Human Caloric Restriction for Retardation of Aging: Current Approaches and Preliminary Data\textsuperscript{1,2}

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As the percentage of the U.S. population over 65 y continues to increase, there is growing recognition that we need to identify effective ways to reduce age-associated morbidity and understand the potential for delaying biological aging to improve health in the later years. Caloric restriction (CR) is the only tested intervention that has been proven to delay biological aging in animal models and thus is a candidate for application to humans.

In animal models, CR opposes the development of a broad spectrum of age-associated pathophysiological changes and increases maximum lifespan \textsuperscript{(1–6)}. As reviewed elsewhere \textsuperscript{(7–12)}, body temperature, total energy expenditure, and metabolic rate fall with CR \textsuperscript{(6,11)}. CR also improves immune function \textsuperscript{(13)} and insulin sensitivity \textsuperscript{(14)} and reduces oxidative stress \textsuperscript{(15,16)}. Recent research has also suggested that the effects of CR may be more than a passive consequence of beneficial changes resulting from lowering energy flux, and several putative antiaging genes have been identified that may actively influence the rate of metabolic aging and are modulated by CR \textsuperscript{(9,17,18)}.

Whether humans experience similar benefits of CR without unacceptable side effects is not known. One small randomized trial reanalyzed by Stunkard suggested beneficial effects of human CR \textsuperscript{(a regimen consisting of reduced energy intake provided by milk and fruit on alternate days)} in a small population of nursing home residents \textsuperscript{(19,20)}, and the Biosphere studies have also indicated beneficial short-term effects of a CR that also involved modulation of dietary composition \textsuperscript{(21)}. There have also been cross-sectional studies suggesting that voluntary CR is associated with longevity \textsuperscript{(22,23)}, and factors such as high insulin sensitivity that have been associated with beneficial effects of CR in animal models have also been reported to be associated with longevity in humans \textsuperscript{(24)}. These observations combined with the recent suggestion of active alterations in aging processes by antiaging genes \textsuperscript{(9,17)} do suggest the potential for significant beneficial effects of CR in humans consistent with the effects that are emerging in the nonhuman primate studies \textsuperscript{(25)}. However, some theoretical analyses alternatively suggest that there may be only a limited potential of CR to extend lifespan and reduce morbidity in humans \textsuperscript{(7,26)}. Moreover, potential adverse effects of CR in humans that would render CR unacceptable \textsuperscript{(such as adverse alterations in mood and cognition)}, even if metabolic benefits were detected, have received almost no attention to date. This symposium was conducted to overview the current state of the art research on human CR, including the NIH-funded CALERIE trials. As summarized elsewhere \textsuperscript{(27–29)}, the CALERIE studies indicate the broad feasibility of long-term human CR trials and provide preliminary data on metabolic rate, oxidative stress, and insulin sensitivity that are broadly consistent with emerging data from the CR trials in nonhuman primates.

\textbf{Literature Cited}


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