Fibrinogen and cardiovascular disease

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Introduction

The clear association between high fibrinogen concentrations and the risk of cardiovascular disease is of increasing practical relevance as well as scientific interest. The relation was first reported in preliminary results from the Northwick Park Heart Study in 1980¹ and later confirmed in its main findings.² Numerous other prospective studies have almost without exception confirmed a strong and independent effect of raised plasma fibrinogen on both the onset and the progression of ischaemic heart disease (IHD), stroke and lower extremity arterial disease.³⁻⁴ The strength of the association is similar to that of cholesterol or blood pressure. Thus, men with plasma fibrinogen concentrations in the upper third of its distribution experience between 2.0 and 2.5 times the incidence of IHD compared with those with values in the lower third; the Framingham study has also confirmed this relation in women.⁵ In one of the studies with data on stroke as well as IHD,⁶ the relation of fibrinogen with the incidence of the former was, if anything, stronger than for blood pressure, thus exemplifying the likely importance of fibrinogen, bearing in mind the predominance of blood pressure as a risk factor for stroke. Fibrinogen is strongly associated with mortality (mostly from cardiovascular causes) in patients with intermittent claudication⁷ and also with venous thrombosis.⁸ It may contribute to age related macular degeneration⁹ in which a vascular element has been suspected for some time though not identified precisely. High fibrinogen concentrations lead to an increased risk of re-occlusion after grafting and angioplasty.¹⁰⁻¹¹ For a variety of reasons, a growing number of centres are now measuring or planning to measure fibrinogen concentrations, the stimulus coming from general physicians, cardiologists, neurologists, vascular surgeons, and chemical pathologists.

As fig 1 shows, fibrinogen stands at a crossroads between a large number of personal and environmental factors influencing its concentration, on the one hand, and several pathways influencing thrombogenicity, on the other.¹² Most of the characteristics associated with clinically manifest IHD seem to influence the fibrinogen concentration in the direction to be expected if fibrinogen is involved—for example, higher concentrations and increasing incidence with advancing age and lower concentrations and a degree of cardioprotection with moderate alcohol consumption. Three features call for special comment. First, an obvious exception from the IHD risk factors in fig 1 is diet. There is by now fairly extensive evidence from randomised trials that fat, carbohydrate and fibre intake do not influence fibrinogen

concentration in humans, at any rate in the short term. The only possible exception is fish oil which may lower the fibrinogen concentration, although the evidence is equivocal.¹² Second, smoking is a particularly important determinant of the fibrinogen concentration, probably exerting its effect on IHD through the haemostatic system rather than through lipids. The time course for the return of fibrinogen to non-smoking concentrations¹³ is similar to that for the decline among ex-smokers in the risk of IHD itself, with an obvious initial fall (in both fibrinogen concentration and risk of IHD) starting quite soon, which does not, however, reach non-smoking levels for several years thereafter. It is possible that residual lung damage resulting in increased cytokine production stimulates fibrinogen synthesis and thus raised plasma concentrations for a considerable time after smoking has been discontinued. Emphasis on the importance of smoking as a determinant of fibrinogen should not, however, obscure the fact that high concentrations also predict IHD in non-smokers.¹⁴ Third, while infection causes many changes in addition to a rise in fibrinogen, it is certainly possible that the latter may partly explain the association of infection with increased IHD and stroke mortality.¹⁵ If this is indeed the case, there may be large and significant implications for reducing the incidence of these conditions.

As fibrinogen is an acute phase protein, the high concentrations associated with IHD and with its risk factors could at least in part be a response to underlying vessel wall disease, which has many of the characteristics of an inflammatory process. It is, however, a mistake to assume that this detracts from the value of measuring fibrinogen for clinical purposes or from the pathogenetic importance of raised concentrations. First, high fibrinogen concentrations provide additional information about risk even if they are simply a marker of atheroma. Second, however, there are reasons for questioning the interpretation of raised concentrations as simply a response to vessel wall changes. These include preliminary animal studies suggesting that atherogenesis may in fact not lead to a rise in fibrinogen concentrations, at any rate in the short term,¹⁶ and the demonstrated genetic component to fibrinogen.¹⁷⁻¹⁸ Finally, whatever their origin—whether as markers of vessel wall disease or as a result of genetic and personal predispositions—high concentrations increase the risk of thrombosis through the variety of mechanisms, as summarised in fig 1. In other words, any component of raised fibrinogen concentrations that may reflect vessel wall pathology is still likely to be of biological importance and should not be overlooked simply because it may not be

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entirely independent of the pathological processes involved. It may well be, though, that raised fibrinogen concentrations, however determined, are thrombogenic only in the presence of underlying atheroma. Particularly high concentrations are found in rural Africans who experience virtually no IHD,¹⁹ the explanation probably being the high prevalence of parasitic infestation in these groups and certainly confirming the well known observation that fibrinogen concentrations do rise in response to a variety of stimuli (many of which are associated with thrombotic events). A somewhat analogous example is the relatively low incidence of IHD in the Japanese who smoke heavily but have a low prevalence of underlying vessel wall disease. This observation is clearly not an argument against the harmful effect of smoking in those who do have the necessary substrate of atheroma, and similarly for raised fibrinogen concentrations.

The associations of fibrinogen with risk factors and with IHD itself are very similar whatever measurement methods have been used, including clot detection, nephelometric and immunological techniques. Clot weight may be the most precise but is labour intensive. Most laboratories are using automated Clauss²⁰ methods with electrical impedance or optical density as the clot detection end point. The effects of fibrin degradation products on different techniques and of different forms of fibrinogen on thrombogenicity are topics of current research which may have a bearing on future methods. The development of a World Health Organisation (WHO) standard for fibrinogen²¹ will increasingly facilitate inter-laboratory comparisons which have so far not been possible because of differences in absolute values (though not, as already indicated, in the nature of associations between fibrinogen and IHD risk or IHD itself). Until laboratories routinely use and are familiar with the WHO (or another) standard, the only way in which an individual laboratory can assess its results is to establish its own reference range by measurements in perhaps 200 healthy subjects of different ages of each sex. At present, a "normal" value of, say, 2.7 g/l from one labora-

tory may be quite a low value from another. Once plasma has been separated, fibrinogen concentrations remain fairly stable for up to about 24 hours but may deteriorate unpredictably thereafter so that beyond this limit standard corrections to allow for delay between taking blood and analysis of fresh samples are not possible. Plasma can, however, be stored at low temperature for analysis later on. As with any other risk factor—for example, cholesterol or blood pressure, more than one measurement of fibrinogen is necessary to determine an individual's true or habitual concentration and, because of the acute phase response, samples should not be taken during or too soon after intercurrent infections, etc.

The topic of fibrinogen and arterial disease is at the same kind of interface between research and service that characterised the discussion of cholesterol 20 years ago—strong observational data not yet confirmed by evidence from trials. For sometime to come, therefore, decisions on the interpretation of fibrinogen concentrations and on clinical management must inevitably be based on incomplete evidence. In particular, the effects on the clinical end points of IHD and stroke of lowering raised fibrinogen concentrations have not yet been established. Apart from ancrod, which is given intravenously and only in emergency situations, there are at present no selective fibrinogen lowering agents. If and when these do become available, their long term safety as well as their effectiveness will have to be established. However, several fibrates developed originally for their lipid modifying properties, of which the most widely used is bezafibrate, lower the fibrinogen concentration by 15% or more,²² an effect which—assuming complete reversibility of the association between fibrinogen and IHD—would confer a substantial benefit. This might be particularly relevant in those at high risk of IHD for whatever reason and in whom reducing this risk is likely to outweigh any increased risk of non-IHD mortality attributable to the first generation of fibrates, especially clofibrate²³ (now rarely used for this reason). Two current trials using bezafibrate (which has a considerably shorter half life compared with

Figure 1 Summary of environmental factors affecting fibrinogen concentrations and the effect of fibrinogen on the risk of developing IHD.

clofibrate), one in patients following myocardial infarction²⁴ and the other in men with lower extremity arterial disease (MRC Epidemiology and Medical Care Unit, work in progress), should clarify this possibility in four or five years' time, provided, which seems likely, that the contributions to any risk reduction can be apportioned between the fibrinogen lowering and lipid modifying properties of bezafibrate.

Meanwhile, establishing that a patient considered to be at increased risk of thrombotic disease does have a habitually raised fibrinogen concentration is new information that it is reasonable to take into account. In these circumstances, particularly direct and intensive counselling would—for example, be indicated for those who smoke. A high concentration may also help in deciding whether to recommend other preventive strategies including the use of aspirin, the safety of which in low risk subjects is still doubtful,²⁵ even though it does not lower the fibrinogen concentration. Pending the results of the trials in progress, the fibrinogen lowering property of agents such as bezafibrate may justify their use in those with particularly high concentrations who have either experienced clinical events of cardiovascular disease or who are at highly increased risk, especially if these are accompanied by lipid abnormalities bearing in mind that these are also likely to improve and will often be found concurrently in those with raised fibrinogen concentrations.

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