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**Diet, kiwifruit and genotypes: their influence on  
lipid profiles and CVD-related metabolic  
markers in hypercholesterolaemic men**



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## Abstract

In New Zealand, cardiovascular disease (CVD) is a major public health concern and a leading cause of death. Lifestyle modification, including dietary change, is a crucial element in the prevention of CVD, with fruit and vegetables key elements of a cardioprotective diet. Kiwifruit is a commonly-consumed, nutrient-dense fruit that contains many components individually shown to have positive effects on CVD risk factors. This study investigated the effects on plasma lipid profiles and other CVD-related metabolic markers of consuming kiwifruit daily in conjunction with a healthy diet. Further, plasma lipid responses were examined according to inflammatory status, *APOE* genotype, and additional high-density lipoprotein cholesterol (HDL-C)-related gene polymorphisms.

Eighty-five hypercholesterolaemic men (low-density cholesterol (LDL-C) >3.0 mmol/L and triglycerides (TG) <3 mmol/L) completed a 4-week healthy diet run-in before randomisation to a controlled cross-over study of two 4-week interventions of two green kiwifruit/day plus healthy diet (intervention), or healthy diet alone (control). Anthropometric measures, blood pressure (BP), heart rate (HR), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR) and fasting blood samples (lipid profile, insulin, glucose, high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, tumour necrosis factor alpha (TNF- $\alpha$ ) and IL-10) were taken at baseline, 4 and 8 weeks. An additional blood sample was taken for genetic testing: *APOE*, *CETP Taq1B*; *APOA1* -75G/A; *LIPC*-514C→T; *LIPG* I24582. Subjects were divided into low and medium inflammatory groups, using pre-intervention hs-CRP concentrations (hs-CRP <1 and 1-3 mg/L, respectively). Repeated measures ANOVA was used to examine genotype/inflammatory status x treatment interactions.

After the kiwifruit intervention, plasma HDL-C concentrations were significantly higher (mean difference 0.04 [95% CI: 0.01, 0.07] mmol/L [ $P=0.004$ ]) and the total cholesterol (TC)/HDL-C ratio was significantly lower (-0.15 [-0.24, -0.05] mmol/L [ $P=0.002$ ]), compared to control. For the total group, there were no significant differences between the interventions for TC, LDL-C, insulin, glucose, hs-CRP, BP, HR, SV, CO and TPR. Lipid responses were modulated according to inflammatory status and *APOE* and *CETP Taq1B* genotypes. The

medium inflammatory group had a significant improvement in CRP with kiwifruit compared to control. Significant inflammatory group x intervention interactions were seen for TC/HDL-C ( $P=0.02$ ), TG/HDL-C ( $P=0.05$ ), and plasma IL-6 ( $P=0.04$ ). Examined by genotype, *APOE4* carriers had significantly decreased TG ( $-0.18$  [ $-0.34$ ,  $-0.02$ ] mmol/L [ $P=0.03$ ]) with kiwifruit compared to control. A significant *CETP Taq1B* genotype x intervention interaction was seen for the TG/HDL-C ratio ( $P=0.03$ ), and *B1/B1* homozygotes had a significantly lower TG/HDL-C ( $-0.23\pm 0.58$  mmol/L,  $P=0.03$ ) ratio after the kiwifruit intervention, compared to control. Lipid response was not affected by other polymorphisms.

In conclusion, kiwifruit independently of a healthy diet containing fruit improved dyslipidaemic profiles, significantly improving mean HDL-C concentration and TC/HDL-C ratio compared with the control intervention. Effects were even more pronounced in men with phenotypes and genotypes which placed them at higher risk of CVD, with more sizeable improvements in HDL-C and TC/HDL-C ratio, and significant decreases in TG concentrations and TG/HDL-C ratio. Although modest, the improvements suggest that regular inclusion of green kiwifruit as part of a healthy diet could translate into a significant reduction of CVD risk in men with high cholesterol concentrations.

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## Table of Contents

Abstract .....	I
Acknowledgements .....	III
List of Tables .....	IX
List of Figures .....	XIII
List of Appendices .....	XIV
List of Abbreviations .....	XV
<b>Chapter 1: Introduction.....</b>	<b>1</b>
1.1 Introduction .....	2
1.2 Aims and objectives .....	8
1.2.1 Primary objective.....	8
1.2.2 Secondary objectives .....	8
1.3 Hypotheses .....	9
1.4 Structure.....	10
References.....	11
<b>Chapter 2: Literature Review.....</b>	<b>15</b>
2.1 Introduction .....	16
2.2 Cardiovascular disease .....	18
2.2.1 Atherosclerosis.....	19
2.2.1.1 Pathogenesis.....	20
2.2.1.2 Risk factors .....	23
2.2.1.3 Role of endothelial shear stress .....	24
2.2.1.4 Nitric oxide, oxidative stress and endothelial dysfunction .....	25
2.2.1.5 Linking oxidative stress with atherogenesis .....	28
2.2.2 CVD as a public health issue and recent trends .....	29
2.2.2.1 Global picture of CVD.....	29
2.2.2.2 United States.....	34
2.2.2.3 New Zealand .....	36
2.2.3 Lipid and lipoprotein metabolism in relation to CVD risk.....	43
2.2.3.1 Lipids, lipoproteins and apolipoproteins .....	43
2.2.3.2 Lipoprotein metabolism .....	47
2.2.3.3 Low-density lipoprotein.....	54
2.2.3.4 High-Density Lipoprotein .....	56
2.2.3.5 Triglycerides.....	62

2.2.3.6 Lipoprotein ratios .....	63
2.2.4 Obesity and inflammation .....	66
2.2.4.1 Measuring obesity.....	70
2.2.4.2 C-reactive protein .....	72
2.2.4.3 Cytokines.....	74
2.2.5 Blood pressure .....	77
2.2.5.1 Blood pressure classification .....	79
2.2.5.2 Pathophysiology of hypertension .....	81
2.2.5.3 Risk factors for hypertension .....	83
2.2.5.4 Blood pressure as CVD risk factor .....	83
2.2.5.5 Indirect measuring of BP and other vascular measures .....	86
2.2.6 Selected genes and CVD risk.....	89
2.2.6.1 Apolipoprotein E protein function and genotype.....	90
2.2.6.2 HDL related genes.....	93
2.3 Diet and CVD .....	99
2.3.1 General dietary recommendations for risk reduction.....	100
2.3.2 Fruit and vegetables and CVD risk reduction.....	104
2.3.2.1 Fibre .....	107
2.3.2.2 Anti-oxidant vitamins - C and E.....	108
2.3.2.3 Polyphenols.....	110
2.3.2.4 Individual whole fruit or juice intervention studies .....	112
2.3.3 Green kiwifruit ( <i>Actinidia deliciosa</i> var Hayward) .....	117
2.3.3.1 Nutrient composition .....	117
2.3.3.2 Kiwifruit intervention studies .....	122
2.3.4 Inter-individual diet responsiveness.....	125
2.3.4.1 APOE genotype and diet responsiveness.....	126
2.3.4.2 CETP Taq1B genotype and diet responsiveness .....	128
2.3.4.3 CRP and diet responsiveness.....	128
2.3.5 The potential role of personalised dietary recommendations .....	132
2.4 Summary .....	134
References.....	136

<b>Chapter 3: Methodology</b> .....	<b>163</b>
3.1 Introduction .....	165
3.2 Subjects .....	165
3.3 Screening .....	167
3.4 Study design .....	167
3.5 Ethics .....	167
3.6 Setting .....	168
3.7 Procedure .....	169
3.8 Interventions .....	170
3.8.1 Healthy diet .....	170
3.8.2 Kiwifruit intervention .....	171
3.9 Assessment methods .....	171
3.9.1 Demographics .....	171
3.9.2 Anthropometric measurements .....	171
3.9.3 Dietary assessment .....	173
3.9.4 Nutrient analysis .....	173
3.9.5 Physical activity assessment .....	174
3.9.6 Blood samples, processing and analysis .....	174
3.9.7 Blood Pressure .....	177
3.9.7.1 Brachial arterial blood pressure .....	177
3.9.7.2 Finger arterial blood pressure, heart rate and other cardiac markers .....	177
3.9.8 Tolerance to the kiwifruit intervention .....	178
3.9.9 Preparation and nutrient analysis of kiwifruit samples .....	178
3.10 Data handling and statistical analysis .....	179
3.10.1 The effects of kiwifruit consumption on plasma lipids, and modulation of response by <i>APOE</i> genotype (Chapter 4) .....	180
3.10.2 The effects of inflammatory status on plasma lipid and inflammatory marker response (Chapter 5) .....	180
3.10.3 The effects of selected HDL-related genes on plasma lipid response (Chapter 6) .....	181
3.10.4 The effects of the kiwifruit intervention on BP and other markers of cardiovascular function as measured by the Finometer (Chapter 7) .....	182
3.11 Provision of results to subjects .....	182
3.12 Funding .....	182
References .....	183

<b>Chapter 4: Kiwifruit consumption favourably affects plasma lipids in a randomised controlled trial in hypercholesterolaemic men.....</b>	<b>185</b>
Abstract.....	186
4.1 Introduction .....	187
4.2 Subjects and methods.....	189
4.3 Results .....	189
4.3.1 Characteristics of subjects.....	189
4.3.2 Effects of the intervention on dietary intake, body weight and blood pressure .	189
4.3.3 Tolerance to the kiwifruit intervention .....	193
4.3.4 Nutrient composition of the green kiwifruit .....	193
4.3.5 Effects on plasma lipid and apolipoprotein concentrations.....	193
4.3.6 <i>APOE</i> genotype-kiwifruit treatment interaction.....	196
4.3.7 Other CVD-related markers .....	196
4.4 Discussion.....	197
References.....	202
<b>Chapter 5: Inflammatory status modulates plasma lipid and inflammatory marker responses to kiwifruit consumption in hypercholesterolaemic men .....</b>	<b>207</b>
Abstract.....	208
5.1 Introduction .....	209
5.2 Subjects and methods.....	210
5.3 Results .....	210
5.3.1 Baseline characteristics of subjects by inflammatory group .....	210
5.3.2 Physical activity measures of subjects by inflammatory group.....	211
5.3.3 Effects of the intervention on dietary intake, body weight and BP by inflammatory group.....	211
5.3.4 Effects of the intervention on lipids by inflammatory group .....	215
5.3.5 Effects of the intervention on inflammatory markers by inflammatory group ....	215
5.4 Discussion.....	218
References.....	221

<b>Chapter 6: <i>Taq1B</i> polymorphism in the <i>CETP</i> gene influences lipid responses to consuming kiwifruit in hypercholesterolaemic men.....</b>	<b>225</b>
Abstract .....	226
6.1 Introduction .....	227
6.2 Subjects and methods.....	228
6.3 Results .....	228
6.3.1 Baseline characteristics of subjects by <i>CETP Taq1B</i> genotype group.....	230
6.3.2 Dietary intakes during the intervention by <i>CETP Taq1B</i> genotype .....	231
6.3.3 Effects of diet run-in period and intervention on body weight by <i>CETP Taq1B</i> genotype group.....	232
6.3.4 Effects of the intervention on lipids by <i>CETP Taq1B</i> genotype group.....	232
6.4 Discussion.....	235
References.....	239
<b>Chapter 7: Effects of kiwifruit consumption on blood pressure and markers of cardiovascular function in men with hypercholesterolaemia</b>	<b>243</b>
Abstract .....	244
7.1 Introduction .....	245
7.2 Subjects and methods.....	246
7.3 Results .....	246
7.4 Discussion.....	249
References.....	252
<b>Chapter 8: Discussion and conclusions, including recommendations for future research .....</b>	<b>255</b>
8.1 Introduction .....	256
8.2 Summary of findings and outcomes of hypotheses.....	256
8.3 Discussion of the main findings.....	259
8.4 Strengths.....	269
8.5 Limitations.....	270
8.6 Future research recommendations.....	272
8.7 Conclusions.....	274
References.....	275

## List of Tables

Table 2.1: CVD related statistics for men from representative countries for 2008* .....	33
Table 2.2: Definitions of poor, intermediate and ideal cardiovascular health for each metric in the AHA 2020 goals .....	35
Table 2.3: Mortality rates for ischaemic heart disease, cerebrovascular and hypertensive disease in NZ in 2009* .....	36
Table 2.4: Screening and optimal lipid profile values .....	38
Table 2.5: Vegetable and fruit intake in males .....	39
Table 2.6: National Nutrition Survey results for selected nutrients in men* .....	40
Table 2.7: National Nutrition Survey mean blood cholesterol results in men ..	41
Table 2.8: Characteristics of main lipoprotein classes .....	45
Table 2.9: Major apolipoproteins and their recognised functions .....	46
Table 2.10: Classification of BP in adults aged 18 years or older* .....	80
Table 2.11: Mortality rates for hypertensive disease in NZ in 2009* .....	85
Table 2.12: Isoform differences of <i>APOE</i> at the transcript and protein level and the resultant changes in LDLR binding and lipoprotein preference .....	91
Table 2.13: MAF of selected HDL-related genes* .....	94
Table 2.14: Examples of dietary patterns for heart health* .....	101
Table 2.15: Flavonoid subclasses and food sources* .....	111
Table 2.16: Whole fruit, fruit extract and juice intervention studies investigating effects on lipids, BP and inflammatory markers. ....	113
Table 2.17: Comparison of the edible portion of kiwifruit and some other commonly consumed fruit* .....	120
Table 2.18: Kiwifruit intervention studies .....	123
Table 2.19: <i>CETP Taq1B</i> studies which have investigated diet-gene interactions .....	129
Table 2.20: Studies which have observed modulation of dietary responsiveness to inflammatory status .....	130

Table 3.1: Summary of methods used for anthropometric, clinical, dietary and other assessments .....	172
Table 3.2: Processing of blood samples.....	175
Table 3.3: Biochemical analysis .....	176
Table 3.4: Methods used for nutrient analysis of kiwifruit.....	179
Table 4.1: Baseline characteristics of subjects* .....	190
Table 4.2: Composition of the diet pre-nutrition consultation and during the intervention* .....	191
Table 4.3: Fruit servings, dietary fibre and vitamin C intakes at baseline 1 to baseline 2, and after the 2 intervention periods* .....	192
Table 4.4: Anthropometric and blood pressure assessments at baseline 1 to baseline 2, and after the 2 intervention periods* .....	192
Table 4.5: Plasma lipid and apolipoprotein concentrations at baseline 1 and 2, and after the 2 intervention periods* .....	194
Table 4.6: The impact of <i>APOE</i> genotype on lipid and apolipoprotein conc. at baseline 1 and 2, and after the 2 intervention periods* .....	195
Table 4.7: CRP at baseline 2 and after the 2 intervention periods* .....	197
Table 4.8: Glucose, insulin and insulin resistance at baseline and after the 2 intervention periods*.....	197
Table 5.1: Baseline characteristics and physical activity measures of subjects by inflammatory group* .....	212
Table 5.2: Dietary intake changes for the 2 intervention periods by inflammatory group* .....	213
Table 5.3: Anthropometric assessments at baseline 1 and 2, and after the 2 intervention periods by inflammatory group* .....	214
Table 5.4: Plasma lipid and apolipoprotein concentration changes for the 2 intervention periods by inflammatory group* .....	216

Table 6.1: Position, genotypic distributions and HDL-C concentration at baseline of selected SNPs.....	229
Table 6.2: Baseline characteristics of subjects by <i>CETP Taq1B</i> genotype* ...	230
Table 6.3: Dietary intake changes for the 2 intervention periods by <i>CETP Taq1B</i> group* .....	231
Table 6.4: Anthropometric assessments at baseline 1 and 2, and after the 2 intervention periods by <i>CETP Taq1B</i> group* .....	233
Table 6.5: Plasma lipid and apolipoprotein concentration changes for the 2 intervention periods by <i>CETP Taq1B</i> genotype* .....	234
Table 7.1: Characteristics of subjects who completed the study* .....	247
Table 7.2: Changes in BP and other markers of cardiovascular function measured by the finometer for the 2 intervention periods* .....	249

## List of Figures

Figure 2.1: Atherosclerosis progression: from atherosclerotic plaque formation through to significant obstruction of the lumen .....	20
Figure 2.2: Stages in the development of atherosclerotic lesions .....	21
Figure 2.3: Risk factors for atherosclerosis .....	24
Figure 2.4: Proposed role of low shear stress in atherosclerosis .....	25
Figure 2.5: Distribution of CVD due to heart attacks, strokes and other cardiovascular diseases in males.....	29
Figure 2.6: Global distribution of ischaemic heart disease mortality rates.....	30
Figure 2.7: Global prevalence of overweight .....	31
Figure 2.8: Death rates from ischaemic heart disease, by sex, 1950-2009* ....	37
Figure 2.9: Lipoprotein metabolism .....	47
Figure 2.10: Comparison of CETP-mediated bidirectional transfer of CEs and TG pathways in normotriglyceridaemia and hypertriglyceridaemia .....	53
Figure 2.11: Main synthesis and metabolism pathways for HDL.....	58
Figure 2.12: Changes in adipose tissue with increasing adiposity .....	67
Figure 2.13: Differences in distensibility and pulse wave velocity between young and old individuals.....	81
Figure 2.14: The prevalence of raised blood pressure in males.....	84
Figure 2.15: Potential genetic, environmental, physiological, and pathological factors influencing inter-individual dietary response .....	125
Figure 3.1 Study flow.....	168
Figure 5.1: The percentage change of plasma inflammatory markers from baseline 2 in subjects with low (hs-CRP <1 mg/L) and medium (hs-CRP 1 to 3 mg/L) inflammatory levels. ....	217

## List of Appendices

Appendix 1: Papers (published or submitted) .....	281
Appendix 2: Conference presentations and abstracts .....	283
Appendix 3 Contribution of Authors (including statements of contribution to doctoral thesis containing publications).....	286
Appendix 4: Screening documents.....	293
Appendix 5: <i>APOE</i> fact sheet.....	300
Appendix 6: Weekly compliance diary.....	303
Appendix 7: Dietary material .....	310
Appendix 8: Teleform and on-line questionnaires .....	317
Appendix 9: Real-time SNP genotyping assay procedure.....	332

## List of Abbreviations

2-MG	2-monoacylglycerol	DASH	Dietary Approaches to Stop Hypertension
AAMI	Association for the Advancement of Medical Instrumentation	DBP	diastolic blood pressure
ABC	adenosine triphosphate-binding cassette	DDAH	dimethylarginine dimethylaminohydrolase
ACE	angiotensin converting enzyme	DGAT	acyl-coenzyme A: diacylglycerol acyltransferase
ADMA	asymmetrical dimethylarginine	DHAH	Diabetes, Heart and Health Survey
AHA	American Heart Association	DNA	deoxyribonucleic acid
Ang	angiotensin	eNOS	endothelial nitric oxide synthase
ANOVA	analysis of variance	ESS	endothelial shear stress
ANZCTR	Australian New Zealand Clinical Trial Registry	FA	fatty acid
Apo	apolipoprotein	FABP	fatty acid-binding protein
APOE	apolipoprotein E	FAO	Food and Agriculture Organization
AT1	angiotensin II type 1-receptor	FFA	free fatty acid
ATP	Adult Treatment Panel	FW	fresh weight
AUC	area under the curve	GAE	gallic acid equivalents
BF	body fat	HDL	high-density lipoprotein
BH <sub>4</sub>	tetrahydrobiopterin	HDL-C	high-density lipoprotein cholesterol
BMI	body mass index	HL	hepatic lipase
BODPOD	air displacement plethysmography	HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
BP	blood pressure	HOMA	homeostasis model assessment
CD36	type B scavenger receptor	HOMA2-IR	homeostasis model assessment 2 computer model for insulin resistance
CDC	Centers for Disease Control and Prevention	HR	heart rate
CE	cholesterol ester	hs-CRP	high-sensitivity C-reactive protein
CETP	cholesteryl ester transfer protein	HSPG	heparin sulphate proteoglycans
cGMP	cyclic guanosine monophosphate	IANZ	International Accreditation New Zealand
CHD	coronary heart disease	ICAM-1	intracellular adhesion molecules 1
CI	confidence interval	IDL	intermediate-density lipoprotein
CM	chylomicron	IHD	ischaemic heart disease
CO	cardiac output	IKK	inhibitor of $\kappa$ kinase
CRP	C-reactive protein	IL	interleukin
CT	computer topography	IR	insulin resistance
CtE	catechin equivalents	IRS-1	insulin receptor substrate 1
CV	coefficient of variation	ISAK	International Society for the Advancement of Kinanthropometry
CVD	cardiovascular disease	ISH	isolated systolic hypertension
DALY	disability-adjusted life year	JNK	c-jun N-terminal kinase

LCAT	lecithin cholesterol acyltransferase	PLTP	phospholipid transfer protein
LDL	low-density lipoprotein	PON1	paraoxonase/arylesterase 1
LDL-C	low-density lipoprotein cholesterol	PR	peripheral resistance
LDLR	LDL receptor	PUFA	polyunsaturated fatty acids
LMIC	low- and middle-income countries	PWV	pulse wave velocity
LOX-1	oxidised LDL lecithin-like receptor-1	RAS	renin-angiotensin system
LPL	lipoprotein lipase	RCT	reverse cholesterol transport
LRP	LDL receptor-related protein	ROS	reactive oxygen species
LV	left ventricle	RPAQ	recent physical activity questionnaire
LXR	nuclear receptor liver X receptor	SBP	systolic blood pressure
MANOVA	multivariate analysis of variance	SD	standard deviation
MAP	mean arterial pressure	SE	standard error of the difference between means
MGAT	acyl-coenzyme A: monoacylglycerol acyltransferase	SFA	saturated fatty acids
MHO	metabolically healthy obese	sLDL	small-dense LDL
MONW	metabolically obese, normal weight	SMCs	smooth muscle cells
MTP	microsomal triglyceride transfer protein	SNP	single nucleotide polymorphism
MUFA	monounsaturated fatty acids	SR-A	type A scavenger receptor
MUHEC	Massey University Human Ethics Committee	SR-BI	scavenger receptor class BI
NADPH	nicotinamide adenine dinucleotide phosphate	SV	stroke volume
NCD	non-communicable diseases	TC	total cholesterol
NCEP	National Cholesterol Education Program	TG	triglycerides
NF- $\kappa$ B	nuclear factor-kappa beta	TGF- $\beta$	transforming growth factor- $\beta$
NHANES	National Health and Nutrition Examination Survey	TGRL	TG-rich lipoproteins
NHLBI	National Heart, Lung and Blood Institute	T <sub>H</sub> 1	T helper 1 cells
NLRP3	nucleotide-binding domain leucine-rich repeat containing (NLR) family, pyrin domain containing 3	TLC	Therapeutic lifestyle changes
NO	nitric oxide	TNF- $\alpha$	tumour necrosis factor alpha
NOX	NADH/NADPH oxidase	TPR	total peripheral resistance
NPC1L1	Niemann-Pick C1-like 1	T <sub>reg</sub>	regulatory T cells
NZ	New Zealand	UK	United Kingdom
NZEO	NZ European and other	US	United States
O <sub>2</sub> <sup>-</sup>	superoxide anion	VCAM-1	vascular cell adhesion molecules 1
ONOO <sup>-</sup>	peroxynitrite	VLDL	very low-density lipoprotein
OECD	Organisation for Economic Co-operation and Development	WC	waist circumference
oxLDL	oxidised LDL	WHO	World Health Organisation
PKR	protein kinase R	WHR	waist/hip ratio