signaling molecules or by inducing a metabolic shift through altered substrate availability? Finally, UCP1 appears to be a major target of EODF, but recent work in this field has also highlighted the importance of UCP1-independent pathways for adaptive thermogenesis (Kazak et al., 2015; Long et al., 2016). In the future, it will be important to determine the relative contributions of these pathways to identify the most relevant target(s) in this paradigm.

In addition to potential therapeutic applicability, can these findings be applied in lifestyle management approaches? As reported previously, EODF is effective at improving overall metabolic health, even in a context of pre-existing HFD-induced obesity and while maintaining a high-fat diet in mice as well as in humans (Longo and Mattson, 2014), suggesting that obese patients likely remain sensitive to stimuli inducing beiging. However, the effects of EODF were not permanent; restarting *ad libitum* feeding induced a steady reduction in beiging and weight gain, returning mice within 15 days to their initial metabolic condition. There is also little evidence that the mechanism of beiging is conserved in humans; studies indicate unchanged energy expenditure and unchanged body temperature in patients following these regimes (Longo and Mattson, 2014). Consequently, it remains to be seen how much of the present findings will translate to humans.

Still, it is highly intriguing that the beneficial metabolic effects of EODF are not observed during fasting per se, but rather during the binge-eating period following the fast. Therefore, while reducing caloric intake remains the best advice for weight loss in obesity, the findings reported here may also be ill-interpreted as "Don't eat that burger today, eat two tomorrow instead."

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Dietary Carbohydrates Impair Healthspan and Promote Mortality

Meenakshi Ravichandran,[1,2] Gerald Grandl,[3] and Michael Ristow[1,*]
[1]Energy Metabolism Laboratory, Institute of Translational Medicine, Swiss Federal Institute of Technology (ETH) Zurich, Zurich-Schwerzenbach 8603, Switzerland
[2]Life Sciences Zurich Graduate School, Molecular and Translational Biomedicine Program, Zurich 8055, Switzerland
[3]Institute for Diabetes and Obesity, Helmholtz Zentrum München, Garching 85748, Germany
*Correspondence: michael-ristow@ethz.ch
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The prospective cohort study, named PURE, found that in >135,000 participants from 18 countries, nutritive carbohydrates increase human mortality, whereas dietary fat reduces it, requesting a fundamental change of current nutritional guidelines. Experimental evidence from animal models provides synergizing mechanistic concepts as well as pharmacological options to mimic low-carb or ketogenic diets.

It has been known since the 1930s that global reduction of food uptake, so-called calorie restriction, extends the lifespan of rodents, other model organisms, including rhesus monkeys, and possibly humans due to an interacting set of experimentally established mechanisms. By contrast and based on observational coincidence rather than prospective causality, dietary recommendations to maintain human health have selectively focused on reduction of nutritive fats, specifically of saturated triglycerides contained within, since the 1970s. An increasing number of prospective studies in large cohorts of humans in the last two decades have repeatedly questioned this practice but have remained widely unnoticed in the general public and also in major parts of the scientific community.

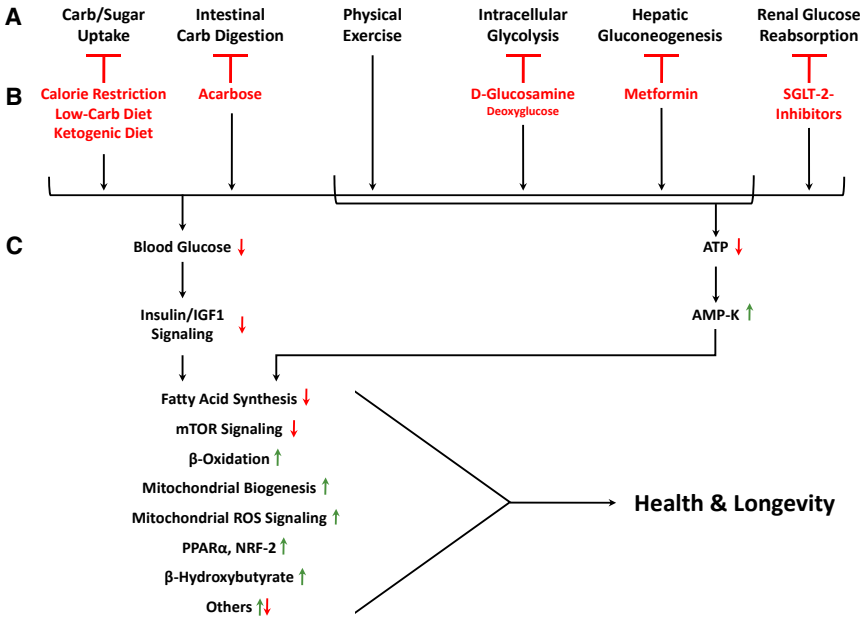

Figure 1. Factors, Modulators, and Executers of Carbohydrate-Mediated Healthspan Regulation

(A) Physiological and environmental factors that may regulate healthspan in relation to carbohydrate uptake or glucose catabolism.

(B) Therapeutic modulators of the individual factors depicted above.

(C) Selected mechanistic regulators that cumulatively mediate the downstream execution of (A) and (B), respectively.

Recently, the findings of the PURE study, consisting of >135,000 individuals recruited from 18 countries of different developmental stages worldwide, has been published (Dehghan et al., 2017). While clinical parameters, socio-economic factors, and detailed food and exercise questionnaires were obtained during initiation of the study, and individuals with pre-existing cardiovascular diseases (but not diabetes) were excluded, after a median follow-up of 7.4 years, together more than 10,000 deaths or events, like myocardial infarction or stroke, had occurred. These were then statistically correlated with the parameters at initiation. Dehghan et al. (2017) found that carbohydrate intake was associated with increased total mortality. By contrast, any (saturated/monounsaturated/polyunsaturated) type of dietary fat reduced the likelihood of dying. Moreover, there was no link to cardiovascular events or related mortality, except for saturated fats, which were unexpectedly associated with a lower risk of stroke. Consistently, Dehghan et al. (2017) conclude that "global dietary guidelines should be reconsidered."

Most dietary carbohydrates relevant for human nutrition contain the monosaccharide D-glucose as a key building block, which, consequently, is transported into the blood to exert release of insulin from the pancreatic β cells. Glucose is ultimately transported into and metabolized within multiple cell types in a partly insulin-dependent fashion. Impaired insulin and/or insulin-like growth factor 1 (IGF-1) signaling has been shown to extend the lifespan of various model organisms (Friedman and Johnson, 1988 and follow-ups). The glucose-induced release of insulin to activate the corresponding signaling cascade may be considered the key reason as to how increased carbohydrate uptake promotes mortality (Figure 1). Conversely, hyperinsulinemia not only is a hallmark of lifespan-impairing type 2 diabetes, but also specifically promotes malignant growth as reflected by an increased incidence of cancers in diabetics. Notably, while the PURE study could not establish an increase in mortality from cardiovascular causes (see above), the observed increase in global mortality likely is related to the second-frequent cause of death, namely cancers, in states of high-carbohydrate uptake.

From a therapeutic perspective, if carbohydrates are relevant factors in promoting mortality, then not only reduced uptake of these, but also inhibition of carbohydrate uptake or glucose catabolism should extend lifespan. This has been experimentally tested (Figure 1).

(1) The conversion of D-glucose into metabolic intermediates, namely glycolysis, can be inhibited by compounds like (the highly efficient but rather toxic) 2-deoxy-D-glucose or (the less efficient but completely harmless) D-glucosamine (GlcN). The latter is widely used to treat arthrosis with the questionable claim of inducing cartilage regeneration. Both compounds have been shown to extend *C. elegans* lifespan (Schulz et al., 2007; Weimer et al., 2014), while only GlcN extends lifespan in rodents (Weimer et al., 2014). Notably, GlcN uptake has been also associated with reduced mortality in a large human cohort (Bell et al., 2012).

(2) Acarbose is an inhibitor of alpha-glucosidase, an enzyme that releases D-glucose from complex nutritive carbohydrates, most importantly starch, in the intestine. It has been used for the treatment of diabetics to prevent absorption of carbohydrates from the gut since the 1980s. Consistent with the role of carbohydrates in impairing health, acarbose has been shown to extend the lifespan of mice (Harrison et al., 2014).

(3) Inhibitors of the renal sodium-glucose co-transporter 2 (SGLT-2) promote removal of D-glucose from the blood via the urine. These rather newly developed inhibitors are being used for the treatment of diabetics. Potential effects on lifespan of model organisms or humans have not been published to date but appear warranted.

(4) The antidiabetic compound metformin, which is currently under prospective investigation in regards to lifespan extension (TAME

study), exerts its action by reducing glucose production (gluconeogenesis) from the liver, and hence to cause a reduction in circulating blood glucose.

Next, a number of studies have evaluated the effects of specific macronutrients on lifespan, initially in *S. cerevisiae* (Lin et al., 2002), subsequently in *C. elegans* (Schulz et al., 2007 and follow-ups), and mice. Out of the latter, two studies in the previous issue of *Cell Metabolism* have studied this in mice starting at 12 months of age. In regards to the PURE study, most notably, the almost complete removal of carbohydrates (<1%) from the diet to generate a ketogenic diet extended lifespan compared to a high-carb diet. However, reconstituting only 10% of energy of the ketogenic diet by sugar abolished this effect (Roberts et al., 2017), suggesting that specifically sugar (rather than carbohydrates in general) has the most relevant effect on lifespan. Along this line, it is also interesting to note that when nutritive sugar content is kept constant, a different (and less extreme) high-carb diet exerts the best effects on murine lifespan. By contrast, a high-fat diet still containing the same amount of sugar, but no other carbs reduced lifespan slightly. Lastly, when combining high-fat and high-carb components from the two previous diets, the worst effect on lifespan was observed (Keipert et al., 2011). Moreover, lifespan extension in mice was also obtained when dietary protein was replaced by carbs, possibly independent of the total uptake in calories (Solon-Biet et al., 2014). Taken together, these studies suggest that dietary sugar may be one important, but not the only, nutritional factor in limiting healthspan in rodents, hence additional studies are definitely required to establish firm evidence in model organisms.

The PURE study has already been criticized for misleadingly generalizing a statistical effect that may be also due to confounding factors. Specifically, income- and geography-dependent nutritional habits of specific subgroups would not be applicable to westernized high-income societies (which, however, had been included into PURE). Indeed, Dehghan et al. (2017) did not analyze which specific source of carbohydrates (e.g., sugar/refined carbs versus whole-grain products) may contribute to the detrimental effects of carbs observed, especially since income and wealth do impact the quality of dietary choices significantly. This criticism, however, misses the fact that a (not immediately accessible) re-analysis additionally adjusting for household income and wealth, as well as for socioeconomic status of the respective country, did not affect the key observations of the study by any means (appendix, p. 34 of Dehghan et al., 2017).

Taking the body of preceding evidence both from model organisms as well as human epidemiology into account, we therefore believe that current nutritional recommendations in regards to macronutrients, but most importantly in regards to refined carbs and sugar, should indeed be fundamentally reconsidered. Moreover, pharmacological options to mimic low-carb nutrition (i.e., without the need for an actual reduction of carbohydrate intake; Figure 1) may offer a promising approach easier to obtain than achieving changes in nutritional habits of the general population.

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