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What We Know, Think We Know, or Are Starting to Know

In nutrition circles, we have almost come to view fruit juices as almost akin to sugar-sweetened beverages [SSB]. The weight of this position has been derived from epidemiology, but even this position is not as clear cut as one might otherwise think.

For example, in an analysis by Mozaffarian et al. on the contributions of foods to weight gain in the US population, 100% fruit juice was associated with weight gain in three U.S. cohorts ⁽¹⁾. However, this analysis did not adjust for total energy intake, a boo-boo for nutritional epidemiology where we want to understand whether the effect of a nutrient or food is independent of total energy intake ⁽²⁾.

The weight of evidence to date does not suggest that fruit juices are inherently associated with weight gain in either adults or children, and the main consideration for young children appears to be the contribution of sugars to tooth decay ^(3,4).

Where there are some epidemiological associations between a sugary food/beverage and weight gain or other outcomes, it has been common to home in on a particular explanation: impacts on blood glucose and insulin levels. So, a relevant research question with regard to fruit juices is whether fruit juices, and the type of juice, have an impact on postprandial glucose and insulin metabolism?

Citrus fruits have attracted some interest due to the content of specific types of (poly)phenols that may exert an influence on glucose metabolism*. The present study compared fresh and processed orange juice on glucose, insulin, and appetite levels.

*Geek Box: Citrus (Poly)phenols and Glucose Metabolism

We love (poly)phenols. And we have, in previous Geek Box's, discussed their effects on neurological processes and on cardiovascular processes, with a focus on their influence on blood flow and blood pressure. However, (poly)phenols also appear to influence carbohydrate digestion and absorption, thus potentially influencing the rate of glucose appearance in the blood [which, in turn, would influence insulin responses]. But recall that each flavonoid subclass behaves somewhat differently, and citrus flavonoids may influence glucose metabolism through other pathways. Animal studies have shown that two citrus flavonoids, hesperidin and naringin, upregulate the GLUT4 transporter that is responsible for bringing glucose into a cell and out of circulation. This appears to be through influencing pathways associated with liver glucose regulation. Also recall that, in the fasted state, the liver is the primary site of glucose production, while in the postprandial period liver glucose production is suppressed in order to process the glucose arriving from the meal. This is what occurs in healthy individuals; in individuals with visceral fat/liver fat and higher adiposity, the liver continues to produce glucose, and this adds to the state of elevated postprandial glucose levels, strain on insulin, and impaired glucose tolerance. It appears that citrus flavonoids may act by influencing liver glucose production. Specifically, citrus flavonoids in animal models upregulate the glucokinase enzymes which result in liver glucose being stored as glycogen. Citrus flavonoids have also been shown to suppress other pathways associated with production of glucose in the liver. Finally, similar to other flavonoid compounds, there is also mechanistic evidence that citrus flavonoids may inhibit digestion and absorption of glucose. Thus, it may be that citrus flavonoids influence postprandial glucose metabolism through a number of potential mechanisms: inhibition of intestinal glucose transport; upregulation of glucose uptake into cells from the blood; suppression of liver glucose production and increased storage of glucose in the liver. The liver mechanisms are similar to the diabetes class of drugs known as thiazolidinediones.

The Study

The intervention was designed to test the effects of orange juice on postprandial metabolism in both lean individuals and individuals with obesity. 36 [18 lean participants and 18 participants with obesity] participants completed 3 separate interventions:

- Fresh orange juice [FOJ]
- Processed [non from concentrate] orange juice [POJ]
- Placebo control

The placebo was matched for sugar and acid content of the orange juices, and was coloured and flavoured to matched the appearance of the orange juices. Participants were provided with 5ml/kg of each drink [e.g., 350ml for a 70kg person], and each participant completed all three phases of the study. Each phase was separated by a 1-week washout period.

For each study phase, participants consumed the drink within 10mins, which was followed by a standardised breakfast 30min later, which was designed to be free from flavonoids. Blood samples were taken immediately before the drinks were consumed, and then at four time-points across 5hrs postprandial.

The primary outcomes were glucose and insulin responses over 5hrs following each drink. Secondary outcomes included antioxidant activity and appetite.

Results: Processing influenced the compositions of the FOJ and POJ. The FOJ had 19% higher vitamin C [ascorbic acid] levels and 66% higher flavones compared to POJ. Conversely, the POJ had 3-fold and 6.5-fold higher levels of hesperidin and narirutin, respectively. Data was analysed separately from lean participants and participants with obesity.

Lean Participants:

- **Glucose/Insulin:** Compared to the placebo control, the blood glucose response over 5hrs was 11% lower after FOJ and 5% lower after POJ. Insulin levels were 27% lower after the FOJ and 29% lower after the POJ.
- **Antioxidant Activity:** Lipid peroxidation [more under Interesting Finding, below] was reduced by 59% following FOJ and 54% following POJ, compared to fasting levels.
- **Food Intake:** Following the placebo control drink, participants consumed 175kcal and 140kcal more at lunch compared to after the FOJ and POJ, respectively.

Participants with Obesity:

- **Glucose/Insulin:** Compared to the placebo control, postprandial glucose was 3% and 7% lower following the FOJ and POJ, respectively. Insulin levels were 21% lower after the FOJ, and 33% lower after the POJ.
- **Antioxidant Activity:** Lipid peroxidation [more under Interesting Finding, below] was reduced by 54% following FOJ and 58% following POJ, compared to fasting levels.
- **Food Intake:** Following the placebo control drink, participants consumed 244kcal and 264kcal more at lunch compared to after the FOJ and POJ, respectively, and 113kcal and 108kcal more at dinner compared to after the FOJ and POJ, respectively.

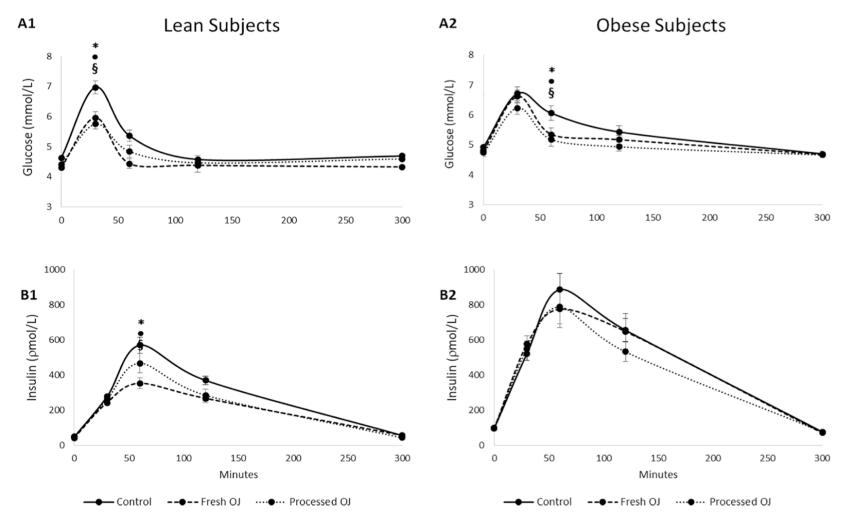


Figure from the paper illustrating the glucose [top] and insulin [bottom] responses over 5hrs in lean participants [left] and participants with obesity [right]. The control group is the solid black line; the FOJ is the long-dashed black line, and the POJ is the short-dashed black line. In the lean participants, a clear difference can be observed following both FOJ and POJ compared to the sugar/acid-matched placebo control drink. What is most striking about the effects of the orange juices is the difference is the magnitude of the blood glucose and insulin responses over the early [0-100min] postprandial period. In relation to insulin in lean participants, this remains elevated over the orange juices even beyond 100min. In participants with obesity, while the total 5hr area-under-the-curve for glucose was not significantly different, there was a significant difference after 60min with both the FOJ and POJ lower than the placebo. Interestingly, it was the POJ which resulted in lower overall insulin levels in participants with obesity.

The Critical Breakdown

Pros: The research question was clearly focused and addressed with the primary and secondary outcomes clearly stated. An appropriate placebo control has been a methodological challenge for all (poly)phenol intervention studies, and the placebo in this study was matched for both sugars and acids with the orange juices [more under *Key Characteristic*, below]. The participants were balanced for sex and BMI, with equal numbers of both in the study cohort. The required sample size was 15 per group, thus the study had adequate statistical power [with 18 in both lean and obese groups]. The 7-day washout between each test day would be expected to ensure no carryover effects of the preceding intervention.

Cons: The design of the study has some questionable execution. For example, the participants were not randomised to groups because they were allocated to a group based on their BMI. The paper states that the order of the intervention was FOJ>POJ>Placebo, then states that the first phase [FOJ] was not randomised, but the other phases were randomised. But how? They have already assigned participants to groups based on BMI, so the only aspect of the design that could be randomised would be the order of the phases, but this is unclear in the paper. The subsequent dietary intake over the day was self-reported, but we don't know what the participants ate [i.e., did they remain in the facility?] and whether their self-selection of different foods may have influenced energy intake. The reporting in the paper also leaves a lot to be desired, with key raw data not presented [i.e., lipid peroxidation] and leaving calculations of differences to the reader.

Key Characteristic

Despite the flaws of the study in factors like randomisation and reporting, the one aspect of the design the researchers deserve credit for is formulating a placebo control that was matched for sugars, acids, and appearance and flavour. This has been a challenge in research on effects of flavonoids, to tease out the independent effects of the flavonoid compounds themselves from other characteristics of the food/drink.

For example, an intervention on the effects of flavonoids on cognitive function failed to match the intervention and placebo for sugar, and glucose could have influenced performance on cognitive tests ⁽⁵⁾. More importantly for the present study, however, is the fact that flavonoids may themselves influence sugar metabolism ⁽⁶⁾. Where the sugar content of each drink was matched in the present study, it indicates that the results are more demonstrable of effect of the other compounds in orange juice, including citrus flavonoids but also pectin and ascorbic acid [vitamin C].

Interesting Finding

The lipid peroxidation finding is interesting, but also an example of where method matters. Lipid peroxidation is the process of fats [lipids] undergoing oxidation by free radicals, creating damaged lipid products that can in turn damage cells in the body. It is a process that is important for cardiovascular disease and metabolic health, and there are a number of dietary compounds that are important to protecting against this process, specifically vitamins E and C, and also (poly)phenols.

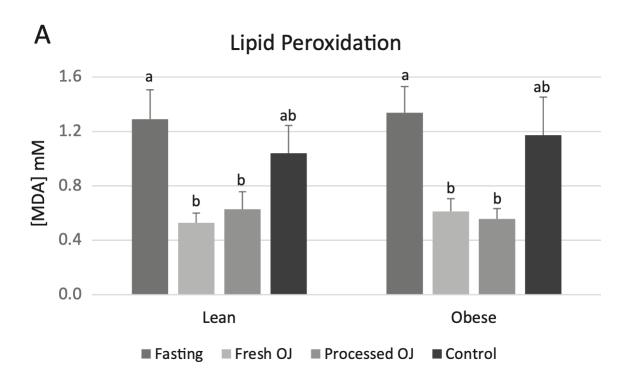


Figure from the paper illustrating the differences in lipid peroxidation when compared to fasting in both lean [left bar chart] and obese [right bar chart] participants. Lipid peroxidation was compared to fasting levels for both the FOJ, POJ, and placebo. Both orange juices, compared to fasting and also compared to the placebo, showed significantly lower levels of lipid peroxidation in this analysis.

So, at first glance the findings of 55-60% lower lipid peroxidation from the FOJ and POJ in both lean participants and participants with obesity seems quite pronounced, and a finding to emphasise. However, and credit to the authors for acknowledging this in their limitations, in this study lipid peroxidation was measured using a laboratory technique known as TBARS [thiobarbituric acid-reactive substances].

The problem is that TBARS is a *non-specific* measure of lipid peroxidation, may measure products other than lipid peroxidation, and may be elevated without concomitant elevations in markers of oxidative stress ⁽⁷⁾. A more accurate way to directly measure oxidative stress is by measuring isoprostanes ⁽⁸⁾. So, while the findings in the present study for lipid peroxidation are interesting, we would want to see them replicated in a study that measures lipid peroxidation using isoprostane markers.

Relevance

The issues with regard to randomisation and allocation mean that the potential for bias in the present study cannot be ruled out entirely, which is a shame given their provision of an appropriate placebo for the two orange juice interventions. Nevertheless, the findings are interesting insofar as they purport to demonstrate an effect of the orange juices that is independent of their sugar and acid content.

It is important to note, however, that the orange juices themselves differed due to their respective processing methods. The FOJ was squeezed from whole oranges by the research team on the morning of the intervention, while the POJ was a non-from-concentrate commercially available orange juice. These resulted in key differences, with the ascorbic acid [vitamin C] and flavone content of FOJ higher than POJ, while the POJ was higher in hesperidin and narirutin.

In relation to postprandial glucose, however, this appears to have resulted in little significant difference between FOJ and POJ, although tipped toward the FOJ having a lower overall postprandial glucose response in lean participants. Given that animal and experimental studies show a specific effect of hesperidin and narirutin on glucose metabolism ⁽⁶⁾, we could have expected to see POJ have a more pronounced effect. This is an example of why simple extrapolation from animal/mechanistic data to humans does not always translate, as the total food/beverage matrix comes into play with *Sapiens*. Ultimately, the differences were small and indicate that some combinations of compounds in orange juice independent of sugar exert beneficial effects on postprandial glucose metabolism.

While we're all about the flavonoids, however, we must also note that good 'ol vitamin C may have contributed to the findings, particularly in relation to insulin. An intervention in older adults with type-2 diabetes showed that 1-month of ascorbic acid supplementation resulting in significantly lower postprandial glucose levels, potentially through insulin-mediated glucose uptake in peripheral tissues [i.e., skeletal muscle] ⁽⁹⁾. To what extend vitamin C and flavonoids may have additive effects would be an interesting question for future research.

Application to Practice

Does fruit juice deserve its bad rep? Arguably, no; certainly not based on the preponderance of evidence available ^(3,10). Sure, from the perspective of tooth decay in children we probably don't want them drinking a lot of sugary beverages or foods. But it is important to recall that the dosage range at which most interventions have used fruit juices, which is usually 200-250ml. And there is scant reason to worry about those kinds of habitual levels, assuming the remainder of the diet is not awash with SSB and Haribo. It would appear that worrying about the blood sugar rollercoaster from fruit juices may also be overstated, and the matrix of ascorbic acid and citrus flavonoids may have favourable effects on postprandial glycaemia, certainly when compared to an equivalent amount of sugar from other drinks.

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