ORIGINAL COMMUNICATION

Effects of moderate weight loss on anginal symptoms and indices of coagulation and fibrinolysis in overweight patients with angina pectoris

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Objective: To evaluate the effects of moderate weight loss, in overweight patients with angina, on plasma coagulation, fibrinolytic indicies and pain frequency.
Design: Single-stranded 12-week dietary intervention, an individualised eating plan with quantitative advice delivered by a dietitian. Target weight loss of 0.5 kg per week.
Setting: Outpatient research clinic.
Subjects: Fifty-four volunteers with angina pectoris were recruited. Five subjects withdrew, so 27 males, 22 females, mean body mass index (BMI) 29.3 (s.d. 4.3) kg/m^2 and age 60.3 (s.d. 6.5) y completed the intervention.
Measurements: Body weight and frequency of anginal pain. Plasma fibrinogen, red cell aggregation (RCA), viscosity, factor VII activity, plasminogen activator inhibitor (PAI) activity, tissue plasminogen activator antigen (t-PA), plasma cholesterol, triglyceride and insulin.
Results: After the 12-week dietary intervention period, mean body weight fell by 3.5 (s.d. 2.6) kg or 4.3% ($P = 0.0001$), range −11.7 to +1.7 kg. Mean angina frequency fell by 1.8 (s.d. 3.6) from 3.2 to 1.4 episodes/week ($P = 0.009$) and plasma cholesterol by 0.4 (s.d. 0.7) from 6.3 to 5.9 mmol/l ($P = 0.0001$). HDL cholesterol and triglyceride were unchanged. Of the coagulation and fibrinolytic factors, factor VII activity and RCA were significantly reduced by 5 (s.d. 20), IU/dl ($P = 0.04$) and 1.3 (s.d. 1.3) arbitrary units ($P = 0.014$), respectively.
Conclusions: A conventional dietetic intervention, resulting in 4% weight loss, offers the potential to reduce atherosclerotic and thrombotic risk, and to reduce pain frequency, in angina patients. Given the importance of this result in a public health context, these results indicate that this may be a fruitful area for future nutrition research.
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Introduction

Relatively modest weight loss is increasingly recognised to have major health benefits for overweight people (Goldstein, 1992). Weight gain leads to a wide range of disabling symp-toms, as well as being an important coronary risk factor (Hubert *et al*, 1983; Higgins *et al*, 1988). Being overweight favours the development of diabetes (Chan *et al*, 1994), which can be controlled with sufficient weight loss (UK PDS. 1995). Other risk factors that are elevated by overweight include hypertension (Ramsey *et al*, 1978), blood lipids and coagulation factors (Williamson *et al*, 1995; Heinrich *et al*, 1993). All improve with loss of 5–10% or 5–10 kg body weight (Goldstein, 1992). Life expectancy is increased with intentional weight loss in overweight people who have obesity-related complications, particularly diabetes (Lean *et al*, 1990; Williamson *et al*, 1995,1999).

As well as promoting a more atherogenic blood lipid profile, overweight promotes coronary heart disease by ele-vating plasma coagulation factor VII activity, fibrinogen,

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measures of blood rheology and impaired fibrinolysis (Le Devehat et al, 1992; Meade et al, 1986). All these changes are associated with increased coronary risk via thrombogenesis (Heinrich et al, 1993; Lowe & Forbes, 1981). Increased visceral fat is particularly associated with impaired fibrinolytic activity (raised levels of plasminogen activator inhibitor, PAI; Kockx et al, 1999). Tissue plasminogen activator antigen (t-PA) and PAI activity, factor VII activity and fibrinogen all show greater elevations in those with known coronary disease and angina (Aznar et al, 1988).

Bahadori et al, (1996) have reported that close to 40% of obese angina patients do not have significant coronary artery disease, and so a clinical benefit from weight loss could be expected without necessarily modifying atheroma. Some previous studies have shown that weight reduction improves established measurements of coagulation, rheology and fibrinolysis (Poggi et al, 1994; Palareti et al, 1994). Most studies used short-term very low calorie diet (VLCD) regimens in otherwise healthy subject groups, where effects from acute, severe energy restriction are likely to confound any effects of weight loss per se. The amount of weight loss in these trials (18% body weight) is more than is achievable in routine practice (Poggi et al, 1994; Palareti et al, 1994).

The aims of the present study were to investigate the effects of moderate weight loss on both established biochemical and haematological risk factors for cardiovascular disease, and on the frequency of chest pain in overweight angina patients already on treatment for coronary heart disease. The dietary advice concerned dietary composition (COMA, 1991) together with an individualised daily energy restriction.

Experimental
Design
A single-stranded study design was employed with paired analysis (before and after the intervention) within subjects.

Patients and methods
Patients actively seeking weight management were recruited by local advertising. All patients had received a previous medical diagnosis of angina pectoris, which was determined from Rose questionnaires (Rose, 1963). An ultrasonic flow detector was used to investigate the presence of peripheral vascular disease (Yao et al, 1969). Each patient was requested to attend the Department of Human Nutrition on five occasions over the 12-week intervention period. Body weight, height, waist and hip circumferences were measured and body mass index (BMI) was calculated (WHO, 1987). Skinfold thicknesses were measured (Lean et al, 1996) and used to estimate body fat as a percentage of body weight. The same observer carried out all measurements without reference to previous measurements. At baseline and after 12 weeks the frequency of anginal pain and use of glyceryl trinitrate (GTN) were recorded alongside food and drink consumption in a 7-day diary.

Dietary intervention
In order to ensure an appropriate dietary prescription to achieve a standard energy deficit in each subject, given that predicted energy requirement figures are those for healthy people, individual dietary prescriptions were based on resting energy expenditure, estimated from indirect calorimetry (Deltatrac). No patients engaged regularly in physical exercise, so an activity factor of $1.3 \times$ resting energy expenditure was used to estimate total daily requirements (COMA, 1991) and a daily energy deficit of 2510 kJ (600 kcal) was applied (Lean & James, 1986). Advised dietary composition was in line with current national dietary guidelines (COMA, 1991); greater than 50% of energy derived from carbohydrate, less than 35% from fat and under 20% from protein. Patients were asked to prospectively record their food intakes using 7 day weighed diaries at baseline and at week 12.

Plasma measures
Fasting blood was sampled from the anticubital vein with minimal stasis between 9 and 11 am following a 5 min supine rest. Measurements were made pre- and post-dietary intervention. Triglycerides and total cholesterol were measured on an automated analysis system (Boehringer Mannheim, Lewes, Sussex, UK) and high density lipoprotein cholesterol (HDL) was measured using β-quantification and ultracentrifugation. Whole blood and plasma-viscosity were measured at high shear rates (over $300 \, s^{-1}$) at $37^{\circ}C$ in a Harkness viscometer (Lowe et al, 1993). Haematocrit was measured with a Hawksley microcentrifuge, RCA was assessed photometrically in a cone-plate aggregometer (Myrenne GmbH, Roetgan, Germany).

Fibrinogen was measured using an automated thrombin-clotting assay (Clauss, 1957). Factor VII activity was measured using a one-stage clotting assay and rabbit thromboplastin and results were recorded as a percentage of a reference plasma pool (Lowe et al, 1997). The total plasma concentrations of t-PA antigen were determined by an ELISA (Tintelize t-PA, Biopool, Sweden). The intra- and inter-assay coefficient of variation were 8.9 and 9.0%, respectively. The plasminogen activator inhibitor activity (PAI-1) was measured using a chromogenic microtitre assay (COAtestPAI, Chromogenix) with an intra-assay coefficient of variation of 7.9% and an inter-assay variation of 8.1%.

Statistical and sample size considerations
The sample size of 45 patients was chosen to provide an 80% power to detect a clinically important difference equal in size to the population standard deviation for factor VII activity,

red cell aggregation and t-PA antigen as principle outcome measures using a 5% significance test (Woodward, 1999).

The data were approximately normally distributed, from inspection of distribution plots. Before and after means were compared using paired Student's *t*-tests. Pearson's correlation coefficient was applied to investigate the relationships between changes in body weight and secondary outcome measurements. Ethical approval for the study design was obtained from the Glasgow Royal Infirmary Joint Ethics Committee and signed informed consent was secured from all patients.

Results

Clinical characteristics of study subjects
Fifty-four patients enrolled in the study, of these five withdrew and 49 overweight, but weight-stable, angina patients (27 male, 22 post-menopausal females) with a BMI $\geq 25 \, kg/m^2$ completed the study. The mean age was 60.3 y (range 41.0–67.5). The prescribed medications for these subjects relevant to their cardiovascular disease were glyceryl trinitrate spray (27), aspirin (20), diuretic (12), β blocking agents (29) and lipid-lowering medications (one). There was no change in any prescribed medications during the study. There were 11 smokers, seven of whom were male. There was no reported change in smoking status during the study. Eleven subjects (two females) showed signs of occlusive peripheral vascular disease with an ankle branchial pressure index (ABPI) below 0.9. Mean ABPI was 0.9 (s.d. 0.2). There was no effect of lowered ABPI measurement on baseline measures or on changes in biochemical measures.

Energy requirements and dietary intake data
Mean daily energy prescription for all patients was 6217 (s.d. 1498; range 4184–1172) kJ; for males, 6941 (s.d. 1292; range 5020–10460) kJ and for females, 5322 (s.d. 1292; range 4184–7949) kJ. At baseline, median energy intake and inter quartile range was 7928 (6564–8865) kJ, which fell to 6108 (5213–8075) kJ ($P < 0.00001$) at week 12. Baseline median dietary fat intake was 33.4 (29.5–38.2)%, which fell to 30.0 (25.9–33.5)% post-intervention.

Weight and body composition
The mean BMI of males was 30.9 (s.d. 4.5) kg/m^2 (range 25.6–40.9), which was greater ($P = 0.04$) than that of females 27.8 (s.d. 2.5) kg/m^2 (range 25.0–32.7). For all patients mean BMI was 29.3 (s.d. 4.3) kg/m^2 (range 25.0–40.9). Mean weight reduction over the 12-week study was 3.5 (2.6) kg, ($P = 0.009$, Table 1), close to 60% of the expected loss (Lean & James, 1986). The frequency of anginal pain between baseline and week 12 was significantly reduced in all participants (Table 1, Figure 1).

Thrombogenic factors
At baseline, mean factor VII activity was higher in females than males, 130 (s.d. 20) *vs* 114 (s.d. 26) IU/dl ($P = 0.04$), but no sex difference was observed in the other measures. Amongst the haemostatic and fibrinolytic indices measured, significant reductions between baseline and week 12 were detected for RCA and factor VII activity (Table 2). There was some evidence for a reduction in PAI activity in males ($P = 0.09$).

Atherogenic factors
Plasma total cholesterol was reduced in all patients ($P = 0.0001$), in males ($P = 0.0019$) and females ($P = 0.011$), separately, although HDL cholesterol and triglyceride were unchanged.

During the course of the study no significant ($P < 0.05$) correlations were found between changes in body weight, or alterations in waist circumference, and changes in angina frequency (Figure 2) or in biochemical measures.

Discussion
The results from this study support the view that modest weight loss can improve clinical and biochemical indices of

Table 1 Mean (s.d.) of cardiovascular risk factors, fasting plasma biochemistry pre- and post-intervention ($n = 49$)

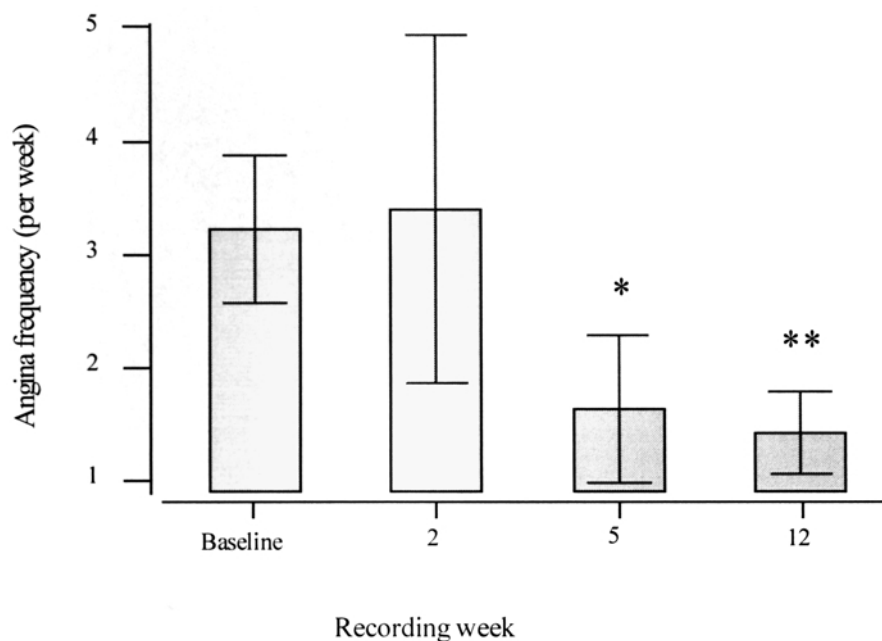|	Baseline	Week 12	Change	95% CI	P-value
Weight (kg)	81.6 (11.7)	78.1 (11.3)	− 3.5 (2.6)	− 4.2, − 2.6	0.0001
BMI (kg/m²)	29.3 (4.3)	28.1 (4.0)	− 1.2 (0.9)	− 1.5, − 0.9	0.0001
Body fat (%)	31.9 (4.8)	31.1 (5.0)	− 0.8 (1.7)	− 1.2, − 0.3	0.0022
Waist circumference (cm)	103.9 (9.3)	101.6 (10.2)	− 2.3 (4.5)	− 3.5, − 1.1	0.0005
Waist-to-hip ratio	1.00 (0.06)	0.99 (0.07)	− 0.01 (0.06)	− 0.02, + 0.01	0.40
Plasma insulin (mU/l)	13.1 (8.1)	11.8 (8.9)	− 1.3 (7.8)	− 3.7, + 1.1	0.29
Total cholesterol (mmol/l)	6.3 (1.1)	5.9 (1.0)	− 0.4 (0.7)	− 0.6, − 0.2	0.0001
HDL cholesterol (mmol/l)	1.3 (0.3)	1.2 (0.3)	− 0.1 (0.6)	− 0.1, + 0.1	0.092
Triglyceride (mmol/l)	1.8 (0.8)	1.7 (1.0)	− 0.1 (0.6)	− 0.3, + 0.1	0.31
Systolic blood pressure (mmHg)	144 (16)	142 (17)	− 2 (17)	− 18.5, + 5.4	0.99
Diastolic blood pressure (mmHg)	86 (10)	85 (18)	− 1 (19)	− 19.5, + 6.5	0.14
Angina frequency (incidents/week)	3.2 (4.5)	1.4 (2.5)	− 1.8 (3.6)	− 2.5, − 0.9	0.009

Figure 1 Angina frequency before and after intervention. * $P < 0.05$, ** $P < 0.01$ when compared to baseline. Data presented of mean (s.e.m.).

Table 2 Mean (s.d.) coagulation and fibrinolytic measures, pre and post-intervention ($n = 49$)

| Measure	Baseline	Week 12	Change	95% CI	P-value
PAI-1 (% pool)	134 (75)	123 (59)	− 11 (57)	− 30.5, +5.73	0.10
t-PA antigen (μg/ml)	10.9 (3.2)	10.6 (3.6)	− 0.3 (2.8)	− 1.0, +0.6	0.21
Fibrinogen (g/l)	3.4 (1.0)	3.6 (0.8)	+0.2 (0.1)	− 0.1, +0.3	0.15
Factor VII activity (IU/dl)	120 (14)	115 (20)	− 5 (20)	− 11.3, +0.8	0.04
Haematocrit (%)	45 (0.1)	40 (0.1)	− 0.5 (0.1)	− 2.1, +1.3	0.32
Red cell aggregation (arbitrary units)	3.9 (1.5)	2.6 (0.6)	− 1.3 (0.6)	− 2.3, − 0.4	0.014
Plasma viscosity (mPa s)	1.30 (0.08)	1.29 (0.08)	− 0.01 (0.08)	− 0.03, +0.02	0.33
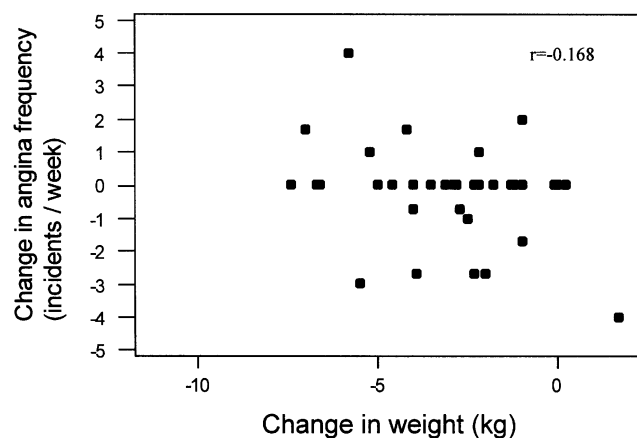
Figure 2 Relationship between the change in body weight and anginal frequency.

CVD risk and, importantly, that there are clinical benefits in terms of symptom reduction for overweight patients with angina. The data cannot, however, be considered definitive because of the range of weight changes, which places severe limits on the power of a study of routine management. A randomised controlled intervention design is the gold standard for testing causality, provided that a fixed treatment is used, and that a placebo or some other control treatment is feasible (Woodward, 1999). As the present study illustrates, in dietary intervention studies the treatment (weight loss) is not fixed. As in any study of this kind, the treatment group includes a wide range of weight changes (in this case from + 1.7 to − 11.7 kg over 12 weeks), which will introduce a wide variability in secondary consequences such as biochemical or clinical outcomes. Furthermore, an untreated control group may be problematic, as in practice medically compromised patients seeking weight management are rightly reluc-

tant to ignore their problem and remain in a control group. Untreated observation 'non-weight loss' control groups usually have a large overlap of weight changes. This has been shown by participants who had volunteered for a weight loss study, but were randomised to be held in a 12 week control period prior to commencing the intervention, whose range of weight changes was -4.9 to $+5.3$ kg (Leslie et al, 2000). Thus the study design chosen, a correlation analysis between weight change and outcome measures, was a pragmatic choice (Lean, 2000). If a clinical trial design were deemed feasible, post-hoc analyses from the current study could be carried out to derive appropriate samples sizes. If a controlled intervention study were deemed feasible, post hoc analyses from the current study could be carried out to derive appropriate sample sizes. For instance, assuming a control group with no average change, results from Table 2 suggest that a sample size of 422 in each group would be expected to be required in order to be 80% sure of detecting a significant difference in PAI-1 (Woodward, 1999).

The mean 3.5 kg (4%) weight loss after dietary intervention during this 12 week study is similar to that achievable by a range of approaches in a variety of patient groups. In a patient group considered as being largely physically inactive, and in whom weight gain frequently occurs, it represents considerable success (Goldstein, 1992). It has been shown that angina can be reduced by other lifestyle interventions (Barnard et al, 1983), but clinical programmes such as cardiac rehabilitation have usually concentrated only on exercise, relaxation and education, without effective dietary or weight management strategies (ASPIRE Steering Group, 1996). The present finding of reduced anginal pain frequency is in accordance with the frequent clinical impression of an immediate benefit from weight loss in those suffering angina.

The finding that only some patients showed any benefit from weight loss suggests that angina patients are a heterogeneous group in terms of the relationship between weight and angina (Figure 2). When patients were recruited, they were not selected for their reported angina frequency, and hence there was a wide range in the frequency of anginal pain (0–70 incidents per week) in the study group. However, as subjects were identified for participation on the basis of having angina, some reduction in frequency could have been attributable to secular factors or 'regression to the mean'. A possible mechanism by which this clinical observation could be explained may involve the effect of weight loss in changing indices of endothelial function. This has been illustrated in type 2 diabetes mellitus patients, also suffering from angina pectoris, who when treated with thiazolidine-dione show a reduction in the frequency of angina pain (Murakami et al, 1999).

In addition to recording the frequency of anginal pain, the participants in the present study were asked to record their frequency of GTN use. However, the majority declined to do this, and hence their record of anginal frequency

provides the most objective measure possible within the confines of this study of free living subjects.

In addition to benefits in anginal episodes, we also observed significant decreases in a number of biochemical measures, known to be CVD risk factors: total cholesterol, factor VII activity and RCA. Reduced plasma cholesterol is an expected benefit of weight loss (Dattilo & Kris-Etherton, 1992). The fact that HDL cholesterol and triglyceride were unaltered is probably because most patients were on lipid-lowering drugs and additional weight loss was insufficient to affect any changes. Additionally, weight loss was completed at 12 weeks and insufficient time was available for weight stability to encourage a rise in HDL (Heinrich et al, 1993). The significant decrease in factor VII activity achieved in the present study supports the findings of other studies where both moderate weight loss (Rissanen et al, 2001, Folsom et al, 1993) and much greater weight loss (18%) have been achieved (Palareti et al, 1994).

In contrast, Baron et al (1989), using a 1200 kcal weight-reducing diet in overweight subjects, failed to demonstrate a significant change in factor VII activity with a similar weight loss. The fall in factor VII activity achieved by Baron et al was below that observed in similar work carried out in healthy overweight subjects: mean BMI 34.9 kg/m^2 (Hankey et al, 1995). The mean baseline factor VII activity was 5% lower than that of the angina patients in the present study.

Red cell aggregation (RCA) is a risk factor for cardiovascular disease (Gillum et al, 1995; Bottiger & Carlson, 1980) and is raised in obesity. The improvement in RCA after weight loss concurs with similar results in healthy adults using a VLCD (Palareti et al, 1994) or in type 2 diabetics (MacRury et al, 1992). The stability of plasma viscosity following modest weight loss is also in accord with previous studies (Fanari et al, 1993). Very substantial weight loss is required to change this measure. A VLCD, with an enormous daily energy deficit is necessary to reduce plasma viscosity in those with raised baseline values compared to the present study (Fanari et al, 1993). Studies which showed falls in fibrinogen or haematocrit have shown greater weight loss (>15 kg), than in the present investigation (Palareti et al, 1994; Poggi et al, 1994; Le Devehat et al, 1992). Thus, the failure of a 4% weight loss to affect plasma fibrinogen in this study, implies only a small effect of dietary intervention and weight loss on plasma fibrinogen concentrations (Palareti et al, 1994; Poggi et al, 1994; Le Devehat et al, 1992; Baron et al, 1989; Lowe et al, 1992; Broadhurst et al, 1990).

A number of studies have succeeded in lowering PAI activity and t-PA antigen, following large weight losses in subjects whose fibrinolytic activity was impaired (Landin et al, 1990; Palareti et al, 1994; Fehily et al, 1982). The PAI activity at baseline for our angina patients was 31% below the values of those 'simple obese' subjects in a previous study (Hankey et al, 1997a,b). The stability of fibrinolytic variables noted here might be due to the unaltered fibrinolytic systems of the subjects, and an insufficient weight loss to change it. Two studies (Rissanen et al, 2001; Folsom et al,

1993) have demonstrated that moderate weight change is associated improvements in PAI-1 and factor VII activity. In addition, Rissanen et al (2001) showed the benefits were still present with long-term maintenance of weight loss.

In conclusion, a weight management programme for overweight patients with angina improves symptoms and some rheological and fibrinolytic and lipid risk factors. These effects of weight may have been masked, or to some degree minimised by drug therapy. Routinely administered advice for weight loss in overweight patients with angina may have important implications for clinical practice by improving patient care and quality of life (Lewin et al, 1995). These outcomes merit further study.

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