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The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy

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SUMMARY

Recent studies confirm that dietary methionine restriction increases both mean and maximal lifespan in rats and mice, achieving "aging retardant" effects very similar to those of caloric restriction, including a suppression of mitochondrial superoxide generation. Although voluntary caloric restriction is never likely to gain much popularity as a pro-longevity strategy for humans, it may be more feasible to achieve moderate methionine restriction, in light of the fact that vegan diets tend to be relatively low in this amino acid. Plant proteins – especially those derived from legumes or nuts – tend to be lower in methionine than animal proteins. Furthermore, the total protein content of vegan diets, as a function of calorie content, tends to be lower than that of omnivore diets, and plant protein has somewhat lower bioavailability than animal protein. Whole-food vegan diets that moderate bean and soy intake, while including ample amounts of fruit and wine or beer, can be quite low in methionine, while supplying abundant nutrition for health (assuming concurrent B12 supplementation). Furthermore, low-fat vegan diets, coupled with exercise training, can be expected to promote longevity by decreasing systemic levels of insulin and free IGF-I; the latter effect would be amplified by methionine restriction – though it is not clear whether IGF-I down-regulation is the sole basis for the impact of low-methionine diets on longevity in rodents.

Low-fat vegan diets may slow human aging

It has been suggested that long-term consumption of a low-fat, whole-food vegan diet, accompanied by regular aerobic exercise training, may at least modestly increase maximal lifespan in humans by down-regulating plasma levels of insulin and free IGF-I [1]. Down-regulation of insulin/IGF-I signaling in Caenorhabditis elegans, Drosophila, and rodents has been found to increase maximal and mean lifespan while slowing key aspects of the aging process; the well documented utility of caloric restriction in this regard is believed to be mediated, at least in part, by down-regulation of such signaling [2–6]. Treatment of various cell lines with serum obtained from calorically-restricted rats or monkeys results in decreased proliferation and increased tolerance to oxidants and heat, relative to cells grown with serum from ad-lib-fed animals; addition of insulin and IGF-I to the calorically-restricted serum largely reverses these effects [7]. Low-fat vegan diets, complemented by exercise, tend to promote leanness and muscle insulin sensitivity; the resulting down-regulation of insulin secretion can be expected to diminish hepatic production of IGF-I while increasing production of its functional antagonist IGFBP-1 [1,8,9]. Moreover, the relatively low content of certain essential amino acids in many vegan diets has the potential to decrease IGF-I synthesis [10–13]. In cross-sectional studies, vegans do indeed tend to have lower plasma IGF-I levels than omnivores or ovo-lacto-vegetarians [14–16]. Barnard has demonstrated that the Pritikin regimen – consisting of a very-low-fat, whole food quasi-vegan diet complemented by ample walking exercise – achieves a rapid down-regulation of plasma levels of insulin and free IGF-I [17–19].

In light of recent evidence, there may be an additional respect in which vegan diets can promote increased maximal lifespan – as contrasted to diets that incorporate animal products, vegan diets tend to be low in methionine (Met).

Methionine restriction boosts longevity in rodents

Over a decade ago, Orentreich and colleagues reported that dietary methionine restriction – cutting the Met content of rodent diets by 80% from 0.86% to 0.17% – was associated with a greater than 40% increase in both mean and maximal lifespan in Fischer 344 rats [20,21]. Importantly, the animals had *ad libitum* access to these diets – they were allowed to eat as much as they wished to achieve satiety. To rule out the possibility that this response reflected impact on a pathology to which this strain of rats is unusually prone, rather than an impact on aging per se (kidney failure, which often can be slowed by protein restriction, is a common cause of mortality in Fischer 344 rats [22]), these researchers have more recently

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tested Met restriction in three other rat strains – Brown Norway, Sprague Dawley, and Wistar Hannover [23]. Although, at time of publication, the studies had not yet progressed far enough to calculate maximal lifespans, the mean lifespans of the restricted rats had clearly been markedly enhanced, and survival curves were quite comparable to those seen with Fischer 344 rats. Meanwhile, other researchers have reported that a Met-restricted diet can increase maximal lifespan in mice [24]. As anticipated, the Met-restricted mice showed lower serum levels of IGF-I, insulin, glucose, and thyroid hormones. The onset of certain markers of aging – lens turbidity and alterations in T cell subsets – was delayed in the restricted mice, who were also noted to have greater resistance to hepatic oxidant stress induced by acetaminophen.

Although ad-lib-fed Met-restricted rats consume fewer calories per day than rats fed control diets, this reflects the fact that they grow slower and achieve a smaller adult size; their calorie consumption adjusted for body mass tends to be slightly greater than than of normally fed rats. Moreover, rats that are pair-fed with Met-restricted rats (but receiving normal chow) do not achieve an increase in longevity [23]. Thus, decreased caloric consumption does not account for the longevity effect of Met restriction.

No doubt, a portion of the impact of Met restriction on maximal longevity is mediated by down-regulation of hepatic IGF-I production. A relative dietary deficiency of any single essential amino acid has this impact in rodents [10–13]. In particular, one study reported that an 80% reduction in dietary Met content was associated with a 42% decrease in plasma IGF-I, as well as a doubling of plasma IGFBP-1 (a functional antagonist of IGF-I) in Wistar rats [13]. However, it is by no means certain that this is the only mechanism at play here, since, aside from its role in supporting protein synthesis and maintaining IGF-1 production – capacities shared by all essential amino acids – Met has a number of additional biological roles; it functions as a methyl donor (via its derivative *S*-adenosylmethionine), and as a precursor for taurine, polyamines, glutathione, and sulfate. (While cysteine can support synthesis of taurine, glutathione, and sulfate, it should be noted that the semi-purified diets used in Met-restriction protocols have not included cysteine or most other non-essential amino acids.) Whether restriction of essential amino acids other than Met might achieve a comparable impact on rodent longevity is not clear; while tryptophan restriction can indeed increase maximal lifespan in mice, it also *increases* mortality early in life, and thus is of little interest from a clinical standpoint [25].

Intriguingly, Pamplona and Barja report that long-term Met restriction reduces *ex vivo* superoxide production by complex I of the mitochondrial respiratory chain, while maintaining efficient state 3 and state 4 respiration; this effect is not seen in the presence of rotenone, suggesting that decreased reduction of the complex I superoxide generator accounted for this effect of Met restriction [26]. They have reported a similar effect for long-term restriction of calories or total protein [26–30]. This effect likely was not mediated solely by IGF-I or insulin down-regulation, since insulin or growth hormone treatment of calorically-restricted mice did not reverse the favorable effect of such restriction on hepatic mitochondrial superoxide production [31]. These favorable effects of calorie, protein, or Met restriction on mitochondrial oxidant stress were associated with a reduction in oxidative damage to mitochondrial DNA and proteins.

There is increasing evidence that the cumulative impact of mitochondrial oxidant stress on the structure and function of mitochondria may play a key role in the aging process, and that progressive mutation or deletion of mitochondrial DNA contributes importantly to aging [32]. Thus, knock-in mice expressing a "sloppy" mutant form of a mitochondrial DNA polymerase prone to proof-reading errors, experience decreased lifespan and signs of accelerated aging [33]. Conversely, mice overexpressing a form of catalase targeted to mitochondria enjoy an increase in median and maximal lifespans [34]. The ability of Met restriction to minimize respiratory electron leak may thus contribute importantly to its impact on longevity.

In light of the prominent antioxidant role of the intracellular reduced glutathione pool, and the fact that Met functions as a glutathione precursor, the impact of Met restriction on glutathione metabolism has been studied in rats. Surprisingly, although Met restriction decreased glutathione levels in liver and kidney, it did not have this effect on other tissues examined – and plasma glutathione levels were actually higher than in control rats [21]! This suggests that, as an adaptive response to Met deficiency, hepatic capacity to synthesize and export glutathione is up-regulated. Furthermore, despite the decrease in the hepatic glutathione pool, Met restriction in mice was associated with increased resistance to hepatic oxidant stress [35].

Of related interest is the intriguing observation that the fraction of Met found in the heart proteins of a species tends to correlate inversely with longevity [36]. This might reflect the fact that oxidation of protein-bound Met is one of the prominent ways in which oxidant stress can disrupt protein function [37]. Indeed, genetically altered mice deficient in the enzyme that repairs methionine sulfoxide residues have a decreased lifespan [38,39] – whereas, in Drosophila, increased expression of this enzyme prolongs survival [40]. It should be noted, however, that this phenomenon is not likely to contribute to the impact of Met restriction on longevity, since such restriction would not be expected to influence the relative expression of Met in tissue proteins.

Vegan diets can be low in methionine

Voluntary caloric restriction, while it may be feasible for some ascetic individuals [41] is unlikely to represent a truly practical technique for life prolongation in humans. Animals subjected to involuntary caloric restriction show signs of ravenous hunger, virtually attacking the food that is presented to them; and the high long-term failure rate of calorie-restricted dieting for weight loss in humans is well known. However, it is inherently easier to control intakes of protein and, in particular, methionine, owing to the fact that many vegan diets are relatively poor sources of methionine. This reflects three phenomena: First, the Met contents of plant proteins tend to be lower than those of animal proteins. Table 1 (calculated from data provided in Ref. [42]) reveals that the Met fraction in representative plant proteins ranges from 0.85% to 2.26%, whereas that of animal proteins falls into the range 2.34–3.11%. The fraction of methionine in legume protein (including

Table 1
Methionine contents of common foods

	% Met in protein	mg Met/kcal
Plant origin		
Wheat (bulgur)	1.55	0.57
Oatmeal	1.87	0.77
Brown rice	2.26	0.52
Corn	2.11	0.64
Soy (tofu)	1.28	1.36
Potato	1.61	0.42
Pinto beans	1.51	0.90
Black beans	1.51	1.01
Lentils	0.85	0.66
Peanuts	1.23	0.49
Almonds	1.15	0.32
Animal origin		
Chicken breast w/o skin	2.77	4.94
Beef, lean ground	2.34	2.05
Tuna	2.96	6.48
Milk, low-fat	2.51	1.97
Eggs	3.11	2.54

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soy) and nut protein is especially low. Secondly, the protein content of plant-derived foods, as a fraction of total calories, tends to be lower than that of animal-derived foods. Only soy products have a protein fraction comparable to that of some animal-derived foods – and soy protein is noted for its low-Met content! As a result, as indicated in Table 1, the Met content expressed as mg Met/kcal tends to be far lower in plant foods than in animal products. And finally, plant proteins tends to be digested less efficiently than animal proteins; animal protein is usually at least 90% available, whereas plant protein may be only about 80% available [43,44]. Thus, the disparities in bioavailable Met content between plant and animal products are actually understated by Table 1.

An additional factor may also be at work. Plant proteins tend to be relatively rich in glycine [45], which can acts as a functional Met antagonist by serving as a methyl group acceptor in a reaction catalyzed by glycine *N*-methlytransferase; this enzyme transfers a methyl group from *S*-adenosylmethionine to the amine group of glycine [46]. In rodents, a high-Met diet tends to elevate circulating cholesterol levels; this effect is antagonized by a concurrent high intake of glycine [47]. Indeed, the Met/glycine ratio of the diet is a determinant of plasma cholesterol in rodents [47,48].

Induction and spread of cancers in rats can be suppressed by feeding them a semi-purified diet in which soy protein is the sole protein source; this benefit is eliminated if extra Met is added to the soy-based diet [49]. As is well known, caloric restriction likewise retards cancer development in rodents. Down-regulation of systemic IGF-I activity is likely to play a role in both of these phenomena [50,51].

Vegans can keep their Met intakes relatively low by moderating their intakes of soy products and legumes, while diluting their total protein intake by ingesting ample amounts of fruit, wine, and/or beer. (Note however the comparatively low-Met density of lentils – on a mg per kcal basis, marginally higher than that of wheat or brown rice – and lower than that of oatmeal!) Protein dilution could also be achieved by including more plant oils in the diet; whether this would be advisable may hinge on the long-term impact of increased oil intake on insulin sensitivity. Very-low-fat diets coupled with exercise training can have a rapid insulin-sensitizing impact and in the longer term promote leanness [52–54] – effects that down-regulate insulin secretion, which should be favorable from a longevity standpoint [1]. However, it is conceivable that some lean, well-exercised individuals could increase their dietary intake of unsaturated oils without notably impairing their insulin sensitivity or leanness – studies have not yet assessed the impact of dietary fat modulation within the context of a vegan diet and regular exercise.

Theoretically, effective Met availability might be further reduced by ingesting supplemental glycine, which is inexpensive, delicious, and has anti-inflammatory effects which are potentially protective [55]. However, since dietary Met has an inductive impact on expression of glycine *N*-methyltransferase [56,57], dietary glycine may be less effective as a functional Met antagonist in the context of a low-Met diet.

Whether a feasible strategy of Met restriction, implemented consistently over most of a lifetime, could have a sufficient impact on Met availability to achieve a meaningful delay in the human aging process, remains a matter of speculation. To date, we still await confirmation that caloric restriction can increase maximal lifespan in primates to a worthwhile extent. Perhaps one way to assess the likely impact of a Met-restricted diet on human longevity would be to examine the long-term impact of such a diet on oxidation of mitochondrial DNA in leukocytes – though whether Met restriction influences this particular parameter in rodents is not yet known, as the relevant studies have targeted mitochondria obtained from liver or heart.

In any case, regular consumption of a low-fat, whole-food vegan diet, coupled with exercise training, is likely to have a favorable impact on *mean* longevity by reducing risk for cancers, coronary disease, and diabetes [45,58–60]. However, low systemic IGF-I activity seems likely to increase risk for hemorrhagic stroke, and possibly ischemic stroke as well, and is associated with poor prognosis following an ischemic stroke [61–65]. Furthermore, in Asian cultures, increasing intakes of animal products and total protein have been associated with declining stroke risk [66–70]. Since stroke is an uncommon cause of death in most strains of rodents, calorie/protein restriction studies in rodents can cast little light on the impact of such measures on stroke risk in humans. Vegans would thus be well advised to keep their blood pressures in the low-normal range throughout life, by employing a potassium-rich, low-salt diet, exercising, and staying lean [61].

Met plays a role in the endogenous synthesis of various "carnitrients", including L-carnitine, creatine, and taurine, that are not supplied by vegan diets, and that may play important roles in health promotion [71]. Thus, supplementation with these agents may be warranted in vegans practicing a Met-restricted diet. Furthermore, since selenium occurs naturally in foods primarily as protein-bound selenomethionine – substituted for Met in proteins – it follows that a low-Met diet is prone to be a low-selenium diet; selenium supplementation may be prudent for vegans who are trying to keep their Met intakes low [72]. Unsupplemented vegan diets are devoid of vitamin D, so vegans who lack access to year-round *uv* light should be sure to include this in their supplementation regimens [73]. And it should go without saying that supplementation with vitamin B12 is mandatory for vegans [74].

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