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Abstract

Epidemiological studies indicate that the increased consumption of sugars including sucrose and fructose in beverages correlate with the prevalence of obesity, type-2 diabetes, insulin resistance, hyperinsulinemia, hypertriglyceridemia, and hypertension in humans. A few reports suggest that fructose extends lifespan in *Saccharomyces cerevisiae*. In *Anopheles gambiae*, fructose, glucose, or glucose plus fructose also extended lifespan. New results presented here suggest that fructose extends lifespan in *Caenorhabditis elegans* (*C. elegans*) wild type (N2). *C. elegans* were fed standard laboratory food source (*E. coli* OP50), maintained in liquid culture. Experimental groups received additional glucose (111 mM), fructose (55 mM, 111 mM, or 555 mM), sucrose (55 mM, 111 mM, or 555 mM), glucose (167 mM) plus fructose (167 mM) (G&F), or high fructose corn syrup (HFCS, 333 mM). In four replicate experiments, fructose dose-dependently increased mean lifespan at 55 mM or 111 m Min N2, but decreased lifespan at 555 mM (*P* < 0.001). Sucrose did not affect the lifespan. Glucose reduced lifespan (*P* < 0.001). Equal amount of G&F or HFCS reduced lifespan (*P* < 0.0001). Intestinal fat deposition (IFD) was increased at a higher dose of fructose (555 mM), glucose (111 mM), and sucrose (55 mM, 111 mM, and 555 mM). Here we report a biphasic effect of fructose increasing lifespan at lower doses and shortening lifespan at higher doses with an inverse effect on IFD. In view of reports that fructose increases lifespan in yeast, mosquitoes and now nematodes, while decreasing fat deposition (in nematodes) at lower...
concentrations, further research into the relationship of fructose to lifespan and fat accumulation in vertebrates and mammals is indicated.

**Keywords**
- biphasic effect
- *Caenorhabditis elegans*
- fructose
- high fructose corn syrup (HFCS)
- lifespan
- obesity

**INTRODUCTION**

In 2012, more than one third of children and adults were estimated to be overweight or obese in the United States (US) (Ogden et al., 2014). Obesity associated health issues are increasing globally, including cardiovascular disease, hypertension, stroke, type 2 diabetes, insulin resistance, impaired glucose tolerance, hyperinsulinemia, hypertriglyceridemia, nonalcoholic fatty liver disease, and ovarian or colorectal cancer (Gerstein, 1997, DiMeglio and Mattes, 2000, Ludwig, Peterson, & Gortmaker, 2001, Elliott et al., 2002, Raben et al., 2002, Bray, Nielsen, & Popkin, 2004, Cordain et al., 2005, Johnson et al., 2007, Schenewerk et al., 2014, Zhang et al., 2014).

Epidemiological studies correlate these obesity-related diseases with sedentary behavior and the consumption of excessive energy-dense diets containing saturated fat, sucrose and high-fructose corn syrup (HFCS) (Burt and Pai, 2001, Ashrafi et al., 2003, Heber, 2010, Mathias, Slining, & Popkin, 2013, Ogden et al., 2014, Zheng et al., 2014, Koutoukidis, Knobf, & Lanceley, 2015, Sample, Martin et al., 2015). Since HFCS intake increased 10-fold in the United States from 1970 to 1990 and accounts for 40% of the consumption of caloric sweeteners, the correlation between increased HFCS consumption and increased obesity has been speculated to have a cause and effect relationship (Bray et al., 2004). Consumption of sucrose decreased 50% as HFCS consumption increased during this time period (DiMeglio and Mattes, 2000, Ludwig et al., 2001, Elliott et al., 2002, Raben et al., 2002, Bray et al., 2004, Johnson et al., 2007, Schenewerk et al., 2014).

The insulin/IGF-1-signaling pathway regulates the lifespan of many organisms including yeast, *Caenorhabditis elegans* (*C. elegans*), mice, and humans (Barbieri et al., 2003, Lee, Murphy, & Kenyon, 2009, Kenyon, 2010, Zheng and Greenway, 2012). In yeast studies, either glucose or fructose at a concentration of 0.5% extends the lifespan of *Saccharomyces cerevisiae* mutants compared with a concentration of 2% due to the effect of caloric restriction (Smith et al., 2007). Interestingly, Anopheles gambiae consuming a diet supplemented with fructose (584 mM) or an equal amount of fructose plus glucose (292 mM) supported life compared with the water only control (Kessler, Vlimant, & Guerin, 2015). Feeding fructose to mice did not change body weight compared to a sugar-free, low-fat dietary control over a 3-month study period, and there was no change in triglycerides, free fatty acids, glucose sensitivity or leptin (Tillman et al., 2014).

*C. elegans* stores energy along the intestinal tract via intestinal fat deposition (IFD), which can be directly quantified photometrically by lipid staining dyes in the intact animal. In the *C. elegans* model, glucose as low as 0.1% (5.5 mM) is sufficient to decrease lifespan by
decreasing expression of the DAF-16/FOXO gene, a homologue of the human gene FOXO, which regulates lifespan, mediates lipid metabolism, regulates insulin/IGF-1 signaling pathways, and controls heat shock transcription factor (HSF-1) activity (Ogg et al., 1997, Lin et al., 2001, Lee et al., 2009, Solis and Petrascheck, 2011, Zheng et al., 2014, Gao et al., 2015a, Gao et al., 2015b, Koutoukidis et al., 2015). C. elegans is a small, multicellular, transparent, free-living, soil nematode that has a completely sequenced genome and conserves 65% of the genes associated with human disease (Fei et al., 2004, Hostetler et al., 2008, Koutoukidis et al., 2015).

Although many studies have addressed the effect of sugars on obesity and diabetes, little is known about the effect of sugars on lifespan. This study evaluated the effects of fructose, glucose, and sucrose sugars on C. elegans lifespan and quantified intestinal fat deposition (IFD) by fluorescence intensity of lipophilic dye Nile red staining in liquid culture (Solis and Petrascheck, 2011).

**MATERIALS AND METHODS**

**C. elegans**

Wild type *C. elegans* (N2) and the standard lab food source *Escherichia coli* (*E. coli*, OP50, *Uracil-auxotroph*) were obtained from the *Caenorhabditis* Genetics Center (University of Minnesota, Minneapolis, MN). The *C. elegans* model does not require Institutional Animal Care and Use Committee (IACUC) approval.

**Culture of *Escherichia coli* (*E. coli*, OP50)**

OP50 were cultured by the standard method described elsewhere (Zheng et al., 2010). Briefly, an *E. coli* pellet was inoculated into a Luria-Bertani (LB) broth solution containing 0.2% streptomycin, incubated at 37°C overnight, and stored at 4°C, before being plated on petrifilm (3M™ Petrifilm™ *E. coli*/Coliform Count Plates 6404, 3M Corp., Minneapolis, MN) at 37°C for 24 h. Densities of 5 × 10⁸ to 5 × 10¹¹ colony forming units (cfu/mL) were selected and fed to *C. elegans ad libitum* (Gruber, Ng et al., 2009, Zheng et al., 2010). The OP50 stock feeding solution was enriched to 2 × 10⁹ cfu/mL by centrifuging at 2,200 g for 10 minutes and washing twice with S-complete buffer (Solis and Petrascheck, 2011).

**Culture of *C. Elegans***

Mature gravid wild type *C. elegans* (N2, Bristol) were treated with NaOH (1M) and sodium hypochlorite solution (5.25%) at 5:2 ratio to dissolve the body and release viable eggs. Eggs were washed with S-complete solution 3 times and hatched overnight at room temperature. The age-synchronized *C. elegans* were diluted to 100 animals/mL, plated in liquid culture in 96-well plate (120 µL/well, 10–15 animals) (Solis and Petrascheck, 2011) with OP50 (10⁹ cfu/mL), and incubated in 20°C (N2) low temperature incubators (Revco Tech., Nashville, NC, USA). Thirty microliters of 5-Fluoro-2’-deoxyuridine (FUDR, 0.6 mM) stock solution were added to each well at larvae 4 stage.
Lifespan Assay

Glucose, fructose, and sucrose were purchased from Sigma-Aldrich (St. Louis, MO, USA) for use in investigating their effect in *C. elegans* (Solis and Petrascheck, 2011). Fifty microliters of the treatments were prepared and fed to the *C. elegans* on day 3. Each group had 60–90 animals (*n* = 10–15/well × 6 well). The control animals were fed with *E. coli* OP50 only. Experimental groups were fed with additional glucose (111 mM), fructose (55 mM, 111 mM, or 555 mM), sucrose (55 mM, 111 mM, or 555 mM), glucose (167 mM) plus fructose (167 mM), or high fructose corn syrup with 60% fructose (HFCS, 333 mM). The 96-well plate was placed on a microtiter plate shaker for 2 min before counting. The numbers of live animals were manually recorded every other day under an inverted microscope with a 4× objective (Nikon Eclipse Ti, Melville, NY, USA) (Lee et al., 2009, Zheng et al., 2014). Animals that did not move were excluded from the survival assay. The animals were returned to the 20°C incubators thereafter.

Fluorescence Microscopy

Lipophilic dye, Nile red, was used to stain for intestinal fat deposition (IFD) and fluorescent intensity was evaluated (Zheng et al., 2010). *C. elegans* in each group were collected after 3 days of treatments, washed with S-Basal solution twice, fixed with paraformaldehyde (4%) over 2 h at 4°C, and washed with PBS for 5 min three times. Nile red (50 µL) was applied to the specimens for 10 min. Ten microliters of Fluoromount-G (Southern Biotechnology Associates, Birmingham, AL) was applied to a glass slide followed by 20 µL of the medium containing Nile red stained *C. elegans*. A cover glass was mounted on the glass slide and the slides were viewed with an epifluorescence microscope (Nikon Eclipse Ti, Melville, NY) equipped with a Texas Red filter. Fluorescent micrographs (*n* = 10–15) were taken with a digital camera (Andor, DU-885k) and analyzed using Nikon-Elements (version 3.22.11). Optical densities (arbitrary units, % of control) of Nile red labeled IFD were determined for *C. elegans* (larvae 4).

Statistical Analysis

Analyses were completed using SAS/STAT® software, Version 9.4 of the SAS System for Windows (Cary, NC, USA). All results were expressed as means ± standard error of the mean (SEM) Survival curves of lifespan were displayed by binomial probabilities as surrogates for survival probabilities and the mean survival time (mean lifespan) was estimated by Kaplan–Meier analysis. The data for fluorescence intensity was analyzed by ANOVA. All *P* values were calculated based on the comparisons to control group. Statistical significance was set at *P* ≤0.05.

RESULTS

Fructose Increased Lifespan and Increased IFD at Higher Doses

Fructose added to the culture significantly and dose-dependently increased mean lifespan up to the 111 mM dose but reduced lifespan at higher doses in a biphasic dose–response relationship. The average probability of survival across the lifespan was increased at lower doses and decreased at a higher dose (Figure 1a). The mean lifespan was increased at lower
doses from 17.3 to 21.1 (55 mM, \( P < 0.0001 \)) or to 25.2 (100 mM, \( P = 0.0002 \)) days, and was decreased at a higher dose from 25.2 to 11.8 (555 mM) days \( (P < 0.00001, \text{Figure 1b}) \).

The intestinal fat deposition (IFD) of \( C. \text{ elegans} \) measured by Nile red staining was not affected by the lower doses of fructose (55 mM or 111 mM, \( P > 0.05 \)), while it was increased 2-fold at the higher dose (555 mM, \( P < 0.0001 \), Figure 2a & b).

**Sucrose Increased IFD**

The average probability of survival across the lifespan was mildly decreased in sucrose treated groups (Figure 3). The mean lifespan was slightly increased from 17.3 to 18.2 (555 mM) days in a dose-dependent trend \( (P > 0.05, \text{Figure 3 & Figure 1b}) \). Inversely to lifespan extension, the IFD was increased by 120% (55 mM), 180% (111 mM), or 90% (555 mM, \( P < 0.0001 \), Figure 2a & b).

**Glucose Reduced Lifespan and Increased IFD**

The average probability of survival across the lifespan was decreased in the glucose treated group (Figure 1a). The mean lifespan was reduced from 17.3 to 9.2 days (111 mM, \( P < 0.05 \), Figure 1b). The IFD was increased by 20%, \( P < 0.05 \), Figure 2a & b).

**Equal Amount of Glucose Plus Fructose (G&F) or High Fructose Corn Syrup (HFCS)-Reduced Lifespan**

The average probability of survival across the lifespan was decreased in the G&F (167 mM & 167 mM) or HFCS (333 mM) treated group (Figure 4a). The mean lifespan was reduced from 11.8 to 8.2 days for each group \( (P < 0.05, \text{Figure 4b}) \).

**DISCUSSION**

In this study, the effects of fructose, sucrose, glucose, glucose plus fructose, or HFCS consumption were evaluated in the \( C. \text{ elegans} \) model by measuring alterations in lifespan and changes in IFD determined by the fluorescent intensity of Nile red. Lifespan was reduced in the glucose treated group as previously reported \( (\text{Lee et al., 2009, Gao et al., 2015a, Gao et al., 2015b}) \). Here we report a biphasic effect of fructose increasing lifespan at lower doses and shortening lifespan at a higher dose. Sucrose had no significant effect on mean lifespan. The mixed glucose & fructose or HFCS treatment reduced lifespan. IFD was increased at the higher dose and by glucose and sucrose in this study.

Although sugars are important energy sources for animals and humans, overconsumption can threaten health. Consumption of sugar-sweetened beverages can increase hyperinsulinemia, heart rate, advanced oxidation of protein products, triacylglycerol in the blood, and oxidative stress markers in rodents \( (\text{Gurecka et al., 2015}) \). Glucose is transported into cells by GLUT-4, an insulin-dependent transport system, while fructose is transported by GLUT-5 \( (\text{Basaranoglu, Basaranoglu, & Bugianesi, 2015}) \). A high ratio of fructose to glucose can lead to glucose addictive behavior and metabolic disorders in the rat \( (\text{Levy, Marshall et al., 2015}) \). An increased fructose-to-glucose ratio in humans increases fasting triglycerides when daily consumption is over 100 g per day, even without a change in body weight.
weight (Livesey and Taylor, 2008). Elevation of blood glucose in humans stimulates insulin secretion which can lead to weight gain. Rats fed a 32% sugar supplemented diet gain significantly more retroperitoneal fat compared to a standard diet (Kanarek and Orthen-Gambill, 1982).

Similarly, consumption of fructose is linked to many adverse events and diseases in humans. Fructose consumption is a risk factor for metabolic syndrome, an accelerated aging process, myocardial infarction, gout, fatty liver disease, impaired adiponectin secretion, cardiovascular disease, hypertension, diabetes, and cancer (Perheentupa and Raivio, 1967, Ames, Cathcart et al., 1981, Hwang, Ho et al., 1987, Sato et al., 1996, Kang et al., 2005, Khosla et al., 2005, Johnson et al., 2007, Sautin, Nakagawa et al., 2007, Gul, Rahman, & Hasnain, 2009, Perez-Pozo, Schold et al., 2010, Van Horn and Dietary Guidelines Advisory, 2010, Suresh and Das, 2012, Kavanagh et al., 2013, Basaranoglu et al., 2015, Levy et al., 2015). Fructose does not stimulate insulin or leptin secretion in vitro and has a limited ability to inhibit food intake, because it is not able to prevent depletion of ATP, which is necessary for a homeostatic response in the brain (Perheentupa and Raivio, 1967, Johnson et al., 2007). Fructose leads to the generation of lactic acid and hyperuricemia which stimulates intestinal epithelial cells and vascular smooth muscle cells to proliferate and release chemotactic and inflammatory substances, induce monocyte chemotaxis, and create oxidative stress in adipocytes (Kang et al., 2005, Khosla et al., 2005, Sautin, Nakagawa et al., 2007).

Citing increased fructose consumption as the cause for the increase in obesity and obesity-associated diseases that are correlated with caloric sweetener use is controversial (Sun and Empie, 2007). Epidemiological studies also find that total energy intake in the U.S. population increased by 515 kcal/day (24%) between 1970 and 2008 (USDA-ERS data). Of the 515 kcal/day increase in caloric intake, only 58 kcal/day were estimated to come from sugar and only half of that, 29 kcal/day, came from fructose, which includes fructose from all sources including raw fruits and vegetables (White, 2011, White, 2012, White, 2013). Moreover, dietary use of fructose peaked in 1999 followed by a 13-year decline of 39 ± 4 g/day today (White, 2011, White, 2012, White, 2013). This decrease in fructose consumption was coincident with an increasing prevalence of obesity, metabolic syndrome, elevated uric acid, and a rising Body Mass Index (BMI) (White, 2011, White, 2012, White, 2013). Some researchers believe that experimental fructose intake representing 24% of total energy is beyond the normal range of human consumption (≈7.9% of energy at 19–22 years of age) which has been claimed to show no detrimental effect on human health and recommended to diabetic individuals (Anderson, Story et al., 1989, Marriott, Cole,&Lee, 2009, Sun, Anderson et al., 2011, Kavanagh et al., 2013, White, 2013). One clinical trial concluded that fructose and other sugars had no effect on fasting plasma glucose, fasting plasma insulin, LDL and total cholesterol, free fatty acids, or leptin (White, 2013, White, 2013). A recent review of 19 articles from 2006 to 2012 concluded that the “six eligible publications” that linked the fructose in HFCS to childhood obesity were based on “inconclusive scientific evidence” (Morgan, 2013). As the sweetest of the nutritive sweeteners, fructose, a simple monosaccharide found in fruits, vegetables, and honey, is bound to glucose forming the disaccharide sucrose. Fructose has a low glycemic index (GI) and is the least cariogenic of the nutritive sugars compared with sucrose and glucose (Cury,
Rebelo et al., 2000, Bantle, 2006, Cozma et al., 2012). Interestingly, in human studies, lower amounts of daily fructose intake (50–100 g) were related to reduced dysglycemia and glycated hemoglobin (HbA\textsubscript{1c}) (Huttunen, 1976, Livesey and Taylor, 2008). Thus, adverse effects of fructose may only occur with preexisting dyslipidemia, as substitution of fructose in isocaloric diets does not cause adverse effects on lipid metabolism (Chiavaroli et al., 2015).

Many studies have addressed the adverse effects of sugars on obesity and diabetes. With this in mind, we tested three common sugars that are used in foods and beverages. To our surprise, provided that we used equal molar amounts of each sugar, we observed heterogeneous effects of the sugars on lifespan and IFD in \textit{C. elegans}. The biphasic dose-response curve seen with fructose, which increased lifespan at lower doses and reduced at higher doses, supported the results of some other studies using low or high doses (Smith et al., 2007, Kessler et al., 2015). The reduced lifespan by glucose & fructose or HFCS may be related to the dose that could be in the declining lifespan range of fructose treatment alone. Our results with fructose differ from the conclusions of epidemiological studies.

Similarly as in humans reporting, where lower amounts of daily fructose intake (50–100 g) reduced dysglycemia and HbA\textsubscript{1c} without having adverse effect on lipid metabolism except preexisting dyslipidemia (Livesey and Taylor, 2008), we observed that lower doses of fructose extended lifespan. Higher dose of fructose reduced lifespan and increased IFD, which is in agreement with results from human studies that have demonstrated elevations of triacylglycerol, body weight, and fat mass at higher doses of fructose (Herman, Zakim, & Stifel, 1970, Elliott et al., 2002). In rats, sucrose supplemented diets shorten mean lifespan and elevate blood pressure. In the fruit fly (\textit{Drosophila melanogaster}) sucrose reduced lifespan and increased levels of body fat (Preuss et al., 1991, Rovenko et al., 2015). Our results showed no change in lifespan with sucrose. Glucose increased intestinal fat deposition and reduced the lifespan in \textit{C. elegans} which is consistent with previous studies (Zheng et al., 2014, Gao et al., 2015a).

In summary, glucose increased IFD and shortened lifespan, sucrose increased IFD without affecting lifespan, and fructose increased lifespan while increasing IFD at higher doses in \textit{C. elegans}. These data, along with results from studies showing increased lifespan with fructose in yeast and mosquitoes, suggest the need to assess the dose response effect of fructose on lifespan and IFD in higher animal models to further evaluate if lower doses of fructose may have implications for humans.

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REFERENCES


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FIGURE 1.
Glucose, fructose, and sucrose affected lifespan of wild-type *C. elegans* (N2) and their mean survival days. (A) Survival curves of lifespan were displayed by binomial probabilities as surrogates for survival probabilities. (B) The mean survival time (mean lifespan) was estimated by Kaplan–Meier analysis. Low doses of fructose (55 mM and 111 mM) increased mean lifespan (*P* < 0.05). The *P* values of lifespan reflect the Kaplan–Meier probabilities (*P* < 0.05).
FIGURE 2.
Glucose, fructose, and sucrose affected intestinal fat deposition (IFD, *P < 0.05). High dose of fructose (555 mM) increased IFD (P < 0.05). All three doses of sucrose (55 mM, 111 mM & 555 mM) increased IFD, and glucose (111 mM) also increased IFD (P < 0.05).
FIGURE 3.
Sucrose did not significantly alter the mean survival time (mean lifespan) estimated by
Kaplan-Meier analysis. Survival curves of lifespan were displayed by binomial probabilities
as surrogates for survival probabilities.
FIGURE 4.
Glucose plus fructose (G&F) or high fructose corn syrup (HFCS) reduced lifespan. (A) Survival curves of lifespan were displayed by binomial probabilities as surrogates for survival probabilities. (B) The mean survival time (mean lifespan) was estimated by Kaplan–Meier analysis. G167 mM & F167 mM and HFCS 333 mM decreased the mean lifespan ($P < 0.05$). The $P$ values of lifespan reflect the Kaplan–Meier probabilities ($^* P < 0.05$).