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ORIGINAL ARTICLE

Diabetes medications as potential calorie restriction mimetics—a focus on the alpha-glucosidase inhibitor acarbose

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Abstract The field of aging research has grown rapidly over the last half-century, with advancement of scientific technologies to interrogate mechanisms underlying the benefit of life-extending interventions like calorie restriction (CR). Coincident with this increase in knowledge has been the rise of obesity and type 2 diabetes (T2D), both associated with increased morbidity and mortality. Given the difficulty in practicing long-term CR, a search for compounds (CR mimetics) which could recapitulate the health and longevity benefits without requiring food intake reductions was proposed. Alpha-glucosidase inhibitors (AGIs) are compounds that function predominantly within the gastrointestinal tract to inhibit α-glucosidase and α-amylase enzymatic digestion of complex carbohydrates, delaying and decreasing monosaccharide uptake from the gut in the treatment of T2D. Acarbose, an AGI, has been shown in pre-clinical models to increase lifespan (greater longevity benefits in males), with decreased body weight gain independent of calorie intake reduction. The CR mimetic benefits of acarbose are further supported by clinical findings beyond T2D including the risk for other age-related diseases (e.g., cancer, cardiovascular). Open questions remain regarding the exclusivity of acarbose relative to other AGIs, potential off-target effects, and combination with other therapies for healthy aging and longevity extension. Given the promising results in pre-clinical models (even in the absence of T2D), a unique mechanism of action and multiple age-related reduced disease risks that have been reported with acarbose, support for clinical trials with acarbose focusing on aging-related outcomes and incorporating biological sex, age at treatment initiation, and T2D-dependence within the design is warranted.

Keywords Calorie restriction mimetic · Macronutrient · Energy balance · Glucosidase

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Calorie restriction and aging

The field of aging research has grown rapidly over the last half-century, coincident with the development and advancement of scientific technologies including multiple areas of molecular biology. These advances have built upon the foundation of nutrition and physiologic research from the early 1900s to characterize more fully the nutrition-based interventions that have been shown to improve health, reduce disease, and ultimately increase lifespan in laboratory organisms. The most well-studied longevity and disease-altering intervention from research studies is the practice of calorie restriction (CR), a major player within the larger intervention toolkit of general "dietary restriction." Despite the knowledge of expected benefit(s) from CR, the implementation of and adherence to CR at a sufficient level of restriction and duration necessary to achieve significant longevity and health benefits is improbable in the modern environment of dietary availability. This is evidenced by the contemporary rise and prevalence of obesity and Type 2 Diabetes (T2D), which are both associated with increased morbidity and mortality. Furthermore, refinement in our understanding of dietary composition and caloric content introduces possibilities for manipulating specific dietary components, and carbohydrates, in particular, to achieve benefits normally observed with traditional CR, which is known to counteract obesity and diabetes. Compounds which could recapitulate the health and longevity benefits of CR, referred to as calorie restriction mimetics (CRM), could target specific macronutrient classes and/or related signaling pathways to mimic CR without requiring food intake reductions. Herein, an update regarding the importance of carbohydrate metabolism in relation to longevity and age-related disease is provided. A specific focus on the antidiabetic agent and alpha-glucosidase inhibitor acarbose is provided, given its robust translational potential and clinical relevance.

Achieving the health benefits of CR through the use of CRMs

Of the many types of dietary restriction interventions that have been studied, CR remains the most highly utilized nutritional method to improve health, reduce disease, and increase lifespan in laboratory research models [1–6]. In practice as an intervention, CR is defined as a significant and sustained reduction in calorie provisions (most simply a proportional reduction of all macronutrient calories) to organisms below what their voluntary (ad libitum) intake would be. While the degree of calorie reduction is related to the health and longevity benefits, there is a level of restriction beyond which health and longevity benefits are lost. As diet provision approaches these greater levels of restriction, a necessary alteration in the proportions of macronutrient (protein preserving) and micronutrient supplementation becomes necessary [1, 7]. The beneficial impact of CR on health applies to many of the highest-ranked disease contributors to morbidity and mortality in the USA including cardiovascular diseases, cancers, and diabetes (specifically T2D) [8–11]. In contrast to CR, overfeeding and diet-induced obesity are shown to increase disease and mortality risk [12–14]. These divergent associations emphasize the need to understand the mechanisms which underlie the health benefits of CR (and conversely, the detrimental effects of diet-induced obesity and T2D) as a means to identify interventions which can mimic the health and longevity benefits of CR.

CRMs were initially proposed as a hypothetical class of compounds that could accomplish these goals and provide significant benefits through translational application [15–17]. Importantly, the benefits of CRMs would not rely on the need for individuals to maintain significant reductions in caloric intake, which remains a challenge in modern society as seen by the high prevalence of obesity and T2D in the modern nutrition environment [18, 19]. Furthermore, a CRM would be broad acting in the ability to slowing aging and improve general health rather than treat or prevent a single, exclusive disease focus. In light of these relationships between calorie intake and obesity/T2D, candidate CRMs were identified by focusing on compounds that showed benefit for treating obesity or T2D via their ability to recapitulate critical aspects of the physiologic responses induced by CR [16, 20–24]. The focus here will be on the class of T2D medications which target alpha-glucosidase inhibition, particularly acarbose [25, 26].

Research from the first half of the 1900s demonstrated the ability of CR to inhibit the outgrowth of transplanted or spontaneous cancers, highlighting the impact nutritional intervention (i.e., limitation) could have on rapidly dividing cells [27–29]. Subsequent longer-term studies revealed that CR reduced the rate of growth and maturation of rodents, coincident with increases in longevity [1, 7, 8]. Over the decades, this

line of CR research has expanded to include "dose-response" assessments of levels of restriction, with carbohydrates identified as a select dietary component that could be reduced (relative to protein levels) to achieve CR longevity benefits even at more extreme levels of CR, achieving further delays and reductions in the magnitude and age of onset for common diseases [1, 7]. Across these studies of disease reduction and longevity extension, a physiologic and molecular signature of metabolic control (i.e., glucose reduction), hormonal regulation (insulin function), stress response, and metabolic rate reductions opened a window of knowledge allowing a view toward interventions that shared similarities with CR-induced molecular and physiologic responses, which would be predictive of health and longevity benefits [30, 31].

Parallel with these years of CR research, epidemiologic observations reported sustained and significant increases in obesity and T2D, which contributed to heightened morbidity and mortality within afflicted populations [18, 32–34]. Recent estimates indicate that approximately 40% of all adults in the USA have obesity [35, 36]. This trend is further exacerbated by the age-related increased risk in T2D, such that over half of the older adult population (> 65 years of age) in the USA are either prediabetic or diabetic [34]. The hyperglycemia associated with T2D is in stark contrast to the reduced glycemia present with CR and is implicated in the biological processes underlying fundamental aging mechanisms and disease phenotypes. Thus, improvements in the metabolism of glucose at the organismal and cellular level might reasonably offer the means not just to address T2D hyperglycemia as a treatment but also to intervene in fundamental glucose metabolism prior to development of an overt disease state, for the purpose of improving the aging trajectory [16, 37]. While a variety of pharmaceutical classes of compounds have been developed to treat T2D (biguanides, sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, sodium-glucose linked transporters 2 inhibitors, etc.), the subsequent focus of this review will be on the alpha-glucosidase inhibitors (AGIs).

Acarbose is a candidate CRM that inhibits alpha-glucosidase activity

Each class of T2D medications works through distinct primary mechanisms of action, with AGIs predominantly functioning in the gastrointestinal (GI) tract [25, 26, 38, 39]. The particular AGI of interest here is acarbose, a pseudo-tetrasaccharide of bacterial origin that competitively inhibits alpha-glucosidase and alpha-amylase enzymatic digestions (Fig. 1). In doing so, acarbose delays and decreases monosaccharide cleavage from complex carbohydrates in the diet, impacting monosaccharide absorption in the gut [25, 40]. This results in a delayed and blunted postprandial glucose response, dampening the variability in blood glucose over the course of the day, particularly after meals that contain high amounts of carbohydrates [40]. In line with the health and longevity benefits observed with fiber supplementation, undigested complex carbohydrates transit further down the GI tract, resulting in an increased fiber-like effect [41–47]. Many of the side effects of acarbose administration (i.e., flatulence, bloating, and diarrhea) are related to its mimicry of a high-fiber diet and diminish over time or may be reduced by utilizing a dose-escalation protocol [25, 40, 48, 49].

Data from single-celled yeast to mammalian models have demonstrated that manipulation of the dietary amount and biochemical complexity of carbohydrates can result in significant impacts on cellular aging and organismal longevity [50–54]. In the budding yeast, *Saccharomyces cerevisiae*, which has been used extensively to study genetic and environmental/nutritional contributors to aging, reducing the starting glucose concentration in the media or increasing the complexity of sugars provided (i.e., by providing di- or tri-saccharides which are enzymatically digested, imported, and metabolized more slowly and efficiently than monosaccharides) both increase lifespan [50, 53]. Consistent with these effects, incorporation of acarbose at 0.1% by weight in a healthful laboratory diet with 66% carbohydrate by calories (21.2% protein and 12.8% fat) significantly increases overall, mean, and maximum lifespan (90th percentile) in non-diabetic male mice (HET3 strain, median: control—807 vs. acarbose—984 days, 22% increase, $p < 0.0001$) and to a lesser but statistically significant extent in female mice (HET3 strain, median: control—896 vs. acarbose—939 days, 5% increase, $p = 0.01$ relative to controls) [55, 56]. These results extend the previous observations of treatment efficacy and longevity promotion (recovery) in a model of diabetes with rats [57].

The benefits of acarbose outside T2D effects on longevity were replicated in a subsequent dose-response study using the same dietary composition

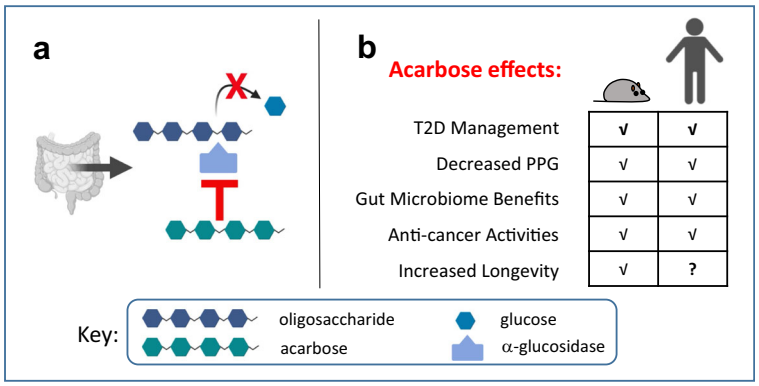

Fig. 1 The antidiabetic agent acarbose is an α-glucosidase inhibitor that provides multiple health benefits. **a** Acarbose is a pseudotetrasaccharide that competitively inhibits the enzymatic activity of α-glucosidases in the gut, thereby delaying and reducing the release of glucose monomers from complex carbohydrates. As a result, less glucose is absorbed in the upper intestines and made available for systemic use. **b** Due to its potent glucoregulatory ability, acarbose use promotes a wide range of health benefits, including type 2 diabetes (T2D) management, and decreased postprandial glucose (PPG). The figure was made with BioRender

formulations with 0.04%, 0.1%, and 0.25% acarbose by weight; where acarbose efficacy was shown to approach a plateau in longevity at 0.1% percent (median lifespan, males: control—830, acarbose [0.04%]—918, acarbose [0.1%]—975, acarbose [0.25%]—964 days; females: control—889, acarbose [0.04%]—887, acarbose [0.1%]—933, acarbose [0.25%]—922 days) [58]. Importantly, coincident with the longevity extension, multiple hormones implicated in lifespan regulation are altered with acarbose treatment [59]. Fasting insulin and insulin-like growth factor-1 (IGF-1) levels were lowered which are associated with lifespan extension that mimics a CR response, whereas fibroblast growth factor-21 (FGF-21) was significantly elevated, in contrast with the lowering of FGF-21 observed with CR [55]. Notably, the mechanism of action for acarbose is such that in these non-diabetic, healthy mice, blood glucose was not significantly lower under fasting conditions [55]. In contrast, acarbose does reduce blood glucose in both diabetic and non-diabetic animals during the postprandial phase [57, 58, 60–64]. This is in agreement with human studies where the primary benefits of acarbose glycemic control are acute following a meal, although longer-term benefits on insulin signaling and body composition may additionally contribute to T2D treatment efficacy [25, 26, 40, 48, 65–67]. Furthermore, no reduction in food intake was necessary for the acarbose-associated longevity benefit, despite animals having lower average body weight and body fat mass relative to untreated controls [55, 56, 58]. Reduced water intake has been reported with acarbose treatment in laboratory models of T2D, coincident with reduced blood glucose and urinary output; however, similar measures have not been routinely reported in non-diabetes focused, pre-clinical studies [64, 68]. Furthermore, the energy balance changes with acarbose treatment initiation appear to be largely explained by alterations in nutrient absorption [69–72], although comprehensive studies of energy expenditure (e.g., metabolic rate) across acute and long-term acarbose treatment are needed.

Systemic or off-target effects of acarbose

Although acarbose has low absorption kinetics with approximately 3% or less absorbed into the systemic circulation, and the primary mechanism of action of AGIs is focused in the GI tract, effects on longevity across multiple organ/systems via the small amount of absorbed acarbose or its secondary metabolites are not fully determined [40, 73]. As with other FDA-approved medications, including T2D medications, simulation work on acarbose protein binding domains and interaction modeling has highlighted additional unexpected potential interactions with "off-target" pathways (i.e., effects independent of alpha-glucosidase and alpha-amylase inhibition), which are frequently not considered when assessing acarbose effects [74]. Proposed off-target effects of interest include 4-α-glucanotransferase and maltose-binding periplasmic protein [74]. Whether mechanisms in addition to alpha-glucosidase inhibition contribute to acarbose's effects independent of T2D amelioration remains to be determined.

Acarbose has distinct metabolomic and gut microbiome effects

In addition to improved glycemic control, acarbose may also modulate metabolism within tissues. Metabolomic profiling of liver and cecal samples from acarbose-treated (0.1% by weight) C57BL/6J mice compared with CR (40% reduction) or ad libitum feed controls uncovered a characteristic signature of amino acid and lipid metabolism [75]. Despite some level of similarity between acarbose and CR responses, unique differences exist in specific amino acids, bile acids, vitamin/cofactor, and xenobiotic compounds. For example, CR treatment resulted in a higher abundance of multiple vitamin/cofactor, dipeptide, and ketone metabolites relative to control and acarbose treatment, while responses within subpathways of metabolites were at times uniquely different with acarbose-treated females which exhibit a smaller longevity benefit, relative to acarbose-treated males and CR-treated males and females (e.g., heme, multiple gamma-glutamyl amino acids) [75]. These results reveal distinct effects of each longevity-promoting intervention at the specific doses of acarbose and CR used in this particular dietary composition (i.e., NIH-31 based 22.4% protein, 12.2% fat, and 65.4% carbohydrates by kcal) [75].

Given the bacterial origin of acarbose (*Actinoplanes* and *Streptomyces* sp.) and as might be anticipated with the change in GI digestion and absorption of complex carbohydrates, acarbose-induced shifts in the fecal microbiome have been reported [76–80]. These are characterized by a relatively greater prevalence of *Bifidobacterium* and lower *Lactobacilli*, likely driven by changes in nutrient substrate availability and the resulting competitive growth advantages to *Bifidobacterium* [76–84]. These microbiota shifts further contribute to metabolite differences observed with acarbose treatment, although the extent, if any, to which specific metabolites or individual bacterial species abundance further improve health or longevity outcomes is not yet determined with acarbose [75, 76, 79, 85–91]. Whether the secondary metabolites related to acarbose administration may have independent and beneficial roles reflective of prior research on short-chain fatty acids and ketone bodies is a further area of research opportunity [92–100].

Evidence for the emerging use of acarbose as an anti-cancer agent

Much like the early work with CR and cancer, the impact of acarbose on glucoregulatory control could be important for cancer control and/or treatment. While acarbose blunts postprandial glucose excursions, the overall effects on 24-h glucose levels tend to be lower, but of a potentially meaningful magnitude [25]. With the high glycolytic demand of tumors, the benefits of blunting postprandial glycemic excursions could, in theory, have implications for cellular proliferation within the tumor microenvironment. In support of this idea, a longitudinal study of over 1.3 million newly diagnosed diabetics illustrated that acarbose use for T2D management reduced the risk of colorectal cancer incidence by 27% [101]. However, a study of newly diagnosed cancer patients in Taiwan found that prior acarbose use was not associated with any change in all-cancer risk, illustrating the need for additional investigation of this question [102]. In rodent models, beneficial anti-cancer effects of acarbose were found in $APC^{+/Min}$ mice that are prone to developing bleeding intestinal neoplasias, which culminate in anemia and shortened lifespan. In this study acarbose use at 935 ppm resulted in decreased tumor formation and increased longevity [103]. Our own research using a pre-clinical model of renal cancer has found that acarbose administration at 0.1% in the diet (1000 ppm) can inhibit renal tumor progression, strengthen protective immune responses against tumors, and augment the efficacy of an immune-based cancer therapy, suggesting that acarbose may have clinical application in the treatment of established renal tumors (Orlandella et al., submitted).

While not the focus of the current review, the biguanide metformin is likely the most highly studied T2D medication regarding effects on cancer and longevity in rodent models [104]. It is of interest that metformin's longevity effects in rodents appear to be somewhat strain-specific, with longevity benefits observed in cancer-prone rodent strains and the extension effect size proportionally larger with shorter-lived strains [104, 105]. In humans, metformin use is associated with a reduced incidence of colorectal cancer, similar to what has been reported with acarbose [106, 107]. In rodent models of established cancer, metformin use has been reported to directly impair tumor cell

proliferation, reduce hypoxia within solid tumors, and improve protective immune responses [108]. The mechanisms of action of metformin for T2D (i.e., inhibition of mitochondrial Complex I, AMP-activated protein kinase activation, and decreased hepatic glucose production) are distinct from those of acarbose [109]. Thus, it may seem surprising that both acarbose and metformin were identified through an in vitro screening for compounds that impacted a genetic model of mitochondrial defect in iron-sulfur cluster formation defects with Friedreich's ataxia [110]. Even more intriguing are the differential and opposing mitochondrial effects that were shown with the two agents. Specifically, acarbose increased mitochondrial function (oxygen consumption) whereas metformin had the opposite effect [110]. Whether acarbose is able to ameliorate the aging deficits observed with mitochondrial diseases or preserve mitochondrial function with advancing age is an area of future interest.

Acarbose effects on other age-related diseases

Early clinical studies supported a role for acarbose as both a treatment after T2D establishment, as well as a preventative intervention for pre-diabetes [67, 111, 112]. While these disease benefits were expected as the focus of acarbose development and use, initially more surprising may have been the cardiovascular-related benefits which have also been observed in patients receiving acarbose for T2D, including reduced cardiovascular disease, myocardial infarction, and hypertension [111, 113–116]. Emerging data suggest that postprandial glucose, triglyceride, and chylomicron responses, along with hormone improvements, may mediate some of these cardiovascular benefits [117–120]. In agreement with the increasingly recognized contribution of T2D to age-related neurologic disease risk (e.g., Alzheimer's, Parkinson's) [121, 122], recent studies highlight the potential reduced risk of onset or progression of dementia in subjects with T2D receiving acarbose treatment [123]. Finally, inflammatory-related diseases like arthritis have growing support for benefits from acarbose use to alleviate symptoms and reduce risk of progression in pre-clinical and clinical models [124–128], expanding the potential utility of acarbose treatment to multiple types of age-related disease mechanisms with human aging relevance.

AGIs beyond acarbose

In addition to acarbose, multiple pharmaceuticals within the AGI class (miglitol and voglibose) remain unreported regarding their ability to enhance longevity, exhibit anti-cancer activity, and achieve CRM status using non-diabetic laboratory models. Additionally, natural AGIs of phytochemical/botanical origin (e.g., cinnamon, tea) are being increasingly identified and experimentally shown to alter and improve glycemic control [129–134]. In fact, multiple botanically derived AGIs show equivalence and/or superiority regarding in vitro pharmacokinetics to acarbose, and combination treatment with acarbose further enhances glycemic suppression [135, 136]. However, less data are available to clarify whether botanical-derived AGIs can similarly improve long-term physiologic, metabolic, and longevity outcomes as seen with acarbose.

Summary and future studies

Additional studies of acarbose effects are needed at all levels of translational science. Existing literature supports consideration of broad health benefits by targeting glucoregulatory control in relation to co-morbidities and diseases (e.g., cardiovascular, neurodegenerative) [37], and may be informative in prioritizing study focus areas. Pre-clinical work has not fully investigated the dietary composition, strain background, and disease-status dependence of acarbose's effects on age-related disease and longevity. The distinct mechanism of acarbose action from other proposed CRM raises the possibility that combinatorial therapies may be superior to any one intervention for addressing the complexity of biological aging across tissue types and organs. This may be particularly relevant in the context of sex-differential benefits observed with lifespan enhancing interventions (e.g., rapamycin, 17-estradiol) [55, 137–139]. Whether other AGIs have similar or greater anti-aging benefits to acarbose, particularly those of natural/botanical origin that are consumed in everyday diets at varying levels, remains understudied. Other T2D medication classes that also reduce postprandial glucose and improve overall glycemia like sodium-glucose-linked transporters 2 (SGLT2) inhibitors, which increases glucose excretion through urine, remain an interesting area of exploration as potential CR mimetics [140–142].

The AGI acarbose has a multi-decade safety profile as an FDA-approved treatment for T2D. While underprescribed in the USA relative to metformin or other T2D medications, a growing body of pre-clinical, clinical, and epidemiologic research highlights the potential for acarbose (Fig. 1) as a stand-alone therapy and/or adjuvant treatment to address some of the most common ailments of biological aging, including age-related diseases and morbidities.

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Compliance with ethical standards

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