optimizing glycemic control, high-dose statins were recommended as first choice, and a combination of statins plus gemfibrozil were recommended as second choice.

At the time when the review was written, these were the drugs available in the U.S. Recently, however, another fibric acid derivative, micronized fenofibrate, has also been approved by the Food and Drug Administration and is now marketed. Because it has been approved for several years in a large number of other countries, there is wide experience with it in the treatment of both those with and those without diabetes. The drug is potent in reducing triglycerides and increasing HDL cholesterol. As well, it has a greater effect in lowering LDL cholesterol than does gemfibrozil. Hence, in future recommendations, it should be considered as first-line not only in the treatment of hypertriglyceridemia that persists after glycemic control is improved, but also as first choice in the treatment of combined hyperlipidemia. Its use as a single agent in the latter condition would avoid the combination of a statin and gemfibrozil, thereby reducing the possibility of myositis.

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References

Association Between Fibrinogen Levels and Insulin Resistance

Imperatore et al. (1) have recently published an impressive cross-sectional study on the relationship between fibrinogen and the metabolic syndrome usually termed “syndrome X.” This study clearly demonstrated in a large and relatively young population that high fibrinogen levels were associated with some symptoms of the metabolic syndrome (high plasma glucose, triglycerides, blood pressure, and low HDL cholesterol) or with their combination, independent of various confounders such as age, smoking, coexisting inflammatory diseases, or use of drugs. Thus, there is now strong evidence that hyperfibrinogenemia is a characteristic of syndrome X, as previously suggested (2). In fact, disturbances of the hemostatic system, i.e., excess of plasma fibrinogen and defective fibrinolysis, have been recently added by Reaven to the revised definition of the metabolic syndrome (3).

As mentioned by Imperatore et al., the link between hyperfibrinogenemia, hyperinsulinemia, and insulin resistance is not fully elucidated. Aside from a single study by Landin et al. (4), there do not appear to be any studies in which direct measurements of insulin sensitivity, such as glucose clamp or minimal model procedure, have been used to evaluate the relationship between fibrinogen and insulin resistance. Landin et al. reported a negative correlation between fibrinogen levels and the rate of glucose disposal during a euglycemic clamp technique (r = −0.35, P < 0.05; 22 men, 11 with mild untreated hypertension). Surprisingly, no correlation was observed between fibrinogen and fasting insulin (r = 0.06, NS).

We have investigated the association between plasma fibrinogen levels, basal insulin, and insulin sensitivity in a random sample of 36-year-old non-diabetic non-hypertensive patients, 20 men and 30 women, with BMIs ranging from 18.6 to 35.9 kg/m². Insulin sensitivity was assessed with the minimal model procedure over a 180-min intravenous glucose tolerance test with iterative sampling, as previously described (5). Plasma insulin was determined by radioimmunoassay and fibrinogen by the method of Clauss. The two major findings of our study were a highly significant negative correlation between fibrinogen and insulin sensitivity (r = −0.76, P < 0.0001) (Fig. 1) and a positive correlation between fibrinogen and basal insulin (r = 0.59, P < 0.0001) (Fig. 2). We performed a partial correlation analysis to assess the influence of BMI on these data: the negative relationship between fibrinogen and insulin sensitivity remained significant after adjustment for BMI (r = −0.64, P < 0.0001). These results provide further evidence for the connection between insulin resistance and hemostatic disorders in the pathogenesis of the metabolic syndrome. Nevertheless, they do not allow analysis in terms of causality.

A role for free fatty acids (FFA) has been proposed to explain the association between fibrinogen and insulin resistance, since hepatic fibrinogen synthesis should be stimulated by FFA (6). A defective fibrinolysis with high plasminogen activator inhibitor-1 (PAI-1) levels may be found in type 2 diabetic patients, in relation to the amount of visceral fat (7). Finally, there is a large body of literature emphasizing the...
Response to Raynaud et al.

We thank Raynaud et al. (1) for their thoughtful comment on the association between insulin resistance and fibrinogen levels. In our work, a large unselected group of normoglycemic men was studied by measuring fasting plasma insulin along with the classical components of the metabolic syndrome (i.e., blood pressure, fasting plasma triglycerides, HDL cholesterol, and glucose); we conclude that it is very likely the condition of insulin resistance rather than hyperinsulinemia per se that is related to hyperfibrinogenemia (2). Raynaud et al., by directly measuring insulin resistance with the minimal model procedure, provide an important and missing piece of information nicely elucidating the up to now poorly investigated issue of the relationships among hyperfibrinogenemia, hyperinsulinemia, and insulin resistance.

We fully agree with Raynaud et al. that these findings should not be interpreted in terms of causality, since cause-effect relationships cannot be established by cross-sectional studies. Furthermore, we would like to expand the interpretation of our own data and that obtained by Raynaud et al. Tough evidence exists supporting a possible role for insulin resistance in the pathogenesis of hyperfibrinogenemia; however, based on current knowledge, other concurrent or alternative interpretations should be explored as well. In particular, because the metabolic syndrome may influence the development of cardiovascular disease, it cannot be ignored that hyperfibrinogenemia may be an epiphenomenon rather than a causative factor in the process of atherogenesis. Plasma fibrinogen is known to rise acutely in response to a number of conditions including endothelial damage and inflammation, both involved in the pathogenesis of atherosclerosis (3). In support of this hypothesis is the independent relation—found in our study after careful exclusion of individuals with clinically evident cardiovascular disease—between fibrinogen levels and some well-established cardiovascular risk factors, such as LDL cholesterol and smoking, which do not cluster with the components of the metabolic syndrome.

In conclusion, a clear association exists between the metabolic syndrome and hyperfibrinogenemia; this association is likely mediated by insulin resistance. Further studies, in particular intervention studies, are needed before either insulin resistance or hyperfibrinogenemia are firmly established as cardiovascular risk factors (4).

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References

Autoimmunity and Intraperitoneal Insulin Treatment by Programmable Pumps

Lack of relationship

Continuous intraperitoneal insulin infusion (CIPII) by programmable pumps is a promising therapy for patients with type 1 (insulin-dependent) diabetes, since it improves metabolic control and decreases the frequency of severe hypoglycemia (1). But this treatment leads to an increase of anti-insulin immunogenicity (2-4), as shown by sustained elevated levels of anti-insulin antibodies. The report of five cases of hyperthyroidism in type 1 diabetic patients treated with intraperitoneal (IP) insulin infusion (5) has raised the question of a more general stimulation by CIPII of autoimmunity in type 1 diabetes.