A Carbohydrate Concentration Regimen that Segregates Protein-Rich Foods into Low-Carb Meals May Represent a More Practical Way to Achieve the Healthspan Benefits Conferred by Calorie Restriction or Alternate-Day Fasting

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Abstract

Daily calorie restriction and alternate-day fasting boost healthspan and lifespan in rodents and other species, by chronically or episodically lowering blood level of insulin, free IGF-I, and glucose. However, these strategies are too draconian and stressful for most people to persist in voluntarily. For this reason, there is considerable interest in defining alternative lifestyle strategies that can provide a measure of the same metabolic benefit, but that are more feasible for people to stick with. Modified episodic fasting regimens, in which a modest calorie intake is allowed on "fasting" days, appear to be less stressful to implement than strict fasting approaches, and are achieving a measure of popularity. Alternatively, strategies which modify the timing or composition of meals in each day, such that insulin, free IGF-I, and glucose are kept relatively low for a number of consecutive hours in each 24 hour period, are also feasible. One simple approach is to eat one large meal daily; this however requires more fortitude than most people can muster. The carbohydrate concentration strategy requires that the bulk of the day's carbohydrate be ingested in one meal daily, and allows subsidiary meals providing protein/fat-rich foods and low-carb vegetables; this has the considerable merit of allowing people to eat their traditional foods dispersed in 3 meals a day. The efficacy of this strategy might be reinforced by segregating protein-rich foods from the carbohydrate-rich meal, as protein can notably boost the insulin response to co-ingested carbohydrate; choosing lower-glycemic index carbohydrate foods can also moderate postprandial insulin levels. Restricting high-quality protein – choosing plant-based foods of moderate protein content – can amplify the benefits of any of these strategies by down-regulating hepatic production of IGF-I. A carbohydrate concentration regimen that also segregates protein-rich foods to low-carb meals could be expected to promote leanness and metabolic benefits, and has the potential to be popular with the general public; formal clinical evaluation of this strategy is called for.

Calorie Restriction and Alternate-Day Fasting Boost Healthspan

Diets and lifestyles which minimize diurnal levels of insulin, free IGF-I, and glucose have potential for boosting lifespan and healthspan by promoting "cell cleaning" autophagy, cancer-preventive apoptosis, and antioxidant defenses. (For the technically inclined – these benefits appear to be achieved, in part, by down-regulation of cellular activities of mTORC1 and Akt, and up-regulation of those of AMPK, Sirt1, and FOXO factors.)[1, 2] These strategies also help to preserve the functional integrity of the brain, and of course tend to promote leanness. In rodent studies, these benefits are most effectively achieved with chronic daily calorie restriction, or with alternate-day fasting. However, aside from a few people who are exceptionally motivated, few humans are likely to voluntarily stick with such lifestyle strategies. Hence, more practical – if presumably somewhat less effective – strategies for repeatedly achieving prolonged

periods of low insulin, free IGF-I, and glucose, conceived of as modifications of the alternate-day fasting paradigm, have been proposed and, to some minor degree, studied clinically.

Episodic Modified Fasting

The Modified Alternate-Day Fasting protocol of Johnson and Laub allows a small number of calories – in the range of 400 kcals, or 20% of usual daily calorie intake - to be ingesting on "fasting"days.[3, 4] In their experience, this is more feasible for most people than total fasting on the fast days. They have demonstrated that this approach has important anti-inflammatory benefit, and in particular can help overweight asthma patients markedly improve their symptoms.[5] Health journalist Michael Mosley has recently proposed a protocol in which very low levels of calories are ingested for two consecutive days per week; a number of people claim to have used this program with good benefit.[6] Dr. Benjamin Horne has published epidemiology suggesting that the traditional Mormon custom of fasting one day per month is associated with a significant reduction in risk for cardiovascular disease and diabetes.[7-9]

Modifying Daily Eating Patterns – Meal Skipping and Carbohydrate Concentration

A different category of "longevity" strategies seeks to configure food consumption within each day so that insulin, free IGF-I, and glucose levels remain relatively low for extended periods. One way to achieve this is to restrict oneself to one large meal a day; Drs. Mark Mattson and Bert Herring have suggested this approach.[10-12] A clinical effort to compare this strategy to standard 3-meal-a-day eating did not have a very impressive outcome, presumably largely because the volunteers in the one-meal-a-day arm were required to consume as many calories in their one meal as the control group did in three; subjects given a free choice would most likely have consumed less, at least until they became exceptionally lean.[13, 14]

Most people are used to consuming three or at least two meals daily, and for this reason it is hard to see a one-meal-a-day plan becoming widely popular, although some individuals can manage it. Carbohydrate concentration diets – initially proposed by Drs. Richard and Rachel Heller in their best-sellling "Carbohydrate Addict's Diet" – require that the large majority of the day's carbohydrate ingestion be confined to one daily "reward meal".[1, 15-17] Other meals or snacks must be comprised of foods high in protein and/or fat, along with some low calorie vegetables. Anecdotally, this strategy often tends to promote weight loss and ancillary metabolic benefits, especially if saturated fat intake is kept relatively low. A study by Sofer and colleagues has recently demonstrated that, within the context of moderate daily calorie restriction, subjects who confine their main carbohydrate intake to one meal a day achieve greater weight loss and metabolic benefit than those eating an identical number of calories per day, but dispersing their carbohydrate intake across several meals.[18] Carbohydrate concentrated diets can be expected to keep insulin, free IGF-I, and glucose levels relatively low for about 19 consecutive hours during each 24 hour period – albeit these reductions will not be so intense as those achieved during alternate-day fasting. The Catalytic Longevity website has posted an extensive essay marshaling suggestive evidence that the carbohydrate concentration strategy may be a more practical way to achieve, at least in some measure, the metabolic benefits associated with daily calorie restriction or episodic fasting.[1] A key merit of this approach, from the standpoint of practicality and compliance, is that it allows people to eat their traditional foods in three daily meals – they only need to alter the distribution of these foods; it is a new way of eating, rather than a new "diet".

The Impact of Protein Consumption – Decreasing IGF-I

Nature and timing of protein intake may also be an important consideration in these respects. In humans, keeping the daily intake of total protein, and most particularly, "high-quality" animal protein, relatively low is associated with a marked decrease in plasma IGF-I levels. Surprisingly, moderate daily calorie restriction, while it tends to lower systemic IGF-I levels in rodents, fails to do so in humans – unless accompanied by protein restriction.[19] This is a key consideration, since systemic IGF-I activity is generally considered to be the chief pace-setter of the aging process, in species ranging from roundworms to rodents and possibly primates.[20] Protein restriction regimens likely lower circulating IGF-I because a relative paucity of essential amino acids sensed by the liver down-regulates the liver's production and secretion of IGF-I.[21, 22] It is however important to note that, to the degree that various "longevity" regimens keep insulin levels low for an extended time, they can be expected to decrease systemic IGF-I *bioactivity*, owing to the fact that the liver secretes a higher amount of the IGF-I antagonist IGFBP-1 when insulin is low.[23, 24] Nonetheless, if this phenomenon is complemented by a reduction in the absolute plasma level of IGF-I, owing to food choices that minimize intake of animal proteins and feature moderate amounts of plant protein, it is evident that a very substantial reduction of systemic IGF-I activity should be achievable.

In this regard, plant-based diets practiced at the Pritikin Clinics have been shown to markedly decrease absolute and free IGF-I levels in heart patients.[25, 26] Although such diets do not entail episodic fasting or carbohydrate concentration, diurnal insulin levels tend to be relatively low because the low ratio of saturated to unsaturated fat in such diets tends to improve muscle insulin sensitivity, leading to a down-regulation of fasting insulin.[27] Emphasis on lower-glycemic-index carb sources also contributes to this benefit – and another phenomenon which we will now discuss also may keep post-prandial insulin levels somewhat lower.

Protein Potentiates the Insulin Response to Carbohydrate

Although pure dietary protein is a relatively weak stimulant to insulin release, a considerable research literature indicates that protein ingestion can quite markedly potentiate the insulin response to co-ingested carbohydrate.[28-31] For example, in a study by Spiller and colleagues, adding about 15 g or more of protein to a meal containing 58 g of carbohydrate was found to approximately double the post-prandial insulin response.[29] This phenomenon is likely to be minimized by vegan meals, unless they include ample amounts of plant-protein concentrates or soy products. Fortunately, beans tend to yield a relatively low "insulin index", likely because both their starch and their protein content are digested and absorbed gradually.[32, 33] Hence, the relatively low quantity of protein in most vegan meals may moderate the post-prandial insulin responses of vegans, not unlikely contributing to their characteristic leanness and favorable risk factor profile.[34]

Remer and colleagues conducted a cross-over study comparing two diets identical in calories.[35] One was essentially vegan, providing 50 g of protein and 282 g of carbohydrate daily. The second diet differed only in that 32 g of egg protein was added, replacing 14 g of fat. The amount of C-peptide in 24 hour urine was used to estimate diurnal insulin secretion (one molecule of C-peptide is produced for each molecule of insulin secreted, and most of this C-peptide is excreted in the urine). Daily C-peptide excretion was found to be 60% greater when the subjects were consuming egg protein. This provides rather cogent evidence that moderating total protein intake can decrease daily insulin secretion.

Protein Segregation Strategies

However, it is not necessary to become vegan – which many people would be loath to do – to take advantage of this phenomenon. If high-protein foods are segregated into meals relatively low in carbohydrates – featuring low-carbohydrate vegetables and salads, for example – and carbohydrate-rich foods are ingested in quasi-vegan meals relatively low in protein, the phenomenon of protein-potentiated insulin release should be minimized, helping to moderate diurnal insulin.[34] Surprisingly, this strategy is a standard tenet of traditional "food combining" diets, and is a feature of the "Fit for Life" diet program promoted by Marilyn and Harvey Diamond.[36] The rationales offered in support of this strategy make no sense from the standpoint of modern physiology – for which reason such diets are often stigmatized as quackish – but in practice this strategy may indeed be useful.

A clinical study published by Dr. Marthinette Slabber and colleagues suggests that the strategy of segregating high-protein foods into low-carbohydrate meals may in fact have merit.[37] These researchers compared two diets of essentially identical, moderately restricted calorie content, ingested over 12 weeks. One diet was a typical mixed diet; the other diet, although similar not only in calorie content, but also the relative proportion of carbohydrate, protein, and fat, was configured to be "low insulin response". This was achieved by recommending lower-glycemic-index starchy foods – and by also banning the co-ingestion of high-protein and high-carbohydrate foods. The carbohydrates were consumed in two quasi-vegan meals daily, and one meal featured a goodly intake of animal protein often accompanied by low-carbohydrate vegetables. (One way to think of this is that "Pritikin" and "Atkins" meals were alternated!) During the twelve weeks, subjects on the low-insulin-response diet lost significantly more weight (9.4 kg vs 7.4 kg, respectively) and achieved greater metabolic benefit; notably, fasting insulin levels dropped by nearly half on the low-insulin-response diet, as opposed to only a 12% drop on the control diet. Yet analysis of food records indicated that the two groups had been eating similar levels of calories. After this initial study, 16 of the subjects, after a washout period, agreed to be crossed over to the other diet for 12 weeks. The results confirmed that the low-insulin-response diet was associated with greater reductions in body weight and fasting insulin. This ground-breaking study appears to have received minimal attention in academic circles or in the popular media.

To provide more conclusive confirmation for the utility of the protein segregation strategy, it would be good to repeat the Slabber study while keeping the glycemic index of the two diets the same. It would also be good to measure body composition rather than just weight, to confirm a greater impact on fat loss.

Hybrid Approaches May Optimize Benefits

It evidently should be feasible to combine some of these principles in hybrid strategies. For example, protein segregation could be practiced on a carbohydrate concentration diet – the high-carb "reward meal" could be quasi-vegan and modest in protein content, to minimize the post-prandial insulin response to this meal. This would however differ from the regimen studied by Slabber in that one rather than two meals daily would highlight carbohydrate. It would also be feasible to configure a carbohydrate concentration diet such that it is vegan or quasi-vegan, and hence down-regulates plasma IGF-I levels. Jenkins and colleagues have described an "eco-Atkins" eating strategy that is relatively low in carbohydrate, but features plant-derived foods – nuts, seeds, soy products, olives, avocadoes, and low-carb vegetables; the metabolic response to such a diet was highly favorable.[38] Such foods could be employed for the low-carb

meals of a carbohydrate concentration diet, such that the diet was vegan or quasi-vegan. And there is no reason why vegan diets couldn't incorporate episodic modified fasting or calorie restriction.

From the standpoint of the American public, a carbohydrate concentrated diet that was also protein segregated – in which the carb-rich meal was quasi-vegan, but animal products could be consumed in the alternate meals, if desired - might have a chance to achieve reasonable compliance and popularity, since people would be allowed to eat most of the same foods they typically eat, dispersed in up to 3 meals daily – only the *pattern* of food consumption would change. And yet a marked reduction in diurnal insulin secretion, with extended periods in which insulin, free IGF-I, and glucose were relatively low, could be anticipated with such a diet. A formal clinical evaluation examining the impact of such a regimen on body composition and risk factors, and assessing its feasibility for motivated people, could prove very worthwhile.

Although purists may be inclined to scoff at strategies which they consider "half-way measures" for healthspan promotion, an analysis of the recent results reported in studies of long-term calorie restriction in rhesus monkeys suggests that, for primates, a relatively modest degree of calorie restriction may achieve near-optimal benefit.[39] Hence, whereas rodents may be markedly benefited by calorie restriction in the 30-40% range, a 10% restriction, analogous to what Okinawans achieved in the mid-twentieth century,[40] may provide about as much benefit as primates – presumably including humans - are likely to receive. If that is the case, then the less draconian, more practical strategies surveyed here may be not too far from the mark with respect to optimizing healthspan in humans.

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