Testosterone and Leptin in Older African-American Men: Relationship to Age, Strength, Function, and Season

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Testosterone (T) and bioavailable testosterone (BT) levels have been shown to decline with aging in Caucasian males. We are unaware of any studies that have examined this in African-American men. Previous studies have suggested a relationship of T to strength and leptin levels, but no such correlation with measured functional tests exists. This study explores these associations in a cross-sectional sample of older African-Americans from the Saint Louis University Inner City Aging Project. The participants were 65 African-American males aged 70 to 102 years. Measurements included T, BT, and leptin levels, isometric muscle strength, and relevant physical impairments. Statistical analysis included a *t* test and simple and multiple ordinary least-squares regression. Age was inversely related to T and BT. Of these older African-American males, 90.7% had a BT value less than the normal range for young males. T correlated with upper- and lower-limb strength and functional tests. Leptin was correlated with the body mass index (BMI) and inversely with T, but not with BT. Circannual rhythms for T, BT, and leptin were present. This study demonstrates for the first time an age-related decrease in T and BT in African-Americans and a circannual rhythm for leptin. T was correlated with upper- and lower-limb strength and functional status.

NUMEROUS CROSS-SECTIONAL studies have now demonstrated that total testosterone (T), bioavailable testosterone (BT), and free T decline with age.[1-11] This has been confirmed by a longitudinal study.[12] The rate of decline is on the order of 1% to 2% yearly after the age of 30 years.[13] There is an increase in sex hormone–binding globulin with age, making the decline in BT and free T greater than the decline in total T levels. Most of the available data on the decrease in serum T with age have been derived from studies in Caucasian males of Western European descent. Little information is available concerning whether this decline in T occurs in persons of other ethnic origins, eg, African-American men.

Cross-sectional[14] and interventional[15-17] studies in whites have suggested an effect of T on muscle mass and strength. However, no studies have examined the relationship of T to functional status.

Leptin is a protein hormone produced by adipose cells that modulates food intake and the metabolic rate.[18] Leptin levels decline with age in females.[19] Females have higher leptin levels even when corrected for adipose tissue mass.[20] Recently, both cross-sectional and longitudinal studies have found that in contradistinction to females, leptin levels increase with age in males.[21-23] T treatment results in a decline in leptin levels in young and older hypogonadal males.[16,24] Thus, there is some evidence that T may regulate leptin levels separately from its effects on adipose tissue mass. Again, most data on leptin levels have been reported in subjects of Caucasian origin, although leptin values in postmenopausal African-American women have been reported.

Our group is in the process of an ongoing epidemiological study of inner-city African-Americans. The full characteristics of this population have been reported previously.[25,26] In this study, we have examined T, BT, and leptin levels in a subset of males in this population. In addition, we have examined the relationship of T and leptin to strength and function in this population. Finally, as samples were obtained at different times during the year, we examined whether there is a circannual rhythm in the serum level of T and leptin.

SUBJECTS AND METHODS

Participants were 65 African-American men aged 70 to 102 years who were recruited from a larger study of frailty in community-dwelling African-Americans living in the inner city of St. Louis. The mean age of this subpopulation was 79.2 ± .9 years. All subjects were free-living in the city of St. Louis.

Strength and Physical Function

The strength assessment was made by testing isometric muscle strength (handgrip strength, shoulder abduction, hip abduction, extension, and flexion, knee extension, and ankle dorsiflexion). Physical function was assessed through timed performance tests (panel of doors) and the following tests of dynamic muscle strength and gait and balance: (1) repetitive sit and stand, (2) walking speed, (3) ''get up and go,'' and (4) one-leg stand. These tests were selected because they measure a spectrum of physical abilities important for daily activities and are easily performed and tested in a clinical setting with simple equipment.

Functional assessment. The following timed tasks were used as part of the performance testing in this study: simulated eating, opening a door knob, closing a door knob, opening a drawer lock, and closing a drawer lock. A single score for all 5 tasks was also created by summing the time required to perform each task. Simulated eating was measured using the method of Jebsen et al,[27] which involves timing subjects as they use a spoon to transfer 5 beans 1 at a time from a bowl to a coffee can. Timing is from the word ''go'' until the last bean is heard hitting the bottom of the can. The panel of doors used in this study (door knob and drawer lock) is similar to the panel of doors used in the short version (Timed Manual Performance Doors Test) by Williams et al[28] (door knob, open round knob, and cabinet lock).

Strength assessment. Handgrip strength was tested using the Jamar handgrip dynamometer (J.A. Preston, Jackson, MS). Two trials were performed with each (right and left) hand, and the better score of 2 trials on the stronger side was recorded.[29] Other tests of strength[30] were

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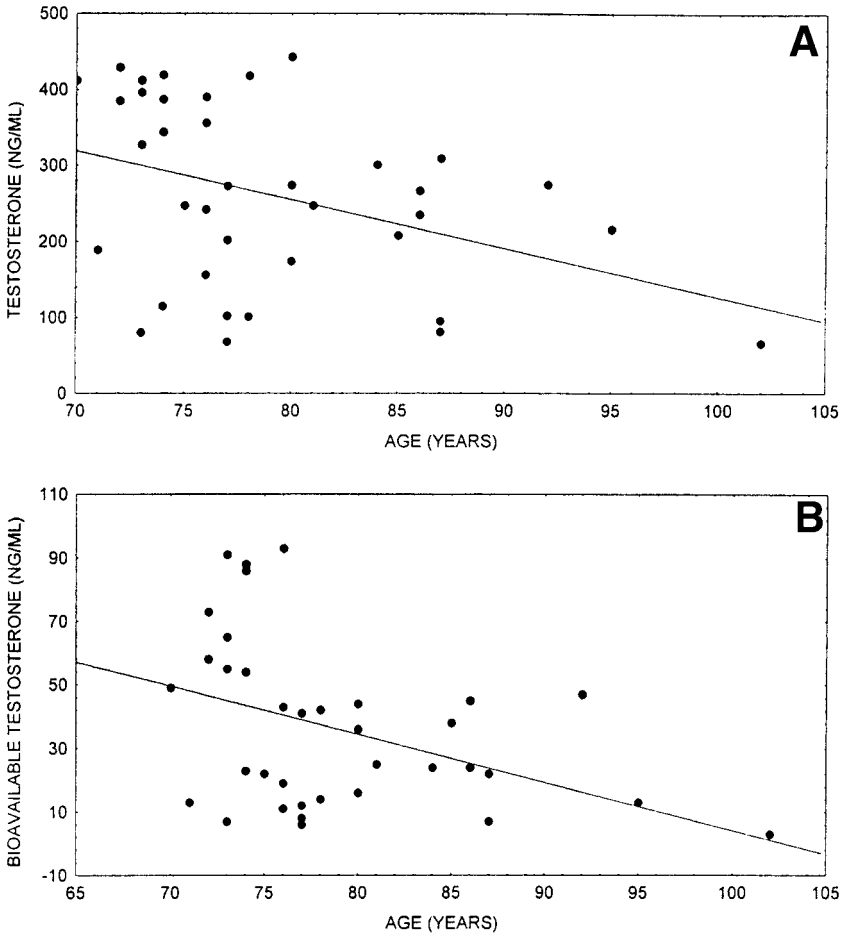

Fig 1. Age versus (A) serum testosterone ($r = -.384$) and (B) serum bioavailable testosterone ($r = -.413$) in older African-American men.

performed using a hand-held isometric dynamometer (Micro-Fet; Hogan Health Industries, Draper, UT) and the break test. These tests were performed once on the right side and once on the left side, and the better performance of the 2 sides was used in the analysis. Shoulder abduction and hip flexion tests were performed with subjects in the seated position using a firm chair without arms with the chair seat 45 cm from the floor. Knee extension and ankle dorsiflexion were performed with the subject sitting on an examination table with the legs dangling freely. Subjects gripped the table sides with their hands for stabilization. Hip abduction was performed with the subject lying on the side on an examination table, and hip extension was examined with the subject lying across the examination table. Shoulder abduction strength was measured with the shoulder abducted 90°, elbows flexed 90°, and palms facing the floor. The dynamometer was placed just proximal to the elbow on the lateral surface of the arm. Hip flexion strength was measured with the knees and hips at 90°, arms at rest, and feet resting on the floor within the margins of the pelvis. The subject then lifted his foot without the help of the arms or other upper-body muscles. The dynamometer was placed just proximal to the knee on the extensor surface of the thigh. Knee extension was performed with hips and knees at 90° and then having the subject bring the knee into full extension and dropping and holding the lower leg at approximately 20°. The dynamometer was placed over the distal one third of the anterior surface of the tibia/fibula. Ankle dorsiflexion was measured with the shoe on and knee extended, and then having the subject pull their toes up and in. The dynamometer was placed along the first metatarsal just proximal to the metacarpophalangeal joint. The researcher used the opposite hand to stabilize the heel and was careful to watch for substitution caused by external rotation of the hip. For each individual strength test, subjects were coached to ''hold, hold, hold'' using the ''break test.''[31] Four individuals outside the study population were each tested five times over a 7-day span using this protocol. The coefficient of variation for each muscle group reported here was as follows: shoulder, 5.8% ± .7% (mean ± SEM); hip, 9.3% ± 2.1%; knee, 8.8% ± 1.9%; and ankle, 4.8% ± 8%.

Performance assessment. The time required for a subject to stand and sit 5 times consecutively was measured. This type of test has been standardized previously (for ages 20 to 85).[32] It assesses physical functional ability, but also has been shown to correlate well with

Table 1. Correlation Coefficients for Strength and T, BT, and Leptin

	Handgrip		Shoulder		Hip Flexors		Hip Extensors		Hip Abductors		Ankle	
Variable	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
T	.391	.009	.386	.010	.329	.04	.451	.006	.456	.005	.379	.018
BT	.257	.091	.348	.021	.294	.070	.495	.003	.360	.031	.312	.053
Leptin	−.077	.629	−.026	.873	−.073	.672	−.043	.817	.151	.401	−.023	.896

Table 2. Correlation Coefficients for Functional Testing and Serum Androgens

	Doors		Walk at Preferred Gait Speed for 6 m		Get Up & Go		5 Chair Stands		Beans	
Variable	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
T	−.306	.049	−.362	.088	−.296	.064	−.341	.027	−.267	.079
BT	−.344	.026	−.506	.007	−.324	.039	−.256	.123	−.233	.154
Leptin	.138	.379	.315	.125	.222	.180	.147	.365	.241	.120

lower-extremity (knee flexor and extensor) muscle strength. For this study, it was categorized as a measure of physical function.

A timed ''get up & go'' test was performed as previously reported[30] by having the subject rise from an armless chair, walk 3 m, turn around, walk back to the chair, and sit down.[33]

Serum Analysis

A nonfasting random blood sample between 8 AM and noon was obtained from each participant. The serum 25-hydroxyvitamin D level was measured in duplicate using a competitive protein binding assay (Incstar, Stillwater, MN). T and BT levels were measured as previously described.[7] The intraassay and interassay coefficient of variation was 5.8% and 10.4% for T and 4.7% and 5.8% for BT. The leptin level was measured as previously described.[34] The intraassay coefficient of variation for leptin was 4.7% and interassay coefficient of variation 5%. The date the sample was obtained was coded by month (January 1 through December 12). The seasons were considered as follows: spring included samples obtained from April 1 to June 30 and summer samples were obtained from July 1 to September 30, etc.

Data Analysis

Data are presented as the mean ± SEM and were evaluated using Student's unpaired *t* test and both simple and multiple ordinary least-squares regression. The analysis was performed on a personal computer using commercially available software (Statistica Statsoft, Tulsa, OK).

RESULTS

Age was significantly and inversely related to serum T and BT (Fig 1). Not surprisingly, T and BT were highly correlated ($r = .774$, $P < .0001$). Overall, 66.1% of the men had T levels below the normal range for young males (300 ng/dL) and 90.7% had BT levels below the normal range for young males (70 ng/dL). Serum T was positively correlated with upper- and lower-extremity strength in all muscle groups tested (Table 1). BT was not correlated with handgrip but was correlated with the other muscle groups tested, although not all *P* values reached

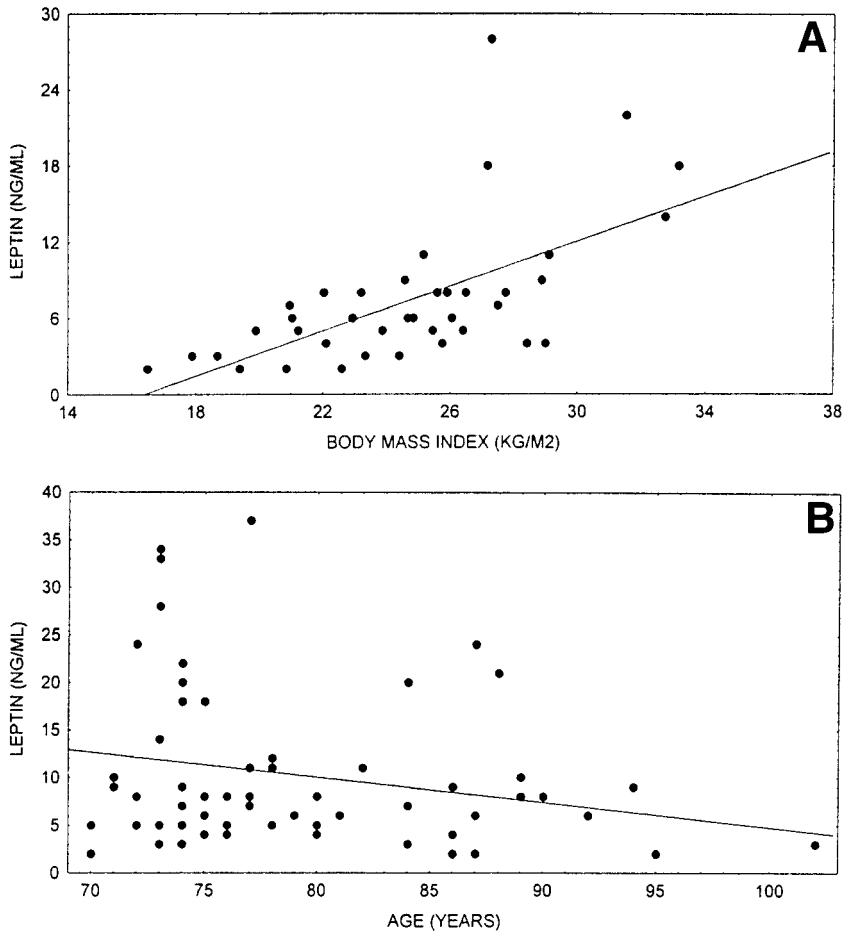

Fig 2. (A) BMI versus leptin ($r = .608$) and (B) age versus leptin ($r = -.224$) in older African-American men.-

conventional levels of statistical significance. The correlations for T with muscle strength were better than those for BT. Both T and BT were correlated with upper-limb functional status using the doors test (Table 2). In addition, T was correlated with lower-extremity function as measured by the 6-m walk, ''get up & go,'' and 5 chair sit/stand tests. BT was significantly correlated with the 6-m walk and ''get up & go'' tests.

Leptin levels were not correlated with strength and function (Tables 1 and 2). There was a highly statistically significant correlation between the body mass index (BMI) and serum leptin ($r = .556$, $P < .001$; Fig 2A). Leptin levels tended to be inversely correlated with age ($r = -.228$, $P = .09$; Fig 2B). This correlation remained when leptin levels were corrected for the BMI. In addition, serum leptin was inversely correlated with serum T ($r = -.32$, $P = .012$; Fig 3A), but not with BT ($r = -.129$, $P = .133$; Fig 3B).

In this study, we analyzed T and BT data for seasonal changes ($r = .406$, $P = .003$ and $r = .362$, $P = .005$, respectively; Fig 4). Both T and BT vary significantly with the seasons. The peak for both occurs in late winter, with the nadir occurring around August. Neither strength nor functional testing were significantly related to season (data not shown). Leptin also varies significantly by season ($r = .297$, $P = .033$; Fig 5), with the peak occurring in September and the nadir in January. The BMI does not vary significantly by season ($r = .06$, NS).

DISCUSSION

This cross-sectional study demonstrates for the first time that T and BT decline with age in African-Americans. The magnitude of the change was similar to that previously reported in persons of Caucasian descent from Europe.[1-11] As in previous reports,[5,7,35] there was a greater percentage of older persons with low BT as compared with low T. This is presumably because sex hormone–binding globulin increases with age, as demonstrated in a longitudinal study.[12]

A previous cross-sectional study has suggested that the decline in muscle mass in older men is related to physical activity, free T, and insulin-like growth factor-I,[14] and in a previous study of highly healthy individuals, we found that BT was the major independent associate of the decline in upper-body muscle strength with age.[7] This study confirms the putative role that T may play as a determinant of both upper- and lower-body strength.[36]

T has well-established anabolic effects on muscle tissue.[36] In addition, interventional trials in older hypogonadal men have demonstrated improved strength with T therapy.[15-17] Thus, our findings further confirm the putative role of T in maintaining strength in older males.

Physical function declines with age, although considerable individual variation is present.[37] Performance tests with function have been shown to correlate well with the self-reported

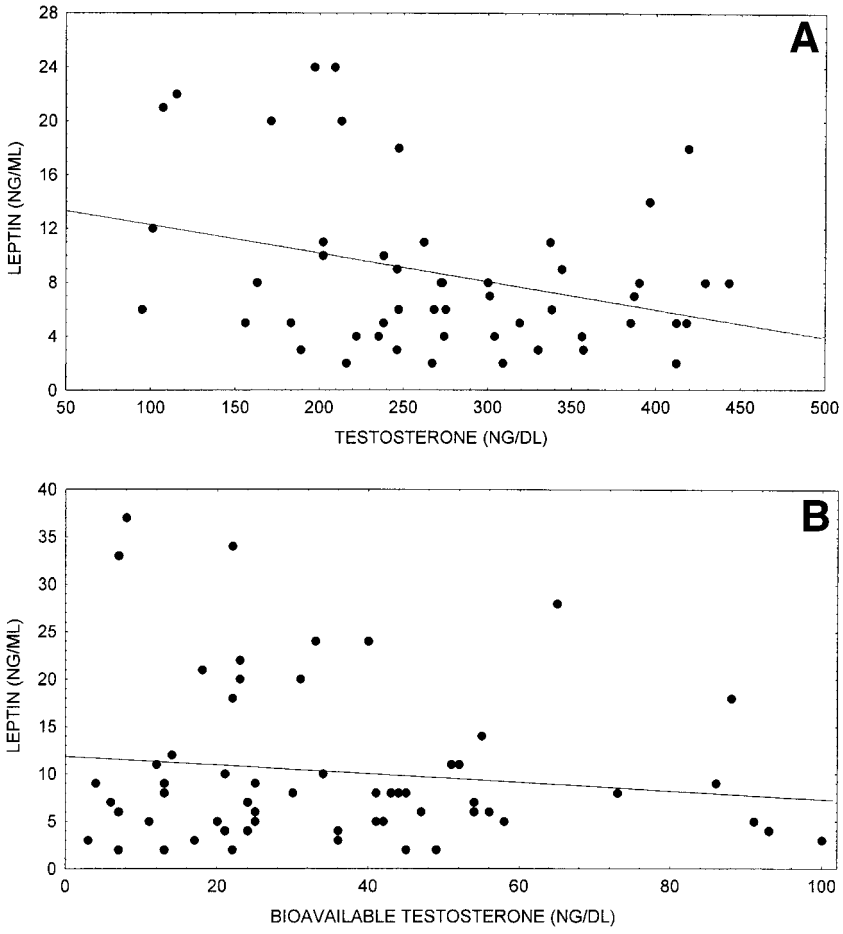

Fig 3. (A) Serum testosterone versus serum leptin ($r = -.320$) and (B) bioavailable testosterone versus serum leptin ($r = -.129$) in older African-American men.

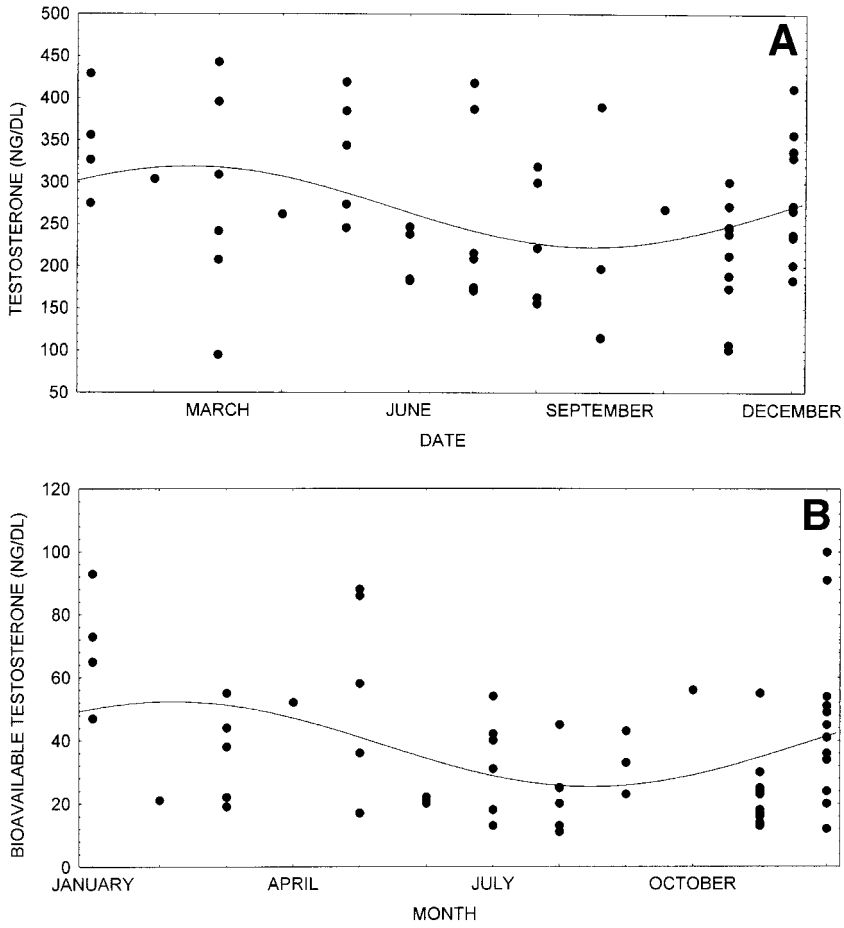

Fig 4. (A) Serum testosterone versus month specimen was obtained (r = .406) and (B) serum bioavailable testosterone versus date obtained (r = .362) in older African-American men.

disability, prediction of mortality, and nursing home admission.[38] The ability to perform satisfactorily on functional testing depends on both muscle strength[39] and, in some cases, cognitive function.[40] Studies in animals and humans have suggested that in addition to enhancing muscle strength, T may improve cognitive function.[41-43] This study demonstrates for the first time a correlation of T with measured upper (doors) and lower functional status. This suggests that the effects of T on other systems are integrated in older persons, and T replacement may improve function in older males.

A number of studies both longitudinal and cross-sectional have suggested that there is a circannual variation in T levels.[44-48] This circannual rhythm persists in older individuals.[49,50] The two most recent studies have found the T nadir to occur in August,[44,45] similar to the finding in our study.

Leptin is a peptide hormone produced by adipose tissue that plays a role in the regulation of food intake and the metabolic rate.[18] Females have higher leptin levels than males, and with aging, circulating leptin levels decline in females.[20,51] In Caucasian males, leptin increases with age both cross-

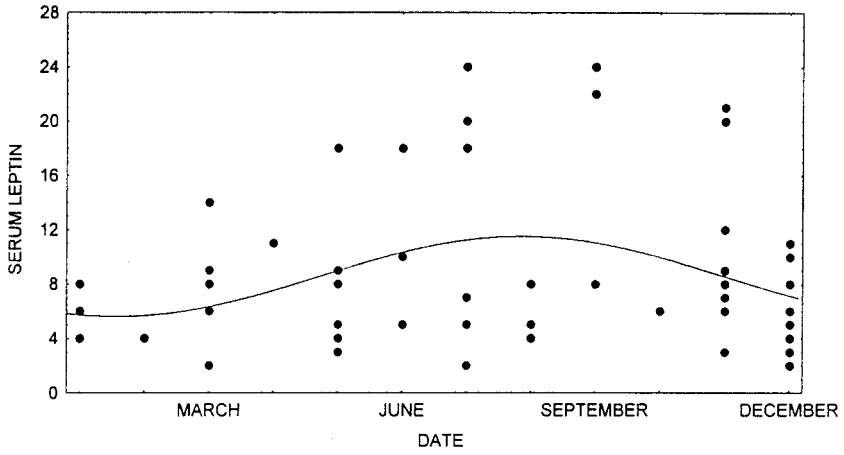

Fig 5. Serum leptin versus month specimen was obtained in older African-American men (r = .297).

sectionally and longitudinally.[21-23] This increase is related to the decline in T with aging.[23] T replacement results in a decrease of leptin levels.[15,24] It has been suggested that the elevated leptin in older males plays a role in the pathogenesis of the anorexia of aging.[52] This study demonstrated an inverse correlation of serum leptin to T in men.

In all studies, leptin is highly correlated with body fat and the BMI.[19,20,23,32] In this study, we found a similar correlation of leptin with the BMI. However, leptin failed to correlate with strength or function in this cohort. Leptin levels demonstrated a mirror image of the circannual rhythm of T. This cross-sectional study represents the first indication that leptin levels have a circannual rhythm. Further studies are necessary to confirm this finding.

It should be recognized that the results of this study are obtained from cross-sectional data and do not provide direct evidence of cause and effect. In addition, our study sample is composed of ambulatory, relatively poor, inner-city community-dwelling African-Americans.[25,26] Many of these adults have borderline self-reported instrumental activities of daily living[25] and are at high nutritional risk.[26] These later factors may have allowed some unmasking of the relationship of functional status to T that would have been less apparent in a healthier population. However, only one of the subjects had an albumin level less than 3.5 g/dL, and there was no relationship between T and albumin ($r = .154$, NS). This suggests that the nutritional status was not a major confounder in this population. However, it is not possible in this population to clearly delineate whether the decrease in T is predominantly due to aging or if disease played a significant role in its decline. Multiple diseases have been associated with decreased T levels,[53] and in our population, diabetes mellitus is associated with poorer functional status.[30] Again, none of the subjects in this subset of the population had severe uncontrolled disease, and all had intact basic activities of daily living.

The decline in muscle mass and strength has been well documented in older males, and there is some evidence that these losses accelerate beyond the age of 65 years.[54] These losses are associated with impaired functional performance and increased disability and falls.[38] This study has demonstrated a strong correlation between the decline in T and the decline in muscle strength and function in males. It also provides further evidence for a role of T in the regulation of leptin production. The available literature suggests that the effect of T on leptin is separate from its effect on adipose tissue mass.[55]

This study is the first to demonstrate a clear age-related decline in T and BT in African-American males. The association of lower T and BT levels with greater physical impairment is also demonstrated for the first time. The circannual rhythm of leptin, which is inversely related to that of T, represents a unique observation requiring further clinical investigation.

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