Dietary factors in thrombosis and hemostasis: summary and conclusions

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ABSTRACT Patients who develop thrombotic vascular occlusions usually have underlying vascular disease. However, the interplay among lipids, atherosclerosis, and thrombosis has proven difficult to define in humans. The evidence for a contribution from individual dietary lipids to thrombogenesis was reviewed in the preceding section of this supplement. Although feeding long-chain fatty acids in animal models may increase the propensity to thrombosis in animal models, the implications of this observation for human diets are obscure. This may reflect the multiple pro- and anticoagulant species that may be regulated by dietary constituents. The role of lipids in the regulation of gene expression is emerging; however, it is unknown what relevance such observations may have for dietary lipids. The study of thrombosis in vivo and, particularly, investigations of the propensity to thrombosis is confounded in many cases by ex vivo platelet activation. Evidence for a prothrombotic state is still controversial. Even the association of elevated fibrinogen with the incidence of coronary disease may not reflect a causative mechanism. Limited information is available as to health benefits of individual lipids, although drugs that lower cholesterol unequivocally reduce the incidence of cardiovascular death, even in patients with moderate hypercholesterolemia.

Am J Clin Nutr 1997;65(suppl):1699S–701S.

KEY WORDS Lipids, diet, thrombosis, platelets, hemostasis

INTRODUCTION

An association between atherosclerosis and thrombosis in patients with acute vascular occlusive events has been well established. Postmortem studies, angiography, angioscopy, and biochemical indexes of platelet activation and thrombin generation provide a consistent picture of plaque rupture, with superimposed thrombosis as the precipitating event that becomes manifest clinically as myocardial infarction or unstable angina (1–4). The functional relevance of these observations is supported by the clinical efficacy of thrombolytic, antiplatelet, and anticoagulant drugs and of lipid-lowering agents in reducing mortality in such patients (5–9).

LIPIDS AND THROMBOSIS

Interest in nonpharmacologic approaches to modifying coronary disease is exemplified by studies of the effects of exercise, stress management, and quitting cigarette smoking on risk (10–12). Given the likely role of lipids in atherogenesis, dietary intervention to modify the lipid profile has also been investigated. However, although strict regimens have been reported to reduce low-density-lipoprotein (LDL) cholesterol coincident with significant regression of coronary vascular disease as assessed by quantitative coronary angiography (13), only treatment with lipid-lowering drugs has been shown to reduce unambiguous clinical endpoints, such as myocardial infarction and death, coincident with a reduction in serum lipids (9, 14). Although the results of such studies imply that lipid reduction by diet, drugs, or both may reduce coronary risk, a much more difficult issue to resolve is how particular lipid constituents of the diet may contribute to coronary risk.

A first step in addressing this issue might be to assess the effects of administration of pharmacologic quantities of lipids in animal models. This type of evidence was well summarized by John Hoak. Essentially, there is fairly good evidence that systemic administration of long-chain saturated fatty acids will increase the propensity to clotting in a variety of animal models of arterial thrombosis. Medium-chain and unsaturated fatty acids are usually without effect. However, the relation of these findings to the clinical setting is constrained by issues such as dose, acuity of administration, species, potentially modifying effects of other dietary constituents, and how closely the model simulates the actual thrombotic event in humans.

An extension of this concept might be to evaluate how individual dietary constituents modify cellular functions relevant to thrombosis and atherosclerosis. Kenneth Mann highlighted many of the features of thrombosis in vivo. These include the interaction of circulating constituents with the vessel wall, the kinetic facilitation of coagulation by the assembly of multimeric complexes on cell membranes, and the coincidental activation of counterbalancing pathways, including vasodilators and platelet inhibitors (eg, prostacyclin and nitrous oxide), anticoagulants (lipoprotein-associated coagulation inhibitor, antithrombin III, and platelet factor 4), and thrombolytics (single-chain urokinase and tissue plasminogen activator). Appreciation of the nonlinear kinetics and redundancies involved in this complex system illustrates the challenge of establishing biochemical markers that might define a prothrombotic state.

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Agreement on what constitutes such a condition of risk for an impending coronary event would permit more precise evaluation of potentially adverse or beneficial maneuvers in the clinic. Norberta Schoene reviewed some of the biochemical and cellular indexes that have been used for this purpose. Perhaps the most common of these is the in vitro platelet aggregation response to agonists. This test is inexpensive and widely available. It is useful in demonstrating inhibition of platelet function ex vivo when a patient has taken an antplatelet drug such as aspirin. Its application to imply a propensity to thrombosis in vivo, on the basis of increased aggregability, however, is much more controversial.

Multiple factors influence aggregability and are rarely standardized, even in small studies conducted in specialized units. Extension of such methodology to multiple centers in field studies only exacerbates the difficulty. There is no reason to suppose that refinements of the basic methods of aggregation in whole blood or filter aggregometry, for example, will solve this problem. Multiple agonists may be used, often with differing results. How to interpret such information is not known. These observations question the validity of comparisons of aggregability across regions with reportedly differing dietary intakes of fat (15, 16). They do give some insight into the likely inhibitory potency of manipulations of dietary lipids on platelet responsiveness. Thus, chronic supplementation of the diet with large and unpalatable quantities of fish oils has a modest inhibitory effect compared with ingestion of a single tablet of aspirin (17).

Other approaches to defining increased platelet reactivity also have limitations. Platelets are highly susceptible to activation during sampling. It is essentially impossible to prevent or quantify this phenomenon or to discriminate it from activation that occurred in vivo when assessing markers of platelet function in blood samples. These limitations undermine the use of plasma thromboxane B₂, β-thromboglobulin, and circulating platelet aggregates.

Activation during sampling is likely to be a problem with the currently fashionable use of flow cytometry to detect activation-dependent epitopes in membrane glycoproteins, with antibodies such as PAC-1 (18). This technology has afforded considerable insight into platelet activation in vitro. The precision of the instrumentation does not address the limitations outlined above when applied to the study of platelet function in vivo. Urinary metabolites of platelet products or their plasma concentrations, if they are not formed in whole blood (19, 20), can provide some insight into platelet activation in vivo (21). However, they suffer from the constraint that their tissue of origin is never definitively established and may vary, dependent on coincident disease. Recently, long-lived cleavage products of coagulation proteins, such as F1.2 and complexes of such proteins with their natural inhibitors, such as thrombin-antithrombin complexes, have been used to investigate thrombotic events in vivo (22, 23). There is some evidence, from using this approach, that some patients who have suffered a myocardial infarction may have sustained elevations in these indexes for months after the event (24). However, a quantitative relation between these markers and the likelihood of a subsequent event has not been established, and this would be a prerequisite for using them to define a prothrombotic state.

The most convincing case for association of a coagulation or platelet factor with coronary risk is for fibrinogen. Thomas Pearson et al reviewed the evidence from several prospective studies that showed an association between elevated fibrinogen and acute vascular events. However, even these have limitations, including a paucity of information on females and non-whites. Pearson et al also draw our attention to the several sources of potential bias that might confound such an association. These include the relation of the risk factor and the event to a distinct, causative factor. Thus, fibrinogen and cardiac disease may both be independently related to cigarette smoking. Pearson et al also highlighted the problem of prevalence-incidence bias. For example, fibrinogen is an acute-phase protein; it may be elevated when one is acutely ill. Thus, elevations in patients with vascular disease may reflect activation of the inflammatory component of atherosclerosis, which may (or may not) predispose one to plaque instability and a clinical event. Alternatively, it may be that patients with established disease have elevated acute-phase proteins compared with healthy individuals with no specific causative link to vascular occlusive events.

Assessment of the health benefits or risks of individual lipids requires interventional studies with unambiguous clinical outcomes. These have not been performed. The closest approximation is the assessment of dietary supplementation with a complex of fish oils on restenosis after coronary angioplasty. Given an appropriate sample size, this intervention was ineffective (25), despite a reasonable mechanistic rationale (26). Retrospective assessment of dietary lipids or dietary counseling have yielded conflicting results on the effect of dietary fish consumption on cardiovascular disease (27–29).

Useful information might be gathered if biochemical or functional indexes that predicted risk were identified. The effects of supplementation with individual or complex dietary lipids might then be assessed more inexpensively to provide a rationale for an interventional trial. Such an approach was used with hypolipidemic and antihypertensive drugs. However, the implications of alterations in indexes of the propensity to thrombosis have not yet been defined as precisely as was the case for LDL cholesterol and blood pressure when they were used as surrogates for clinically important vascular events.

CONCLUSIONS

The coincidence of atherosclerosis and thrombosis in patients suffering from unstable coronary artery disease is well established. Molecular links have been shown between the two processes, as exemplified by the discovery of lipoprotein(a) (30), concentrations of which may predict the rate of progression of vascular pathology (31). However, the direct effect of individual dietary lipids on platelet function and the coagulation pathway has been difficult to discern and the molecular basis for the interplay between lipids and the coagulation system is largely obscure. For example, we know that procoagulant complexes assemble efficiently on cell membranes. However, little is known about how the lipid composition or status of those membranes affects the function or interaction of these proteins (32). It is likely that reasonable hypotheses will emerge from studies of the basic mechanisms involved. Extension of these hypotheses into the clinical domain may require the definition of more precise biochemical or cellular indexes of thrombotic risk in vivo than are available currently (33, 34).
HEMOSTASIS SECTION: SUMMARY

REFERENCES


