Influence of dietary fructose on lipid profile and glycaemic control in healthy individuals

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Thesis submitted in fulfilment of the requirements for the
Degree of Doctor of Philosophy

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October 2015
Statement of originality

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University’s Digital Repository subject to the provisions of the Copyright Act 1968.
Acknowledgments

The end of an arduous journey of completing a PhD thesis calls for a pause and rewind; and for expressing my heartfelt gratitude to those without whose support, this project would not have come to fruition. I want to acknowledge all those moments, circumstances and people who have helped me accomplish this rather ambitious goal.

Firstly, I owe the biggest debt of gratitude to Professor Manohar Garg, who has contributed significantly to my development through his guidance, encouragement and support. His intellectual inputs, expertise and positive outlook have inspired me to keep going, and those much needed pep talks have given me the confidence to overcome even the most difficult of challenges with relative ease.

I would also like to thank my co-supervisor, Associate Professor Lisa Wood for her patience, invaluable feedback and passionate mentoring. She is a remarkable role model who has inspired me to think laterally and aim higher.

My sincere thanks to the Hunter Medical Research Institute (HMRI) for helping me recruit participants for my research. I would like to express my sincere gratitude to all the wonderful participants who selflessly committed their time towards my research.

I will be ever indebted to Jennie Thomas Trust Fund (via HMRI) and the University of Newcastle scholarships without whose support completing a PhD would have remained a dream.

I have been very fortunate to be a part of Nutraceuticals Research Group. A big ‘thank you’ to my colleagues: Jency, Cintia, Rohith, Fatimah, Jess and Kylie. They have been immensely helpful, supportive and encouraging. Special thanks also to Melissa Fry and Melinda Phang, who always listened patiently to all my woes and provided their useful suggestions.

Last but not the least; I would also like to thank my family and friends for their ongoing encouragement, support and prayers and for believing in me when I had moments of doubt. A special thanks to my wife Sameena and my little boy Ayaan. Thank you Sameena for always believing in me and encouraging me to be the best that I can be. I would have never been able to come so far without your constant support and love and putting my work as a priority ahead of our life.
Publication and presentations central to this thesis

Refereed journal publication:

Jameel F, Phang M, Wood LG and Garg ML; Acute Effects of Feeding Fructose, Glucose and Sucrose on Blood Lipid Levels and Systemic inflammation Lipids in Health and Disease 2014, 13:195

Conference Abstracts:

F. Jameel, M. Phang, L. G. Wood, M. L. Garg; Fructose consumption modulates postprandial lipid levels and inflammatory mediators in healthy subjects, Nutrition Society of Australia and New Zealand ASM (Dec 2013), Brisbane.


F Jameel, LG Wood, ML Garg; Dietary supplementation with fructose or glucose does not influence blood lipids and C-reactive protein in healthy subjects, Nutrition Society of Australia and New Zealand ASM (NOV 2014), Hobart.
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### Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AGEs</td>
<td>Advanced glycation end products</td>
</tr>
<tr>
<td>AOPP</td>
<td>Advanced oxidation protein products</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under Curve</td>
</tr>
<tr>
<td>BFM</td>
<td>Body Fat Mass</td>
</tr>
<tr>
<td>BIA</td>
<td>Bioimpedance analysis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CETP</td>
<td>Cholesteryl ester transfer protein</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DHAP</td>
<td>Dihydroxy acetone phosphate</td>
</tr>
<tr>
<td>DNL</td>
<td><em>de novo</em> lipogenesis</td>
</tr>
<tr>
<td>FAS</td>
<td>Fatty acid synthase</td>
</tr>
<tr>
<td>Ga-3-P</td>
<td>Glyceraldehyde-3-Phosphate</td>
</tr>
<tr>
<td>GLUT 2</td>
<td>Glucose Transporter 2</td>
</tr>
<tr>
<td>GLUT 5</td>
<td>Glucose Transporter 5</td>
</tr>
<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
</tr>
<tr>
<td>HEAC</td>
<td>Human aortic endothelial cells</td>
</tr>
<tr>
<td>HFCS</td>
<td>High Fructose Corn Syrup</td>
</tr>
<tr>
<td>HOMA</td>
<td>Homeostatic model assessment</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>high-sensitivity CRP</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>Intercellular adhesion molecule-1</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon gamma</td>
</tr>
<tr>
<td>IHCL</td>
<td>Intra hepatocellular lipids</td>
</tr>
<tr>
<td>IKKβ</td>
<td>IκB kinase</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Inter Leukin-1β</td>
</tr>
<tr>
<td>IL-6</td>
<td>Inter Leukin-6</td>
</tr>
<tr>
<td>IL-8</td>
<td>Inter Leukin -8</td>
</tr>
<tr>
<td>IMCL</td>
<td>Intra-myocellular lipids</td>
</tr>
<tr>
<td>JNKs</td>
<td>c-jun N-terminal kinase</td>
</tr>
<tr>
<td>LCAT</td>
<td>Lecithin cholesterol acyltransferase</td>
</tr>
<tr>
<td>LDL</td>
<td>Low Density Lipoprotein</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>LPL</td>
<td>Lipoprotein Lipase</td>
</tr>
<tr>
<td>LTs</td>
<td>Leukotrienes</td>
</tr>
<tr>
<td>MCP-1</td>
<td>Monocyte chemotactic protein 1</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>NASH</td>
<td>Non-alcoholic steatohepatitis</td>
</tr>
<tr>
<td>NEFA</td>
<td>Non-esterified fatty acids</td>
</tr>
<tr>
<td>PBF</td>
<td>Percent body fat</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s Disease</td>
</tr>
<tr>
<td>PDH</td>
<td>Pyruvate dehydrogenase</td>
</tr>
<tr>
<td>PFK</td>
<td>Phosphofructokinase</td>
</tr>
<tr>
<td>PGE2</td>
<td>Prostaglandin E2</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
<tr>
<td>SGLT1</td>
<td>Sodium Glucose Transporter 1</td>
</tr>
<tr>
<td>sICAM</td>
<td>Soluble intercellular adhesion molecule</td>
</tr>
<tr>
<td>SREBP-1</td>
<td>Sterol regulatory element binding protein-1</td>
</tr>
<tr>
<td>SREBP-1c</td>
<td>Sterol regulatory element binding protein-1 c</td>
</tr>
<tr>
<td>T2DM</td>
<td>Type II Diabetes Mellitus</td>
</tr>
<tr>
<td>TBARS</td>
<td>Thiobarbituric acid reactive substances</td>
</tr>
<tr>
<td>TCA cycle</td>
<td>Tricarboxylic acid cycle</td>
</tr>
<tr>
<td>TG</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll-like receptors</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumour Necrosis Factor α</td>
</tr>
<tr>
<td>USD</td>
<td>United States Dollar</td>
</tr>
<tr>
<td>WHR</td>
<td>waist: hip ratio</td>
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</table>
Synopsis

Fructose is commonly known as ‘fruit sugar’, but is also a major component of table sugar and high fructose corn syrup. The way the human body absorbs and metabolises fructose is different from any other sugar molecule. Absorption of fructose is enhanced in the presence of glucose and unregulated, due to its passive diffusion into the blood stream. Similarly, excess fructose intake is metabolised in a way that may contribute to the development of chronic diseases. A review of the literature has shown positive associations between high fructose intake and cardiovascular disease risk factors, i.e. increased TG, HDL, total cholesterol and LDL & reduced HDL blood lipids [1-4] [5-9], development of insulin resistance [10-15], alteration in the production of satiety hormones: insulin [6] [16], leptin [6, 17] and ghrelin [6, 18, 19], increase in the level of inflammatory biomarkers (TNF-α, IL-6 etc.) [20-23] and increase in body weight or obesity [10, 24-28], in some but not all studies.

Extensive literature review has revealed that no work has been done on restricting fructose intake and its effect on disease risk in healthy individuals. We hypothesised that restricting dietary fructose intake would result in improved glycaemic indices, reduced circulating lipid levels and low grade inflammation in healthy individuals.

Prior to testing the effect of restriction of fructose consumption in the diet, we looked at the effect of acute and chronic consumption of fructose in healthy individuals. In the acute study (Chapter 3, published: Lipids in Health and Disease 2014, 13: 195), fructose was consumed as the sole source of energy without an accompanying meal. The reason for the increase in postprandial levels of total, LDL and HDL cholesterol in subjects who consumed fructose in the acute study is not known. Since no nutrients, other than sugars, were included in the test beverages, the lipoproteins measured were almost exclusively of hepatic origin. The lipemic
effects of fructose may depend on the dose and duration of fructose feeding and whether fructose is consumed in the presence or absence of other energy nutrients and also whether consumed as a substitute for another sugar or as a supplement in excess of energy requirements.

In the chronic study (chapter 4), fructose was used to supplement usual diets for a period of 4 weeks. When fructose was consumed for 4 weeks in addition to the usual diet, it was found to cause significant changes in glucose metabolism without causing any significant change in lipid and hs-CRP levels. It appears that at the dose and duration used in chronic study, the type of sugar (fructose or glucose) consumed increases fasting blood glucose levels but does not modulate other CVD risk factors such as lipid profile, insulin and low grade inflammation in healthy individuals. Hence consumption of a diet containing fructose at these moderate levels does not increase CVD risk in healthy individuals.

Conversely, the fructose restriction study (chapter 5) demonstrated that consumption of a low fructose diet (< 8g/day, less than 2% energy from fructose) resulted in a statistically significant decrease in BFM, BMI and a small decrease in weight (statistically non-significant). This suggests the potential for clinically important weight reduction to be observed if the duration of intervention was increased. There was no significant difference in other parameters of anthropometric measurements, body composition and blood biomarkers of lipids or systemic inflammation.

In conclusion, as fructose is metabolised differently to other sugars, this becomes important in ascertaining the effect of sugar consumption on cardiovascular health [29]. However, fructose when substituted for glucose in isocaloric diets and not consumed as excess energy, may not increase the risk of developing cardio-metabolic disease.
Thesis structure and overview

This thesis consists of six chapters including one published study in Lipids in Health and Disease. The thesis begins with an introduction and review of the literature (Chapter 1) followed by the methodology undertaken in the conduct of the research (Chapter 2). The introduction, methods, results, discussion and implications of the research conducted for this thesis are then presented as a series of three chapters (Chapter 3 to 5). This thesis presents work from a body of research comprised of three human research studies; (i) an acute fructose supplementation study (chapter 3), a chronic fructose supplementation study (chapter 4) and a fructose restricted study (chapter 5). An overall discussion of the findings from this body of research and its implications are provided as the final chapter of the thesis (chapter 6).