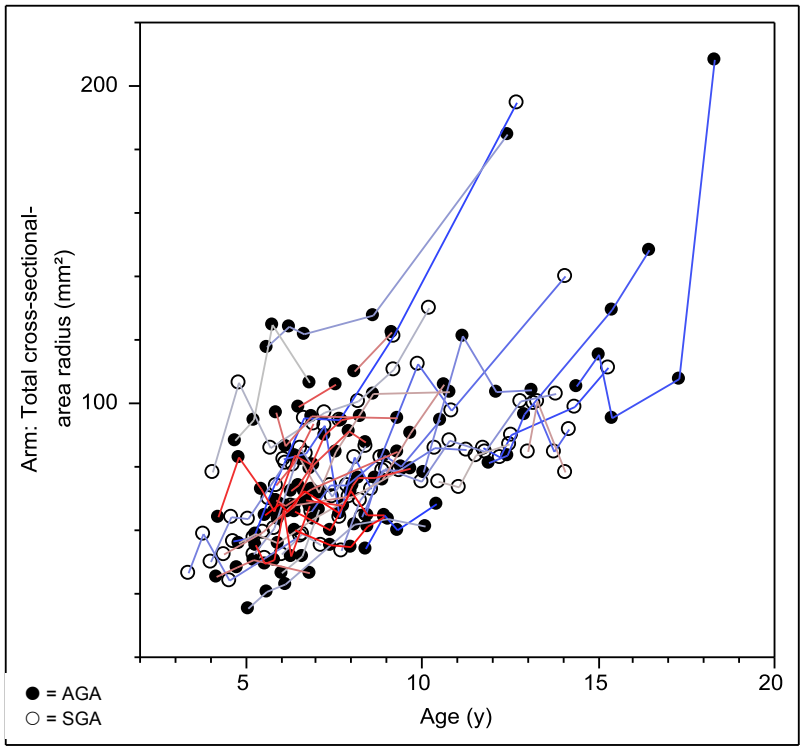


FIGURE 58: Fat area (mm²) to age (y) (arm and leg pQCT)



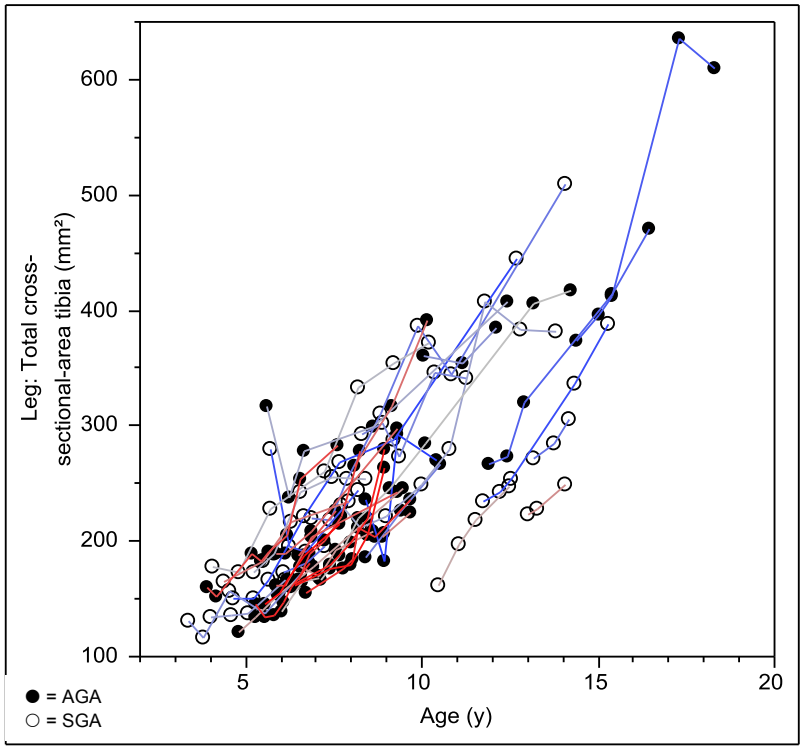
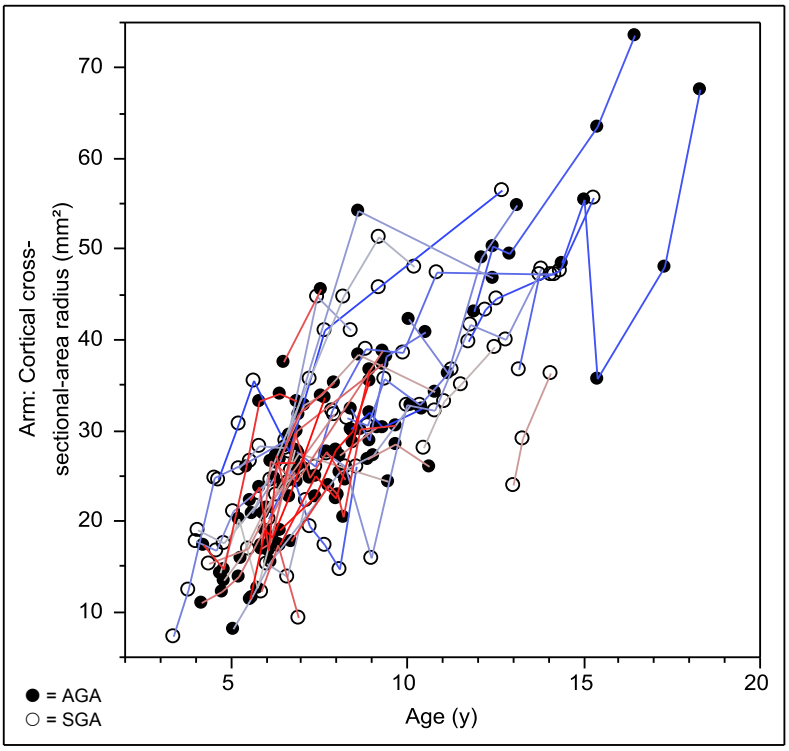


FIGURE 59: Total CSA (mm²) to age (y) (arm and leg pQCT)



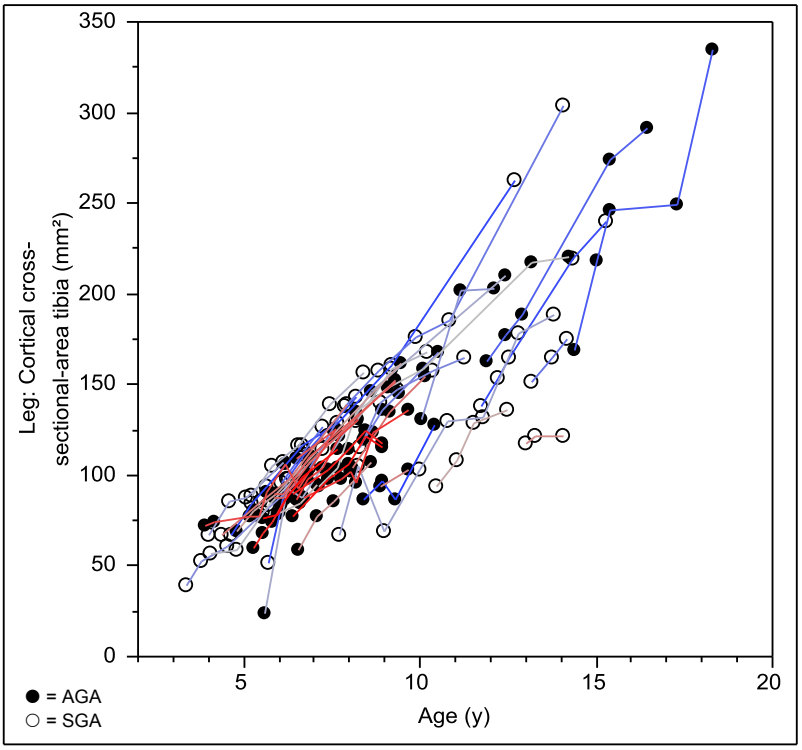


FIGURE 60: Cortical CSA (mm²) to age (y) (arm and leg pQCT)

8 Deutsche Zusammenfassung

Titel: Größe, Muskel- und Fettmasse sowie Knochenzusammensetzung unter Wachstumshormonbehandlung bei ehemaligen früh- und mangelgeborenen Kindern und SGA Kindern mit einem Geburtsgewicht bis 1500 g sowie fehlendem Aufholwachstum.

Hintergrund: Ein Teil der SGA (small for gestational age: zu klein in Bezug auf das Gestationsalter) geborenen Kinder und ein Teil der unreif AGA (appropriate for gestational age: normal groß in Bezug auf das Gestationsalter) geborenen Kinder mit einem Geburtsgewicht bis 1500 g werden zu kleinwüchsigen Kindern und weisen einen Mangel an Muskelmasse und –kraft auf. Eine Wachstumshormonbehandlung ist bisher nur für kleine SGA Kinder zugelassen, jedoch nicht für kleine AGA Kinder mit einem Geburtsgewicht bis 1500 g.

Zielsetzung: Diese Studie untersucht, wie sich eine Wachstumshormonbehandlung auf Größenzuwachs, Muskelmasse, –kraft sowie Knochendichte und –geometrie an kleinen SGA und AGA Kindern mit einem Geburtsgewicht bis 1500 g auswirkt.

Studiendesign: Diese longitudinale Kontrollstudie wurde in der Abteilung für Pädiatrische Endokrinologie und Diabetologie der Kinderklinik des Universitätsklinikum Tübingen durchgeführt. Daten wurden zu Beginn und während des ersten Behandlungsjahres erhoben, in einigen Fällen darüber hinaus.

Patientengruppe: Die Patientengruppe besteht aus 44 präpubertären kleinen Kindern mit einem Geburtsgewicht unter 1500 g. Die Gruppe teilt sich in 17 SGA Kinder (6 Mädchen) und 27 AGA Kinder (12 Mädchen) auf. Die Berechnung der Mittelwerte zum Therapiebeginn ergab: Alter 6.9 J. AGA; 7.1 J. SGA; Größe SDS -3.3 AGA; -3.3 SGA; Knochenalter 5.8 J. AGA; 4.3 J. für SGA und Geburtsgewicht SDS -0.96 für AGA und -3.2 für SGA.

Intervention: Die mittlere Wachstumshormondosis lag sechs Monate nach Behandlungsbeginn bei 54 µg/kg/d in der AGA Gruppe (SD 12) und 51 µg/kg/d in der SGA Gruppe (SD 11).

Methode: Mittels peripherer quantitativer Computertomografie (pQCT) (XCT 2000; Stratec, Inc., Pforzheim, Germany) wurden die Querschnittsflächen von Unterarm und Unterschenkel gemessen. Daten zur Körperzusammensetzung von Fett-, Muskel- und Knochenmasse sowie Wassergehalt wurden mittels DXA-Scan und BIA gemessen. Die maximale isometrische Handkraft (MIGF) wurde mit dem Jamar Dynamometer (Preston, Jackson, MI) und die Hautfaltendicke mit dem Holtain/Tanner-Whitehouse Skinfold Caliper gemessen. Die IGF-1 und IGFBP-3 Werte wurden im Hormonlabor der Tübinger Kinderendokrinologie ermittelt. Alle Messdaten wurden zu Beginn der Wachstumshormontherapie, nach zwölf Monaten und in einigen Fällen darüber hinaus ermittelt.

Ergebnisse: Zu Beginn der Wachstumshormonbehandlung wiesen beide Gruppen gleiche Charakteristika im Wachstumsverhalten auf. Größe, Gewicht und Wachstumsgeschwindigkeit waren erniedrigt. Muskelmasse und Knochendicke und –dichte waren erniedrigt, jedoch gleich in der AGA und SGA Gruppe. Beide Gruppen zeigten unter Wachstumshormonbehandlung eine ähnliche Zunahme an Größe und Gewicht. Im ersten Jahr unter Wachstumshormonbehandlung stieg der SDS der Muskelfläche von -2.2 auf -0.73 in der AGA Gruppe ($p = 0.0010$) und von -3.2 auf -1.2 in der SGA Gruppe ($p = 0.060$), (AGA vs. SGA $p = 0.61$); der SDS der Fettfläche fiel von -1.1 auf -1.8 in der AGA Gruppe ($p = 0.054$) und von -0.62 auf -1.7 in der SGA Gruppe ($p = 0.12$), (AGA vs. SGA $p = 0.65$) und der SDS der Wachstumsgeschwindigkeit stieg in der AGA Gruppe von -0.0015 auf 4.2 ($p < 0.0001$), in der SGA Gruppe von -0.18 auf 3.3 ($p < 0.0001$), (AGA vs. SGA $p = 0.36$). Veränderungen im größenabhängigen-SDS für Kortikalisdichte und im größen- und altersabhängigen SDS für Fettfläche in der AGA Gruppe waren statistisch signifikant. Die Veränderungen unter Wachstumshormonbehandlungen während des ersten Jahres ergaben im Vergleich beider Gruppen miteinander keine signifikanten Unterschiede. Die Auswertungen der pQCT Messungen des Beines konnten nicht in SDS dargestellt werden, da bisher keine Normalwerte für diese Messungen an Kindern existieren. SSI, polares Trägheitsmoment, Kortikalisfläche,

Mineralgehalt der Kortikalis und MIGF zeigten eine positive Korrelation mit Muskelfläche der Arm- und Bein pQCT Messungen zu Beginn und während der Wachstumshormonbehandlung.

Zusammenfassung: Präpubertäre Kinder mit fehlendem Aufholwachstum und einem niedrigen Geburtsgewicht weisen, unabhängig davon ob sie zu klein oder normal groß für ihr Geburtsalter waren, ein gleichermaßen eingeschränktes Wachstum und veränderte Körperzusammensetzung der Muskel- und Knochenparameter auf.

Die zwei Gruppen unterscheiden sich nicht hinsichtlich ihres Ansprechens auf eine Wachstumshormonbehandlung. Insofern erscheint die Zulassung einer Wachstumshormonbehandlung für SGA Kinder aber nicht für AGA Kinder bei einem Geburtsgewicht unter 1500 g arbiträr.

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11 Erklärung zum Eigenanteil

Die dieser Dissertation zugrunde gelegten Daten sind in einer Gemeinschaftsarbeit erhoben worden.

Das Paper **“**Height, muscle, fat and bone response to growth hormone in short children with very low birth weight (VLBW) born appropriate for gestational age (AGA) and small for gestational age (SGA)” von Berndt C, Schweizer R, Binder G und Martin D wurde im Januar 2014 von Hormone Research in Pediatrics (Ms No.: 201301022) zur Veröffentlichung angenommen.

Das Studiendesign stammt von Prof. Dr. D. Martin und Dr. R. Schweizer. Die Untersuchungen wurden von Prof. Dr. D. Martin und Dr. R. Schweizer durchgeführt.
Die Datenrecherche und Auswertung der Patientendaten und der pQCT-Daten dieser Dissertation wurde von C. Berndt durchgeführt. Die Daten wurden von Dr. R. Schweizer und Prof. Dr. D. Martin zur Verfügung gestellt.
Die Studie, das Erstellen der Veröffentlichung und diese Dissertation wurden durch Prof. Dr. D. Martin betreut. Das Manuskript wurde von Prof. Dr. G. Binder und Prof. Dr. D. Martin korrigiert.

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