Why do smokers have higher plasma fibrinogen levels than non-smokers?

Plasma fibrinogen is an independent predictor of cardiovascular disease, including coronary heart disease (CHD) [1,2], stroke [3] and peripheral arterial disease [4]. Its predictive value for CHD is similar to that of classical risk factors, such as smoking habit, blood pressure or serum cholesterol, and adds to risk prediction from these three variables [5]. Plasma fibrinogen levels show a dose-dependent increase in smokers; following smoking cessation, levels decrease towards similar values in those who have never smoked. In parallel with the fall in risk of CHD, an early rapid reduction is followed by a slower reduction over 10–15 years [5–7]. Plasma fibrinogen levels may promote cardiovascular disease through several biological mechanisms, including atherogenesis, thrombogenesis and increased blood viscosity, which may reduce blood flow [7]. It has been estimated that up to 50% of the increase in CHD risk associated with smoking could be attributed to the effects of smoking on fibrinogen [8,9]. However, the causal significance of fibrinogen levels in cardiovascular disease remains to be established by large randomized trials of fibrinogen reduction [1–7].

Why do smokers have higher plasma fibrinogen levels than non-smokers? Increased fibrinogen synthesis in the liver, rather than decreased fibrinogen catabolism, has long been suspected, but there is a lack of published studies addressing this hypothesis. In the April issue of Clinical Science, Hunter et al. [10] report two studies of fibrinogen synthesis in male smokers. In the first study, current smokers had higher absolute fibrinogen synthesis rates than non-smokers, which were correlated with increased fibrinogen levels. In the second study, 2 weeks’ abstinence from smoking in current smokers reduced both absolute synthesis rates and plasma fibrinogen levels. The authors conclude that increased fibrinogen synthesis plays a primary role in the increased plasma fibrinogen level associated with smoking. This is an important step in elucidating the pathways through which smoking increases fibrinogen levels.

Hunter et al. [10] also discuss such pathways, including the possibility that the effects of smoking on fibrinogen synthesis are part of a generalized inflammatory reaction (e.g., to smoking-induced injury to the respiratory tract, blood vessels or other organs). Other measures of inflammation are also predictive of cardiovascular risk, including C-reactive protein, leucocyte counts and low serum albumin [2], as well as plasma viscosity and the erythrocyte sedimentation rate (which are determined by plasma levels of fibrinogen and other macromolecules) [11]. Similarly to fibrinogen, such measures also show a dose-dependent increase in smokers and decrease following smoking cessation [12–15]. As discussed by Hunter et al. [10], cytokines, such as interleukin-6, are important mediators of these measures of the inflammatory response, including fibrinogen synthesis [16–17].

Future studies of smoking, smoking cessation and plasma fibrinogen are required to define their relationship to other acute-phase markers and inflammatory cytokines. Fibrin degradation produces, such as D-dimer, may also play a role in fibrinogen synthesis and inflammatory reactions; D-dimer is also elevated in smokers and weakly related to plasma levels of fibrinogen [18] and C-reactive protein [15].

Hunter et al. [10] also discuss the possible role of catecholamines in smoking-induced hyperfibrinogenemia. However, studies to date [19] have shown variable effects of adrenergic-blocking drugs in reducing plasma fibrinogen levels.

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REFERENCES

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