# A low-fat, whole-food vegan diet, as well as other strategies that down-regulate IGF-I activity, may slow the human aging process

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**Summary** A considerable amount of evidence is consistent with the proposition that systemic IGF-I activity acts as pacesetter in the aging process. A reduction in IGF-I activity is the common characteristic of rodents whose maximal lifespan has been increased by a wide range of genetic or dietary measures, including caloric restriction. The lifespans of breeds of dogs and strains of rats tend to be inversely proportional to their mature weight and IGF-I levels. The link between IGF-I and aging appears to be evolutionarily conserved; in worms and flies, lifespan is increased by reduction-of-function mutations in signaling intermediates homologous to those which mediate insulin/IGF-I activity in mammals. The fact that an increase in IGF-I activity plays a key role in the induction of sexual maturity, is consistent with a broader role for-IGF-I in aging regulation. If down-regulation of IGF-I activity could indeed slow aging in humans, a range of practical measures for achieving this may be at hand. These include a low-fat, whole-food, vegan diet, exercise training, soluble fiber, insulin sensitizers, appetite suppressants, and agents such as flax lignans, oral estrogen, or tamoxifen that decrease hepatic synthesis of IGF-I. Many of these measures would also be expected to decrease risk for common age-related diseases. Regimens combining several of these approaches might have a sufficient impact on IGF-I activity to achieve a useful retardation of the aging process. However, in light of the fact that IGF-I promotes endothelial production of nitric oxide and may be of especial importance to cerebrovascular health, additional measures for stroke preventionmost notably salt restrictionmay be advisable when attempting to down-regulate IGF-I activity as a pro-longevity strategy.
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## IGF-I ACTIVITY MAY BE A PACESETTER FOR AGING

There is growing evidence that IGF-I activity may be a major pacesetter of mammalian aging. Three different monogenic mutant strains of mouse – growth hormone receptor knock-out (Laron dwarf) mice (1–4), as well as the *Prop-1*(Ames dwarf) and *Pit-1* (Snell dwarf) strains (5–11), in which pituitary dysdifferentiation leads to re- duced production of growth hormone (GH), prolactin, and thyrotropin, are characterized by lifelong reductions in IGF-I levels as well a marked increase in lifespan (up to 60%). The only other monogenic mutation currently known to increase lifespan in mice is a loss-of-function mutation in p66Shc (12,13) – a possible mediator of IGF-I signaling. Caloric restriction markedly down-regulates IGF-I activity in mammals, both by reducing hepatic production of this growth factor (14–17), and also presumably by up-regulating IGFBP-1 production (a predictable consequence of the very low diurnal insulin levels in calorically restricted animals) (18–23); there is evidence that this down-regulation of IGF-I activity is primarily responsible for the prevention or retardation of tumor onset associated with caloric restriction (16,24).

Although GH production initially declines in young calorie-restricted rats, it eventually returns to control levels and by middle age exceeds the control value, owing to a marked retardation of the age-related decline in GH secretion; nonetheless, IGF-I levels remain below control levels throughout life in the restricted animals, consistent with the thesis that low IGF-I activity, rather than GH deficiency per se, is crucial to the prolongevity effect (17).

Hepatic IGF-I production also decreases when animals are fed diets deficient in one or more essential amino acids (25,26); a substantial increase in lifespan has been observed in rats fed low-methionine diets throughout life, despite calorie consumption that was high on a per-weight basis (27,28). Low-tryptophan diets likewise have increased maximal longevity in rats (29,30). Small breeds of dogs have longer lifespans than larger breeds – and lower levels of IGF-I (31–35). Conversely, strains of mouse selected for rapid early growth and maturity – likely indicative of increased IGF-I activity-have considerably reduced lifespans (36,37). Lifelong feeding of chromium picolinate (1 ppm chromium in the diet) to Long Evans rats, has been reported to increase median and maximal lifespan by 25%, while cutting serum insulin levels in half (38); this latter effect, other factors being equal, would be expected to decrease IGF-I activity by up-regulating hepatic production of IGFBP-1. Similarly, a modest increase in lifespan associated with decreased insulin secretion has been reported in mice treated throughout life with the drug phenformin (39).

Moving a bit further afield, in both worms (*Caenerhabditis elegans*) and Drosophila, mutations in the signaling pathways mediating the effects of hormones homologous to mammalian insulin/IGF-1, are associated with increased lifespan – as well as delayed or diminished fertility (40–43). Even in yeast, reduction-of-function mutations in signaling pathway components homologous to those involved in insulin/IGF-I signaling, are associated with increased stress resistance and longer post-mitotic survival (40,44). Bartke comments that 'these findings indicate that aging might be controlled by homologous genes and by similar metabolic mechanisms in organisms ranging from unicellular yeast to mammals.....insulin-IGF signaling is causally linked to aging across taxa' (42). Other scientists likewise point to insulin and IGF as key mediators of the aging process (40,41,43,45–47).

## WHY IGF-I?

IGF-I – arguably the 'universal growth factor' – can be viewed as a signal that integrates information regarding the availability of calories, stored fat, and protein, and relays this information to nearly every tissue in the body. A high IGF-I activity essentially implies that it is a propitious time for an animal to grow, achieve sexual maturity, and breed. Indeed, a boost in IGF-I activity appears to play a crucial role in initiating puberty and menarche (48–52). It is not likely to be coincidental that the current epidemic of childhood overnutrition, manifesting as increased rates of obesity and type 2 diabetes, has coincided with progressive reductions in the age of onset of sexual maturity (53,54). Conversely, low IGF-I activity signals that sexual maturity should be postponed until conditions are more favorable. If IGF-I acts as a pacesetter of development in early adulthood, it is not unreasonable to expect it to influence subsequent developmental milestones in the aging process.

As stated previously: 'In contradiction to the stochastic/error accumulation theories of aging, the aging process should be viewed as the latter part of a developmental continuum that commences with embryogenesis'. Aging doubtless reflects 'pre-programmed' subtle shifts in the differentiation state of stem cells and long-lived cells that ultimately (and inexorably) compromise the efficiency of organ function. Just as growth factor exposure regulates milestones in development – such as organogenesis and the onset of puberty – it is not unreasonable to expect such exposure to likewise regulate the pace of the yet-to-be-characterized differentiation shifts that constitute aging (47).'

Although a decrease in IGF-I activity appears to be a common theme in animals that, owing to genetic alterations or environmental conditions, achieve increased longevity, final proof that IGF-I is a pacesetter of aging may require the production of monogenic mutants of the IGF-I gene or IGF-I receptor gene that are characterized by partial loss of IGF-I function. If such animals can be shown to have increased longevity, this should constitute the definitive proof that IGF-I activity is a key determinant of the rate of development and aging.

What component(s) of the IGF-I signaling pathway is most crucial to its putative effects on the aging process–and thus needs to be down-regulated to optimize lifespan? The IRS/PI3K/Akt pathway does not seem to be a likely candidate in this regard, since down-regulation of this pathway would compromise glycemic control–resulting in the glucotoxicity characteristic of diabetes – while inducing a compensatory increase in insulin secretion. On the other hand, the pathway which activates the p42/p44 MAP kinases (via Shc (or IRS) and Ras) seems a more likely possibility, particularly in light of the greater lifespan enjoyed by loss-of-function p66Shc mutants (12,13). However. it has recently been reported that interaction between the EGF receptor and p66Shc fails to activate Ras or the MAP kinases; in this respect, p66Shc differs markedly from other, shorter products of the Shc gene, p52/p46Shc, that efficiently

activate Ras (55). The interaction between IGF-I and p66Shc has so far received little study, and the functional consequences of this interaction are unknown. p66Shc has been shown to act as a mediator of apoptosis in cells exposed to oxidants, which possibly explains why mice homozygous for p66Shc deficiency have increased tolerance for oxidant chemicals (12); this function of p66Shc is contingent on a serine phosphorylation of this molecule, and might be independent of any interaction with tyrosine kinase receptor activity. Thus, it is conceivable that the pro-longevity effect of p66Shc deficiency is unrelated to any impact on IGF-I activity. It should also be noted that IGF-I signals by some pathways that are independent of either IRS or the various isoforms of Shc (56); could these still obscure pathways play a role in the aging process? Evidently, further studies with genetically altered mice will be required to unravel this mystery. (In Drosophila and *C. elegans*, mutations of the Akt pathway are associated with increased lifespan (40,41) – but these animals presumably do not need to worry about diabetes!)

As is well known, the insulin receptor is a close relative of the IGF-I receptor, and signals by some of the same path way (e.g. IRS-1/2, Shc). Thus, it is conceivable that down-regulation of insulin secretion – independent of the suppressive impact that this has on free IGF-I levels – will complement the impact of IGF-I down-regulation on aging regulation. Of course, this should be achieved by measures that preserve good glucose control – measures which sensitize skeletal muscle to insulin (and thus down-regulate insulin secretion), that lessen the prandial stimulus to insulin release, or that decrease hepatic glucose output. The very marked reduction of fasting insulin noted in calorically restricted rodents (57), presumably reflects a marked decrease in postabsorptive hepatic glucose output; this evidently necessitates a strong down-regulation of insulin secretion to prevent hypoglycemia.

## PRACTICAL STRATEGIES FOR SLOWING HUMAN AGING

If we assume that IGF-I activity is indeed a pacesetter of aging, it follows that some healthful measures which down-regulate IGF-I activity may literally slow the aging process. As originally suggested by Parr (45), measures more practical and less draconian than lifelong semi-starvation may be useful in this regard.

There is considerable reason to suspect that a very-low-fat, whole-food vegan diet can down-regulate IGF-I activity – and that this effect may be largely responsible for the low risk for 'Western' cancers enjoyed by many rural Third World cultures (58,59). Such diets are likely to be characterized by decreased diurnal insulin secretion – attributable to the characterisitc leanness and insulin sensitivity of people who habitually consume very-low-fat vegan diets (60–64), to the typically lower glycemic index of whole foods, as well as to the absence of the potentiating impact of animal protein on postprandial insulin secretion (65). (With respect to the latter effect, Remer has reported that 24-h urine C-peptide levels increase by about 60% after egg protein is added to a low-protein quasi-vegan diet (66).) Furthermore, the so-called 'poor quality' of the protein supplied by vegan diets – i.e. the relative paucity of certain essential amino acids, including methionine – might be expected to decrease hepatic production of IGF-I whilst increasing that of its key antagonist IGFBP-1 (25,26,67). Indeed, the serum IGF-I levels of British vegans are reported to be significantly lower than those of age- and sex-matched controls whose habitual diets are omnivore or lacto-ovo-vegetarian (68). Thus, it is reasonable to expect that long-term practitioners of very-low-fat, whole-food vegan diets will tend to have lower serum levels of IGF-I and (owing to decreased insulin secretion) higher levels of IGFBP-1 – implying a rather substantial net reduction in circulating IGF-I activity (21,23). Such an effect is consistent with the fact that growth and achievement of sexual maturity are significantly delayed in rural Third World children as well as in children raised on macrobiotic vegan diets (69) – and it provides a satisfying explanation for the substantially lower rates of 'Western' cancers enjoyed by traditional Third World societies (58,70). The remarkably favorable vascular risk factor profile observed in macrobiotic vegans (71,72),the marked improvements in these risk factors (and in survival) achieved in heart patients following the quasi-vegan Pritikin or Ornish regimens (63,73–75), and the likely beneficial impact of such diets on risk for diabetes (76) and cancer, all strongly suggest that lifelong consumption of a low-fat, whole-food vegan diet should increase healthful survival, whether or not it impacts 'aging' per se. (A crucial proviso is that vegan diets require supplementation with vitamin B12.)

Moderation in calorie intake also evidently will decrease insulin secretion and IGF-I activity; this may be the mechanism whereby caloric restriction promotes longevity in rodents. However, it is not likely that healthy humans could voluntarily restrict their calorie intakes to a degree that would have a marked influence on lifespan; calorically restricted animals appear to be famished, quickly attacking food that is offered to them. In general, it is easier to control the *type* of food that one consumes, than the *quantity* of it. High-protein diets tend to have a superior satiating effect that, at least temporarily, is associated with decreased calorie intake (77,78); however, such diets would also likely promote increased hepatic IGF-I production. Meals that are high

in fiber, low in fat caloric density, or low in glycemic index also tend to decrease daily calorie intakes (79–84). Supplemental glucomannan has been shown to decrease calorie intake and promote weight loss in obese subjects (85–88). Anchors has suggested the use of safe appetite-suppressant drugs with durable efficacy (e.g phentermine + fluoxetine) (89) as a strategy for achieving modest chronic caloric restriction in non-obese subjects. A transgenic mouse that has diminished appetite, known as alpha MUPA, consumes 20% fewer calories than control mice when fed ad libitum – a phenomenon associated with a 20% increase in longevity (90).

Exercise training also down-regulates insulin secretion by promoting muscle insulin sensitivity and, in the longer term, leanness. It is notable that the Pritikin program, which incorporates daily walking exercise, achieves marked reductions in the fasting insulin levels of hyperinsulinemic patients (63). However, the increased calorie intake which strenuous exercise mandates would be expected to have a countervailing impact on insulin secretion that might blunt the overall benefit.

In addition to appropriate diet and exercise, there are additional practical measures that have the potential to down-regulate IGF-I activity. Agents which promote insulin sensitivity – and thus down-regulate insulin secretion-such as chromium picolinate (91,92) or thiazolidinediones (93), may have some utility in this regard-presuming that they do not also sensitize the body to IGF-I activity or boost hepatic production of IGFBP-1. Agents which blunt hepatic glucose output (such as metformin (94) or high-dose biotin (95)) may also decrease insulin secretion and thus diminish IGF-I activity. The postprandial insulin response can be dampened by supplementing meals with soluble fiber (96–98) – glucomannan generates the highest viscosity, and thus may be most practical in this regard (96) – and with vinegar (99–101); how vinegar decreases postprandial insulin secretion (without compromising glycemic control) is not yet clear.

Furthermore, there are certain phytochemicals, hormones, and drugs that act directly on the liver to decrease hepatic IGF-I secretion by unknown mechanisms; these include flax lignans (secoisolariciresinol diglucoside – SDG (102)), oral estrogen (103–105) and tamoxifen (106,107). Unfortunately, the lifespan-enhancing benefits of estrogen replacement are compromised by the fact that oral estrogen has pro-thrombotic effects (108) and can directly promote estrogen-responsive tumors; moreover, it is not appropriate for use by men. Tamoxifen has the shortcoming of increasing risk for endometrial cancer (109). However, flax lignans might not have these drawbacks, as they show versatile anticarcinogenic and cancer-retardant effects in rodent studies (110–114). Once SDG is available in sufficient quantities,

it will be of great interest to evaluate the clinical effects of this agent–and to note its impact on longevity in rodents.

Presumably, concurrent use of several appropriate measures may be required to achieve a marked down–regulation of IGF-I activity. Thus, one can envision a lifestyle incorporating a low-fat, whole-food vegan diet, exercise training, and a supplementation program that might include glucomannan, chromium picolinate, and flax lignans. It would be of considerable interest to determine how effectively such a program could decrease diurnal insulin and free IGF-I levels.

## A PROVISO IGF-I AND VASCULAR HEALTH

It should be acknowledged that low IGF-I activity may not be an altogether unmixed blessing. In particular, IGF-I promotes nitric oxide (NO) production by vascular endothelium – it increases the activity of the endothelial NO synthase by an Akt-mediated phosphorylation (115,116). That this phenomenon is of physiological importance is suggested by the fact that whole-body NO production, as well as endothelium-dependent vasodilation, are subnormal in patients who are GH-deficient – whereas GH administration rapidly corrects these abnormalities (117,118). Furthermore, IGF-I may aid vascular elasticity by inducing vascular elastin synthesis (119). On the other hand, IGF-I can also act directly on vascular smooth muscle cells and macrophages to promote intimal hyperplasia (120), and, in excess (as in acromegaly) it induces cardiomegaly (121). In humans, both deficiency and excess of GH are associated with increased vascular risk (122–125); in hypopituitary patients (receiving glucocorticoid/thyroid replacement), an increase in cerebrovascular mortality is particularly prominent (123). The adverse impact of GH deficiency on vascular health may be largely reflective of increased visceral adiposity (presumably attributable to the loss of GH's pro-lipolytic impact on visceral adipocytes) that gives rise to insulin resistance syndrome (126). However, the loss of IGF-I's favorable influence on endothelial function very likely plays a role as well.

A number of epidemiological studies have concluded that short humans tend to survive longer than tall humans (127). However, other studies (in Western populations) find that short stature, while protective in regard to cancer risk, is associated with increased vascular mortality (128–130). Perhaps this simply reflects the fact that a genetic tendency to produce lesser amounts of GH and/or IGF-I constitutes a risk factor for vascular disease.

The regimen for IGF-I down-regulation advocated here almost certainly has a net favorable impact on cardiovascular health – albeit for reasons that may have nothing to do with decreased IGF-I activity. And, most

likely, this regimen will tend to *increase* GH production, since, by decreasing serum levels of free IGF-I and free fatty acids, it can be expected to alleviate feedback suppression of GH release; indeed, much of the age-related decline in GH production may be secondary to the onset of visceral obesity, which increases this feedback suppression (131). However, it is conceivable that the decrease in IGF-I activity per se is not favorable to vascular health.

Societies which practice low-fat vegan diets throughout life enjoy excellent insulin sensitivity, are very lean, have very low LDL cholesterol levels, and are virtually immune to coronary disease; any adverse effect of a relatively low IGF-I activity on coronary health appears to be overwhelmed by countervailing protective effects. On the other hand, strokes–for which LDL cholesterol is not a prominent risk factor–is by no means rare in these societies, at least in those that consume salted diets. Over the last few decades, the incidence of stroke has dropped markedly in Japan, concurrent with an increase in animal product consumption; although decreased salt consumption and better pharmacological control of hypertension has contributed importantly to this effect, many researchers suspect that the increase in animal product intake has contributed to this favorable trend (132–134). Arguably, low IGF-I activity, aside from adversely impacting vascular NO production, could also render the cerebrovasculature more prone to rupture in the context of hypertension; hemorrhagic stroke is much more common in Japan than in the US. On the other hand, vegetarian and especially vegan diets, as well as exercise training, are associated with decreased blood pressure and good insulin sensitivity, both of which should lower stroke risk.

Perhaps the 'take-home' lesson should be that people who undertake to down-regulate IGF-I activity as a pro-longevity measure should take particular care to control their blood pressure and preserve their cerebrovascular health – in particular, they should keep salt intake relatively low while insuring an ample intake of potassium. It is notable that stroke and senile dementia appear to be virtually absent in Kitava, an Oceanic culture whose quasi-vegan traditional diet is very low in salt and very rich in potassium (135,136). Endothelial NO synthase activity can also be increased by statin therapy (137), estrogen replacement (138), and possibly policosanol (139).

A further potential drawback of low IGF-I activity is that it may not be consistent with optimally efficient wound healing (140,141). However, this issue is easily addressed by boosting IGF-I activity temporarily when faced with surgery or significant trauma. In this regard, when calorically restricted aging mice were temporarily fed ad libitum, their capacity for wound repair was found to be superior to that of mice of comparable age who had been fed ad libitum throughout life (142).

With respect to other putative beneficial effects of IGF-I on health, a recent study in elderly postmenopausal women has concluded that one year of IGF-I injections had no evident favorable impact on bone density, body composition, or psychological function (143). While it may be rash to jump to conclusions based on just one study, these findings suggest that the normal age-related decrease in serum IGF-I levels does not have the global negative impact on physiological structure and function that some have postulated. Benefits achieved with GH administration to the elderly may be largely independent of increased hepatic IGF-I production.

## CODA

Evidently, these speculations have taken us rather far out on a theoretical limb – we do not yet have clinching proof that caloric restriction increases lifespan in primates, or that down-regulation of insulin/IGF-I mediates its pro-longevity benefits in other species. But it seems rather likely that we are in fact 'barking up the right tree' on these issues – that IGF-I does indeed act as a pacesetter for the aging process. Provided that additional feasible measures are taken to promote cerebrovascular health, the lifestyle and supplementation regimen suggested here may have considerable potential for optimizing human 'healthspan'. For those who have the desire and self-discipline to adhere to such a lifestyle, the prospects for staying lean, smart, spry, and healthy into a very ripe old age may be better than most would suspect.

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