Review

Targeting glucose metabolism for healthy aging

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Abstract. Advancing age is the greatest single risk factor for numerous chronic diseases. Thus, the ability to target the aging process can facilitate improved healthspan and potentially lifespan. Lack of adequate glucoregulatory control remains a recurrent theme accompanying aging and chronic disease, while numerous longevity interventions result in maintenance of glucoregulatory control. In this review, we propose targeting glucose metabolism to enhance regulatory control as a means to ameliorate the aging process. We highlight that calorie restriction improves glucoregulatory control and extends both lifespan and healthspan in model organisms, but we also indicate more practical interventions (i.e., calorie restriction mimetics) are desirable for clinical application in humans. Of the calorie restriction mimetics being investigated, we focus on the type 2 diabetes drug acarbose, an α-glucosidase inhibitor that when taken with a meal, results in reduced enzymatic degradation and absorption of glucose from complex carbohydrates. We discuss alternatives to acarbose that yield similar physiologic effects and describe dietary sources (e.g., sweet potatoes, legumes, and berries) of bioactive compounds with α-glucosidase inhibitory activity. We indicate future research should include exploration of how non-caloric compounds like α-glucosidase inhibitors modify macronutrient metabolism prior to disease onset, which may guide nutritional/lifestyle interventions to support health and reduce age-related disease risk.

Keywords: Glucose, aging, diabetes, disease, glucosidase inhibitor, insulin, calorie restriction

Non-Standard Abbreviations:

ACA   acarbose
CR   calorie restriction
CRM   calorie restriction mimetic
T2D   type 2 diabetes
PPG   post-prandial glucose

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1. Aging as a risk factor for disease

Aging is considered the largest risk factor for a variety of chronic and metabolic diseases [1]. More than any other individual factor, advancing age increases the risk for type 2 diabetes (T2D), neurodegenerative diseases (i.e., Alzheimer's disease, Parkinson's disease), cancer, heart disease, and stroke [2–6]. Unlike many risk factors (i.e., smoking, diet, weight gain), aging, by strict definition as the act of growing old, has not historically been considered to be modifiable. Aging and risk of disease

development are so well intertwined that skepticism surrounding the idea of longevity extension persists, as a longer lifespan is considered by some as simply a prolonged opportunity to develop additional age-related diseases [7, 8]. Despite this concern, contemporary pursuit of methods to increase lifespan and healthspan through the process of slowing the accumulation of age-related damage to cells and tissues continues [9].

Conceivably, an intervention to extend lifespan and/or healthspan would act through slowing the fundamental aging process(es) rather than preventing a single disease [10]. It is possible that interventions to slow the aging process may result in an individual experiencing an extension of healthspan without significant increases to lifespan, as it is currently unknown if maximal lifespan can be extended in humans. Therefore, an individual might experience a compressed window of morbidity by living the great majority or potentially the entirety of lifespan without developing the disorders now commonly associated with aging.

A common co-morbidity observed in aging is metabolic dysfunction [11, 12]. While metabolic (e.g., glucose and mitochondrial) dysfunction is frequently associated with aging, the causal relationship between aging and metabolic dysfunction remains to be fully understood [13, 14]. The risk relationships among age and metabolic associated diseases suggest some factors may be better primary targets for longevity interventions than others. For instance, curing cancer may not necessarily be expected to significantly affect the subsequent risk for T2D or cardiovascular disease [15]. In contrast, cardiovascular disease and T2D are more widely recognized as possible contributors to neurological disease risk and when remediated, could reduce the risk of dementia and neurodegenerative disease [16–18]. Considering the coordinate increase in risk for a number of chronic diseases with advancing age and given the unclear interrelationship between these diseases, a stronger case might be made for targeting glucoregulatory control to decrease disease risk and consequently improve longevity (Fig. 1). In fact, T2D is a significant risk factor for most other age-related diseases (e.g., cardiovascular disease, neurodegenerative disease, cancer, kidney disease) [17, 19–22]. If glycemic control were successfully maintained with advanced chronological age, this might slow the aging process, potentially delaying or preventing the development of multiple age-related diseases, allowing an individual to live healthier for longer (Fig. 1).

Exactly which cellular or molecular mechanism(s) is primarily responsible for the associations of elevated glucose with chronic disease risks is not fully understood. Proposed causative mechanisms leading to accelerated aging include direct methods such as amplified and inappropriate glycosylation events, along with the production of advanced glycation end products that damage cellular functions from DNA repair to structural integrity [23] and indirect contribution to the production of reactive oxygen species [24, 25]. Alternatively, maintenance of glycemic control may function as a biomarker of health maintenance from the cell to the organismal level. As such, one might expect a range of interventions targeting diverse mechanisms could share this glucoregulatory phenotype, resulting from some combination of maintained integrity of the cell, organelles, hormonal signaling or other factors coordinating metabolism and ultimately aging across the organism. Thus by indirect means, changes in glucose levels could significantly impact transcriptional programs or hormonal signaling to coordinately regulate processes currently known (or unknown) to influence the aging process (e.g., mitochondrial function, autophagy) [26–30].

2. Glucose regulation in aging

Glucose dysregulation, measured as either hypoglycemia or hyperglycemia, can result from problems along the entire glucose uptake, production, and metabolism spectrum. Hyperglycemia is commonly associated with advancing age and can occur as a result of decreasing insulin release in response to glucose and/or increased insulin resistance by tissues [31, 32]. T2D is diagnosed by chronically elevated blood glucose, either as a fasting blood glucose level greater than 126 mg/dL or a 2-hour post-oral glucose tolerance test blood glucose level greater than 200 mg/dL, while impaired fasting glucose is the recommended diagnosis for elevated blood glucose from 110–125 mg/dL [33], both of which may be accompanied by hyperinsulinemia and/or insulin resistance.

Recent surveys of the adult population in the United States suggest that ≥50% of individuals over 45 years of age have T2D or prediabetes [34]. This prevalence is greater with increasing age, with ∼80% of older adults (age > 65) showing glucose dysregulation. Thus, impaired glycemic control is approaching epidemic proportions both in the U.S. and throughout the world [35–37]. Although the source of the
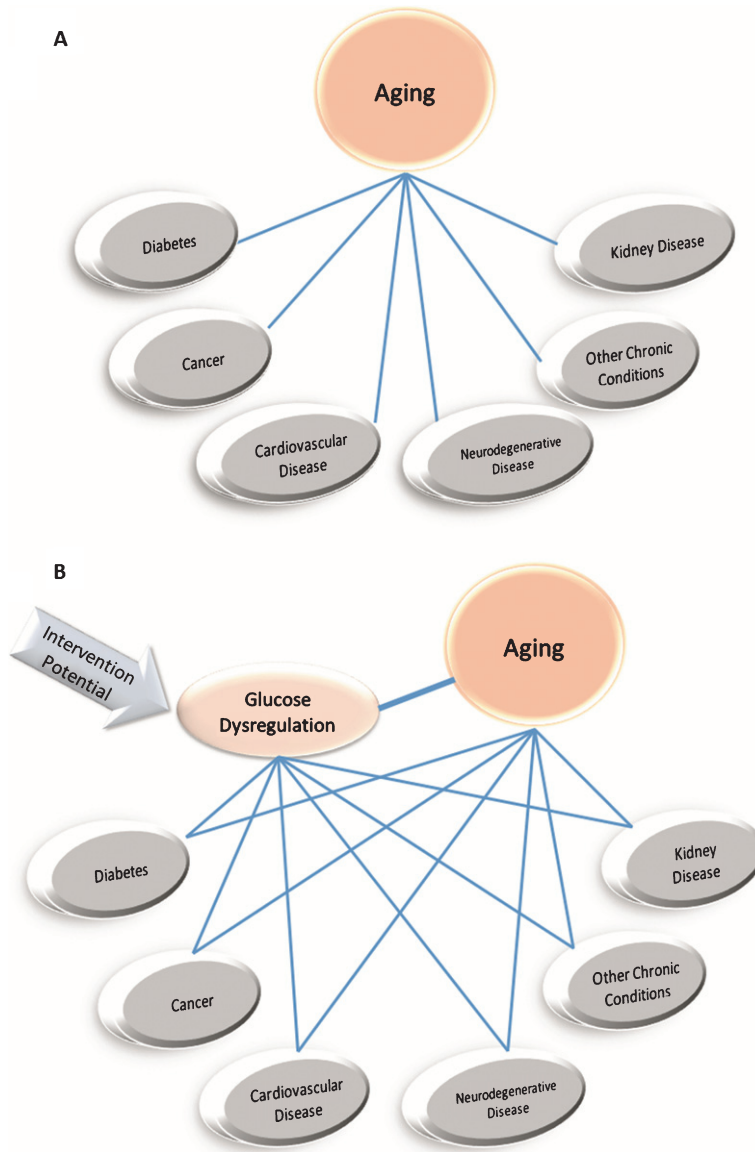
Fig. 1. Aging as a risk factor for chronic disease. A. Aging is the number one risk factor for the most prevalent metabolic and chronic diseases in developed countries. B. Glucose dysregulation, however, is also a major risk factor for many of these same "age"-related diseases, suggesting interventions that maintain or improve glucoregulatory control to prevent, delay or treat T2D (e.g., acarbose, metformin) may have manifold benefits related to other chronic diseases associated with aging.

metabolic imbalance driving glucose dysregulation may have multiple contributors, a surfeit of energy intake with increasing body weight and BMI are proposed to contribute [38]. Considering the advancing wave of senior adults in the "baby boomer" generation with their current health and fitness status, interventions targeting protection and improvements in glycemic control should hold high priority [39].

3. Glycemic control in nutrition and genetic aging interventions

At a metabolic level, improved glucoregulatory control is a hallmark of successful aging in multiple nutrition and genetic models across model organisms. Improved glycemic control is often present despite no obvious or significant reductions in relative

body fatness, suggesting, independent of adiposity, glucose levels may serve as a biomarker of factors downstream or in addition to the glucose metabolism (e.g., insulin sensitivity and hormonal signaling) which may be mediating a portion of this relationship [40]. For instance, multiple pre-clinical, rodent models with improved longevity profiles have coincident improvements in glucose levels or insulin responsiveness, despite the nutrition or genetic interventions targeting a multiplicity of alternative pathways. Table 1 presents an overview of selected lifespan-extending interventions, summarizing the diversity of interventions with similar glucose responses. However, improved insulin sensitivity is not universally the case, as a few genetic and pharmaceutical models of increased longevity have been observed to induce insulin resistance, albeit at times still in the context of reduced circulating glucose [41–45]. These less common exceptions where longevity extension is uncoupled from improved glucose metabolism include cases where the insulin signaling pathway in the brain is disrupted resulting in increased longevity (relative to within study controls) despite mild glucose intolerance, or where downstream signaling is inhibited with normal glucose metabolism, as compared with whole body effects where insulin sensitivity is improved concomitant with increased lifespan [43, 46]. Similarly, inhibition of TOR (target of rapamycin) activity through rapamycin treatment and/or genetic means has been reported to extend lifespan in healthy, non-diabetic mice under normal laboratory conditions despite inducing some level of glucose intolerance and insulin resistance, particularly in male mice, which may be moderated (glucose intolerance) or corrected (insulin resistance) during 20 weeks of rapamycin treatment [47–50]. Additionally, intermittent rapamycin exposure may provide longevity benefits without inducing insulin resistance or glucose intolerance in mice [51]. However, other reports suggest these glucose/insulin phenotypes progress to diabetes and preempt any longevity benefit when using healthy mice under alternative housing conditions or genetic models of T2D [52–54]. Human studies of rapamycin administration following organ transplantation have also noted a predisposition to development of diabetes and poor lipemic control [55, 56]. If the results are consistent in individuals not undergoing organ transplant, and given the hypothesis that rapamycin may be particularly detrimental to insulin regulation in conditions requiring an adaptive β-cell response [57], the metabolic dysfunction as a

Table 1
Selected lifespan extending interventions and glucose response

Organism	Intervention		Glucose Level**
	Diet§	Genetic	
Yeast	GR		▼ [189, 190]
Worms	GR		▼ [191]
Mice/Rats	DR		▼ [192, 193]
	MR		▼ [194, 195]
	ADF		▼ [196, 197]
		Ames dwarf	▼ [198]
		Snell dwarf	▼ [199, 200]
		GHR mutant	▼ [201]
		FIRKO	▼ [120, 202]
		AC5 – KO	▼ [203–205]
		Atg5 OE	▼ [206]
		Fgf21 OE	▼ [207]
		αMUPA OE	▼ [208]
		S6K1 KO	▼ [209]
		RIIβ KO	▼ [210]

§GR = glucose restriction, MR = methionine restriction, DR = dietary restriction, ADF = alternate day fasting. **Represents either decreased glucose level or increased glucose tolerance/clearance.

result of rapamycin treatment may limit its wider use. To what extent the rodent model is more permissive of glucose intolerance than the adult human and how the interplay between glucose and insulin mediates the longevity effects of these specific interventions over the full life course remains to be fully quantified and understood.

One of the most direct methods of maintaining glucose homeostasis is through diet/nutritional interventions. Paramount among these is the dietary restriction (DR) or calorie restriction (CR) paradigm. Generally speaking, CR-related increases in healthy aging and lifespan are inversely related to the amount of restriction (fewer calories = longer lifespan) and positively related to the duration of the intervention (longer duration = larger benefit) [58–60]. Within the group of homeotherms ("warm blooded" organisms), the magnitude of the benefit appears largest in smaller organisms and when started in early life [61]. While not all reports have shown longevity benefits with CR, some even display negative health and longevity responses [62–67], the majority of publications demonstrate within-study increases in both health and longevity, albeit in laboratory strains that are most often less genetically diverse than wild populations, including humans. In most rodent CR studies, CR initiation results in temporary negative energy balance accompanied by body weight reduction (both lean and fat mass) with weight stabilization occurring within the first one to two months after

CR initiation. This re-establishment of energy balance is maintained for the majority of the lifespan, albeit accompanied by chronic hunger, with a lower restriction limit of ~60% below *ad libitum (AL)* (up to ~80% below AL with essential dietary component supplementation) before overt health detriment is observed in the lab [58, 61, 68, 69].

Despite these reported health benefits, life-long dietary restriction in humans remains challenging given the current state of modern society in developed countries that has shifted from a limited food supply a century ago to nutritional excess today. Additionally, it is ethically questionable whether, similar to protocols in the majority of laboratory animal models, such restriction could and/or should be enforced from a young age in humans, particularly given more recent results in non-human primate studies which provide limited support for health benefits achieved relative to a healthful diet consumed in moderation [70–72]. Therefore, the identification of interventions that promote health and longevity independent of obligatory food intake reductions has been proposed as an alternative means to "mimic" the physiologic benefits of CR and reap health and longevity gains – a hypothetical class of compounds termed calorie restriction mimetics (CRMs) [73–79].

Multiple compounds have been proposed as potential CRM, with many fewer demonstrating the unique capacity to increase health and lifespan significantly without inducing calorie intake reductions. Of potential CRMs targeting glucose metabolism, multiple approaches might be pursued: 1) the reduction of cellular glucose utilization with glycolytic inhibitors, 2) the reduction of circulating glucose through increased utilization or storage (e.g., insulin sensitizers) or 3) the reduction of dietary glucose access and utilization. Examples of tested glycolytic inhibitors include 2-deoxyglucose (2DG, a non-metabolizable glucose analog) and glucosamine, both of which recapitulate some of the cellular and physiologic effect of CR [80–83]. However, the ability to successfully modulate cellular glycolysis without inducing toxic side effects remains a hurdle for the non-metabolizable inhibitors like 2DG [80]. Although these compounds may have relevance to inhibiting tumor growth and specific disease states [84, 85], alternatives like glucosamine have shown promise for lifespan extension [86]. While we might suspect many compounds that modulate glucose metabolism could function as CRM (natural compounds or pharmaceuticals for T2D treatment), for the remainder of this review, we will focus largely on the third category of potential CRMs that reduce dietary access or utilization of glucose.

4. Targeting glucoregulatory control in aging

The similarities between glucose dysregulation in aging and glucose dysregulation with T2D have led to the hypothesis that an effective CRM could be found by targeting glucoregulatory control [87]. If an intervention is able to improve glucose regulation to treat or prevent T2D, it may prevent development of glucose dysregulation commonly observed with aging (Fig. 1). The most well-known T2D drug that has been tested as a CRM is metformin [88]. Metformin is reported to act through multiple pathways; however, the best-characterized pathway is through the activation of the cellular energy regulatory sensor AMP-activated protein kinase (AMPK) [89]. AMPK has wide-reaching effects, including increasing fatty acid oxidation, autophagy and glucose uptake by skeletal muscle, as well as inhibiting gluconeogenesis in the liver [89]. As such, metformin is a first-line drug therapy in T2D hyperglycemia treatment, with over 50% of individuals receiving metformin when beginning glucose-lowering treatment [90–92]. Metformin has been shown to extend lifespan in some rodent models [88], including a possible reduction in age-related diseases with long-term use [93]. However, the benefit of metformin has been most pronounced in disease-prone, accelerated aging or short-lived models [94]. In longer-lived, non-disease rodent strains, metformin has limited health and longevity benefits, with potential dose-dependent toxicity (similar results in *Drosophila*), suggesting metformin may be more effective at suppressing diseases, such as cancer, than slowing aging and extending lifespan itself [88, 95–97]. However, the extensive safety records, widespread clinical use, low cost, and presence of multiple chronic conditions with advancing age has been used to support further testing of metformin in individuals with accelerated aging or early-onset aging-related disease risk. More recent pre-clinical work has highlighted another class of diabetic control agents that work upstream of insulin (and presumably metformin-related targets) while providing health and longevity benefits in lab models – namely the α-glucosidase inhibitor acarbose.

5. An overview of acarbose

Acarbose (ACA), originally BAY 5421, was isolated and identified from bacterial cultures in 1977

by Bayer and is currently marketed in the United States for T2D under the brand name Precose [98, 99]. ACA is produced commercially from bacterial strains of Actinoplanes sp. SE50/110, though it is also produced naturally by other strains of Streptomyces and Actinoplanes bacterial species [100, 101]. ACA is a pseudo-tetrasaccharide composed of an unsaturated cyclitol unit bound to a 4,6-dideoxy-D-glucopyranose, followed by a chain of three D-glucopyranose sugars connected via α-1,4 linkages [98]. The initial two sugars form the functional inhibitory site of ACA, with the nitrogen linkage preventing hydrolysis by α-1,4 linkage-cleaving α-glucosidases and α-amylases. When consumed with a complex carbohydrate-containing meal, ACA acts as a competitive inhibitor to carbohydrate breakdown along the brush border of the small intestine, with a 15,000x greater affinity than sucrose for α-glucosidase, resulting in reduced enzymatic degradation and absorption of glucose from complex carbohydrates [102]. This inhibitor effect lowers the post-prandial blood glucose elevation in a dose-dependent manner. ACA remains bound to brush-border enzymes only transiently, then is released and transits further down the gastrointestinal tract, resulting in metabolism by microbiota in the colon and cecum or elimination in the feces. No significant metabolism of ACA appears to occur when ACA is administered intravenously and 90% of ACA in the bloodstream is excreted in urine within 24 hours, with an elimination half-life of approximately 30 minutes [103].

Studies with non-diseased humans and rodents, as well as diabetic individuals, have described beneficial metabolic effects, most notably as reduced post-prandial blood glucose excursions with ACA [104, 105]. Insulin sensitivity is slightly improved with ACA, though post-prandial insulin levels do not show a consistent significant decrease [104, 106]. Glucoregulatory outcomes are sufficiently effective as to improve metabolic parameters in diabetic animal models and to decrease the number of progressions from pre-diabetes to T2D compared to a placebo in human trials [107–109]. Additionally, in a large placebo-controlled randomized clinical trial, ACA reduced risk of cardiovascular events in patients with impaired glucose tolerance, with specific decreases in risks of myocardial infarction and development of hypertension [110]. The most commonly reported side effects, as might be expected based on the mechanism of action, are flatulence, abdominal distension, and loose stools, though in rare cases ileus has been

reported as well [105, 111]. Many of these side effects can be lessened through a gradual increase in ACA administration or modification of complex carbohydrate intake [112]. ACA administration typically involves a pill consumed at the start of each meal, though the most effective administration (i.e., post-prandial blood glucose mediation) occurs when powdered ACA is mixed directly into food [113].

While the molecular, inhibitory action of ACA is well-detailed, fewer studies have attempted to explore the effect ACA has on specific nutrient retention from the diet and specifically if the weight loss sometimes reported with ACA administration is the result of reduced overall energy retention from the diet. Higher levels of starches have been observed in stool of humans and animals receiving ACA compared to placebo control [114, 115] and one non-controlled feeding human study reported a slight, but non-significant, increase in total energy, nitrogen, and fat excreted [116]. Studies in our lab with mice have confirmed increased excretion of calories and carbohydrates in the feces, including glucose; however, this was balanced by increased food intake, resulting in a similar number of calories retained from the diet both with and without ACA [117]. In contrast, no alteration to caloric intake nor percentage of macronutrients utilized from the diet were observed in humans [118]. Therefore, it is unlikely that ACA acts through a simple reduction in calorie intake, availability or retention. Instead, given the important roles of insulin signaling and IGF1 in body weight homeostasis [119] and longevity [120, 121], the benefits of ACA are more likely a result of the slowed uptake of sugars from the diet, resulting in lower post-prandial glucose excursions and moderated insulin responses.

6. Acarbose and aging – current evidence

In addition to the immediate, short-term effects on postprandial circulating glucose and insulin levels, long-term treatment with ACA produces physiologic responses that are expected with reduced calorie 'availability' [104, 105]. In rats fed a standard chow diet supplemented with ACA (0.15% w/w), a significant reduction in body weight gain occurred despite a significant increase in food intake compared to the controls [122]. The preponderance of reports for both mice and rats suggest that food intake is increased (or unchanged) while body weight is decreased (or unchanged) compared to controls [104, 105, 115,

122–125]. In contrast to some other T2D medications which result in weight gain, ACA has also frequently been reported to reduce body weight in human studies [126–130]. In addition to the post-prandial response with ACA, some long-term reports have shown that fasting glucose and insulin levels are reduced by ACA supplementation (although the duration of fasting and body composition should be carefully considered in these relationships). Furthermore, age-related dysregulation of glucose and insulin is partially offset by ACA supplementation [122, 131]. This parallels nicely with the effect of CR on glucose and insulin responses in rodents and primates [132–134]. The systemic effects of ACA treatment on reduced glucose metabolism are further supported by the commonly reported reduced levels of glycated HbA1c [104, 105]. Thus, both short and long-term treatment with ACA supplementation appears to partially 'mimic' the glucose regulatory benefit observed with CR.

In 2013, a longevity study of ACA administration in healthy, non-diabetic mice was published using the F1 generation of a four-way cross of BALB/cByJ, C57BL/6J, C3H/HeJ, and DBA/2J strains (UM-HET3 mice) [135]. Mice in the study received 0.1% ACA in chow, beginning at four months of age. Median lifespan was significantly extended in both sexes with ACA, with a greater effect size in males (22% increase vs. controls) than females (5% increase), but resulting in similar median lifespans for both sexes (984 vs. 939 days, males vs. females). Additionally, both male and female mice exhibited ∼10% maximum lifespan increase (11% and 9%, respectively) compared to controls [135]. The differences between sexes in the early- versus late-life benefits and overall magnitude of the lifespan extension in response to ACA may have several contributing explanations. For instance, sex differences in natural longevity of UM-HET3 mice, where control females generally achieve longer median and maximum lifespans than males [135, 136] may obscure early- to mid-life benefits in females. Additionally, fasting insulin and IGF-1 are noted to be lower in females in this strain, along with better glucose tolerance [48, 135]. These factors may suggest females possess improved glucose handling, and the margin for further improving glucose control compared to males is reduced. Given the relative equivalence of longevity extension with calorie restriction previously reported in both sexes of the UM-HET3 strain [137], one might speculate a sex-differential response to specific dietary components

like glucose for males and maybe protein/amino acid levels for females. Whether other longevity extending interventions that target specific pathways of nutrient signaling which show the opposite sex-preferential bias in effects (e.g., rapamycin with greater effects in females) might be pointing to such an explanation will require further study. Although a direct comparison of longevity outcomes with metformin versus acarbose has not be reported, a previous report testing 0.1% metformin treatment in one of the founding strains (C57BL/6) reported a small (5.8%), but statistically significant benefit on mean lifespan in males; however, female mice were not included in the report [88]. Considered as a whole, even in the absence of overt disease, these data suggest targeting glucoregulatory maintenance by acarbose or other means may be a viable nutritional target for maintaining health and delaying aging.

7. Possible alternatives to acarbose

With the primary indication of ACA for treatment of glucose control and its mechanism of action, other treatments acting through similar glucoregulatory effects may result in beneficial outcomes as well. Three main effects of ACA include decreased post-prandial glucose (PPG) response, increased carbohydrate fermentation, and increased short-chain fatty acid (SCFA) production.

Post-prandial hyperglycemia is associated with multiple negative macro- and microvascular complications [138], thus a reduction in PPG may be expected to protect against such negative effects. ACA slows the breakdown of oligosaccharides and polysaccharides, leading to slower uptake of dietary carbohydrates and decreased PPG elevation. However, decreasing PPG can be achieved not only through a slowing of carbohydrate uptake, but also through increasing clearance or elimination rates of blood glucose. For example, sodium/glucose cotransporter 2 (SGLT2) inhibitors are able to decrease recovery of glucose from the glomerular filtrate, increasing glucose excretion [139]. They have also shown potential for improving glucose control and decreasing risk of cardiovascular disease [140, 141]. Whether an improved mechanism of glucose clearance by SGLT2 inhibition will recapitulate the health and longevity benefits observed with reduced glucose uptake remains to be demonstrated.

The main side effects of ACA (i.e., gastrointestinal discomfort, flatulence, loose stools) are due in

part to increased microbial fermentation in the lower gut [142]. Absent ACA, most intestinal fermentation occurs as a result of dietary fiber intake, with soluble fiber generally the main source [143]. Moderate levels of dietary fiber have been proposed to be beneficial for both gut and overall organismal health [144–146], and early work by McCay et al. demonstrated extension of lifespan in rats when the diet was supplemented with 10 to 20% cellulose [146].

Resistant starches, a group of starches indigestible by human enzymes due to their structure [147], also increase fermentation in the gut when included in the diet [148]. When assessed in both pre-clinical and clinical studies, resistant starches have been associated with decreased rates of colon cancer, decreased cholesterol levels, and moderation of blood glucose levels [149–151]. Additionally, resistant starch feeding in aged mice results in improved performance on functional assessments [152] and increases in positive health-marker associated gut bacterial genera [153]. Several theories have been put forth regarding mechanisms through which resistant starches may act to improve healthspan [154] or lifespan, including more beneficial gut microbiome profiles [153, 155] and increased production of secondary metabolites such as butyrate [156–159]. To what extent resistant starches and fiber provide specific lifespan benefits similar to ACA requires further investigation.

While not directly involved with glucoregulatory control, recent studies have concluded that short chain fatty acids (SCFA) may play an important role in suppression of inflammation [160, 161]. Inflammation has been proposed as a risk factor for both aging and age-related diseases [162]; in particular, T2D displays characteristics of being both induced by and causing inflammatory states [163]. A main source of SCFA in the body derives from the byproducts of carbohydrate fermentation by gut microbiota [164]. Following production by fermentation, SCFA can be used by colonic epithelial cells as a fuel source and/or absorbed into the blood stream with subsequent tissue distribution [165]. Therefore, SCFA produced in the gut or supplemented in the diet may activate suppressors of inflammation, leading to decreased chronic inflammation and delayed development of age-related diseases. The availability of carbohydrates for fermentation in the colon may support shifts in gut microbial communities and facilitate SCFA production. ACA treatment in rats leads to increased levels of SCFA in the colon [115], and shifts in microbial communities with increased *Bifidobacteria* have been documented in T2D patients

receiving ACA supplement to anti-diabetic medications [166], as well as both increased *Lactobacilli* and *Bifidobacteria* in hyperlipidemic patients with ACA [167]. Additional human studies of ACA supplementation have also demonstrated increased colonic butyrate production, likely from the observed concurrent increases in starch-fermenting bacteria as a percentage of total fecal anaerobes [114]. The degree to which ACA alone (as a compound produced by bacteria) or SCFA production drives changes in the gut microbial community remains to be determined. However, reduced inflammatory cytokines (i.e., LPS) have been noted in T2D patients given ACA supplement to prescribed anti-diabetic medications [166]. It is becoming increasingly clear that our understanding of interactions and dependence of glucose-lowering drugs on the gut and resident microbiota with health outcomes is still far from complete. For instance, the longevity benefit of metformin in the *C. elegans* model depends on alterations in bacterial metabolism ultimately affecting the host lifespan [168]. Furthermore, the glucose-lowering mechanism of metformin appears to be significantly influenced by the lower gut and bacterial populations associated with SCFA production [169, 170]. Future studies using gnotobiotic or germ-free rodent models may be able to further clarify the contribution of microbial fermentation byproducts in the health and longevity benefits of ACA and alternative interventions.

8. Naturally-occurring acarbose mimetics

While ACA is bacterially derived and purified, other compounds with similar α-glucosidase or α-amylase inhibitory activity are found in multiple naturally-occurring dietary sources. In particular, a variety of leguminous plants contain inhibitory activity against both α-glucosidases and α-amylases [171]. Animal studies have confirmed the ability of many of these naturally occurring α-glucosidase or α-amylase inhibitors to reduce blood glucose levels and improve overall health status [172–175]. In fact, based on *in vitro* and *ex vivo* testing, plant-derived α-glucosidase or α-amylase inhibitors from seeds, bark, leaves, and fruits of many plant varieties often have equivalent or greater inhibitory activity than ACA and related pharmaceutical compounds [176–178]. Cinnamon in particular has gained recent attention as an effective α-glucosidase and α-amylase inhibitor significantly reducing PPG in response to maltose and

sucrose-load in diabetic rats [179, 180], with clinical data showing similar possibilities [181].

Considering the number of α-glucosidase and α-amylase inhibitors identified from such a diverse selection of plants, it is likely additional compounds with similar inhibitory properties may be present, but currently unidentified, in many commonly eaten foods. Eating a diet rich in foods containing botanicals with sufficient concentrations/activity of these phytochemicals may conceivably provide α-glucosidase and α-amylase inhibitor outcomes equal to or greater than those achieved through pharmaceutical interventions as monotherapies (e.g., ACA at specific dosages). Anecdotal evidence potentially supports this notion. For instance, Okinawan cohorts recognized for exceptional health and longevity previously consumed high levels of sweet potatoes in their diet relative to the general population in Japan and other contemporary cohort countries, estimated to previously constitute ∼69% of total daily dietary calories [182, 183]. Sweet potatoes *(Ipomoea batatas)* are rich in fiber, with higher vitamin and mineral concentrations than many other natural starches such as rice or refined carbohydrates [184]. Additionally, sweet potatoes come in a variety of colors with diverse phytochemicals (e.g., anthocyanins and polyphenols), which have multiple proposed biochemical and health benefits, with particularly remarkable α-glucosidase and α-amylase inhibitory activity [185–187]. Similarly, curcumin-rich foods, best known for antioxidant properties, were also a staple for the Okinawan cohorts [183], and also contain α-glucosidase inhibitory properties [188]. Moving beyond the simple calorie, macronutrient, and micronutrient composition of a given food to a deeper understanding of the biologically active and non-caloric compounds present in foods, as well as how those modify nutrient access and utilization, would build on longstanding knowledge and tradition of healthy dietary components.

9. Conclusions

ACA has proven to be an effective means for reducing PPG and improving glucose regulation in individuals with T2D. Additionally, animal work has demonstrated a role for ACA in extending both healthspan and lifespan of non-diabetic models. These positive outcomes with ACA may result from a combination of several biological mechanisms; however, multiple health and longevity extending interventions (nutrition and genetic) support the idea that the benefits of ACA reflect improved glucose regulation. ACA trials in non-diabetic human populations could be further explored, given the potential for beneficial health and aging outcomes, the limited side effects, extensive clinical history of use for T2D, and minimal costs. Such trials may be especially relevant to address the pre-diabetic state of metabolic syndrome in middle age or older populations. Additionally, as multiple compounds in plants and foods exhibit similar inhibitory properties, increased research into these naturally occurring compounds seems warranted. A greater understanding of how non-caloric compounds like α-glucosidase or α-amylase inhibitors modify macronutrient metabolism holds promise for nutritional/lifestyle interventions as a form of preventative medicine to support health and reduce age-related disease risk.

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