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Inhibition of the glycaemic response by onion: a comparison between lactose-tolerant and lactose-intolerant adults

Richard Hoffman, Golnaz Ranjbar and Angela M. Madden

School of Life and Medical Sciences, University of Hertfordshire, AL10 9AB, UK

Corresponding author

Richard Hoffman

School of Life and Medical Sciences, University of Hertfordshire, Hatfield, AL10 9AB, UK

Tel. +44 1707 284526

Fax: +44 1707 285046

E-mail: r.hoffman@herts.ac.uk

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This pilot study compared inhibition of the glycaemic response to glucose by a dietary source of quercetin glucosides (onion) in lactose-tolerant adults (n = 12) and lactose-intolerant adults (n = 12). We hypothesised that lactose-intolerant people (who do not express lactase) will retain intact quercetin glucosides that can inhibit glucose uptake via the glucose transporter SGLT1 whereas lactose-tolerant people (who do express lactase) will hydrolyse quercetin glucosides to free quercetin which does not inhibit glucose uptake. In a glucose tolerance test, reduction of peak glucose levels by an onion meal was higher in lactose-intolerant people than lactose-tolerant people (44.2% versus 19.3%, p = 0.04). Incremental area under the blood glucose curve was reduced more in lactose-intolerant people, but was not statistically significantly (54.5% versus 42.1%, p = 0.42). A diet containing quercetin glucosides may be of greater benefit for glycaemic control in lactose-intolerant people than in lactose-tolerant people.

INTRODUCTION

A recent consensus report concluded that there is convincing evidence that a low glycaemic index (GI) diet reduces the risk of type 2 diabetes and coronary heart disease, probably reduces the risk of obesity and possibly reduces the risk of some cancers.[1] Some dietary polyphenols can modify the apparent GI of foods by reducing glucose absorption.[2] These include quercetin glucosides, which have been shown to inhibit the active transport of glucose from the luminal side of the brush border into the small intestine via the sodium-dependent glucose transporter SGLT1. By contrast, free quercetin does not inhibit SGLT1.[3,4]

Onions are a major dietary source of quercetin glucosides, and the glucosides in an onion meal can be completely hydrolyzed in the human small intestine to quercetin, as demonstrated in ileostomy patients.[5] The β-glycosidase lactase phlorizin hydrolase (LPH) is responsible for hydrolysis on the luminal side of enterocytes.[6] LPH is expressed in lactose-tolerant people but not in lactose-intolerant people. Hence, we hypothesised that quercetin glucosides may be less effective at blocking glucose uptake in lactose-tolerant people (because they can hydrolyse quercetin glucosides to the aglycone with LPH) compared to lactose-intolerant people. We tested this hypothesis using an onion meal, since onions are a rich source of quercetin glucosides (mainly quercetin-4'-O-glucoside and quercetin-3,4'-O-diglucoside), but contain very little free quercetin [7] , and onions with a higher flavonoid content have been shown to inhibit glucose uptake to a greater extent than onions containing lower concentrations. [8]

METHODS

Participants

The characteristics for the lactose-tolerant and lactose-intolerant participants respectively were (SD): Age: 27.6 (4.6) years (8 F; 4 M) and 29.8 (7.4) (7 F, 5 M) ($p = 0.4$); BMI (kg/m^2) (SD): 22.0 (3.4) and 24.2 (4.3) ($p = 0.18$). Exclusion criteria: under 18 years; pregnant; diabetic, history of blood disorders. Data on contraceptive pill use was not collected. All participants gave written consent and participant information was coded. The protocol was approved by University of Hertfordshire Ethics Committee (protocol number: LMS/PG/UH/00187).

Onion meal

Fresh red onions, bought locally, were peeled, homogenised in water (23% w/v), boiled for 15 min, cooled to room temperature and filtered. Quercetin and quercetin glucosides were analysed by reverse phase HPLC.[7]

Lactose Tolerance Test

Lactose intolerance was measured by a hydrogen breath test using a Gastro® analyser (Rochester, England). Lactose (25g dissolved in 220 ml water) was given to participants after an overnight fast and breath hydrogen was measured over 2 hours. Hydrogen levels 20 ppm above baseline were classified as lactose intolerance.[9]

Glucose Tolerance Test

Participants fasted overnight for at least 10 h before the study commenced (between 09.00 and 09.30) and were allowed to eat their normal evening meal. Finger prick capillary blood samples were obtained after the overnight fast and at 15, 30, 60, 90 and 120 minutes after drinking a glucose solution (50 g food grade glucose (Holland and Barrett, UK) dissolved in 220 ml water). The same blood collection regime was then repeated on a subsequent day after participants had consumed 220 ml of a filtered onion meal (23% w/v) containing glucose (50 g). Participants were not randomised: all participants were designated as either lactose-tolerant or lactose-intolerant and all received glucose alone and glucose plus filtered onion meal ie participants acted as their own controls. Glucose was measured with an EKF glucose analyser (Cardiff, UK). Incremental area under the time glucose curve (IAUC) was calculated using a linear trapezoidal method in Excel, taking the fasting blood glucose concentration as baseline. The study was conducted at University of Hertfordshire.

Statistical analysis

Percentage changes in peak glucose and blood glucose IAUC values were calculated for glucose control versus glucose plus onion with each participant acting as their own control. The mean changes for peak glucose and blood glucose IAUC were then compared between lactose-tolerant and lactose-intolerant groups in Excel by paired two-tailed t-tests and using two-sample unequal variance. Quality of variance was tested for by an F test. Two-way repeated measures ANOVA was performed to examine interactions between time and treatment (SPSS version 22; IBM Corp., Armonk, New York, USA).

Because these interactions were significant, Fisher's least significant difference post-hoc analysis was used.

RESULTS

The onion meal contained 2.0 µg/ml quercetin, 39.5 µg/ml quercetin-4'-O-glucoside, 3.5 µg/ml quercetin-3-O-glucoside and 26.5 µg/ml quercetin-3,4'-O-diglucoside. Consuming an onion meal reduced the glycaemic response in both lactose-tolerant and lactose-intolerant people as determined by glucose IAUC and peak blood glucose concentration (Fig. 1 and Table 1). There was a statistically significant greater reduction in glycaemic response, as measured by changes in peak blood glucose using paired t-tests, by the onion meal in lactose-intolerant people compared to lactose-tolerant people (44.2% and 19.3% respectively, $p = 0.04$) (Table 1). The onion meal also caused a greater reduction in blood glucose IAUC in lactose-intolerant people compared lactose-tolerant people, but this was not statistically significant (54.5% versus 42.1% respectively, $p = 0.42$) (Table 1). In two-way repeated measures ANOVA, interactions between time and glucose ± onion treatment were highly significant for lactose-tolerant participants ($p = 0.007$) and for lactose intolerant participants ($p = 0.007$). Post-hoc comparisons showed that inhibition of glucose uptake by the filtered onion meal occurred from 30 minutes to 120 minutes in the lactose-tolerant participants whereas in the lactose-intolerant group it only lasted until 60 minutes (Fig. 1).

DISCUSSION

In this pilot study we found a significantly greater inhibition of peak glucose concentrations by an onion meal in lactose-intolerant people compared to lactose-tolerant people. This supports our hypothesis that LPH in lactose-tolerant people is hydrolysing quercetin glucosides in the onion meal and that this reduces the ability of the quercetin glucosides to inhibit glucose uptake. Nevertheless, the onion meal inhibited glucose uptake in both groups, and various factors may have contributed to this. Firstly, reduced glucose uptake in lactose-tolerant people may be related to inhibition of GLUT2 by quercetin produced from the hydrolysis of quercetin glucosides by LPH. Quercetin has been shown to inhibit GLUT2, and transport of glucose from the gut to the blood stream requires not only luminal glucose uptake into enterocytes via SGLT1, but also release from the basal membrane of enterocytes into the blood stream via GLUT2.[4] Secondly, both lactose-tolerant and intolerant people may express other glucosidases able to cleave quercetin glucosides. Thirdly, onions are rich in the soluble fibre inulin, and some types of dietary fibre reduce postprandial glycaemia. However, current results on the glucose-lowering effects of inulin are inconsistent.[10]

Consuming dietary flavonoid glucosides is an interesting approach to reducing the glycaemic response to a meal, and this aligns with a recent conclusion of the International Carbohydrate Quality Consortium that overall diet, rather than just the GI values of individual foods, is important when evaluating the potential health risks of sugary foods consumed as part of a meal.[1] Our small pilot study cannot rule out that other components in the onion meal are responsible for the reduced glucose uptake in the presence of onion.

Nevertheless, it does raise the possibility that a diet containing quercetin glucosides (and possibly other flavonoid glucosides hydrolysed by LPH) may be of greater benefit for glycaemic control in lactose-intolerant people than for lactose-tolerant people. Hence, lactose tolerance could be a confounding factor in studies that compare glycaemic responses to diets between regions of the world where lactose tolerance is low, such as the Mediterranean basin, with regions where lactose tolerance is high, such as Northern Europe.

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REFERENCES

1 Augustin LS, Kendall CW, Jenkins DJ, Willett WC, Astrup A, Barclay AW *et al.* Glycemic index, glycemic load and glycemic response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutr Metab Cardiovasc Dis* 2015; **25:** 795-815.

2 Hanhineva K, Torronen R, Bondia-Pons I, Pekkinen J, Kolehmainen M, Mykkanen H *et al.* Impact of dietary polyphenols on carbohydrate metabolism. *International journal of molecular sciences* 2010; **11:** 1365-1402.

3 Cermak R, Landgraf S, Wolffram S Quercetin glucosides inhibit glucose uptake into brush-border-membrane vesicles of porcine jejunum. *The British journal of nutrition* 2004; **91:** 849-855.

4 Johnston K, Sharp P, Clifford M, Morgan L Dietary polyphenols decrease glucose uptake by human intestinal Caco-2 cells. *FEBS Lett* 2005; **579:** 1653-1657.

5 Walle T, Otake Y, Walle UK, Wilson FA Quercetin glucosides are completely hydrolyzed in ileostomy patients before absorption. *J Nutr* 2000; **130:** 2658-2661.

6 Day AJ, Canada FJ, Diaz JC, Kroon PA, McLauchlan R, Faulds CB *et al.* Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. *FEBS Lett* 2000; **468:** 166-170.

7 Lombard KA, Geoffriau E, Peffley E Flavonoid Quantification in Onion by Spectrophotometric and High Performance Liquid Chromatography Analysis. *Hort Sci* 2002; **37:** 682–685.

8 Johnston KL, Clifford MN, Schylen EWG, Kik C, Bovy AG, Morgan LM Differences in intestinal glucose absorption, and insulin and GIP secretion in volunteers following consumption of isogenic onions differing in flavonoid contents. *Proc Nut Soc* 2002; **61:** 124A.

9 Eisenmann A, Amann A, Said M, Datta B, Ledochowski M Implementation and interpretation of hydrogen breath tests. *J Breath Res* 2008; **2:** 046002.

10 Bonsu NK, Johnson CS, McLeod KM Can dietary fructans lower serum glucose? *J Diabetes* 2011; **3:** 58-66.

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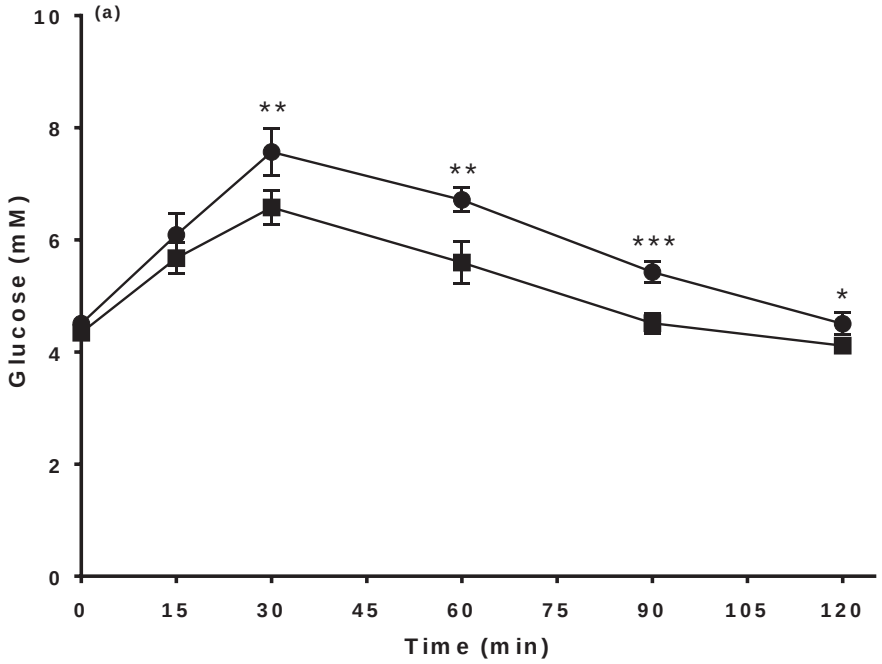
197 *Legend to Figure 1*

198 Blood glucose concentrations after consumption of glucose (•) or glucose plus
199 an onion meal (■) in (a) lactose-tolerant adults and (b) lactose-intolerant
200 adults. Data are means ± SEM (n = 12). Post-hoc Fisher's least significant
201 difference test * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.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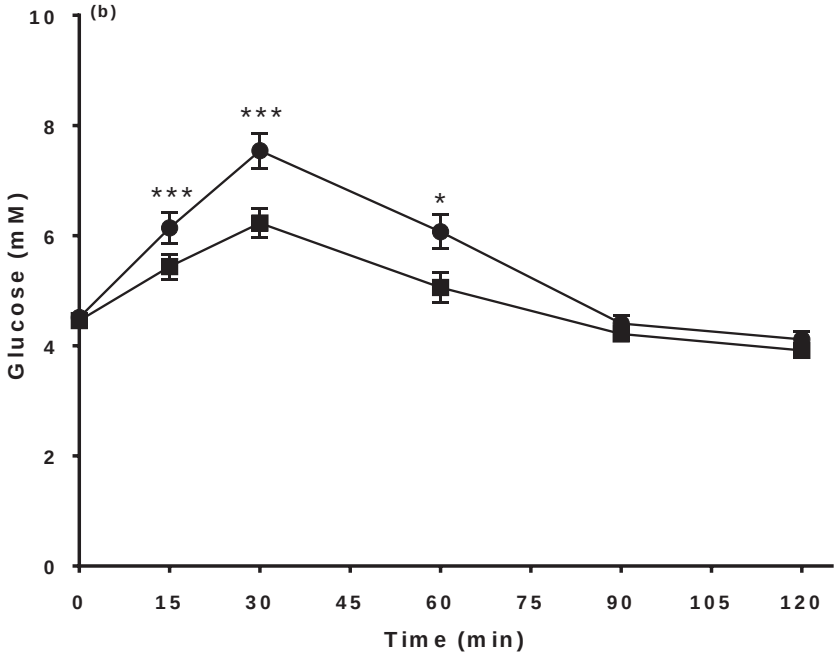
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Table 1. Effects of an onion meal on peak rise in blood glucose and incremental area under the blood glucose - time curve (IAUC) in lactose-tolerant and lactose-intolerant adults.

	IAUC (mM x min)			Reduction in IAUC by onion		**Δ** Blood glucose (mM)[a]			Reduction in **Δ** glucose by onion	
	Glucose control	Glucose + onion	p	%	p[b]	Glucose control	Glucose + onion	p	%	p[b]
Lactose-tolerant	186.4 (16.74)	109.3 (16.77)	0.0037	42.06 (7.50)		3.06 (0.34)	2.24 (0.26)	0.083	19.28	
Lactose-intolerant	130.2 (14.20)	57.1 (16.01)	0.0034	54.53 (12.72)	0.425	3.03 (0.25)	1.77 (0.27)	0.0038	44.19	0.042

Values are expressed as means (SEM). [a] Peak glucose at 30 min minus fasting glucose. [b] Lactose-tolerant versus lactose-intolerant