Calories and Longevity: Do They Really Matter?

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Abstract

Calorie restriction extends the life span of laboratory animals, and now scientists are beginning to discover the molecular basis for this phenomenon. The findings so far indicate that there are genes that respond to stressors (like calorie restriction) by turning on cell survival mechanisms. Outright skeptics of calorie restriction argue that the practice will not work in humans, while those more dubious contend that if the practice works at all, the addition of time to the life span will be minimal compared with the sacrifices endured by adhering to such a rigid dietary regimen. In fact, several studies have indicated that those classified as overweight (according to body mass index) have at least as low a risk of premature death as those of normal weight, and despite the "obesity epidemic" in the United States, life expectancy continues to rise. Nevertheless, the goal of scientists is to devise ways to target the newfound "longevity genes" in order to achieve the alleged life-extending effects without actually restricting calories. So, does longevity depend on eating less or eating more, or maybe in the future, taking a pill? Science and society are precariously close to seeking longevity simply for longevity's sake. Where does happiness fit into the equation?

Introduction

That life is good and preferable to death is a widely shared sentiment. It is a philosophy that makes the quest for longevity logical and sensible to most people. Arguably, there are probably few who would not choose to extend precious time with friends and family. What happens after death is unknown and somewhat frightening to contemplate. Even if faith dictates a blissful and contented afterlife, there is sorrow and sadness when someone dies. To want to prolong life seems only natural, but where does the pursuit appropriately end? At what point are science and society seeking longevity simply for longevity's sake, just to see if it can be done? Are lives that are longer somehow better than those that are shorter? Is it a symbol of status to live long? Are people that live longer also happier, and is it worth it if they are not? Do longevity and happiness depend on one another, or are they independent?

It is not surprising that longevity and ways to achieve it are subjects of intense research and speculation, because of the widespread human contention that living longer is worth the effort. Consequently, there are reports of and recommendations for life strategies that are purported to extend the human life span beyond what is normally expected. However, in today's age of instant food, instant gratification and instant information, the very term "life strategy" becomes problematic, and the pursuit of longevity falls victim to the same must-have-it-now and must-have-it-all mentality prevalent in so many other aspects of society, creating the new oxymoron "instantaneous longevity." Long term life strategies, if not quickly circumvented by shortcuts, invariably fail. What's more, building a life of happiness is often left completely out of the equation, as if it is beside the point and has nothing to do with either the quality or quantity of life. Perhaps it is assumed that longevity begets happiness. Armed with the attitude that longevity is something for which to strive, consumers are barraged with messages touting ways to go about achieving it, even if happiness is forsaken in the process. After all, should the journey toward longevity become uncomfortable, there is always a shortcut. This paper examines a strategy that has the potential to enhance longevity, and even delay age-related disease symptoms. Even though scientific evidence is still confusing and contradictory, plans for future shortcuts are plentiful.

Calorie restriction has been shown in numerous organisms, including mammals, to extend the life of lab animals significantly.1[1][,2[2],3[3]] Physiological parameters

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associated with age-related chronic diseases, such as diabetes, cancer, arthritis and cardiovascular disease, are improved by calorie restricted diets in lower organisms and mammals, including rats, mice and humans.4[4],[5[5],6[6],7[7],8[8]] The hope that life span extension will also hold true in humans is the basis for the Calorie Restriction Society. Unfortunately, calorie restriction as a life span-extending tool has yet to be proven in humans, and there is controversy over whether it even has the potential to work in humans.9[9] Meanwhile, even devoted followers of calorie restriction admit near-constant hunger, low libido, decreased cold tolerance, and moodiness, at least at first.10[10] Unreported but logical concerns regarding the practice might include questions concerning impaired fertility, exacerbation of eating disorders, and malnutrition in some individuals. Even if calorie restriction is found to significantly extend the human

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life span, it is highly debatable whether an appreciable number of people would be able to put up with such a strict dietary regimen, which is typically about two-thirds of one's normal caloric intake while maintaining nutrient sufficiency. Thus, scientists are understandably interested in finding out how calorie restriction works at the molecular level so that they can devise drugs to mimic calorie restriction while maintaining normal caloric intake.11[11],12[12],13[13],14[14] Such a drug would be the magic bullet that pharmaceutical companies and consumers would need in order to "have their cake and eat it, too."

There are many theories that attempt to explain the life span-prolonging effects of calorie restriction, but exact mechanisms have been difficult to pinpoint. Many if not all of the hypotheses are interconnected, and the scientific literature has revealed some conflicting data. Because food shortage is a cell stressor, there are probably a number of cellular responses to the stress. Some mechanisms that have been proposed to be part of the explanation of increased life span in response to caloric deprivation include: decreased oxidative damage,15[15],16[16],17[17],18[18] increased nitric oxide

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synthesis,19[19] reduced pituitary hormone secretion,20[20] changes in adipose tissue,21[21],[22][22] manipulation of cell apoptosis,23[23],[24][24] increased insulin sensitivity and improved blood glucose control,25[25],[26][26],[27][27] and others. A great deal of research has focused on a set of genes that code for proteins called sirtuins, which are

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thought to be at least in part responsible for cells' response to various stresses, including lack of food. In particular, the gene sir2 (in lower organisms) and its mammalian counterpart, sirt1, are thought to mediate many of the life extending effects of calorie restriction. It has been shown that when sir2(sirt1) expression is up-regulated by calorie restriction, the life spans of yeast, flies, worms and mammals are significantly increased.28[28]'[29] It has also been reported that increased sir2 transcription is necessary for the life span-extending effect of calorie restriction.30[30] However, recent research has called that necessity into question, since sir2-independent life span elongation in response to calorie restriction has been demonstrated.31[31]'[32],[33] In yeast, scientists are now distinguishing between reproductive life span and chronological life span. Recent studies have shown that increasing sir2 expression extends the reproductive life span but actually blocks extension of the chronological life

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span.34[34],35[35] Decreased sir2 expression, on the other hand, delayed chronological aging in yeast, as did decreased activity of another nutrient-responsive pathway, TOR.36[36],37[37]

The genetics of longevity and the connection with calorie restriction are intriguing. It will be interesting to follow the research and see how the pieces of the puzzle connect as the story unfolds. It is clear that there is much yet to be unraveled. In the meantime, as no one is entirely confident that calorie restriction will increase longevity in humans, it may be rash to be devising shortcuts to circumvent the discomfort of the practice. For example, there was initial excitement about the compound resveratrol, a small molecule found in grape juice, red wine and peanuts. Reported to activate sirtuin genes and enhance longevity in flies, worms, and yeast, resveratrol was suspected of acting as a substitute for calorie restriction. There have since been serious questions raised about its ability to do so in vivo in flies, worms, and yeast.38[38] If resveratrol has a life-extending effect in these organisms, a different mechanism than sirtuin gene activation must be considered. Making assumptions about a dietary or drug

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substitute for calorie restriction in humans after confounding studies in lower eukaryotes would be a leap of faith at best.

Even if calorie restriction does eventually pan out and is shown to extend the life span of human beings, there are several factors to consider. Might a significant portion of the life-extending benefits of calorie restriction simply be due to causing people to lower their body weights? Overweight and obesity make front page news every day, along with all the implications for early disease onset, aging, and premature death. Surely reducing people's waistlines would in itself have a life-prolonging effect. Unfortunately, this presumption is rife with ambiguity. First, this appears not to be the case in rats, where low body weight resulting from calorie restriction accounted for only a modest portion of the increased longevity caused by calorie restriction.39[39] Second, life expectancy in the U.S. is increasing despite the obesity crisis, as deaths from cardiovascular disease, cancers and stroke decrease.40[40] Third, it has been shown that those in the overweight category according to body mass index are not at increased risk for mortality compared with those in the normal weight category.41[41],42[42] Although it is clear that increased mortality rates are associated with the obese category of body

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mass index, increased mortality is also associated with the underweight category, a fact that has been largely ignored in the thin-obsessed U.S.43[43],44[44] Further, high body mass indices correlate much more strongly with mortality in whites than in blacks, so there appear to be racial differences to consider as well.45[45]

The relationship between body weight and mortality is further muddied by reports that indicate that dieting itself imparts health risks and may contribute to higher mortality, especially compared with those who maintain a constant weight throughout life.46[46],47[47],48[48],49[49],50[50] Given that achieving permanent weight loss by dieting is most often a fruitless endeavor, any putative health benefits brought about by temporary weight loss are overshadowed by the rather dismal long term prognosis of future weight gain, more dieting, and increased mortality rates. It is apparent that the connections

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among longevity, body weight, and caloric intake are still incredibly indistinct. Other than avoiding the extremely high or very low body mass index categories, there is no clear consensus from the scientific and medical communities about what to do to achieve longevity, and hopefully good health along with it.

Conclusion

The body weight quandary faced by consumers is exacerbated by the perhaps overblown and over-hyped health risks of excess pounds and the consequent admonitions to lose weight or suffer the consequences. Fashion-conscious ideals of thinness only add to the pressure and confusion, as do the promises of weight loss diet regimens. Even a strategy like calorie restriction, which has some interesting scientific basis, feeds into the weight loss and longevity frenzy when questionable future pills that will manipulate longevity genes are peddled prematurely. In light of the push to pursue health and longevity by losing weight and/or restricting calories, it is interesting that so little is made of the finding that underweight is as dangerous as obesity with respect to mortality. Despite all the propaganda to lose weight for health and longevity, there is precious little evidence that dieting alone will result in health and longevity, even in the unlikely event that it is successful.

An important question to ask, then, is whether the effort is justified. It seems as though longevity is something that is automatically viewed as "good," so striving for it is a noble thing to do. However, many of the strategies advertised as a means for achieving it involve regimens that are either "too good to be true" or are boring, uncomfortable, and restrictive. If a strategy is successful, has happiness been sacrificed in the quest for longevity? If one is unwilling to submit to discomfort and restriction, are years of life lost? Alternatively, is there a shortcut that promises the best of both worlds, and if so,

will it really deliver? In the worst case scenario, if a strategy fails, has all hope for either happiness or longevity disappeared?

Happiness, though an emotion difficult to quantify, has been positively associated with living longer.51[51],[52[52],53[53],54[54]] The current drive to extend the human life span has disappointingly centered on longevity as the primary goal, with the unspoken assumption that happiness will inevitably follow if one lives for a long time. Simultaneously, the diet industry has pushed weight loss using outward appearance as the driving force, again with happiness to follow if one is successful at it. Perhaps the order should be reversed. Happiness seems too central a human necessity to relegate it to a consequential afterthought. Outward appearance is too superficial a trait to guarantee true happiness. Longevity in and of itself does not guarantee either health or happiness. Perhaps the most important goal in life should be the attainment of joy and contentment. If life was premised on building happiness first and foremost, maybe obesity and longevity wouldn't be such major concerns. Conceivably, if happiness came first, then healthy, non-self-destructive lifestyles, healthy body weights and longevity would follow naturally.

Maintaining a healthy lifestyle and body weight does require a conscious effort, attention to detail, and dedication, but the investment pays off with improved physical and mental

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health. This sets up a powerful positive feedback loop with happiness at the core. When one is happy, lifestyle goals are more likely to be accomplished, setting the stage for better mental and physical health, which in turn result in more happiness and satisfaction, all of which contribute to greater longevity. The analogous loop based on sadness is typically self-defeating. Sadness causes self-destructive lifestyle behaviors, which result in decreased mental and physical health, which in turn lead to more sadness, which all contribute to premature death.

Counting on rigid diet plans and short cut pills to break free of the sadness cycle is so often ineffectual because, even if they could potentially work, the sadness and self-destructive behaviors are never evaluated or changed. There is no incentive to do so, only promises of everything for nothing (or something so problematic it can't be maintained). Perhaps it is time to reassess what is truly important and what should be emphasized in the quest for longevity. Promising immediate or drastic results is unrealistic, gives false hope, and is highly prone to failure. Establishing a generally happy life with healthy habits is pragmatic and straightforward. Reaping both tangible and intangible rewards from accomplishments achieved by doing so can last a long and healthy lifetime.

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