MEDICINE

Biomarkers of Caloric Restriction May Predict Longevity in Humans

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The most robust intervention for slowing aging and maintaining health and function in animals is dietary caloric restriction (CR) (*1*). Although most studies of this phenomenon have been conducted in rodents and lower animals, data accumulating from rhesus monkeys suggest that CR may also be relevant for primates, including humans (*2–5*). These findings include CR-induced attenuation of age changes in plasma triglycerides (*2*) and melatonin (*3*) as well as oxidative damage (*4*) and glucose tolerance (*5*). Current mortality data from our ongoing studies in rhesus monkeys, although not yet statistically significant, reveal that mortality in CR monkeys is about half of that observed in controls (15% compared with 24%, respectively).

Moreover, because we have already demonstrated that two of the most robust biomarkers of CR in rodents, reduced body temperature and plasma insulin, also occur in rhesus monkeys on CR (*2*), it became important to assess their association with human survival. CR also slows the rate of decline in serum dehydroepiandrosterone sulfate (DHEAS) such that restricted monkeys maintain more youthful levels of this adrenal steroid (*2*). DHEAS, which declines in both rhesus monkeys and humans during normal aging, may be important in health maintenance and may serve as another potential longevity marker (*6*). All three biomarkers indicate that CR causes a fundamental shift in metabolic processes.

Figure 1, A to C, shows the effects of CR on body temperature, insulin, and DHEAS in male rhesus monkeys, and Fig. 1, D to F, compares survival of healthy men in the Baltimore Longitudinal Study of Aging (BLSA) (*7*) who are in the upper and lower halves of the distributions for the corresponding markers. Consistent with the beneficial effects of CR on aging and lifespan in other animals, men with lower temperature and insulin and those maintaining higher DHEAS levels have greater survival than respective counterparts.

Because all analyses are corrected for initial subject age, any differences between upper and lower halves for the respective markers would not influence interpretation of survival differences. In fact, only subjects in the DHEAS study exhibited a significant difference in initial age for upper and lower halves. Moreover, if subsets of these individuals with identical initial age distributions or subject pairs matched for initial age from the upper and lower halves are examined, significant survival differences persist, as would be expected from age-adjusted analyses. It should also be noted that DHEAS sampling times were comparable between comparison groups, so that data might alternatively be expressed as rates of change or slopes. In this case, however, because insulin and temperature measures refer to actual values, rather than rates of change, the DHEAS data are expressed accordingly for more relevant comparison.

To our knowledge, the BLSA men are not CR. However, whatever environmental or genetic factors result in CR-like effects on the physiological markers examined here would appear to be related to longevity and therefore worthy of further investigation. Moreover, the fact that monkeys on CR exhibit reduced insulin, body temperature, and decline in DHEAS further supports the likelihood that this nutritional treatment will enhance survival in these primates.

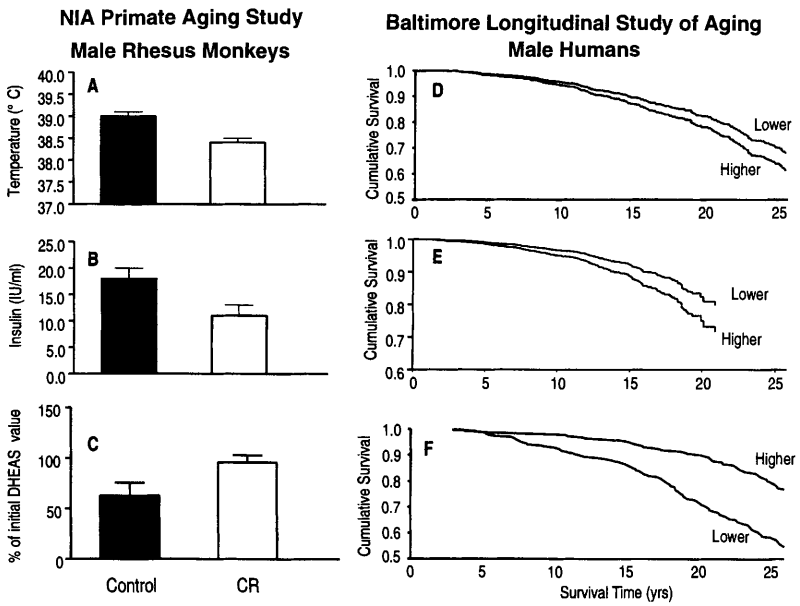

Fig. 1. Values for male rhesus monkeys are means ± standard errors for 20 to 30 animals in each group, after 3 to 5 years of 30% CR. Numbers of BLSA men having died in the temperature, insulin, and DHEAS studies were 324, 199, and 192, respectively. Only those individuals surviving at least 3 years were followed in the DHEAS study, and all subjects were in good health as evaluated by extensive medical assessment. Subject age in the three data sets ranged from 19 to 95 years. All analyses are significant to at least $P < 0.05$ by t test or proportional hazard model, corrected for initial subject age. BLSA data are divided into upper and lower halves for better comparison with the two monkey groups, although all three age-adjusted variables exhibit significant, continuous effects for temperature, insulin, and DHEAS on mortality in humans. Additional experimental details are given in (*2*, *5*).

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