Hyperlipidemia and Thrombotic Complications in Patients With Membranous Nephropathy

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Membranous nephropathy (MN), the most common cause of adult-onset nephrotic syndrome (NS) in Caucasians, is associated commonly with the secondary complications of hyperlipidemia and hypercoagulability. These may increase the risk for cardiovascular disease, alter the rate of progression of renal disease, and raise the risk for thromboembolic events. The treatment of these secondary effects remains controversial. Although no clear practice guidelines are available to assist the clinician in deciding how and when to start disease-modifying therapies, the literature provides enough information to make reasonable decisions in most clinical scenarios. Prospective trials in the future will provide definitive information on how to best treat these abnormalities.

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As the most common entity associated with adult-onset idiopathic nephrotic syndrome (NS), membranous nephropathy (MN) and its attendant complications of hyperlipidemia and increased thrombotic risk are familiar to nephrologists. These complications are believed to be secondary to the proteinuria that results in homeostatic disturbances causing decreased circulating plasma volume, enhanced hepatic production of proteins and lipids, decreased lipid catabolism, and loss of specific proteins in the urine. Despite the potential risks associated with hyperlipidemia and hypercoagulability, treatment of these 2 entities in MN is controversial and no practice guidelines have been established. In this article, we review available information concerning the clinical significance, pathogenesis, and treatment of these secondary complications commonly associated with MN.

MN and Hyperlipidemia

The hyperlipidemia of NS and its treatment has gained increasing attention over the past decade. Although its causative mechanisms are not yet completely delineated, plausible mechanisms of its development have been postulated and studied. Hyperlipidemia is of particular concern in patients with NS because it is a risk factor for atherosclerotic cardiovascular disease, the most common cause of mortality in end-stage renal disease patients. Hyperlipidemia in nephrotic patients also has been related to increased endothelial dysfunction, which can be corrected through treatment of the hyperlipidemia by use of HMG-CoA reductase inhibitors.1,2 It may also be a risk factor for the initiation and progression of renal disease.3-8

As with other forms of NS, lipid abnormalities may be quite striking in nephrotic patients with MN. Lipid levels generally correlate inversely with the serum albumin concentration and plasma oncotic pressure.9 Total cholesterol and low density lipoproteins (LDL) are abnormal in about two thirds of the patients and are elevated about 2-fold. In one study of 100 consecutive new adult nephrotic patients with either MN or focal glomerulosclerosis, 87% of all patients and 93% of the membranous patients had a serum cholesterol level greater than 200 mg/dL, whereas 53% of all patients and 66% of the membranous patients had a total cholesterol level of greater than 300 mg/dL.10 LDL cholesterol was greater than 160 mg/dL in 65% of all patients and 70% of the membranous patients in this study. Very low density lipoproteins (VLDL) and lipoprotein a (Lp(a)) also typically are elevated in nephrotic patients with MN. However, levels of high-density lipoprotein (HDL) cholesterol are often in the normal range. These abnormalities are believed to result from multiple concurrent mechanisms (vide infra).

Significance of Hyperlipidemia in MN

The evidence supporting elevated risks for cardiovascular disease in nephrotic patients has been conflicting. Associations of an increased risk for cardiac events at younger than expected ages for subjects with NS have been noted. However, there also have been studies that have found no association with an increased risk for cardiovascular-
related mortality. A convincing argument for an increased risk for cardiovascular disease was made by a prospective cohort study of 142 nephrotic patients and 142 controls followed-up for 5.6 years to assess nonfatal coronary events, and 7.8 years to assess mortality. Twenty-eight percent of the nephrotic patients were diagnosed with MN, and patients with diabetes as a cause of the NS were excluded. In the adjusted analysis, the relative risk for myocardial infarction in nephrotic patients versus controls was 5.5 (95% confidence interval, 1.6-18.3), cardiac death was 2.8 (95% confidence interval, 0.7-11.3), and all-cause mortality was 7.2 (95% confidence interval, 3.6-14.2). More, there is no reason to believe patients with idiopathic NS and MN would be at less risk for cardiovascular disease in the presence of an unfavorable lipid profile than any other population.

Experimental models in both animals and humans also have suggested that hyperlipidemia propagates renal injury. Samuelsson et al followed-up 73 adult nondiabetic patients with primary chronic renal disease for an average of 3.2 years. Approximately half of the cohort had chronic glomerulonephritis as the cause of their renal disease. The findings indicated that independent of glomerular filtration rate (GFR) at study initiation, abnormal lipid profiles independently contributed to the decline in GFR. The ability to preserve GFR by treating lipid abnormalities has been studied. Although no large randomized trials exist, a number of small trials have been conducted. A meta-analysis of 13 prospective trials studying the effects of antihyperlipidemic agents on renal function, proteinuria, and microalbuminuria concluded that lipid reduction may assist in GFR preservation.

Mechanisms of Hyperlipidemia in the NS

Elevated VLDL levels are secondary to both an increase in synthesis and a decrease in catabolism. Endothelial-bound lipoprotein lipase (LPL) and apolipoprotein C-II (apoC-II) are necessary for VLDL metabolism. LPL, produced in adipose and muscle tissue, binds to endothelial tissue where it can encounter, bind, and metabolize VLDL particles. In NS, abnormalities in LPL messenger RNA levels and LPL attachment to endothelium have been found. LPL synthesis and release are not thought to be impaired. But, secondary to reduced LPL-endothelial binding, VLDL cannot be metabolized.

The role of HDL in the development of lipid abnormalities in the NS centers on a defect in its ability to shuttle apoC-II from remnant particles to VLDL and chylomicrons. This shuttling process is dependent on lecithin:cholesterol acyltransferase. In the NS, lecithin:cholesterol acyltransferase activity is reduced secondary to decreased binding of lyssolecithin to albumin. This prohibits the maturation of HDL particles to the form most effective in transporting apoC-II, and results in an accumulation of atherogenic cholesterol particles. Moreover, cholesterol ester transfer protein levels are elevated markedly in nephrotic patients and may be responsible for shuttling cholesterol from HDL to VLDL and LDL.

The elevation in LDL is believed to be caused by its hepatic overproduction. The stimulatory mechanisms responsible for its overproduction remain unclear. Hypoalbuminemia, reduced oncotic pressure, and loss of regulatory proteins in the urine of nephrotic patients all have been suggested as driving mechanisms for the enhanced hepatic synthesis.

Lp(a) serum levels in nonnephrotic individuals are dependent on and vary inversely with isoform molecular weight. The molecular weight in each individual is genetically determined. In the NS, Lp(a) levels increase independently of isoform size. The increase in Lp(a) concentration is dependent only on an increased synthetic rate by the liver.

Treat the Hyperlipidemia in MN

The decision to treat hyperlipidemia in MN patients is based on information from studies showing the contribution of lipid abnormalities to both the risk for cardiovascular disease and for the progression of renal disease. The treatment of lipid abnormalities in patients with MN rests primarily on treatment of the underlying NS. However, additional measures usually are required. These include dietary interventions, medications to reduce proteinuria, and specific antihyperlipidemic medications. Dietary therapy with a low saturated fat, low-cholesterol diet should be initiated in all patients with MN with serum cholesterol levels greater than 200 mg/dL or LDL cholesterol values greater than 130 mg/dL. Although such therapy may lower total and LDL cholesterol levels by
approximately 30%, it often will fall short of the goals set for such patients. The use of angiotensin converting enzyme inhibitors, A-II receptor antagonists, or their combination will reduce proteinuria, increase serum albumin levels, and decrease serum cholesterol and LDL levels. HMG Co-A reductase inhibitors are effective in treating the hyperlipidemia of NS. Trials of statin use document a 20% to 30% decrease in total and LDL cholesterol levels with increases in the HDL cholesterol level. Moreover, higher doses of more potent statins can decrease total cholesterol level by over 50% in patients with idiopathic NS including MN (personal observations) (Fig 1). Other antihyperlipidimic agents used in MN include fibric acid derivatives, bile acid sequestrants, and agents used to block intestinal absorption of cholesterol. There are no published data on ezetimibe in nephrotic patients, but it may lead to major lipid lowering, especially if combined with low-dose statin therapy. Statins must be used with caution in patients receiving fibric acid derivatives and/or the calcineurin antagonists, cyclosporine and tacrolimus.

MN AND THE HYPERCOAGULABLE STATE

The risk for thromboembolic phenomena and its attendant morbidity and mortality are of considerable concern in MN. Deep venous thrombosis (DVT) and renal vein thrombosis (RVT) occur more frequently in MN than in other patterns of NS. The risk for DVT has been estimated at 11%, clinically significant pulmonary embolism (PE) at 11%, and RVT at 35%. The decision to initiate prophylactic anticoagulation with warfarin at diagnosis of MN or to postpone treatment until a thrombotic event occurs is controversial. Given the high risk for thrombosis in MN it would seem that the benefits of prophylaxis in some patients should outweigh the hemorrhagic risks. However, no consensus has emerged.

Risk for Thromboembolic Complications

The reported prevalence of true RVT in MN with NS ranges from 5% to 60%. The prevalence of thrombotic complications from other sites range from 8.5% to 44%. Multiple studies have estimated the incidence of RVT and DVT in MN compared with other types of the NS. The incidence of thrombosis in MN versus other types of NS, in terms of events per 100 patient-months, is approximated at 0.5 versus 0.08 for clinically apparent RVT and 1 versus 0.6 for clinically apparent DVT. The varied reported incidence in MN in part can be attributed to the vigor with which clotting events are sought by the investigator. For example, selective renal branch vein catheterizations to look for RVT clearly will yield a higher positive percent than Doppler ultrasound, a commonly used screening technique. The risk for thrombosis also correlates with the degree of hypoalbuminemia. Thromboembolic events become more common with lower serum albumin levels and especially with levels less than 2.0 g/dL.

The risk for PE after RVT or DVT varies in the literature. Estimates range from 20% to 40% for untreated RVT and 50% for untreated DVT. The mortality associated with PE is high. Patients who present with acute PE and are treated have a
mortality of 2.5% to 8%. In some series those patients with unrecognized PE are at risk for the development of recurrent emboli and a subsequent mortality of 32%.45,46 However, it is unclear if the mortality and morbidity figures applied to the overall population with PEs applies to those with MN.

**Etiologies of Hypercoagulability in the NS**

The mechanisms of heightened thrombotic risk in NS are multifactorial. One primary etiology of the clotting abnormalities are thought to arise from glomerular injury with proteinuria resulting in the loss of antithrombotic proteins, such as antithrombin III. Also, the hypoalbuminemic state results in platelet hyperactivity, changes in the fibrinolytic pathway, and increased synthesis of procoagulant proteins.34 Glomerular injury also results in activation of the glomerular hemostasis system, stimulating thrombin formation. Other mechanisms of hypercoagulability in the NS are believed to result from a decrease in renal vein perfusion pressure secondary to the lowered oncotic pressure, and a possible genetic predisposition to clotting abnormalities. Why patients with MN with the same degree and duration of serum hypoalbuminemia have a much higher incidence of thrombotic events and especially RVT than do other nephrotic patients is unclear.

**Treatment of Hypercoagulability in MN**

Despite an increased incidence of thrombosis in MN compared with other forms of NS, the timing of antithrombotic therapy initiation is controversial owing to the potential hemorrhagic risk associated with long-term warfarin therapy.36,41,47 The rationale to initiate anticoagulation therapy is to decrease the incidence of thromboembolism and lessen its associated morbidity and mortality. However, anticoagulation therapy may itself be associated with life-threatening bleeding complications. Hemorrhage from anticoagulation therapy generally correlates with the degree of anticoagulation and underlying comorbid conditions.48-50 The average hemorrhagic risk from long-term anticoagulation for hypoalbuminemic patients is thought to be higher than nonhypoalbuminemic patients secondary to altered warfarin pharmacokinetics. However, no clear data exist to support this theory.

The literature specifically examining the efficacy and risks for long-term anticoagulation therapy in patients with NS is scant. Sarasin and Schifferli51 used a decision-analysis model to quantify the risk benefits of prophylactic therapy in which oral anticoagulation was started at diagnosis of MN versus initiation of anticoagulant therapy after the first clinically apparent event. Although the sensitivity analysis concluded that the overall number of fatal embolic events prevented by anticoagulation exceeded that of fatal bleeding events, the quality-adjusted life expectancy was only 2.5 months greater in the prophylaxis group.

The paucity of data surrounding the appropriate timing of when to start anticoagulant therapy and which patients would benefit most from prophylactic therapy in MN makes it difficult to develop treatment guidelines. Some clinicians recommend prophylactic anticoagulation in all MN patients, others only on those with a serum albumin less than 2 g/dL, and others only in those who have already experienced a thromboembolic event.52,53 Prospective trials are needed to address the risk-benefit ratio of this therapy, the level of anticoagulation most appropriate, and the factors that elevate the risk for thrombotic events in this group of patients.

**CONCLUSION**

It is clear the complications of hyperlipidemia and hypercoagulability can have significant deleterious effects on the course of patients with MN. Moreover, therapy of these complications can pose major therapeutic challenges. Evidence for routine and vigorous therapy of lipid abnormalities is strong in MN patients with NS. Persistent lipid abnormalities elevate the long-term risk for cardiovascular complications, and also may accelerate the rate of progression of renal disease. Treatment with diet, nonspecific agents to reduce proteinuria, and lipid-lowering medications such as statins can improve the lipid abnormalities. Once patients have achieved a remission of their proteinuria through treatment of the basic glomerular disease process, the lipid abnormalities will dissipate and no longer require treatment. Those patients who remain nephrotic with large amounts of proteinuria will benefit the most from long-term antihyperlipidemic therapy.

The initiation and timing of anticoagulation therapy in MN is more controversial. The lack of prospective randomized trials assessing prophylactic therapy versus watchful waiting prohibits definitive criteria for treatment. A high level of sus-
picion for thrombotic complications in these patients is necessary. Patients who do not respond to antiproteinuric therapy and remain nephrotic with very low serum albumin levels and large amounts of proteinuria likely represent those at greatest risk for thrombotic complications. Whether or not to initiate prophylactic anticoagulation before the development of a thrombotic complication in this population must remain up to the discretion of the treating nephrologist until more data is available.

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