



NORTH-WEST UNIVERSITY
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Effect of dietary fibre on selected haemostatic variables and C-reactive protein

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M.Sc. in Nutrition

Thesis submitted for the degree
Philosophiae Doctor in
Nutrition at the School of
Physiology, Nutrition and
Consumer Science of the
North-West University
(Potchefstroom Campus)



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Potchefstroom
South Africa
2006



Dedication

To my wonderful husband Benni and children Robert-Reece and Catherine for their love, patience and unfailing support throughout this study and the sacrifices made during the completion of the thesis.

Acknowledgements

I wish to sincerely thank:

- Prof. Johann Jerling as promoter and Prof. Christine Venter as co-promoter, for their guidance, inspiration and pleasant dispositions. It was a privilege to work under your leadership. The assistance Prof. Venter gave with the reference list is greatly appreciated.
- My mother for her ongoing motivation and belief in me.
- Prof. Lesley Greyvenstein for the language editing.
- Family and friends for their support and encouragement.
- The staff of the Ferdinand Postma Library for their invaluable and friendly assistance.
- Above all, I want to honour the Lord for giving me the strength and ability to finish this study.

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Abstract

Motivation

Cardiovascular heart disease (CVD) is the leading cause of death worldwide. Risk markers for CVD include, amongst others, the haemostatic factors tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor type 1 (PAI-1), factor VII (FVII) and fibrinogen and more recently, C-reactive protein (CRP), a sensitive marker of inflammation. Epidemiological studies have demonstrated an inverse association between dietary fibre (DF) consumption and risk factors for CVD and CVD prevalence. Some research indicates that this protection may be related to favourable changes in the haemostatic profile and inflammatory markers. This is applicable for the consumption of total DF, as well as soluble and insoluble fibre. However, clinical intervention trials report conflicting data on the effects of DF on t-PA, PAI-1, FVII, fibrinogen and CRP. In addition, available literature is not clear on the mechanisms through which DF may have favourable effects.

Objective

The main objective of this study was to review the results of randomised controlled trials systematically on the effects of DF on the above-mentioned selected haemostatic variables and CRP in healthy adults and subjects with hypertriglyceridaemia and the metabolic syndrome.

Methods

Human adult intervention trials, at least two weeks in duration, with an increased and measurable consumption of DF were included. Electronic databases were searched from the earliest record to May/July 2006 and supplemented by crosschecking reference lists of relevant publications. From the literature search, two reviewers identified studies that were rated for quality based on the published methodology. No formal statistical analysis was performed due to the large differences in the study designs of the dietary intervention trials. The primary outcome measures were percentage changes between intervention and control groups, or baseline to end comparisons for t-PA, PAI-1, FVII, fibrinogen and CRP.

Results

t-PA activity increased significantly (14-167%) over the short and long-term following increased fibre intakes. PAI-1 activity decreased significantly between 15-57% over periods ranging from two to six weeks. These favourable changes in t-PA and PAI-1 occurred in healthy, hypertriglyceridaemic and metabolic syndrome subjects following consumption of diets containing ≥ 3.3 g/MJ DF and ≥ 4.5 g/MJ DF respectively. Mechanisms through which DF may affect t-PA and PAI-1 include its lowering effect on insulinaemic and glycaemic responses, decreasing triglycerides which are a precursor of very-low-density lipoproteins, fermentation of DF to short-chain fatty acids, which may reduce free fatty acid concentrations, as well as the role of DF in promoting weight loss.

High DF intakes did not have a significant effect on fibrinogen concentrations possibly because of relatively little weight loss, too low DF dosages and maintaining a good nutritional status. Inadequate study designs deterred from meaningful conclusions. Significant decreases in FVII coagulant activity (6-16%) were observed with DF intakes of ≥ 3.3 g/MJ and concomitant decreased saturated fat intakes and weight loss in healthy and hypertriglyceridaemic subjects. Confounding factors include weight loss and a simultaneous decreased intake of saturated fats. The type of fibre seems to play a role as well. Mechanisms through which DF may reduce FVII concentrations include its effects on triglyceride-rich lipoproteins, insulin and weight loss.

Increased DF consumption with dosages ranging between 3.3-7.8 g/MJ were followed by significantly lower CRP concentrations (25-54%), however, simultaneous weight loss and altered fatty acid intakes were also present in all the studies. Mechanisms are inconclusive but may involve the effect of DF on weight loss, insulin, glucose, adiponectin, interleukin-6, free fatty acids and triglycerides.

Conclusions

Epidemiological evidence indicates an association between DF and the CVD risk factors t-PA, PAI-1, FVII, fibrinogen and CRP. In general, the risk of CVD may improve with high-fibre intakes as indicated by the favourable changes in some of the parameters. However, simultaneous reduced fat intakes and weight loss presented difficulties in separating out the effects of specific components. Furthermore, DF is consumed in a variety of different forms and different dosages that may have different effects. Overall, the study designs used in the intervention trials prevented significant conclusions. DF

did, however, play a role in modifying t-PA, PAI-1, FVII and CRP. Potential effects on fibrinogen were not quantifiable.

Recommendations

The results from this investigation provide the motivation for additional controlled clinical research to establish the effect and mechanisms of DF on haemostatic variables and CRP. A critical aspect of future studies would be to set up suitable protocols. The amount of subjects, duration of the trials, confounding factors such as weight loss and altered fat intakes and differentiation between types and dosage of DF are important. DF supplemental studies are recommended as they may be the most suitable method to reach meaningful conclusions.

Key words: Dietary fibre, tissue-type plasminogen activator, plasminogen activator inhibitor type 1, factor VII, fibrinogen, C-reactive protein, systematic review.

Opsomming

Afrikaanse titel

Die effek van dieetvesel op uitgesoekte hemostatiese veranderlikes en C-reaktiewe proteïen

Motivering

Die vernaamste oorsaak van dood in die wêreld is kardiovaskulêre siektes (KVS). Risikomerkers vir KVS sluit onder andere die volgende hemostatiese veranderlikes in: weefsel-tipe plasminogeenaktiveerder (t-PA), plasminogeenaktiveerderinhibeerder tipe 1 (PAI-1), faktor VII (FVII) en fibrinogeen. C-reaktiewe proteïen (CRP), 'n sensitiewe merker van inflammasie, is onlangs ook as 'n risikomerker van KVS erken. Epidemiologiese studies toon 'n omgekeerde verwantskap tussen dieetveselinname en risikofaktore vir KVS aan. Sommige navorsing dui aan dat die beskermende effek van verhoogde dieetveselinname moontlik toegeskryf kan word aan gunstige veranderinge in die hemostatiese profiel en inflammatoriese merkers. Dit geld vir die inname van totale, sowel as oplosbare en onoplosbare dieetvesel. Daar is egter kliniese proefnemings wat teenstrydige bevindings aangaande die effek van dieetvesel op t-PA, PAI-1, FVII, fibrinogeen en CRP rapporteer. Beskikbare literatuur verskaf ook nie duidelikheid oor potensiële meganismes waardeur dieetvesel gunstige veranderinge kan meebring nie.

Doelwit

Die doelwit van die studie was die uitvoering van sistematiese oorsigte oor die resultate van ewekansige, gekontroleerde studies van die effekte van dieetvesel op bogenoemde geselsteerde hemostatiese veranderlikes en CRP in gesonde volwassenes en diegene met hipertriglisëridemie en die metaboliese sindroom.

Metodes

Menslike intervensiestudies wat ten minste twee weke geduur het en wat 'n meetbare toename in dieetveselinname gerapporteer het, is ingesluit. Elektroniese databasisse is van die begin van die databasis tot Mei/Julie 2006 gebruik vir 'n literatuursoektog en aangevul deur die bronnelyste van geskikte publikasies na te gaan. Hierdie artikels is gekeur en gegradeer deur twee navorsers na aanleiding van die metodologie soos dit in

die publikasie voorgekom het. Geen formele statistiese analise is uitgevoer nie weens die aansienlike verskille in die studie-ontwerpe van die dieetintervensies. Die primêre uitkomstes was die persentasie veranderinge tussen die intervensie en kontrole groepe, of vergelykings van basis-na-eindwaarde vir t-PA, PAI-1, FVII, fibrinogeen en CRP.

Resultate

t-PA-aktiwiteit het betekenisvol verhoog (14-167%) in kort- en langtermynstudies na 'n verhoogde inname van dieetvesel. PAI-1-aktiwiteit het betekenisvol verlaag (15-57%) gedurende tydperke van twee tot ses weke. Hierdie gunstige veranderinge in t-PA en PAI-1 is aangetoon in gesonde, hipertriglisieridemiese- en metaboliese sindroom-pasiënte na verhoogde dieetveselinname van ≥ 3.3 g/MJ en ≥ 4.5 g/MJ onderskeidelik. Meganismes waardeur dieetvesel t-PA en PAI-1 mag beïnvloed sluit vesel se verlagende effek op insulien en glukemiese reaksies in, sowel as verlaagde konsentrasies in trigliseriede wat 'n voorloper van baie-lae-digtheidlipoproteïene is. Die fermentasie van dieetvesel tot kortkettingvetsure wat verlaagde vryvetsuurkonsentrasies tot gevolg kan hê en die rol van dieetvesel in gewigsverlies mag ook 'n rol speel.

Hoë veselinnames het nie 'n betekenisvolle effek op fibrinogeenkonsentrasies gehad nie. Dit is waarskynlik as gevolg van onvoldoende gewigsverlies, te lae dieetveseldosisse en die goeie voedingstatus van die proefpersone. Ontoereikende studie-ontwerpe het sinvolle gevolgtrekkings bemoeilik. Betekenisvolle verlagings in FVII-koagulantvlakke (6-16%) is waargeneem in gesonde en hipertriglisieridemiese proefpersone met dieetveselinnames van ≥ 3.3 g/MJ gepaardgaande met 'n verlaging in versadigde vetsuurinname en gewigsverlies. Die tipe vesel mag moontlik 'n rol speel. Meganismes waardeur vesel FVII-konsentrasies mag verlaag sluit die effek van vesel op trigliseridiedryke lipoproteïene, insulien en gewigsverlies in.

'n Verhoogde dieetveselinname in dosisse van 3.3-7.8 g/MJ is gevolg deur betekenisvolle verlagings in CRP-konsentrasies (25-54%). Die gunstige veranderinge het egter met gewigsverlies en veranderde vetsuurinnames gepaard gegaan, wat gevolgtrekkings bemoeilik. Daar is nie uitsluitel oor moontlike meganismes nie maar dit mag die effek van dieetvesel op gewigsverlies, insulien, glukose, adiponektien, interleukins-6, vrye vetsure en trigliseriede behels.

Gevolgtrekkings

Epidemiologiese studies dui 'n verwantskap tussen dieetvesel en die KVS-risikofaktore t-PA, PAI-1, FVII, fibrinogeen en CRP aan. Oor die algemeen kan 'n verlaagde risiko vir KVS verwag word met 'n verhoogde dieetveselinname soos waargeneem in die gunstige veranderinge in sommige van die parameters in die studie. Die gelyktydige vermindering van vetinname en gewigsverlies wat in sommige studies voorgekom het, bemoeilik gevolgtrekkings oor die afsonderlike invloed wat die verskeie faktore tot gevolg mag hê. Daarbenewens word dieetvesel in verskeie vorms ingeneem en in verskillende dosisse wat verskillende effekte tot gevolg kan hê. In geheel gesien het die studie-ontwerpe wat gebruik is, voorkom dat duidelik omskrewe gevolgtrekkings gemaak kon word. Dieetvesel speel wel 'n rol in gunstige veranderinge in t-PA, PAI-1, FVII en CRP. Moontlike veranderinge in fibrinogeen kon nie bepaal word nie.

Aanbevelings

Die resultate van hierdie studie dui aan dat verdere gekontroleerde kliniese intervensiestudies nodig is om die effek van dieetvesel op die hemostatiese veranderlikes en CRP te bepaal. Dit is belangrik dat geskikte studie-ontwerpe in toekomstige navorsing gebruik moet word. Die aantal proefpersone, duur van die studies, gewigsverlies en veranderde vetinnames, onderskeiding tussen verskillende tipes vesel en dosisse is belangrik. Studies wat gebruik maak van suplemente word aanbeveel aangesien dit waarskynlik die mees geskikte model sal bied om sinvolle gevolgtrekkings te maak.

Sleutelwoorde: Dieetvesel, weefsel-tipe plasminogeenaktiveerder, plasminogeenaktiveerderinhibeerder tipe 1, faktor VII, fibrinogeen, C-reaktiewe proteïen, sistematiese oorsig.

Preface

Results of this study will be reported as manuscripts in article format as required by the regulations of the North-West University.

The articles were prepared according to the following journals' specifications:

- Chapter 2: Nutrition, metabolism, and cardiovascular diseases
- Chapter 3: Annals of internal medicine
- Chapter 4: Annals of internal medicine.

Co-authors

The principal author of this thesis is Ms CJ North. In the table that follows contributions of the co-authors are summarised.

The following is a statement from the co-authors confirming their role in the study and giving their permission that the manuscripts form part of this thesis.

I declare that I have approved the above-mentioned manuscripts, that my role in the study as indicated is representative of my actual contribution and that I hereby give my consent that they may be published as part of the Ph.D. thesis of Christa North.

Co-authors and their contributions

Chapters 2, 3 and 4	
Co-author	Contribution
CJ North (Dietician)	Responsible for literature searches, designing, planning, collection and analysis of data, execution, interpretation and documentation of the reviews
Prof JC Jerling (Nutritionist)	Promoter, assisting in all aspects: designing, planning, execution, interpretation and documentation of the reviews and provision of significant advice
Prof CS Venter (Dietician)	Co-promoter, assisting in all aspects: designing, planning, execution, interpretation and documentation of the reviews and provision of significant advice



Prof. JC Jerling
Promoter



Prof. CS Venter
Co-promoter

List of abbreviations

Abbreviation	Description
↑	increase/high
↓	decrease/low
↑-fat	high-fat
↓-fat	low-fat
a	controlled feeding trials
AI	adequate intake
ALC	alcohol
b	studies conducted under free-living conditions
BMI	body mass index
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults Study
CHD	coronary heart disease
CHO	carbohydrates
CI	confidence interval
CRP	C-reactive protein
CVD	cardiovascular disease
d	day/daily
DF	dietary fibre
DRI	Dietary Reference Intakes
e.g.	<i>example gratia</i> (for example)
FFA	free fatty acids
FVII	factor VII
FVIIa	factor VII activity
FVIIag	factor VII antigen
FVIIc	factor VII coagulant activity
g	gram
g/d	gram per day
g/L	gram per litre
g/MJ	gram per megajoule
GI	glycaemic index
GL	glycaemic load
HOMA	homeostasis model assessment
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
IHD	ischaemic heart disease

Abbreviation	Description
IL-18	interleukin-18
IL-6	interleukin-6
IU/mL	international units per millilitre
kg	kilogram
LDL	low-density lipoproteins
M	men
MeSH	medical subject headings
MI	myocardial infarction
MJ	megajoule
Mo	month(s)
MUFA	monounsaturated fatty acids
n-3	omega-3
n-6	omega-6
n3-PUFA	omega-3-polyunsaturated fatty acids
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NR	not reported
NS	not significant
OR	odds ratio
PAI-1	plasminogen activator inhibitor type 1
PAI-1a	plasminogen activator inhibitor-1 activity
PAI-1ag	plasminogen activator inhibitor-1 antigen
PRO	protein
PUFA	polyunsaturated fatty acids
QS	quality score
Ref	reference study
RR	relative risk
SCFA	short-chain fatty acids
SD	standard deviation
SFA	saturated fatty acids
TC	total cholesterol
TG	triglyceride/triacylglycerol
t-PA	tissue-type plasminogen activator
t-PAa	tissue-type plasminogen activator activity
t-PAag	tissue-type plasminogen activator antigen
VLDL	very-low-density lipoprotein
vs	<i>versus</i>
W	women
wk	week(s)
y	year(s)

1

Introduction

1.1 Background and motivation of the study

This thesis reports on the effects of dietary fibre (DF) on selected haemostatic variables and C-reactive protein (CRP). In this chapter the significance of each one of these variables in relation to cardiovascular disease (CVD) will be discussed, the objectives of the study will be stated and the structure of the thesis explained. Below follows a motivation for this project.

CVD is the leading cause of death worldwide (World Health Organization, 2004) and refers to various medical conditions that affect the heart and blood vessels. These conditions include coronary artery disease (CAD), myocardial infarction (MI), angina, congestive heart failure, hardening of the arteries, stroke and peripheral vascular disease. CVD has a multifactorial aetiology, as illustrated by the existence of numerous risk indicators, many of which can be influenced by dietary means. However, only after a cause-and-effect relationship has been established between the disease and a given risk indicator, can modifying this factor be expected to affect disease morbidity and mortality. Half of all MIs occur in people in whom plasma lipids are normal (Braunwald, 1997), therefore, other markers have been proposed in an effort to identify individuals at risk better. The haemostatic system contributes to atherogenesis and controls intravascular thrombus formation and thus plays an important role in the development of coronary heart disease (CHD) (Fuster *et al.*, 1992). It is, therefore, of utmost importance to gain insight into the possible modification of the haemostatic system to pave the way for prevention of CVD. In addition, inflammation is believed to play a role in the pathogenesis of cardiovascular events and markers of inflammation have been put forward as another method of prediction of risk of these events (Ridker *et al.*, 2000). The Centres for Disease Control and Prevention and the American Heart Association published the first set of guidelines in January 2003 to endorse the use of high sensitivity C-reactive protein (hsCRP) as an adjunct to traditional risk factor screening (Pearson *et al.*, 2003).

Many of the risk factors for heart disease are either preventable or controllable through dietary factors such as fibre which has been found to be inversely associated with risk factors for CHD (Watts *et al.*, 1992; Feskens *et al.*, 1994; Djousse *et al.*, 1998). Fibre may play a greater role in determining CVD risk than total or saturated fat intake as indicated in epidemiological studies (Ascherio *et al.*, 1996; Rimm *et al.*, 1996; Ludwig *et*

al., 1999). Some researchers have suggested that this protection may be mediated by improvements in haemostasis (Fehily *et al.*, 1982; Boman *et al.*, 1994) and inflammation (Ajani *et al.*, 2004) with increased fibre intake, but is not conclusive. The five variables that have been investigated in this study were selected based on their predictive value as risk markers of CVD. An overview of the selected haemostatic factors' involvement in coagulation and fibrinolysis is schematically represented in **Figure 1.1**.

The public is repeatedly exposed to conflicting claims about the effectiveness of dietary components in preventing disease. An understanding of the role of fibre in CHD risk can help clarify and reinforce dietary recommendations. The mechanisms of how DF may reduce CVD risk are not yet fully understood. Insights into the mechanisms of fibre's protective effect may lead to better dietary recommendations and new prevention strategies. Increasing the fibre content of a diet is relatively low-cost and safe with minimal side effects, making it a feasible option for a large proportion of the population. If DF is truly protective, even if only modestly so, it may have a large impact on disease rates at the population level because the prevalence of low-fibre diets is substantial as will be indicated in Chapter 5.

1.1.1 Tissue-type plasminogen activator and plasminogen activator inhibitor type 1

Tissue-type plasminogen activator (t-PA) converts inactive plasminogen to active plasmin, the enzyme that degrades fibrin. Free active t-PA is difficult to measure in plasma (Booth, 1999). Clinical studies tend to measure circulating t-PA antigen (t-PAag) values (de Bono, 1994; Booth, 1999) which are mainly markers of the complex formation between t-PA and plasminogen activator inhibitor type 1 (PAI-1), its major inhibitor. A relation between circulating t-PAag levels and subsequent CVD has been reported in epidemiological studies (Francis, Jr. *et al.*, 1988; Yamauchi *et al.*, 1992; Smith *et al.*, 1997; Thogersen *et al.*, 1998; Gram *et al.*, 2000), although not consistently (Ridker *et al.*, 1993; Wiman *et al.*, 2000). This might be because previous studies involved in general too few CHD cases to give a reliable indication of the relationship between t-PAag and the incidence of CHD. A recent meta-analysis of 12 studies found a statistically significant association between circulating concentrations of t-PAag and subsequent CHD (Lowe *et al.*, 2004). In a comparison of men in the top third (>13.0 ng/ml) compared with those in the bottom third (<8.4 ng/ml) of baseline t-PAag values, the odds ratio (OR) for CHD was 2.20 [95% confidence interval (CI), 1.70; 2.85] after

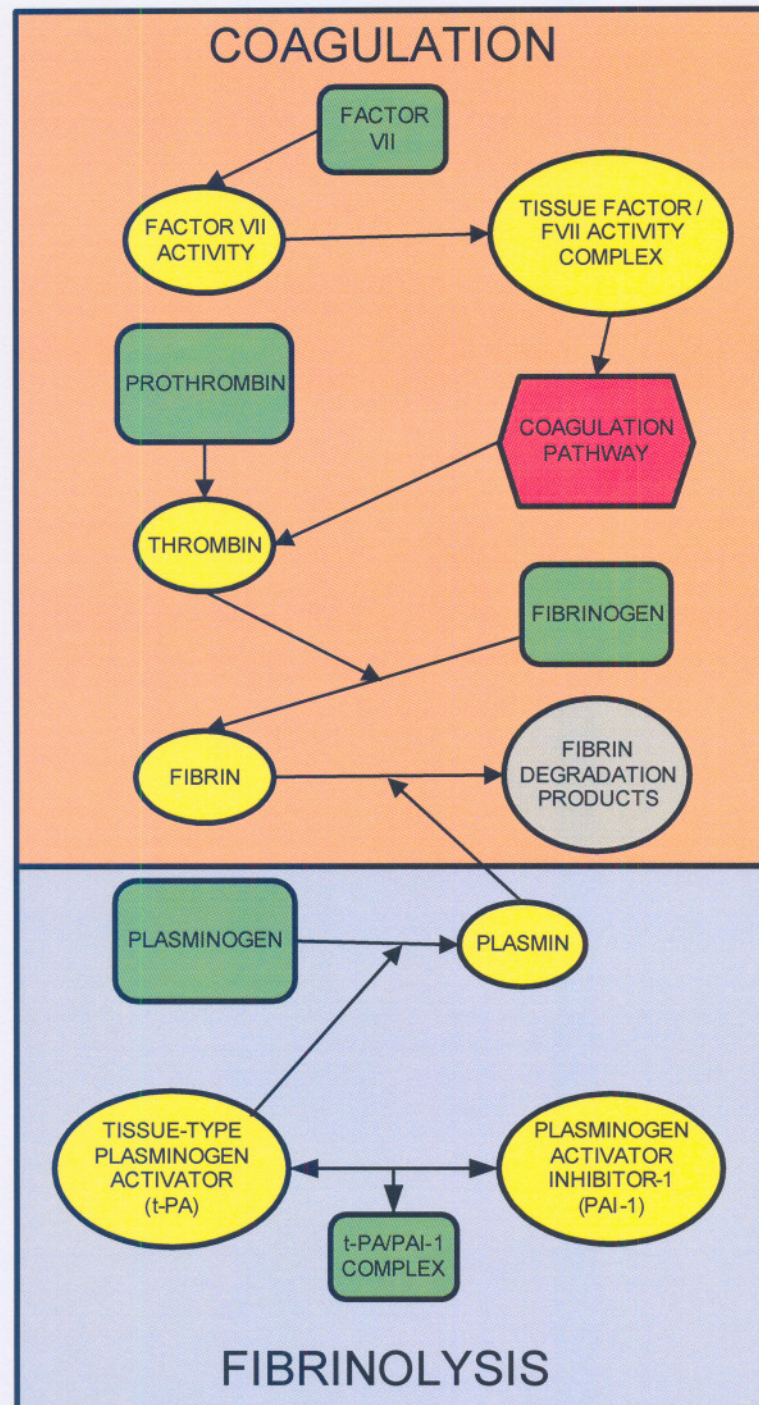


Figure 1.1 Schematic representation of selected key factors involved in coagulation (top section) and fibrinolysis (bottom section). “Coagulation Pathway” represents a series of reactions involved in the coagulation cascade including the activation of factors V, VII, VIII, IX and X. Ovals represent activated enzymes or complexes and boxes represent inactive enzymes or complexes. Adapted from Lefevre *et al.* (2004).

adjustment for age and town which fell to 1.48 (95% CI, 1.09; 2.01) after further adjustment for classical risk factors (high-density lipoprotein cholesterol, triglycerides, body mass index, blood pressure and physical activity) (Lowe *et al.*, 2004). Analysis of t-PA as a continuous variable gave similar results (Lowe *et al.*, 2004). Whether DF influences the fibrinolytic activity of t-PA significantly and independently in clinical trials remains, however, inconclusive (Marckmann *et al.*, 1993b; Sundell & Ranby, 1993; Lindahl *et al.*, 1999; Turpeinen *et al.*, 2000) and, therefore, t-PA was selected to be included in the current study.

PAI-1, the primary inhibitor of tissue- and urinary-type plasminogen activator, plays a key role in fibrin homeostasis by controlling plasmin formation. Raised PAI-1 levels are associated with an increased CVD risk (Jansson *et al.*, 1993) such as in acute (Almer & Ohlin, 1987) and recurrent MI (Hamsten *et al.*, 1987), atherosclerosis (Robbie *et al.*, 1996) and CAD (Olofsson *et al.*, 1989). Furthermore, low PAI-1 levels were observed in a population “free” from CVD (Lindeberg *et al.*, 1997). In intervention trials, higher fibre intakes were followed by lower PAI-1 concentrations in some studies (Nilsson *et al.*, 1990; Sundell & Ranby, 1993; Boman *et al.*, 1994; Lindahl *et al.*, 1999) but not in others (Sundell *et al.*, 1988; Lindahl *et al.*, 1998). Given these inconsistencies and the association between CVD risk, t-PAag and PAI-1 complexes, PAI-1 was selected as a parameter to investigate systematically.

1.1.2 Factor VII and fibrinogen

Prospective investigations report that higher fibrinogen (Danesh *et al.*, 2005) and plasma factor VII coagulant activity (FVIIc) concentrations (Junker *et al.*, 1997; Rudnicka *et al.*, 2006) are associated with a greater risk of CVD. FVII is of particular interest in defining a hypercoaguable state as it is the enzyme responsible for initiating clotting (Tracy *et al.*, 1999). The role of FVII as an independent risk factor for CHD is controversial (Marckmann *et al.*, 1998). Some studies such as the Northwick Park Heart Study (Meade *et al.*, 1986) and the PROCAM study (Heinrich *et al.*, 1994) demonstrated a strong relationship between the level of FVIIa and the later incidence of ischaemic heart disease (IHD)/CHD in healthy males. An estimated increase of one standard deviation (approximately 25%) in FVIIa may increase the risk of fatal CHD within 5 years by 55% (Meade *et al.*, 1986). Since subsequent studies showed discrepancies (Folsom *et al.*, 1997; Junker *et al.*, 1997; Tracy *et al.*, 1999), the recently published cohort that investigated the relationship of fibrinogen and FVIIc with the risk of

CHD and stroke was received with much anticipation (Rudnicka *et al.*, 2006). Study subjects were 22715 men (aged 45-69 years), followed-up over a period of 15 years (Rudnicka *et al.*, 2006). A small effect of FVIIc on CHD after adjusting for age and trial treatment was found (OR, 1.07; 95% CI, 1.01; 1.12), but no association independent of other risk factors (Rudnicka *et al.*, 2006). In a community-based case-control study of women aged ≤ 65 years, the OR for CHD for the highest *versus* the lowest quartile of factor VII antigen (FVIIag) was 1.75 (95% CI, 1.05; 2.92) (Eriksson-Berg *et al.*, 2001). The adjusted OR was 0.76 (95% CI, 0.28; 1.98) after controlling for other CVD risk factors (Eriksson-Berg *et al.*, 2001). The corresponding ORs for FVIIa were non-significant. Thus, FVIIa was not significantly increased in women with CHD and FVIIag levels, although elevated, were not independently associated with apparent disease (Eriksson-Berg *et al.*, 2001). Low-fat/high-fibre diets may lower fasting FVIIc by 5-15% in healthy (Marckmann *et al.*, 1993b), mildly hypercholesterolaemic (Brace *et al.*, 1994) and severe hypertriglyceridaemic individuals (Simpson *et al.*, 1983). In contrast, others reported no significant deviation from baseline measurements with a high DF intake (Marckmann *et al.*, 1993a; Sundell & Ranby, 1993). Therefore, FVII was included in this study.

Fibrinogen plays a key role in platelet aggregation, the final step of the coagulation cascade and is a major determinant of plasma viscosity. Fibrinogen is, furthermore, a primary, independent risk factor for CVD (Meade *et al.*, 1986) including stroke and MI (Wilhelmsen *et al.*, 1984) and is associated with IHD (Danesh *et al.*, 2005). A large cohort in men showed a persistent association between fibrinogen and CHD beyond ten years that may imply a causal effect (Rudnicka *et al.*, 2006). Modifications of fibrinogen concentrations would thus be valuable in the prevention of CVD and, therefore, were included in this study. James *et al.* (2000) reported that in free-living subjects high DF intake was associated with low fibrinogen levels. This was also found in other cross-sectional studies (Fehily *et al.*, 1982; Yarnell *et al.*, 1983). There are indications that high-fibre interventions in children (Koepp & Hegewisch, 1981) and animals (Vorster *et al.*, 1985; Venter *et al.*, 1991) lower fibrinogen concentrations, but so far results in adults are less promising (Simpson *et al.*, 1982).

1.1.3 C-reactive protein

Since elevated CRP concentrations increase PAI-1 expression and activity (Devaraj *et al.*, 2003) and thus have a connection with haemostasis, CRP was included in this

study. In addition, CRP is a sensitive circulating marker of inflammation that is used as a predictor of the risk of future CVD (Ridker *et al.*, 2000; Pearson *et al.*, 2003; Willerson & Ridker, 2004) and CHD events (Koenig *et al.*, 1999; Danesh *et al.*, 2004). It is important, however, to distinguish between its role as a risk marker and that of a risk factor, that directly causes a biological effect because this will determine optimal therapeutic intervention (Paffen & de Maat, 2006). The identification of modifiable factors, such as diet, that influence serum CRP concentrations may provide the means for reducing the risk of CVD. Recent findings indicate that fibre intake, including total (Jenkins *et al.*, 2003; King *et al.*, 2003; Ajani *et al.*, 2004; Ma *et al.*, 2006), soluble and insoluble fibre (Ma *et al.*, 2006), is independently associated with serum CRP concentrations, although this has not been a consistent finding (Lopez-Garcia *et al.*, 2004).

1.2 Aims and objectives of the study

In large cohort studies high-fibre intakes have been associated consistently with a reduction in CHD risk (Watts *et al.*, 1992) and CHD risk factors (Ludwig *et al.*, 1999). The effects of DF on lowering cholesterol (Brown *et al.*, 1999) alone do not explain the decrease in risk for coronary events following increased DF intake. Other factors are thus likely to be involved to explain the association between fibre and CVD.

The Food and Nutrition Board of the Institute of Medicine included fibre for the first time in the Dietary Reference Intakes (DRI) in 2002 and determined that the Adequate Intake (AI) of fibre for females (31 - 50 years) is 25 g per day and for males 38 g per day (31 - 50 years) (Institute of Medicine, 2002). The question may be asked whether these amounts are enough to alter CVD risk indicators? In addition, it is of interest to investigate the possible mechanisms of interaction between DF and these factors/markers. The aim of this study was to review the effects of DF on selected haemostatic variables and CRP systematically.

1.2.1 Objectives

The objectives of this study were to review the results of randomised controlled trials on the effects of DF on PAI-1 and t-PA, FVII and fibrinogen and CRP systematically in healthy adults and those with hypertriglyceridaemia and the metabolic syndrome, identify possible mechanisms through which DF may have these effects and to present the findings in article format.

1.2.2 Overall methodology of the study

The steps followed in this study included:

- Formulating the research questions and protocols
- Locating and selecting suitable studies
- Assessing quality and rating selected studies
- Collecting and sorting data
- Analysing results
- Interpreting results
- Writing reviews and thesis.

1.3 Definitions of terms

Multiple definitions of DF have been developed since its original use in 1953 (Hipsley, 1953). The definitions varied according to substances that were considered to be fibre, the analytical methods used to identify and measure fibre and whether physiological criteria were part of the definition (Jones *et al.*, 2006). The history of defining DF was recently reviewed and the latest definition is from the Dietary Reference Intakes (DRI) Panel on Macronutrients (Trumbo *et al.*, 2002):

- *Dietary fibre* consists of non-digestible carbohydrates and lignin that are intrinsic and intact in plants.
- *Functional fibre* consists of isolated, non-digestible carbohydrates that have beneficial physiological effects in humans.
- *Total fibre* is the sum of DF and functional fibre.

However, the studies included in this review used the terms *soluble* and *insoluble* fibre, which are defined based on the physical properties and the physiological roles of the fibre (Mahan & Arlin, 1992).

- *Soluble fibre* includes pectins, gums, mucilages and some hemicelluloses and examples of food sources include fruit, vegetables, oat bran, barley and legumes. Soluble fibre has the ability to hold water and form gels and acts as a substrate for colonic fermentation.

- *Insoluble fibre* consists primarily of cellulose and hemicelluloses. It lends structure to plant cells and is found in the bran of cereal grains. Lignin can be found in edible skins and seeds.

Furthermore, definitions applicable to other terms used in the framework of this thesis are indicated in **Table 1.1**.

Table 1.1 Definitions used in the context of this study

Risk factor	A risk factor is defined as any factor with a causal association with a disease.
Risk marker	A risk marker marks an aspect of the disease so that it could be related either to the risk factor or the disease process or outcomes.
Cardiovascular disease	CVD is a general category consisting of several separate diseases of the heart and circulatory system. The terms of the type of CVD have been used as per the original articles.
Coagulation	The set of enzymatic reactions that result in thrombin production and fibrin formation.
Fibrinolysis	The set of enzymatic reactions that result in plasmin production and fibrin degradation.
Haemostasis	The arrest of blood flow, either from a vessel or within a vessel.

1.4 Structure of thesis

This thesis is constituted by chapters written specifically to comply with the requirements of the North-West University (Potchefstroom Campus) and the journals to which manuscripts were submitted for publication. In particular, directives in terms of language usage, formatting and bibliography were strictly adhered to. All chapters and manuscripts have their own reference index. The articles were prepared according to the following journals' specifications:

- Chapter 2: Nutrition, metabolism, and cardiovascular diseases
- Chapter 3: Annals of internal medicine
- Chapter 4: Annals of internal medicine.

The current chapter is introductory in nature and presents the background and motivation of the study and sets out the objectives and methodology. The next three chapters are systematic review articles about selected clinical trials with high-fibre interventions that measured PAI-1 and t-PA (Chapter 2), FVII and fibrinogen (Chapter 3) and CRP (Chapter 4). These chapters also highlight possible mechanisms whereby DF may influence the mentioned risk factors of CVD. Chapter 5 focuses on DF and integrates the results of Chapters 2 – 4. The scientific contribution, strengths and limitations of this study are discussed and recommendations regarding further research are made in Chapter 5.

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Instructions for authors:
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2

Dietary fibre, tissue-type
plasminogen activator and
plasminogen activator
inhibitor type-1

A systematic review of the effects of dietary fibre on tissue-type plasminogen activator and plasminogen activator inhibitor type-1 in humans

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Abstract and key words

Aims

Cardiovascular disease (CVD) is one of the major causes of death worldwide and high-fibre intakes have consistently been associated with a reduction in CVD risk. According to epidemiological research, high levels of tissue-type plasminogen activator (t-PA) antigen and raised plasminogen activator inhibitor type 1 (PAI-1) concentrations are related to an increased cardiovascular risk. The objective of this study was to systematically review the scientific evidence from clinical trials that is related to the influence of dietary fibre (DF) on t-PA and PAI-1.

Data synthesis

Significant elevations of t-PA activity (14-167%) was observed over the short-term and long-term subsequent to increased fibre intakes. PAI-1 activity decreased significantly between 15-57% over periods ranging from two to six weeks. These favourable changes occurred following consumption of diets containing ≥ 3.3 g/MJ DF and ≥ 4.5 g/MJ DF in t-PA and PAI-1 respectively, in healthy, hypertriglyceridaemic and metabolic syndrome subjects.

Conclusion

Mechanisms through which DF may affect t-PA and PAI-1 include its lowering effect on insulinaemic and glycaemic responses; decreasing triacylglycerols which are a precursor of very low density lipoproteins; fermentation of DF to the short-chain fatty acids, which may reduce free fatty acid concentrations, as well as the role of DF in promoting weight loss. Additional clinical trials are needed to study the potential favourable effects of DF on t-PA and PAI-1 observed in this review.

KEY WORDS: Dietary fibre, tissue-type plasminogen activator, plasminogen activator inhibitor type 1, cardiovascular disease, diet, systematic review.

Introduction

Cardiovascular disease (CVD) remains one of the major causes of death worldwide [1]. Many of the risk factors for heart disease are either preventable or controllable through dietary factors such as fibre, which is inversely associated with risk factors for CVD [2]. The haemostatic system is assuming an increasingly prominent role in the pathogenesis and progression of cardiovascular diseases [3]. A recent review reported a significant association between circulating tissue-type plasminogen activator antigen (t-PAag) concentrations and subsequent coronary heart disease (CHD) as seen in epidemiological studies [4], but conflicting data prevail [5]. Raised plasminogen activator inhibitor type 1 (PAI-1) concentrations are associated with an increased cardiovascular risk such as in acute [6] and recurrent myocardial infarctions [7], ischaemic heart disease (IHD) [8], atherosclerosis [9] and coronary artery disease (CAD) [10]. Dietary fibre (DF) intake studies show an independent, inverse relationship between the level of total DF [11-13], water-soluble DF [14], cereal fibre [13], whole-grain intake [15] and risk of subsequent CHD [12-14], IHD [15] and myocardial infarction [11]. Some researchers have suggested that this protection may be mediated by improvements in haemostasis with an increased fibre intake [16]. Higher daily DF intakes are related to lower t-PAag concentrations [16]. Whether DF influences the fibrinolytic activity of tissue-type plasminogen activator (t-PA) significantly and independently remains, however, inconclusive [17-19]. Higher fibre intakes are inversely associated with PAI-1 in some studies [16,18,20] but not in others [21,22]. The aim of this systematic review is to evaluate scientific data to determine the effects of DF on t-PA and PAI-1.

Methods

Subjects

The data of 289 subjects (153 men, 125 women, 11 mixed) were included from eight intervention studies summarised in this systematic review. Participants with metabolic syndrome (n=108) and high triacylglycerol (TG) concentrations (n=25) made up 46% of the study population. The remainder of participants were healthy.

Inclusion and exclusion criteria

Human adult (men and women) trials with a duration of two weeks or longer, and fibre supplementation or clinical studies involving interventions with an increased and measurable consumption of DF with an intake higher than habitual were included. Subjects were excluded if diabetic, suffering from CHD or had had a heart attack.

Outcome measures

The primary outcome measures were percentage changes between intervention and control groups, or baseline to end comparisons for tissue-type plasminogen activator activity (t-PAa), t-PAag, plasminogen activator inhibitor-1 activity (PAI-1a) and plasminogen activator inhibitor-1 antigen (PAI-1ag).

Data sources

To identify potential studies, literature searches were performed in electronic databases. EbscoHost was used as a gateway to the records in MEDLINE [Pubmed], Academic Search Premier, Clinical Pharmacology, Health Source: Nursing/Academic Edition, Health Source: Consumer Edition and Biological & Agricultural Index. In addition, The Cochrane Library, Science Direct, Web of Science and EMBASE were also searched. Databases were searched from the earliest record to May 10, 2006. Reference lists of relevant publications were crosschecked manually to ensure that all applicable papers were included. Search terms used included plasminogen activator inhibitor-1 (PAI-1), tissue-type plasminogen activator (t-PA), dietary fibre (fiber), non-digestible carbohydrate(s), lignin(s), non-starch polysaccharide(s), functional fibre (fiber), haemosta*, nutrition*, food. Medical subject headings (MeSH) such as 'haemostatic' and 'hemostatic' were combined with the key search words in the Medline search.

Study selection and data extraction

Two assessors screened the studies identified to determine eligibility for inclusion into the review. Using a standardised form, data was extracted to determine the quality of all the identified intervention studies.

Data synthesis

A rating based upon the methodology as it appeared in the publication was given to each of the selected studies. The following criteria for quality assessment of the intervention trials were used (adapted from Verhagen *et al.*[23]): (1) the study was controlled; (2) justified sample size; (3) groups were similar at baseline regarding the most important prognostic indicators; (4) compliance was acceptable; (5) randomisation was performed; and (6) in case of cross-over trials: no order of treatment effect. The following quality scores were assigned: 1 = if all the above criteria were present / if the study was controlled and one criterion was missing; 2 = if the study was controlled and two criteria were missing; 3 = if the study was not controlled or ≥ 3 criteria were missing. Furthermore, the letter *a* was assigned to controlled feeding trials and *b* to studies conducted under free-living conditions. No formal statistical analysis was performed due to the large differences in study designs of the clinical trials.

Results

From the literature search 345 articles were screened (titles, abstracts, original research and review articles). Consequently eight original research papers were identified that were suitable for inclusion. Of the eight selected studies, four received a “1” or “2” rating. **Table 1** presents a summary of the baseline characteristics of the studies and participants. The experimental design of these studies was variable, subjects’ characteristics differed, as did the amount and type of fibre, duration of the studies, the control diets and sample sizes. Most of the intervention diets in the included studies were also low in fat. **Table 2** summarises the sources of fibre and macronutrient compositions of the diets.

The duration of the studies varied between two to 35 weeks. The length of the shortest dietary intervention period in this systematic review ($n=2$ weeks) was sufficient to achieve stabilisation of PAI-1 and t-PA [24,25]. The number of subjects per study ranged between 11 and 108. According to power calculations (80% power at 5% significance), two studies [17,20] did not have adequate power to detect clinical significant changes in PAI-1. The characteristics of subjects in each study are shown in **Table 3**.

Table 1 Summary of baseline characteristics including all studies and participants

	Summary result	Number of studies reporting (n=8)
Fibre intake g/MJ/d [mean (range)]	4.8 (2.5-10.7)	8
Supplement [mean (range)]	3.5 (2.5-4.5)	2
Dietary intake [mean (range)]	5.2 (3.3-10.7)	6
Study duration (weeks) [mean (range)]	7.4 (2-35)	8
Supplement (weeks) (range)	4 (2-6)	2
Dietary intake (weeks) (range)	8.5 (2-35)	6
Participants completed (n) (dropouts)	289 (39)	8
Supplement (n) (dropouts)	35 (4)	2
Dietary intake (n) (dropouts)	254 (35)	6
Age men (years) [mean (range)]	46.5 (20-72)	8
Age women (years) [mean (range)]	54.6 (17-72)	5

Abbreviation: g/MJ/d, gram per megajoule per day.

Favourable increased t-PAa concentrations were seen in three studies after the high-fibre interventions (**Table 4**). A dietary intervention with 4.5 g/MJ DF increased t-PAa by 167% [17]. A low-fat/high-fibre diet with 3.3 g/MJ DF raised t-PAa with 14% which was significantly different from the high-fat/low-fibre (fat 39% of total energy) control diet [26]. The afore-mentioned studies were rated high in their study designs. In the lower quality supplemental study (10g oat husk fibre/day) the 6% increase in t-PAa did not reach significance [20]. t-PAa showed no difference comparing rye with whole-wheat bread in another good quality study [19]. The diet in the clinical trial of Mehrabian *et al.* [27] had a very high DF content namely 8.3-10.7 g/MJ and produced a significant decrease in t-PAag after three weeks in the obese participants (quality rating = low). However, two further high quality studies produced opposite results in t-PAag, although none of the changes were significant [17,26]. Possible explanations for inconsistent results between studies are given in the discussion.

As shown in **Table 5**, the four low-quality rated clinical trials reported a significant decrease of PAI-1a when increased DF dosages ranging from 4.5-10.7 g/MJ DF were consumed by healthy [20], obese [27], hypertriglyceridaemic [28] and metabolic syndrome subjects [21]. Also in a high-quality study a significant decrease in PAI-1a during treatment with guar gum compared to the placebo in a DF supplement study was

found [29]. No change in PAI-1 was seen in the study comparing rye with whole-wheat bread (quality rating = high) [19]. The favourable results from the insufficiently designed oat husk supplemental study should be interpreted with caution as it was an uncontrolled study and had a small number of subjects (n=11) [20]. In the two studies that measured PAI-1ag, no significant changes were observed [17,26].

Changes in body weight are known to have an impact on PAI-1a and t-PA concentrations [41]. The weight losses seen in studies included in this review were not consistent with favourable changes in PAI-1 and tPA. In a highly rated study that reported a significant difference in t-PAa comparing two interventions, a significant reduction in body weight occurred [26]. In another study (quality rating = 2) with a significant increase in t-PAa, weight loss was not statistically significant [17]. Only one study observed a significant decrease in t-PAag and the significance of the weight loss was not reported [27]. A high-quality study with a significant reduction in PAI-1a reported unchanged body weight [29] whereas simultaneous significant reductions in both PAI-1a and body weight were seen in some [21,28], but not all of the remaining lower quality studies [20,27].

Discussion

This review of eight clinical trials indicated that diets high in DF may favourably affect PAI-1a and t-PAa concentrations. t-PAa showed an upward trend following DF intakes of 3.3 and 4.5 g/MJ [17,20,26]. PAI-1a decreased following DF intakes ranging from 4.5-10.7 g/MJ DF [20,21,27,28] and a significant difference was seen in PAI-1a comparing two groups with a DF supplement (2.5g/MJ) [29]. Insignificant changes of PAI-1 were observed in three studies with healthy subjects [17,19,26].

Inconsistent results could possibly be explained in a number of ways. Insignificant changes in t-PAag concentrations following DF intakes of 3.3-4.5 g/MJ DF were seen in two studies [17,26]. It seems reasonable to presume it would be more difficult to change t-PAag concentrations in these subjects as they were healthy, non-obese and had baseline t-PA values within reference range [17,26]. Moreover, it might be that the dosage of DF was too low to have a substantial effect, as consumption of a slimming diet with 8.3-10.7 g/MJ DF did cause a significant decrease in t-PAag [30].

Table 2 Macronutrient composition of diets in dietary intervention trials investigating the effect of dietary fibre on tissue-type plasminogen activator and plasminogen activator inhibitor type-1

Type / source of dietary fibre / Reference study	DF g/MJ	PRO %	CHO %	FAT %	Compliance	Control diet / type / source of dietary fibre	DF g/MJ	PRO %	CHO %	FAT %
INTERVENTION						CONTROL				
SUPPLEMENTAL STUDIES										
Guar galactomannan Landin <i>et al.</i> , 1992 [29]	2.5 *	2	63.4	29.5	Good Remaining granulate was weighed	Placebo	NR	2.1	63.9	28.1
Oat husk † Sundell & Ranby, 1993 [20]	4.5	14.5	54.6	29.4	Not reported Four were excluded do to failure to comply	Habitual diet (No control group)	2.3	15.2	55.3	29.5
DIETARY INTERVENTION STUDIES										
Mostly vegetarian Mehrabian <i>et al.</i> , 1990 [27]	8.3-10.7	13	77	<10	Good Controlled feeding trial	Controls (n=2) habitual diet	Not reported			
Low-fat, high-fibre Marckmann <i>et al.</i> , 1993 [17]	4.5	14	58	26	Good Controlled feeding trial	Habitual diet	2.2	14	47	35
Bread, cereals, fruit, vegetables Marckmann <i>et al.</i> , 1994 [26]	3.3	14	57	28	Good Controlled feeding trial	Not reported	2.1	13	47	39
Vegetables, root vegetables, breakfast fibre Lindahl <i>et al.</i> , 1998 [21]	5.1	18	64	18	Good Controlled feeding trial	Not reported				
Whole-meal rye bread Turpeinen <i>et al.</i> , 2000 [19]	M 3.6 W 3.7	M 17 W 17	M 49 W 49	M 31 W 33	Good Food diaries kept	Low-fibre wheat bread	M 1.6 W 1.7	M 17 W 16	M 48 W 51	M 33 W 32
Whole-grain bread and cereal, vegetables, fruit, specially formulated muesli Junker <i>et al.</i> , 2001 [28]	↑-fat 5.0 ↓-fat 5.4	↑-fat 20.2 ↓-fat 18.4	↑-fat 40.3 ↓-fat 54.2	↑-fat 39.3 ↓-fat 27.2	Good Part of foodstuffs provided to subjects	Habitual diet	2.5	16.8	41.1	37.0

Abbreviations used: NR, not reported; M, men; W, women; DF, dietary fibre; PRO, protein; CHO, carbohydrates; ↑-fat, high-fat; ↓-fat, low-fat, g/MJ; gram per megajoule.

* Excluding fibre from diet † 99% insoluble fibre

Mehrabian *et al.*, 1990 [27] Daily portion of milk and 85g fish/chicken per week.

Marckmann *et al.*, 1993 [17] Alcohol: Intervention, 2%; Control, 4%.

Marckmann *et al.*, 1994 [26] Alcohol: Intervention and Control, 1%.

Junker *et al.*, 2001 [28] Alcohol: Intervention, 0.2%; Control, 5.2%.

Turpeinen *et al.*, 2000 [19] Alcohol: Intervention, Men 4.6%, Women 2.2%; Control, Men 4.1%, Women 3.6%.

Table 3 Characteristics of participants per study

Mean amount of fibre (g/MJ) of intervention group(s) Intervention diet Study design Reference study	Number of participants that completed intervention (n{total dropouts})	Selected inclusion criteria of studies	Participant characteristics: nationality, mean age, BMI	Duration of intervention	Comparison made	Quality score
SUPPLEMENTAL STUDIES						
2.5 g/MJ supplement (excluding dietary intake) Very low protein (1-2%) Cross-over Landin <i>et al.</i>, 1992 [29]	n=25M [0]	Healthy, non-obese	Sweden 52 y BMI: 25	6 wk	Placebo	1b
4.5 g/MJ 10 g/d supplement Within subject comparison Sundell & Ranby, 1993 [20]	n=11 M&W [4]	Healthy, non-obese	Sweden 32 y BMI: NR	2 wk	Baseline	3b
DIETARY INTERVENTION STUDIES						
8.3-10.7 g/MJ Mostly vegetarian (low-fat/high complex CHO) Parallel Mehrabian <i>et al.</i>, 1990 [27]	n=27: 12M, 15W [0]	Obese	United States of America 58 y BMI: NR	3 wk	Prudent diet	3a
4.5 g/MJ Low-fat/high-fibre diet Parallel Marckmann <i>et al.</i>, 1993 [17]	n=32M [0]	Healthy, non-obese	Denmark 24 y BMI: 21	8 mo	Control	2a
3.3 g/MJ Low-fat/high-fibre diet Cross-over Marckmann <i>et al.</i>, 1994 [26]	n=21: 10M, 11W [1]	Healthy, non-obese	Denmark 53 y BMI: 23	2 wk	High-fat, low-fibre diet	1a
5.1 g/MJ Low-fat diet/high-fibre Within subject comparison Lindahl <i>et al.</i>, 1998 [21]	n=108: 31M, 77W [31]	Overweight, hypertension, atherogenic lipid profile and/or impaired glucose tolerance	Sweden 49 y [M], 47 y [W] BMI: 34 [M], 33 [W]	1 mo	Baseline	3a
3.6-3.7 g/MJ High-fibre from whole-meal rye Cross-over Turpeinen <i>et al.</i>, 2000 [19]	n=40: 18M, 22W [3]	Healthy TC<7.5 mmol/L TG<2.5 mmol/L	Finland 43 y BMI: 20-32	4 wk	Low-fibre diet from wheat	1b
5.0 g/MJ High-fat diet rich in PUFA and MUFA 5.4 g/MJ Low-fat diet/high-fibre Within subject comparison Junker <i>et al.</i>, 2001 [28]	n= 25M [0]	Non-obese, TG>2.3 mmol/L	Germany 40 y BMI: 26	3 wk	Baseline diet	3b

Abbreviations used: M, men; W, women; DF, dietary fibre; CHO, carbohydrates; ↑-fat, high-fat; ↓-fat, low-fat; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; TG, triacylglycerols; TC, total cholesterol; a, controlled feeding trials; b, studies conducted under free-living conditions; NR, not reported; g/MJ; gram per megajoule. Quality score: 1 = high; 3 = low.

Table 4 Effect of fibre on tissue-type plasminogen activator activity (IU/ml) and tissue-type plasminogen activator antigen (ng/ml) in intervention studies

Mean amount of fibre (g/MJ) intervention groups Intervention diet Reference study	Baseline [mean (SD) or median (range)]	Trial end [mean (SD) or median (range)]	% change from baseline to end † (p-value or significance) or difference between groups ‡	Baseline [mean (SD) or median (range)]	Trial end [mean (SD) or median (range)]	% change from baseline to end (p-value or significance)	Summary of results	Quality score	
	INTERVENTION			CONTROL					
t-PAa (IU/ml)									
4.5 g/MJ 10 g/d supplemental study Sundell & Ranby, 1993 [20]	0.98 (0.2)	1.04 (0.32)	+6.1 † NS	No control group			Non significant increase in t-PAa after 2wk supplement	3b	
4.5 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1993 [17]	0.94 (0-4.3)	2.5 (0-9.7)	+167.0 † p<0.008	0.93 (0-6.75)	Not reported	NS p=0.53	Significant increase in t-PAa after 8mo low-fat/high-fibre diet	2a	
3.3 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1994 * [26]	Period 1 0.134	Period 1 0.153	+14.2 ‡ NR	Period 1 0.111	Period 1 0.044	-60.4 NR	Significant difference (p=0.02) between diets after 2wk (low-fat(28%) /high-fibre diet vs high-fat diet 39%)	1a	
3.6-3.7 g/MJ High-fibre from whole-meal rye Turpeinen <i>et al.</i> , 2000 [19]	No baseline measure	Men 0.26(0.04) Women 0.4(0.06) All 0.33(0.04)	Men 0(0) ‡ NS Women 0.07(0) ‡ NS All 0.03(0.01) ‡ NS	No baseline measure	Low-fibre wheat Men 0.26(0.04) Women 0.33(0.04) All 0.3(0.03)		No significant differences between high-fibre rye and low-fibre wheat (1.6-1.7 g/MJ bread) after 4wk	1b	
t-PAag (ng/ml)									
8.3-10.7 g/MJ Mostly vegetarian (low-fat/high complex CHO) Mehrabian <i>et al.</i> , 1990 [27]	11.5 (4.9)	8.2 (3.7)	-28.7 † p=0.0001	Not reported (n=2)		NS	Significant decrease in t-PAag after 3wk high complex carbohydrate, low-fat diet	3a	
4.5 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1993 [17]	3.1 (0.4-5.6) (no venous occlusion) 11.8 (4-24.2) (venous occlusion)	2.0 (0.0-5.1) (no venous occlusion) 9.0 (0-19) (venous occlusion)	-35.5 † p=0.08 -23.7 † p=0.25	3.7 (2.0-5.9) (no venous occlusion) 9.5 (4.8-16.4) (venous occlusion)	Not reported		NS p=0.32	Insignificant decrease in t-PAag after 8mo low-fat/high-fibre diet	2a
3.3 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1994 [26]	Period 1 4.2 (1.2-10.6) Period 2 4.4 (0.6-11.5)	5.3 (2.6-6.2)	Period 1 +26.2 † NS Period 2 +20.5 † NS	Period 1 4.2 (1.2-10.6) Period 2 4.4 (0.6-11.5)	4.0 (2.4-6.0)	Period 1 -5 NS Period 2 -10 NS	Insignificant increase in t-PAag after 2wk low-fat/high-fibre diet	1a	

Reference values: t-PAa 0.2-20 IU/ml, t-PAag: 3.2-4.9 ng/mL [7,39]. The formula used was: (End value – Baseline value)/Baseline value x 100.

Abbreviations used: IU/ml, international units per milliliter; t-PAa, tissue-type plasminogen activator activity; t-PAag, tissue-type plasminogen activator antigen; a, controlled feeding trials; b, studies conducted under free-living conditions; g/MJ, gram per megajoule; NR, not reported; wk, weeks; mo, months; NS, not significant; †, % change from baseline to end; ‡, % difference between groups. * Due to carry-over effects only data from the first experimental period were used for statistical analysis. A significant difference between the two groups (high-fibre and low-fibre) was found. Quality score: 1 = high; 3 = low.

Table 5 Effect of fibre on plasminogen activator inhibitor-1 activity (U/ml) and plasminogen activator inhibitor-1 antigen (ng/ml) in intervention studies

Mean amount of fibre (g/MJ) intervention groups	Baseline [mean (SD) or median (range)]	Trial end [mean (SD) or median (range)]	% change from baseline to end † (p-value or significance) or difference between groups ‡	Baseline [mean (SD) or median (range)]	Trial end [mean (SD) or median (range)]	% change from baseline to end (p-value/significance) or difference between groups	Summary of results	Quality score
Intervention diet	INTERVENTION			CONTROL				
Reference study	PAI-1a (U/ml)							
8.3-10.7g/MJ Mostly vegetarian (low-fat/high complex CHO) Mehrabian <i>et al.</i> , 1990 [27]	15.3 (14.4)	10.2 (7.8)	-33.3 † p=0.0117	Not reported (n=2)		NS	Significant decrease in PAI-1a after 3wk high complex carbohydrate, low-fat diet	3a
2.5 g/MJ supplement (excluding dietary intake) Very low protein (1-2%) Landin <i>et al.</i> , 1992 [29]	No baseline values taken	Supplement 12.1 (6.1)	-2.9 (4.9) † p<0.01	No baseline values taken	Placebo 14.5 (8.2)		Significant decrease in PAI-1a after 6wk supplement compared to placebo	1b
4.5 g/MJ 10 g/d supplemental study Sundell & Ranby 1993 [20]	5.8 (3.2)	2.5 (2.4)	-56.9 † p<0.05	No control group			Significant decrease in PAI-1a after 2wk supplement	3b
4.5g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1993 [17]	4.5 (0.0-12.9)	Not reported	NS † p=0.63	4.1 (1.3-13.8)	Not reported	NS p=0.47	Insignificant changes in PAI-1a in a random subsample (n=8) after 8mo low-fat/high-fibre diet	2a
3.3 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1994 [26]	Period 1 7.7(0-40.4) Period 2 6.4(0-28.8)	8.7 (3.6-12.4)	Period 1 +13 † NS Period 2 +35.9 † NS	Period 1 7.7(0-40.4) Period 2 6.4(0-28.8)	7.8 (4.1-13.1)	Period 1 +1 NS Period 2 +21.8 NS	Insignificant increase in PAI-1a after 2wk low-fat/high-fibre diet	1a
5.1 g/MJ Low-fat diet/high-fibre Lindahl <i>et al.</i> , 1998 [21]	26.7 (2.0)[W] 30.0 (3.4) [M]	22.6(1.5) [W] (1 mo) 26.3(2.0) [W] (12 mo) 25.1(4.4) [M] (1 mo) 28.4(4.3) [M] (12 mo)	-15.4 (W) † p<0.05 NS NS	No control group			Significant decrease in PAI-1a after 1 mo low-fat diet in women, at 12mo PAI-1a reverted to entry levels	3a
3.6-3.7 g/MJ High-fibre from whole-meal rye Turpeinen <i>et al.</i> , 2000 [19]	No baseline values taken	Men 12.9(2.6) Women 7.8(1.1) All 10.1(1.4)	Men -1.3(0) ‡ NS Women 1.1(0.2) ‡ NS All 1.2(0) ‡ NS	Men 14.2(2.6) Women 8.9(1.3) All 11.3(1.4)	Not reported		Insignificant differences between high-fibre rye and low-fibre wheat (1.6-1.7 g/MJ bread)	1b
5.0 g/MJ High-fat diet rich in PUFA & MUFA 5.4 g/MJ Low-fat diet/high-fibre Junker <i>et al.</i> , 2001 [28]	High-fat /high-fibre diet 29.2(3.9-50.0) Low-fat diet/high-fibre 13.6 (1.0-49.3)	High-fat /high-fibre diet 13.6 (1.0-49.3) Low-fat/high-fibre diet 13.6 (2.7-27.8)	-53.4 † p<0.05 NS	No control group			Significant decrease in PAI-1a after 3wk high-MUFA, n-3 period, PAI-1a remained unchanged after low-fat/high-fibre period	3b
PAI-1ag (ng/ml)								
4.5 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1993 [17]	4.9 (0.5-10.3)	4.5 (0.0-18.7)	-8.2 † p=0.67	Not reported	Not reported	NS p=0.78	Insignificant decrease in PAI-1ag after 8mo low-fat/high-fibre diet	2a
3.3 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1994 [26]	Period 1 7.0 (1.1-45.3) Period 2 7.5 (1.9-25.6)	7.8 (3.5-11.7)	Period 1 +11.4 † NS Period 2 +4 † NS	Period 1 7.0 (1.1-45.3) Period 2 7.5 (1.9-25.6)	8.1 (3.4-14.2)	Period 1 +15.7 NS Period 2 +7.4 NS	Insignificant increase in PAI-1a after 2wk low-fat/high-fibre diet	1a

Reference values PAI-1a: 2.6-13.2 U/ml; PAI-1ag: 4.1 ng/mL [6,9,39]. The formula used was: (End value – Baseline value)/Baseline value x 100. † % change from baseline to end; ‡ % difference between groups

Abbreviations used: W, women; M, men; wk, weeks; mo, months; n-3, omega-3; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; PAI-1a, plasminogen activator inhibitor-1 activity; PAI-1ag, plasminogen activator inhibitor-1 antigen; U/ml, international units per milliliter; a, controlled feeding trials; b, studies conducted under free-living conditions; g/MJ; gram per megajoule. Quality score: 1 = high; 3 = low.

Furthermore, in both the aforementioned studies alcohol was allowed and it has been shown that t-PAag increase significantly after alcohol consumption in healthy people [31]. The lack of an effect of DF on t-PAa in the supplemental study by Sundell and Ranby [20] could be because this uncontrolled study consisted of a small number (n=11) of healthy, non-obese, subjects with baseline concentrations within the reference range of both t-PA and PAI-1. Also, insoluble fibres such as the oat husk used in the experiment are reported to have primarily bulk effects [32].

t-PA and PAI-1 concentrations showed no considerable differences comparing groups consuming rye and low-fibre whole-wheat in another study [19]. This might be due to the relatively low levels of fibre in the rye diet (3.6-3.7g/MJ) in comparison to the fibre content of other studies which reported significant changes in t-PA namely 4.5g/MJ [17] and 8.3-10.7g/MJ [27]. In addition the healthy subjects who participated in this study probably had baseline values falling within the reference range of t-PA and PAI-1. Also, the increase in fibre in this study was mostly contributed by insoluble fibre (220% increase) and a more modest raise in soluble fibre (65%) [19]. The lack of significant lowering of PAI-1a in the long-term study of eight months comparing 4.5 g/MJ DF with a control group consuming 2.1 g/MJ DF could be because PAI-1a concentrations were determined in a small sub sample (n=8) of the 16 participants [17]. That is not sufficient power to detect a significant clinical change compromised further by the well-known large intra-individual variations in PAI-1 that commonly occur [33]. Furthermore, ineffective randomisation could have contributed to the insignificant lowering of PAI-1a concentrations in addition to baseline differences in habitual nutrient intakes seen in the experimental group [17]. Lastly, the study population was made up of healthy, young, non-obese subjects with low baseline PAI-1 concentrations [17]. The insignificant increase in PAI-1a in another study may be explained by the higher carbohydrate content of the experimental group (57% versus 47% of control group) [26]. High carbohydrate diets generally have a hypertriglyceridaemic effect [34] and TG concentrations correlate with PAI-1a [35]. Also, the experiment was done on healthy, non-obese participants in whom it might be more difficult to lower PAI-1 concentrations. Significant baseline differences in some of the anthropometrical measurements (weight and waist-hip ratio) between the groups might have led to insignificant changes [26]. Daily supplementation of 4g of polyunsaturated fatty acids (PUFA) was shown to increase PAI-1a in healthy volunteers [36]. Consideration should thus be given to the 24g total PUFA consumed daily by the participants in the long-term study [17], as well

as the 16.5g (mostly linoleic acid) [26] and 10.5g PUFA [19] in the other two studies that could have had opposing effects in PAI-1. Turpeinen *et al.* [19] and Marckmann *et al.* [17] did not differentiate between omega-3 (n-3) and omega-6 (n-6) PUFA. Although the results seen in the study by Junker and colleagues [28] may have been attributed to high n-3 PUFA intakes, there is not consistent evidence about the effect of n-3 PUFA on PAI-1 [36]. Lastly, alcohol was allowed in all three studies and could have influenced PAI-1a concentrations. Regular alcohol consumption is followed by increased plasma PAI-1a while binge drinking appeared to have no effect on PAI-1 concentrations [37].

Body weight

t-PA and PAI-1 are associated with body mass index (BMI) [21,35,38], waist-hip ratio [21,22,35], obesity [39,40] and central body fat distribution [40]. Weight reduction is associated with a reduction in PAI-1a and t-PA concentrations [41]. Two studies included in this review showed simultaneous significant changes in body weight and PAI-1a and t-PAag [21,27]. The remainder of the studies that had significant changes in t-PA and PAI-1 reported insignificant changes in body weight [17,20,29] or ruled the influence thereof out statistically by multiple regression analysis [28]. Epidemiological support that DF consumption prevents obesity is strong [42,43] and in clinical studies body weight decreased on high-fibre diets [44]. Potential mechanisms through which DF can assist in weight loss can be categorised as hormonal, intrinsic and/or colonic [45]. These include the effects of DF on gastric emptying [46], satiety [47], gut hormones such as cholecystokinin [48] and an altered glycaemic index (GI) or insulin response [49]. Increased ileal fat losses were seen following an addition of 15g citrus pectin per day in ileostomy patients [50]. Alginate (7.5 g/d) supplementation of a low-fibre diet has previously been shown to more than double (140% increase) mean fatty acid excretion in the digesta of a small cohort (n = 6) of human ileostomy patients [51]. Possible mechanisms that may clarify the effect of DF on fat absorption include steatorrhoea caused in part by malabsorption or maldigestion [52], a reduced bile flow [51] and/or increased concentrations of faecal bile and cholesterol excretion [53]. Lastly, weight reduction is associated with reduced intra-abdominal fat depots, at least in females [54]. Intra-abdominal fat represents a metabolically active depot that mobilizes free fatty acids (FFA) into the portal circulation [55]. Whether this FFA exposure stimulates PAI-1 secretion is not known. It is possible that human visceral

adipose tissue secretes PAI-1 [56] possibly through increased gene expression in adipocytes [57].

Insulin

PAI-1a [21,58] and t-PA [22,59] correlate strongly with insulin and insulin resistance. Acute decreases in the insulin concentrations lead to rapid alterations in the fibrinolytic system, namely PAI-1 decreases while t-PAa increases [60]. Insulin possibly regulates plasma PAI-1a directly by enhancing production and secretion of PAI-1 from endothelial cells [61] or hepatocytes [40,61]. Some of the ways that diet may affect insulin include modulating insulin secretion, affecting insulin action at peripheral sites, and/or influencing obesity or body weight [2]. It is generally accepted that DF exerts a major effect on the glycaemic and, therefore, insulinaemic response to high-carbohydrate intakes [62,63] and clinically significant reductions in insulin, glucose and TG are seen following high-fibre intakes [63] while insulin sensitivity increases [64]. Soluble fibre is fermented by anaerobic bacteria in the colon to short-chain fatty acids [65]. Acetate, a short-chain fatty acid, inhibits serum FFA release from adipocytes and results in lower FFA concentrations [66] which lead to increased insulin sensitivity [67] and may subsequently decrease PAI-1 concentration, given the positive correlation between hyperinsulinism and PAI-1 [35]. It seems that glucose also influences PAI-1 gene expression in vascular smooth muscle cells, which may explain increased PAI-1 concentrations in hyperglycaemia and diabetes [68]. Differences in GlIs in the different studies may contribute to differences seen in insulin and glucose responses. One of the three studies in this systematic review that measured insulin was a well-controlled, clinical trial and reported a significant decrease [21]. The other two studies were both supplemental studies, one in which insulin increased significantly after a five week adaptation period with insoluble oat husk fibre [20]. In the other instance insulin concentrations were unchanged [29]. A phenomenon has been observed that for some parameters, individuals with the highest initial concentrations are also the most responsive [27]. Conversely, in healthy, non-obese patients with already low baseline concentrations of insulin it evidently was not possible to lower insulin further with high-fibre intakes, even if glucose utilisation in the skeletal muscles and adipose tissue was enhanced [29].

Triacylglycerols and very low-density lipoprotein

Positive correlations between TG concentrations and those of t-PAag [38] and PAI-1a [38] have been demonstrated in several studies, including those being reviewed here [17,20,21,27]. Therefore, the possibility of improving and even normalising fibrinolytic potential through the reduction of hypertriglyceridaemia was suggested [69]. Studies investigating this relation with TG brought forward the following factors to consider: duration of high carbohydrate consumption, type and amount of carbohydrates consumed as well as the baseline TG status of the individual. Short-term studies consistently show that raising the carbohydrate content of the diet increases serum TG concentrations [34,63] but not over the long-term [17,70,71]. This interim rise in serum TG concentrations seems to be dependant on the total (moderate *versus* high), as well as type (sugar *versus* low-GI starches) of carbohydrates consumed [72,73]. The mechanism by which high-GI starches increase TG concentrations appears to involve their effect on glycaemia and insulinaemia [74]. It was suggested that soluble fibre might counteract the hypertriglyceridaemic effect of carbohydrates [71] because low-GI foods and high DF intakes are known to reduce serum insulin and glucose responses [63]. TG is a precursor for the hepatic synthesis of VLDL [75] and a rise in TG will thus be accompanied by increased VLDL concentrations. Increased VLDL concentrations (*in vitro* [76] and *in vivo* [77]) increase the production and/or release of PAI-1. A population-based study indicated that insulin may regulate plasma PAI-1a indirectly by increasing the synthesis of TG-rich VLDL from the liver [40]. The ability of insulin to increase TG elimination and to inhibit FFA release from fat cells might also play a role [60]. Furthermore, there are substantial differences in various aspects of coagulation and fibrinolysis between patients with hypertriglyceridaemia and normolipidaemic subjects [78]. A significant lowering of TG was found in a three-week study of obese, hypertriglyceridaemic subjects which showed a correlation between TG and both t-PAag and PAI-1a before and after the high complex carbohydrate dietary intervention [27]. Similarly, Jenkins *et al.* [79] showed that low-GI diets decrease serum TG concentrations in patients with hypertriglyceridaemia. In contrast, studies of non-obese participants with baseline TG concentrations falling within the reference values, showed increased TG concentrations during the first few weeks on an increased DF intake [20,26]. In a study by Marckmann *et al.* [26] the rise in TG was accompanied by a decrease in coagulability, as indicated by factor VII values and increased fibrinolytic activity. Thus, an elevated fasting TG concentration caused by the introduction of a

low-fat/high-fibre diet seems to be associated with decreased blood thrombogenicity and might have physiological implications different from those of hypertriglyceridaemia from other causes [26]. Changes in t-PA that did not correlate with TG [80] may indicate that dietary changes can favourably affect fibrinolysis independent of blood lipids. Studies included in this review with significant decreases in PAI-1 also showed significant decreases in TG from baseline to end [21,27,28] or significant differences between groups [29]. In the three studies that did not show a significant effect on PAI-1, TG concentrations were unchanged [17,19] or showed a significant increase compared to concentrations on a low-fibre diet [26].

The possible mechanisms through which DF may have influenced PAI-1 and t-PA include effects on insulin, TG-rich lipoproteins, FFA and changes in body weight as shown schematically in **Figure 1**.

Dosage

The minimum daily DF intake that showed significant changes in t-PA and PAI-1 in studies included in this review were 3.3 g/MJ DF and 4.5 g/MJ DF respectively in healthy, obese and metabolic syndrome subjects. The Dietary Reference Intake (DRI) for male adults (19-50 years) is 38g DF/day and 25g DF/day for females [81] and is compared to the fibre intakes of studies in this review in **Table 6**. The DRI recommendations may be sufficient to alter t-PA, but not PAI-1 concentrations.

Future studies and limitations

Future studies should attempt to reduce the large intra-individual variability by using repeated measurements on every intervention level. Since t-PA and PAI-1 have a strong circadian pattern [87] it is essential that studies of this system are properly controlled. It is advisable, therefore, to define the 24-hour pattern of plasma t-PA and PAI-1 in patient groups before concentrations based on a single blood sampling time are compared to those of a control population [88]. The possible confounding effect of weight loss should also be investigated. Differentiation between the possible effects of the different types of DF and dosage thereof will be useful.

A limitation of this study is that we could not account for possible genetic differences and the possibility of publication bias remains. Data analysis was limiting since most of the comparisons were within groups and effect sizes could not be calculated due to lack of information on control groups. Lack of placebo's prevented meaningful conclusions. The dietary interventions were restrictive as we were unable to determine whether individual components of the diet accounted for the changes observed or whether the changes in t-PA and PAI-1 are a result of the sum of all the dietary and/or lifestyle changes.

Conclusions

This systematic review concludes that increased intakes of DF reduces PAI-1a and increases tPAa and in doing so supports observational data suggesting a role of DF in CVD risk reduction. Diets with daily DF intakes containing ≥ 3.3 g/MJ and ≥ 4.5 g/MJ had significant effects on t-PAa ($\uparrow 14$ -167%) and PAI-1a ($\downarrow 15$ -57%) respectively. Diets high in DF are often low in fat, making it difficult to separate the individual effects. However, supplemental fibre administered with meals in a way that decreases their effective GIs/glycaemic loads is also useful for influencing haemostatic variables favourably [20,29] without altering other components of the diet. The physiological mechanism of DF is mainly via its effects on insulinaemic and glycaemic responses, TG-rich lipoproteins, FFA and changes in body weight. Additional research is needed before firm conclusions can be made about the potential favourable effects of DF on t-PA and PAI-1.

Acknowledgements

None.

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Several guidelines and checklists are available for the reporting of essential elements of randomized, controlled trials, including cluster trials (11-15); meta-analyses of randomized, controlled trials (16); meta-analyses of observational studies (17); observational studies (18); nonrandomized evaluations of behavioral or public health interventions (19); economic analyses (20); case reports of adverse drug reactions (21); diagnostic test studies (22); and guidelines (23, 24). We expect authors of reports in one of these categories to include the elements suggested by the guidelines.

We advise authors to arrange components of manuscripts in the following order (see below for further instructions): title page, abstract, text, acknowledgements (if any), references, tables in numerical sequence, figure legends, figures in numerical sequence, and appendices (if any). Number all pages consecutively, starting with the title page. List the word count of the text of the manuscript at the bottom of the title page. Double space the text of the manuscript.

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Systematic Reviews, including Meta-Analyses

Background, Purpose, Data Sources, Study Selection, Data Extraction, Data Synthesis, Limitations, Conclusions.

Manuscript text

For original articles, economic analyses, systematic reviews, and meta-analyses, use 4 main headings when arranging text: Introduction, Methods, Results, and Discussion. Aim for clear and concise and logically organized presentations. Avoid convoluted sentences and use active voice, whenever possible. Specific guidance regarding text content follows.

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Results: Fully describe the study sample so that readers can gauge how well the study findings apply to their patients (external validity). Then present primary findings followed by any secondary and subgroup findings. Use tables and figures to demonstrate main characteristics of participants and major findings. Avoid redundancy between text and tables and figures.

Discussion: Consider structuring the discussion according to the following sequence. First, provide a brief synopsis of key findings, with particular emphasis on how the findings add to the body of pertinent knowledge. Second, discuss possible mechanisms and explanations for the findings. Third, compare study results with relevant findings from other published work. Briefly state literature search sources and methods (e. g. , English-language MEDLINE search to January 2007) that identified previous pertinent work. Use tables and figures to help summarize previous work when possible. Fourth, discuss the limitations of the present study and any methods used to minimize or compensate for those limitations. Fifth, mention any crucial future research directions. Sixth, conclude with a brief section that summarizes in a straightforward and circumspect manner the clinical implications of the work.

Acknowledgements section

Acknowledge only persons who have contributed to the scientific content or provided technical support. Authors should obtain written permission from anyone who they wish to list in the Acknowledgements section. The corresponding author must also affirm that he or she has listed everyone who contributed significantly to the work in the Acknowledgements.

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3

Dietary fibre, factor VII and fibrinogen

Systematic review:
**The effects of dietary fibre on factor VII and
fibrinogen in humans**

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Abstract

Background

Epidemiological studies show that higher plasma factor VII coagulant activity (FVIIc) and fibrinogen concentrations are associated with greater risk of cardiovascular disease (CVD), the major cause of death worldwide. High-fibre intakes have consistently been associated with a reduction in CVD risk.

Purpose

The objective of this study was to assess the evidence from clinical trials that is related to the influence of dietary fibre (DF) on factor VII (FVII) and fibrinogen.

Data Sources

Electronic databases were searched from the earliest record to May 10, 2006 and supplemented by crosschecking reference lists of relevant publications.

Study Selection

Human intervention trials with an increased and measurable consumption of DF were included.

Data Extraction

From the literature search, 10 studies were identified that were rated based on the methodology as it appeared in the publications.

Data Synthesis

No formal statistical analysis was performed due to the large differences in study designs of the dietary intervention trials. High DF intakes did not have a significant effect on fibrinogen possibly because of relatively little weight loss, too low DF dosages and maintaining a good nutritional status. Inadequate study designs hinder conclusions. Significant decreases in FVIIc (6-16%) were observed with ≥ 3.3 g DF/MJ and concomitant decreased saturated fat intakes in healthy and hypertriglyceridaemic subjects. Confounding factors include weight loss and decreased intake of saturated fats. The type of fibre seems to be a factor as well. Mechanisms through which DF may reduce FVII concentrations include its effects on triglyceride-rich lipoproteins, insulin and weight loss.

Limitations

Limitations of the studies reviewed include inadequate study designs, possible publication bias, not able to determine whether individual components of the diet accounted for the changes observed or whether the changes in FVII are a result of the sum of all the dietary changes, namely reduced saturated fat and increased DF intakes.

Conclusions

Appropriately designed intervention trials are needed to elucidate the epidemiological relation between DF and fibrinogen and study the potential favourable effects of DF on FVII observed in this review and to isolate the effects of DF from that of low-saturated fat intakes.

KEY WORDS: Systematic review, dietary fibre, factor VII, FVII, fibrinogen

Introduction

Prospective investigations report that higher fibrinogen (1;2) and plasma factor VII coagulant activity (FVIIc) concentrations (2;3) are associated with a greater risk of cardiovascular disease (CVD) which continues to be the major cause of death worldwide (4). Fibrinogen, the soluble protein that polymerises to form fibrin networks, has been studied extensively. Plasma fibrinogen is a foremost, independent risk factor for CVD including stroke and myocardial infarction and is associated with ischaemic heart disease (IHD) (1). Elevation of one standard deviation in fibrinogen is associated with an increased risk of 84% for IHD within five years (5). Factor VII (FVII) is the plasma serine proteinase responsible for initiating clotting (6). FVII activity (FVIIa) is the first enzyme of the blood coagulation system and serves a priming function for triggering of the clotting cascade. FVIIc is the total activity of factor VII in plasma. The Northwick Park Heart Study (5) demonstrated a strong relationship between the level of FVIIa and the later incidence of IHD and coronary heart disease (CHD) in healthy males and estimated that an increase of one standard deviation (approximately 25%) in FVIIc will increase the risk of fatal IHD within 5 years by 55% (5). However, subsequent studies showed discrepancies (2;6;7). More recently, the prospective relationship of fibrinogen and FVIIc with the risk of CHD and stroke was investigated in a cohort of 22715 men (aged 45-69 years) over a period of 15 years (3). A persistent association between fibrinogen and CHD beyond ten years was found and may imply a causal effect (3). There was a small effect of FVIIc on CHD after adjusting for age and trial treatment, but no association was found independent of other risk factors (3). Similar results have been reported in a community-based case-control study of women aged ≤ 65 years (8). The odds ratio (OR) for CHD for the highest *versus* the lowest quartile of factor VII antigen (FVIIag) was 1.75 [95% confidence interval (CI), 1.05; 2.92] (8). The adjusted OR was 0.76 (95% CI, 0.28; 1.98) after controlling for other cardiovascular risk factors (8). The corresponding ORs for FVIIa were non-significant. Thus, FVIIa was not significantly increased in women with CHD and FVIIag levels, although elevated, were not independently associated with apparent disease (8).

Emphasis on dietary factors is one of the approaches currently advocated to prevent CVD (9). Data from the Atherosclerosis Risk in Communities Study obtained from over 12000 men and women indicate that elevations in FVII and fibrinogen may be modifiable through changes in the diet (10). In large cohort studies high-fibre intakes

have consistently been associated with reduction in CHD risk factors (11;12). DF intake studies show an independent, inverse relationship between the level of total DF (13-15), water-soluble DF (16), cereal fibre (15), whole-grain intake (17) and risk of subsequent CHD (14-16), IHD (17) and myocardial infarction (13). Nearly two decades ago researchers suggested that this protection with an increased fibre intake may be mediated by improvements in haemostasis (18).

In cross-sectional (19) and experimental studies (20-24), high-fibre intakes are associated with lower FVIIc concentrations (5-15%) in healthy (19-22) mildly hypercholesterolaemic (23) and severe hypertriglyceridaemic individuals (24). In contrast, others researchers reported no significant deviation in FVII from baseline levels with a higher DF intake (25;26). High DF intake is, furthermore, correlated with low fibrinogen concentrations (27;28). The aim of this systematic review is to evaluate scientific data to determine if, and if so to what extent, DF affects FVII and fibrinogen concentrations.

Methods

Subjects

A total of 428 subjects (282 men, 135 women, 11 mixed) were included in the studies summarised in this systematic review. Participants with high triglyceride (TG) concentrations (n=25) made up 6% of the study population. The remainder of participants were healthy.

Inclusion and exclusion criteria

Human adult (men and women) trials with a duration of two weeks or longer in fibre supplementation or clinical studies involving interventions with an increased and measurable consumption of DF, with an intake higher than the habitual were included. Subjects were excluded if diabetic, suffering from CHD or had had a heart attack.

Outcome measures

The primary outcome measures were percentage differences between intervention and control groups, or baseline to end comparisons for factor VII coagulant activity (FVIIc), activated factor VII (FVIIa) and fibrinogen.

Data sources

To identify potential studies, literature searches were performed in electronic databases. EbscoHost (29) was used as a gateway to the records in MEDLINE [Pubmed], Academic Search Premier, Clinical Pharmacology, Health Source: Nursing/Academic Edition, Health Source: Consumer Edition and Biological & Agricultural Index. In addition, The Cochrane Library (30), Science Direct (31), Web of Science (32) and EMBASE (33) were also searched. Databases were searched from the earliest record to May 10, 2006. Reference lists of relevant publications were crosschecked manually to ensure that all applicable papers were included. Search terms included fibrinogen, factor VII (FVII), dietary fibre (fiber), non-digestible carbohydrate(s), lignin(s), non-starch polysaccharide(s), functional fibre, haemosta*, nutrition*, food. Medical subject headings (MeSH) such as 'haemostatic' and 'hemostatic' were combined with the key search words in the Medline search.

Study selection and data extraction

Two assessors screened the identified studies to determine eligibility for inclusion into the review. Using a standardised form, data was extracted to determine the quality of all the selected intervention studies.

Data synthesis

A rating based upon the methodology as it appeared in the publication was given to each of the selected studies. The following criteria for quality assessment of the intervention trials were used [adapted from Verhagen *et al.* (34)]: (1) the study was controlled; (2) justified sample size; (3) groups were similar at baseline regarding the most important prognostic indicators; (4) compliance was acceptable; (5) randomisation was performed; and (6) in case of cross-over trials: no order of treatment effect. The following quality scores were assigned: 1 = if all the above criteria were present or if the study was controlled and one criterion was missing; 2 = if the study was controlled and

two criteria were missing; 3 = if the study was not controlled or ≥ 3 criteria were missing. Furthermore, the letter *a* was assigned for controlled feeding trials and *b* for studies conducted under free-living conditions. No formal statistical analysis was performed due to the large differences in study designs of the clinical trials. This study had no external funding source.

Results

Of the 1306 articles screened (titles, abstracts, original research and review articles) 10 original research papers were identified that were suitable for inclusion in this systematic review. Of the 10 studies, seven received a “1” or “2” rating. **Table 1** presents a summary of the attributes of the studies and participants. The experimental design of these studies was variable, subjects' characteristics differed, as did the amount and type of fibre consumed, duration of the studies, the control diets and sample sizes. In this review, the majority of the DF intervention studies were also low in total fat. **Table 2** summarises the macronutrient composition of dietary intakes, sources of fibre, compliance and weight loss in each study.

Table 1 Summary of characteristics of studies and participants

	Summary result	Number of studies reporting (n=10)
Fibre intake gram per megajoule/day [mean (range)]	4.4 (2.5 [*] -10.7)	10
Studies using supplements [mean (range)]	3.5 (2.5-4.5)	2
Studies utilising diets [mean (range)]	4.6 (3.2-10.7)	8
Study duration (weeks) [mean (range)]	6.6 (2-35)	10
Studies using supplements (weeks) (range)	4 (2-6)	2
Studies utilising diets (weeks) (range)	7.3 (2-35)	8
Participants completed (n) (dropouts)	428 (19)	10
Studies using supplements (n) (dropouts)	36 (4)	2
Studies utilising diets (n) (dropouts)	392 (15)	8
Age men (years) [mean (range)]	40.3 (18-72)	9
Age women (years) [mean (range)]	41 (18-72)	7

* excluding fibre from dietary intake

Table 2 Macronutrient composition, dietary fibre intake, compliance and weight loss reported in intervention trials

	Intervention								Control					
Reference study	Type / source of dietary fibre	DF g/d	DF g/MJ	PRO %	CHO %	FAT %	Compliance	Weight change (kg) Significance	Control diet / type / source of dietary fibre	DF g/d	DF g/MJ	PRO %	CHO %	FAT %
SUPPLEMENTAL STUDIES														
Landin <i>et al.</i> , 1992 (35)	Guar galactomannan	30*	2.5*	2	63.4	29.5	Good Remaining granulate was weighed	Unchanged	Placebo	NR	NR	2.1	63.9	28.1
Sundell & Ranby, 1993 (26)	Oat husk †	35	4.5	14.5	54.6	29.4	Not reported Four were excluded due to failure to comply	+ 0.2 NS	No control					
DIETARY INTERVENTION STUDIES														
Fehily <i>et al.</i> , 1986 (36)	High cereal fibre (whole-meal bread, whole-grain cereals, bran)	31	3.2	15.0	47.3	36.9	Good Food diaries kept and weighed inventories	+0.3 p<0.05	Low cereal diet	19	1.9	14.2	45.9	38.5
Mehrabian <i>et al.</i> , 1990 (37)	Mostly vegetarian	NR	8.3-10.7	13	77	<10	Good Controlled feeding trial	-4.6 NR	Controls (2) habitual diet					
Marckmann <i>et al.</i> , 1993 (20)	Low-fat, high-fibre	56	4.5	14	58	26	Good Controlled feeding trial	M -0.3 W -0.9 NR	Habitual diet	28	2.2	14	47	35
Marckmann <i>et al.</i> , 1994 (38)	Bread, cereals, fruit, vegetables	34	3.3	14	57	28	Good Controlled feeding trial	-0.5 p<0.05	Average Danish diet	22	2.1	13	47	39
Marckmann <i>et al.</i> , 2000 (21)	Low-fat, high-fibre	31	3.4	13	59	28	Good Feeding trial Prepackaged food and left-overs recorded	-0.7 p<0.05	High-sucrose diet	20	1.9	13	59	29
									High-fat diet	22	2.2	13	41	46
Turpeinen <i>et al.</i> , 2000 (39)	Whole-meal rye bread	M 31 W 26	M 3.6 W 3.7	M 17 W 17	M 49 W 49	M 31 W 33	Good Food diaries kept	Unchanged	Low-fibre wheat bread	M 15 W 12	M 1.6 W 1.7	M 17 W 16	M 48 W 51	M 33 W 32
Junker <i>et al.</i> , 2001 (22)	Whole-grain bread and cereal, vegetables, fruit, specially formulated muesli	↑-fat 50 ↓-fat 51	↑-fat 5.0 ↓-fat 5.4	↑-fat 20 ↓-fat 18	↑-fat 40 ↓-fat 54	↑-fat 39 ↓-fat 27	Good Part of foodstuffs provided to subjects	↑-fat: -1.5 p<0.001 ↓-fat: -0.8 p<0.05	Habitual diet	26	2.5	17	41	37
Most <i>et al.</i> , 2005 (40)	Defatted rice bran incorporated into muffins, cookies and breads	33	2.7 - 3.6	13	51	37	Good Controlled feeding trial	Unchanged	Low-fibre diet	17	1.3 - 1.8	12	51	37

Abbreviations used: M, men; W, women; ↑, high; ↓, low; g/MJ, gram per megajoule; g/d, grams per day; kg, kilograms; NR, not reported; DF, dietary fibre; PRO, protein; CHO, carbohydrates; NS, not significant.

* excluding fibre from dietary intake

† 99% insoluble fibre

Fehily *et al.*, 1986 (36) Intervention: Alcohol 11.5 g/day; Control: Alcohol 13.6 g/day

Mehrabian *et al.*, 1990 (37) Daily portion of milk and 85g fish/chicken per week

Marckmann *et al.*, 1993 (20) Intervention: Alcohol 2%; Control: 4%

Marckmann *et al.*, 1994 (38) Intervention and control: Alcohol 1%

Junker *et al.*, 2001 (22) Intervention: Alcohol 0.2%; Control: Alcohol 5.2%

The duration of the studies varied between 2-35 weeks. The length of the shortest dietary intervention period in this systematic review, namely two weeks, was sufficient to achieve stabilisation of FVII (41-44). Fibrinogen is an acute phase reactant whose plasma level is highly labile and can be rapidly increased (within one day) by a variety of stimuli (45). The number of subjects per study ranged between 11 and 201. This may have been sufficient to detect clinically significant changes in FVII and fibrinogen with the exception of one study (n=11) (26). Calculations with 80% power at 5% significance indicated that 12 study subjects are required to detect clinically significant changes in fibrinogen and 15 for FVII. Selected characteristics of each study and their subjects are shown in **Table 3**. Excluding one trial, all the other studies were older than five years. Possible explanations for inconsistent results found between studies are given in the discussion.

Only one study (with a low quality score) assessed FVIIa concentrations and found a significant decrease on a high-fat/high-fibre diet (5.0 g/MJ DF) (22) (**Table 4**). Following the first intervention, a low-fat/high-fibre diet (5.4 g/MJ DF) in the same study produced a non-significant increase in FVIIa (22). **Table 4** presents the data of seven studies that measured FVIIc. The effect of an insoluble oat husk supplement was researched in healthy individuals and a non-significant increase in FVIIc was seen (26). The research group of Junker *et al.* (22) found a significant decrease ($p<0.001$) in FVIIc concentrations on a high-fat/high-fibre (5.0 g/MJ) diet in hypertriglyceridaemic men. The sequential low-fat/high-fibre (5.4 g/MJ) diet that followed immediately, could not produce a significant change in FVIIc (22). Both the afore-mentioned studies had low quality scores. Marckmann and colleagues carried out three high quality studies. In the first of these, a parallel study, they compared changes in FVIIc from baseline to end in healthy men over a period of eight months with 4.5 g/MJ DF (intervention group) (20). A highly significant ($p<0.0001$) decrease in FVIIc was found (20). After comparing two study groups in a cross-over trial, a significant difference ($p<0.05$) between the values of FVIIc were reported with consumption of 3.3 g/MJ DF (88% FVIIc) compared to 2.1 g/MJ DF (96% FVIIc) (38). In another study a significant difference between groups (3.4 *versus* 1.9 *versus* 2.2 g/MJ DF) was found in the postprandial state, but not in fasting FVIIc concentrations (21). As indicated in **Table 2**, these three studies reported reductions in body weight which were significant in two instances. FVII concentrations differed insignificantly between groups in a study (quality score = 1) comparing rye with whole-wheat bread with no changes in body weight (39). Lastly, no significant

Table 3 Characteristics of studies and participants

Mean amount of fibre (g/MJ) consumed in intervention groups	Intervention diet	Cross-over / Parallel	Reference study	Total number of participants that completed the study (number of Men/Women [total dropouts])	Selected inclusion criteria	Participant characteristics: nationality, mean age and BMI	Duration of intervention	Comparison made	Quality score
SUPPLEMENTAL STUDIES									
2.5 g/MJ supplement (excluding dietary intake)	Very low protein intake (1-2%)	Cross-over	Landin <i>et al.</i> , 1992 (35)	n=25M	Healthy, non-obese	Sweden BMI: 25 52 y	6 wk	Placebo	1b
4.5 g/MJ	10 g/d supplement	Within subject comparison	Sundell & Ranby, 1993 (26)	n=11 M&W	Healthy, non-obese	Sweden BMI: NR 32 y	2 wk	Baseline	3b
DIETARY INTERVENTION STUDIES									
3.2 g/MJ	High cereal fibre diet	Cross-over	Fehily <i>et al.</i> , 1986 (36)	n=201: 147M, 54W	Healthy	England BMI: NR 36 y [M], 41y [W]	4 wk	Low cereal fibre diet	1b
8.3-10.7 g/MJ	Mostly vegetarian (low-fat/high complex carbohydrate)	Parallel	Mehrabian <i>et al.</i> , 1990 (37)	n=27: 12M, 15W	Obese	USA BMI: NR 58 y	3 wk	Prudent diet	3a
4.5 g/MJ	Low-fat/high-fibre diet	Parallel	Marchmann <i>et al.</i> , 1993 (20)	n=32M	Healthy, non-obese	Denmark BMI: 21 24 y	8 mo	Control	2a
3.3 g/MJ	Low-fat/high-fibre diet	Cross-over	Marchmann <i>et al.</i> , 1994 (38)	n=21: 10M, 11W	Healthy, non-obese	Denmark BMI: 24[M], 23[W] 53 y	2 wk	High-fat, low-fibre diet	1a
3.4 g/MJ	High-fibre starch diet	1.9 g/MJ	High-sucrose diet	2.2 g/MJ	High-fat diet	Denmark BMI: 23 39 y	2 wk	High-sucrose and high-fat diets	1a
3.6-3.7 g/MJ	High-fibre intake from whole-meal rye	n=40: 18M, 22W	Healthy, non-obese	TC: 5.5-7.5 mmol/L TG < 2.5 mmol/L	Finland BMI: 26[M], 24 [W] 43 y	4 wk	Low-fibre wheat diet	1b	
5.0 g/MJ	High-fat diet rich in PUFA & MUFA	n=25M	Non-obese	TG > 2.3 mmol/L	Germany BMI: 26 40 y	3 wk	Baseline diet	3b	
2.7-3.6 g/MJ	High-fibre diet with defatted rice bran	n=26: 13 M, 13W	Healthy, non-obese	LDL < 4.9 mmol/L TG < 90 th percentile	USA BMI: 24 33 y	5 wk	Control diet	1a	
Mostafaei <i>et al.</i> , 2005 (40) Parallel									

Abbreviations used: M, men; W, women; wk, week(s); mo, months; y, years; g/MJ, gram per megajoule; BMI, body mass index; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; NR, not reported; USA, United States of America; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoproteins; a, controlled feeding trials; b, studies conducted under free-living conditions. Quality score of publication: 1=high; 3=low.

Table 4 Effect of fibre on factor VII coagulant activity (%) and activated factor FVII (mU/ml) in intervention and dietary supplemental studies

Mean amount of fibre in intervention groups Intervention diet Reference study	INTERVENTION			CONTROL			Summary of results	Quality score
	Baseline [mean (SD) or median (range)]	Trial end [mean (SD) or median (range)]	% change from baseline to end * (p-value or significance) or difference between groups † (p-value or significance)	Baseline [mean (SD) or median (range)]	Trial end [mean (SD) or median (range)]	% change from baseline to end (p-value or significance)		
FVIIc (%)								
4.5 g/MJ 10 g/d supplemental study Sundell & Ranby, 1993 (26)	89.3 (13.3)	95.6 (36.2)	+7.1 * NS	No control			Non significant increase in FVIIc after 2 wk supplement	3b
4.5 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1993 (20)	93 (67-128)	84 (69-103)	-9.7 * p<0.0001	100 (57-123)	97 (72-169)	NS p=0.75	Significant decrease in FVIIc after 8 month low-fat/high-fibre diet	2a
3.3 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1994 (38)	Period 1: 104 (74-150) Period 2: 102 (83-150)	88 (84-110)	Period 1: -15.4 * Period 2: -13.7 * p=0.002	Period 1: 104 (74-150) Period 2: 102 (83-150)	96 (91-114)	Period 1: -7.7 NR Period 2: -5.9 NR	Significant decrease in FVIIc after 2 wk low-fat/high-fibre diet	1a
3.4 g/MJ High-fibre starch diet 1.9 g/MJ High-sucrose diet 2.2 g/MJ High-fat diet Marckmann <i>et al.</i> , 2000 (21)	No baseline values taken	<u>Fasting:</u> Starch: 97 (3.7) <u>Non-fasting:</u> Starch: 99 (4.4)	<u>Fasting:</u> Starch – Sucrose: -6.7 † NS Fat – Starch: 3.4 † NS Fat – Sucrose: -2.9 † NS <u>Non-fasting:</u> Starch – Sucrose: -9.8 † p=0.004 Fat – Starch: 9.6 † p=0.003 Fat – Sucrose: 2.1 † p=0.63	No baseline values taken	<u>Fasting:</u> Sucrose: 103 (3.6) Fat: 101 (3.6) <u>Non-fasting:</u> Sucrose: 107 (4.6) Fat: 109 (4.9)		High-fibre, high-starch intake was associated with lower non-fasting FVIIc than high-sucrose and high-fat diets after 2 wk	1a
3.6-3.7 g/MJ High-fibre from whole-meal rye Turpeinen <i>et al.</i> , 2000 (39)	Men 99.7 (4.7) Women 103.6 (4.1) All 101.9 (3.1)		Men 2.1 † Women 4.5 † All 3.4 †	Men 101.8 (3.3) Women 108.1 (5.6) All 105.3 (3.4)			No significant differences between high-fibre rye and low-fibre wheat bread (1.6-1.7 g/MJ)	1b
5.0 g/MJ High-fat diet rich in PUFA & MUFA 5.4 g/MJ Low-fat/high-fibre diet Junker <i>et al.</i> , 2001 (22)	High-fat, high-fibre diet 129.1 (27.6) Low-fat, high-fibre diet 108.7 (19)	High-fat, high-fibre diet 108.7 (19) Low-fat, high-fibre diet 109.8 (20.4)	High-fat, high-fibre diet -15.8 * p<0.001 Low-fat, high-fibre diet +1 * NS	No control group			Significant decrease in FVIIc after 3 wk high-fat/high-fibre period	3b
2.7-3.6 g/MJ High-fibre diet with defatted rice bran Most <i>et al.</i> , 2005 (40)	81.7 (3.3)	85.5 (5.2)	+5 * NS	81.7 (3.3)	80.9 (5.6)	-1 NS	No significant differences from baseline to end after 5 wk rice bran	1a
FVIIa (U/ml)								
5.0 g/MJ High-fat diet rich in PUFA & MUFA 5.4 g/MJ Low-fat/high-fibre diet Junker <i>et al.</i> , 2001 (22)	High-fat, high-fibre diet 63.7 (11.4-148) Low-fat, high-fibre diet 59.9 (12.8-100.8)	High-fat, high-fibre diet 59.9 (12.8-100.8) Low-fat, high-fibre diet 63.9 (13-131.1)	High-fat, high-fibre diet -6 * p<0.05 Low-fat, high-fibre diet +6.7 * NS	No control group			Significant decrease in FVIIa after 3 wk high-fat/high-fibre period	3b

Reference value: FVIIc 108% (3).

The formula used was: (End value– Baseline value)/Baseline value x 100.

Abbreviations used: M, men; W, women; NR, not reported; NS, not significant; FVIIc, factor VII coagulant activity; FVIIa, activated factor VII; g/d, grams per day; g/MJ, gram per megajoule; SD, standard deviation; wk, week(s); CHO, carbohydrates; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; a, controlled feeding trials; b, studies conducted under free-living conditions. * % change from baseline to end † % difference between groups. Quality score of publication: 1=high; 3=low.

differences in FVIIc or body weight were seen following a five-week intervention with defatted rice bran in healthy subjects compared to baseline in a study with a high quality score (40).

The findings observed from the studies that measured fibrinogen, revealed an unfavourable significant change in one of the studies. An increase of 18% in fibrinogen concentrations ($p<0.05$) subsequent to a high-fat/high-fibre intervention (5.0 g/MJ) providing 3.6–4g of omega-3 fatty acids in men with hypertriglyceridemia was found (22). Daily supplementation with 4g omega-3 fatty acids has been previously reported to be associated with increased fibrinogen concentrations (46), a trend also observed cross-sectionally (47). The remainder of the studies did not have significant changes in fibrinogen as shown in **Table 5**.

Discussion

This review indicates that increasing DF intake may play a role in lowering FVII concentrations. This is supportive of cross-sectional data such as that of 3007 subjects, in which fibre intake was strongly and inversely associated with FVIIc in both men (0.31; 95% CI, -0.57; -0.06) and women (-0.36; 95% CI, -0.63; -0.09) (48). In contrast, no significant decreases were observed in fibrinogen concentrations following increased DF consumption.

Factor VII

Inconsistent results in FVIIc concentrations can be explained in a number of ways. The common denominator between the studies that did not show significant FVII changes seems to be higher levels of what was previously defined as insoluble fibre. Insoluble fibres such as the oat husk used in one of the studies are reported to have primarily bulk effects (49). The increased fibre intake in the study comparing rye with low-fibre whole-wheat was mostly contributed by insoluble fibre (220% increase) and a more modest soluble fibre increase (65%) (39). Similarly, defatted rice bran consumed in the study by Most *et al.* (40) is known to contain negligible amounts of water-soluble β -glucans and larger amounts of insoluble DF (50;51). In addition, lower saturated fat intakes were found in the studies that reported significant decreases in FVII (20-22;38)

Table 5 Effect of fibre on fibrinogen (g/L) in dietary intervention and supplement studies

Mean amount of fibre in intervention groups Intervention diet Reference study	INTERVENTION			CONTROL			Summary of results	QS
	Baseline [mean (SD) or median (range)] g/L	Trial end [mean (SD) or median (range)] g/L	% change from baseline to end * (p-value or significance) or difference between groups † (p-value or significance)	Baseline [mean (SD) or median (range)] g/L	Trial end [mean (SD) or median (range)] g/L	% change from baseline to end (p-value or significance) or difference between groups (g/L)		
3.2 g/MJ High cereal fibre diet Fehily <i>et al.</i> , 1986 (36)	High-fibre first: 3.34 (0.66) Low-fibre first: 3.37 (0.85)	High-fibre first: 3.30 (0.66) Low-fibre first: 3.33 (0.83)	High-fibre first: -1.2 * NS Low-fibre first: -1.2 * NS	Low-fibre first: 3.30 (0.66) High-fibre first: 3.30 (0.83)	Low-fibre first: 3.27 (0.70) High-fibre first: 3.37 (0.85)	Low-fibre first: -0.9 NS High-fibre first: -2.1 NS	High-cereal fibre diet had no detectable effect on fibrinogen	1b
8.3-10.7 g/MJ Mostly vegetarian (low-fat/high complex CHO) Mehrabian <i>et al.</i> , 1990 (37)	3.95 (0.69)	3.65 (0.79)	-7.6 * p=0.07	Not reported (n=2)			Non significant decrease in fibrinogen after 3 wk high complex carbohydrate, low-fat diet	3a
2.5 g/MJ supplement (excluding DF intake) Very low protein intake (1-2%) Landin <i>et al.</i> , 1992 (35)	NR	2.3 † (0.6)	NR	NR	2.4 (0.5)	0.1 NS	Unchanged fibrinogen levels after 6wk fibre supplement	1b
4.5 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1993 (20)	2.04 (1.43-3.27)	1.97 (1.6-2.82)	-3.4 * p=0.45	2.21 (1.87-3.4)	NR	NS p=0.60	Non significant decrease in fibrinogen after 8 month low-fat/high-fibre diet	2a
3.3 g/MJ Low-fat/high-fibre diet Marckmann <i>et al.</i> , 1994 (38)	Period 1: 2.07 (1.5-2.79) Period 2: 2.38 (1.46-3.64) p=0.01 between baseline values	2.18 (2.01-2.52)	Period 1: +5.3 * NS Period 2: -8.4 * NS	Period 1: 2.07 (1.5-2.79) Period 2: 2.38 (1.46-3.64) p=0.01 between baseline values	2.18 (2.01-2.45)	Period 1: +5.3 NS Period 2: -8.4 NS	No changes in fibrinogen after 2 wk low-fat/high-fibre diet	1a
3.4 g/MJ High-fibre starch diet 1.9 g/MJ High-sucrose diet 2.2 g/MJ High-fat diet Marckmann <i>et al.</i> , 2000 (21)	No baseline values taken	Fasting: Starch: 2.62 (0.12) Non-Fasting: Starch: 2.55 (0.14)	No baseline values taken	Fasting: Sucrose: 2.65 (0.12) Fat: 2.55 (0.12) Non-Fasting: Sucrose: 2.55 (0.13) Fat: 2.45 (0.11)	Fasting: Starch – Sucrose: 0.01 † NS Fat – Starch: 0.07 † NS Fat – Sucrose: 0.09 † NS Non-Fasting: Starch – Sucrose: 0.01 † NS Fat – Starch: 0.1 † NS Fat – Sucrose: 0.07 † NS	No baseline values taken, no significant differences between groups after 2 wk intervention	1a	
3.6-3.7 g/MJ High-fibre from whole-meal rye Turpeinen <i>et al.</i> , 2000 (39)	No baseline values taken	Men 3.61 (0.2) Women 3.33 (0.1) All 3.46 (0.1)	No baseline values taken	Men 3.22 (0.2) Women 3.26 (0.1) All 3.24 (0.1)	Men 0.39 † NS Women 0.07 † NS All 0.22 † NS	No significant differences between high-fibre rye and low-fibre wheat bread (1.6-1.7 g/MJ)	1b	
5.0 g/MJ High-fat diet rich in PUFA & MUFA 5.4 g/MJ Low-fat/high-fibre diet Junker <i>et al.</i> , 2001 (22)	High-fat/ high-fibre 2.45 (0.43) Low-fat/ high-fibre 2.89 (0.81)	High-fat/ high-fibre 2.89 (0.81) Low-fat/ high-fibre 2.74 (0.68)	High-fat/ high-fibre +18.0 * p<0.05 Low-fat/ high-fibre -5.2 * NS	No control group			Significant increase in fibrinogen after 3 wk high-fat/high-fibre period	3b

Reference value of fibrinogen: 2.8 g/L (3). The formula used was: (End value - Baseline value)/Baseline value x 100. Abbreviations used: NS, not significant; NR, not reported; DF, dietary fibre; CHO, carbohydrates; g/MJ, gram per megajoule; SD, standard deviation; wk, week(s); MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; g/L, gram per litre; a, controlled feeding trials; b, studies conducted under free-living conditions; QS, quality score; *, % change from baseline to end; †, % difference between groups. Quality score of publication: 1=high; 3=low.

compared to those which did not (39;40) (**Table 6**). This is consistent with a recent review by Lefevre *et al.* (2004) that identified a trend that saturated fats have adverse consequences on FVII whilst mono and omega-3 polyunsaturated fats do not (52). Two studies had poor quality study designs (22;26). One of the supplemental studies (26) with insignificant changes in FVIIc used a small study population of 11 healthy, non-obese subjects (26). That is not sufficient power to detect a clinical significance change in FVII. Furthermore, the absence of a placebo in this study made it impossible to draw meaningful conclusions (26). The type of assay used may also affect the results. Difficulties with blood sampling and assays exist because drawing blood by its nature tends to activate the haemostatic system. FVII was assayed in some of the studies (20; 21) by a test that measures clotting time in which both factor VII and factor VIIa contribute in unknown proportions (53).

The mechanism to explain the association of FVIIc and DF is unknown so far. TG may be involved since successful treatment of hypertriglyceridaemia is associated with a reduction in FVIIc, and FVII and TG are correlated (24). Very low-density lipoprotein (VLDL) is secreted by hepatocytes in response to endogenously synthesised TG (54). A rise in TG will thus be accompanied by increased VLDL concentrations (55). TG-rich lipoproteins may affect the extent of FVII activation (41) leading to an increase in the hepatic synthesis of vitamin K-dependent proteins such as FVII (56). Furthermore, Anderson *et al.* (2000) reviewed intervention studies and found that high-carbohydrate/low-fibre diets increase TG on average by 53% (95% CI, 34; 71) whereas, high-carbohydrate/high-fibre diets lead to a mean decrease of 10% (95% CI, -11; -71) (57).

The studies in this review that reported significant lowering in FVIIc levels had varying responses in TG levels. The only significant reduction in TG was observed in a low-quality score study and could be because hypertriglyceridaemic patients were used as the study subjects in whom it may be easier to lower TG concentrations (22). In the long-term study of eight months, TG levels remained unchanged (20) whilst TG increased in the remaining short-term studies (two weeks) (21;38). This is expected since it is well known that raising the carbohydrate content of the diet increases serum TG concentrations in the short-term (58) but not over the long-term (59;60). This interim rise in serum TG concentrations seems to be dependant on the total (moderate *versus*

Table 6 Total, saturated, monounsaturated and polyunsaturated fat content of the intervention and control studies and summarised outcomes of factor VII coagulant activity and fibrinogen

	INTERVENTION							CONTROL				
Reference study	Type / source of dietary fibre	SFA %	MUFA %	PUFA %	FAT %	Quality score and FVIlc result	Quality score and fibrinogen result	Control diet / type / source of dietary fibre	SFA %	MUFA %	PUFA %	FAT %
SUPPLEMENTAL STUDIES												
Landin <i>et al.</i> , 1992 (35)	Guar galactomannan	Not reported			29.5	FVIlc not measured	1b Unchanged fibrinogen levels after 6wk fibre supplement	Placebo	Not reported			28.1
Sundell & Ranby, 1993 (26)	Oat husk	P/S ratio: 0.59			29.4	3b Non significant increase in FVIlc after 2 wk supplement	3b Unchanged fibrinogen concentrations after 6 wk fibre supplement	No control				
DIETARY INTERVENTION STUDIES												
Fehily, <i>et al.</i> , 1986 (36)	High cereal fibre (whole-meal bread, whole-grain cereals, bran)	Not reported			36.9	FVIlc not measured	1b High-cereal fibre diet had no detectable effect on fibrinogen	Low cereal diet	Not reported			38.5
Mehrabian <i>et al.</i> , 1990 (37)	Mostly vegetarian	P/S ratio: 2.4			<10	FVIlc not measured	3a Non significant decrease in fibrinogen after 3 wk high complex carbohydrate, low-fat diet	Controls (n=2) habitual diet	Not reported			
Marckmann <i>et al.</i> , 1993 (20)	Low-fat, high-fibre	8.4	NR	6.3	26	2a Significant decrease in FVIlc after 8-month low-fat/high-fibre diet	2a Non significant decrease in fibrinogen after 8-month low-fat/high-fibre diet	Habitual diet	13.7	NR	5.1	35
Marckmann <i>et al.</i> , 1994 (38)	Bread, cereals, fruit, vegetables	8	8	6	28	1a Significant decrease in FVIlc after 2 wk high-fibre, low-fat/high-fibre diet	1a No changes in fibrinogen after 2 wk low-fat/high-fibre diet	Control diet	13	12	6	39
Marckmann <i>et al.</i> , 2000 (21)	Low-fat, high-fibre	9.8	11.2	7	28	1a High-fibre, high-CHO starch intake was associated with lower non-fasting FVIlc than high-CHO, high-sucrose and high-fat diets after 2 wk	1a No baseline values taken - no significant differences between groups after 2 wk interventions	Sucrose diet	11	10.7	7.5	29
								Fat diet	21	17	8.3	46
Turpeinen <i>et al.</i> , 2000 (39)	Whole-meal rye bread	M 12.3 W 13.3	M 10.4 W 10.9	M 4.5 W 4.5	M 31 W 33	1b No significant differences between high-fibre rye and low-fibre wheat bread (1.6-1.7 g/MJ)	1b No significant differences between high-fibre rye and low-fibre wheat bread (1.6-1.7 g/MJ)	Low-fibre wheat bread	M 12 W 12.6	M 10.8 W 9.6	M 4.5 W 3.5	M 33 W 32
Junker <i>et al.</i> , 2001 (22)	Whole-grain bread and cereal, vegetables, fruit, specially formulated muesli	8.3	15	16	39	3b Significant decrease in FVIlc after 3 wk high-fat/high-fibre period	3b Significant increase in fibrinogen after 3 wk high-fat/high-fibre period	Habitual diet	13.9	12.5	10.6	37
Most <i>et al.</i> , 2005 (40)	Defatted rice bran incorporated into muffins, cookies and breads	14.5	11.3	10.6	37	No significant differences from baseline to end after 5 wk rice bran	Fibrinogen not measured	Low-fibre control diet	14.6	11.4	10.6	37

Abbreviations used: NR, not reported; CHO, carbohydrates; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; FVIlc, factor VII coagulant activity; g/MJ, gram per megajoule; wk, week(s); P/S, polyunsaturated to saturated fatty acid ratio; a, controlled feeding trials; b, studies conducted under free-living conditions. Quality score of publication: 1=high; 3=low.

high), as well as type [sugar *versus* low glycaemic index (GI) starches] of carbohydrates consumed (21;61). The mechanism by which high-GI starches increase TG concentrations appears to involve its effects on glycaemia and insulinaemia (62). It was suggested that soluble fibre might counteract the hypertriglyceridaemic effect of carbohydrates (60) because low-GI foods and high-DF intakes are known to reduce serum insulin and glucose responses (58). The ability of insulin to increase TG elimination may also play a role (63). An accompanying decrease in coagulability as indicated by reduced factor VII values and increased fibrinolytic activity were seen in two of the studies, even though TG levels increased or remained unchanged (20;38). Thus, an elevated fasting TG concentration caused by the introduction of a low-fat/high-fibre diet seems to be associated with decreased blood thrombogenicity and might have physiological implications different from those of hypertriglyceridaemia from other causes (38). The simultaneous introduction of a low-fat diet in some of the studies needs further examination (20;21;38). A variety of studies have explored the potential effects of fat and its differential fatty acids compositions on FVII and were recently reviewed (52). Observations from population studies show a positive association between intakes of saturated fat and plasma levels of factor VII (47;48). FVII levels seem unaffected by omega-3 fatty acids (64;65) and monounsaturated fatty acids (MUFA) (66) in intervention trials but decline modestly with reductions in saturated fat intake (41). Replacement of saturated fat with either carbohydrate, MUFA, or polyunsaturated fatty acids (PUFA) produces essentially the same results (67-69), indicating that the effects seen are independent of total fat intake (67;68;70). A similar tendency was noted in the present investigation with the studies reporting significant lowering of FVIIc with simultaneous decreased saturated fat and increased DF consumption (20-22;38) (**Table 6**). However, one of the reviewed studies received a low quality score (22) while another found the significant change in FVIIc only in the postprandial state (21). Studies reporting unchanged FVII levels did not have differences in saturated fat intakes between intervention and control groups (39;40). A mechanism through which FVIIc may be influenced by saturated fats is via the release of free fatty acids (FFA) during lipolysis of TG-rich lipoproteins (68). In one of the intervention studies the reduction in FVIIc with saturated fat reduction was accompanied by a decrease in FVIIag, suggesting that these effects are the result of lower protein levels and not decreased activation (38).

Body weight

Body weight and BMI (body mass index) are positively associated with FVIIc (10) and decline when obese individuals lose weight (71). Significant weight loss was found in the four studies in this review that reported significant changes in FVII (Table 2) (20-22;38). One low quality score study ruled the influence of weight loss statistically out by multiple regression analysis (22). In a long-term study, subjects with a baseline BMI of 21 had lower mean body weight midway through the study, as were FVII concentrations, but at the end of the study body weight did not differ from initial mean body weight, even though lower FVIIc concentrations remained significantly lower (20). Weight loss could thus be a confounding factor that needs to be taken into consideration when studying FVII and dietary intervention trials. DF could play a role in the management of body weight through its effect on gastric emptying (72), satiety (73), gut hormones such as cholecystokinin (74;75) and an altered GI or insulinaemic response (76).

In summary, the suggested mechanisms through which DF might affect FVII include its effects on TG, insulin and reduced body weight and are presented in Figure 1. In the present investigation this transpired with a simultaneous decrease in saturated fat intake.

Fibrinogen

In the Coronary Artery Risk Development in Young Adults Study (CARDIA), a multicentre population-based cohort with 2909 participants, DF intake was associated with fibrinogen (11). Older epidemiological studies also reported an inverse relation (28;86), whereas data from the National Heart, Lung, and Blood Institute Family Heart Study (n=1999) did not find an association between fibrinogen and DF intake (80). The clinical studies in this review and in others (87;88), did not find any significant reductions in fibrinogen with higher intakes of DF (Table 5). Several explanations for this finding are possible. Vorster *et al.* (1988) (18) hypothesised that insulin resistance may affect hepatic synthesis of fibrinogen indirectly by increasing circulating FFA, a known stimulant of fibrinogen synthesis (45). Therefore, DF, which is known to decrease insulin requirements (58) and circulating FFA by means of microbial fermentation (89), is expected to lower fibrinogen levels via its effects on insulin sensitivity. However, several studies suggested that proinsulin is more important than insulin levels in the

determination of plasma fibrinogen (90-93). Only the two supplemental studies measured insulin, reporting a significant increase after five weeks of 5g oat husk intake during the adaptation phase (26) and improved insulin sensitivity with unchanged fasting insulin levels following 30 g/d guar gum intake for six weeks (35). None of the reviewed studies measured FFA. Also, it is now considered that the increased fibrinogen levels usually seen in metabolic syndrome patients are determined by overall adiposity rather than insulin resistance (94), shifting the attention to weight loss (95). Mean plasma fibrinogen levels tend to be lower following weight reduction (96). However, substantial weight loss of at least 10% of body weight seems necessary to lower fibrinogen levels significantly (97-100) and was not achieved in the studies included in this review [-1.1% (21); -1.7% (high-fat diet), -0.9% (low-fat diet) (22); -4.6% (37); -0.4% (males), -1.4% (females) (20) weight loss of total body weight]. The association between DF and weight regulation have often been reviewed, consistently validating the role of DF (72;101-104).

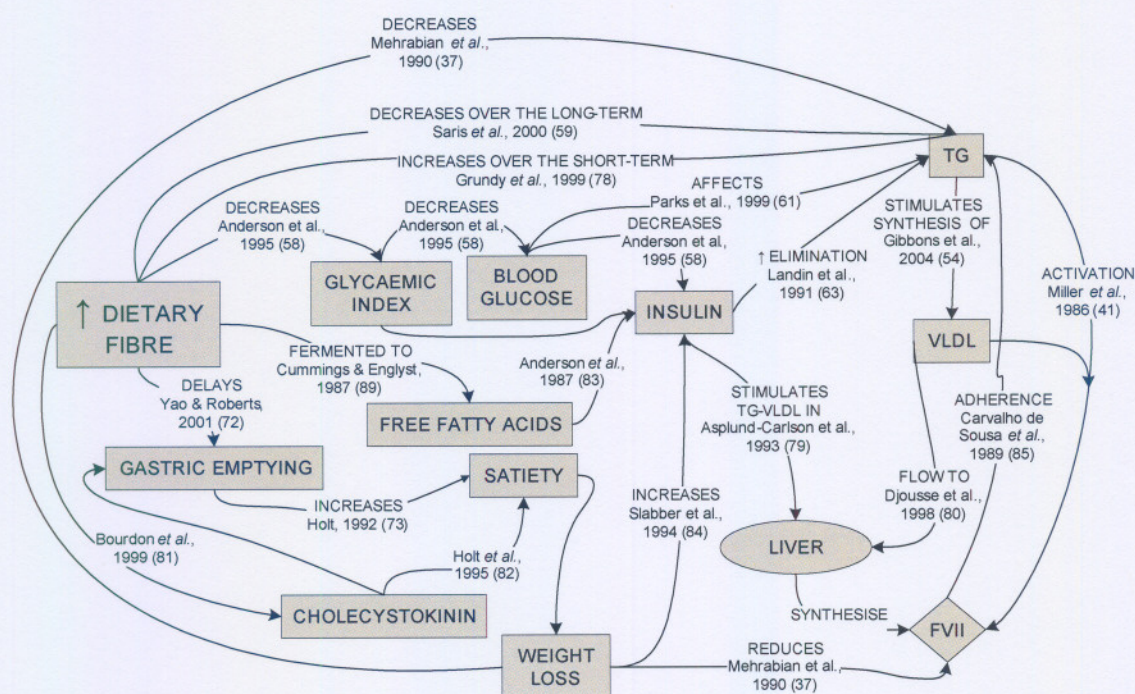


Figure 1 Schematic representation of possible mechanisms through which dietary fibre may affect factor VII

Abbreviations used: TG, triglycerides; VLDL, very low-density lipoprotein; FVII, factor VII; ↑, increase.

A newly identified determinant of plasma fibrinogen levels is the overall nutritional status (27) and may partially explain the results found in the intervention studies included in this review. In a cross-sectional survey of 1854 African men and women, it was reported that subjects with the worst nutritional status (over and undernutrition) had the highest fibrinogen levels (27). It is, therefore, possible that the subjects used in the studies reviewed here had optimal or at least a satisfactory nutritional status as they were described as "healthy" and mostly non-obese. Since the dietary interventions in general were in line with prudent dietary guidelines, the interventions were unlikely to have influenced the total nutritional status. This is also reflected in most of the studies as mean baseline fibrinogen levels fell within normal ranges (105). It has been shown to be difficult to improve a "normal" physiological parameter by means of increased DF intake (106;107).

Whether increased fibrinogen concentrations are a consequence or a cause of CHD remains debatable as contrasting evidence is available (1;3;108-111). It is possible that a high fibrinogen level may be both a marker and contributor of the inflammatory consequence of atherogenesis and (3), at the same time, a cause of CHD through its effect on thrombus formation (112).

Supplemental intervention trials in children (113) and animals (114-116) demonstrated lower fibrinogen concentrations with an increased fibre intake. In these studies DF came mostly from soluble gel-forming fibre sources [guar gum (113) and konjac-glucomannan (114-116)] compared to mixed sources in the studies reviewed here (**Table 2**). In addition, the amount of total DF ingested was relatively high, namely 34 g/d in baboons (mean weight 19kg) (115), 8.5 g/d in rats (116) and up to 20 g/d supplemented guar in 7-10 year old children (113), evaluated against the total DF intakes in this study in human adults ranging from 29-56 g/d (**Table 2**). The Dietary Reference Intake (DRI) for male adults (19-50 years) for DF is 38g/day and 25g/day for females (117) and are compared to the range of fibre intakes of studies in this review in **Table 7**. The reviewed studies with the highest dosages of DF received the lowest quality score hindering a meaningful deduction about the effect high dosages of DF might have. There is some evidence that increased intake of the saturated fatty acid, stearic acid, increases fibrinogen levels (42;118;119), however, due to differences in study designs and limited information about the fatty acid content, it is difficult to conclude what the effect of a particular fatty acid will have on fibrinogen from the

available literature (**Table 6**). Lastly, the widely-accepted influence of the specific genetic makeup of an individual on fibrinogen (120) seems mostly applicable to smokers (121-123) and interindividual variations (124) may also affect fibrinogen concentrations, most markedly during periods of rapid weight loss (96).

Table 7 Comparison of Dietary Reference Intakes for total fibre (g/MJ) per recommended energy intake in adults (40 years, 165 cm) with the range of fibre consumption in studies reviewed

Dietary Reference Intakes for dietary fibre (g/MJ)			Dietary fibre content from studies reviewed (g/MJ)
Physical activity levels	Men	Women	Men and women
	BMI: 18.5 - 25		Normal weight to obese
Sedentary	4.0 – 4.6	3.1 – 3.4	2.5* (35) – 10.7 (37)
Low active	3.7 - 4.2	2.8 – 3.1	
Active	3.3 - 3.8	2.5 – 2.7	

* Excluding fibre from dietary intake

Abbreviations used: g/MJ, gram per megajoule; BMI, body mass index.

Future studies and limitations

Future studies should attempt to distinguish between the effects of DF, weight loss and dietary fat intake on FVII and could be achieved through carefully designed supplemental studies. Mechanisms are not clear, as is the role of different dosages of DF on both FVIIc and FVIIa. Studies in this review with higher levels of insoluble fibre, did not show a significant lowering of FVIIc concentrations (39), indicating that protection from CHD is thus more likely to come from soluble fibre sources (26) and warrants further investigation (40). Appropriately designed intervention protocols, most likely supplementary in nature, are required to study the epidemiological relation between high DF intakes and fibrinogen on a clinical level.

Limitations of the studies reviewed include that they did not account for possible genetic differences (120;125) or differentiate between results per gender. Design problems exist with many of the trials including inadequate sample size, incomparable differences in dietary compositions and potential confounding variables such as weight loss. Data analysis was limiting since most of the comparisons were within groups and effect sizes

could not be calculated due to incomplete information on control groups. Lack of placebo's prevented meaningful conclusions and the possibility of publication bias remains. The dietary interventions were restrictive as we were unable to determine whether individual components of the diet accounted for the changes observed or whether the changes in FVII are a result of the sum of all the dietary changes, namely reduced saturated fat and increased DF intakes.

Conclusions

To date, fibrinogen appears to be resistant to change with increased DF intakes in human adults, however, poor study designs hampered advancement in this area. Considering the studies included in this review, unchanged fibrinogen concentrations are possibly due to the relatively little weight loss seen, too low a dosage of DF and sustaining a good nutritional status during intervention. The reviewed clinical studies support the epidemiological associations between lower FVII concentrations and higher intakes of DF, however, in the presence of decreased saturated fat intake. A significant reduction (6-16%) in FVIIc concentrations can be achieved following a dietary change to lower saturated fat and increased fibre content (3.3-4.5 g/MJ) (20-22;38). Furthermore, the type of fibre (soluble *versus* insoluble) seems to play a role with weight loss as a potential confounding factor. The potential mechanisms through which increased DF can affect FVII include changes in TG-rich lipoproteins and insulin, but much work is needed in carefully controlled studies to expand knowledge in this important area. Based on the findings in this review it seems justified to conclude that the optimal diet for lowering FVII is a combination of a diet lower in saturated fat and rich in DF of a mixed origin.

Acknowledgements

None.

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4

Dietary fibre and C-reactive protein

Systematic review: The effects of dietary fibre on C-reactive protein in humans

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Abstract

Background

C-reactive protein (CRP), a sensitive marker of inflammation, is an independent predictor of future cardiovascular disease (CVD), a major cause of death worldwide. High-fibre intakes have consistently been associated with reduction in CVD risk.

Purpose

The objective of this study was to assess the influence of dietary fibre (DF) on CRP in clinical trials.

Data Sources

Databases were searched from the earliest record to May 2006 and supplemented by crosschecking reference lists of relevant publications.

Study Selection

Human adult intervention trials, at least two weeks in duration, with an increased and measurable consumption of DF were included.

Data Extraction

From the literature search, two reviewers identified studies that were rated for quality based on the methodology and included sample size, baseline comparisons between groups, compliance, randomisation, order of treatment effect and control of the study.

Data Synthesis

Five clinical trials were included and reported significantly lower CRP concentrations of 25% - 54% with increased DF consumption with dosages ranging between 3.3 - 7.8 g/MJ. Weight loss and altered fatty acid intakes were present in all the studies.

Limitations

Limitations include possible genetic differences, publication bias, lack of reporting on control groups and the inability to determine whether individual components of the diet accounted for the changes observed.

Conclusions

In the presence of weight loss and modified saturated, monounsaturated and polyunsaturated fat intakes, significantly lower CRP concentrations (↓ 25-54%) are seen with increased fibre consumption (≥ 3.3 g/MJ). Mechanisms are inconclusive, but may involve the effect of DF on weight loss, insulin, glucose, adiponectin, interleukin-6, free fatty acids and triglycerides. Well-designed, supplemental studies are recommended to investigate the potential favourable effects of DF on CRP as observed epidemiologically.

KEY WORDS: Dietary fibre, C-reactive protein, cardiovascular disease, fat intake, weight loss, systematic review.

Introduction

Cardiovascular disease (CVD) remains one of the major causes of death worldwide (1). Many of the risk factors for heart disease are either preventable or controllable through dietary factors such as fibre, which is inversely associated with risk factors for coronary heart disease (CHD) (2). The Centres for Disease Control and Prevention and the American Heart Association published the first set of guidelines in January 2003 to endorse the use of high sensitivity C-reactive protein (CRP), a sensitive circulating marker of inflammation, as an adjunct to traditional risk factor screening (3) since research indicated that fibre intake is independently associated with serum CRP concentrations in clinical (4) as well as cross-sectional trials (5). In a recent meta-analysis an elevated CRP concentration as risk marker for CHD shows an odds ratio (OR) of 1.45 [95% confidence interval (CI), 1.25; 1.68] after adjustment for established risk factors (6). There are now over 30 prospective studies that have all come to the conclusion that CRP is one of the most consistent risk stratifiers available (7), but the distinction between its role as a risk marker or risk factor is important (8). In large cohort studies high-fibre intakes have been associated consistently with a reduction in CHD risk (9) and CHD risk factors (10) and a recent prospective study suggests that dietary fibre (DF) is protective against high CRP concentrations (11). In this study multiple dietary and CRP measurements were taken and an inverse association between DF intake in both cross-sectional and longitudinal analyses was found (11). Compared to subjects in the lower quartile of total fibre intake, participants in the highest quartile had a 63% lower chance of having elevated CRP concentrations in the adjusted (OR, 0.37; 95% CI, 0.16; 0.87) and unadjusted models (OR, 0.27; 95% CI, 0.12; 0.57) (11). Factors adjusted for included BMI, age, tobacco use, self-reported infection and season of the year (11). Furthermore, the risk reduced by 61% (p for trend = 0.006) for subjects in the highest quartile of water-soluble intake and 75% (p for trend < 0.01) for insoluble fibre (11). DF may thus play an important role in mediating the relation between diet, inflammation and CVD (12). The investigation of Ludwig *et al.* (1999) (10) together with that of the Health Professionals' Follow-up Study (13) raise the interesting possibility that fibre may play a greater role in determining CVD risk than total or saturated fat intake. DF intake studies show an independent, inverse relationship between the level of total DF (13-15), water-soluble DF (16), cereal fibre (15), whole-grain intake (17) and risk of subsequent CHD (14-16), ischaemic heart disease (IHD) (17) and myocardial infarction (13). Emphasis on dietary factors is one of

the approaches currently advocated to prevent CVD (2). Over a period of two years it was demonstrated that a Mediterranean-style diet rich in whole-grains, fruits, vegetables, legumes, walnuts and olive oil may be responsible for a cardio-protective effect through the reduction of low-grade inflammation (18). The aim of this systematic review was to assess the influence of DF on CRP in clinical trials.

Methods

Subjects

A total of 387 subjects (151 men and 236 women) participated in the studies summarised in this systematic review. Participants with metabolic syndrome (n=180) (18), high triglyceride (TG) concentrations (n=25) (19) and hyperlipidaemia (n=46) (4) made up 65% of the study population. The remainder of participants were healthy.

Inclusion and exclusion criteria

Human adult (men and women) trials with a duration of two weeks or longer in fibre supplementation or clinical studies involving interventions with an increased and measurable consumption of DF with an intake higher than the habitual were included. Subjects were excluded if diabetic, suffering from CHD or had had a heart attack.

Outcome measures

The primary outcome measures were percentage changes in CRP between intervention and control groups or baseline to end comparisons.

Data sources

To identify potential studies, literature searches were performed in electronic databases. EbscoHost (20) was used as a gateway to the records in MEDLINE [Pubmed], Academic Search Premier, Clinical Pharmacology, Health Source: Nursing/Academic Edition, Health Source: Consumer Edition and Biological & Agricultural Index. In addition, The Cochrane Library (21), Science Direct (22), Web of Science (23) and EMBASE (24) databases were also searched. Databases were searched from the earliest record to July 2006. Reference lists of relevant publications were crosschecked manually to ensure that all applicable papers were included. Search terms used included C-reactive protein (CRP), dietary fibre (fiber), non-digestible carbohydrate(s), lignin(s), non-starch polysaccharide(s), functional fibre (fiber), nutrition*, food. Medical

subject headings (MeSH) such as 'fibre' and 'fiber' were combined with the key search words in the Medline search.

Study selection and data extraction

Two assessors screened the potential studies identified to determine eligibility for inclusion in the review. Using a standardised form, data was extracted to determine the quality of all the identified intervention studies.

Data synthesis

A rating based upon the methodology as it appeared in the publication was given to each of the selected studies. The following criteria for quality assessment of the intervention trials were used [adapted from Verhagen *et al.* (25)]: (1) the study was controlled; (2) justified sample size; (3) groups were similar at baseline regarding the most important prognostic indicators; (4) compliance were acceptable; (5) randomisation was performed; and (6) in case of crossover trials: no order of treatment effect. The following quality scores were assigned: 1 = if all the criteria were present/if the study was controlled and one criterion was missing; 2 = if the study was controlled and two criteria were missing; 3 = if the study was not controlled or ≥ 3 criteria were missing. Furthermore, the letter *a* was assigned for controlled feeding trials and *b* for studies conducted under free-living conditions. No formal statistical analysis was performed due to the large differences in study designs of the clinical trials. This study had no external funding source.

Results

Of the 2121 articles screened (titles, abstracts, original research and review articles), five original research papers were identified that were suitable for inclusion in this review. **Table 1** presents a summary of the baseline characteristics of the studies and participants. The experimental designs of these studies were variable, subjects' characteristics differed, as did the amount and type of fibre consumed, duration of the studies, the control diets and number of subjects. Four of the five studies received a "1" quality score. The macronutrient composition and sources of fibre in each study are summarised in **Table 2**.

Table 1 Summary of baseline characteristics of studies and participants

	Summary result Number of studies reporting (n=5)
Fibre intake (gram per megajoule/day [mean (range)])	4.8 (3.3 - 7.8)
Study duration (weeks) [mean (range)]	45.8 (3 - 104)
Participants completed studies (n) (dropouts)	387 (33)
Men (n)	151
Women (n)	236
Age (years) [mean (range)]	44.9 (32 - 85)

The duration of the studies were three (19), four (4) and 14 weeks (27) and 24 months (18;26), which were sufficient time to achieve stabilisation of CRP. CRP is an acute phase protein with serum concentrations peaking around 48 hours after a single stimulus (28) and concentrations of pro-inflammatory cytokines and adipokines have been reported to change in response to individual meals (29). The number of subjects who completed the high-fibre interventions ranged between 16 and 90 per study, which have been adequate to detect clinically significant changes in CRP. As per power calculations (80% power at 5% significance), a minimum of 16 participants are required. The characteristics of studies and subjects are shown in **Table 3**.

The results of the studies reviewed are summarised in **Table 4**. Increased consumption of DF to dosages of 3.3, 3.6, 3.7, 5.0 and 7.8 g/MJ significantly lowered CRP concentrations by 25%, 34.4%, 39.3%, 25.9% and 54% respectively, comparing baseline to end. Concentrations of CRP were also significantly reduced when comparing intervention and control groups following two Mediterranean-style diets reporting a difference in CRP of -0.8 (95% CI, -2.0; -0.4; p=0.008) (26), -1 (95% CI, -1.7; -0.3; p=0.01) (18). Furthermore, a significance of p<0.005 was reached following a vegetarian intervention comparing groups (4). In this review there was a tendency in the high-quality score studies that the higher the fibre intake, the bigger reduction in CRP. One study reported that without a concomitant decrease in body weight, a low-

fat/high-fibre (3.3 g/MJ) did not alter CRP concentrations (27). The baseline CRP concentrations in that study were low in the non-obese, healthy subjects. Reductions in body weight were seen in all the other studies and are specified in **Table 4**.

Table 2 Macronutrient compositions of diets used in intervention trials investigating the effect of dietary fibre on C-reactive protein

Reference study	INTERVENTION GROUPS						Compliance	CONTROL GROUPS					
	Type / source of DF	DF	PRO	CHO	FAT	ALC		Control diet / Type / source of DF	DF	PRO	CHO	FAT	ALC
		g/MJ	%	%	%	g/d			g/MJ	%	%	%	g/d
Junker <i>et al.</i> , 2001 (19)	Whole-grain bread and cereal, vegetables, fruit, specially formulated muesli	↑-fat: 5.0 ↓-fat: 5.4	↑-fat: 20.2 ↓-fat: 18.4	↑-fat: 40.3 ↓-fat: 54.2	↑-fat: 39.3 ↓-fat: 27.2	↑-fat: 0.7 ↓-fat: 0.7	Good Part of foodstuffs provided to subjects	Habitual diet	2.5	16.8	41.1	37.0	19
Esposito <i>et al.</i> , 2003 (26)	Fruits, vegetables, bread and other cereals, beans, nuts and seeds	3.6	17	55 (48)*	28	NR	Good Monthly and bi-monthly meetings and completion of diet diaries	Advised on healthy food choices but not individualised diets	1.9	14	58 (38)*	28	NR
Jenkins <i>et al.</i> , 2003 (4)	Viscous fibers from oats, barley, psyllium, additional eggplant and okra	7.8	21.7	48.0†	30.0	0.4	Good Compliance: 93%	Vegetarian Step II diet (NCEP), whole-grain cereal, bread and muffins	5.6	22.2	52.8†	24.6	0.3
Esposito <i>et al.</i> , 2004 (18)	Fruit, vegetables, whole-grains and walnuts	3.7	14.0	58.0 (50)*	28.0	38	Good Monthly and bi-monthly meetings and completion of diet diaries	Advised on healthy food choices but not individualised diets	1.9	13.5	57.1 (42)*	30.0	38
Koren <i>et al.</i> , 2006 (27)	Whole-grain cereal, bread, granola bar, fruit and vegetables	3.3	20	65	15	NR	Good Controlled feeding trial	Whole-grain bread, fruit and vegetables	2.1	20	45	35	NR

* Complex carbohydrates † Available carbohydrates

Abbreviations used: DF, dietary fibre; PRO, protein; CHO, carbohydrates; ALC, alcohol; ↑-fat, high-fat; ↓-fat, low-fat; g/MJ, gram per megajoule; g/d, gram per day; NCEP, National Cholesterol Education Program; NR, not reported.

Table 3 Characteristics of studies and participants

Mean amount of fibre (g/MJ) in intervention groups Intervention diet Study design Reference study	Number of participants who completed intervention (n [total dropouts])	Selected inclusion criteria	Participants characteristics: nationality, baseline mean age and BMI	Duration of intervention	Comparison made (DF intake)	Quality score
5.0 g/MJ High-fat diet rich in PUFA and MUFA 5.4 g/MJ Low-fat/high-fibre diet Within subject comparison Junker <i>et al.</i> , 2001 (19)	n= 25 M [0]	Non-obese, TG > 2.3mmol/L	Germany 40 y BMI: 26	3 weeks	Habitual diet [high-fat (37%), high-SFA, low-fibre 2.5 g/MJ]	3b
3.6 g/MJ Mediterranean-style diet rich in complex carbohydrates and fibre Parallel Esposito <i>et al.</i> , 2003 (26)	n=57 W [3]	Healthy, obese	Italy 34 y BMI: 35	24 months	Baseline and control (1.9 g/MJ)	1b
7.8 g/MJ Diet high in plant sterols, soy protein, viscous fibre and almonds Parallel Jenkins <i>et al.</i> , 2003 (4)	n=16: 7 M, 9 W [2]	Healthy, overweight LDL > 4.1mmol/L	United States of America 59 y BMI: 28	1 month	Control diet (milled whole-wheat cereals, low-fat dairy foods, very low in SFA); Lovastatin with control diet (5.6 g/MJ)	1b
3.7 g/MJ Mediterranean diet rich in MUFA, PUFA and fibre Parallel Esposito <i>et al.</i> , 2004 (18)	n=82 M&W [8]	Metabolic syndrome	Italy 44 y BMI: 28	24 months	Baseline and control (Prudent diet 1.9 g/MJ)	1b
3.3 g/MJ Low-fat/high-fibre diet Cross-over Koren <i>et al.</i> , 2006 (27)	n=16: 2 M, 14 W [0]	Healthy, overweight	United States of America 46 y BMI: 27	3½ months	High-fat (35%)/ low-fibre diet (2.1 g/MJ)	1a

Abbreviations used: g/MJ, gram per megajoule; M, men; W, women; DF, dietary fibre; CHO, carbohydrates; ↑-fat, high-fat; ↓-fat, low-fat; y, years; BMI, body mass index; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; TG, triglycerides; LDL, low-density lipoprotein cholesterol; a, controlled feeding trials; b, trials conducted under free-living conditions. Quality score: 1 = high; 3 = low.

Table 4 Increased dietary fibre intake and changes in CRP concentrations (mg/L) in clinical trials

Mean amount of fibre (g/MJ) intervention groups Intervention diet Reference study	INTERVENTION					CONTROL			Summary of results	QS
	% increase in fibre intake compared to baseline	Baseline [mean (SD) or median (range)]	Trial end [mean (SD) or median (range)]	% change from baseline to end (p-value or significance)	Weight loss (kg) significance	Baseline [mean (SD) or median (range)]	Trial end [mean (SD) or median (range)]	% change from baseline to end (p-value or significance)		
5.0 g/MJ High-fat diet rich in PUFA and MUFA 5.4 g/MJ Low-fat/high-fibre diet Junker <i>et al.</i> , 2001 (19)	100	↑-fat/ ↑-fibre: 2.7 (0.9-49.8) ↓-fat/ ↑-fibre: 2.0 (0.8-24.1)	↑-fat/ ↑-fibre: 2.0 (0.8-24.1) ↓-fat/ ↑-fibre: 2.3 (0.7-57.5)	↑-fat/ ↑-fibre: -25.9 p<0.05 ↓-fat/ ↑-fibre: +15.0 NS	-1.5 p<0.001 -0.8 p<0.05	No control group			Significant decrease in CRP after 3wk high-fat PUFA and MUFA period	3b
3.6 g/MJ Mediterranean-style diet rich in complex carbohydrates and fibre Esposito <i>et al.</i> , 2003 (26)	56	3.2 (1.5-8.4)	2.1 (0.9-7.1)	-34.4 p=0.01	-14 p<0.001	3.4 (1.4-8.3)	3.1 (1.3-8.2)	-8.8 p=0.19	Significant decrease in CRP baseline to end in intervention group. Significant decrease in CRP after 2y Mediterranean-style diet compared to control group, p=0.08.	1b
7.8 g/MJ Diet high in plant sterols, soy protein, viscous fibre and almonds Jenkins <i>et al.</i> , 2003 (4)	178	2.4	1.1	-54.2 p<0.005	-0.4 p=0.06	1.4	1.1	-21.4 NS	Significant decrease in CRP after 4wk diet with plant sterols, soy protein, viscous fibre and almonds baseline to end. Significant difference in CRP comparing groups, p<0.05.	1b
3.7g/MJ Mediterranean diet rich in MUFA, PUFA and fibre Esposito <i>et al.</i> , 2004 (18)	129	2.8 (0.7-5.4)	1.7 (0.4-4.9)	-39.3 p=0.01	-4 p<0.001	2.9 (0.5-5.7)	2.8 (0.5-5.5)	-3.4 NS	Significant decrease in CRP after 2y, high n3-PUFA and MUFA diet baseline to end in intervention group. Significant decrease in CRP after 2y Mediterranean-style diet compared to control group, p=0.01.	1b
3.3 g/MJ Low-fat/high-fibre diet Koren <i>et al.</i> , 2006 (27)	56	↓-fat/ ↑-fibre: (ad libitum): 1.6 (3.3)	↓-fat/ ↑-fibre: (ad libitum): 1.2 (2.0)	↓-fat/ ↑-fibre: (ad libitum): -25.0 p=0.03	-4.1 NR	↓-fat/ ↑-fibre: (8400 kJ): 1.4 (3.3)	↓-fat/ ↑-fibre: (8400 kJ): 1.6 (3.3)	↓-fat/ ↑-fibre: (8400 kJ): +14.3 NS	Significant decrease in CRP after 3mo low-fat/high-fibre diet (ad libitum)	1a

Reference values CRP: 1 - 3 mg/L.

The formula used was: (End value – Baseline value)/Baseline value x 100.

Abbreviations used: g/MJ, gram per megajoule; wk, week(s); mo, month(s); y, years; kg, kilograms; kJ, kilojoule(s); MUFA, monounsaturated fatty acids; n3-PUFA, omega-3 polyunsaturated fatty acids; SD, standard deviation; NS, not significant; CRP, C-reactive protein; ↑-fat/↑-fibre, high-fat/high-fibre; ↓-fat/↑-fibre, low-fat/high-fibre; NR, not reported; a, controlled feeding trials; b, trials conducted under free-living conditions; QS, quality score. Quality score: 1 = high; 3 = low.

Discussion

The five clinical trials reviewed report significantly lower CRP concentrations following increased fibre consumption, altered fat intakes and weight loss. There were substantial differences between the studies in terms of dietary interventions, study designs and subjects. Participants included hyperlipidaemic subjects consuming a vegetarian diet (4), Mediterranean-style intakes in metabolic syndrome (18) and overweight/obese subjects (26), as well as hypertriglyceridaemic patients consuming a high-fat/high-fibre diet with resultant decreased CRP concentrations, which remained low after the subsequent low-fat/high-fibre diet (19). Koren *et al.* (2006) found no effect on CRP following a lower carbohydrate (45%) intake with 2.1 g/MJ DF during isocaloric feeding in overweight subjects (27). However, *ad libitum* feeding on a high carbohydrate intake (65%) with 3.3 g/MJ DF during the subsequent three-month phase of the trial resulted in significantly lower CRP levels (27). These experimental studies strengthen the epidemiological data indicating that DF is inversely associated with CRP concentrations (5;12).

Suggested mechanisms

Weight loss

A positive correlation exists between CRP and body mass index (BMI) (30) and ample clinical evidence indicates that weight loss results in decreased CRP concentrations as reviewed recently (31). This is also applicable to the studies reviewed here (4;18;19;27). Elevated levels of interleukin-6 (IL-6) are also reduced in serum and subcutaneous adipose tissue of obese women after weight loss (32). This is to be expected since IL-6 is in part produced by adipose tissue (33). Dietary interventions that reduce body weight are thus likely to be effective in lowering CRP and the relation between DF and body weight has been often reviewed (34-36). Mechanisms through which DF can assist in weight loss include, but are not limited to the effects of DF on gastric emptying (37), satiety (38), gut hormones such as cholecystokinin (39) and an altered glycaemic index (GI) or insulin response (40). In some instances, however, significance in both weight loss and CRP were not achieved. In hyperlipidaemic subjects CRP concentrations reduced significantly following a very high-fibre vegetarian intake of 7.8 g/MJ DF compared to the control group with insignificant weight loss ($p=0.06$) (4). Koren *et al.* (2006) found no effect on CRP following a lower carbohydrate

(45%) intake during two weeks of isocaloric feeding in overweight subjects (27). However, CRP lowering was seen with *ad libitum* feeding on a high carbohydrate (65%) intake, accompanied by weight loss (significance not reported), during the next phase of the trial (27). In another long-term study the significant favourable results in CRP and IL-6 were adjusted for body weight and the authors attributed the favourable findings to the Mediterranean-style diet, largely independent of the changes in body weight (18).

Macronutrients

The differences seen between macronutrient intakes in the comparative groups need some consideration (**Table 2**). Two studies reported substantial differences in the total fat intake between the control and intervention groups (4;27). In one instance the authors concluded that plasma CRP concentrations are not affected by isocaloric dietary fat reduction (27). In the other, caution should be taken because of the substantial but non-significant difference in baseline CRP values between comparative groups. Other literature indicates that in young adults (mean age 18 years) saturated fat emerged as the single most important nutrient contributing to increases in CRP levels (41), whereas a modest association in adults is found (12). Other dietary fatty acids that showed a weak inverse relation with CRP include monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and omega-3 PUFAs in females (42). In a study where men were randomly assigned to consume *ad libitum* a moderately low-fat (26%) or a high-fat (40%) diet rich in MUFA for 6-7 weeks, neither diets affected the plasma CRP concentration (43). A role of omega-3 PUFA in lowering CRP levels has also been shown in clinical trials (44-46) and cross-sectionally (47). Increases in MUFA and PUFA and a decrease in saturated fatty acids (SFA) occurred in some instances in the trials reviewed here as indicated in **Table 5**. The differences in consumption of MUFA, PUFA and SFA between the intervention and comparative diets were significant in one instance (18), in SFA for another (26), but not reported for the remainder of the studies (4;19;27). The lowering of CRP could thus in part have been attributed to changes in fatty acids intake.

In addition to fat another major difference in macronutrients occurs in one study in the form of carbohydrates (27). Isocaloric substitution of carbohydrates for fat caused no change in CRP (27). After 12 weeks of *ad libitum* consumption of a low-fat (15%)/high-carbohydrate (65%) diet, both body weight and CRP reductions reach significance (27).

CRP concentrations were measured retrospectively in baseline and 3-month samples from 41 obese women completing a randomised trial comparing a low-fat (28%)/high-carbohydrate (54%) diet and a very low-carbohydrate (15%)/high-fat (57%) diet (48). Both interventions led to significantly lower CRP concentrations (48). These effects were proportional to the amount of weight lost but independent of dietary macronutrient composition (48). In the context of weight loss, macronutrient composition is probably not important in lowering CRP.

Table 5 Total fat and fatty acid compositions of control and intervention diets

Mean amount of fibre (g/MJ) intervention groups Intervention diet Reference study	INTERVENTION				CONTROL				CRP: % change from baseline to end (p-value)	Quality score
	SFA (%)	MUFA (%)	PUFA (%)	Total fat (%)	SFA (%)	MUFA (%)	PUFA (%)	Total fat (%)		
5.0 g/MJ High-fat diet rich in PUFA and MUFA Junker <i>et al.</i> , 2001 (19)	8.3	15	16	39.3	13.9	12.5	10.6	37	-25.9 p<0.05	3b
3.6 g/MJ Mediterranean-style diet rich in complex carbohydrates and fibre Esposito <i>et al.</i> , 2003 (26)	8	13	7	28	11	11	7	28	-34.4 p=0.1	1b
7.8 g/MJ Diet high in plant sterols, soy protein, viscous fibre, almonds Jenkins <i>et al.</i> , 2003 (4)	6.3	12.7	10.1	30	4.5	10.3	8.4	24.6	-54.2 p<0.005	1b
3.7 g/MJ Mediterranean diet rich in MUFA, PUFA and fibre Esposito <i>et al.</i> , 2004 (18)	8	12.4	7.6	28	13.7	9.6	6.7	30	-39.3 p=0.01	1b
3.3 g/MJ Low-fat diet/high-fibre Koren <i>et al.</i> , 2006 (27)	4.9	5.7	2.9	15	11.9	12.5	8.3	35	-25.0 p=0.03	1a

Abbreviations used: SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; g/MJ, gram per megajoule; CRP, C-reactive protein; a, controlled feeding trials; b, trials conducted under free-living conditions. Quality score: 1 = high; 3 = low.

Adiponectin

Adiponectin is an adipocyte-derived hormone with insulin sensitising and anti-atherogenic properties and may mediate some of its cardioprotective effects through its anti-inflammatory effects (49). Reducing adipocyte mass via liposuction does not increase adiponectin or affect CRP (50). Havel (2004) hypothesises in his review that adiponectin is regulated by adipocyte size and that a substantial reduction in adipocytes size is required to increase adiponectin production and circulating levels (51). Only one study reviewed here measured adiponectin, reporting a significant increase in adiponectin together with the highest mean weight loss (14kg) compared to the other studies (**Table 4**) (26). CRP and adiponectin changes were also significant when comparing the intervention to the control group that also experienced a significant weight loss (3kg) (26). In diabetics, cross-sectional data demonstrates that adiponectin levels are related to insulin sensitivity and negatively correlated with TG and CRP, independent of body adiposity (52), thus other pathways are likely to exist. It was found that the higher the quantity of fibre in the diet, especially cereal fibre (53), the greater the stimulation of adiponectin (29), whereas a diet with a high GI might adversely affect plasma adiponectin in diabetic men (53).

Interleukins

Cytokines, such as the interleukins, are regulatory proteins that are released by cells of the immune system and act as intercellular mediators in the generation of an immune response. The sole determinant of CRP is its synthesis rate (54), which thus directly reflects the intensity of the pathological processes stimulating CRP production. Interleukin-6 (IL-6) seems to be the chief stimulant to hepatic production of CRP (55). Modulation of the fibre content of a meal may influence the cytokine milieu: increasing the fibre content of a meal from 4.5g to 16.8g was associated with a significant reduction of circulating interleukin-18 (IL-18) concentrations in healthy and diabetic subjects (29). IL-18 is a potent pro-inflammatory cytokine that may be important in the process of plaque destabilisation and hence in predicting cardiovascular death in patients with acute coronary syndromes (56). The intestinal flora, which are dependant on DF (57), may also contribute in preventing inflammation by reducing the production of inflammatory cytokines by altering the intralumen bacterial environment (58). With fewer inflammatory cytokines produced in the bowel, the liver may produce less CRP,

resulting in lower concentrations of CRP (59). In agreement with a recent review (60), two studies in this review found simultaneous reductions in CRP and IL-6 (18;26).

Insulin and glucose

Positive correlations exist between CRP/IL-6 and insulin resistance (61) and interventions that alter insulin resistance may also alter CRP concentrations (62). A significant reduction in insulin and glucose is seen following high-fibre intakes (63;64). Recent data from a study on 244 apparently healthy women suggest that the intake of rapidly digested and absorbed carbohydrates with a high dietary glycaemic load (GL) is associated with increased CRP concentrations (65). Esposito *et al.* (2002) showed that intravenous glucose administration increases concentrations of the pro-inflammatory markers IL-6 and IL-18 (66) and hypothesise that low-fibre diets can thus contribute to hyperglycaemia with resultant increases in the mentioned cytokines (18). Since insulin is known to stimulate IL-6 secretion (67), it can be predicted that diets that induce a relatively low post-prandial insulin response will be associated with below-average serum concentrations of IL-6 and CRP. Therefore, it may be possible to moderate CRP concentrations by avoiding high-insulin-response starchy foods (high-GI foods) and emphasising whole-grain foods rich in amylose and fibre (4). The studies reviewed here did not determine the GIs or GLs and the relevance of this as potential mechanism in these studies couldn't be determined. Even in the short-term (72 hours), insoluble fibre (31.2g) has been shown to improve whole-body insulin sensitivity in obese and overweight women (68). In a cross-sectional analysis of 780 diabetic men, high GI and GL were associated with lower concentrations of plasma adiponectin (53) and positive associations between cereal fibre and plasma adiponectin were observed (29;69). In insulin-resistant states, insulin has an anti-inflammatory effect producing more cytokines (70). McLaughlin *et al.* (2002) showed that with weight loss, CRP levels are decreased only in insulin-resistant, but not in insulin-sensitive, obese subjects (71). Insulin and IL-6 were measured in two of the studies reviewed here and these reported significant decreases in insulin, IL-6 and body weight (18;26).

Free fatty acids and triglycerides

In a recent clinical trial the changes in CRP were best described by changes in free fatty acids (FFA), TG and waist circumference (72). IL-6 (26) and CRP (73) are significantly

associated with FFA concentrations in women. Increased IL-6 and decreased adiponectin concentrations from an excess of adipose tissue may have a convergent increased effect on FFA (26) which affects insulin sensitivity negatively (74). Soluble fibre is fermented by anaerobic bacteria in the colon to short-chain fatty acids (75), including acetate which inhibits serum FFA release from adipocytes (76;77) resulting in increased insulin sensitivity (74). It is possible that the resultant lower insulin levels can reduce the amount of IL-6 produced as shown *in vitro* (78;79) and *in vivo* (67) and thus subsequently CRP. Furthermore, adiponectin may lower circulating FFA concentrations by increasing fatty acid oxidation by skeletal muscle (80) and by increasing hepatic FFA extraction directly (81). Cereal fibre may affect adiponectin by reducing the FFA available for storage in adipose tissue by promoting the clearance of lipids (82). FFA acts as ligand for the upstream regulation of adiponectin expression (83). Lower adiponectin concentrations following high-carbohydrate, low-fibre meals were found in diabetic patients (29). Altogether, this information warrants more research to investigate the effect DF on adiponectin and FFA.

A positive correlation between CRP/IL-6 and TG concentrations exists (42). Dietary carbohydrates stimulate TG production in the liver and may cause secondary hepatic inflammation with associated higher CRP concentrations (84;85). This increase in TG seems to be intermittent and the concentrations decrease again over time (86;87), indicating that DF might counteract the hypertriglyceridaemic effect of carbohydrates (86). An association observed between high adiponectin and low TG concentrations was independent of insulin sensitivity (88). There is also evidence that adiponectin lowers circulating FFA concentrations by decreasing TG content in muscle and liver (80). TG decreased significantly in all (18;19;26) but one (4) of the studies reviewed here that measured TG. In the latter study, the short duration of the intervention could explain the lack of significance (4). In another study that was short in duration, the subjects had very high baseline TG levels (19) and thus likely to have had higher responsiveness during interventions. However, this is insufficient information to advocate a satisfactory mechanism for the link between TG and CRP. To integrate the possible mechanisms through which DF may affect CRP via its effects on weight loss, insulin, glucose, FFA, TG, adiponectin and IL-6, a schematic representation is shown in **Figure 1**.

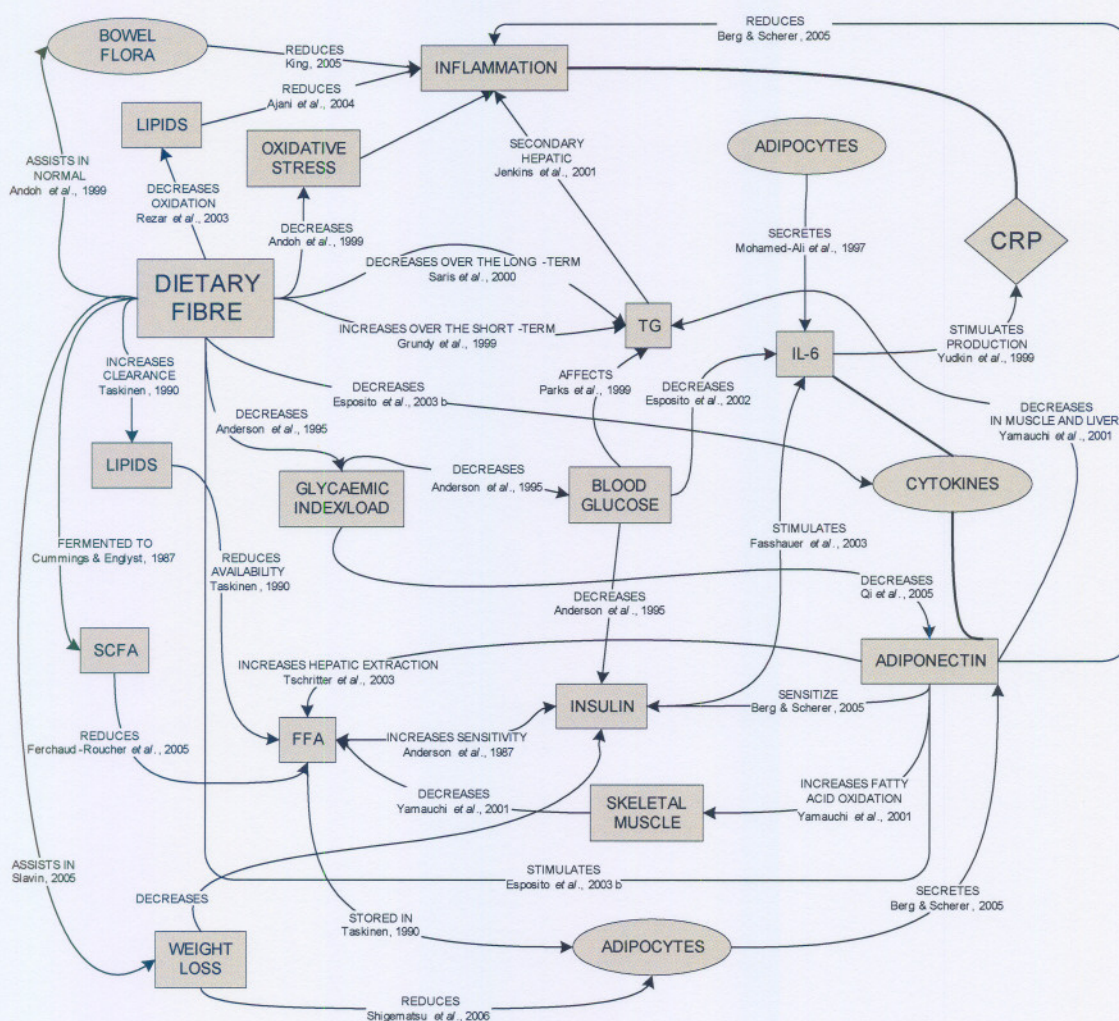


Figure 1 Schematic representation of the mechanisms through which dietary fibre may influence CRP

Abbreviations used: SCFA, short-chain fatty acids; FFA, free fatty acids; TG, triglycerides, IL-6, interleukin-6; CRP, C-reactive protein.

Type of fibre

A recent prospective study differentiated between the association of CRP and that of total fibre intake and as far as is known for the first time between soluble and insoluble fibre (11). The studies included in this review could not make a distinction between types of fibre as they were part of the same foods and included fruit, vegetables, oats, barley, psyllium, nuts, muesli, whole-grain bread and cereal. Epidemiological (98;99) and experimental (53;100) studies indicate a stronger inverse association of cereal fibre with type 2 diabetes, CHD and lower CRP concentrations than other types of fibre, however, the mechanisms are unclear. Since 2002, DF is defined as the nondigestible carbohydrates and lignin that are intrinsic and intact in plants (101). Functional fibre is

defined as isolated, nondigestible carbohydrates that have been shown to have beneficial, physiological effects in humans (101). Total dietary fibre is the sum of dietary and functional fibre (101).

Other factors

Other factors that may influence CRP include physical activity (7), moderate alcohol consumption (102), anti-oxidants (103), postmenopausal hormone replacement therapy (104) and smoking (42). Race and ethnicity can lead to differences in factors that affect both CRP concentrations (105) and fibre consumption (106). Furthermore, it might be difficult to reduce low or normal CRP concentrations as observed in the baseline measurements of the studies in this review (4;18;19;26;27). For half the populace studied in three large populations (Women's Health Study, PRINCE cohort, Physicians' Health Study), the variance in CRP is attributable to lifestyle factors e.g. smoking, diet, exercise; the other half is primarily inherited (7). Twin studies show a significant heritable component in baseline CRP values that is independent of age and BMI (107). It is well known that foods high in fibre content are rich in phytic acid, saponins, tannins, flavonoids, phytoestrogens and protease as well as amylase inhibitors, lignans and lectins (13) that also contribute to the effects of high-fibre foods. Conflicting results have been reported with soy intake and CRP concentrations (31). Because of the anti-inflammatory role of DF in intestinal functions (57), it can be speculated that the fibre content of a high-fibre diet, eventually magnified by some other components with anti-oxidant capability (103), can enhance the body's defense mechanisms against oxidative stress (108).

Future studies and limitations

There is a pressing need to determine whether DF can affect CRP since existing epidemiological (5;12) and clinical data (19;109) are promising, but lack appropriate study designs that prevent conclusions. Weight loss and simultaneous changes in the fatty acid intakes were prominent confounders in the studies reviewed here. Well-controlled isocaloric trials with DF as the only variable, such as in supplemental studies, are recommended to explore the relation between CRP and DF and identify physiological mechanisms. Differentiation between the effects of the different types of DF will be valuable. A trend was observed that with higher DF dosages, higher reductions in CRP occurred and needs further investigation. For future studies, it is

important to realise that the CRP response is triggered by many disorders unrelated to CVD and a stable baseline with multiple measurements is recommended (28;110).

A limitation of this study is that we could not account for possible genetic differences. Effect sizes could not be calculated due to lack of reporting on control groups and the possibility of publication bias remains. The dietary interventions were restrictive as we were unable to determine whether individual components of the diet accounted for the changes observed.

Conclusions

This review demonstrates that in the presence of weight loss and modified saturated, MUFA and PUFA intakes, increased fibre consumption (≥ 3.3 g/MJ) is associated with significantly lower CRP concentrations ($\downarrow$ 25-54%). Due to confounding factors and differential study designs, the physiological mechanisms of the effects of DF on CRP are inconclusive in this review. Potential mechanisms that need investigation include insulin, glucose, adiponectin, IL-6, FFA and TG. Well-designed, supplemental studies are recommended to explore the potential favourable effects of DF on CRP as seen epidemiologically.

Acknowledgements

None.

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5

Discussion and conclusions

5.1. Introduction

In this chapter the main findings of the studies are summarised, strengths and limitations are discussed and conclusions and recommendations for future research are made.

The overall purpose of this study was to review systematically whether increased dietary fibre (DF) consumption has an effect on selected haemostatic variables and the inflammatory marker, C-reactive protein (CRP). It resulted in three articles reporting on the effects of DF and possible mechanisms through which DF may affect:

- tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) (Chapter 2),
- factor VII (FVII) and fibrinogen (Chapter 3), and
- CRP (Chapter 4).

5.2. Summary of the main findings

The first systematic review demonstrated that increased DF intakes of ≥ 3.3 g/MJ and ≥ 4.5 g/MJ may assist in increasing tissue-type plasminogen activator activity (t-PAa) concentrations between 14-167% and reduce plasminogen activator inhibitor type-1 activity (PAI-1a) levels by 15-57%. The main physiological mechanisms of DF that are proposed are via its effects on insulinaemic and glycaemic responses, triglyceride (TG)-rich lipoproteins, free fatty acids (FFA) and a reduction in body weight.

Based on the current weight of evidence it does not seem as if an increase in DF intake has a measurable effect of fibrinogen. The modest weight loss as well as the assumingly good nutritional status of the participants may have concealed the potential effects. Furthermore, as discussed in Chapter 3, the dosages consumed in the studies reviewed might have been too small to have an effect on fibrinogen. Compared to previous clinical investigations that found lower fibrinogen concentrations following DF supplementation (Koepp & Hegewisch, 1981; Vorster *et al.*, 1985; Venter *et al.*, 1990b; Venter *et al.*, 1991), the highly-rated quality studies that have been reviewed in this study reported relatively modest DF intakes (2.5-3.7 g/MJ) (Fehily *et al.*, 1986; Landin *et al.*, 1992; Marckmann *et al.*, 1994; Marckmann *et al.*, 2000; Turpeinen *et al.*, 2000).

These dosages will be compared to the DRI and current intakes around the world in sections 5.9 and 5.10.

Dietary modifications with ≥ 3.3 g/MJ DF may have significant effects on factor VII coagulant activity (FVIIc), decreasing it by 10-16%. Differences in the type of fibre seem to play a role. The potential mechanisms through which increased DF may affect FVII include changes in TG-rich lipoproteins and body weight. The simultaneous reduction in saturated fat intake and weight loss may have accounted for some of the effects.

The third review showed that in the presence of weight loss and modified saturated, monounsaturated and polyunsaturated fat intakes, significantly lower CRP concentrations (25-54%) can be expected with increased fibre consumption (≥ 3.3 g/MJ). Mechanisms are inconclusive but may involve the effect of DF on weight loss, insulin, glucose, adiponectin, interleukin-6, FFA and TG. Well-designed, supplemental studies are recommended to investigate the potential favourable effects of DF on CRP as observed epidemiologically.

The diversity of the study designs used in the intervention trials resulted in various quality ratings and presented a hindrance for drawing conclusions. Overall, confounding factors such as simultaneous reductions in body weight and adjustments in other components of dietary interventions such as a reduced fat intake, may have masked the protective effects of DF. Therefore, suitably designed studies are the key to address this important topic in the future. Moreover, different types of fibre could have different effects on the parameters, as could different dosages of DF. Isocaloric, supplemental studies could be a suitable vehicle to investigate this further. The outcomes may be different in healthy, non-obese patients *versus* obese and/or hypertriglyceridaemic or metabolic syndrome subjects, which highlights the importance of appropriate study protocols.

5.3. Scientific contribution of the study

The topics addressed by the three reviews are unique and relevant and it is the first time that an attempt has been made to deal with the topic in such a systematic manner. The results of the reported studies here are valuable in augmenting the current

knowledge about the protective effect of DF and how it may impact health. Furthermore, the haemostatic factors associated with the development of cardiovascular disease (CVD), namely fibrinogen, t-PA antigen, PAI-1 and factor VII are all interrelated with inflammatory markers, most notably CRP (Kannel, 2005). The thesis attempts to integrate the role of DF in the prevention of CVD with the role of the haemostatic system in CVD by providing balanced information on effects of DF from clinical intervention trials.

Furthermore, these systematic reviews offer the following advantages (adapted from Greenhalgh, 1997):

- Explicit methods limited bias in identifying and rejecting studies and increase the precision of the overall result.
- Conclusions are more reliable and accurate because of the systematically documented methods used.
- Results of different studies are formally compared to establish generalisability of findings and consistency of results.
- Reasons for heterogeneity (inconsistency in results across studies) are identified and the impact discussed.
- Clear guidelines for future research protocols can be made.

5.4. Limitations

The following limitations were identified in the clinical studies that were reviewed:

- Study design inadequacies in some of the trials included small sample size, incomparable differences in dietary compositions and potential confounding variables such as weight loss.
- Genes coding for the variables were not taken into account in any of the studies. Firstly, polymorphisms can influence the structure and function of gene products and secondly, may have a regulatory influence. In the latter instance it would modify the level of the product coded for by a gene with its influence being on plasma level (Davey-Smith & Ebrahim, 2003), which, had it been measured, would have been useful in this study. As reviewed recently, a reasonable

amount of polymorphisms have already been identified for PAI-1, t-PA, FVII, fibrinogen (Ajjan & Grant, 2006; Ye *et al.*, 2006) and CRP (Kushner *et al.*, 2006).

- Publication bias (the tendency on the part of investigators, reviewers and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings) cannot be ruled out and could have played a role in the data available for analysis.
- Data analysis was limiting since most of the comparisons were within groups and effect sizes could not be calculated due to lack of information on control groups.
- The lack of proper placebo controlled trials but also the lack of proper placebos for fibre limits the strength of conclusions that can be made.
- The inability to determine whether individual components of the diet accounted for the changes observed or whether the changes were a result of the sum of all the dietary and/or lifestyle changes.
- Differentiation between the effects of different types of fibre might be important but was unattainable in the present study.
- Overall, the length of the intervention periods of the clinical trials in the systematic reviews was sufficient to achieve stabilisation of the variables. Sustainability of the outcomes could not be evaluated for those studies of shorter duration (n=2 weeks).

5.5. Epidemiological studies

A large set of studies report a reduction of fatal and non-fatal CHD events as a function of increased intake of DF or selected fibre-rich foods such as cereals and legumes (Flight & Clifton, 2006). The degree of risk reduction varies from 20% (Khaw & Barrett-Connor, 1987) to 50% (Humble *et al.*, 1993). In the Nurses' Health Study the age-adjusted relative risk (RR) for major CHD events was 0.53 [95% confidence interval (CI), 0.40; 0.69] for women in the highest quintile of total DF intake (22.9 g/d) compared to women in the lowest intake quintile (11.5 g/d) (Wolk *et al.*, 1999). This translates to a 34% lower risk of CHD and is associated with cereal fibre and whole-grains (Wolk *et al.*, 1999). This observation has been confirmed by another survey of adult women in the USA (Liu *et al.*, 2002a). A four-fold lower cardiovascular death rate in men ingesting high amounts of DF (>37 g/d) compared with those ingesting the lowest amounts (<20 g/d) were found in the 1980's (Kromhout *et al.*, 1982). In a 6-year prospective study investigating a large cohort of adult men aged 40–75 years, an inverse relationship

between fibre intake and cardiovascular death was found, with an odds ratio (OR) of 0.6 for a fibre intake of about 30 g/d compared to the lowest quintile (10–17 g/d) (Rimm *et al.*, 1996). In a multicentre population-based study changes in CVD risk factors were observed over a period of 10 years (Ludwig *et al.*, 1999). Fibre consumption predicted CVD risk factors more strongly than total or saturated fat consumption (Ludwig *et al.*, 1999). More recently in a pooled analysis of 10 studies, it was found that DF from cereals and fruits, but not from vegetable fibre, is inversely associated with risk of CHD (Pereira *et al.*, 2004). After adjustment for demographics, body mass index (BMI) and lifestyle factors, each 10 g/d increment of energy-adjusted and measurement error-corrected total DF was associated with a 14% (RR, 0.86; 95% CI, 0.78; 0.96) decrease in risk of all coronary events and a 27% (RR, 0.73; 95% CI, 0.61; 0.87) decrease in risk of coronary death (Pereira *et al.*, 2004). Male health professionals (n=42850) aged 40–75 years at baseline in 1986 and who were free from CVD, cancer and diabetes were followed up after 14 years in a prospective cohort (Jensen *et al.*, 2004). After CVD risk factors and the intakes of bran and germ added to foods were controlled for, the RR of CHD between extreme quintiles of whole-grain intake was 0.82 (95% CI, 0.70; 0.96) (Jensen *et al.*, 2004). The RR of CHD in men with the highest intake of added bran was 0.70 (95% CI, 0.60; 0.82) compared with men with no intake of added bran (Jensen *et al.*, 2004). The bran component of whole-grains could thus be a key factor in the protective relationship against CHD (Jensen *et al.*, 2004). Furthermore, in a meta-analysis using data of 13 studies the protective effect of DF against CVD was confirmed (Anderson, 2003). The study found that subjects in the highest compared to those in the lowest quintile for whole-grain intake, had a 29% reduction in risk for atherosclerotic CVD (RR, 0.72; 95% CI, 0.48; 0.94) (Anderson, 2003). The risk reduction for CHD associated with total DF intake was 0.73 (95% CI, 0.73; 0.83), thus virtually identical to that provided by whole-grains (Anderson, 2003). Also in people older than 65 years, cereal fibre consumption is inversely associated with incident CVD with 21% lower risk (RR, 0.79; 95% CI, 0.62; 0.99) in the highest quintile of intake, compared with the lowest quintile (Mozaffarian *et al.*, 2003). Collectively, these findings suggest that DF and/or foods rich in DF may protect against the number one cause of death worldwide (World Health Organization, 2004). As a result of the epidemiological nature of these studies, causality cannot be established, but it clearly implies that including high-fibre food options in the habitual diet is a possible mechanism for reducing risk factors for CVD.

5.5.1 Haemostatic variables

Epidemiological data on the relation between DF and haemostatic variables is scarce. Haemostatic factors associated with the development of CVD include, amongst others, fibrinogen, t-PA, PAI-1 and FVII. Each SD increment of these increases the association by 24-30% (Kannel, 2005). Data from the National Heart, Lung and Blood Institute Family Heart Study showed an inverse relation between PAI-1 and age and energy-adjusted indexes of fibre intake for both men and women (Djousse *et al.*, 1998). DF intakes also correlate negatively with t-PA (-0.29 ; 95% CI, -0.45 ; -0.10 ; $p < 0.01$) (Rankinen *et al.*, 1994). Similarly, DF intake is inversely associated with factor VIIc in both men (-0.31 ; 95% CI, -0.57 ; -0.06) and women (-0.36 ; 95% CI, -0.63 ; -0.09) (Mennen *et al.*, 1997). Cross-sectional studies (Fehily *et al.*, 1982; Yarnell *et al.*, 1983; James *et al.*, 2000) indicate that DF is negatively associated with fibrinogen, although not found consistently (Djousse *et al.*, 1998). Very recently the results of a large prospective cohort in men investigating the relationship of fibrinogen and VIIc with risk of CHD and stroke over a period of 15 years were published (Rudnicka *et al.*, 2006). After adjusting for age, trial treatment group, conventional CHD risk factors and regression dilution bias, the hazard ratio (HR) for fibrinogen was 1.52 (95% CI, 1.37; 1.70) for all CHD and 1.36 (95% CI, 1.09; 1.69) for all strokes (Rudnicka *et al.*, 2006). Excluding events within the first ten years a persistent association between CHD and fibrinogen, with an adjusted HR of 1.93 (95% CI, 1.42; 2.64) was shown (Rudnicka *et al.*, 2006). The HR for FVIIc adjusting for age and trial treatment was 1.07 (95% CI, 1.01; 1.12) for all CHD and 1.07 (95% CI, 0.97; 1.20) for all strokes and the fully adjusted HRs respectively were 0.97 (95% CI, 0.84; 1.05) and 1.07 (95% CI, 0.85; 1.33) (Rudnicka *et al.*, 2006). Thus, according to the authors, the continuous association between fibrinogen and CHD beyond ten years may imply a causal effect, whereas a small effect of FVIIc on CHD after adjusting for age and trial treatment was seen, but no association independent of other risk factors (Rudnicka *et al.*, 2006).

5.5.2 C-reactive protein

Using data from the National Health and Nutrition Examination Survey (1999-2000), DF intake was found to be inversely associated with serum CRP concentrations (Ajani *et al.*, 2004). The OR for increased CRP concentration (>3.0 mg/L) was 0.49 (95% CI, 0.37; 0.65; p for trend < 0.001) for the highest quintile of fibre intake compared with the lowest (Ajani *et al.*, 2004). Adjustment for age, gender, race, education, smoking,

physical activity, BMI, total energy and fat intake resulted in a slight attenuation (Ajani *et al.*, 2004). In the Nurses' Health Study intakes of whole-grains and bran were both associated with significantly decreasing trends of CRP (p for trend = 0.03 and 0.007, respectively) in 902 diabetic women (Qi *et al.*, 2006a). High intake of cereal fibre was also inversely associated with the lower levels of CRP (p for trend = 0.03) (Qi *et al.*, 2006a). The concentrations of CRP were 18% lower in the highest quintile of cereal fibre compared to the lowest quintile (Qi *et al.*, 2006a). More recently, this inverse association was also seen between intake of total DF, soluble and insoluble fibre in both cross-sectional and longitudinal analyses (Ma *et al.*, 2006). The likelihood of elevated CRP concentrations was 63% lower (OR, 0.37; 95% CI, 0.16; 0.87) in participants in the highest quintile of total fibre intake than in participants in the lowest quintile (Ma *et al.*, 2006).

These epidemiological associations suggest, therefore, that increased DF consumption might influence CRP and the mentioned haemostatic factors.

5.6. Clinical trials

Intervention trials report that increased DF intakes result in increased t-PA (Boman *et al.*, 1994) and lower PAI-1 concentrations (Boman *et al.*, 1994; Lindahl *et al.*, 1999). Similarly, reductions in FVIIc concentrations are seen following high-fibre intakes (Simpson *et al.*, 1982; Simpson *et al.*, 1983; Brace *et al.*, 1994). On the other hand, a number of intervention trials in adults following high-fibre intakes did not induce a significant decrease in fibrinogen concentrations (Simpson *et al.*, 1982; Fehily *et al.*, 1986; Miller *et al.*, 1986; Djousse *et al.*, 1998; Junker *et al.*, 2001). Recent findings indicate, furthermore, that fibre intake is independently associated with serum CRP concentrations in clinical trials (Jenkins *et al.*, 2003) and can be modulated by the consumption of fruit and vegetables (Watzl *et al.*, 2005). DF may thus play a role in mediating the relation between diet, inflammation and CVD (King *et al.*, 2003).

As indicated in Chapters 2-4, many of the clinical trials reviewed in this study reported similar favourable results for t-PA (Marckmann *et al.*, 1993; Marckmann *et al.*, 1994), PAI-1 (Mehrabian *et al.*, 1990; Landin *et al.*, 1992; Sundell & Ranby, 1993; Lindahl *et al.*, 1998; Junker *et al.*, 2001), FVIIc (Marckmann *et al.*, 1993; Marckmann *et al.*, 1994; Marckmann *et al.*, 2000; Junker *et al.*, 2001) and CRP (Junker *et al.*, 2001; Esposito *et*

al., 2003b; Jenkins *et al.*, 2003; Esposito *et al.*, 2004; Koren *et al.*, 2006). High-fibre interventions did not induce lower fibrinogen levels (Fehily *et al.*, 1986; Mehrabian *et al.*, 1990; Landin *et al.*, 1992; Marckmann *et al.*, 1993; Sundell & Ranby, 1993; Marckmann *et al.*, 2000; Turpeinen *et al.*, 2000; Junker *et al.*, 2001).

5.7. Mechanisms

A discussion of the mechanisms through which DF may affect selected haemostatic variables and CRP follows and is schematically summarised in **Figure 5.1**.

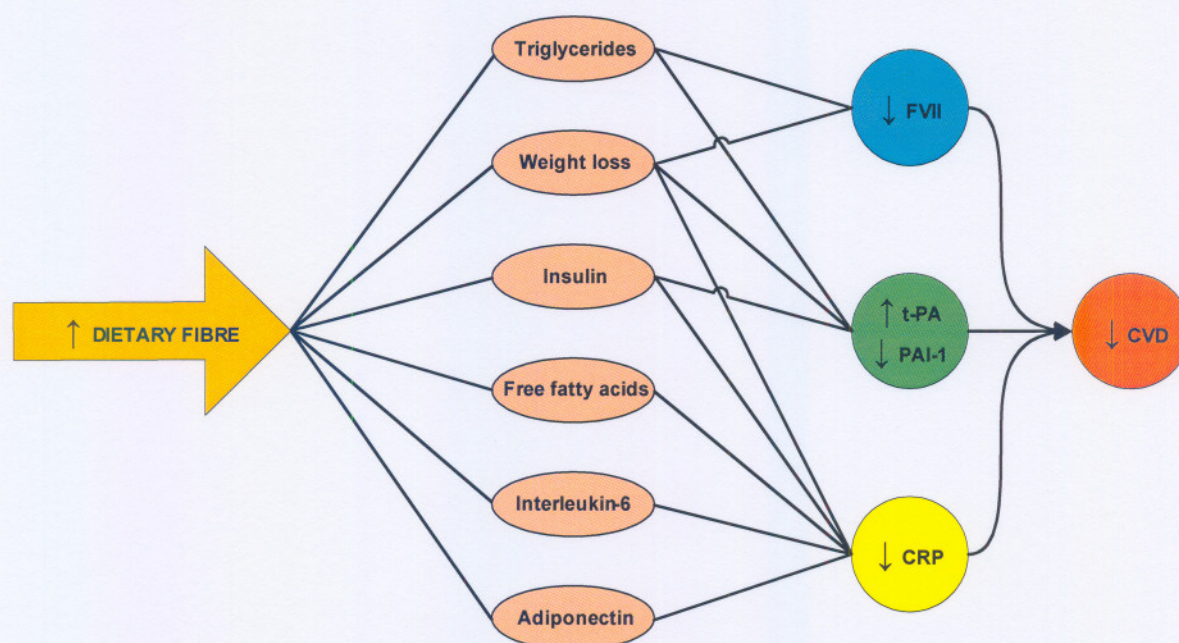


Figure 5.1 Schematic representation of the mechanisms through which dietary fibre may affect tissue-type plasminogen activator, plasminogen activator inhibitor type 1, factor VII and C-reactive protein to reduce the risk of CVD

Abbreviations used: CVD, cardiovascular disease; CRP, C-reactive protein; t-PA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor type 1; FVII, factor VII; ↑, increase; ↓, decrease.

5.7.1 Weight loss

BMI is positively associated with PAI-1 (Yarnell *et al.*, 2000), FVIIc (Folsom *et al.*, 1991), CRP (Ford, 2003) and inversely with t-PA (Yarnell *et al.*, 2000) and these variables improve with weight loss in several (Folsom *et al.*, 1993) but not all instances (Landin *et al.*, 1992; Marckmann *et al.*, 1993; Sundell & Ranby, 1993; Juhan-Vague & Alessi, 1996; Junker *et al.*, 2001; Esposito *et al.*, 2003b; Jenkins *et al.*, 2003). Some of the studies reviewed in this research project showed improvements in t-PA, PAI-1 (Mehrabian *et al.*, 1990; Lindahl *et al.*, 1998), FVII (Marckmann *et al.*, 1993; Marckmann *et al.*, 1994; Marckmann *et al.*, 2000; Junker *et al.*, 2001) and CRP (Junker *et al.*, 2001; Esposito *et al.*, 2004; Koren *et al.*, 2006) with a simultaneous increase in fibre intake and weight loss. The reductions in weight loss were not in proportion to the improvements in the haemostatic variables and CRP. Obesity affects fibrinogen concentrations (Reinhart, 2003) which tends to be lower following weight loss (Vorster *et al.*, 1989). A significant reduction of fibrinogen levels appears to be dependant on weight loss of at least 10% of body weight (Primrose *et al.*, 1992; Fanari *et al.*, 1993; Ditschuneit *et al.*, 1995; Marckmann *et al.*, 1998) and was not seen in the studies reviewed. Weight loss remains, however, a confounding factor that needs to be taken into consideration when studying these haemostatic parameters and CRP in dietary intervention trials. The effect of DF on energy intake or body weight has been the subject of numerous clinical studies. Epidemiological support that high DF consumption prevents obesity is strong (Kimm, 1995; Lissner *et al.*, 1998) and in intervention trials body weight decreases on high-fibre diets (Mueller-Cunningham *et al.*, 2003). A recent study identified dietary patterns predictive of subsequent annual weight change (Schulz *et al.*, 2005b). Study subjects were 24958 middle-aged men and women of the European Prospective Investigation into Cancer and Nutrition-Potsdam cohort (Schulz *et al.*, 2005b). In non-obese subjects, a food pattern of a high consumption of whole-grain bread, fruits, fruit juices, grain flakes/cereals and raw vegetables and of low consumption of processed meat, butter, high-fat cheese, margarine and meat was predictive of subsequent weight change (Schulz *et al.*, 2005b). Thus, food consumption characterised by high-fibre and low-fat food choices can help to maintain body weight or at least prevent excess body weight gain. The EPIC-Oxford study including over 5000 participants between the ages of 20 and 89 years indicated that, of all of the components of the diet, DF contributed the most to the observed age-adjusted differences in BMIs (Appleby *et al.*, 1998). Furthermore, a review suggested that with *ad libitum* intake, the consumption of an additional 14 g/d DF is associated with a 10%

decrease in energy intake and a body weight loss of 1.9 kg over 3.8 months (Howarth *et al.*, 2001). Reviews on DF and weight regulation are thorough and plentiful (Leeds, 1987; Howarth *et al.*, 2001; Pereira & Ludwig, 2001; Yao & Roberts, 2001; Slavin, 2005) and some of the suggested mechanisms through which DF can assist in weight loss are shown in **Table 5.1**.

Table 5.1 Potential mechanisms through which dietary fibre can aid weight loss

Reference study	Suggested mechanisms
Heaton, 1973	Increased mastication time promoting satiation
Isaksson <i>et al.</i> , 1983	Altered fat absorption via malabsorption or maldigestion
Jenkins & Jenkins, 1984	Reduced gastric emptying
Spiller <i>et al.</i> , 1988	Reduced small bowel transit time
Howarth <i>et al.</i> , 2001	Increased satiety
Sandberg <i>et al.</i> , 1994	Increased ileal fat losses
Sandberg, 1994	Altered fat absorption via reduced bile flow
Baer <i>et al.</i> , 1997	Inverse relation between fat and protein digestibility
Bourdon <i>et al.</i> , 2001	Increased gut hormones such as cholecystokinin
Anderson <i>et al.</i> , 2004	Altered glycaemic index or insulin response
Rolls <i>et al.</i> , 2004	Reduced energy density

5.7.2. Insulin

The specific role of DF in modifying insulin sensitivity has challenged investigators for decades. Nonetheless, clinically significant reductions in insulin and glucose are seen following high-fibre intakes (Anderson *et al.*, 1995; Chandalia *et al.*, 2000) with resultant increased insulin sensitivity (Fukagawa *et al.*, 1990). t-PA (Sundell *et al.*, 1988; Smith *et al.*, 1995), PAI-1a (Landin *et al.*, 1990; Lindahl *et al.*, 1998), fibrinogen (Festa *et al.*, 2002), CRP (Chambers *et al.*, 2001) and interleukin-6 (IL-6) (Bastard *et al.*, 2000) correlate with insulin and insulin resistance. It is thus expected that interventions that alter insulin resistance can also alter the investigated parameters. Only a few studies

assessed in this review measured insulin or insulin resistance and reported varied responses (Landin *et al.*, 1992; Sundell & Ranby, 1993; Lindahl *et al.*, 1998; Esposito *et al.*, 2003b; Esposito *et al.*, 2004).

Insulin resistance and hyperinsulinaemia are associated with an increased risk of CVD (Golden *et al.*, 2002). In observational studies, high DF intakes have been inversely associated with rates of insulin resistance as measured by homeostasis model assessment (HOMA) and fasting insulin concentrations (Ludwig *et al.*, 1999; Fung *et al.*, 2002; McKeown *et al.*, 2004). After adjustment for potential confounding variables, intakes of total DF, cereal fibre, fruit fibre and whole-grains were inversely associated, whereas glycaemic index (GI) and glycaemic load (GL) were positively associated with HOMA insulin resistance (McKeown *et al.*, 2004). In the Insulin Resistance Atherosclerosis Study, whole-grain intake was significantly associated with insulin sensitivity (0.08, $p=0.0005$) and insulin (-0.06, $p=0.019$) (Liese *et al.*, 2003). Inclusion of fibre and magnesium removes the association, indicating that these factors may account for some of the effect of whole-grains on insulin sensitivity (Liese *et al.*, 2003). In another study a high dietary GL from refined carbohydrates increases the risk of CHD independently of known coronary disease risk factors (Liu *et al.*, 2000). Even in the short-term (72 hours), insoluble fibre (31g) has been shown to improve whole-body insulin sensitivity in obese and overweight women (Weickert *et al.*, 2006).

The intake of DF is inversely associated with the GI (Schulz *et al.*, 2005a). The GI corresponds to the increase in blood glucose concentration after the ingestion of the corresponding food (standardised to obtain 50g carbohydrates) as compared to the increase in blood glucose after the ingestion of glucose or white bread (Jenkins *et al.*, 1981). DF and its composition are important determinants of the GI (Bjorck & Elmstahl, 2003), although the total glucose seems to be the major determinant (Englyst *et al.*, 2003). The GI is subject to many different influences such as the food particle size for instance in whole-grains (Liljeberg *et al.*, 1992; Jarvi *et al.*, 1995), the amount of soluble and viscous fibre (Torsdottir *et al.*, 1989), food processing (Ross *et al.*, 1987; Granfeldt *et al.*, 1994), starch gelatinisation (more compact granules) as well as interactions with other food components including fat and protein (Augustin *et al.*, 2002; Hu & Willett, 2002). Adding fibre-rich foods or isolated fibre (e.g. β -glucan) to high-GI foods reduces the GI (Jenkins *et al.*, 2002). The factors resulting in the production of slow-releasing carbohydrate foods are thus interconnected and in many studies it is not easy to

separate the different effects of viscous fibre and low-GI foods. One of the metabolic advantages of low-GI foods is the lowered insulin demand (Jenkins *et al.*, 1990). Postprandial insulin levels are lower after high-fibre test meals (Bourdon *et al.*, 1999; Lu *et al.*, 2000; Wolever *et al.*, 2004) and an increased insoluble DF intake significantly improved whole-body insulin sensitivity after three days (Weickert *et al.*, 2006).

Experimentally, low-GL diets are known to decrease PAI-1 concentrations in young, healthy, obese adults (Ebbeling *et al.*, 2005) and diabetic patients (Jarvi *et al.*, 1999; Rizkalla *et al.*, 2004). In 2002 a study was published investigating the relationship of CRP and GL in 244 healthy middle-aged women (Liu *et al.*, 2002b). Using multiple regression models, a strong and statistically significant positive association between GL and plasma CRP were found after adjusting for conventional risk factors for ischaemic heart disease (IHD) (Liu *et al.*, 2002b). The median CRP concentration for the lowest quintile of GL was 1.9 mg/L and for the highest quintile was 3.7 mg/L (Liu *et al.*, 2002b).

5.7.3. Free fatty acids, adiponectin and interleukin-6

High PAI-1 levels are associated with increased plasma concentrations of FFA and TG in type 2 diabetes mellitus (Reaven, 1988; McGarry, 1992). FFA contributes to the short-term regulation of fibrinogen fractional synthesis rate in healthy volunteers (Freyse *et al.*, 2003). Recently the changes in CRP in a clinical trial were best described by changes in FFA and TG (Dvorakova-Lorenzova *et al.*, 2006) and others also reported an association between IL-6 (Esposito *et al.*, 2003b), CRP (Florez *et al.*, 2006) and FFA concentrations.

Soluble fibre is fermented by anaerobic bacteria in the colon to short-chain fatty acids (Cummings & Englyst, 1987). Acetate, a short-chain fatty acid, inhibits serum FFA release from adipocytes and results in lower FFA concentrations (Ferchaud-Roucher *et al.*, 2005), which leads to increased insulin sensitivity (Anderson *et al.*, 1987) and may subsequently affect t-PA, PAI-1 and CRP concentrations, given the positive correlation between hyperinsulinism and these factors as discussed earlier. In addition, with high-fibre consumption more propionate is produced inhibiting glucose production in hepatocytes which may improve glucose tolerance (Anderson & Bridges, 1984; Venter *et al.*, 1990a). FFA in plasma may promote FVII activation (Tholstrup *et al.*, 2003). It was also shown that a reduction in FVIIc following a lower intake of saturated fat may

be instigated via the release of FFA during lipolysis of TG-rich lipoproteins (Mitropoulos *et al.*, 1994).

Lower adiponectin concentrations following high-carbohydrate, low-fibre meals in diabetic patients were reported (Esposito *et al.*, 2003a). Adiponectin is an adipocyte-derived hormone with insulin sensitising, anti-atherogenic and anti-inflammatory properties (Berg & Scherer, 2005). In cross-sectional studies high intakes of cereal fibre are associated with increased plasma adiponectin levels after adjustments for lifestyle factors and GL (Richter *et al.*, 2004; Qi *et al.*, 2005). In one instance adiponectin levels were 19% higher in the highest quintile than in the lowest quintile (Qi *et al.*, 2005). Diets low in GL and high in DF may increase plasma adiponectin and thus improve insulin sensitivity, reduce inflammation and ameliorate glycaemic control (Esposito *et al.*, 2003a; Qi *et al.*, 2005). There is also evidence that adiponectin lowers circulating FFA concentrations by decreasing TG content in muscle and liver (Yamauchi *et al.*, 2001). Furthermore, adiponectin may lower circulating FFA concentrations by increasing fatty acid oxidation by skeletal muscle (Yamauchi *et al.*, 2001) and by increasing hepatic FFA extraction directly (Tschritter *et al.*, 2003). Cereal fibre may affect adiponectin by reducing the FFA available for storage in adipose tissue by promoting the clearance of lipids (Jenkins *et al.*, 2001). FFA acts as ligand for the upstream regulation of adiponectin expression (Iwaki *et al.*, 2003).

IL-6, a regulatory protein that is released in response to the immune system, is the principal stimulant of hepatic production of CRP (Castell *et al.*, 1989). Increased IL-6 and decreased adiponectin concentrations from an excess of adipose tissue may have a convergent increased effect on FFA (Esposito *et al.*, 2003b) which affect insulin sensitivity negatively (Trowell, 1975). Since insulin is known to stimulate IL-6 secretion (Krogh-Madsen *et al.*, 2004), it can be predicted that diets that induce a relatively low insulin response, will be associated with below-average serum concentrations of IL-6 and CRP. In insulin-resistant states, insulin has an anti-inflammatory effect producing more cytokines (Fernandez-Real & Ricart, 2003). Data indicate that whole-grains and a low-GI diet may reduce systemic inflammation among women with type 2 diabetes (Qi *et al.*, 2006a).

5.7.4 Triglycerides

The review by Silveria (2001) highlights the work done on the associations between TG, PAI-1, FVII and underlying CHD. Associations of FVII with TG and increased plasma FVII levels in groups with CHD or at risk of CHD were reported in cross-sectional studies (Hoffman *et al.*, 1988; Hoffman *et al.*, 1989; Broadhurst *et al.*, 1990; Suzuki *et al.*, 1991). PAI-1 is positively associated with very-low density lipoprotein (VLDL)-TG (Hamsten *et al.*, 1985) which seems to be the major determinant of PAI-1 activity (Asplund-Carlson *et al.*, 1993). In addition, a positive correlation between CRP/IL-6 and TG concentrations exists (Fredrikson *et al.*, 2004).

High-carbohydrate diets commonly elevate plasma VLDL-TG concentrations (Coulston *et al.*, 1989; Rivellesse *et al.*, 1990; Parks *et al.*, 1999) and may cause secondary hepatic inflammation with associated increased CRP concentrations (Solga *et al.*, 2004; Kerner *et al.*, 2005). Cross-sectional studies show an inverse association between TG and increased fibre consumption (Ylonen *et al.*, 2003). It was shown that a high-fibre (44 g/d) diet compared to a low-fibre (16 g/d) diet, followed for eight weeks each in type 2 diabetic patients consistently induced lower mean TG concentrations (Hagander *et al.*, 1988). With very high-fibre intakes (50 g/d) reduced insulin requirements, improved glycaemic control and lower fasting serum TG values can be expected (Chandalia *et al.*, 2000). Several review articles considered this relationship between TG and fibre intakes and a brief discussion of the findings follows. Diets enriched with wheat bran and guar gum have the ability to blunt the hypertriglyceridaemic effects of diets high in carbohydrate and low in fibre (Vinik & Jenkins, 1988). Fructo-oligosaccharides, a saccharide polymer found in many vegetables, also appear to reduce serum TG for reasons that are not entirely clear (Jenkins *et al.*, 2000). The review by Fried and Rao (2003) established that the hypertriglyceridaemic effects of high-carbohydrate diets may dissipate with time as also shown in clinical trials (Marckmann *et al.*, 1993; Rivellesse *et al.*, 1994), indicating that DF might counteract the hypertriglyceridaemic effect of increased carbohydrates. Changes in TG correlate with changes in insulin levels (Pieke *et al.*, 2000). Acute hyperinsulinism induces a decrease in hepatic VLDL production and secretion (Malmstrom *et al.*, 1997; Harbis *et al.*, 2001) but, in the long-term and in insulin-resistant conditions, insulin may induce a chronic stimulatory effect on TG synthesis (Cummings *et al.*, 1995; McLaughlin *et al.*, 2000). Low-GL diets also reportedly lead to a significant decline in plasma TG in clinical trials (Ebbeling *et al.*, 2005).

Studies included in this review with significant decreases in PAI-1 also showed significant decreases in TG from baseline to end (Mehrabian *et al.*, 1990; Lindahl *et al.*, 1998; Junker *et al.*, 2001) or significant differences between groups (Landin *et al.*, 1992). In the three studies that did not show a significant effect on PAI-1, TG concentrations were unchanged (Marckmann *et al.*, 1993; Turpeinen *et al.*, 2000) or showed a significant increase compared to concentrations on a low-fibre diet (Marckmann *et al.*, 1994). TG decreased significantly in all (Junker *et al.*, 2001; Esposito *et al.*, 2003b; Esposito *et al.*, 2004) but one (Jenkins *et al.*, 2003) of the studies reviewed that measured TG and CRP. In the latter study, the short duration of the intervention could explain the lack of significance (Jenkins *et al.*, 2003).

5.8. Types of fibre

DF has recently been redefined since the terms “soluble” and “insoluble” fibre did not provide an appropriate physiochemical characterisation (Trumbo, 2002). DF is now defined as the nondigestible carbohydrates and lignins that are intrinsic and intact in plants (Trumbo *et al.*, 2002). Functional fibre is defined as isolated, nondigestible carbohydrates that have been shown to have beneficial, physiological effects in humans (Trumbo *et al.*, 2002). Total DF is the sum of dietary and functional fibre (Trumbo *et al.*, 2002). Most of the studies included in this review did not make a distinction between types of fibre, as they were part of the same foods.

DF intake studies show an independent, inverse relationship between the level of total DF (Pietinen *et al.*, 1996; Rimm *et al.*, 1996; Wolk *et al.*, 1999), water-soluble DF (Bazzano *et al.*, 2003), cereal fibre (Wolk *et al.*, 1999), whole-grain intake (Jacobs, Jr. *et al.*, 1998) and risk of subsequent CHD (Pietinen *et al.*, 1996; Wolk *et al.*, 1999; Bazzano *et al.*, 2003), IHD (Jacobs, Jr. *et al.*, 1998) and myocardial infarction (Rimm *et al.*, 1996). No consistent advantage of either soluble or insoluble fibre could be found (Pietinen *et al.*, 1996; Rimm *et al.*, 1996; Wolk *et al.*, 1999; Liu *et al.*, 2002a; Pereira *et al.*, 2004). Data from adults participating in the National Health and Nutrition Examination Survey I (NHANES I) revealed during an average follow-up of 19 years that the RR for CHD for those in the highest quintile for soluble fibre intake (5.9 g/d) compared with those in the lowest (0.9 g/d) was 0.85 (95% CI, 0.74; 0.98; $p=0.004$ for

trend) for CHD events and 0.90 (95% CI, 0.82; 0.99; $p=0.01$) for CVD events (Bazzano *et al.*, 2003).

The inverse relation between cereal fibre and CHD risk has often been reviewed (Truswell, 2002; Anderson, 2003) and in experimental studies an inverse association of cereal fibre with the risk of developing type 2 diabetes and CHD has been reported (Schulze *et al.*, 2004; Ostman *et al.*, 2006; Qi *et al.*, 2006b). Results from some epidemiological studies suggest that cereal fibre, which contains mostly insoluble fibre, has less influence on CHD risk or CHD death than other components such as total fibre (Pietinen *et al.*, 1996; Anderson *et al.*, 2000; Mozaffarian *et al.*, 2003; Pereira *et al.*, 2004). Jacobs *et al.* (2000) demonstrated that a similar amount of total cereal fibre had dissimilar associations with total mortality, depending on whether the fibre came from foods that contained primarily whole-grain or refined grain. Cereals are mostly grasses cultivated for their edible grains or seeds, such as maize, wheat, barley, sorghum, oats, rye, buckwheat and rice. Cereal grains contain several protective compounds such as antioxidants, unsaturated fatty acids, phytosterols and DF (Slavin, 2003). Whole-grains are cereal grains that retain the bran and germ as well as the endosperm, in contrast to refined grains that retain only the endosperm. Common whole-grain products include oatmeal, popcorn, brown rice, whole-wheat flour, sprouted grains and whole-wheat bread. Whole-grains consist of many components and the DF part thereof may assist in ways including enzyme-modulator, lipid-lowering, gut modifier and hormonal effects (Slavin *et al.*, 1999). The result of a meta-analysis including 13 studies conclude that whole-grains are more effective in reducing the risk of CVD than fruit or vegetables and that this effect is independent of cereal fibre. The RR for whole-grains comparing the lowest and highest groups of whole-grain intake was 0.71 (95% CI, 0.48; 0.94) and in sharp contrast, cereal fibre had a RR of 0.9 (95% CI, 0.8; 1.01). It, furthermore, reports the RR for total DF intake as 0.73 (95% CI, 0.73; 0.83) and for fruit and vegetable intake as 0.77 (95% CI, 0.70; 0.86) and 0.86 (95% CI, 0.77; 0.96) respectively for a reduction in CHD risk. Cereal fibre alone is thus not protective against CVD suggesting that the bran and outer germ are important factors in the protective mechanisms associated with whole-grains (Anderson, 2003). Many antioxidants, phytosterols and other phytochemicals are concentrated in the bran or germ of most cereals (Miller *et al.*, 2000). In a large prospective cohort of 42850 male health professionals, the association between the daily intake of whole-grains, additional bran and germ and CHD risk was investigated. It was found that a median intake of 11.1g of added bran

reduced the risk of CHD by 30% (RR, 0.70; 95% CI, 0.6; 0.82) compared to whole-grains with a RR of 0.82 (95% CI, 0.70; 0.96) (Jensen *et al.*, 2004).

Studies in this review with higher levels of insoluble fibre did not show a significant lowering of FVIlc concentrations (Sundell & Ranby, 1993; Turpeinen *et al.*, 2000; Most *et al.*, 2005). A recent prospective study differentiated between the association of CRP and that of total, soluble and insoluble fibre (Ma *et al.*, 2006). The likelihood of elevated CRP concentrations was 63% lower (OR, 0.37; 95% CI, 0.16; 0.87) in participants in the highest quintile of total fibre intake than in participants in the lowest quintile.

5.9. Dosage of fibre

The Dietary Reference Intake (DRI) for male (38 g DF/day) and female (25 g DF/day) adults (Institute of Medicine, 2002) is compared to the fibre intakes of studies in this review in **Table 5.2**. Studies showed that a diet containing at least 37g/d DF may be protective against CHD in Western societies (Kromhout *et al.*, 1982), thus lending support to the DRI recommendations. The minimum daily DF intake in studies with significant changes in t-PA, FVIlc and CRP in studies included in this review were 3.3 g/MJ DF and for reductions in PAI-1, 4.5 g/MJ DF. However, simultaneous reductions in fat intakes and weight loss probably played a role in affecting these factors, making it difficult to isolate the effect of DF. In the high-quality trials included in this review a trend was observed that the higher the fibre intake, the higher the reduction in CRP. A review published in 2006 examined the relationship of risk CHD to whole-grain intake and reported a protective association that acts in a dose-response manner (Flight & Clifton, 2006). After adjustments for demographics, BMI and lifestyle factors, a pooled analysis of DF and its subtypes and risk of CHD showed that each 10 g/d increment of energy-adjusted and measurement error-corrected total DF was associated with a 14% (RR, 0.86; 95% CI, 0.78; 0.96) decrease in risk of all coronary events and a 27% (RR, 0.73; 95% CI, 0.61; 0.87) decrease in risk of coronary death (Pereira *et al.*, 2004). For cereal, fruit and vegetable fibre intake (not error corrected), RRs corresponding to 10 g/d increments were 0.90 (95% CI, 0.77; 1.07), 0.84 (95% CI, 0.70; 0.99) and 1.00 (95% CI, 0.88; 1.13) respectively, for all coronary events and 0.75 (95% CI, 0.63; 0.91), 0.70 (95% CI, 0.55; 0.89) and 1.00 (95% CI, 0.82; 1.23) respectively for deaths (Pereira *et al.*, 2004). Results were similar for men and women (Pereira *et al.*, 2004). Estimates from the large prospective cohort of the Nurses' Health Study predict that an additional

5g of cereal fibre per day will reduce the risk of CHD by 37% (RR, 0.82; 95% CI, 0.70; 0.96) (Wolk *et al.*, 1999). More recently the risk of CVD and CHD and DF in 9776 adults participating in the NHANES I Epidemiologic Follow-up Study were examined (Bazzano *et al.*, 2003). They found that consumption of 0.6 g/MJ cereal fibre was associated with a nonsignificant 20% lower risk of CHD.

Table 5.2 Comparison of Dietary Reference Intakes for total fibre (g/MJ) per recommended energy intake in adults (45 years, 165 cm) with fibre consumption in studies with significant changes in t-PA, PAI-1, FVIIc, FVIIa and CRP

Physical activity levels	Dietary Reference Intakes for dietary fibre (g/MJ)		Dietary fibre content from studies reviewed (g/MJ)				
	Men	Women	t-PA	PAI-1	FVIIc	FVIIa	CRP
	BMI: 18.5 - 25		Normal weight to obese men and women				
Sedentary	4.1 - 4.7	3.2 - 3.5	3.3 - 10.7 ^a	4.5 - 10.7 ^b (2.5 ^c)	3.3-4.5 ^d	5.0 ^e	3.3 - 7.8 ^f
Low active	3.8 - 4.3	2.9 - 3.1					
Active	3.4 - 3.9	2.5 - 2.8					

a (Mehrabian *et al.*, 1990; Marckmann *et al.*, 1993; Marckmann *et al.*, 1994)

b (Mehrabian *et al.*, 1990; Sundell & Ranby, 1993; Lindahl *et al.*, 1998; Junker *et al.*, 2001)

c supplement (excluding dietary intake) (Landin *et al.*, 1992)

d (Marckmann *et al.*, 1993; Marckmann *et al.*, 1994; Marckmann *et al.*, 2000; Junker *et al.*, 2001)

e (Junker *et al.*, 2001)

f (Junker *et al.*, 2001; Esposito *et al.*, 2003b; Jenkins *et al.*, 2003; Esposito *et al.*, 2004; Koren *et al.*, 2006)

Abbreviations used: t-PA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor-1; FVIIc, factor VII coagulant activity; FVIIa, factor VII activity; CRP, C-reactive protein; g/MJ, gram per megajoule; BMI, body mass index.

5.10. Current fibre intakes

In Paleolithic times man ate an estimated 77-120g fibre daily (Eaton *et al.*, 1996). The majority of the recommendations in modern times fall in the range of 25-35 g/d (Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults, 2001; Marlett *et al.*, 2002; Institute of Medicine, 2002). **Table 5.3** summarises the DF fibre intake of men and women in countries across the world from a number of selected studies published since 2000. In the majority of cases, women consumed a higher amount of fibre per energy intake than men. It is clear, however, that in general DF

intakes are too low to be effective in averting CVD. The method of assessment of DF intake is included in the table. Although there is no data to show which is the best instrument to assess fibre intake, a single 24-hour dietary recall may result in misclassification of usual DF intake (Flight & Clifton, 2006).

5.11. Recommendations

The results from this investigation provide the impetus for additional controlled clinical research for the effects of DF on haemostatic variables and the inflammatory marker, CRP, a more recent addition to the CHD risk factor profile (Pearson *et al.*, 2003).

Future studies should consider the following recommendations:

- Set up a suitable protocol for intervention trials with at least 20 men and 20 women matched in each of a control and intervention group with DF intake as the only variable differing between the groups. The duration of studies should be at least two weeks, however, long-term studies are necessary to determine the sustainability of outcomes.
- Simplify observations with supplemental studies in which differing DF dosages and different types of DF can be manipulated in double-blind, placebo-controlled studies. However, to find a suitable source for the placebo for DF supplementation is challenging. It will probably require large and numerous capsules that may affect compliance. It, furthermore, presents a functional problem in dietary intervention trials since increasing the DF will also affect the nutrient distribution, therefore, complicating the interpretation of the contributions of different components.
- Prevent the possible confounding effect of weight loss with isocaloric studies.

Table 5.3 Dietary fibre intake (g/MJ) in various countries for men and women

Reference study	Country	Method of nutritional assessment	Number and gender of subjects	Dietary fibre intake (g/MJ)
Bes-Rastrollo <i>et al.</i> , 2006	Spain	Validated semi-quantitative food-frequency questionnaire	11707 M&W 5094 M 6613 W	1.6 – 3.1 1.9 – 3.5
Davis <i>et al.</i> , 2006	USA	Block 60-item food frequency questionnaire	104 M&W 52 overweight M&W 52 normal weight M&W	2.1 3.0
Kagawa <i>et al.</i> , 2006	Australia and Japan	Four-day dietary records	216 subjects 65 Japanese M living in Australia 81 Japanese M living in Japan 70 Australian M Caucasians	2.1 1.1 2.4
Howarth <i>et al.</i> , 2005	USA	Two-day average intakes	1932 M&W 1108 M 824 W	1.7 1.9
Lairon <i>et al.</i> , 2005	France	Validated, computerised questionnaires	4080 M&W 2168 M 1912 W	2.2 2.4
Mammas <i>et al.</i> , 2004	Greece	24-hour dietary recalls	951 M&W 500 M 451 W	1.6 2.0
Capita <i>et al.</i> , 2003	Spanish	Seven non-consecutive daily dietary records	100 M&W 24 M 76 W	1.7 1.7
Liu <i>et al.</i> , 2003	USA	Validated food-frequency questionnaires	74091 W	1.8 – 2.7
Kabagambe <i>et al.</i> , 2002	Costa Rica	Validated food-frequency questionnaire	503 M&W Rural Suburban Urban	2.6 2.5 2.4
Zhang <i>et al.</i> , 2002	Chinese	Baseline and follow-up food-frequency questionnaires over eight years	262 M&W 136 M 126 W	Baseline to Follow-up: 2.4 to 2.8 2.5 to 3.0
Galvin <i>et al.</i> , 2001	Ireland	7-day food diaries	1379 M&W 662 M 717 W	2.2 2.3
Evans <i>et al.</i> , 2000	Australia	24-hour dietary recalls	6255 M&W 3021 M 3234 W	2.2 2.6
Vorster <i>et al.</i> , 2000	South Africa	Validated and culture-sensitive questionnaires	1854 M&W Deep rural M / W Farms M / W Informal housing M / W Urban townships M / W Urban professional M / W	2.0 / 2.0 1.7 / 1.9 1.9 / 2.1 1.9 / 2.1 2.0 / 2.1

Abbreviations used: M, men; W, women; g/MJ, gram per megajoule.

- Ensure that macronutrients and fatty acid intakes are similar in intervention and control groups.
- Differentiate between the effects of DF in different types of patients e.g. healthy *versus* those with CVD risk factors.
- Validate suggested mechanisms through which changes may be achieved.
- Use reliable methods to determine DF intake in dietary intervention studies.
- Multiply measurements of the variables to obtain a stable baseline values for haemostatic variables.

An increase in fibre intake from a variety of foods is likely to decrease the CVD risk and should thus be recommended on a population basis especially in subjects who have a high risk for CVD. There is, furthermore, a need for epidemiological studies to investigate the relationship of DF and the haemostatic parameters.

5.12. Conclusions

Epidemiological studies substantiate the association between DF and the CVD risk factors t-PA, PAI-1, FVII, fibrinogen and CRP. In this study, definitive clinical evidence of a high-DF consumption favourably affecting these factors was, in general, compromised by the study designs used in the intervention trials. The complexity of relations between DF and other aspects, such as simultaneous reduced fat intake and weight loss, posed difficulties in disentangling the effects of DF. Appropriately designed studies are thus the key to address this important topic in the future. Furthermore, DF, which consists of different components, was consumed in various forms and dosages in the studies, stressing the importance of a suitable designed protocol. DF, however, played a role in modifying t-PA, PAI-1, FVII and CRP. Potential effects on fibrinogen were not quantifiable. This study makes a contribution to the strengthening of the recommendations to consume a high-fibre diet and supports the recent inclusion of fibre into the DRI (Institute of Medicine, 2002). In this context health professionals should encourage healthy, non-obese as well as obese/hypertriglyceridaemic/metabolic syndrome subjects to increase their consumption of DF to levels of at least or more than the DRI.

5.13. References

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