S pc A c

Rare sugars and their health effects in humans: a systematic review and narrative synthesis of the evidence from human trials

Amna Ahmed, Ta eef A. Khan, D. Dan Ramdath, C il W.C. Kendall, and John L. Sie enpipe

Affiliation: *A. A , T.A. K a , C.W.C. K , and J.L. S* a e ith the De a tment of N t itional Science , Teme t Fac lt of

INTRODUCTION

As rates of obesity and type 2 diabetes continue to rise globally, the role of excess sugars in the diet has become a focus of intense concern.[1] Most of the attention has centered on the adverse health effects of the common sugars – fructose, sucrose, and high-fructose corn syrup (HFCS).[2] Rare sugars, defined as "monosaccharides and

Tab 2

Tab 2 **Continued**

St d , ea	Pa ticipant	Setting	Mean age, ea (SD o ange)	Mean BMI, kg/m^2 (SD)	De ign	Feeding cont ol	Randomi ation	Ra e ga do e (g)	Inte ention o cont ol	Follo - p	F nding o ce	Main finding
Inte ention								3	3 g L-a abino e + 75 g c o e in 300 mL ate			
Cont ol									75 g c o e in 300 mL ate			
Shibanuma et al (2011)[11]	21 H (18 M, 3 F)	OP, Jap an	NR	NR	C o o e	S pp	No			120 min	NR	Red ction in blood gl co e le - el at 120 min follo ing L- a abino e con mp tion ($P < 0.05$)
Inte ention								2	2 g L-a abino e + 40 g c o e di - ol ed in 108 g deioni ed ate			
Cont ol									40 g c o e in a 150 g c o e ol tion			
Halschou Jensen et al (2018)[38]	17 H (17 M, 0 F)	OP, Denma k	22.5 (2.6)	22 (1.22)	C o o e	S pp	Ye			5 h	I	No change in p eak pla ma gl - co e o gl co e iAUC
Inte ention								2.5 o 2.9	B eakfa t and l nch meal pple- mented ith 5% a abino e b eight			
Inte ention								4.9 o 5.9	B eakfa t and l nch meal pple- mented ith 10% a abino e b eight			
Cont ol									B eakfa t and l nch meal			
L-a ab , ( )												
Yang et al (2013)[12]												
Inte ention	30 MetS (20 M, 10 F)	OP, China	49.9 (9.9)	NR	Open t d	S pp	N/A	40 o 45	20 g t ice dail o 15 g th ice dail of L- a abino e	6 mo	I	Red ction in ai t ci c mfe ence ($P < 0.01$), total chole te ol ($P < 0.05$), and fa ting gl co e ($P < 0.01$)
Cont ol									None			
D- a a , (ac)												
Buemann et al (2000)[39]	20 H (20 M, 0 F)	OP, Denma k	25.7 (4)	24 (2.2)	Pa allel	S pp	NR	29		13 h	I	Red ced appetite and intake at dinne ($P < 0.05$)
Inte ention									29 g tagato e added to a continental b eakfa t			
Cont ol									29 g c o e added to a continental b eakfa t			
Kwak et al (2013)[15]	52 H (27 M, 25 F)	OP, Ko ea	35.8 (10.5)	23.7 (3.9)	C o o e	S pp	Ye	5		120 min	A	Red ction in p o t-te t meal gl - co e iAUC ($P < 0.05$)
Inte ention									5 g tagato e eetened d ink + MTT			
Cont ol									Placebo eetened (e th itol + 0.004 g c alo e) d ink + MTT			
Kwak et al (2013)[15]	33 p e-diabete / T2DM (18 M, 15 F)	OP, Ko ea	57.2 (9.8)	25 (2.6)	C o o e	S pp	Ye	5		120 min	A	Red ction in p o t-te t meal gl - co e iAUC ($P < 0.05$)
Inte ention									5 g tagato e- eetened d ink + MTT			
Cont ol									Placebo eetened (e th itol + 0.004 g c alo e) d ink + MTT			
Wu et al (2012)[14]	10 H (7 M, 3 F)	OP, A t alia	28.8 (12.6)	25.5 (4.7)	C o o e	S pp	Ye			240 min	NR	Red ced gl co e iAUC, e m in- lin le el , and lo e ga t ic emp t ing follo ing the te t meal ($P < 0.05$)
Inte ention								16	40 g tagato e and i omalt lo e mi t e di ol ed in 400 mL ate			
Cont ol									60 g c alo e di ol ed in 400 mL ate			
D- a a , ( )												
Boesch et al (2001)[16]	12 H (12 M, 0 F)	OP, S it e land	(21 30)	<								

Tab 2 **Continued**

St d , ea	Pa ticipant	Setting	Mean age, ea (SD o ange)	Mean BMI, kg/m^2 (SD)	De ign	Feeding cont ol	Randomi ation	Ra e ga do e (g)	Inte ention o cont ol	Follo - p	F nding o ce	Main finding
												hemoglobin ith tagato e con mption
Cont ol									None			
Ensor et al (2015)[20]	356 T2DM	OP, India & USA	51.7 (10.4)	28.3	Pa allel	S pp	Ye			40 k	A, I	Red ction in bod eight ($P < 0.05$) and non ignificant ed ction in gl co lated he- moglobin ith tagato e con mption
Inte ention								45	15 g tagato e di ol ed in 125 250 mL of ate 3 time /da			
Cont ol									1.5 g Splenda di ol ed in 125 250 mL of ate 3 time /da			
Saunders et al (1999)[18]	8 H (4 M, 4 F)	OP, USA	43.6 (5.1)	NR	Pa allel	S pp	Ye			8 k	NR	No change in blood gl co e le - el , lipid le el , o ic acid le el
Inte ention								75	25 g tagato e added to 3 meal dail			
Cont ol									25 g c o e added to 3 meal dail			
Saunders et al (1999)[18]	8 T2DM (4 M, 4 F)	OP, USA	53.8 (11.9)	NR	Pa allel	S pp	Ye			8 k	NR	No change in blood gl co e le - el , lipid le el , o ic acid le el
Inte ention								75	25 g tagato e added to 3 meal dail			
Cont ol									No ga pplementation			
T a , -ac												
Maki et al (2009)[22]	23 OB (23 M, 0 F)	OP, USA	49.8 (10.9)	34.9 (0.7)	C o o e	S pp	Ye			120 min	I	Lo e i e in pla ma gl co e and in lin le el ($P < 0.05$)
Inte ention								75	75 g t ehalo e in a 414 mL be e age			
Cont ol									75 g gl co e in a 414 mL be e age			
van Can et al (2012)[21]	10 OW (6 M, 4 F)	OP, Nethe land	56 (8)	30.8 (4.9)	C o o e	S pp	Ye			3 h	I	Lo e i e in pla ma gl co e ($P < 0.01$) and in lin le el ($P < 0.05$)
Inte ention								75	75 g t ehalo e di ol ed in 400 mL ate			
Cont ol									75g gl co e di ol ed in 400 mL ate			
T a , (/(764.1490TD(75)-133.9a)												

Tab 2 **Continued**

St d , ea	Pa tici ant	Setting	Mean age, ea (SD o ange)	Mean BMI, kg/m^2 (SD)	De ign	Feeding cont ol	Randomi ation	Ra e ga do e (g)	Inte ention o cont ol	Follo - F nding o ce		Main finding
Cont ol									B eakfa t, l nch, and afte noon nack lemented ith c o e			
Kendall et al (2018)[26]	77 H (18 M, 59 F)	OP, Ne Zealand	21.9 (5.6)	23.7 (3.6)	C o o e	S	Ye			120 min	A	
Inte ention								73.2	T ifle containing 73.2 g i omalt lo e			Red ction in blood gl co e le - el at 60 min follo ing i omal- t lo e con m tion ($P < 0.001$)
Cont ol									T ifle containing 73.2 g c o e			
Maeda et al (2013)[32]	10 H (10 M, 0 F)	OP, Ja an	46.6 (7.7)	21.1 (1.6)	Pa allel	S	NR			180 min	A	
Inte ention								50	50 g i omalt lo e di ol ed in 300 mL di tilled ate			Red ction in o t andial la ma in lin and gl co e le el fol- lo ing i omalt lo e con m - tion ($P < 0.05$)
Cont ol									50 g c o e di ol ed in 300 mL di -			

consumption of 5 g allulose, compared with that of 10 mg of aspartame, administered as preloads, on the postprandial glycemic response to a test meal consisting of rice and hamburger steak. They showed a reduction in plasma glucose at 90 minutes following the test meal.[58] Furthermore, ingestion of allulose as a preload resulted in an increase in fat energy expenditure (but a decrease in carbo.5(an)-315a
decreaseate[(dnse)7((but)]TJ-32

Tab *4* **Rare sugars and their effects in human studies**

Ra e ga	Health- elated effect			Side effect
	Health indi id al	Obe e/o e eight indi id al	Indi id al ith t pe 2 diabete / bo de line t pe 2 diabete	
Allulose	Ac te: - ed ced pla ma gl co e po t-te t meal[58,59] -no effect on pla ma gl co e[60] -inc ea ed FEE, dec ea ed CEE[58] Longe te m: - ed ced BF[41]	Long te m: -Red cedeffh 2d9T0 g(Longe)-2413834.9-05224.9008Tm0.00031 g(41)Tj098-937160.7244309.0897Tm00TJT(-Red cedfatec ea 9(ma 253		

intervention. Han et al assessed the effect of two allu-

L-arabinose

Results from a total of three acute studies and one longer-term human study on L-arabinose and cardiometabolic risk factors have been reported (Table 2). L-arabinose is a monosaccharide and aldopentose found naturally in certain plant cell walls, including many grains and plant gums. It has half the sweetness of sucrose and has been shown in animals to be less metabolizable compared with glucose. With no caloric value, most of the studies examining consumption of L-arabinose in humans are acute post-prandial studies, and they demonstrate a benefit on glycemic control in healthy individuals. All acute trials examining the effect of L-arabinose in humans were conducted using a randomized controlled crossover design. Krog-Mikkelson et al showed that a number of doses of L-arabinose reduced insulin and glucose peak in healthy males when given prior to a test meal, compared with sucrose. In a similar study design, Shibanuma et al 2010 also found that, in both males and females, consumption of 2 g of L-arabinose before a 40 g sucrose test beverage led to reduced blood glucose levels at 2 hours compared with a control of water.[11] However, Halschou-Jensen et al were unable to confirm this effect and found that a breakfast meal supplemented with L-arabinose resulted in no changes in the peak plasma glucose or glucose iAUC compared with a sucrose-supplemented meal in healthy participants.

Yang et al examined the longer-term effect of L-arabinose supplementation in individuals with metabolic syndrome who consumed 40 g–45 g L-arabinose (dissolved in water) daily for 6 months with no alteration in lifestyle habits.[12] This intervention resulted in a reduction in waist circumference, total cholesterol, and fasting glucose, showing an overall benefit in participants with metabolic syndrome.[12] However, since this study lacked a control arm and participants were all diagnosed with metabolic syndrome, it is difficult to extend these results to a larger population. Regardless, the study results promise a novel approach to reducing cardiometabolic risk factors in persons suffering with metabolic syndrome.

No study has specifically examined the side effects of arabinose consumption, though they may occur: the abovementioned study by Krog-Mikkelsen et al showed that out of 15 participants, one experienced mild nausea after 1 g of arabinose, one experienced mild diarrhea after 2 g of arabinose, and another experienced a severe stomach ache and diarrhea after 2 g of arabinose.[13] Yang et al also noted that, with doses of either 40 or 45 g daily, 13 out of the 30 participants had mild nausea and diarrhea following treatment.[12] A study that specifically examined the gastrointestinal tolerance of arabinose would be helpful in determining arabinose's side effects and also the maximum recommended dose.

The mechanism by which L-arabinose affects glucose and insulin release in humans is unknown, but in rodent studies it has been shown to inhibit the brush border enzyme sucrose, which can reduce glucose absorption.[2] Further high-quality studies in humans will be needed to confirm its acute effects and help us to better understand the long-term effects of regular L-arabinose consumption on cardiometabolic outcomes.

D-tagatose

Table 2 shows the study characteristics of 4 acute and 6 longer-term human studies that have reported results for D-tagatose consumption and cardiometabolic risk factors. D-tagatose, a monosaccharide, is a C-4 epimer of D-fructose that is found primarily in whey milk protein and is 92% as sweet as sucrose.[42] While it has been

improved metabolic profile seen in many studies.[69] Overall, while in the literature there is a lack of isomaltulose's effect on body weight, there appears to be an improvement in insulin resistance in several studies, and therefore it may be of some benefit to individuals with type 2 diabetes, though more research is warranted.

Less-studied rare sugars

While there are numerous rare sugars that have yet to be studied in detail, there are a few that show potential in nonhuman studies (cell culture or animal studies). These include kojibiose, sorbose, and allose. Kojibiose, a glucose disaccharide connected by an α1-2 glycosidic

study. **A.A.** is funded by a Toronto 3D MSc Scholarship Award. **T.A.K.** is funded by a Toronto 3D Post-doctoral Fellowship Award. **J.L.S.** is funded by a Diabetes Canada Clinician Scientist award. The sponsors did not have a role in design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, approval of the manuscript, or decision to publish, or any other aspect of the present study.

Declaration of interest. **A.A** declares no relevant competing interests with the present work.

T.A.K. has received research support from the CIHR and an unrestricted travel donation from Bee Maid Honey Ltd. He has also spoken as an invited speaker at a Calorie Control Council annual general meeting for which he received an honorarium.

D.D.R. has received research support from Pulse Canada, the Saskatchewan Pulse Growers Association, and the Ontario Bean Growers Association. He has no other conflict of interest to declare.

C.W.C.K. has received grants or research support

Association for the study of Diabetes (EASD), Canadian Cardiovascular Society (CCS), and Obesity Canada/ Canadian Association of Bariatric Physicians and Surgeons. He serves or has served as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of ILSI North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of AB InBev.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **Search term strategy to identify the effects of rare sugars in human studies**

Figure S1 **Flow of the literature**

REFERENCES

1. Mitchell NS, Catenacci VA, W att HR, et al. Obe it : o e ie of an epidemic. *P, c a C N A* . 2011;34:717 732.
2. Van Laa ADE, G ootae t C, Van Camp J. Ra e mono- and di accha ide a health alte nati e fo t aditional ga and eetene ? *C R F Sc N* . 2021;61:713 741.
3. Ha a hi N, Yamada T, Takamine S, et al. Weight ed cing effect and afet e al ation of a e ga p b a andomi ed do ble-blind, pa allel-g o p t d in h -

41. Han Y, Choi B, Kim S, et al. Ga t ointe tinal tole ance of D-all lo e in health and o ng ad lt . A non- andomi ed cont olled t ial. *N* , . 2018;10:2010.
42. X Z, Li S, Feng X, et al. L-a abino e i ome a e and it e fo biotechnological p od ction of a e ga . *A* *M c b B c* . 2014;98:8869 8878.
43. T ck D, B e on J, B lingame B, et al. Scientific Opinion on the ene g con e - ion facto of D-tagato e fo labelling p po e . *EFSA J.* 2016;14:e04630.
44. Go e nment of Canada. A chi ed no el food info mation. A ailable at: http ://.canada.ca/en/health-canada/ e ice /food-n t ition/geneticall -modified-food -othe -no el-food /app o ed-p od ct /t ehalo e.html. Acce ed Septembe 24, 2020.
45. Chattopadh a S, Ra cha dh i U, Chak abo t R. A tificial eetene a e ie . *J F Sc T c* . 2014;51:611 621.
46. Ma e ch CC, Pet SF, Thei S, et al. Lo gl cemic inde p otot pe i omalt lo e pdate of clinical t ial . *N* , . 2017;9:381.
47. Lina BAR, Jonke D, Ko iano ki G. I omalt lo e (Palatino e®