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Vitamin D Receptor Gene Polymorphism Is Associated with Birth Height, Growth to Adolescence, and Adult Stature in Healthy Caucasian Men: A Cross-Sectional and Longitudinal Study*

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ABSTRACT

Vitamin D receptor (VDR) polymorphism has been associated with bone mineral density (BMD), but recent data indicate association to parameters of body constitution and growth. We investigated VDR gene polymorphism, defined by *Bsm*I and *Taq*I, in 90 healthy Caucasian males and any relation with parameters of body constitution at birth, and to parameters of body constitution, BMD and bone area, at age 16.9 ± 0.3 yr (mean ± SD) and at age 19.2 ± 0.7. Using PCR and the restriction enzyme *Bsm*I and *Taq*I, the allelic variants BB, Bb, and bb, and TT, Tt, and tt were identified. Height (cm) and weight (kg) were measured using standardized equipment, and BMD of the total body, lumbar spine, and femoral neck, and bone area (cm^2) of the total body, humerus, femur was measured using dual-energy x-ray absorptiometry. *Bsm*I and *Taq*I genotypes were related in 89 of the 90 cases; hence, the same associations were found for both genotypes. Boys with the BB genotype were shorter at birth ($P = 0.01$) and grew less from birth to age 16.9 ± 0.3 ($P = 0.01$) than their Bb and bb counterparts. Both during puberty (age 16.9 ± 0.3) and after puberty (age 19.3 ± 0.7), the BB boys were shorter ($P = 0.005$–0.008) and had lower bone area of the humerus, femur, and total body ($P < 0.05$) than the Bb and bb boys. The allelic variants were not related to BMD at any site. A prediction model including parental height, birth height, birth weight, and VDR alleles could predict up to 39% of the total variation in adult height in our population. The VDR allelic variants alone contributed to 8% of the total variation. (*J Clin Endocrinol Metab* **85:** 1666–1671, 2000)

THE ASSOCIATION between Vitamin D receptor (VDR) gene polymorphism and bone mineral density (BMD) has been investigated extensively in several populations, without resulting in any conclusive evidence (1–5), but recent data have indicated that VDR polymorphism could rather be related to growth and parameters of body constitution (6–9). Vitamin D has direct effects on the skeleton, and the active metabolites regulate differentiation, proliferation, and migration of osteoblasts and of chondrocytes of the epiphyseal growth plate, cells determining skeletal growth (10–12). Probably of greater importance, vitamin D affects skeletal metabolism indirectly via regulating calcium and phosphate homeostasis through stimulation of intestinal absorption of these ions (12). Vitamin D deficiency causes growth failure, as seen in rickets (12, 13). Vitamin D is believed to affect intrauterine growth, and infants with low levels at birth show inhibited postnatal growth (14). VDR gene polymorphism has been associated with parameters of body size in both female and male infants (6, 7).

Because vitamin D is likely to regulate growth via effects on bone size, we hypothesized that any association of VDR polymorphism and growth in our population would be observed most clearly by investigating bone size in relation to VDR genotypes. In the present study, we have investigated whether VDR polymorphism is associated with birth height, and with parameters of body growth and size, such as height, weight, and bone size, as well as BMD, during and after puberty, in a group of 90 healthy Caucasian boys.

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Subjects and Methods

Subjects

From advertisement and information in schools and local sports clubs, 96 healthy Caucasian boys participated in a longitudinal study investigating the influence of puberty on bone density at our Department. Of these boys, 92 could be reached and were asked to participate in the present study, and 91 boys volunteered. One of these boys was excluded because it was judged that he had not passed the pubertal growth spurt, leaving 90 boys [age, 16.9 ± 0.3 yr (mean ± SD)] for the present study. None of the subjects had any disease or medication known to affect bone metabolism. Weight and height were measured using standardized equipment. The subjects were divided into different pubertal stages, according to Tanner (15), by the same physician. All participants were judged to have passed the pubertal growth spurt period and were at least Tanner stage 4, based on at least two measurements of weight and height during 1 yr. Sixty-seven boys were judged to have passed puberty (Tanner 5), whereas the remaining 23 boys had not (Tanner 4). Approximately 2 yr later, a follow-up was conducted, and 88 boys were reached and could participate. At that time, the mean age of the 88 boys was 19.3 ± 0.7 yr (mean ± SD), and all boys had passed puberty and attained their approximate peak bone mass (16, 17). The 2 subjects not participating in the follow-up were both heterozygous for *Bsm*I and *Taq*I and were

not different in physical characteristics, bone area, or BMD, at age 17, than the other subjects in the heterozygote group. Using a questionnaire, the average amount of weight bearing physical activity per week was assessed during the last year. Parents of 60 of the subjects were measured for height, and the height of the parents of 13 subjects was obtained through interviews. All data concerning height and weight of the 90 boys studied at birth were collected through interviews with the parents. Informed written consent was given by all the participants, and the study protocol was approved by the Ethical Committee of the Medical Faculty, Umeå University.

Techniques for estimating bone density and body constitution parameters

BMD (g/cm^2) of the total body, femoral neck, and lumbar spine was measured using a DPX-L dual-energy x-ray absorptiometer (Lunar Corp., Madison, WI), software version 1.3y. The bone area of the total body, humerus, and femur was measured using the same equipment and the region-of-interest option. The precision of this method has previously been discussed in detail by others (18, 19). The CV-value (SD/mean) for repeated measurements is 0.7–2.0% in our laboratory, depending on application (20). All analyses were made by the same investigator.

Genomic DNA analysis

Genomic DNA from the 90 boys was isolated from EDTA-stabilized blood, using the Wizard Genomic DNA Purification Kit (Promega Corp., Madison, WI). Determination of the VDR restriction fragment length polymorphisms (RFLPs) was performed as previously described, with some modifications (1, 21).

Genomic DNA (30 ng) was amplified in a 50-μL reaction mixture, consisting of 0.4 μmol/L forward primer, 0.4 μmol/L reverse primer, and 0.2 mmol/L each of dATP, dCTP, dGTP, dTTP, 1× PCR buffer, and 2.5 U *Taq* polymerase (Roche Molecular Biochemicals, Stockholm, Sweden).

The 825-bp region, in the intron separating exon VIII and IX, containing the polymorphic *Bsm*I site, was amplified using primers 5′-CAACCAAGACTCAAGTACCGCGTCAGTGA-3′ and 5′-AACCAGC GGAAGAGGTCAAGGG-3′ in 35 cycles of 30 sec denaturation at 94 C, 30 sec annealing at 60 C, and 30 sec elongation at 72 C (Peltier Thermocycler; MJ Research, Inc., Watertown, MA).

The 740-bp region, in the intron separating exon VIII and IX and a part of exon IX, spanning the *Taq*I polymorphic site, was amplified with primers 5′-CAGAGCATGGACAG-GGAGCAAG-3′ and 5′-GCAACTC-CTCATGGCTGAGGTCTCA-3′ in 35 cycles of 30 sec denaturation at 94 C, 30 sec annealing at 67 C, and 30 sec elongation at 72 C.

To assure the validity of the PCR amplifications, random samples of each polymorphic region were sequenced (Big Dye sequencing chemistry and ABI 377; Perkin-Elmer Corp., Stockholm, Sweden), and no discrepancies were found, compared with expected sequences.

The amplified products were cleaved with *Bsm*I, and *Taq*I, overnight, according to the manufacturer's recommendations (Roche Molecular Biochemicals), and electrophoresed and analyzed on ethidium bromide-stained agarose gel. The RFLPs were coded Bb and Tt, for *Bsm*I and *Taq*, respectively, where capital letters represent absence and small letters represent presence of restriction fragment sites. To validate the accuracy of the RFLP determination, 8 random patients (of the total 90 patients) were redetermined for all polymorphic sites described above. No discrepancies were found.

Statistical analysis

Differences in physical characteristics, bone density, and bone area between the three groups defined by the VDR genotypes were then investigated using an ANOVA, with Bonferroni's correction for multiple comparisons. A multiple regression analysis was used to estimate the variation in the boys' adult height explained by birth height, birth weight, the parents' mean height, and the VDR genotypes. The VDR genotypes were included as absence (BB) or presence (Bb, bb) of restriction site. The package for PC (SPSS, Inc., Chicago, IL) was used for the statistical analysis. A *P*-value less than 0.05 was considered significant.

Results

The RFLPs were coded B or b for (*Bsm*I). The VDR genotypes were in linkage disequilibrium, and *Bsm*I and *Taq*I genotypes were related in 89 of 90 cases; hence, the same associations were found for both *Taq*I and *Bsm*I alleles. The frequency measurements of the *Bsm*I allelic variants were 14% (BB), 44% (Bb), and 41% (bb).

The *Bsm*I allelic variants were significantly related to birth height and weight increase from birth to age 16.9 ± 0.3 yr (mean ± SD; Table 1). At birth, boys with the BB genotype were shorter than boys with Bb and bb genotypes ($P = 0.01$). Boys with the BB genotype showed less height and weight gain, from birth to age 16.9 ± 0.3 yr (mean ± SD), than their Bb and bb counterparts ($P < 0.05$; Table 1).

Physical characteristics, bone area, and BMD of the 90 boys [age, 16.9 ± 0.3 yr (mean ± SD)] are presented in Table 2. Boys with the BB genotype were significantly shorter ($P = 0.005$) and had lower bone area of the total body ($P = 0.006$), humerus ($P = 0.006$), and femur ($P = 0.007$) than boys with the Bb or bb genotypes (Table 2).

At the follow-up, when all boys had passed puberty and were 19.3 ± 0.7 yr old (mean ± SD), boys with the BB genotype were still shorter ($P = 0.008$) and had lower bone area of the total body ($P = 0.004$), humerus ($P = 0.01$), and femur ($P = 0.02$), compared with boys with the bb genotype (Table 3).

In 73 of the boys, midparent height [(mother's height + father's height)/2], birth height, birth weight, and the VDR allelic variants were used to explain the boys' adult height at 19 yr of age, using multiple regression. Together, these factors explained 39% of the variation in the boys' adult height ($P < 0.0001$). Midparent height (regression coefficient β =

TABLE 1. Birth weight, birth height, weight gain (Δweight), and increase in height (Δheight) since birth, in relation to *Bsm*I polymorphism, in 90 adolescent (17-year-old) boys.

Number of subjects:	90 (total)	Allelic variants			Significance	
		BB 13	Bb 40	bb 37	Whole model	Presence of b allele
Birth height (cm)	50.7 ± 2.2	49.3 ± 2.7	50.7 ± 2.3	51.2 ± 1.8	0.03[a]	0.01[b]
Birth weight (g)	3524 ± 516	3448 ± 591	3485 ± 551	3592 ± 452	0.57	0.57
ΔHeight (cm)	128.6 ± 5.1	125.4 ± 4.9	129.4 ± 4.9	128.9 ± 5.1	0.04[c]	0.01[b]
ΔWeight (kg)	69.0 ± 9.6	63.7 ± 6.5	70.5 ± 11.0	69.2 ± 8.3	0.08	0.03[b]

Means, SDs, and *P* values are presented.
[a] bb > BB.
[b] (bb + Bb) > BB.
[c] Bb > BB.

TABLE 2. Age, anthropometric data, physical activity, bone area, and bone density, in relation to *Bsm*I polymorphism, in 90 17-yr-old men.

Number of subjects:	90 (total)	Allelic variants			Significance
		BB 13	Bb 40	bb 37	
Age (yr)	16.9 ± 0.3	16.8 ± 0.3	16.9 ± 0.4	16.8 ± 0.3	$P = 0.43$
Subjects past puberty (Tanner 5)	67 (74%)	11 (85%)	28 (70%)	28 (76%)	$P = 0.57$
Weight (kg)	72.5 ± 9.6	67.1 ± 6.5	74.0 ± 11.0	72.8 ± 8.3	$P = 0.08$
Height (cm)	179 ± 6	175 ± 6	180 ± 5	180 ± 5	$P = 0.005^a$
Physical activity (h/w)	6.7 ± 4.0	6.0 ± 3.7	7.1 ± 4.3	6.6 ± 3.7	$P = 0.84$
Bone area (cm^2)					
Total body	2643 ± 212	2472 ± 214	2671 ± 208	2673 ± 191	$P = 0.006^a$
Femur	209 ± 23	191 ± 16	214 ± 25	209 ± 21	$P = 0.007^a$
Humerus	75.0 ± 7.9	68.7 ± 8.0	75.6 ± 7.5	76.6 ± 7.5	$P = 0.006^a$
Bone density (g/cm^2)					
Total body BMD	1.22 ± 0.08	1.21 ± 0.06	1.22 ± 0.08	1.22 ± 0.09	$P = 0.78$
Neck BMD	1.22 ± 0.14	1.21 ± 0.14	1.21 ± 0.15	1.24 ± 0.12	$P = 0.65$
Spine BMD	1.25 ± 0.12	1.26 ± 0.12	1.25 ± 0.12	1.25 ± 0.12	$P = 0.91$

Differences were investigated using an ANOVA, with Bonferroni's correction for multiple comparisons. Means and SDs are presented.
[a] BB < Bb, bb.

TABLE 3. Age, anthropometric data, physical activity, bone area, and bone density, in relation to *Bsm*I polymorphism, in 88 19-yr-old men.

Number of subjects:	88 (total)	Allelic variants			Significance
		BB 13	Bb 38	bb 37	
Age (yr)	19.3 ± 0.7	19.5 ± 0.9	19.2 ± 0.6	19.4 ± 0.8	$P = 0.18$
Weight (kg)	78.4 ± 11.8	72.5 ± 8.2	79.9 ± 14.0	78.9 ± 9.9	$P = 0.14$
Height (cm)	181 ± 6	176 ± 5	182 ± 6	181 ± 5	$P = 0.008^a$
Physical activity (h/w)	6.4 ± 3.7	5.5 ± 3.8	6.6 ± 3.5	6.4 ± 3.8	$P = 0.63$
Bone area (cm^2)					
Total body	2788 ± 192	2626 ± 152	2816 ± 178	2815 ± 196	$P = 0.004^a$
Femur	229 ± 27	209 ± 20	233 ± 27	231 ± 27	$P = 0.02^a$
Humerus	88.1 ± 10.5	80.9 ± 8.5	87.8 ± 9.7	90.8 ± 11	$P = 0.01^b$
Bone density (g/cm^2)					
Total body BMD	1.29 ± 0.08	1.27 ± 0.06	1.29 ± 0.08	1.30 ± 0.08	$P = 0.50$
Neck BMD	1.26 ± 0.15	1.26 ± 0.14	1.24 ± 0.17	1.28 ± 0.13	$P = 0.53$
Spine BMD	1.32 ± 0.13	1.35 ± 0.14	1.31 ± 0.12	1.33 ± 0.13	$P = 0.59$

Differences were investigated using an ANOVA, with Bonferroni's correction for multiple comparisons. Means and SDs are presented.
[a] BB < Bb, bb.
[b] BB < bb.

0.46, $P < 0.0001$), birth height ($\beta = 0.41$, $P = 0.006$), and the vitamin D receptor allelic variants ($\beta = 0.22$, $P = 0.03$) were found to be independent predictors. The VDR allelic variants alone contributed to 8% of the total variation.

Discussion

Being able to estimate adult stature is crucial when evaluating GH treatment in children with reduced growth. Parental height and birth height are known to be strong predictors of adult stature (22, 23). According to our prediction model, the VDR genotypes have a substantial explanatory importance (8% of the total variation in adult height) and can, together with birth height, birth weight, and parental height, explain up to 39% of the variation in adult height in our population of men.

A plethora of evidence indicates that vitamin D affects body growth. Vitamin D status is believed to affect intrauterine and postnatal growth (14). Further, vitamin D deficiency, either resulting from insufficient vitamin D dietary intake and deprivation of sunlight exposure or from hereditary defects in the synthesis of 1,25-dihydroxyvitamin D, is associated with growth failure (12, 13). Vitamin D metabolites are crucial in the normal differentiation of chondrocytes in the growth plate (24, 25), and injection of active vitamin D metabolites into the reserve zone of rachitic cartilage promotes endochondral bone formation, because of differentiation of cartilage cells (26, 27). Experimental studies in mice with targeted ablation of the VDR show development of hyperparathyroidism in response to hypocalcemia, and these mice fail to grow as rapidly as their VDR-sufficient littermates, weighing 10% less and having approximately 15% shorter tibias and femurs after 91 days of age (28). A diet known to prevent hyperparathyroidism in vitamin D-deficient rats was able to normalize growth in these animals (29), suggesting that hypocalcemia is the predominate cause of the inhibited skeletal growth, apart from the direct actions of vitamin D metabolites on bone. Recent data show that VDR poly-

morphism, defined by *Bsm*I and Fok1 (30, 31), is associated with intestinal calcium absorption in children and in women, and *Bsm*I alleles have been associated with renal absorption of inorganic phosphate in men (32). If these findings are of physiological importance, they could explain the difference in growth and stature seen in our population.

It has been suggested that the association between VDR gene polymorphism and BMD is influenced by differences in body size (8) or is attributable to variations in bone area (33), among the VDR allelic variants. In the present study, bone area of the total body, humerus, and femur was highly significantly associated with the VDR allelic variants, defined by *Bsm*I, both during late puberty (17-yr-old boys) and after accretion of their approximate peak bone mass (19-yr-old boys) (16, 17), whereas no association with BMD was found.

VDR gene polymorphism has previously been associated with parameters of body size in both female and male infants (6, 7) and adults, but many of these findings are limited by inadequate sample size and homogeny and are not conclusive (8, 9, 33, 34). In 10-month-old boys, the BB genotype was associated with lower body surface area and weight, but not with length, compared with bb boys (6). To our knowledge, there are no previous studies investigating the *Bsm*I alleles and association with growth from infancy to adulthood. In our homogenous population, though limited in size, the BB boys had lower height at birth, less growth up to late puberty (at age 17), and shorter adult stature (at age 19) than their bb counterparts.

It is not known whether the VDR polymorphisms cause functional differences of the VDR, or whether the polymorphisms are merely markers of variations in other genes, causing the phenotypic differences observed in association studies such as the present study. The *Bsm*I polymorphism is located in an intron and the *Taq*I polymorphism in an exon of the VDR. The *Taq*I polymorphism does not cause any amino acid change in the VDR protein (35). Intronic sequences have been shown to be able to alter transcriptional activity (36), resulting in varying messenger RNA levels. It has been reported that there are no differences, with respect to *Bsm*I allelic variants, in levels of VDR expression in either the intestine (37) or in peripheral blood mononuclear cells (38). As of now, no data is available on possible association of the VDR polymorphisms with VDR expression levels in other tissues or cells known to contain VDR, such as the kidney, osteoblasts, or chondrocytes (12).

In conclusion, we show here that VDR gene polymorphism is associated with height at birth, with adult stature, and with bone size both during and after puberty in healthy Caucasian males, implying a significant role of VDR polymorphism in skeletal growth and introducing a new parameter in the prediction model for adult stature.

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Erratum

Corrections have been made to the figure legends in the article "Lactate and glycerol release from subcutaneous adipose tissue in black and white lean men" by Maria-Terésa van der Merwe, Per-Anders Jansson, Nigel J. Crowther, Ivan H. Boyd, I. Peter Gray, Barry I. Joffe, and Peter N. Lönnroth (*The Journal of Clinical Endocrinology & Metabolism* **84:**2888–2895). The authors regret the errors.

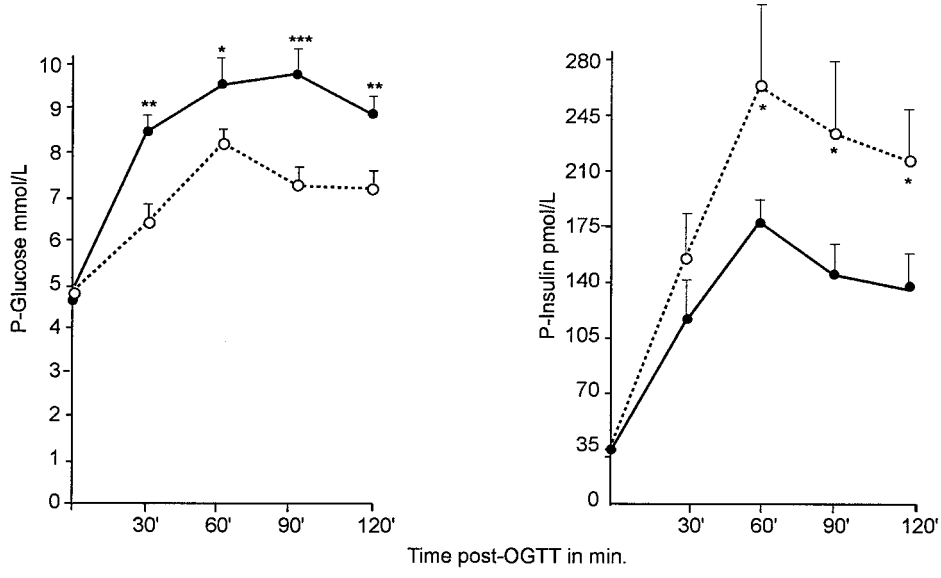

FIG. 1. Glucose and insulin levels during fasting and for 2 h post-OGTT. –■–, Black men (BM); –□–, white men (WM). Data are means ± SEM. Student's unpaired *t* test: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.0001$.

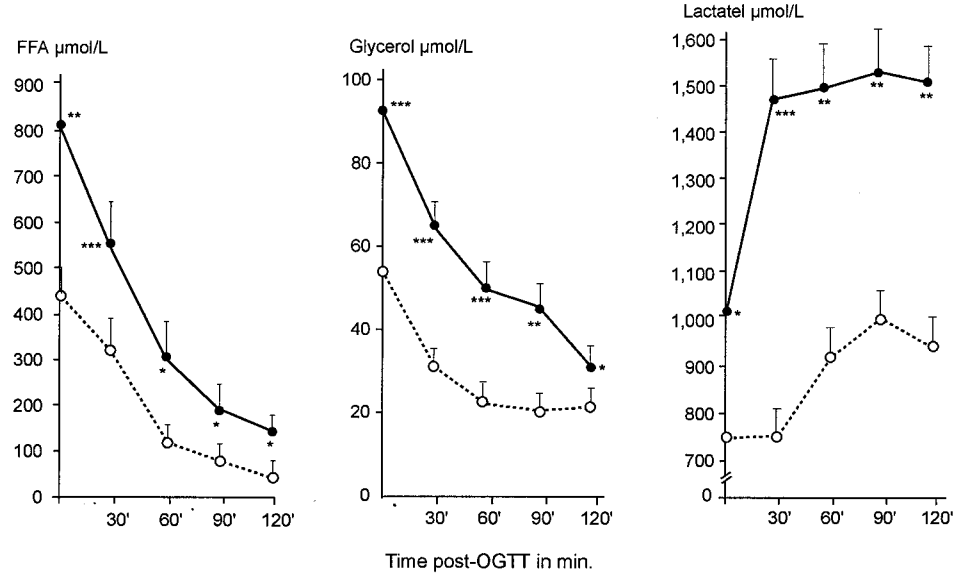

FIG. 2. Plasma FFA, glycerol, and lactate levels during fasting and for 2 h post-OGTT. –■–, Black men (BM); –□–, white men (WM). Data are means ± SEM. Student's unpaired *t* test: for FFA: *, $P < 0.05$; **, $P < 0.005$; ***, $P < 0.001$; for glycerol: *, $P < 0.005$; **, $P < 0.0001$; ***, $P < 0.0001$; for lactate: *, $P < 0.05$; **, $P < 0.001$; ***, $P < 0.0001$.

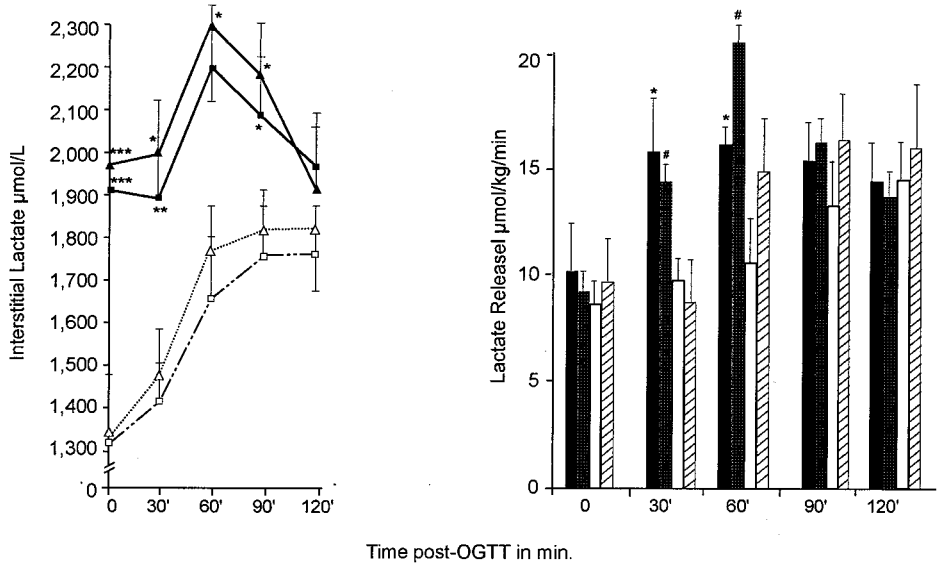

FIG. 3. Interstitial adipocyte lactate levels (*left*) and lactate release from adipose tissue (*right*) during fasting and for 2 h post-OGTT. Black men: ■ –■–, femoral; ▩ –▲–, abdominal. White men: □ –□–, femoral; ▨ –△–, abdominal. Data are means ± SEM. Student's unpaired *t* test: for interstitial lactate values: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$; for lactate release values: *, $P < 0.05$; #, $P < 0.05$.

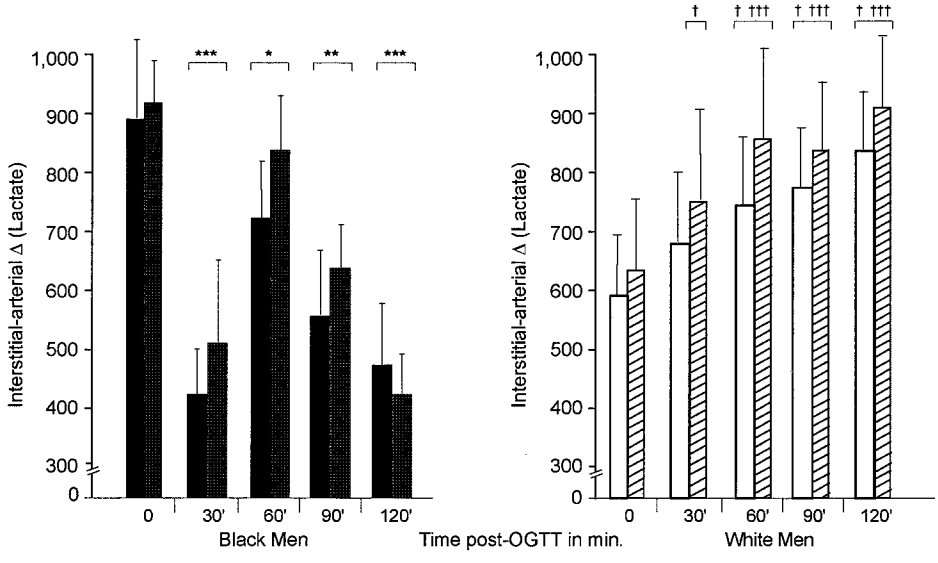

FIG. 4. Interstitial-arterial differences in lactate values for black men (*left*) and white men (*right*). Black men: ■ –■–, femoral; ▩ –▲–, abdominal. White men: □ –□–, femoral; ▨ –△–, abdominal. Data are means ± SEM. *P* = ANOVA for data in each group compared to time 0. For black men: *, $P < 0.05$; **, $P < 0.005$; ***, $P < 0.0005$. For white men: †, $P < 0.05$; ††, $P < 0.01$; †††, $P < 0.005$.

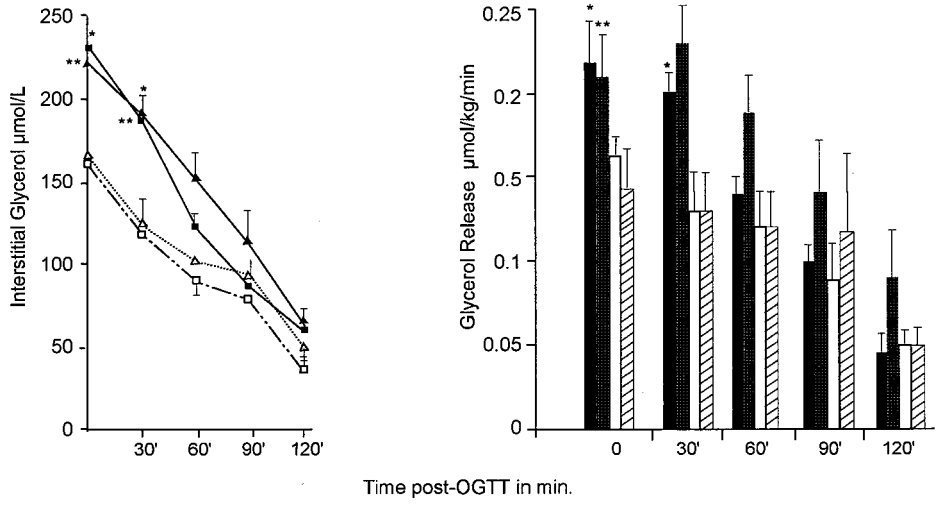

FIG. 5. Interstitial-adipocyte glycerol levels (*left*) and glycerol release values (*right*) during fasting and for 2 h post-OGTT. Black men: ■ –■–, femoral; ▩ –▲–, abdominal. White men: □ –□–, femoral; ▨ –△–, abdominal. For interstitial glycerol values: *, $P < 0.05$; **, $P < 0.01$. For glycerol release values: *, $P < 0.05$; **, $P < 0.01$.