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Resting Metabolic Rate and Respiratory Quotient in Human Longevity

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Significant changes in body composition, body fat distribution, and resting metabolic rate (RMR) occur with aging. Interestingly, studies on human longevity pointed out that long-lived subjects are less prone to the anthropometrics and metabolic derangement normally observed in the elderly. Indeed, the relationship between energy expenditure and longevity has been poorly investigated. Thus, energy expenditure parameters of 28 long-lived subjects were assessed and compared with those of 26 adults and 27 younger elderly. All subjects enrolled were female.

In the whole population, RMR was negatively correlated with age ($P < 0.05$), waist to hip ratio (WHR) ($P < 0.001$), fat mass ($P < 0.001$), and percent body fat ($P < 0.03$); respiratory quotient (Rq) displayed an age-related decrease ($P < 0.001$) and was negatively correlated with WHR ($P < 0.001$) and fat-free mass (FFM) ($P < 0.006$). In multivariate analysis, both RMR and Rq had FFM, WHR, but not body mass index as significant and independent determinants. Splitting the whole study group into subgroups according to age, long-lived subjects had oxygen volume, carbon dioxide volume, and Rq significantly higher than aged subjects but lower than adult subjects. In addition, long-lived subjects had total volume of expired air and RMR greater than aged subjects but not different from ones found in adults. In long-lived subjects, Rq was negatively correlated with percent body fat ($P < 0.02$), plasma glucose ($P < 0.05$), free fatty acid ($P < 0.05$), and WHR ($P < 0.05$), whereas RMR was negatively correlated with WHR ($P < 0.05$). No significant associations of RMR and Rq with FFM were found. In conclusion, our data demonstrate that human longevity seems protected toward an age-related decline. It is likely that the lack of the anthropometrics derangement may preserve long-lived subjects from the age-related decrease in energy metabolism. (*J Clin Endocrinol Metab* 90: 409–413, 2005)

AGING HAS BEEN frequently associated with significant changes in body composition, body fat distribution, and resting metabolic rate (RMR) (1–5).

Interestingly, previous evidence has shown that RMRs decrease with age (1–5) and that this reduction is dependent on the relationships among energy intake, energy expenditure, changes in body composition, and physical activity (6–9). In particular, it has been hypothesized that age-related loss of muscle mass may influence energy expenditure involving both central as well as peripheral cellular mechanisms (10, 11). Indeed, further studies (12, 13) have also underlined the influence of fat distribution, demonstrating that the correlation between fat-free mass (FFM) and RMR is relatively modest.

Previous studies on human longevity (3) focused their attention on anthropometrics (3) and endocrine (14, 15) and metabolic (16–18) characteristics of long-lived subjects and pointed out that such a group of subjects are less prone to the anthropometrics and metabolic derangement normally observed in the elderly. In particular, human longevity has been shown to be associated with lower body fat and waist to hip ratio (WHR) and with preserved insulin action compared with aged subjects. Due to the impact that anthropometrics features have on energy expenditure, one would also expect that human longevity is also associated with different energy expenditure and respiratory quotient (Rq) than ones reported in the elderly.

Notwithstanding, the relationship between energy expenditure and longevity has been poorly investigated. To address such an aim, RMR and Rq were evaluated in human longevity and compared with those in adults and aged subjects.

Subjects and Methods

Subjects

Eighty-one females were divided into three groups: adults (<65 yr old; n = 26), aged subjects (age range 66–94; n = 27), and long-lived subjects (>95 yr old; n = 28) volunteered for the study. All subjects enrolled were prescreened to evaluate their eligibility to participate to the study. Clinical information was obtained by routine laboratory analyses, anamnesis, and physical examination. Hypertensive and diabetic patients or subjects with secondary or Alzheimer dementia or using medications affecting body composition or RMR or Rq were excluded from the study. Furthermore, all subjects that conducted a vigorous physical activity as well as the subjects confined to bed were also excluded from the study. Long-lived subjects conducted a sedentary life but were all self-sufficient. Inclusion criteria were a stable body weight (±2 kg) in the last 6 months, no smoking, and liver, kidney, and thyroid functions within normal range.

All subjects that respected the inclusion criteria were enrolled, assigned, and underwent, for a 2-wk period before the calorimeter eval-

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Abbreviations: %BF, Percent body fat; BMI, body mass index; FFA, free fatty acid; FFM, fat-free mass; FM, fat mass; RMR, resting metabolic rate; Rq, respiratory quotient; TV, total volume of expired air; VCO_2, carbon dioxide volume; VO_2, oxygen volume; WHR, waist to hip ratio.

uation, to a standard diet (50% carbohydrates, 27% fats, and 23% proteins) with daily caloric value of 1500 kcal, according to previous World Health Organization recommendations (19, 20) and considering both the mean age (73 ± 20 yr) and the mean body mass index (BMI) (22.9 ± 2.4 kg/m^2) of our study population.

At the end of the 2 wk, blood samples were collected in the morning after the participants had been fasting for at least 12 h and the day before they underwent the calorimeter evaluation. Glucose level was immediately quantified by an enzymatic colorimetric assay. Several 0.5-ml aliquots of serum were immediately processed and stored at −20 C and subsequently used for the assessment of total cholesterol, triglycerides, free fatty acid (FFA), and total proteins. Premenopausal women had all measurements made during the follicular phase of the menstrual cycle, whereas postmenopausal women were not receiving hormone replacement therapy.

All subjects gave written informed consent to participate in the study, which was approved by our Ethical Committee.

Anthropometrics parameters

Weight and height were measured by using a standard beam balance scale. BMI was calculated as body weight (kilograms) divided by height squared (meters). Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest and hip circumference at trochanter level. Both circumferences were measured to the nearest 0.5 cm with a plastic tape, and the ratio between them provided the WHR.

Skinfold thickness measurements were taken from the triceps and subscapular with a Harpenden (British Indicators Ltd., London, UK) skinfold caliper. All skinfold thickness measurements were taken on the right side of the body. With the elbow extended and relaxed, the triceps skinfold thickness was measured on the midline of the posterior aspect of the upper arm. The subscapular skinfold thickness was measured as a diagonal fold 1–2 cm from the inferior angle of the scapula.

Anthropomorphic techniques including measurements of skinfold thickness at various sites are used in various equations to predict body density and body fat. Due to its ease of use, measurements of skinfold thickness are one of the most commonly used techniques.

The equation of Durnin and Womersley (21) predicts body density (kilograms per liter) and follows the form: $A - B \times \log C$, where A and B are constants depending on the subject's age and gender, and C is the sum of triceps and subscapular skinfold measurements in mm. To convert body density to percent body fat (%BF), the Brozek equation was used: %BF = (457/body density) − 414.2 (22). FFM was calculated as the difference between each subject's characteristics body weight and body fat mass (FM).

Despite all limitation related to derived body composition equation, we chose to use the simplest technique available allowing us to estimate body composition even in long-lived subjects contacted at home or in institutions. In fact, due to all the difficulties related to very old people such as long-lived subjects, more accurate techniques for the assessment of body composition, such as DEXA and doubly labeled water, would not be easily applicable to our study population.

Analytical methods

Fasting plasma glucose, total cholesterol, triglycerides, FFAs, total proteins, albumin concentrations, and blood cells counts were determined by routine laboratory methods. All plasma samples for metabolites determinations were drawn after a 12-h overnight fast. Twenty-four-hour collection of urine urea nitrogen was obtained in all subjects.

Mini Mental State Examination was used to assess cognitive function.

Energy expenditure analysis

RMR was assessed by a portable indirect calorimeter (Cosmed K4 b2, Cosmed, Rome, Italy) for 60 min. The device is a lightweight system that measures the total volume of expired air (TV), oxygen volume (VO_2) consumed in liters per minute, carbon dioxide volume (VCO_2) expired in liters per minute, Rq as the ratio of VCO_2 to VO_2, heart rate, and respiratory frequency. It consists of a face mask (with the photoelectric turbine which measures minute ventilation), a portable unit, an electrode to record heart rate, and a battery pack. Each morning before the RMR measurements, K4 was calibrated by using a calibration gas mixture with the known composition (16% O_2; 5% CO_2).

The test was made in a comfortable supine position, with an environmental temperature of 22–23 C. All measurements were done in the morning (0700–0900 h) after a 12-h fast and a minimum of 8 h sleep.

Abstention (12 h) from any strenuous exercise before the RMR and Rq measurements was also requested for aged and adult subjects. The last 30 min of steady state of each experiment was kept for measurement.

To test the precision and accuracy of measurements made by the K4 system, 21 subjects in random order had respiratory parameters compared with those obtained by another device (Deltatrac II Monitor, Datex, Helsinki, Finland), which is an open-circuit ventilated canopy measurement system. A significant correlation ($r = 0.9$, $P < 0.001$) between the two apparatus was found.

Statistical analyses

Data were analyzed by using the SPSS for Windows (version 10, SPSS Inc., Chicago, IL) statistical software package. ANOVA for evaluating differences among the three study groups was used. Pearson product-moment correlation was calculated to test associations among variables. Partial correlation analysis allowed us to evaluate the association among indirect calorimetry variables and anthropometric and metabolic parameters after controlling for BMI and TV. Furthermore, multivariate linear regression analyses were used to test the independent association

TABLE 1. Clinical characteristics of the study groups

	All subjects (n = 81)	Adult subjects (n = 26)	*P*	Aged subjects (n = 27)	*P*	Long-lived subjects (n = 28)
Age (yr)	73 ± 20	49 ± 6	0.001	73 ± 6	0.001	97 ± 2[a]
Body weight (kg)	61.1 ± 9.7	67.2 ± 7.3	NS	64.9 ± 6.3	0.001	51.6 ± 7.1[a]
BMI (kg/m^2)	22.9 ± 2.4	24.2 ± 2.4	NS	23.2 ± 2	0.008	21.6 ± 2.1[a]
WHR	0.82 ± 0.002	0.81 ± 0.009	0.001	0.84 ± 0.01	0.001	0.80 ± 0.01
Triceps skinfold thickness (mm)	21.5 ± 2.6	24 ± 0.8	0.001	21 ± 1.2	0.001	18 ± 0.9[a]
Subscapular skinfold thickness (mm)	18.4 ± 3.0	20 ± 2	0.001	18 ± 3	0.02	16 ± 3[a]
% BF	23.4 ± 2.0	20 ± 0.4	0.001	24 ± 0.4	0.001	25 ± 0.7[a]
FM (kg)	14.2 ± 2.0	13.9 ± 1.5	0.001	15.7 ± 1.5	0.001	13.1 ± 1.8
FFM (kg)	46.8 ± 8.1	53.3 ± 5.8	0.007	49.2 ± 4.7	0.001	38.5 ± 5.2[a]
Fasting plasma glucose (mg/dl)	98 ± 13	99 ± 3	0.002	105 ± 7	0.001	90 ± 19[a]
Fasting total cholesterol (mg/dl)	184 ± 32	188 ± 28	NS	198 ± 15	0.001	168 ± 40[a]
Fasting triglycerides (mg/dl)	110 ± 24	111 ± 19	NS	122 ± 21	0.001	98 ± 25[a]
FFAs (mmol/liter)	357 ± 31	341 ± 8	0.001	398 ± 12	0.001	331 ± 10[a]
Fasting total protein (g/liter)	7 ± 0.4	7 ± 0.2	NS	6.9 ± 0.2	NS	7 ± 0.7
Fasting plasma albumin (g/liter)	3.8 ± 0.6	3.9 ± 0.4	NS	3.7 ± 0.5	NS	3.8 ± 0.7
Mini Mental State Examination	27 ± 1	29 ± 1	0.001	26 ± 1	0.01	25 ± 1[a]

NS, Not significant.

[a] Significantly different from adult subjects, $P < 0.05$.

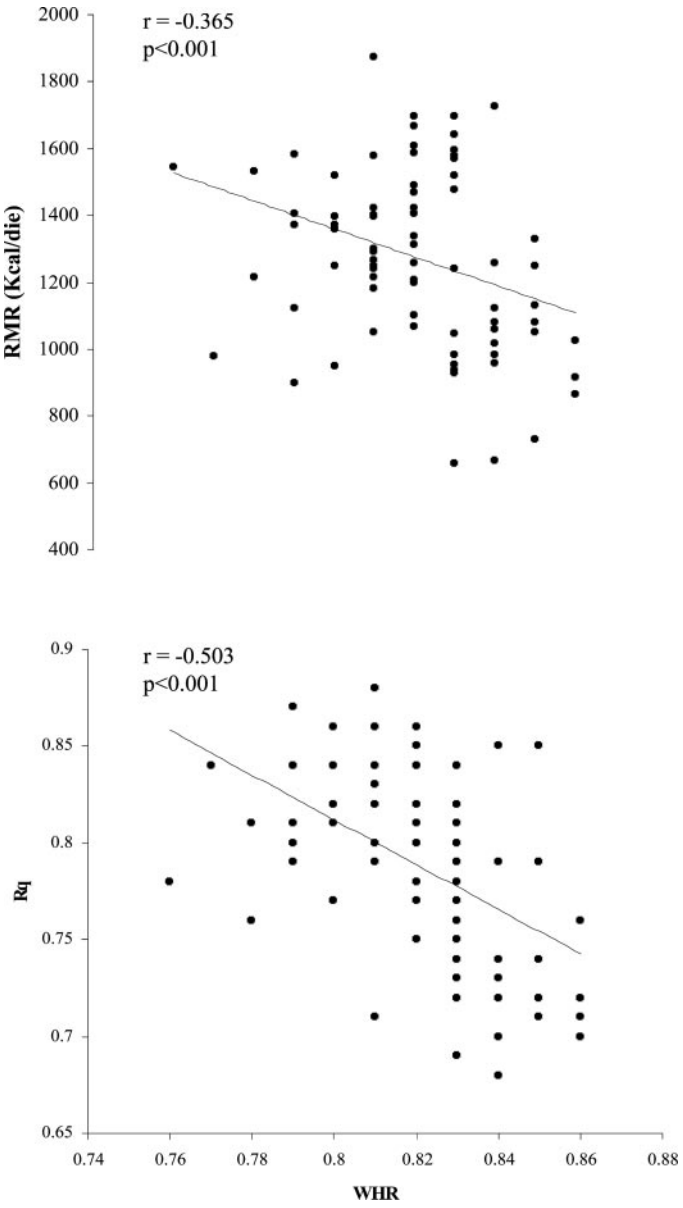

FIG. 1. Simple correlation analysis among WHR, RMR, and Rq.

of age, BMI, WHR, FFM, plasma glucose levels, and TV with RMR and Rq. All data are presented as mean ± SD.

Results

All subjects (n = 81) were not obese or malnourished and had plasma glucose and lipid parameters within laboratory range (Table 1). Cognitive function was also normal after correction for age and scholarity. In such study group, RMR was negatively correlated with age ($r = -0.561$, $P < 0.05$), WHR ($r = -0.365$, $P < 0.001$) (Fig. 1), FM ($r = -0.387$, $P < 0.001$), and %BF ($r = -0.240$, $P < 0.03$); similarly, Rq displayed an age-related decrease ($r = -0.240$, $P < 0.001$) and was negatively correlated with WHR ($r = -0.503$, $P < 0.001$) (Fig. 1), FM ($r = -0.302$ $P < 0.006$), %BF ($r = -0.483$, $P < 0.001$), and glucose plasma levels ($r = -0.291$, $P < 0.001$). All these associations were also independent of BMI and TV (data not shown). To evaluate the relationship between RMR or Rq and anthropometrics parameters, multiple regression analyses (n = 81) were also made. In such analyses, RMR and Rq were the dependent variables, whereas age, BMI, FFM, plasma glucose levels, and TV were the independent variables. The whole model explained almost 40% variability for both RMR and Rq. In particular, WHR, FFM, and TV were significant determinants of RMR, whereas age, WHR, FFM, and plasma glucose levels were significant determinants of Rq (Table 2).

Splitting the whole study group into three subgroups according to age and human longevity was associated with a significant lower body weight, BMI, FFM, FM, fasting plasma glucose, FFAs, total cholesterol, and triglyceride levels than ones found in aged and adult subjects (Table 1). In contrast, %BF had an opposite trend. Furthermore, in human longevity, WHR was significantly lower than aged subjects but not significantly different from ones of adults (Table 1).

Indirect calorimetry parameters for each age group are reported in Table 3. Long-lived subjects had VO_2, VCO_2, and fasting Rq significantly higher than aged subjects but lower than adult subjects. In addition, long-lived subjects had TV and RMR greater than aged subjects but not different from ones found in adults. Difference in RMR between long-lived subjects and aged subjects persisted after adjustment for TV (1292 ± 235 *vs.* 1164 ± 301 kcal/diet; $P < 0.05$). No differences in respiratory frequency among the three age groups were found.

In long-lived subjects (n = 28), Rq was negatively correlated with %BF ($r = -0.420$, $P < 0.02$), fasting plasma glucose ($r = -0.596$, $P < 0.05$), FFA ($r = -0.389$, $P < 0.05$), and WHR ($r = -0.582$, $P < 0.05$), whereas RMR was negatively with WHR ($r = -0.603$, $P < 0.05$). Such correlations were still significant after correction for TV (data not shown). No significant associations of RMR ($r = -0.012$, $P < 0.95$) and Rq ($r = 0.095$, $P < 0.63$) with FFM were found. In contrast, WHR was significantly correlated to FFA ($r = 0.430$, $P < 0.02$).

Discussion

The major finding of our study is that the long-lived female seems protected from a metabolic age-related decline com-

TABLE 2. Linear multiple regression analyses with RMR and Rq as dependent variables (n = 81)

	RMR				Rq			
	β	t	P	r^2 0.40	β	t	P	r^2 0.46
Age	−0.236	−2.648	0.10		−0.192	−2.719	0.010	
BMI	−0.029	−0.216	0.281		−0.149	−1.218	0.227	
WHR	−0.242	−2.381	0.016		−0.464	−5.044	0.000	
FFM	−0.180	−2.811	0.009		0.330	1.989	0.050	
Glucose levels	0.022	0.212	0.833		−0.305	−3.244	0.002	
TV	0.401	3.864	0.000		0.181	1.718	0.070	

TABLE 3. Indirect calorimetry in the different study groups

	Adult subjects	*P*	Aged subjects	*P*	Long-lived subjects
RF (breaths/min)	18 ± 2	NS	19 ± 2	NS	18 ± 2
TV (liters)	0.471 ± 0.1	0.001	0.349 ± 0.07	0.001	0.443 ± 0.09
VO_2 (ml/min)	232.2 ± 26.1	0.001	170.5 ± 28.7	0.001	216.2 ± 28.5[a]
VCO_2 (ml/min)	192.1 ± 20.6	0.001	126.7 ± 24.5	0.001	172.4 ± 25.3[a]
Rq	0.82 ± 0.02	0.001	0.74 ± 0.04	0.001	0.79 ± 0.03[a]
RMR (kcal/diet)	1404 ± 216	0.001	1065 ± 303	0.002	1324 ± 222

NS, Not significant.
[a] Significantly different from adult subjects, $P < 0.05$. All determinations were made after an overnight fast.

pared with aged females. Despite the fact that in the whole group of subjects an age-related decline in RMR and Rq was found, the analysis restrained to long-lived subjects showed in this group RMR and Rq greater than that found in aged subjects. Such a difference might be explained by the changes in anthropometrics features because long-lived subjects had lower BMI, FFM, and WHR than aged subjects.

Our results suggest that long-lived subjects are less prone to the metabolic derangement, normally occurring with age. To this regard, previous studies on human longevity have underlined the role of various metabolic (16–18), endocrine (14, 15), and biological factors as potential determinants of a successful ageing.

Indeed, the relationship between energy expenditure and longevity has been poorly investigated. Rothenberg *et al.* (23) demonstrated in very old individuals (age range 91–96 yr) a lower total energy expenditure, activity energy expenditure, and physical activity level, whereas RMR was not substantially different from that of younger elderly. Notwithstanding, this report provided only little information in very (over 95 yr) old subjects, and the control subjects of the study come from different trials and were studied with different procedures.

In our study, energy expenditure parameters of 28 long-lived subjects were assessed and compared with those of adult and younger elderly groups. The analysis performed showed that despite an age-related decline in energy metabolism parameters, long-lived subjects had greater RMR and Rq than aged subjects.

Several researchers (6–9) but not all (12, 13) have attributed the age-related decrease in RMR to change in body composition and especially in FFM, confirming the significant contribution of skeletal muscle to the variance in RMR. To this regard, it has been hypothesized that loss of muscle mass with age may influence RMR involving both central and peripheral cellular mechanisms (10, 11). Our findings confirm such previous evidence, showing the FFM significantly and independently associated with RMR.

Interestingly, in our study, different body composition and fat distribution between aged subjects and long-lived subjects have been found, with long-lived subjects having lower BMI, WHR, and FFM. Thus, the difference between aged and long-lived subjects in energy metabolism parameters might be explained by the different FFM and fat distribution. Such a hypothesis is strengthened by the evidence that in multivariate analysis, both RMR and Rq had FFM, WHR, but not BMI as significant and independent determinants.

Notwithstanding, when the analysis was restrained to long-lived subjects, only WHR and not FFM was significantly associated with RMR and Rq, thus suggesting a predominant contribution, in such age group, of body fat distribution. Such findings are in agreement with previous ones showing that RMR not only depends on FFM but is also influenced by FM, especially by fat distribution (24) Due to the key role of FFM in the RMR regulation and due to its age-related decline, such results are undoubtedly unexpected. Furthermore, the potential mechanism by which lower WHR, despite the lower FFM found in long-lived subjects, may preserve energy metabolism remains to be elucidated. Indeed, the fact that longevity is associated with a greater Rq is in agreement with previous findings on human longevity, showing a preserved glucose metabolism in long-lived subjects (25, 26). The latter relationship is also supported by the evidence that in our study, Rq was found to be negatively associated with fasting plasma glucose levels. Thus, in long-lived subjects, a preserved Rq may reflect both a predominant use of carbohydrate and a reduced rate of fat oxidation due to the presence of low levels of circulating FFAs; in turn, they may associated with the low fat stores and low WHR observed in those individuals.

We acknowledge that the association design is a potential limitation of our study. Indeed, our results are compatible with a better ability of long-lived subjects to preserve energy metabolism, our findings showing for the first time a relationship between energy expenditure and longevity.

In conclusion, our data demonstrate that human longevity seems protected toward an age-related decline. The exact mechanisms of the preservation of the metabolic changes need to be further elucidated by future studies. It is likely that the lack of the anthropometrics derangement found in long-lived subjects may preserve these individuals from the age-related energy expenditure derangement. However, because our findings were obtained from cross-sectional data, this hypothetical cause-effect relationship can be emphasized but not definitely proved. Notwithstanding, it is likely that variants of gene involved in the regulation of energy expenditure and substrate oxidation might help to explain for the unexpected phenotype found in long-lived subject and justify the potential link between WHR and energy metabolism, independently of FFM.

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