Title Page

Nutrition and vascular function

A thesis submitted to the University of Adelaide by

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For the degree of

Doctor of Philosophy

October 2007

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For Peter who believed I could do it

Declaration of originality

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Jennifer Beatrice Keogh

Date………………………..

October 2007

Publications arising from this thesis

Keogh JB, Grieger JA, Noakes M, Clifton PM. Flow-mediated dilatation is impaired by a high-saturated fat diet but not by a high-carbohydrate diet. Arteriosclerosis Thrombosis and Vascular Biology 2005; 25(6):1274-1279. Impact Factor: 7.053

Clifton PM, Keogh JB, Foster PR, Noakes M. Effect of weight loss on inflammatory and endothelial markers and FMD using two low-fat diets. Int J Obes (Lond). 2005;29(12):1445-51. Impact factor 3.5

Keogh JB, Brinkworth GD and Clifton PM. Effects of weight loss on a low carbohydrate diet on flow mediated dilatation, endothelial markers and adiponectin. Br J Nutr. 2007 Oct;98(4):852-9. Epub 2007 May 10 Impact Factor: 2.967

Keogh JB, Luscombe-Marsh ND, Noakes M, Wittert GA, Clifton PM. Long-term weight maintenance and cardiovascular risk factors are not different following weight loss on carbohydrate-restricted diets high in either monounsaturated fat or protein in obese hyperinsulinaemic men and women. Br J Nutr. 2007;97(2):405-10. Impact Factor:2.967

In press

Keogh JB, Ho JT, O'Loughlin P, Bornstein SR, Lewis JG, Torpy DJ and Clifton PM. Moderate weight loss reduces renin and aldosterone but does not influence basal or stimulated pituitary-adrenal axis function. Horm Metab Res. Accepted January 2007 Impact Factor: 2.049

Keogh JB, Brinkworth GD, Noakes M, Belobrajdic DP, Buckley JD, CliftonPM

Effects on endothelial function and markers of cardiovascular disease risk in subjects

with abdominal obesity of weight loss on a very low carbohydrate diet. AJCN.

Accepted January 2007 Impact Factor: 6.562

Published abstracts arising from this thesis

Keogh JB and PM Clifton. Adiponectin blood pressure and weight loss. Asia Pac J Clin

Nutr 2006;15(Suppl):50

Keogh J, Luscombe N, Foster P, Noakes M, Wittert G, Clifton P

Long term weight maintenance with two carbohydrate restricted diets.

Obesity Reviews 2005;6(Suppl):6

Keogh JB, Torpy DJ, Brinkworth GD, PM Clifton. Salt and blood pressure: relationship

with obesity, weight loss and direct effects on vascular function. Asia Pac J Clin Nutr

2005;14(Suppl):59

Clifton P, Keogh J, Brinkworth G, Torpy D, Ho J. Salt and blood pressure. Relationship

with obesity, weight loss and direct effects on vascular function. Circulation 2005;

112(17):U741

Acknowledgements

from this study was writted by Jennifer Keogh. Further details of Jennifer's role to this study are outlined below in the contribution.

In chapters 3, 4, 5 and 6 FMD and PWV were measured by Ms Jodie Avery, Dr Grant Brinkworth and Mr Tom Wycherley respectively. Dr Brinkworth also measured the AI in chapter 5.

Contribution

Jennifer Keogh's contribution to the studies in the thesis

Chapter 3
The effect of a high saturated fat diet compared with a high MUFA, high PUFA or a high carbohydrate diet on FMD
Protocol design and development
Ethics submission
Development and implementation of the dietary protocol
Counselling of volunteers
Performed the data entry from the food records
Performed statistical analysis and interpretation of the study data
Write-up of the study data for publication
Presented data at national conferences

Chapter 4
The effect of weight loss on inflammatory and endothelial markers and FMD and PWV using two low fat diets
Performed data entry from the food records
Performed statistical analysis and interpretation of the study data
Write-up of the study data for publication
Presented data at national and international conferences

Chapter 5
Effects of weight loss on a low carbohydrate/low saturated fat diet on FMD, adhesion molecules, adiponectin, AI, BP and PWV following short-term weight loss and long-term follow-up
Protocol design and development
Ethics submission
Dietary protocol design
Counselling of volunteers
Performed waist, BIA and seated blood pressure measurements
Performed the data entry from the food records
Performed statistical analysis and interpretation of the study data
Write-up of the study data for publication
Presented data at national conferences
Presented at the European Congress on Obesity 2007

Chapter 6
Effect of a very low carbohydrate/ high saturated fat diet during weight loss on FMD, AI, BP, adiponectin and adhesion molecules during weight loss
Participation in protocol design and development
Development of the dietary protocol
Performed all augmentation index measurements before and after weight loss
Performed laboratory analyses for lipids, CRP, adiponectin, PAI-1, tPA, CAMs
Performed statistical analysis and interpretation of the study data
Performed write-up of the study data for publication
Presented at the European Congress on Obesity 2007

Chapter 7
Effects of weight loss on AI and the BP response to salt in adults
Protocol design and development
Ethics submission
Development and implementation of the dietary protocol
Counselling of volunteers
Performed blood (seated) pressure measurements
Performed the data entry from the food records
Performed statistical analysis and interpretation of the study data
Performed write-up of the study data for publication
Presented data at national conferences

Chapter 8
Effect of long term weight maintenance on CVD risk factors
Counselling of volunteers
Performed data entry from the food records
Performed statistical analysis and interpretation of the study data
Write-up of the study data for publication
Presented at the European Congress on Obesity 2006
Presented data at national conferences

Index of tables and figures

Abbreviations

Acetylcholine (ACh)

Angiotensin converting enzyme (ACE)

Augmentation index (AI)

Australian Clinical Trials Registry (ACTR)

Blood Pressure (BP)

Body mass index (BMI)

Cardiovascular disease (CVD)

Cellular adhesion molecules (CAMS)

Cholesteryl ester transfer protein (CETP)

Coefficient of variation (CV)

Coronary artery disease (CAD)

C-reactive protein (CRP)

Diabetes Mellitus (DM)

Diastolic Blood Pressure (DBP)

Dietary Approaches to Stop Hypertension (DASH)

Disability-adjusted life years (DALYs)

Docosahexaenoic acid (DHA)

Eicosapentaenoic acid (EPA)

Enzyme-Linked ImmunoSorbent Assay (ELISA)

Endothelial NO synthase (eNOS)

Flow independent dilatation (FID)

Flow mediated dilatation (FMD)

Gylceryl trinitrate (GTN)

High density lipoprotein cholesterol (HDL-C)

3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA)

Impaired fasting glucose (IFG)

Impaired glucose tolerance (IGT)

Intercellular adhesion molecule-1 (ICAM-1),

Low density lipoprotein cholesterol (LDL-C),

Methacholine (MCh)

Monounsaturated fat (MUFA)

Myocardial Infarction (MI)

Nitric oxide (NO)

Plasma renin activity (PRA)

Plasminogen activator inhibitor 1 (PAI-1),

Polycystic ovarian syndrome (PCOS)

Polyunsaturated fat (PUFA)

Pulse wave velocity (PWV)

Relative risk (RR)

Systolic Blood Pressure (SBP)

Tissue plasminogen activator (tPA)

Total cholesterol (TC)

Trans fatty acids (TFA)

Transient ischaemic attacks (TIA)

Triglyceride (TG)

Tumour necrosis factor-alpha (TNFα)

UK Prospective Diabetes Study (UKPDS))

Vascular cell adhesion molecule-1 (VCAM-1)

Very low density lipoprotein (VLDL)

Thesis summary

Common risk factors for CVD such as hyperlipidaemia, hypertriglyceridemia, low HDL-C, obesity, insulin resistance, impaired glucose tolerance, inflammation and hypertension may increase the risk of atherosclerosis through altering vascular function. Modification of dietary intake and weight loss can ameliorate these risk factors and may impede the development of atherosclerosis. CVD risk can be assessed by measurement of both traditional e.g. lipid levels, glucose and blood pressure and novel risk markers of CVD e.g. FMD, levels of adhesion molecules, inflammatory markers and adipokines. Changes in these measurements are used to determine effects, if any, of dietary interventions. The studies in this thesis focus on the relationship between nutrition and vascular function and the effects of modifying dietary composition either with, or without weight loss. The primary hypotheses addressed were that a high saturated fat diet would have adverse effects on markers of CVD risk., that short and long term weight loss would have beneficial effects on these markers, that a conventional low fat, high glycaemic load diet would also have adverse effects on these markers and that weight loss would attenuate the BP response to salt. Six studies were conducted to address these hypotheses.

The effects of saturated fat were investigated in chapters 3 and 6. In chapter 3, a high saturated fat diet impaired FMD and increased the level of the adhesion molecule P-selectin compared with a high MUFA, a high PUFA, or a low fat, high glycaemic load diet in weight stability. The high fat, high glycaemic load caused increases of 23-39% in TG and decreases of 10-15% in HDL-C but despite these adverse effects there was no change in FMD. In chapter 6, subjects on a very low carbohydrate/high saturated fat diet lost approximately 1 kg more weight over 8 weeks than those on a conventional low fat diet. While other CVD risk factors, glucose, insulin, E and P-selectin, ICAM-1 and

PAI-1 levels all improved FMD did not change in either diet. Reductions in LDL-C and CRP were greater on the conventional diet.

The effects of weight loss on CVD risk factors were also investigated in the studies in chapters 4, 5, 7 & 8. In chapter 4, moderate weight loss using 2 different low fat diets resulted in improvements in PAI-1 and sICAM-1 but there was no change in FMD. Similarly in chapter 5 weight loss on a low carbohydrate/low saturated fat diet did not change FMD but there were other benefits including reductions in glucose and insulin, LDL-C, adhesion molecules, VCAM1 and ICAM1. Adiponectin did not change after short term weight loss in either of the studies in chapters 5 or 6. In chapter 7 salt loading increased ambulatory day time BP and this response was not altered by short term moderate weight loss. The long term effects of weight loss were investigated in chapters 5, 7 and 8. In chapter 5, after 52 weeks, there was sustained weight loss of 5% but no change in FMD while adiponectin levels increased and LDL-C and insulin were substantially reduced. In chapter 7 the BP response to salt loading remained unchanged despite weight loss maintenance. Finally in chapter 8 weight loss was predicted by protein intake and there were reductions in CVD risk demonstrated by decreases in insulin, TG and CRP and increases in HDL-C.

The studies in this thesis demonstrate that moderate weight loss has beneficial effects on traditional and novel cardiovascular disease risk markers but does not have a beneficial effect on FMD regardless of dietary composition. A high saturated fat diet has detrimental effects on novel CVD risk markers in weight stability but weight loss attenuates this effect. A high saturated fat diet may have detrimental effects on adhesion molecules in weight stability and may attenuate the beneficial effects of weight loss on LDL-C and CRP. Moderate long term weight loss maintenance has beneficial effects on most but not all CVD risk markers.

Nutrition and vascular function

Chapter 1 Review of the Literature

Introduction

Nutritional factors such as obesity, hyperlipidaemia, hypertriglyceridemia, low HDL-C, insulin resistance, impaired glucose tolerance, hypertension and inflammation can play a major role in modulating risk factors for CVD. These risk factors may increase the risk of atherosclerosis through altering vascular function. This review discusses the association between nutrition and CVD risk factors, in particular vascular function and the effects of nutritional intervention. For the purposes of the review vascular function includes blood pressure, endothelial function and arterial stiffness.

Nutrition, lipids and cardiovascular risk factors

The fundamental role of an elevated serum cholesterol level in the aetiology of atherosclerosis and CAD is well known (Levine 1995). Kannel et al (1971) reported a strong direct correlation between TC and the development of CAD in more than 5,000 subjects followed for 14 years in the Framingham Heart Study. In almost 400,000 men screened for the Multiple Risk Factor Intervention Trial (MRFIT), Martin et al (1986) reported an unequivocal relationship between base-line serum cholesterol levels and mortality from CAD during a six-year period. Increased risk was associated with TC levels as low as 4.68 mmol/L and the risk increased progressively with higher TC levels. This has been confirmed in other epidemiologic and observational studies (Pekkanen 1990, 1992, Rose 1986, Goldbourt 1990, Isles 1989).

There are large benefits to be gained from LDL-C reduction and intervention studies have demonstrated a reduction in the incidence of ischemic cardiac events and a reduction in mortality from cardiovascular disease (Brown 1998 a, b). In a recent meta-analysis of 23 randomized lipid trials Brown et al (2006) conclude that epidemiology suggests that the cardiovascular event rate is reduced by nearly 1% for each 1%

reduction in LDL-C and by at least 1% for each 1% increase in HDL-C. The potential benefit may be greater as data from the Helsinki Heart Study and the Veterans Affairs HDL Intervention Trial indicate that a 1% increase in HDL- contributes a 3% reduction in heart disease risk (Boden 2000).

The reduction in total and LDL-C levels by 11.8 and 18.9% with a combination of diet and cholestyramine in the Lipid Research Clinics Coronary Primary Prevention Trial achieved a 19% reduction in nonfatal MI and a 24 % reduction in deaths from CVD; this is a direct effect of reducing LDL-C and is not confounded by the pleiotropic effects of the statin drugs (Lipid Research Clinics Program 1984).

The discovery in 1971 of 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitors by Dr Akira Endo and their subsequent development into drugs such as lovastatin, atorvastatin, pravastatin, simvastatin and more recently the more powerful rosuvastatin which achieves up to 60% LDL-C lowering has revolutionised the management of LDL-C levels (Endo 1992). Their effectiveness in a secondary prevention trial has been demonstrated in the Scandinavian Simvastatin Survival Study, (4S study) in which 4444 patients with angina pectoris or previous MI were randomly assigned to treatment with either simvastatin or placebo (Scandinavian Simvastatin Survival Study Group 1994). Treatment with simvastatin for 5.4 years reduced overall mortality by 30% due to the reduction in fatal ischemic cardiac events. There were reductions of 25 and 35% in total and LDL-C levels, respectively, and an 8 % increase in HDL-C levels with no changes in the placebo group. The simvastatin group had a 37% reduction in nonfatal MI, a 37 % decrease in the need for revascularization and a 42% reduction in deaths ascribable to ischemic heart disease. The West of Scotland Coronary Prevention Study of 6595 men was a primary prevention study designed to determine whether the use of pravastatin in men with hypercholesterolemia but no

history of MI reduced the incidence of both nonfatal MI and death from CAD

(Shepherd 1995). After 4.9 years pravastatin lowered plasma cholesterol levels by 20%

and LDL-C levels by 26%, whereas there was no change with placebo. There were

reductions in the risk of nonfatal MI of 31%, death from CAD of 33% and death from

all CVD causes of 32%. There was also a 22% reduction in the risk of death from any

cause in the pravastatin group.

Summary

It is clear that reduction in LDL-C has life saving and disease preventing importance

(Brown 2006, Shepherd 1995, Lipid Research Clinics Program 1984).

Diet and lipids

There is a large body of data on the effect of diet on lipids with several hundred

intervention trials. Mensink et al (2003) conducted a meta-analysis of 60 trials to

estimate the effects of dietary fatty acids and carbohydrates on serum lipids. The results

indicate that a decrease of 0.032 mmol/L in LDL-C can be expected for every 1%

decrease in energy from saturated fat and replacement by carbohydrate in weight

stability. Decreasing fat intake by 1% energy also decreases HDL-C by 0.01, 0.008 and

0.006 mmol/L for saturated fat, MUFA and PUFA respectively and increases TG by

0.021, 0.019 and 0.026 mmol/L. In a Cochrane review of 27 intervention trials Hooper

et al (2001) conclude there was a small reduction in CVD risk with reduction or

modification of dietary fat intake which was seen particularly in trials of longer

duration.

Other dietary factors such as plant sterols (Gerber 2006), soluble dietary fibre (Ripsin

1992), soy protein (Reynolds 2006) and foods such as pulses (Anderson 2002) and

almonds (Jenkins 2002) also reduce lipid levels. Composite diets containing all these

foods have been shown to be as effective as a low dose of statin medication at reducing

LDL-C, by 30% (Jenkins 2003a) and almost 3 fold more effective than conventional dietary advice (Jenkins 2003b). However these large reductions in LDL-C were not sustained after 3 and 12 months of follow-up in a free living environment when LDL-C reduction was 14% and 13% respectively (Jenkins 2006, Gerber 2006).

Summary

Dietary composition in particular the reduction in saturated fat and the addition of plant sterols have an important role to play in LDL-C reduction (Mensink 2003,).

Weight loss and lipids

Weight loss is generally associated with improvements in lipid profile in both short and long term studies. A systematic review by Poobalan and colleagues (2004) of 13 long term studies reported that change in LDL-C has a significant relationship with weight change (r = 0.9, P < 0.001) where change in weight explains about 80% of the LDL-C difference variation. In contrast, the results for HDL-C indicated a weak negative relationship with weight change (r=-0.3, NS) (Poobalan 2004). In an earlier meta-analysis Dattilo and Kris-Etherton (1992) report on results collated from 70 studies that for every kilogram decrease in body weight a 0.009-mmol/L increase (P ≤ 0.01) in HDL-C occurred for subjects at a stabilized, reduced weight and a 0.007-mmol/L decrease (P ≤0.05) for subjects actively losing weight. They report that a reduction in LDL-C of -0.039 mmol/L per kg weight loss may also be expected.

In studies not included in these meta-analyses HDL-C was improved when measured 12-18 months after a weight loss intervention in people with diabetes (Brinkworth 2004 a, b, Ash 2003, Lovejoy 2003). In the study by Ash and colleagues (2003) HDL-C had significantly increased by approximately 15% at 18 months but weight had returned to pre intervention levels with no change in total or LDL-C or triglycerides (Ash 2003). Subjects in the study by Brinkworth et al (2004) had maintained a 3kg weight loss after

64 weeks and had an increase in HDL-C of 17% (0.16 mmol/L) also with no change in total or LDL-C or triglycerides (Brinkworth 2004). The change in HDL-C was not correlated with change in body weight. In a second long term study Brinkworth and colleagues (2004) observed a similar phenomenon in obese hyperinsulinemic subjects who also had an increase in HDL-C of 15%, 52 weeks after a 12 week weight loss intervention with maintained fat loss of approximately 3.5kg. Similarly Lovejoy et al (2003) found that HDL-C increased by about 9% after 9 months with weight loss between 1.8-6.3 kg. These increases if sustained could translate into a substantial reduction in CVD risk. (Brown 2006, Boden 2000).

A potential mechanism for the increases in HDL-C observed is the reduction in CETP seen after weight loss as CETP transfers cholesteryl ester from HDL to apolipoprotein B-containing lipoproteins (VLDL and LDL) and plays an important role in regulating the concentration and composition of HDL (Ebenbichler 2002, Tzotzas 2006). Concerns have been expressed about the use of very low carbohydrate diets and the potential detrimental effect they may have on cholesterol levels. This topic has recently been reviewed by Noakes and Clifton (2004) who observed that LDL-C level did not increase in many of the studies reviewed and that triglyceride levels fell in all studies. In an 8 week study not included in this review Noakes et al (2006) found that LDL-C increased significantly (7%) on a very low carbohydrate diet as did HDL-C (5%) and TG was lowered by 40% (Noakes 2006). In one of the few one-year studies of low carbohydrate diets Foster et al (2003) found no significant differences in total or LDL-C concentrations after 3 or 12 months, in subjects following either a very low carbohydrate high-protein, high-fat diet or a low-calorie, high-carbohydrate, low-fat (conventional) diet. The increase in HDL-C concentrations and the decrease in TG concentrations were greater in subjects on the low-carbohydrate diet than in those on the

conventional diet throughout most of the study. However adherence to the diet was poor at the end of the study (Foster 2003).

The benefits of LDL-C reduction with diet are likely to be considerable. A sustained modest reduction of 5% such as can be achieved with inclusion of 2g plant sterols/day has been estimated to lead to a reduction of 117,000 cases of CAD over 10 years and an estimated cost benefit of €1.3 billion (Gerber 2006). In this study the 10-year CAD risks were 6.1% in the margarine group compared with 6.5% in controls. It was estimated that the use of sterol containing margarine would avoid 1 case of CAD per 217 subjects thus 117,000 CAD cases could be avoided over 10 years from a prevalence of 25.35 million cases (Gerber 2006).

The LDL-C change that can be achieved with weight loss is in this range (Poobalan 2004). A recent Cochrane review found 23 trials in which healthy free living adults were randomly assigned to receive dietary advice or no dietary advice which on average achieved a 0.13 mmol/l (1.8-2.8%) reduction in TC and a similar LDL-C reduction and that this reduction in cholesterol had the potential to reduce CVD incidence by 5% (Brunner 2005).

Summary

Both reduction in dietary saturated fat and weight loss are associated with improvements in LDL-C (Mensink 2003, Poobalan 2004). The addition of plant sterols increases this benefit in weight stability but this had not been well explored in weight loss (Gerber 2006). The benefits or otherwise of other weight loss dietary interventions such as very low carbohydrate diets have yet to be fully clarified.

Nutrition and hypertension

Hypertension is a leading cause of death and disability. Lawes et al (2006) reported that the estimated global burden of disease in populations with a mean SBP > than 115

mmHg for adults aged $\geq$ 30 years was that approximately 2/3 of stroke and ½ of CAD were attributable to non-optimal blood pressure. Worldwide 7.1 million deaths (approximately 12.8% of the global total) and 64.3 million disability-adjusted life years (DALYs) (4.4% of the global total) were estimated to be due to non-optimal blood pressure. In the MRFIT study of 5362 with a prior MI there was substantial excess mortality risk associated with high blood pressure (Flack 1995).

Hypertension is also a risk factor for stroke (Lindenstrom 1995). In the Copenhagen City Heart Study of 19,698 subjects the relative risk for the highest SBP (3% of the population) was 4.0. In the lower 60% of the population the RR of stroke was constant and the attributable risk of SBP in the upper 40% of the population was 22% (Lindenstrom 1995).

Blood pressure reduction has the potential to reap large benefits. MacMahon and colleagues (1990) found that in nine studies comprising 420,000 individuals, there were 843 strokes, and 4856 CAD events over 6-25 (average 10) years of follow-up and that prolonged differences in usual DBP of 5, 7.5, and 10 mm Hg were respectively associated with at least 34%, 46%, and 56% less stroke and at least 21%, 29%, and 37% less CAD. These results suggest that for the large majority of individuals a lower blood pressure should eventually confer a lower risk of vascular disease (MacMahon 1990). In the UKPDS every 10 mm Hg decrease in SBP was associated with risk reductions of 12% for any complication of diabetes, 15% for diabetes related deaths , 11% for MI and 13% for microvascular complications (Adler 2000). Furthermore Cook et al (1995) reporting on data from Framingham Heart Study and the National Health and Nutrition Examination Survey II (NHANES II) found that a sustained reduction of 2 mmHg DBP would result in a 17% decrease in the prevalence of hypertension as well as a 6% reduction in the risk of CAD and a 15% reduction in risk of stroke and transient

ischaemic attacks. The authors suggest that adding a population-based intervention such as salt reduction to existing levels of treatment could prevent an estimated additional 67,000 CAD events (6%) and 34,000 stroke and TIA events (13%) each year among all those aged 35 to 64 years in the United States. Murray et al (2003) estimated that community health interventions such as salt reduction could avert over 21 million DALYs per year worldwide and treatment for people at risk of a cardiovascular event could avert 63 million DALYs per year worldwide (Murray 2003).

There are also important health benefits to be gained from reducing blood pressure in people with DM as reductions in SBP of 10 mm Hg have been shown to lower the risk of MI in people with diabetes by 21% in the UKPDS (UK Prospective Diabetes Study Group 1998).

Obesity and hypertension

There is a well established association between obesity and hypertension. In a screening study of more than 1 million people Stamler et al (1978) found that the prevalence of hypertension in overweight people was up to twice that in normal weight people. The potential mechanisms for the hypertension of obesity include hyperinsulinemia leading to insulin induced sodium retention and increased sympathetic tone both of which are strongly related to central fat accumulation (Berchtold 1983, Krieger 1988). Obesity is also associated with stimulation of the renin-angiotensin-aldosterone system (Dornfeld 1987, Rocchini 2002). One of the hypotheses in this thesis was that weight loss would reduce renin-angiotensin-aldosterone system activity as this had not been examined in overweight adults before. After we commenced the study Engeli et al (2005) published a study showing that reduction in weight of 5% was associated with reductions in angiotensinogen, renin, aldosterone and angiotensin-converting enzyme (ACE) activity levels of 27%, 43%, 31%, and 12% respectively. It has been suggested that there is

hyperactivity of the hypothalamic-pituitary-adrenal axis which contributes to elevating blood pressure (Pasquali 1993). Ruano et al (2005) found high levels of plasma renin activity (PRA), aldosterone and ACE with sodium retention, potassium loss and high insulin levels in patients with central but not peripheral obesity. After gastric bypass, these abnormalities were reduced (Ruano 2005). Reisin (1990) has suggested that abnormal sodium/potassium exchange and sodium/calcium exchange heightens vessel wall tension. Reisin postulated that insulin increases absorption of sodium in the distal nephron of the kidney with consequent water retention and that increased SNS activity may also cause increased vascular peripheral resistance. Water retention in obese subjects increases absolute blood volume that is redistributed in the cardiopulmonary area, leading to augmented venous return and cardiac output (Reisin 1990).

It has been suggested that obese subjects have an enhanced sensitivity to dietary salt through failure to suppress renin and angiotensin and that weight loss attenuates this increased sensitivity (Rocchini 1989).

Hypertension is seen in patients with obstructive sleep apnoea (OSA) (Budhiraja 2007). Is also directly associated with CAD (Parish 2007, Budhiraja 2007). Potential mechanisms linking OSA with increased CAD include hypoxia, obesity, inflammation, sympathetic activation and endothelial dysfunction (Hargens 2006). In a recent review Wolf et al (2007) suggests that a causal relationship exists between OSA and hypertension. However hypertension, obesity and OSA often coexist. It has been reported that there is a higher prevalence of the metabolic syndrome in patients with OSA (Parish 2007, McArdle 2007). Parish et al reported that of 146 patients with OSA 60% had metabolic syndrome, compared to 40% without OSA with similar BMI The proportion with hypertension in this study was higher in the patients with OSA, 77% compared to 51%. McArdle et al (2007) found that men with OSA and no CAD had

increased insulin resistance compared with age- and BMI-matched men without OSA. Weight loss is usually part of the treatment strategy for patients with OSA and it has been established that weight loss has a beneficial effect on OSA symptoms suggesting that obesity may be a cause of OSA (Grunstein 2007, Fritscher 2007, Haines 2007).

Weight loss and hypertension
Weight loss can achieve reductions in blood pressure thus improving CVD risk (Krebs 2002). Short term weight loss decreases BP by 1mm Hg per 1 kg of weight lost however this effect reduces over time such that with sustained weight loss of 10kg, the effect on BP is halved after two years (Aucott 2005). Lantz et al (2003) observed in a study of patients who used a very low calorie diet for weight loss and maintenance that both SBP and DBP decreased up to 1 year of follow-up but not after 2 years (Lantz 2003). Similarly the Trial of Antihypertensive Interventions and Management (Davis 1993) demonstrated that modest weight reduction (2 to 3 kg) was effective for maintaining blood pressure in the normal range either alone or in combination with drug therapy. The benefit achieved by weight loss may be lost altogether as seen in the Swedish Obese Subjects Study in which there was no effect on SBP after prolonged (10 years) weight loss of 16% of initial body weight (Sjostrom 2004). However this is not always the case and in a 4 year follow-up of subjects using meal replacements for weight loss and maintenance the authors observed a continuing reduction in SBP at 4 years (Fletcher-Mors 2000).

In The Trials of Hypertension Prevention (TOHP) weight loss in the intervention group was 0.2 kg at 3 years and blood pressure was significantly lower in the intervention group than in the usual care control (n = 596) groups. The risk ratio for hypertension in the intervention group was 0.58 (95% CI, 0.36 to 0.94) at 6 months, 0.78 (CI, 0.62 to 1.00) at 18 months, and 0.81 (CI, 0.70 to 0.95) at 36 months. In subgroup analyses,

intervention participants who lost at least 4.5 kg at 6 months and maintained this weight

reduction for the next 30 months had the greatest reduction in blood pressure and a

relative risk for hypertension of 0.35 (CI, 0.20 to 0.59) Stevens (2001).

Type of diet during weight loss can influence the blood pressure to weight loss as seen

in a study by Nowson et al (2005) who assessed the effect on blood pressure of 2

weight-reduction diets either a low-fat diet or a moderate-sodium, high-potassium, high-

calcium, low-fat diet similar to that used in the DASH study. Weight decreased by

approximately 5 kg in both groups but there was a greater decrease in blood pressure in

the low-fat DASH diet group than in the low fat group SBP –7.6 mmHg compared with

–2 and DBP –5.4 and –1.0 mmHg respectively however this may be because of a lower

sodium intake in the low-fat DASH diet group (Nowson 2005).

A one year follow-up of the DASH-sodium study showed that despite higher sodium

intake and some rebound in blood pressure the DASH –sodium diet group had

reductions in SBP and DBP from baseline of ~ 7 and 8 mmHg respectively although it

is not clear from the paper whether these are statistically different from baseline (Ard

2004).

The PREMIER trial showed that after 6 months, SBP was lowered by 3.7 mm Hg in the

group following a multi-component behavioural intervention and by 4.3 mm Hg

(P<.001) in the multi-component behavioural intervention plus DASH group. The

prevalence of hypertension was reduced from 38% to17% and 12% in the intervention

groups (Appel 2003). After 18-months relative to the advice only group, the odds ratios

for hypertension were significantly reduced for the established plus DASH group only

at 0.77 (CI, 0.62 to 0.97) (Elmer 2006).

Salt and hypertension

There is a long established link between dietary salt intake and blood pressure. In a recent Cochrane systematic review of 17 trials, He and McGregor (2005) report a reduction in SBP of -4.97 mmHg and DBP of -2.74 mmHg when urinary sodium was reduced by 78mmol sodium/day in hypertensive individuals. In normotensive individuals the reduction in SBP was -2.03 mmHg and DBP was 0.99 mmHg with a reduction of 74mmol sodium/day.

There are large variations in sodium excretion as seen in the Intersalt study in which sodium excretion ranged from 0.2 mmol/24 h (Yanomamo Indians, Brazil) to 242 mmol/24 h (north China). In those centres with very low sodium excretion, a low blood pressure with little or no increase in blood pressure with age was seen. In the other 48 centres sodium was significantly related to the slope of blood pressure with age. Further analyses of this study by Elliott and colleagues (1996) showed that higher sodium excretion was associated with higher systolic/diastolic blood pressure both within and between populations and the associations were stronger with increasing age (Elliott 1996). Within populations a 100 mmol higher 24 hour urinary sodium excretion was associated with SBP/DBP higher on average by 3/0 - 6/3 mm Hg and between populations this difference in 24 hour sodium excretion was associated with a higher median SBP/DBP of 5-7/2-4 mm Hg, and an estimated average difference in SBP/DBP of 10-11/6 mm Hg at age 55 compared with age 25.

Population interventions to reduce salt intake can be effective in reducing hypertension (Karppanen 2006). In Finland, a one-third decrease in the average salt intake achieved over 30 years has been accompanied by a more than 10mm Hg fall in the population average of both SBP and DBP and a 75% to 80% decrease in both stroke and CAD mortality although no all of this can be attributable to salt (Karppanen 2006).

However public health messages to reduce salt intake in the absence of active measures to reduce salt in the food supply have largely been unsuccessful (Karppanen 2006). In Australia the national target for sodium intake, ≤100 mmol/day, 6g of salt/day, is achieved by only 6% of men and 36% of women (Beard 1997). In this study of 194 participants the mean sodium excretion was 170 mmol/day (range 39-337 mmol/day) and 118 mmol/day (range 26-241 mmol/day) for men and women respectively.

Weight loss and salt reduction
The Trials of Hypertension Prevention (TOHP) combined weight loss and salt reduction over a 3 – 4 year period in 2382 subjects who achieved a weight loss of approximately 2 kg at 36 months in both the weight loss and the combined groups. Sodium excretion was decreased by 40 mmol/d at 36 months and BP decreased by 1.3/0.9 mm Hg in the weight loss group, 1.2/0.7 mm Hg in the sodium reduction group and 1.1/0.6 mm Hg in the combined group. Differences were statistically significant for systolic and diastolic BP in the weight loss group and for systolic BP in the sodium reduction group. At 4 years, the incidence of hypertension (BP > or = 140 mm Hg systolic or > or = 90 mm Hg diastolic or the use of antihypertensive drugs) was significantly lower in each active intervention group than the usual care group (average relative risks, 0.78-0.82) (TOHP 1997). At 7 years follow-up of subjects from the Trials of Hypertension Prevention weight and urinary sodium were not different among the groups but the incidence of hypertension was 18.9% in the weight loss group and 40.5% in its control group and 22.4% in the sodium reduction group and 32.9% in its control group (He 2000). The odds of hypertension were reduced by 77% (odds ratio 0.23; 95% confidence interval 0.07 to 0.76; P=0.02) in the weight loss group and by 35% (odds ratio 0.65; 95% confidence interval 0.25 to 1.69; P=0.37) in the sodium reduction group compared with

their control groups suggesting that lifestyle modification such as weight loss may be effective in long-term primary prevention of hypertension.

In the Trial of Nonpharmacologic Interventions in the Elderly (n=975) (TONE) hazard ratios for the combined outcome measure of diagnosis of high blood pressure at 1 or more follow-up visits, or treatment with antihypertensive medication, or a cardiovascular event during follow-up, among the obese participants were 0.60 (95% CI, 0.45-0.80; P<.001) for reduced sodium intake alone, 0.64 (95% CI, 0.49-0.85; P=.002) for weight loss alone, and 0.47 (95% CI, 0.35-0.64; P<.001) for reduced sodium intake and weight loss combined compared to usual care (Whelton 1998). However despite these differences the frequency of cardiovascular events during follow-up (15-36 months, median follow-up 29 months) was similar in each of the 6 treatment groups although the numbers are low with only 145 events during the follow-up period.

In a 3-year lifestyle dietary intervention trial of sodium reduction Cook et al (2005) found a 187 mmol/24 hr baseline mean sodium excretion, which decreased by 44 mmol/24 hr at 18 months and 38 mmol/24 hr at 36 months in compared with usual care. Decreases in SBP/DBP were 2.0/1.4 mmHg at 18 months, and 1.7/0.9 mmHg at 36 months. Estimated SBP decreases per 100 mmol/24 h reduction in sodium excretion at 18 and 36 months were 2.2 and 1.3 mmHg before and 7.0 and 3.6 mmHg after correction for measurement error respectively. Incremental decreases in BP with lower sodium excretion were observed in these overweight non-hypertensive individuals (Cook 2005).

Other nutritional interventions and hypertension
Other dietary interventions include the Dietary Approaches to Stop Hypertension (DASH) trial which assessed the effect of a diet rich in fruits, vegetables, and low-fat

dairy products and with reduced saturated and total fat and sodium intake of 3000mg (130 mmol/day) and found that SBP and DBP were reduced by 5.5 and 3.0 mm Hg more than control with greater reductions (11.4 and 5.5 mm Hg more) in hypertensives (Appel 1997). An additional study, the DASH-Sodium found that reducing the sodium intake from the high to the intermediate level, 150 to 100 mmol Na/day reduced SBP by an extra 1.3 mm Hg (P=0.03) during the DASH diet and reducing the sodium intake from the intermediate to the low level (100 to 50 mmol Na/day) caused additional reductions of 1.7 mm Hg. The low sodium DASH diet led to a mean systolic blood pressure that was 7.1 mm Hg lower in participants without hypertension, and 11.5 mm Hg lower in participants with hypertension (Sacks 2001).

A similar dietary pattern has been tested in an Australian study (Nowson 2004). This study compared the effect on BP of a low-sodium (50 mmol/day), high-potassium diet and a high-calcium diet (126mmol/day) to a DASH-type (92 mmol/day) diet. There was a fall in SBP on the DASH-type diet of -1.8 ± 0.5 mm Hg and compared with this diet BP fell on the a low-sodium, high-potassium diet by -3.5 and -1.9 ± 0.7 mmHg, SBP and DBP respectively and increased during the high-calcium diet by $+3.1$ and $+0.8$ mm Hg, SBP and DBP respectively.

The OmniHeart study compared 3 different dietary patterns a diet high in carbohydrates, protein or MUFA (Appel 2005) and found that partial substitution of carbohydrate with either protein or MUFA lowered blood pressure, improved lipid levels, and reduced estimated cardiovascular risk compared to a high carbohydrates diet. Data from the INTERSALT Study (Stamler 1996) also found that higher dietary protein intakes were likely to have favourable effects on blood pressure. Significant independent inverse relationships were found between both systolic and diastolic blood pressure and urinary nitrogen (Stamler 1996). In a recent intervention study in hypertensive subjects

Hodgson et al (2006) found that systolic blood pressure was reduced by 5 mm Hg on a high protein intake (increased by 5% of energy) compared with control (no diet intervention).

Other dietary factors such as n-3 fatty acids and alcohol also have an effect on blood pressure (Ueshima 2007, Beilin 1993, Puddey 1985, Puddey 1987). Data from the INTERMAP study, a cross-sectional study of 4680 men and women, found that omega-3 fatty acid intake was inversely related to blood pressure. The overall effect was small -0.55/-0.57 mm Hg in SBP and DBP respectively with 2 SD higher (0.67% energy) intake of omega-3 fatty acids. Mori et al (1999) demonstrated that 4g/day of docosahexaenoic acid lowered ambulatory BP by 5.8/3.3 mm Hg SBP/DBP. Regular alcohol consumption raises blood pressure and contributes to the prevalence of hypertension (Beilin 1993). In a randomised controlled trial Puddey et al (1987) demonstrated that a reduction in alcohol consumption from 452 ml to 62 ml ethanol/ week resulted in a reduction of -5.0/-3.0 mm Hg SBP/DBP respectively after 6 weeks. In a systematic review of lifestyle interventions to reduce BP that included 105 trials (6805 participants) Dickinson et al (2006) found significant effects for a healthy diet, aerobic exercise, alcohol and sodium restriction and fish oil supplements reporting reductions of between -5.0 - and 2-.3 mmHg SBP of respectively.

Nutrition and novel cardiovascular risk factors

Endothelial function

The endothelium is a single layer of specialised cells that form the boundary between the circulating blood and the vascular media. These cells are involved in many aspects of vessel function and are essential for vasodilatation in response to the shear stress caused by increases in blood flow known as endothelium-dependent flow-mediated vasodilatation (FMD) (Smiesko 1985, Pohl 1986, Rubanyi 1986) and in response to

other physiological mediators such as acetylcholine (ACh) (Mullen 2001, Joannides 2002).

The endothelium produces a variety of vasoactive molecules including nitric oxide (NO) which has an important role in protecting the endothelium. NO is a potent vasodilator and inhibitor of vascular smooth muscle cell growth and of platelet and leukocyte adhesion and aggregation (Laroia et al 2003). The endothelium produces vasodilators, which includes prostacyclin and endothelium-derived hyperpolarizing factor as well as NO, and vasoconstrictors, including endothelin, angiotensin II and vasoconstrictor prostaglandins (Mombouli and Vanhoutte 1999).

The endothelium is also involved in coagulation and fibrinolysis, producing tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1), von Willebrand factor and thrombomodulin (Lijnen and Collen 1997).

Endothelial dysfunction is characterised by impaired vasodilation in response to physiological and pharmacological mediators and increased adhesion molecule expression (Zeiher et al 1996), which contribute to atherosclerotic plaque formation (Widlansky 2003).

One of the primary mechanisms of endothelial dysfunction is thought to be the diminished bioavailability of NO and risk factors for coronary atherosclerosis, such as hypercholesterolemia, impair NO bioavailability (Casino 1993, Britten et al 1999). Endothelial dysfunction is seen in patients with existing cardiovascular disease and FMD may be a useful predictor of cardiovascular events in this group (Lieberman 1996, Neunteufl 1997). It has also been observed prospectively in patients with peripheral vascular disease just prior to surgery when FMD was lower (4.4%) in patients who subsequently experienced a cardiac event compared with those without an event (7%) (Gokce 2003). However the study was relatively small with 199 patients who were

followed for 1.2 years during which time 35 patients had a cardiovascular event and these results need to be interpreted with caution.

Endothelial dysfunction in the coronary arteries, assessed by the response to infused ACh, independently predicts cardiovascular and cerebrovascular events in patients with and without coronary artery disease (Targonski 2003, Halcox 2002).

Cross-sectional studies have also reported impaired FMD in patients with risk factors for cardiovascular disease such as low HDL-C, hypertriglyceridemia, hypercholesterolaemia, elevated LDL-C and homocysteine hyperglycaemia and type 2 diabetes and hypertension (Lupattelli 2002, 2003, Toikka 1999, Lewis1999, Steinberg 1997, Thomas 2004, Makimattila 1999, Schlaich 2000, Watts 1996, Jensen-Urstad 1997, Woodman 2006). These risk factors will be explored in more detail in the next section.

Measurement of endothelial function

Celermajer et al (1992) devised a non-invasive method for measuring endothelial function, using high-resolution ultrasound to measure the diameter of the superficial femoral or brachial arteries, measurements are taken at rest, during reactive hyperaemia which leads to increased blood flow causing endothelium-dependent dilatation, and after sublingual GTN which causes endothelium-independent dilatation (Celermajer 1992). Reactive hyperaemia creates a large transient shear stress stimulus that produces an NO-dependent response allowing the FMD measurements to be used as an assay of NO bioavailability (Pyke 2005). The major advantage of this method is that it is completely noninvasive, accurate, and reproducible. The major disadvantage is that the coronary arteries cannot be imaged directly with ultrasound, and therefore the test is usually applied to peripheral arteries, such as the brachial or femoral conduit vessels and

is thought to correspond to the response in the coronary arteries (Anderson 1995, Kuvin 2001). The advantages and disadvantages of technique are discussed in greater detail in the discussion.

Endothelial function can also be assessed by the response to the neurotransmitter acetylcholine (Ach) which is injected into large blood vessels or by iontophoretic administration in the microvascular circulation (Hansell 2004).

Flow independent dilatation (FID)

As flow induced dilatation is NO dependent it is also important to establish that the artery is able to respond to NO. GTN is a nitric oxide donor which causes flow independent dilatation and is used to demonstrate that the blood vessel is capable of flow independent dilatation (Celermajer 1992).Reported FID is approximately twice the magnitude of FMD in control subjects and 3 - 4 times that of subjects with impaired FMD (Celermajer 1993). Reduced endothelial independent vasodilation has been reported in men with type 2 DM compared with controls and in patients with type 1 DM with microalbuminemia compared with controls (Watts 1996, Dogra 2001). In contrast Lambert et al (1996) found that in patients with type 1 DM FMD and FID were not different to controls when the difference in baseline vessel was accounted for.

Lipids and endothelial function
In studies investigating endothelial dysfunction, elevated total or LDL-C has been shown to be negatively related to FMD in the majority of them (Wissing 2006, Kuvin 2005, Corrado 2005, Shechter 2000, Yataco 1999, Tan 1999, Celermajer 1994) with some negative studies (Schnell 1999, Viiri 2006, Dalton 2005). Compared with controls children with FH have impaired FMD which is independent of TC, LDL-C and HDL-C levels (de Jongh 2002, Sorensen 1994, Celermajer 1992). Interventions to reduce total

and LDL cholesterol have been shown to improve endothelial function (Dupuis 1999, Dupuis 2005, Cohen 2000, Sebestjen 2002, Kuvin 2002, Alonso 2001).

Treatment with HMGCoA reductase inhibitors such as pravastatin, atorvastatin, simvastatin or fluvastatin which reduce total and LDL-C have been shown to improve FMD (Dupuis 1999, Dupuis 2005, Sebestjen 2002, John 1998, Beckman 2004). However in the majority of these studies there was no correlation between the change in FMD and the change in lipids or CRP (Dupuis 1999, Dupuis 2005, Sebestjen 2002, Beckman 2004). In the study by John et al (1998) there was a correlation between the increase in blood flow in response to ACh and the decrease in serum cholesterol levels. Nitric oxide synthesis, assessed by the FMD response before and after inhibition by NO inhibition by NG-monomethyl-L-arginine (L-NMMA) infusion, increased suggesting that the improvement in FMD was mediated by increased availability of NO (John 1998). Endothelium-dependent vasodilation has been shown to improve early in statin treatment, after 3 days and after two weeks at which points LDL-C had also decreased and similarly to the earlier study this improvement was inhibited by L-NMMA infusion. John et al (2001, 2005).

The effects on endothelial function may be independent of the reductions in total and LDL-C as there is some in vitro evidence that statins increase NO availability by upregulating endothelial NO synthase (eNOS) (Kaesemeyer 1999) and have been shown to restore eNOS activity in the presence of oxidized LDL (Laufs 1998). However it is also of importance that in the studies discussed above, different methods were used to measure endothelial function i.e. FMD and forearm plethysmography, which may have a bearing on these results (Dupuis 1999, Dupuis 2005, Sebestjen 2002, Beckman 2004, John 1998, 2001, 2005).

One of the few long term interventions with FMD as an endpoint has demonstrated a correlation between improvements in FMD and reduction in LDL-C (Cohen 2000). Not all studies with HMGCoA reductase inhibitors show an improvement in FMD. Stein et al (2001) investigated the effect of both statin (pravastatin or simvastatin therapy) and antioxidant vitamins (vitamin E or vitamins C and E) on FMD finding that while both drugs reduced total and LDL-C levels there was no change in FMD (Stein 2001). However the subjects in the study were elderly (76 years) 83% had hypertension and 24% had known CAD, and may have had a limited capacity to improve FMD from the impaired baseline level of 2.2% (Stein 2001).

An association between reduced HDL-C and impaired FMD has also been observed in cross-sectional studies (Lupattelli 2002, 2003, Kuvin 2003, Toikka 1999, Sarabi 2001, Packard 2005). Lupatelli et al (2003, 2002) found that hyperlipidemic patients free of cardiovascular disease with low HDL-C had lower FMD and that HDL-C was an independent predictor of FMD (Lupatelli 2002, 2003). Similarly Sarabi et al (2001) and Packard et al (2005) also observed this in apparently healthy subjects and Toikka et al found impaired FMD in young men known to have consistently low HDL-C over 2 years (Toikka 1999). Similar findings, that HDL –C was an independent predictor of FMD, were observed by Kuvin et al (2003) in patients with CAD (Kuvin 2003). Increasing HDL-C generally improves FMD (Kuvin 2002, Spieker 2002, Bisoendial 2003, de Roos 2001, Andrews 1997). In patients with existing CAD, Kuvin et al (2002) found that FMD improved from 7% to 12% when HDL-C levels increased (by 50%) following 3 months treatment with niacin (Kuvin 2002). In an acute study over 4 hours, infusion of reconstituted HDL which increased HDL-C (from 1.3 to 2.2 mmol/L), also had a beneficial effect on FMD improving it from 2.7% to 4.5% (absolute) (Spieker 2001). Bisoendial et al (2003) also reported that infusion of apolipoprotein A-

I/phosphatidylcholine which increased plasma HDL from 0.4 to 1.3 mmol/L improved forearm blood flow responses assessed by venous occlusion plethysmography which examines the response of small resistance arteries to infused ACh (Bisoendial 2003). However Andrews et al (1997) found no difference in FMD at the end of a placebo controlled intervention study of gemfibrozil ± niacin ± cholestyramine despite improvements in LDL and HDL-C (Andrews 1997). FMD was measured at the end of the intervention period and the two groups compared as there was no baseline FMD and it has to be assumed that the groups were the same before the intervention commenced. The study was also reasonably large with 53 subjects in the intervention group and 47 controls (Andrews 1997).

High TG levels have also been shown to be associated with impaired FMD in the majority of studies that have examined triglyceride levels (Dart 1999, Lewis 1999, Schneider 2003, de Man 2000, Chowienczyk 1997). However Schnell et al (1999) did not observe this in patients with raised LDL-C and triglycerides.

Interventions to improve triglyceride levels have demonstrated improvements in FMD (Okumura 2002, de Man 2000). Okumura et al (2002) observed that reduction in triglyceride levels of 31% using eicosapentaenoic acid improved endothelial function and treatment with atorvastatin which reduced both triglyceride (43%) and total TC (38%), improved endothelial function (de Man 2000).

Summary

Elevated TC or LDL-C has been shown to be negatively related to FMD in seven out of ten studies and in general interventions to reduce total and LDL-C have been shown to improve endothelial function in six out of seven studies. Low levels of HDL-C are associated with impaired FMD and increasing HDL-C generally improves FMD. The association between high triglycerides and FMD are less clear.

Insulin resistance and endothelial function

Insulin has an important role in vascular function. It is a potent vasodilator in skeletal muscle in healthy subjects mediated by stimulation of nitric oxide (Scherrer 1994, Scherrer and Sartori 1997, Baron 1994, 1995). Insulin's ability to stimulate blood flow in insulin sensitive tissues is impaired in states of insulin resistance such as obesity and type 2 diabetes (Laakso 1990, Baron 1994, McVeigh 1992) suggesting impaired NO production in these conditions.

In a cross-sectional study of 47subjects, body mass index (BMI) 25-30 kg/m^2, Ardigo et al (2006) reported decreased FMD which correlated with waist circumference, higher fasting plasma insulin and triglycerides and lower HDL-C but only plasma insulin was independently negatively associated with FMD (Ardigo 2006). Steinberg et al (1996) observed that obesity and insulin resistance impaired both endothelium-dependent vasodilation via methacholine (MCh) and insulin-mediated augmentation of endothelium-dependent vasodilation finding that MCh induced increments in leg blood flow were lower in obese and subjects with type 2 diabetes by 40% and 55% respectively, compared with C (P < 0.05). Euglycemic hyperinsulinemia augmented endothelium dependent leg blood response to MCh by 50% in controls (BMI<28 kg/m^2) but not in obese or diabetic subjects (Steinberg 1996). In contrast Wendelhag et al (2002) found that while FMD in 60-year-old men was impaired no relationship was observed between FMD and insulin-mediated glucose uptake and subjects with insulin resistance and FMD did not differ compared with those with no risk factors (Wendelhag 2002).

In several cross-sectional euglycemic, hyperinsulinemic clamp studies, insulin impaired FMD in both insulin sensitive and insulin resistant subjects (Campia 2004, Arcaro 2002, Balletshofer 2003).

Free fatty acids, which may be elevated in obesity, inhibit NO production from cultured bovine pulmonary artery endothelial cells in vitro thus potentially contributing to endothelial dysfunction (Davda 1995). However this relationship has not been demonstrated in vivo. Vollenweider et al (1995) infused insulin/glucose with fat emulsion (Intralipid 20%) in lean subjects which attenuated carbohydrate oxidation but had no effect on insulin-induced vasodilation. However it is not clear from the study whether heparin was added to the fat emulsion and levels of free fatty acids were not measured so it unclear whether free fatty acids levels were increased substantially by the infusion. Balletshofer et al (2003) observed a reduction in FMD in insulin resistant subjects (n=30) compared with insulin sensitive subjects (n=61) using a euglycemic, hyperinsulinemic glucose clamp to determine insulin resistance. The insulin resistant group were also heavier and had a greater percent body fat than the insulin sensitive group; they also had higher glucose values 2 hours after an OGTT although within the normal range. There were also more women in the insulin resistant group and their high body fat may have confounded the results. Impaired FMD has also been reported in women with polycystic ovarian syndrome (PCOS) a syndrome characterised by insulin resistance (Carmina 2006, Brinkworth 2006).

Hyperglycaemia and endothelial function
Impaired glucose tolerance (IGT) is common and in 2002 was estimated to be 10.6% in the Australian population (Dunstan et al 2002). Hyperglycemia is known to be associated with endothelial dysfunction in both cross-sectional studies (Rodriguez 2005, Thomas 2004) and acute post prandial or post GTT studies (Kawano 1999, Akbari 1998, Kim 2003, Williams 1998). Rodriguez and colleagues (2005) found IFG in 16% (95of 579) of healthy subjects and that FMD was significantly lower in those 95, (4.9% compared to 6.1%) than in the 478 subjects with normal glucose tolerance, suggesting

that chronic hyperglycaemia impairs FMD. For each 10% increase in plasma glucose a 0.24% absolute decrease in FMD was seen. However the group with IFG also had significantly more hypertension, higher TC and TG all of which are also associated with impaired FMD. While multivariate analysis controlling for age, BMI, and hypertensive status revealed that higher fasting blood glucose independently predicted decreased FMD, when LDL-C, HDL-C and triglycerides were included in model, the effect of glucose was weakened ($p = 0.068$) (Rodriguez 2005).

Similarly Thomas et al (2004) report decreasing FMD across the glucose continuum with higher levels being associated with decreasing FMD, tertile 1 (n=70), glucose 4.9 mmol/L, FMD 9.5%, tertile 2 (n=84), glucose 5.4 mmol/L, FMD 9.2% and tertile 3 (n=74) glucose 6.0 mmol/L FMD 7.7% (Thomas 2004). FMD in tertile 3 was significantly different to FMD in both tertiles 1 and 2 but they were not different to each other. Some of the subjects in tertile 3 would have had IFG according to the World Health Organisation (WHO) criteria which states that 6.1 mmol/L is the cut-off for IFG as the mean fasting plasma glucose was 6.0 ±0.3mmol/L (WHO 1999).

A number of studies have shown that endothelial function is impaired by hyperglycaemia induced by an oral glucose load in subjects with and without IGT (Kawano 1999, Akbari 1998, Kim 2003, Wascher et al 2005, Title 2000). However FMD is not always impaired by acute hyperglycaemia (Bagg et al 2000, Williams 1998). Bagg et al (2000) saw no difference in FMD when either glucose or normal saline was infused. Williams et al (1998) report that endothelial function was impaired only when insulin secretion, which has been observed to be a potent vasodilator (Scherrer 1994, Scherrer and Sartori 1997), was blocked by octreotide infusion suggesting that during hyperglycaemia in normal subjects, insulin has a protective effect on the endothelium (Williams 1998).

Interventions which lower glucose have been shown to have a beneficial effect on FMD in several acute studies in subjects with IGT (Wascher 2005, Schmoelzer 2006). Acarbose, which partially inhibits carbohydrate digestion, prevented the acute hyperglycaemia following 100g sucrose and attenuated the reduction in FMD (Wascher et al 2005). Schmoelzer et al (2006) found that repaglinide, which stimulates insulin release, resulted in a reduction of plasma glucose after an oral glucose tolerance test (OGTT) of 75 g glucose and prevented the 2% fall in FMD that occurred without the drug. Regression analysis demonstrated a strong negative association between the changes in plasma glucose and FMD however the study is limited by the small sample size of 12 subjects (Schmoelzer 2006).

Diabetes Mellitus and endothelial function
Subjects with type 2 diabetes have been shown to have impaired FMD (Ravikumar 2002, Ifrim 2004). In the study by Ravikumar et al (2002) of 50 people with diabetes and 50 matched controls, FMD was correlated with age, fasting plasma glucose, HbA1c and systolic blood pressure. In a smaller study Ifrim et al (2004) found that subjects with diabetes had impaired FMD compared with controls (5.7% compared with 7.1%). Impaired FMD has also been reported in type 1 DM (Johansson 2003). In a 14 year follow up of subjects with type 1 diabetes patients who had received either intensive or conventional treatment of their diabetes, cholesterol and HbA1c correlated inversely with FMD which was significantly impaired at approximately 3% in both intensive and conventional groups. Henry et al (2004) in a cross-sectional study found impaired FMD of 3% only in subjects with diabetes and not in subjects with IGT which is in contrast to the study by Rodriguez et al (2005) referred to earlier. However in the study by Henry et al (2004) FMD was lower in the normal subjects and those with IGT at 4.5% and 4.2% respectively in contrast to the FMD of 6.1 % and 4.9 % in the normal subjects and

those with IGT respectively in the study by Rodriguez suggesting that they are some way a different population although they are of similar age.

Improving insulin sensitivity has been shown to improve FMD (Caballero 2003, Hetzel 2005). Troglitazone (an insulin sensitising agent) has been shown to improve FMD but only in patients recently diagnosed and not in those with long standing diabetes (Caballero 2003). In this study regression analysis showed that change in insulin levels significantly contributed to the FMD change. The only change in lipids observed was an increase in TC in patients with long-term diabetes without macrovascular disease. There was a significant improvement in FMD from 4.4 to 5.4% in placebo-treated patients with long-term diabetes without macrovascular disease. Patients with macrovascular disease were older when compared with the other patients and also had an increase in body weight of 2 kg. The results of this study are of interest however the numbers in each group were small and there are confounding factors such as age, weight gain and an increase in TC that make the negative results in patients with long-term diabetes somewhat difficult to interpret. Hetzel et al (2005) reported an improvement in FMD from 5% to 9% after 3 weeks treatment with rosiglitazone with no change in glucose or insulin but with reductions in CRP and sE-selectin suggesting that these agents have a direct effect on endothelial function. Similarly Martens et al (2005) observed that FMD was increased by 4 weeks of treatment with pioglitazone compared with placebo (FMD 5.4 % vs 3.1 %). While pioglitazone treatment reduced insulin, FFA and CRP concentrations compared with control and increased plasma adiponectin concentration no correlations were found between these changes and the improvement in FMD suggestion that pioglitazone may have a direct effect on endothelial function.

Summary

Insulin resistance is associated with impaired FMD in seven of the eight studies discussed. Hyperglycemia per se is also associated with impaired FMD in both cross-sectional and acute studies and two interventions which lowered glucose in people with IGT have been shown to have a beneficial effect on FMD. Both type 1 and type 2 diabetes mellitus are associated with impaired FMD. People with diabetes often have other risk factors associated with impaired FMD such as hyperlipidaemia. As seen previously in subjects with IGT, insulin sensitising agents also appear to improve in FMD in diabetes.

Hypertension and endothelial function

Endothelial dysfunction has been reported in people with hypertension (Andrews 1997, Lind 2006, Ceravolo 2003, Perticone 2001, Suzuki 2004, Lauer 2005). Antihypertensive treatment has been shown to improve FMD although this is not always the case (Tomiyama 1998, Topal 2006, Sola 2005, Rajagopalan 2002). The studies do not always adjust for all variables that may influence FMD in subjects with hypertension. Andrews et al (1997) report that a history of hypertension was a highly significant predictor of FMD while Ceravolo et al (2003) report that endothelial dysfunction was predicted by pulse pressure (SBP-DBP) after adjusting for other variables. Suzuki et al (2004) observed that FMD was independently related to steady-state plasma glucose and SBP and Lauer et al (2005) reported that peripheral flow reserve in resistance vessels was a strong independent variable determining the extent of FMD. Higashi et al (2001) reported that the maximal forearm blood flow response to ACh correlated independently with age, obesity, HOMA index and mean BP suggesting that both obesity and hypertension are independently involved in abnormal endothelium dependent vasodilation both in large conduit arteries (FMD) and smaller resistance

vessels. Similarly Lteif et al (2005) reported that endothelium-dependent vasodilation, (leg blood flow in response to MCh) was reduced in subjects with the metabolic syndrome and after multivariable regression analysis the only independent relationship was with SBP (Lteif 2005).

It has been postulated that the vascular damage and predisposition to the development of atherosclerosis seen in hypertension may be mediated through high levels of adhesion molecules such as P-selectin although this remains to be clarified (Lip 1995, Verhaar 1998). Tomiyama et al (1998) observed that markers of fibrinolysis were elevated in hypertensive patients with t-PA and PAI-1 both being elevated and on multiple regression analysis endothelial function was negatively correlated with t-PA activity and antigen (Tomiyama 1998). Antihypertensive treatment has also been shown to have a beneficial effect on PAI-1 and the cellular adhesion molecules VCAM-1 and ICAM-1 (Sola 2005, Rajagopalan 2002).

Weight loss may have a beneficial effect on endothelial function in obese hypertensives as Sasaki et al (2002) observed that weight loss reduced blood pressure and enhanced the response of forearm blood flow to Ach. However this was a small study over two weeks and it needs to be determined if these benefits are sustained (Sasaki 2002).

Summary

Endothelial dysfunction is associated with hypertension and antihypertensive treatment has generally been shown to improve FMD.

Nutrition and hypertension and the effects of salt and weight loss are discussed in a separate section.

Obesity and endothelial function

Obesity per se has been reported to impair vascular endothelial function (Brook 2006). However the effects of the risk factors that may co-exist with obesity have not always

been adjusted for in the analysis (Williams 2006, Arcaro 1999). William et al (2003) reported reductions in FMD in subjects prior to bariatric surgery for obesity but these obese subjects also had cardiovascular disease risk factors including hypertension, impaired glucose metabolism and increased inflammatory markers which are also associated with impaired FMD. Arcaro et al (1999) also found that FMD was impaired in obese compared to age matched lean women and was inversely correlated with visceral fat (r=0.624, P<0.01) whereas other variables such as age, BP, fasting plasma glucose, insulin, and lipids did not correlate with FMD (Arcaro 1999).

In contrast Joseph et al (2002) found no relationship between measures of body fatness *per se* and FMD in obese older men in whom only glucose area under the curve correlated with FMD. FMD was 7.6% which is higher than in similar aged subjects (Jensen-Urstad 2001) and similar to non-obese younger subjects (Hashimoto 1998). However there was no lean control group in the study with which to compare the results from the obese group (Joseph 2002). Jensen-Urstad et al (2001) observed that while FMD was reduced (3 % in men and 2.6 % in women) in an older group of subjects (55yr) it was not correlated with conventional CVD risk factors. FMD was significantly different between younger (35 yr) and older women, 5.7% and 2.6% respectively, but was not different in the 35 year old men FMD (3.1%) compared to the 55 year olds, despite higher BP, BMI, glucose, TC and LDL-C and lower HDL-C in the older men. It is not clear why the FMD is so low in this group of young men. Hashimoto et al (1998) observed that FMD was impaired in younger men (37years) with visceral obesity compared to subjects with subcutaneous obesity, and non-obese subjects 3.1%, 7.9% and 8.9% respectively. The obese subjects also had a low HDL-C, 1.13 and 1.10 mmol/L compared with 1.51 mmol/L in the non obese group which was also associated

with impaired FMD but it appears that this was not accounted for in the analysis (Hashimoto 1998).

In a study of 24 young (31 years) obese women and 14 age matched lean controls Oflaz et al (2003) found that brachial artery FMD was lower, 13.3 % compared with 25.2 %, in obese and lean subjects respectively. Lipid profile, BP, HOMA and anthropometric parameters did not predict the FMD or in the obese and lean women (Oflaz 2003). Central adiposity is associated with reduced FMD (Hashimoto 1998, Wendelhag 2002, Brook 2001, Arcaro1999).

Brook et al (2001) found no correlation between BMI and FMD but obese subjects with a WHR ≥0.85 had a significantly reduced FMD, 3.9% compared with 8.3 %, compared with those with a WHR <0.85. Traditional CVD risk factors, CRP, postprandial lipemia, and LDL particle size did not predict FMD.

Impaired FMD can occur early in life. Cross sectional studies have reported impaired FMD in obese children and in young adults with a family history of premature heart disease (Meyer 2006, Zhu 2005, Kapiotis 2006, Gaeta 2000). The children in these studies had other risk factors which are also associated with impaired FMD e.g. increased levels of adhesion molecules, C-reactive protein and dyslipidaemia (Meyer 2006, Zhu 2005, Kapiotis 2006). Similarly the young adults in the study by Gaeta 2003 had higher TC (P=0.06), apolipoprotein B and serum Lp (a) lipoprotein which may have accounted for some of the impaired FMD which was 5.7% compared to 10.2% (absolute) in controls.

Summary

Obesity is associated with impaired FMD however this is not independent of other obesity related risk factors for impaired FMD. Fat distribution is important as central adiposity is associated with reduced FMD. There is wide variability in reported FMD in

the literature however while the absolute values may be different the changes are in the same direction.

Weight loss and endothelial function

The data on whether weight loss per se improves FMD is not clear cut. There are a number of positive studies (Vazquez 2005, Ziccardi 2002, Hamdy 2003, Shechter 2006, Williams 2005, Sasaki 2002) and two negative studies (Brook 2004 Dengel 2006). The studies differ in both their design and the method used to measure endothelial function which makes direct comparison of the results somewhat difficult.

Two studies have been undertaken in patients who required bariatric surgery for obesity (Vazquez 2005, Williams 2005). Vazquez and colleagues (2005) observed an average weight loss of 26kg in 26 patients 4 months after bariatric surgery for obesity with improvements of 20% in the endothelium dependent, vasodilatory response to bradykinin in a hand vein (measured by an indirect electrical technique), were observed after weight loss. Williams et al (2005) reported that FMD improved from 5 to 10% after weight loss of 23kg in a small study of 6 patients who lost weight after bariatric surgery. However it contains a very small number of patients and the exclusion of 2 subjects from the data weakens the study considerably. While the method of assessing endothelial function differs in these 2 studies the results suggest that large amounts of weight loss are effective in improving FMD.

Four studies have used FMD as the method by which to assess endothelial function (Hamdy 2003, Shechter 2006, Williams 2005, Raitakari 2004). Hamdy et al (2003) conducted a 6 month weight loss study with both a reduced energy diet and 30 mins of exercise daily (60-80% maximal heart rate) in people with impaired glucose tolerance and found that FMD improved from 8 to 13% with a weight loss of 7kg (6.6%). In a multiple regression model percentage reduction in body weight, reduction in fasting

plasma glucose, reduction in serum TC and reduction in diastolic blood pressure were significant predictors of the improved brachial FMD. There was no control group in this study and it is not clear whether weight loss of this relatively modest amount without improvements in lipids and glucose would have had the same effect on FMD. Shechter et al (2006) in a study of 80 obese subjects with CAD on either sibutramine or usual care for 4 months achieved weight loss of approximately 11kg on sibutramine and 2kg in the usual care group. FMD improved from a baseline of 5% to 9% in the sibutramine group only. These studies support the finding that weight loss of relatively modest amounts with or without an exercise component are also effective in improving endothelial function assessed by FMD.

Raitakari et al (2004) reported improvements in FMD from 5.5% to 8.8% after weight loss of 11kg in 67 subjects on a very low calorie, low carbohydrate (70g/day) diet but this correlated with reductions in fasting glucose concentrations and not with weight loss per se. These results also support the view that weight loss, because of its effect on fasting glucose levels, contributes to improved endothelial function. This finding is supported by results of studies by Schmoelzer 2006 and Wascher et al 2005 which showed that reduction of hyperglycemia by repaglinide or acarbose reduced endothelial dysfunction.

Another method used to assess change in endothelial function is the forearm blood flow response to intra-arterial infusions of acetylcholine Ach (Sasaki 2002, Bergholm 2003). Sasaki 2002 reported that forearm blood flow response to ACh was attenuated in 11 obese hypertensive patients compared to 15 healthy controls at baseline and weight loss of only 4 kg was associated with enhanced forearm blood flow response to Ach and decreases in BP, fasting insulin, TC and LDL-C. However whether the changes in the

response to ACh were associated with any of the other changes achieved was not discussed.

Bergholm et al (2003) also reported improvements in endothelium-dependent vasodilatation assessed by this method following modest amounts of weight loss in a parallel study of weight loss using orlistat or placebo. While weight loss was similar in both groups, approximately 7kg, responses to ACh improved by 41% in the low and 33% in the high dose orlistat group only. There was a reduction in LDL-C of 14% in the orlistat group which correlated with the improvement in the blood flow response to ACh but not with weight loss or other measures of body composition. These results support the view that weight loss, because of its effect on LDL-C, contributes to improved endothelial function although it is not clear why the placebo group did not have a reduction in LDL-C as weight loss usually achieves this (Noakes & Clifton 2000) and the study diet which was fat restricted was the same for both groups. There are no measures of dietary compliance reported so it unclear whether dietary intake was different although the overall energy deficit was similar as demonstrated by the same amount of weight loss in both groups.

Intravenous infusion of L-arginine, the precursor of nitric oxide, is also used to assess endothelial function (Giugliano 1997). Ziccardi et al (2002) found that vascular responses to intravenous L-arginine improved in 56 obese women after 10kg weight loss over a year on a diet and exercise program. Weight loss was also associated with reductions in fasting glucose and insulin levels, TNF-α, IL-6, and adhesion molecules. Improvements in vascular responses to L-arginine correlated with reductions in BMI and WHR, increases in physical activity and the decline in serum TNF-α and IL-6. These results add support the view that weight loss improves endothelial function and in

addition increased physical activity and reduced levels of cytokines may have an additional effect but there was no control arm in the study.

However it needs to be borne in mind that the mechanism of the vascular responses to endothelium-dependent FMD, intravenous arginine, bradykinin or ACh may differ, even if nitric oxide acting on vascular smooth muscle is the final pathway. Certainly the site of action differs in FMD studies (conduit arteries) and intra arterial infusions (small muscular arteries).

There are two studies which did not show improvements in FMD with weight loss (Brook 2004, Dengel 2006). Forty-three subjects lost 6kg (6%) over 12 weeks using a calorie-restricted diet and orlistat. While TC, HDL-C & LDL-C and insulin levels fell by 7%, 4%, 9% and 16% respectively FMD did not change after weight loss (3.86 +/- 3.54 vs 3.74 +/- 3.78%, p = 0.86). It is unclear why the results of this study differ from those of Bergholm et al (2003) except that the reduction in LDL-C was greater than in the study by Brook et al (2004) and different methods were used to assess endothelial function. In a study by Dengel et al (2006) 12 obese adults lost 7kg over 6 months with no change in FMD (5.5±1.1 vs 6.3±1.2) despite improvements in insulin sensitivity, reductions in TC of 16.7%, LDL-C of 17.9%, and TG of 29.4% with change in HDL-C. Blood pressure and brachial artery compliance and distensibility improved indicating improvements in vascular function without effect on FMD but this is a small study (n=12).

Summary

The majority of the studies discussed support the view that weight loss has a beneficial effect on endothelial function although it is not clear whether this is due to weight loss per se or the metabolic benefits of weight loss. However while weight loss has been

shown to reduce abdominal fat studies of weight loss and FMD have not generally measured body fat distribution and this requires further investigation.

Dietary composition and endothelial function

Studies of the effect of medium or long term change in dietary macronutrient composition on endothelial function are relatively few and have generally been conducted in a weight stable design rather than in weight loss (Fuentes 2001, de Roos 2001a, Ros 2004). Fuentes et al (2001) conducted a study which included an initial 28-day period on a diet high in saturated fat after which subjects were randomised in a crossover design to two diets for two 28-day periods, either a low fat or a high MUFA, low saturated fat diet. FMD increased from 9.9% to 13.5% after the high MUFA compared to the high saturated fat but did not change on the low fat diet, despite similar falls in LDL-C (15%) on both diets and no change in HDL-C (Fuentes 2001).

de Roos et al (2001a) fed 32 subjects either a low fat or a high MUFA diet for 1 week in a randomised cross-over design. HDL-C was lower after the low-fat diet than after the high MUFA diet and serum TG were higher after the low-fat diet. Despite these potentially undesirable changes FMD was not impaired after the low-fat diet which was 4.8% compared with 4.1% after the high MUFA diet.

Ros et al (2004) reported improved FMD, from 3.6 to 5.9% and reduced levels of VCAM-1 in a randomised cross-over design study of a high polyunsaturated fat (PUFA) diet achieved using 40 to 65 g walnuts/day for 4 weeks compared to a high MUFA diet in hypercholesterolemic subjects. The high PUFA diet reduced TC and LDL-C by 4.4 and 6.4% respectively. It is unclear why the two diets had different effects on endothelial function and it is possible that the walnut intake which increased dietary L-arginine by 0.9 to 1.4 g/d contributed extra substrate for NO production. It would have

been useful to have a high PUFA fat diet in which the arginine content was kept similar to the high MUFA diet in order to help clarify this.

Long-term dietary change and endothelial function has only rarely been investigated. Raitakari et al (2005) examined endothelial function in 11year olds after dietary intervention which commenced in infancy and hypothesised that decreasing saturated fat would lead to improved FMD. There were 289 children in the intervention and 325 control children who were examined at age 11 years and there were FMD measurements available for 179 children. Dietary advice given in infancy was in accordance with the Nordic Dietary Recommendations and families completed food records for 4 days twice/year. Based on these 4-day food records, the fat intake of the intervention children was 30% of the energy intake, whereas it was 2 - 3 % of energy higher (P<0.001) in the controls (Talvia 2004). The intervention children consumed 2 - 3 % less saturated fat and 0.5 to 1.0% of energy more PUFA fats than controls. At aged 5 both parents of the intervention children consumed less saturated fat (*P*<0.001) than control parents (Talvia 2004). FMD was greater in boys 9.6%compared to 8.4% (P<0.05) but not in girls, 8.8% and 8.4% intervention and controls respectively. Despite data from the diet records that both boys and girls in the intervention maintained a significantly lower saturated fat intake than controls (girls 11.5 ±2.9 vs 12.8 ±2.7%, P<0.001 boys 10.8 ±2.1 vs 13.2 ±2.9, P<0.0001, intervention vs controls), TC was 5% lower in intervention boys compared to controls but not girls. Similarly LDL-C was 10% lower in the intervention boys only which may account for the difference in FMD between boys and girls.

Trans fatty acids
The consumption of trans fatty acids (TFA), produced by hydrogenation of polyunsaturated vegetable oil (Lichtenstein 1993), are known to increase the risk of cardiovascular disease (Willett 1993, Ascherio 1996, Clevidence 1997, Clifton 2004).

The effect of TFA on FMD has been examined in several studies (de Roos 2001b, 2002). de Roos et al (2001b) observed that FMD was impaired by the replacement of saturated fat in the diet by TFA which caused a fall in HDL-C of 21% (0.39mmol/L) with no change in LDL-C or triglyceride concentrations (de Roos 2001b). Volunteers (n=29) consumed 2 controlled diets in a 2x4-week randomized crossover design, a diet which contained 9.2% energy from TFA or a diet replacing the TFA with saturated fatty acids. FMD was 4.4% after the high TFA diet vs 6.20% after the high saturated fat diet. In a study designed to reduce HDL-C over 4 weeks de Roos et al (2003) found that replacement of 10% of energy from saturated by trans fatty acids by TFA decreased serum HDL-C by 21% and impaired FMD. The replacement of MUFA by carbohydrates decreased serum HDL-C by 13% but did not impair FMD. The role of serum HDL-C is unclear in these circumstances

Summary

The effect of dietary fat type on FMD is uncertain. One study found in improvement in FMD after MUFA and no change after a low fat diet whereas another found no change after either MUFA or a low fat diet (Fuentes 2001, de Roos 2001a). A high PUFA diet improved FMD compared with a high MUFA diet (Ros 2004). In the only long-term study a low saturated fat diet improved FMD in boys but not girls (Raitakari 2005). It appears that the consumption TFA has a more detrimental effect on FMD than saturated fat (de Roos 2003). While low HDL-C appears to be associated with lower FMD yet a low fat diet which lowered HDL-C did not impair FMD suggesting that the relationship between HDL-C and FMD is complex.

Effect of fat on FMD in acute studies

In acute studies the effect of different types of fat on FMD and the effect of addition of other macronutrients to test meals has been investigated (de Roos 2002, Tushuizen 2006, Giannattasio 2005, Westphal 2006, West 2005, Vogel 2000, Raitakari 2000).

de Roos (2002) followed up on the earlier longer study with an acute study in which 21 healthy men were given test meals with 0.9-1.0 g fat/kg body weight (75-83.5g) in random order either high in saturated fatty acids or TFA. The test meals comprised a milkshake (33 g fat/average portion), bread plus spread (45 g fat/average portion), and preserves. The type of fat was the only difference between the test meals. FMD did not change after either test meal despite a 48% greater increase in TG after the TFA test meal compared with the saturated fat test meal (de Roos 2002).

Similarly Raitakari et al (2000) observed that FMD did not change after a either a high MUFA (61 g fat, 85% MUFA, 10% saturated, 5% PUFA) or high saturated test meal (61g fat, 48% saturated, 40% MUFA, 7.4% PUFA, 4.6% trans fatty acids).

Tushuizen et al (2006) fed volunteers 2 high fat meals (breakfast and lunch, both of which contained 50g (30g saturated) fat, 55 g carbohydrate and 30 g protein) and found that FMD was impaired from 6.9 to 3.7%, 6 hours after the first meal compared with a second day when the subjects remained fasted.

Cortes et al (2006) substituted walnuts (40g, 230gPUFA) for olive oil (25g, 20g MUFA) in a randomized crossover study of 2 high-fat meals (80 g fat, 35% saturated fat) in 12 patients with hypercholesterolemia and 12 controls. FMD was reduced in both hypercholesterolemic patients and controls after the olive oil meal by comparison with the walnut meal. Fasting, but not postprandial TG concentrations correlated inversely with FMD. It may be that the extra NO was produced from the arginine in the walnuts had a protective effect. E-selectin decreased after the walnut meal (P<0.05). It is unclear

why the change in E-selectin might have occurred and may be chance alone given the multiple tests performed.

Nicholls et al (2006) found that FMD was decreased by a saturated fat meal by 2.2% (compared with baseline) and did not change after a high PUFA meal in a randomised study in which 14 subjects consumed 2 isocaloric meals containing either PUFA from safflower oil or saturated fat from coconut oil (1 g of fat/kg of body weight). After the saturated fat meal HDL was less effective than HDL from fasting plasma in its ability to inhibit expression of ICAM-1 and VCAM-1 in human umbilical vein endothelial cells, whereas HDL collected after the PUFA meal had a greater inhibitory activity that than that of fasting HDL. Consumption of saturated fat appears to impair FMD and reduce the anti-inflammatory potential of HDL which may be another potential mechanism for the atherogenic effect of a high saturated fat diet. These effects need to be tested in a long term study.

In subjects at increased risk of CVD Giannattasio et al (2005) observed that after an oral fat load (680 kcal, 62g fat/m^2 body surface) FMD was lower than in subjects with high TG than in controls. These results suggest that a high fat intake may be detrimental in subjects with high TG; however the controls were younger and were all male and it is known that FMD is related to both age and gender so caution is needed when interpreting these results. The type of fat used in the study was not discussed in the paper and different types of fat may have different effects in subjects with high TG.

The effect on FMD of omega-3 fatty acids has been examined by West et al (2005) who measured FMD before and after 3 test meals (50 g fat, 2,615 kJ) high in MUFA, high in MUFA with added docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) or high in MUFA with alpha-linolenic acid in 18 healthy adults with type 2 diabetes. FMD was not impaired by any of the test meals. In 8 subjects who had high fasting TG, FMD

was reduced at baseline compared with the subjects with normal fasting TG and the high omega-3 fatty acid meals increased FMD (2% absolute change) but the meals high in MUFA alone had no significant effects on FMD (West 2005). Westphal et al (2006) investigated the effect of including protein with fat on postprandial FMD and found that FMD was reduced after the fat (cream) meal. This reduction was not observed when either casein or soy protein was added to the cream meal. The addition of protein decreased triglycerides and free fatty acids and increased insulin concentrations. Vogel et al 2000 studied the postprandial effect of components of the Mediterranean diet on endothelial function. Subjects ate five meals containing 900 kcal and 50 g fat. Three meals contained different fat sources: olive oil, canola oil, and salmon (as fish rather than just oil). Two olive oil meals also contained additional antioxidant vitamins (C and E) or foods (balsamic vinegar and salad). The olive oil meal reduced FMD from 14.3 to 9.9% but the other four meals did not reduce FMD. As indicated by the study by Westphal et al (2006) the addition of protein from salmon may have attenuated any reduction in FMD and the addition of vinegar to food is thought to delay gastric emptying (Liljeberg 1998) although it is not clear why olive oil and canola oil provoked different responses and this is different to the results found by West et al (2005).

Brook et al (2001) measured FMD before and 4 hours after a high-fat meal (71g fat (25.5g saturated), carbohydrate 189g, protein 65g) in 32 overweight/obese subjects and found no change in postprandial FMD from the fasting value (6.25 to 6.31%).

Other dietary factors such as frying foods in previously used cooking oil or the composition of mixed meals may affect FMD. Williams et al (2001) investigated the effect of meals high in used olive or safflower oil and found no difference either between fasting and postprandial FMD or between the meals suggesting that these used oils do not adversely affect FMD. Sarabi et al (2001) observed a transient decrease in

endothelium-dependent vasodilation after a mixed meal (900 kcal, 34% of energy as fat) at 60 min after the meal which had returned to the fasting level at 120 min. Steer et al (2003) found that endothelium-dependent vasodilation decreased at 1 hour after a meal containing 34% energy from fat but approached fasting levels after 2 hours and did not change after a meal containing 20% energy from fat meal, and increased after a meal containing 3% energy from fat suggesting that the effect of mixed meals on endothelium-dependent vasodilation is related to the fat content of the meal.

Summary

The post prandial effect of fat on FMD is confusing, in 2 studies fat impaired FMD (Giannattasio 2005, Westphal 2006), in 4 studies fat had no effect on FMD (de Roos 2002, Raitakari 2000 West 2005, Brook et al (2001) whereas in one study there were different responses to olive and canola oil (Vogel 2000). A high PUFA meal, with walnuts did not decrease FMD whereas a high MUFA meal did and in another study a high saturated fat meal decreased FMD and a high PUFA meal did not (Cortes 2006, Nicholls 20063). In addition used oils did not adversely affect FMD and mixed meals may have a transient adverse effect on endothelium-dependent vasodilation related to the fat content of the meal (Williams 2001, Sarabi 2001, Steer 2003).

Homocysteine and folate

Data from the Framingham studies demonstrates an increased RR for both all cause and CVD mortality of homocysteine levels in the upper quartile (>14.26 µmol/L) versus the lower 3 quartiles (<14.26 µmol/L) of 1.54 for total and 1.52 for CVD mortality, adjusted for age, sex, SBP, diabetes, smoking and total and HDL-C (Selhub 2006). Elevated homocysteine has been shown to be independently associated with impaired endothelium dependent vasodilation as assessed by intra-arterial infusion of ACh after adjustment for other variables such as age, BP, BMI, LDL- C, HDL-C and TG

(Schlaich 2000). However, when homocysteine levels were increased after a methionine load in an acute study by Olthof and colleagues (2006a), there was no adverse effect on FMD. Measures to decrease homocysteine such as folic acid supplementation generally improve FMD (Doshi 2002, Title 2000, Moat 2006, Bellamy 1999, Pena 2004). In two of these studies (Doshi 2002, Moat 2006) folic acid increased plasma folate, lowered homocysteine and improved FMD but the improvement in FMD was not correlated with homocysteine reduction whereas in the study by Title et al (2000) improvements in FMD in patients with coronary artery disease correlated with homocysteine reduction. However in a second study the same authors found no relationship between homocysteine reduction and improvement in FMD following folic acid supplementation in patients with type 2 diabetes (Title 2006). Pena et al (2004) observed improvements in FMD in adolescents with type 1 diabetes following folic acid supplements and this change in FMD was related to change in serum folate. Coronary artery blood flow has also been shown to improve with homocysteine reduction following folic acid supplementation (Willems 2002). The amount of folate needed is also important as both 400 ug/day and 5 mg day of folic acid have been shown to increase plasma folate and decrease plasma homocysteine but FMD improved only after treatment with the 5 mg day (Moat 2006). In contrast to these studies no change in FMD was seen in several studies following folic acid supplementation at either recommended daily dietary intake (400 ug/day) or therapeutic doses (1400 ug/day) in older people with impaired FMD and in apparently healthy subjects 0.8 mg/d of folic acid had no effect on FMD despite a reduction in homocysteine (Carlsson 2004, Olthof 2006b). Similarly Woodman et al (2004) found no effect on FMD of folic acid supplements in subjects with hyperhomocysteinaemia but without other CAD risk factors. In another study of 90 patients with CAD, Thambyrajah et al 2001, found an equivocal result with folic acid of

5 mg/day with a trend for a greater increase in FMD from baseline in the folic acid group (1.2%, P = 0.07) compared to placebo.

Whether increased levels of homocysteine which are sometimes seen after weight loss have an adverse effect on FMD has not been examined.

Trials of folate supplements have failed to show a protective effect on clinical cardiovascular endpoints or mortality (Davey-Smith and Ebrahim 2005). Bonaa et al (2006) investigated homocysteine-lowering with B vitamins for secondary prevention in 3749 patients who had had an acute MI. While the mean total homocysteine level was lowered by 27 % the treatment had no effect on recurrence of CVD (Bonaa 2006). In addition a recent meta-analysis by Bleys et al (2006) showed no evidence of a protective effect of antioxidant vitamin-mineral or B vitamin supplementation on the progression of atherosclerosis or the prevention of restenosis after coronary angioplasty.

Summary

In one cross-sectional study homocysteine was independently associated with impaired FMD and one acute study showed no adverse effect of increasing homocysteine on FMD. Six out of nine studies have shown a benefit on FMD of folic acid supplements which reduced homocysteine. To date trials of folate supplements have failed to show a protective effect on clinical cardiovascular endpoints or mortality

C reactive protein

The acute phase reactant CRP has gained strength as a predictor of cardiovascular and cerebrovascular events in healthy subjects and in those with known coronary disease (Ridker 2003). CRP levels are higher in obese subjects and this link is thought to be because of increased interleukin-6 (IL6) production from adipose tissue (Clifton 2003). CRP levels are also associated with impaired endothelial function in adults and children but this was not independent of other risk factors (Vitale 2003, Kang 2002, Brevetti

2003, Suheyl Ezgu 2002). Interventions that improve insulin resistance, such as weight loss and exercise are likely to improve CRP and this has been reported frequently in the literature in recent years (Clifton 2003, Dvorakova -Lorenzova 2006, Raitakari 2004, Jae 2006). Clifton (2003) first reported on CRP changes in 403 overweight and obese subjects before and after weight loss observing a gender difference such that despite a similar BMI, CRP was higher in women than men. Following weight loss of 7 kg over 12 weeks CRP fell by 0.8 ± 5.1 mg/L. Similarly Dvorakova -Lorenzova et al (2006) found that CRP decreased 30% after weight loss as did Raitakari et al (2004) who observed a reduction in CRP of 31% after weight loss of 11 kg and Jae et al (2006) also found that 7kg weight loss following a diet and exercise program was associated with a decrease in CRP of 25%.

The effect of dietary macronutrient composition on CRP during weight loss has also been investigated (Clifton 2003, Wood 2006, O'Brien, Cardillo 2006). In the study by Clifton (2003) discussed previously weight loss was achieved on two different dietary patterns but change in CRP was related to change in weight with no difference between high or low-carbohydrate diets which supports the view that while weight loss lowers CRP, the type of diet is not influential. Likewise Wood et al (2006) observed a reduction in CRP of 8% in a study in 29 men consuming an ad libitum carbohydrate restricted diet (13% energy). O'Brien et al (2005) compared a low-fat diet with a very low-carbohydrate diet during weight loss and observed a decrease in CRP with no diet effect. Koren et al (2006) also found that CRP was not reduced by isocaloric dietary fat reduction without weight loss in overweight subjects and 3 months of ad libitum low-fat diet resulted in a 4 kg weight loss and decrease in CRP.

CRP reductions persist with weight loss maintenance suggesting long term benefits of relatively small amounts of weight loss although this is not always the case (Brinkworth

2004 a, b, Cardillo 2006, Li 2005). Brinkworth et al (2004a) followed 43 subjects for 68 weeks after which time they had lost 3.5kg and maintained reduced CRP levels. This phenomenon was also observed in subjects with type 2 with a continuing reduction in CRP after 64 weeks with maintenance of ~3kg weight loss (Brinkworth 2004b). Li et al (2005) observed a reduction in CRP of 25% with a relatively small amount of weight loss, 5%, achieved with a meal replacement strategy after 12 months which was not seen in the control group who lost 2% of their initial weight. In contrast Cardillo et al (2000) found that weight loss of 4 kg after 3 years was not associated with a reduction in CRP however the subjects in the study remained very overweight at approximately 130 kg. Shechter et al (2006) observed a reduction in CRP of 44% in a group treated with the weight loss drug sibutramine in whom weight loss was 11% compared with 2% in the control group.

Summary

It has been established that CRP is raised in obesity, that weight loss is effective at reducing CRP, that this reduction is sustained with long term maintenance of small amounts of weight loss and that macronutrient composition is not influential.

Cellular adhesion molecules

Endothelial function can also be assessed by circulating levels of cellular adhesion molecules (CAMs) which are intrinsic membrane proteins that are shed into the circulation. The cellular adhesion molecules are important for capturing white cells, particularly monocytes, as part of the inflammatory response in arteries. CAMs include intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E and P selectin and are thought to be involved in the pathogenesis of atherosclerosis (Hope and Meredith 2003a). Adhesion molecules are found mainly on the endothelium but ICAM-1 and VCAM-1 have also been found in intimal smooth

muscle cells in atherosclerotic lesions (Hope and Meredith 2003a). Adhesion molecules are shed from the cell surface and found in soluble form in the plasma where their levels can be measured as a surrogate for direct assessment of endothelial function. However the relationship between plasma levels and cell surface activity is unclear (Ridker 2001). Mice deficient in CAMs develop fewer atherosclerotic lesions than wild-type mice, and the administration to mice of antibodies directed against CAMs decreases the vascular inflammatory response seen after vessel-wall injury (Ridker 2001). It has been shown that P-selectin-deficient mice on an atherogenic diet formed significantly smaller fatty streaks than P-selectin-positive mice (Johnson 1997).

In humans the reported associations between levels of ICAM-1, VCAM-1, E and P-selectin and coronary risk factors have been examined in a number of cross-sectional studies (Hwang 1997, Hajilooi 2004, Demerath 2001). In these studies ICAM-1 and E-selectin were higher in patients with CAD and were independently associated with CAD (Hwang 1997, Hajilooi 2004). Demerath et al (2001) found significant independent associations between ICAM-1, VCAM-1, E and P selectin and risk factors for CAD such as smoking, waist-hip ratio, blood pressure, HDL-C and TC. Prospective studies have also found relationships between CAMs and cardiovascular disease risk (Blankenberg 2001, Ridker 2001, Ridker 1998, Luc 2003, Shai 2006). In these studies the relative risk of cardiovascular events ranged from 2.2 times higher in the highest quartile of P-selectin compared with those in the lowest quartile after controlling for other risk factors to 1.9 for ICAM-1 and 1.34 for sVCAM-1, (Ridker 2001, Luc 2003, Ridker 1998, Shai 2006). In contrast Malik et al (2001) found no significant relationships with ICAM-1, VCAM-1, E-, and P-selectin in a prospective study of men who developed CAD (Malik 2001). A meta-analysis of 5 studies by the same authors supported these observations (Malik 2001). Meigs et al (2004) has shown that levels of

E-selectin, ICAM-1, and VCAM-1, independently predicted type 2 diabetes in the Nurses' Health Study. The adjusted relative risks for diabetes in the top quintile compared with the bottom quintile were 5.43 for E-selectin and 3.56 for ICAM-1. High levels of sICAM-1 and sVCAM-1 have also been associated with impaired FMD in subjects with hypertriglyceridemia which in itself is an independent risk factor for death from CVD (Lupattelli 2000, Czernichow 2006).

Obesity is independently associated with increased levels of cellular adhesion molecules in adults (Mora 2006, Miller 2006). A similar association was also seen in obese children compared with controls however this was not independent of other risk factors obesity (Meyer 2006, Glowinska 2005). Weight loss of 7 – 18% following either lifestyle programs or bariatric surgery, has been shown to reduce the cellular adhesion molecules for ICAM-1 VCAM-1 and E-selectin by 15 - 28%, 15%, 20% - 35% respectively (Ito 2002, Ferri 1999, Pontiroli 2004, Vazquez 2005). After weight loss of 24 kg Vazquez and colleagues (2005) observed that E & P selectin, improved after weight loss, but ICAM-1 levels did not change and VCAM rose, PAI-1 and CRP fell but TNFα and IL6 did not change (Vazquez et al 2005).

There are a small number of studies exploring the effect of dietary composition on CAMs (Bemelmans 2002, Lewis 1999). Bemelmans et al (2002) found a reduction in saturated fat intake over 2 years in a dietary intervention study was associated with reduced levels of sICAM-1 whereas Lewis et al (1999) found there was no significant difference in sICAM-1 or sVCAM-1 concentrations between the SFA diet and the Mediterranean diet over 28 days in hypercholesterolemic men (Bemelmans 2002, Lewis 1999).

Summary

Increased levels of cellular molecules are seen in obesity and are associated with increased risk for cardiovascular disease. Weight loss in four out of four studies has been shown to decrease levels of these molecules but the effect of dietary composition is largely unexplored.

Plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA)

Plasminogen, a plasma glycoprotein synthesized mainly in the liver, endothelial cells and thrombocytes, is the inactive precursor of plasmin which is a potent protease required for the dissolution of fibrin blood clots. Tissue-type plasminogen activator (t-PA) is required for the dissolution of fibrin in the circulation (Lijnen 1995). t- PA and plasminogen activator inhibitor (PAI) are secreted by endothelial cells and provide anticoagulant and procoagulant regulatory mechanisms respectively (Lijnen 1997). PAI-1 is the most important inhibitor of plasma fibrinolytic activity (Skurk 2004). Studies in human adipocytes indicate that PAI-1 synthesis is upregulated by insulin and by cytokines such as TNFα, metformin and the thiazolidinediones which reduce insulin resistance, reduce adipose expression and circulating levels of PAI-1 (Skurk 2004, Kruszynska 2000, Dolezalova 2006). High PAI-1 levels have been reported in obesity (Sasaki 2001) and subjects with DM and CAD (Davi 1991), and the metabolic syndrome .

PAI-1 is expressed in adipose tissue and visceral adipose tissue has a higher capacity to produce PAI-1 than subcutaneous adipose tissue (Skurk 2004). Visceral fat has been shown to correlate with PAI-1 in obese diabetic and non-diabetic adults and in obese children (Mertens 2001, Kockx 1999, Giltay 1998, Ferguson 1998, Natali 2006).

In cross-sectional studies levels of PAI-1 and tPA antigen have been found to be higher in subjects with glucose intolerance compared with subjects with normal glucose

tolerance (Meigs 2000) and tPA and PAI-1 activity have been shown to be associated with BMI and serum TG levels and SBP (Eliasson 1994a, b, Farhan 2006, Sundell 1989, Urano 1993). In a prospective study of 2,924 subjects in the Framingham Offspring Study the relative risk of DM was increased with increasing levels of PAI-1 and that this effect remained after further adjustment for other diabetes risk factors (Meigs 2006).

In a cross-sectional study of 50 mildly hypertensive patients and 10 age matched controls Tomiyama et al (1998) found that compared to controls tPA activity & antigen was increased in hypertensives and endothelial function was negatively correlated with tPA activity & antigen. Anti hypertensive treatment improved insulin sensitivity and reduced PAI-1 activity by ~ 20% however tPA activity also fell by ~ 40% & antigen levels by ~8% so the net effect on these markers is not clear.

Weight loss in children and adults has been shown to lower PAI-1 levels (Kockx 1999, Sudi 2001, Lindahl 1999, Charles 1998, Sylvan 1992, Svendsen 1996, Mavri 2001,). The beneficial effect of weight loss was not sustained after 6 months in the study by Svendsen et al (1996) however whether weight was completely regained was not reported.

Summary

PAI-I levels are associated with BMI, visceral fat, insulin resistance, triglycerides and on multiple regression is most closely associated with insulin resistance and visceral fat and weight loss lowers PAI-1.

Adiponectin

Adiponectin is an adipocyte specific secretory protein implicated as a mediator of systemic insulin sensitivity with liver and muscle as target organs (Pajvani 2003a). It inhibits liver gluconeogenesis and promotes fatty acid oxidation in skeletal muscle and

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also counteracts the pro-inflammatory effects of TNF-α on the arterial wall and may protect against the development of arteriosclerosis (Bastard 2006). Increasing adiponectin levels in apoE-deficient mice inhibited atherosclerotic lesion formation by 30% (Okamoto 2002).

It is found as two forms in serum, a lower molecular weight trimer-dimer and a high molecular weight complex. Female mice have higher levels of the high molecular weight complex than males and levels are significantly reduced in response to infused insulin (Pajvani 2003). This gender difference has also been observed in human subjects however it may be disrupted in women with diabetes (Cnop 2003, Ryan 2003a, Yamamoto 2002, Putz 2004, Laughlin 2006, Matsubara 2002a). A number of cross-sectional studies ranging in number of subjects from 73 to 967, in subjects with and without DM have reported correlations between adiponectin concentrations and insulin sensitivity, glucose utilisation and HDL-C and negative correlations with BMI, percent body fat, subcutaneous and intra-abdominal fat, SBP, DBP, lipids, glucose and insulin levels (Yamamoto 2002, Cnop 2003, Ryan 2003a, Matsubara 2002b, 2003, Inoue 2005, Vendrell 2004, Im 2006). In a prospective study Lara-Castro et al (2006) found similar associations and that the quantity of high molecular weight adiponectin rather than total adiponectin that seems to be responsible for these relationships.

In a recent study of young obesity-discordant and concordant twins Pietilainen et al (2006) found that while the heavier co-twins of the discordant pairs had significantly lower whole body insulin sensitivity than the leaner co-twins blood flow in response to Ach was not altered by obesity. However the duration of obesity may be a determinant of endothelial dysfunction and the mean duration of overweight was only 6.5 years in the heavier co-twins. Adiponectin was 20% lower and intra-abdominal fat volume was 95% greater in the heavier co-twin. Intra-pair differences in serum adiponectin were

positively correlated with intra-pair differences in blood flows during Ach and intrapair difference in serum CRP was inversely correlated with differences in blood flow during ACh infusion. These data suggest that low adiponectin and high CRP, together with large amounts of intra-abdominal fat mass, may be associated with early signs of endothelial dysfunction.

It has been suggested that adiponectin is related to endothelial function (Buras 2005) but the increase in adiponectin levels of 75% seen after troglitazone treatment was not correlated with an improvement in the endothelium-dependent vasodilation. This is in contrast to the findings of Caballero et al (2003) who observed an improvement in FMD following treatment with troglitazone.

Hypoadiponectinemia has also been shown to be associated with hypertension (Iwashima 2004, Della Mea 2005, Patel 2007). It has been speculated that hypoadiponectinemia may underline the mechanisms conferring increased vascular risk in hypertension, as adiponectin *per se* may have direct antiatherogenic effects (Patel 2007). Iwashima et al (2004) found that adiponectin was lower in hypertensives compared to normotensives adjusted for age, BMI and TC and BP was inversely associated with adiponectin concentration in normotensives regardless of insulin resistance (Iwashima 2004). Della Mea et al (2005) also found that adiponectin was lower and insulin higher in subjects with more severe hypertension i.e. persistently elevated blood pressure over 24 hrs (nondippers).

Despite the proposed relationships between adiponectin levels and cardiovascular disease risk factors, adiponectin has not been reported as having a protective effect on cardiovascular disease risk in several case control studies (Pilz 2006, Menon 2006, Lawlor 2005, Sattar 2002, Laughlin 2007).

Pilz et al (2006) report that high adiponectin levels independently predicts all-cause, cardiovascular, and noncardiovascular mortality in individuals with coronary artery disease in a large study (n=2473) followed for > 5years. There were 427 deaths in this period and an increase of 1 sd in adiponectin was associated with fully adjusted hazard ratios for all cause mortality of 1.22 and for death from cardiovascular causes of 1.23. Menon et al (2006) report a similar finding in a study in patients with chronic kidney disease in which a 1μg/ml increase in adiponectin was associated with a 3% increased risk for all-cause and 6% increased risk for CVD mortality.

Lawlor et al (2005) report that adiponectin did not predict CAD events in adjusted analyses in a prospective case (n = 167) control (n = 334) study. The relative risk ratio for a doubling of adiponectin was 0.93 (95% confidence interval, 0.78, 1.11).

Likewise Lindsay et al (2005) also in a case control study (n=251 cases and controls) report that baseline adiponectin concentrations were similar in cases and controls and showed no significant association with development of coronary heart disease after additional adjustment for other covariates (odds ratio 0.91) or in subgroups of those with (0.92) or without diabetes (0.82).

Sattar et al (2006) also in a case control study of 589 men with fatal coronary heart disease or nonfatal myocardial infarction and 1231 controls found that no significant difference between median adiponectin levels at baseline was observed between cases and controls (10.2 versus 10.8 μg/mL; P = 0.5), despite the fact that BMI, HDL-Cand CRP were all significant predictors of events. The odds ratio for CAD was 0.89 (95% CI, 0.67 to 1.18 comparing men in the top third of adiponectin concentrations with those in the bottom third. The authors report that these results were similar to a meta-analysis they conducted of 7 studies which included this study, of 1318 CAD cases in which the odds ratio was 0.84 (95% CI, 0.70 to 1.01).

Laughlin et al (2006) reporting on a 20 year prospective analyses, report that adiponectin levels in the highest sex-specific quintile, as compared with lower levels, were independently associated with almost 40% increased risks of CVD disease death (n = 441) and death from all causes (n = 925).

Cavusoglu et al (2006) also observed that a higher adiponectin independently predicted all-cause mortality, cardiac mortality, and MI and that the 24-month survival rates for patients in the lower, middle, and upper tertiles of plasma adiponectin values were 95.0, 90.4, and 83.5%, respectively.

To date only one study by Pischonet al (2004) has reported a protective effect of adiponectin. In a case-control study of 266 men with nonfatal MI and 532 controls, those in the highest compared with the lowest quintile of adiponectin levels had a significantly decreased risk of MI (RR, 0.41) after adjustment for family history of MI, BMI, alcohol consumption, physical activity and history of DM and hypertension. Adjustment for LDL-C and HDL-C levels attenuated this protection (RR, 0.56).

Summary

To date the body of evidence does not support the assertion that adiponectin protects against heart disease.

Weight loss and adiponectin

There have been four weight loss studies that have observed an increase in adiponectin Baratta 2004, Vendrell 2004, Raitakari 2004, Balagopal 2005 and four observing no change Dvorakova -Lorenzova 2006, Ryan 2003b, Spranger 2004.

In the positive studies Baratta et al (2004) measured adiponectin before and after bariatric surgery for obesity in 95 patients. Weight loss was 19kg (16.8%) after 6-12 months and adiponectin increased by 3.1μg/ml (22%) (Baratta 2004). Similarly Vendrell et al (2004) measured adiponectin in 34 morbidly obese patients before and 6

months after gastric bypass surgery. Weight loss was 38.5kg, adiponectin doubled and insulin resistance improved which correlated with increased adiponectin (Vendrell 2004). Raitakari et al (2004) used a very low calorie diet (580 kcal or 2.3 MJ/day) to achieve weight loss of 11 kg (-12%) in six weeks and adiponectin increased by 26%. Balagopal et al (2005) found that a three month lifestyle intervention with exercise and general diet advice produced a 34% increase from 4.44 to 5.95 μg/litre in adiponectin concentration with no weight loss but with reductions in fat mass from 45.5 to 39 kg and increases in lean mass from 51.9 to 58.3 kg in 16 yr old adolescents. These increases in lean mass seem very large considering that the exercise intervention was only 45mins, 3 times per week for only 3 months.

In the negative studies Dvorakova -Lorenzova et al (2006) achieved weight loss of 7kg, (8%) after 9 weeks on diet and aerobic exercise but adiponectin did not change. Ryan et al 2003 conducted a weight loss study in 3 different groups, weight loss (n=15), weight loss and aerobic exercise (n=16) and weight loss with resistance exercise (n=9) in obese women. Weight loss was 6 kg, (7%) after 6 months, with no differences between groups and adiponectin did not change. Cardillo et al (2006), in a 36 month weight loss study of 132 obese adults randomised to either a low carbohydrate diet or a low fat energy restricted diet observed weight loss of 4 kg which was the same in both group. Despite sustained weight loss adiponectin and CRP did not improve and insulin was higher at 36 months (Cardillo 2006).

There are few studies of the effect on adiponectin of diet composition and they are cross-sectional observational studies rather than intervention studies (Pischon 2005, Qi 2005). Both studies reported that adiponectin was independently inversely related to glycemic load. Pischon et al (2005) also found a positive association between plasma

adiponectin concentrations and alcohol intake while Qi et al (2005) observed that a high intake of cereal fibre was associated with increased plasma adiponectin levels.

Summary

There are four studies that observed an increase in adiponectin after weight loss and four that did not. In the studies where adiponectin increased there was a wide range of weight loss (0 – 38.5 kg over 6 weeks-12 months) including one were there no net weight loss but a reduction in fat mass of 6.5 kg and an increase in lean mass of 6 kg. The amount of weight loss in the negative studies was relatively small, 1.76 – 7kg and it may be that a larger amount of fat loss than is likely to have been achieved is needed to achieve improvements in adiponectin.

Effects of long term weight maintenance on CVD risk factors

In general weight loss studies of 3-6 months are focussed on weight loss as a primary outcome while studies of 6-12months or more focus on maintenance of the early weight loss. There are few studies of 6 months duration or more to establish whether weight loss is preferentially maintained on higher protein diets (Lejeune 2005, Brinkworth 2004a, Stern 2004, Due 2004 Foster 2003). Lejeune et al (2005) showed improved weight maintenance when protein was 18% of energy compared to 15% in a 6 month study. However Due et al (2004) observed that while weight loss was greater after 6 months on a higher protein diet compared to a conventional low fat diet at six months this difference was not sustained at 12 months. The high protein group had a greater abdominal fat loss suggesting a long-term metabolic advantage of the diet. In a study of weight maintenance from our group of either a high protein or high carbohydrate diet fat loss of ~3kg was maintained as were improvements in CVD risk factors without any effect of diet (Brinkworth 2004). Foster (2003) reported greater weight loss at 6 months in subjects on a very low carbohydrate, high protein, high fat diet but there was no

difference at 12 months. Stern (2004) also found that weight loss at 1 year was not different in subjects advised to follow a low carbohydrate (<30g/day) compared to a conventional diet. There were differential effects such that triglycerides decreased more and HDL-C decreased less on the low carbohydrate diet, suggesting there may be some long term metabolic benefits of this dietary pattern. It is thought that a high fat intake *per se* will promote weight gain and low fat weight loss diets are the recommended option (Astrup 2000). However a high MUFA diet is recommended for people with metabolic syndrome and diabetes in order to avoid the TG increasing and HDL-C lowering effects of low fat diets (Garg 1998). Despite this to our knowledge there are few if any studies of the long term effect of a reduced carbohydrate, high MUFA diet.

Scope of the studies in the thesis
The effect on FMD of dietary composition in both weight stability and during weight loss needs to be clarified further and whether weight loss has a beneficial effect on FMD also requires elucidation and several of the studies in this thesis will attempt to do this. The studies in this thesis will help address some of the gaps and inconsistencies in the literature. Three studies will focus on weight loss *per se* as well as on the effect of dietary composition during weight loss thus helping to clarify the inconsistencies in the literature regarding weight loss and FMD. The effect of saturated fat will be examined in two chronic studies with and without weight loss in an attempt to clarify the role of saturated fat in endothelial dysfunction. The potential deleterious effect on FMD of HDL-C reduction will be examined both in weight loss and weight stability in order to help clarify the effect of HDL-C reduction of a low fat diet.

The effect of weight loss on the blood pressure response to a high salt diet and the long term effects of weight loss will be investigated.

The effects of weight loss and dietary composition on adiponectin, cellular adhesion molecules PAI-1 and tissue plasminogen activator will be explored further.

Hypotheses

The focus of the studies in this thesis is to investigate the effect of dietary composition and weight loss on both novel and traditional markers of risk of CVD.

The specific hypotheses are that

1. A diet which lowers HDL-C and increases TG (such as a high carbohydrate diet) will impair FMD compared with diets that do not induce these lipid changes

2. A high saturated fat diet will impair FMD compared with diets high in MUFA and PUFA fat

3. Weight loss will improve endothelial dysfunction

4. A low carbohydrate/low saturated fat weight loss diet will be associated with improvements in FMD and endothelial markers after short and long term weight loss compared with a high carbohydrate diet

5. A very low carbohydrate high saturated fat during weight loss diet will to impair endothelial function

6. The increase in BP in response to salt loading will be attenuated by weight loss

7. Sustained weight loss will result in reduction in CVD risk factors and that a higher protein intake will be associated with reduced blood pressure

Chapter 2

Common Methodology

The methodologies described in this chapter are common to the studies presented in Chapters 3 to 8. If a method was used in one chapter only this is indicated or if different methods of measurement of a particular variable were used in different studies this is also indicated.

Ethics approval

All protocols were approved by the Human Research Ethics Committee of the CSIRO and written informed consent was obtained from all volunteers.

Assessment of vascular function

FMD

In Chapters 3 to 6 subjects underwent assessment of endothelium-dependent FMD of the right brachial artery, as described by Celermajer et al (1992). Subjects were kept quiet for 5 minutes before FMD measurements which were taken in the morning after an overnight fast. Measurements were taken using a 7.5 MHZ linear array transducer of an Accuson Aspen Duplex ultrasound machine (Mountain View, CA USA). Subjects lay supine with their right arm extended at 90º. The examiner held the ultrasound transducer on the distal third of the upper arm to locate a clear, longitudinal 2 dimensional image of the brachial artery. A clamp was used to fix the ultrasound transducer in place, after which 3 baseline images were recorded. A blood pressure cuff was then placed around the subjects' forearm approximately 2 cm distal to the olecranon and inflated to 200 mmHg for 5 minutes. Following cuff release, ultrasound examination continued for the next 3 minutes with images recorded at 15 second intervals. After 5 minutes rest allowing the artery diameter to return to baseline, 3 images were recorded. Exclusion criteria in the studies were the use of long acting

nitrates, sildenafil, or tadalafil, a previous adverse reaction to GTN, unstable blood pressure and frequent syncope.

FID

GTN, a nitric oxide donor and was used to achieve endothelium independent dilation. A 300μg GTN tablet was administered under the tongue after the 5 minutes rest period. Images were recorded 30 seconds before administration of GTN and then recorded for 4 minutes at 15 second intervals.

Anterior to posterior medial diameters were measured off-line for all images, at end-diastole as deduced by the ECG.

Endothelium dependent and independent dilatations were expressed as percentage change relative to the average baseline diameter. The coefficient of variation (CV) for this technique with different operators was 10% (n = 6) chapter 3, 15% (n = 6), chapter 4, 8.4% (n = 6) chapter 5, and 8% (n=6) chapter 6.

PWV

Using a Doppler probe (Accuson Aspen Duplex, Mountain View, CA, USA.) aortic PWV was measured via recordings of arterial sound waves produced at the carotid and femoral arteries. Approximately 10 consecutive beats were recorded. A simultaneous ECG recording was used to calculate the time between the R-wave and the upstroke of each sound wave. The difference between the average pulse time delays for the arteries was calculated. PWV was then determined by dividing the measured distance between carotid and femoral arteries (using a tape measure, meters), by pulse time. The baseline measurement of arterial length was used throughout.

AI

Vascular measurements were performed as previously described by van Trijp et al (2005) using the SphygmoCor™ blood pressure analysis system (AtCor Medical, Sydney, Australia). The pressure waveforms obtained by aplanation tonometry on the radial artery were calibrated with a peripheral BP value of the brachial artery. Subsequently, the radial pressure waveforms were transformed into a single calibrated waveform. Ascending aortic pressure was derived from the central pressure waveform, using a generalized transfer function that is incorporated in the SphygmoCor device (Chen 1997). Finally, AI (the difference between early and late pressure peaks divided by pulse pressure) was calculated and expressed as a percentage.

The coefficient of variation for this technique was 16.8%, measured in 6 people on 3 separate occasions.

Different operators who were blinded to the study treatments performed FMD, PWV and AI.

BP

Resting blood pressure (mean of 3 measurements) was measured by automated oscillometry (Dinamap™, 845XT/XT-IEC, Tampa, Florida) with subjects in a seated position for 5 minutes before blood pressure measurement.

24 hr ambulatory BP

Ambulatory blood pressures were measured with ambulatory BP devices (Meditech Ltd. Budapest, Hungary). The measurement interval was set at 30 minutes while the subject was awake and 60 minutes while asleep. Subjects were educated on how to use the BP monitor by a registered nurse.

Body weight and height

Fasting body weight was measured to the nearest 0.05 kg using calibrated electronic digital scales (Mercury digital scales, model AMZ14, Japan) in light clothing without shoes at baseline and every 2 weeks during weight loss and monthly during follow-up. Height was measured to the nearest 0.1 cm using a stadiometer (Seca, Germany) at baseline with participants barefoot in the free-standing position.

Body mass index (BMI) was calculated by weight (kg)/height (m^2).

Waist circumference

Waist circumference (cm) was recorded as the smallest measurement (mean of three) between the iliac crest and the lateral costal margin.

Body composition measurements

Dual-energy X-ray absorptiometry (DEXA)

In Chapter 6 body composition was assessed using Dual Energy X-ray Absorptiometry (DEXA), General Electric, Lunar Prodigy, Madison, WI, USA). The errors for DEXA assessments of body composition performed in 11 overweight/obese subjects not involved in this study on consecutive days were 0.87% for %body fat, 0.53 kg (1.6%) for fat-mass, 1.05 kg (2.3%) for lean mass, and 0.02 g/cm^2 (1.3%) for bone mineral density.

In Chapter 8 body composition (total fat mass and total lean mass) was assessed by DEXA (Norland densitometer XR36; Norland Medical Systems, Fort Atkinson, Wisconsin, USA; CV of 2.3 ± 0.7% for total body fat mass and 2.1 ± 0.4% for lean mass.

Bioelectrical Impedance Analysis (BIA)

In chapter 7 total fat mass (TFM) and total fat-free mass (TFFM) and percent body fat were measured by using bioelectrical impedance analysis (Bioimpedance meter IMP5; Impedimed Pty Ltd, Mansfield, Brisbane, Australia); CV of 1.2 ± 1.2% for TFFM and 1.9±3.54% for TFM..

Laboratory Analysis

Fasting blood samples were collected into tubes without additive for lipids, apolipoprotein B (ApoB), insulin, hsCRP, adiponectin and adhesion molecules, sodium fluoride/EDTA for glucose, homocysteine, folate and ketone body measurements or tubes containing 0.11 M sodium citrate with theophylline, adenosine and dipyridamole (CTAD) a platelet activator inhibitor in 300μl of solution for PAI-1 and tPA (CTAD was added to the tubes by the manufacturers).

Plasma or serum was isolated by centrifugation at 2,500 rpm at 4ºC for 10 minutes at 5ºC (Beckman GS-6R centrifuge, Beckman, Irvine, CA). Aliquots were frozen at -80 ºC until analysis.

Biochemical assays were performed in one run at the completion of the studies.

Lipids

In Chapter 4 and 8 serum TC and TG concentrations were measured using a Cobas-Bio centrifugal analyser (Roche Diagnostica, Basel, Switzerland) using commercially available enzymatic kits (Hoffmann-La Roche Diagnostica, Basel, Switzerland) and control sera. Roche immunoturbidimetric assay kits were used for measurement of ApoB and Hs-CRP concentrations (Roche Diagnostics Co, Indianapolis, IN).

In chapter 4 serum HDL-C concentrations were measured after precipitation of LDL-C and VLDL-C with polyethylene glycol 6000 solution.

In Chapters 3, 5 and 6 serum lipids, hs-CRP, ApoB and glucose concentrations were measured on a BM/Hitachi 902 Automatic Analyser using standard Roche enzymatic kits for lipids and glucose and a Roche immunoturbidimetric assay kit for ApoB (Roche Diagnostics Co, Indianapolis, IN).

LDL-C concentrations were calculated using a modified Friedwald equation [(TC-HDL-C) – (TG x 0.45)] (Friedwald 1972).

Glucose, insulin and ketone bodies

Plasma glucose concentrations were measured using either a Cobas-Bio centrifugal analyser (Roche Diagnostica, Basel, Switzerland) (Chapters 4 and 8) or a BM/Hitachi 902 Automatic Analyser (Chapters 3, 5 and 6) using commercially available enzymatic kits (Hoffmann-La Roche Diagnostica, Basel, Switzerland) and control sera.

Serum insulin was determined using either a radioimmunoassay kit (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) (Chapter 4) or enzyme linked immunosorbent assay (ELISA) kit (Mercodia Insulin ELISA Cat# 10-1113-10, Mercodia AB, Sylveniusgatan 8A, SE-754 50 Uppsala, Sweden) (Chapters 3, 5 and 6).

Plasma ketone levels were analysed using a RANBUT D-3-Hydroxybutyrate kit (RANDOX Laboratories Ltd., Co. Antrim, United Kingdom).

Plasma homocysteine and folate

Plasma homocysteine concentrations were measured by Fluorescence Polarization Immunoassay (FPIA) (AxSYM Abbott Ireland Diagnostics Division, Co. Longford

Ireland) by a certified commercial laboratory (Institute of Medical and Veterinary Science (IMVS), Adelaide, Australia).

Plasma folate concentrations were measured by IMVS by Chemiluminescent Microparticle Immunoassay (CMIA) (ARCHITECT® Abbott Ireland Diagnostics Division Co. Longford Ireland) by IMVS.

t-Pa and PAI-1, sVCAM1, ICAM1, CRP and IL6

In chapter 4 the following tests were performed by ELISA: Coaliza® t-Pa and PAI-1 (Chromogenix, Sweden), sVCAM1, and ICAM1 (Immunokontact); CRP (Alpha Diagnostic International, Texas) and IL6 (Sapphire Bioscience, Sydney, Australia)

In chapter 5 concentrations of sICAM-1, sVCAM-1, E - P-selectin and adiponectin were determined by an ELISA (ImmunoKontact, Wiesbaden, Germany,

In Chapter 6 E-selectin, P-selectin and I-CAM were measured in serum (diluted 1:50) using the Fluorokine multianalyte profiling human adhesion molecule panel (R&D systems, Minneapolis, MN). The mean intra- and inter-assay CVs were 4% and 6% for E-selectin, 4% and 8% for P-selectin and 5% and 6% I-CAM-1 respectively.

Serum concentrations of adiponectin and PAI-1 (diluted 1:60) were analysed using the human Fluorokine multianalyte profiling human obesity panel (R&D systems, Minneapolis, MN), according to manufacturer's instructions. The mean intra- and inter-assay CVs were 4% and 6% for adiponectin and 5% and 4% for PAI-1. Multianalyte profiling was performed on the Luminex-200 system and fluorescence data were analysed by the Liquichip analyser (Ver. 1.0.5; Qiagen, Australia).

VCAM-1 was measured in serum (diluted 1:20) by ELISA (R&D systems, Minneapolis, MN). The mean intra- and inter-assay CVs were 7% and 3% respectively.

Renin and aldosterone

Plasma renin concentration was measured by the Nichols Advantage direct renin assay (Nichols Institute Diagnostics, San Clemente, CA).

Plasma aldosterone was measured by the Nichols Advantage aldosterone assay (Nichols Institute Diagnostics, San Clemente, CA).

Urinalysis

In chapters 4 -6 and 8, 24-hour urine samples were collected for urea, creatinine and sodium excretion and also for potassium excretion in chapter 7. Urine was collected in 4L bottles without preservatives. Collections started after the first voiding of urine on the morning of the collection and included the first voiding of urine on the second day. Volunteers noted the time the collection started and finished on the urine bottle. The urine volume was recorded and aliquots were frozen until analysis. Urea concentration was measured on a Boeringer Mannheim Hitachi 902 automatic analyser. Sodium and creatinine were measured using by IMVS a certified commercial laboratory.

Food frequency questionnaire

Usual dietary intake was assessed at baseline in chapter 5 & 6 using the Anti Cancer Council of Victoria Food Frequency Questionnaire (ACCV FFQ) (Hodge 2000).

Weighed food records

Three day weighed food records (consecutive days, one weekend and 2 weekdays) were analysed from food records kept by the volunteers weekly in chapters 3 and 7 (during the salt protocol), monthly in chapter 4 and every 3 months in chapter 8.

Subjects were shown how to undertake the weighed food records in a standardized manner by a research dietitian and to record the food items eaten with as much description as possible in the booklet provided. Weighing scales were provided for this purpose.

In chapters 5 - 7 volunteers completed daily structured checklists of all foods eaten. Each checklist contained a sample plan of the prescribed diet with either weights or household measures of the food to be included in the diet. Subjects were shown how complete these checklists by a research dietitian and three consecutive days (one weekend and 2 weekdays) were analysed in each 2-week period

Dietary analysis

Food records were analysed using either Diet/1 Version 4.2 dietary analysis software, (Xyris software, Highgate Hill, Australia) (chapters 3 and 8) or FoodWorks Professional Edition, versions 3.1 (chapters 4, 5 and 7) or 4.0 software (chapter 6) (Xyris Software, Highgate Hill, Australia) computerized dietary analysis packages based on a database of Australian foods (NUTTAB Food Standards Australia end New Zealand, Canberra, Australia).

Diet data entry was completed by a qualified dietitian while the volunteer was present to help ensure accuracy and completeness of the data

Measures of compliance

Compliance sheets of the prescribed test foods were completed daily in chapter 3 to aid compliance.

During the salt intervention in Chapter 7 sufficient salt tablets for 1 week at a time were issued in bottles and volunteers returned the bottles and any unused tablets were counted.

24 hr urine collections for urea/creatinine ratio to assess protein intake (Chapter 5, 6 and 8) and sodium and potassium excretion (Chapter 7) were used to assess compliance to the dietary protocol.

Chapter 3 The effect of a high saturated fat diet compared with a high monounsaturated fat, high polyunsaturated fat or a high carbohydrate diet on flow-mediated dilatation

Chapter 4 The effect of weight loss on inflammatory and endothelial markers and flow mediated dilatation and pulse wave velocity using two low fat diets

Chapter 5 Effects of weight loss on a low carbohydrate/low saturated fat diet on flow mediated dilatation, adhesion molecules, adiponectin, augmentation index, blood pressure and pulse wave velocity following short-term weight loss and long-term follow-up

Keogh, J.B., Brinkworth, G.D. and Clifton, P.M. (2007) Effects of weight loss on a low carbohydrate diet on flow-mediated dilatation, endothelial markers and adiponectin.
British Journal of Nutrition, v. 98 (4) pp. 852-859, September 2007

Chapter 6: Effect of a very low carbohydrate/high saturated fat diet during weight loss on flow mediated dilatation, augmentation index, blood pressure, adiponectin and adhesion molecules

Chapter 7 Effects of weight loss on augmentation index and the blood pressure response to salt in adults

Chapter 8 Effects of long term weight maintenance on cardiovascular risk factors

Published as

Chapter 9

Discussion

The main findings of the studies were

1. Under weight stable conditions a diet high in saturated fat impaired FMD by 50% but a low fat diet did not impair FMD despite increases in TG levels and decreases in HDL-C.

2. Moderate weight loss (6.3±3.7 kg) did not change FMD but resulted in significant improvements in the cardiovascular risk markers PAI-1, sICAM1 and PWV.

3. A low carbohydrate/low saturated fat weight loss diet did not improve FMD after either short or long term weight loss but the adhesion molecules VCAM1 fell by 14% and ICAM1 by 13% (both P<0.05) after short term weight loss and ICAM remained reduced after 52 weeks.

4. Weight loss on a very low carbohydrate /high saturated fat diet was greater than on a high carbohydrate diet but FMD did not change after weight loss on either diet. PWV was 11% slower after weight loss. CRP was reduced with weight loss but with a significantly smaller reduction on the low carbohydrate diet. E and P-selectin, (ICAM-1), PAI-1 and tPA levels all decreased after weight loss with no effect of diet. LDL-C reduction was less on the low carbohydrate/high saturated fat diet

5. Weight loss (8.5 ± 0.8 kg) did not alter the elevation in BP (6/3 mmHg) in response to salt loading at 12 or 52 weeks after weight loss. Plasma aldosterone and renin levels fell with weight loss.

6. Long term weight loss maintenance was associated improvement in CVD risk factors i.e. reductions in insulin, TG and CRP levels and increased HDL-C level.

Discussion

The focus of the studies in this thesis was to investigate the effect of dietary

composition and weight loss on both traditional and novel markers, particularly those

related to vascular function, of risk for CVD. The studies in this thesis support the proposition that a diet high in saturated fat under weight stable conditions adversely affects endothelial function which in turn contributes to increased risk of CVD. There appeared to be no benefit of a high PUFA or MUFA diet compared with a high carbohydrate diet despite differences in HDL-C and TG. However a diet containing a large amount of saturated fat (20% of energy) during weight loss did not have an adverse effect on FMD. Modest weight loss *per se* did not improve FMD in our hands but other markers of endothelial function were improved. Weight loss did not ameliorate the BP response to a high salt intake but in the short term BP was improved by weight loss and this may be mediated by reductions in renin and aldosterone. Overall both traditional and some novel CVD risk markers were improved by weight loss.

Flow mediated dilatation

In a relatively short-term weight stable study a low fat diet which reduced HDL-C and increased TG did not have an adverse effect on FMD. It is important to establish that this dietary pattern does not have adverse effects on FMD in the longer term as a low fat diet is still the dietary pattern recommended for cardiovascular disease prevention. Therefore further studies of this dietary pattern with FMD as the main outcome measure under weight stable conditions would help clarify this question.

The lack of effect of weight loss on FMD observed in the studies in this thesis, are in accord with one other study in this area. However the absence of evidence is not necessarily evidence of absence and there have been a number of positive studies showing a benefit of weight loss on FMD but in general these have been studies with larger amounts of weight loss or weight loss plus exercise. Thus the effects of moderate weight loss alone on FMD are not yet clear. There are few studies that measure FMD

after long term weight loss maintenance and while we did not see any effect after 52 weeks very few subjects remained in the study. It would be important to conduct a long term study of the very low carbohydrate/high saturated fat diet to establish that this dietary pattern does not impair FMD in the long term.

It is possible that our studies were underpowered to detect an effect and this will be discussed in greater detail in the section discussing the FMD technique. FMD may not be the best technique for measuring small changes in endothelial function because of its variability (discussed below) and measurements of bioactive molecules produced by the endothelium may be a more reliable method of measuring changes that are potentially beneficial. Other methods of assessing vascular dilatation such as plethysmography may be more accurate.

Sodium

We observed reductions in blood pressure after short term weight loss that were not maintained after long term follow-up at 52 weeks despite continuing weight loss maintenance of 5 kg. Blood pressure remained responsive to a salt intake after both short and long term weight loss. There were also secondary findings such that a high salt intake appeared to have an adverse effect on FMD - observations that merit further investigation with the effect of a high salt intake on FMD as the primary hypothesis. It is not clear why the beneficial effects of weight loss on blood pressure are lost after weight maintenance and it remains to be determined whether a continuing high salt intake has a role to play in this. However the most important barrier to long term maintenance of a reduced salt intake is the high salt content of manufactured food in Australia and the difficulty in obtaining low salt or salt reduced staple foods.

Adiponectin

It is of interest that in two of the studies adiponectin did not rise after short term weight loss but had risen after 12 months of weight maintenance. These results suggest that the adiponectin response to weight loss does not appear to occur during negative energy balance/energy restriction and it is important to investigate adiponectin in energy balance. There also appeared to be a relationship with salt as a correlation was observed between the reduction in urinary sodium output and an increase in adiponectin. This was unexpected and warrants further investigation.

Cellular adhesion molecules, PAI-1 and tPA

Weight loss had beneficial effects on cellular adhesion molecules, PAI-1 and tPA which were maintained after long term weight loss. There was also an indication that the amount of weight loss was important and it needs to be clarified whether this is an effect of energy restriction or amount of weight lost.

Limitations of the studies in the thesis

The limitations that will be discussed are

FMD technique

AI technique

Cellular adhesion molecules

Study duration

Dietary intake methodology

Lack of control group

FMD technique

Ultra sound measurement of FMD of the brachial artery was one of the key techniques used in the studies in this thesis. First developed in 1992, it is a well established technique used for the assessment of endothelial function and thus potential

cardiovascular risk (Celermajer 1992). The non-invasive nature of the technique has lead to its widespread use but concerns have been expressed about its reproducibility (Bots 2005, Hardie 1997). CVs for the technique as high as 29% and 50% have been reported suggesting that the technique is very variable thus making it difficult to detect small changes in endothelial function (West 2004, de Roos 2003). West et al (2004) measured FMD in 18 subjects with type 2 DM on 3 occasions finding a CV for FMD of 29.7%. In 13 subjects who had FMD measurements repeated 6 times (FMD 5.60 ± 2.15%) de Roos et al (2003) reported a within-subject SD of 2.8 %, resulting in a CV of 50.3%. Based on these CVs they stated that the number of subjects needed to detect an absolute treatment difference of 2 % with a probability of 0.05 and a power of 0.80 would be 31 in a crossover design and 62 per group in a parallel design for group comparisons (de Roos 2003). There are similar numbers to those recruited in our weight stable study in which FMD was impaired by a high saturated fat diet but greater numbers than in some of the weight loss studies. The power calculations in our studies were based on a CV of the technique in our hands of 10-15%.

Similarly to the studies in the thesis Brook et al (2004) found no improvement in FMD in the brachial artery after weight loss (-6.6%) in a study with 43 subjects which had 80% power to detect a 1.5% absolute change in FMD based on a SD of 3.5%. The mean values presented in the study were not different after weight loss (3.86 +/- 3.54 ve 3.74 +/- 3.78%, p = 0.86) and there was no statistical trend to suggest that a change would be detected with a larger numbers. Other researchers have decided that a CV of 19% for FMD measurement was too variable to be reliable in clinical research studies (Hardie 1997).

If FMD of the radial artery were measured instead of in the brachial artery the numbers of subjects required to detect a treatment difference of 2% would be greater as Brook et

al (2005) has estimated this to be 118 subjects for a crossover design and 234 for a parallel design study.

The CVs of the operators in the studies in Chapters 3, 4, 5 & 6 were 15%, 10%, 8% and 8.4% (n=9) study. In each study the same operator measured FMD before and after the intervention so that there was no inter-operator variability to confound the results. However we are aware that we may have over estimated the confidence we have in the ability of the measurement to detect change as the number of individuals studied and replicates were low. Nevertheless we saw absolutely no differences in the mean values before and after treatment in the weight loss studies and no statistical trends to suggest that the negative studies were underpowered. The subject numbers in our weight loss studies are similar to or greater than the subject numbers in other studies in which FMD improved with weight loss: these are Hamdy 2003 n=24, Vazquez 2005 n =26, Williams 2005 n=6, Raitakari n=67, or did not change: Brook n=43. One weight loss study in which FMD improved had a larger sample size n=80 (Shechter 2006). Shorter term studies examining the effect of fatty acid composition on FMD generally have smaller sample sizes than those in this thesis viz Fuentes 2001 n=22, de Roos 2001 n=29, de Roos 2002 n=21, Ros 2004 n=21. Similarly acute studies of the effect of fat on FMD tend to have similar sample sizes, de Roos 2002 n=21, Cortes 2006 n=24, Nicholls 2006 n=14, West (2005) n=18, Brook et al (2001) n=32 and Vogel n=10. It is also important to acknowledge that the blood vessels being measured by this technique are very small only 3-4mm in diameter and small changes in endothelial response of e.g. 0.1 - 0.5mm, equivalent to 3-5% absolute change, are difficult to detect and that this is likely to contribute to the variability of the results reported in the literature.

Whether FMD is mechanically more difficult to measure in obese subjects has not been well documented. In key studies e.g. Celermajer et al (1992) BMI of the subjects is not

reported but it is likely that some of the controls and subjects with CAD were overweight or obese suggesting that obesity *per se* is not a limitation of the technique. Similarly Järvisalo et al (2000) in a study examining the FMD methodology in 148 middle-aged men obtained satisfactory measurements in all subjects but did not report BMI suggesting that weight was not a limiting factor of the technique. Woodman et al (2001), in their study using edge detection and wall tracking software (see below) report that their subjects had a BMI of 26.9 ± 2.8 kg/m^2, but did not discuss experiencing any difficulty with the measurement in more overweight subjects. We have not experienced more difficulty with obese compared with lean subjects.

Edge detection software

The use of edge detection and wall tracking software may make the technique more accurate and reproducible. Using this type of software Woodman et al (2001) reported CVs of 14.7 and 17.6% for FMD and response to GTN (n=24, tested twice) which is similar to the CVs of our group using the manual technique. They report though that only 8 subjects and matched controls are needed to detect an absolute change in FMD of 2.5% in a parallel study (assuming 80% power and an alpha of 0.05).

It is of concern that the FMD technique apparently conducted in the same way produces very different values leading to disagreement on what a "normal" FMD value is. In our hands we have consistently found values of approximately 5% for FMD in middle aged overweight subjects (Clifton 2005, Brinkworth 2006). Other workers have reported different values (Joseph 2002, Jensen-Urstad 2001, Oflaz 2003). Joseph et al (2002) report a value for FMD 50% higher that ours of 7.6 ± 0.7% in obese men aged 68yr describing it as impaired. Jensen-Urstad et al (2001) report FMD in a population sample, of 3.1 % of men and 2.6 % in women aged 55 yr, 40% lower that our results,

and values of 5.7% and 3.1% in 35 year olds. In contrast Oflaz et al (2003) report FMD

values of 13.3 % and 25.2 % in young (31 years) obese and lean subjects respectively.

AI

There are few dietary or weight loss intervention studies in which AI is an outcome

measure. In the present studies AI, using the same equipment, was similar to that

reported in people with diabetes (27.5±7.4%) who were of a similar age but who were

considerably thinner (BMI 24.8±4.0 kg/m^2) than our subjects (Ravikumar 2002). In

subjects without DM who were the same age and BMI (23.9±3.7 kg/m^2) AI was

19.1±8.2% suggesting that the presence of diabetes rather than weight per se was

associated with higher AI. In non diabetic subjects, AI was positively correlated with

fasting plasma glucose, whereas in diabetic subjects, only age correlated with AI. Suh et

al (2005) reported a similar AI among younger (34 yr) obese (21.9±8.8%) and age

matched lean women (19.2±10.3%), In a weight loss intervention study in the same

group of obese women Park and Shim (2005) observed no change in AI after weight

loss (-8 kg) (22.6±11.3 vs 22.9±9.1%,).

However reported values for AI vary widely. Ryan et al (2006) reported a much lower

AI of ~ 15% in lean (BMI 23.4 kg/m^2) and 17.5% in obese (BMI 32.1 – 35.4 kg/m^2),

46-50 year old subjects. These values are very different to those seen in our studies in

subjects of similar age and weight using the same methodology. AI improved to 10%

from 16% with improved insulin sensitivity. However we observed no change in AI

despite reductions in insulin levels.

Maple-Brown (2007) reported AI among 162 Indigenous Australians (60 with type 2

diabetes) and 121 European Australians (38 with diabetes) of 32±12 versus 24±2 % (P <

0.0001. These values are in a similar range to those reported in this thesis in Chapter 7

(28.6 and 28.2% LC vs HC).

We had sufficient power to detect a change if one occurred as the CV for AI in the thesis was 17% and with 95 people we had 80% power to see a 10% change, P<0.05.

Cellular adhesion molecules

Concerns have been expressed about whether plasma levels of cellular adhesion molecules are a reflection of numbers of molecules available for binding leucocytes at the endothelial cell surface (Ridker 2001, Hope and Meredith 2003). The relationship between cellular adhesion molecule protein synthesis and cell surface activity is influenced by the rate of surface shedding. Work by Rasmussen et al (2001) shows that the inhibition of HMG-CoA reductase in endothelial cells attenuates VCAM-1 expression, but increases E-selectin expression and that these effects were associated with modulation of the surface removal of E-selectin. The effects of mevastatin were reversed by mevalonate Rasmussen et al (2001). In the absence of other data we can only assume a lower plasma level of adhesion molecules implies lower expression on the endothelial surface and a healthier cell.

Study duration

The majority of studies in the thesis were of relatively short duration and while they have provided valuable information it is important to understand the long term effects of changes in dietary composition on endothelial function and risk for cardiovascular disease. Two studies followed subjects for a year and sufficient weight loss was maintained to confer continuing health benefits. Unfortunately there were high attrition rates in these studies of approximately 50% of the original participants.

Dietary intake methodology

A limitation of the studies was the reliance on 3 day weighed food records to capture dietary intake as it is well known that self-reporting leads to under-reporting of food intake and as duration increases so does the inaccuracy (Hill 2001). In chapter 6 there

was a difference in weight loss of approximately 1kg between the diet groups despite no difference in reported energy intake. The approximate energy intake difference between the groups should have been in the order of 700kJ/day to account for this weight loss difference. In the short term it is likely that it is easier to both comply with and accurately record a diet that has fewer food choices e.g. a very low carbohydrate diet than a diet with greater variety. In the long term follow-up study reported energy was ~8200 kJ for men (97kg) and 6700 kJ for women (85 kg) whereas energy requirements for weight maintenance were likely to be closer to 11,000 kJ for men and 9000 kJ for women based on their weight and an activity factor of estimated BMR X 1.4 for a sedentary lifestyle and higher than this if in positive energy balance. Biomarkers such as weight loss and lipid changes during active weight loss make the need for recording and analysis of weighed food questionable. While it is thought they may help the volunteers comply with the dietary protocol there is no evidence that this is the case. The dietary intake data in the long term study may provide some insight into the macronutrient profile of the dietary intake at the end of the study and whether dietary intake retains any of the features of the originally prescribed diet which would be important if a potentially detrimental diet had been used e.g. a high saturated fat diet. We have some evidence that subjects reporting a higher protein intake also report higher energy intakes and it may be that this dietary pattern may be easier to record accurately. However a food frequency questionnaire which is less invasive may be as informative.

Lack of control groups
A limitation of the weight loss studies is the lack of a control group. While it would have added strength to the studies to be able to assess the effect of time alone, especially on FMD but it is difficult to recruit volunteers to a weight loss study and then

randomise them to a control group as their intention to lose weight is likely to influence their behaviour despite being allocated to no intervention.

Future directions and conclusion

Longer term studies are needed to clarify the effects of a low carbohydrate/high saturated fat diet during weight loss on endothelial function and also to clarify the effects of sodium reduction on FMD during and after weight loss.

The studies in this thesis have contributed to the understanding of how nutrition affects vascular function. The key findings were that; weight loss improves some aspects of endothelial function but in our hands does not improve FMD, weight loss does not attenuate the BP response to salt and a high saturated fat diet in weight stability but not in weight loss impairs FMD.

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