Higher Energy Expenditure in Humans Predicts Natural Mortality

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Context: Higher metabolic rates increase free radical formation, which may accelerate aging and lead to early mortality.

Objective: Our objective was to determine whether higher metabolic rates measured by two different methods predict early natural mortality in humans.

Design: Nondiabetic healthy Pima Indian volunteers (n = 652) were admitted to an inpatient unit for approximately 7 d as part of a longitudinal study of obesity and diabetes risk factors. Vital status of study participants was determined through December 31, 2006. Twenty-four-hour energy expenditure (24EE) was measured in 508 individuals, resting metabolic rate (RMR) was measured in 384 individuals, and 240 underwent both measurements on separate days. Data for 24EE were collected in a respiratory chamber between 1985 and 2006 with a mean (SD) follow-up time of 11.1 (6.5) yr and for RMR using an open-circuit respiratory hood system between 1982 and 2006 with a mean follow-up time of 15.4 (6.3) yr. Cox regression models were used to test the effect of EE on natural mortality, controlled for age, sex, and body weight.

Results: In both groups, 27 natural deaths occurred during the study period. For each 100-kcal/24 h increase in EE, the risk of natural mortality increased by 1.29 (95% confidence interval = 1.00–1.66; $P < 0.05$) in the 24EE group and by 1.25 (95% confidence interval = 1.01–1.55; $P < 0.05$) in the RMR group, after adjustment for age, sex, and body weight in proportional hazard analyses.

Conclusions: Higher metabolic rates as reflected by 24EE or RMR predict early natural mortality, indicating that higher energy turnover may accelerate aging in humans. (***J Clin Endocrinol Metab* 96: E972–E976, 2011**)

Higher energy turnover is associated with shorter lifespan in animals, but evidence for this association in humans is limited. Over a century ago, the German physiologist Max Rubner linked body size and energy turnover with lifespan (1), and Benedict's mouse-elephant curve extended these findings by demonstrating that smaller animals expend relatively more energy per body mass and have a shorter life span than larger animals (2). The physiological underpinnings of the theory that lifespan is determined by a rate of living, however, are not clear. The free radical theory of aging proposes that aging is accelerated by the accumulation of cellular metabolites, in particular toxic free radicals (3). Free radicals in the form of reactive oxygen species (ROS) accumulate more quickly with higher metabolic rates and are responsible for various types of oxidative damage in the cell (4). To investigate the hypothesis that higher metabolic rate is associated with aging, we examined whether energy expenditure (EE), measured in a metabolic chamber over 24 h and during rest predicts natural mortality in nondiabetic Pima Indians from the Gila River Indian Community.

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Abbreviations: CI, Confidence interval; DS-1, dataset 1; EE, energy expenditure; FFM, fat-free mass; FM, fat mass; HRR, hazard rate ratio; RMR, resting metabolic rate; ROS, reactive oxygen species; SG, study group; SLEEP, sleep EE.

Subjects and Methods

Study participants

Nonsmoking Pima Indian volunteers (n = 652), healthy by laboratory testing, history, and physical examination were admitted to our clinical research unit. Body composition was assessed by dual energy x-ray absorptiometry and glucose regulation by a 75-g oral glucose tolerance test. After 5 d, EE was measured over 24 h (24EE) and/or in the resting state [resting metabolic rate (RMR)]. All subjects were followed biennially in a longitudinal outpatient study of risk factors for diabetes and obesity that included history, physical exam, and an oral glucose tolerance test with measurement of glucose and insulin concentrations. The data presented derive from a prospective analysis of this study. Vital status was confirmed through December 31, 2006, and date and cause of death were ascertained by the examination of health records and death certificates. Terminology and codes of the ninth revision of the *International Classification of Disease* (5) were used for recording causes of death and other diagnoses. Deaths were considered natural if they were due to disease or nonnatural if they were due to external causes. All study participants provided written and informed consent. The study was approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases.

Energy expenditure

The 24EE was measured in a metabolic chamber as described previously (6). Sleep EE (SLEEP) was defined as the average EE of all 15-min periods between 2330 and 0500 h when spontaneous activity was less than 1.5% as quantified by radar sensors. RMR was measured using a respiratory hood system as described elsewhere (7). Overall, 508 individuals with measurements of 24EE and SLEEP [study group (SG)-1] and 384 individuals with measurements of RMR (SG-2) were included in this analysis. Simultaneous measurements of both 24EE/SLEEP and RMR were obtained in 240 individuals who, therefore, are represented in both datasets.

Statistical analysis

SAS Enterprise Guide version 4.1 (SAS Institute Inc.,Cary, NC) was used for data analyses. Student's *t* test or Kruskall-Wallis test was used for normally distributed or skewed variables. Proportional hazard models were used to test the measurements of EE as predictors of mortality. The time between measurement of EE and death or December 31, 2006 was counted as survival time. The proportionality assumption was tested by assuring linearity in the Weibull plot. Age, gender, and body weight were used as covariates in the models. Because the number of events was small, there is potential for overfitting the models. Therefore, body weight served as a proxy for fat mass (FM) and fat-free mass (FFM) to reduce the number of covariates. Additionally, bootstrap analyses were used to examine the validity of the prediction model by creating 1000 replicates by random sampling with replacements from the original dataset. Details of this method are described elsewhere (8). The data from SG-1 and SG-2 were pooled with larger datasets including participants with the same measurements of EE [24EE and SLEEP in dataset 1 (DS-1) and RMR in DS-2] but no follow-up for mortality, to allow for adjustment of further covariates. Linear regression models adjusted for age, gender, FM, FFM, and physical activity were used to calculate residuals for 24EE. Similar models (physical activity excluded) were used to extract residuals for RMR and SLEEP. The residuals of EE traits from the original datasets were then extracted and analyzed in proportional hazard models. Because this approach does not require inclusion of covariates in the proportional hazard models, it avoids overfitting. α was set at $P < 0.05$.

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Results

Subject characteristics of SG-1 and SG-2 are presented in Table 1. Causes of death in both SG-1 and SG-2 are listed in Table 2. Overall, 43 nonnatural deaths in SG-1 and 53

TABLE 1. Group characteristics

	SG-1			SG-2		
	Survived	**Died**	***P* value**	**Survived**	**Died**	***P* value**
n (male)	438 (243)	27 (19)	NA	304 (173)	27 (20)	NA
Age at time of measurement (yr)	27.8 ± 7.0	30.9 ± 7.5	0.03	25.3 ± 5.5	27.8 ± 7.3	0.12
Body weight (kg)	96.7 ± 24.8	92.6 ± 24.3	0.34	92.5 ± 22.7	102.8 ± 26.9	0.06
Body fat (%)	33.5 ± 8.1	30.5 ± 8.2	0.06	32.6 ± 8.5	33.5 ± 8.7	0.62
Body mass index (kg/m^2)	34.7 ± 8.6	33.2 ± 7.4	0.46	33.2 ± 7.3	36.8 ± 8.9	0.06
Fasting glucose (mg/dl)	90 ± 11	95 ± 7	<0.01	86 ± 9	88 ± 5.4	0.12
2-h glucose (mg/dl)	121 ± 30.6	133 ± 30.6	0.05	117 ± 29	121 ± 29	0.55
24EE (kcal)	2376 ± 413	2370 ± 418	0.94	NA	NA	NA
SLEEP (kcal)	1688 ± 296	1694 ± 306	0.93	NA	NA	NA
RMR (kcal/24 h)	NA	NA	NA	1765 ± 333	1908 ± 330	0.03
Follow-up time (yr)	11.6 ± 6.5	11.3 ± 5.9	0.82	17.7 ± 3.3	19.1 ± 3.3	0.22

SG-1 includes individuals with measurements of 24EE and SLEEP by indirect calorimetry in a metabolic chamber; SG-2 includes individuals with measurements of RMR by indirect calorimetry using an open-circuit hood system (values are extrapolated to a 24-h interval); the first row of the column 'Died' shows number of deaths by external causes in parentheses, data shown in this column derive from 27 individuals who died from natural causes. Two-hour glucose is plasma glucose 2 h after a 75-g oral glucose load. Data are depicted as mean ± SD. For conversion of glucose values to SI units, multiply by 0.0555. NA, Not available.

TABLE 2. Causes of death

Nomenclature	ICD-9 codes	SG-1	SG-2
Toxic organ failure	303.0	1	1
Cardiovascular disease	414.0; 431.0; 557.0; 425.5	4	3
Infections	038.1; 038.4	2	2
Malignancy	151.9; 186.9	1	2
Diabetes/obesity	250.4; 278.0	1	3
Liver disease	571.2	15	12
Lung disease	486.0; 516.3; 518.89	3	3
Undiagnosed disease	799.9	0	1
External	806.2; 812.0; 812.1; 814.7; 816.0; 816.1; 816.9; 819.0; 819.1; 821.0; 850.2; 858.9; 860.0; 860.1; 860.9; 888.0; 890.2; 900.0; 910.9; 928.9; 950.0; 950.4; 953.0; 955.0; 963.0; 965.1; 965.2; 965.4; 966.0; 968.2; 968.9; 980.4	43	53
Natural deaths		27	27
Total deaths		70	80
Survived[a]		438	304

SG-1 includes individuals with measurements of 24EE and SLEEP by indirect calorimetry in a metabolic chamber; SG-2 includes individuals with measurements of RMR by indirect calorimetry using an open-circuit hood system. ICD-9: *International Classification of Diseases, 9th Revision*.

[a] Survival until end of ascertainment period (December 31, 2006).

occurred in SG-2, whereas 27 natural deaths were ascertained in each study group. Death due to alcohol-related causes predominated in both groups. As shown in Supplemental Table 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org), baseline characteristics did not differ between SG-1 and DS-1, although individuals in DS-1 were slightly older. In DS-2, individuals were also slightly older and had slightly higher fasting glucose levels compared with SG-2.

In proportional hazard models adjusted for age, sex, and body weight, higher 24EE increased the risk of natural mortality [hazard rate ratio (HRR) = 1.29 with 95% confidence interval (CI) = 1.00–1.66; $P < 0.05$ for each 100-kcal increase in 24 h] but not all-cause mortality [HRR = 1.06 (95% CI = 0.90–1.24); $P = 0.47$]. Additional adjustment for fasting glucose did not change the results. Bootstrap replicates revealed 496 of 1000 *P* values were below 0.05, with a median *P* value of 0.052. Likewise, RMR predicted natural mortality with HRR = 1.25 (95% CI = 1.01–1.54) and $P = 0.04$ for each 100-kcal increase in 24 h but not all-cause mortality [HRR = 0.97 (95% CI = 0.86–1.09); $P = 0.56$]. After bootstrapping, 506 of 1000 *P* values were below 0.05, with a median *P* value of 0.046. Results were similar for 24EE and RMR if FM and FFM were substituted for body weight in the models [HRR = 1.30 (95% CI = 1.00–1.67), $P < 0.05$; and HRR = 1.24 (95% CI = 1.00–1.54), $P < 0.05$]. Further adjustment for fasting glucose or 2-h glucose did not change the results for 24EE or RMR. However, SLEEP was not a predictor of either natural mortality [HRR = 1.00 (95% CI = 0.99–1.00); $P = 0.89$[or all-cause mortality [HRR = 1.10 (95% CI = 0.94–1.30); $P = 0.24$].

To adjust for additional covariates, measures of EE were adjusted for age, sex, physical activity (for 24EE only), FM, and FFM in the larger cohorts as described above. After including the extracted residuals in a proportional hazard model for survival time, 24EE modestly predicted natural mortality with a HRR of 1.29 (95% CI = 0.99–1.68; $P = 0.06$) and RMR remained a significant predictor of natural mortality with a HRR of 2.30 (95% CI = 1.04–5.10; $P < 0.05$). Additional adjustment for fasting glucose did not change the results. However, SLEEP was still not a predictor of natural mortality [HRR = 1.14 (0.87–1.49); $P = 0.35$].

Discussion

In this longitudinal study, we found that 24EE and RMR, measured on different days, predict natural mortality in Pima Indians. These results are consistent with previously described data for RMR in an older population (9). In the present study, EE was measured in a younger population, and two different measures of EE provided consistent results.

Increased EE and ATP turnover increase free radical formation, and this is proposed as a mechanism for accelerated aging and increased mortality (3). Furthermore, studies in animals indicate that reduced metabolic rate after caloric restriction has beneficial effects on lifespan (10). However, recent studies using knockout models of key antioxidant genes in the worm *Caenorhabditis elegans* and data from long-lived mouse models have produced inconsistent results, therefore calling this oxidative damage theory into question (11).

Importantly, studies in which energy turnover is willfully increased (via physical activity) demonstrate clear metabolic benefits (12). Therefore, our results do not ap-

ply to increased energy turnover due to exercise. This belief is supported by two recent reports showing that 1) excess fat intake (which increases metabolic rates) leads to increased ROS production, which links overnutrition to insulin resistance, whereas 2) transient elevations in ROS induced by physical exercise may be essential for training-induced insulin sensitivity (13, 14). Thus, a transient elevation of ROS, as seen during physical exercise, could have beneficial effects on human health, whereas sustained elevations in ROS due to higher metabolic rates as a consequence of macronutrient excess could be harmful. Recent experiments have shown that transgenic hypermetabolic mice with increased uncoupling from ectopically expressed uncoupling protein 1 live longer than their wild-type counterparts (15, 16). Despite higher metabolic rates, these mice show substantial reductions in mitochondrial ROS production (17). Together these data indicate that the effect of elevated metabolic rate on cell/organ damage over a lifespan needs to be viewed against the background of ROS production.

Because exams were performed at a young age, the number of natural deaths was low, allowing for a limited number of covariates in our regression analyses, which could result in some residual confounding (18). However, additional adjustments in larger cohorts and bootstrap analyses indicated that the results remained robust to further adjustments. Although causes of death were spread among many diagnoses, liver disease due to exogenous exposure was very common. This outcome might be expected in a cohort where early nontraumatic mortality is more likely to be due to long-term effects of exogenous exposures (such as alcohol). However, increased EE could explain greater susceptibility to liver disease in the setting of alcohol exposure. The combination of an exogenous toxin (such as alcohol) with the accumulation of free radicals could result in chronic low-grade damage by accrual of these metabolites and result in greater hepatic injury (19). It should be acknowledged that chronic alcohol use is known to increase metabolic rate. However, Levine *et al.* (20) have shown that this effect disappears after only 4 d of abstinence. Because all measurements were performed at least 5 d after admission and we have confirmed our findings in two assessments of EE done on separate days, it seems unlikely that alcohol use or previous overeating would have affected the EE measurements. Furthermore, we found that RMR but not SLEEP predicted mortality. Because SLEEP is a measurement carved from the 24EE based on a defined time period and low activity, it may have more variability and less accuracy compared with RMR, accounting for our lack of an association with mortality. Individual EE measurements can vary from day to day. However, under the conditions on our unit, the reproducibility of our measurements is high with an intra-individual coefficient of variation of approximately 2% (6).

Conclusions

Two different measurements of EE (24EE and RMR) measured on different days predict natural mortality in Pima Indians, supporting a role for increased energy turnover as a risk factor for accelerated aging and early mortality.

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