3-1-2014

Treatment of nephrotic syndrome: Retrospection

Jerry Yee
Henry Ford Health, JYEE1@hfhs.org

Recommended Citation
Yee J. Treatment of nephrotic syndrome: Retrospection. Advances in Chronic Kidney Disease 2014; 21(2):115-118.

ACKD Advances in Chronic Kidney Disease
A Journal of the National Kidney Foundation™
Vol 21, No 2, March 2014

EDITORIAL

Treatment of Nephrotic Syndrome: Retrospection

In this issue of *Advances in Chronic Kidney Disease*, the guest editors, Drs. Radhakrishnan and Bomback, have assembled a retinue of glomerulologists to advance the theme of essentially "what's new" in the treatment of glomerulonephritis—a truly heterogeneous group of disorders. The 10 papers contained herein do just that, informing the reader of novel therapies and breakthroughs that have demonstrated efficacy in the treatment of the various glomerulonephritides, ranging from well-known disorders to ultraorphan diseases,[1] which affect less than 0.0020% of a defined population. One such example where a new understanding of the pathogenesis of the disease gives rise to innovative therapy is membranoproliferative glomerulonephritis from dense deposit disease, a form of C3 glomerulopathy stemming from continuous complement activation from a genetically altered factor H.[2]

Current treatments for glomerulonephritis involve conventional, nonspecific and newer, specific therapies. For many of the glomerulonephritides, nonspecific, therapeutic strategies remain the cornerstone of management, and several of these will be discussed. The nonspecific ones are those that are employed to ameliorate the signs, symptoms, and consequences of glomerulonephritis, and these are encountered most prominently in nephrotic syndrome (NS). Per the Kidney Disease: Improving Global Outcomes initiative, the definition of NS in adults is "proteinuria >3.5 g per 24 hours plus hypoalbuminemia and edema."[3] Notably, nearly all of these manifestations are engendered by albuminuria, arising from multiple, potential disease-specific derangements: (1) endothelial dysfunction[4]; (2) glomerular basement membrane disruption[5]; (3) podocyte and slit diaphragm impairment(s), which frequently coincide with cytoskeletal disruption[6,7]; and (4) immune- and complement-mediated disorders.

In general, CKD is often marked by hypertriglyceridemia, but hypercholesterolemia is a hallmark of nephrosis, the result of high-grade proteinuria. Previously, in nephrosis, the serum cholesterol level was considered a function of the renal albumin clearance (Table 1)[8]; however, others have speculated that the urinary losses of other, nonalbuminous proteins may be critical to the pathogenesis of nephrotic dyslipidemia.[9] The nephrotic kidney initiates the biochemical alterations that beget the dyslipidemia of NS, but the nephrotic liver perpetuates it. Urinary loss of a lipid metabolism regulator, possibly lecithin cholesterol acyl transferase (LCAT), may trigger the abnormal hepatic lipid metabolism that can be divided experimentally into two phases: hypercholesterolemia and hypertriglyceridemia, via early phase upregulation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and acyl CoA:diacylglycerol acyltransferase, respectively, and chronic phase maintenance of hypercholesterolemia via hepatic acyl CoA: cholesterol acyltransferase upregulation. In concert, there is low-density lipoprotein (LDL) receptor and high-density lipoprotein (HDL) receptor downregulation, rendering a more atherogenic profile. Furthermore, LCAT loss impairs HDL-mediated cholesterol uptake by extrahepatic tissues and reduces liver disposal of triglyceride and HDL cholesterol (Fig 1). Finally, a low-protein diet may attenuate this pathophysiological sequence, but this tactic is often averted for fear of instigating protein malnutrition and immune incompetence, a concern that may be an exaggerated fear, given the difficulties in practice of achieving dietary protein restriction.[10]

The subject of impaired immunity is important because advanced CKD is associated with immune compromise. The relative immunodeficiency state is amplified in heavy proteinuria with urinary losses of immunoglobulin. Recall that infection in children afflicted with minimal change disease was once the primary cause of death.[11] The relative risk amplification is significant, 6.74 for immunoglobulin G levels below 600 mg/dL versus above this threshold.[12] Consequently, it may be prudent to use a more aggressive vaccination strategy in nephrotic patients, especially those with lower

1548-5595/$36.00
http://dx.doi.org/10.1053/j.ackd.2014.01.012

Table 1. Albumin Synthesis and Serum Lipid Concentrations in Nephrotic Syndrome Treated by Low and High Protein Diets

Parameter	Low-Protein Diet	High-Protein Diet
Albumin synthetic rate (g/1.73 m^2/24 h)	12.61 ± 1.2	17.60 ± 1.25
Triglycerides (mg/dL)	265 ± 65	306 ± 75
Cholesterol (mg/dL)	325 ± 44	376 ± 55

Changes in albumin synthetic rates and serum lipid concentrations from 8 patients with nephrotic syndrome treated with low- and high-protein diets. Total serum cholesterol concentrations were dependent only on kidney clearance of albumin by multiple regression analysis ($P < .001$). Adapted from data from Kaysen GA, Gambertoglio J, Felts J, Hutchison FN. *Kidney Int.* 1987;31(6):1368-1376.[8]

glomerular filtration rates. Such a decision would be tempered by the anticipated duration and severity of the albuminuria. Also, "live" vaccines should be avoided during immunosuppressive therapy that is used to treat many of the glomerulonephritides.[13]

Hypercholesterolemia in NS is primarily due to elevations of LDL cholesterol, and this is often treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). However, clinical trials evidence supporting the use of statins for retarding progression of disease in NS or reducing cardiovascular events in NS is limited.[14] Recent meta-analyses support the utility of statins in pre-dialysis.[15] Because one hopes to induce remission of NS as quickly as possible, endpoint analysis of hard cardiovascular endpoints is impossible to ascertain when glomerulonephritis responds to therapy rapidly: clinical trial participant numbers are small and natural vacillations in the course of disease confound analysis of treatment efficacy. In essence, any hypocholesterolemic therapy should be targeted toward reduction of albuminuria, not the height of the LDL cholesterol, which is rarely normalized by treatment. When albuminuria is heavy and hypercholesterolemia is present, statin therapy may significantly retard albuminuria. Among the statins, atorvastatin appears to consistently yield an antiproteinuric effect, and this may be related to an augmentation of the production of endothelial nitric oxide, the deficit of which fosters transendothelial passage of albumin.[4]

Monotherapeutic renin-angiotensin-aldosterone system inhibition rapidly and effectively reduces albuminuria via beneficial alterations of intraglomerular pressure and glomerular permeability.[16] Trials of dual, anti-RAAS therapy have shown more harm than benefit in type 2 diabetes, although similar observations have not been rigorously tested in non-diabetic glomerular disorders. The Veterans Administration Diabetes in Nephropathy (VA Nephron-D) study was powered to detect an 18% relative risk reduction in its composite endpoint of a decline in GFR, ESRD, or death. The trial of type 2 diabetics with albuminuria of at least 300 mg/g demonstrated some benefit in nearly all subgroups, but the risk reduction was less than 18%. Overall, any improvements were small and outweighed by mild increases in CKD progression and the onset of AKI as well as more frequent episodes of hyperkalemia.[17] Notably, none of these trials targeted nephrotic individuals. Nephrotic patients treated by dual, anti-RAAS therapy with an ACEI and ARB consistently experience greater proteinuria reductions than with either agent alone.

The level of evidence admonishing the dual anti-RAAS therapy is Level 1, Grade A. Nonetheless, even at this level of strength of evidence, the Kidney Disease: Improving Global Outcomes initiative has the rejoinder that "… most people in your situation would want the recommended course of action and only a small proportion would not."[3] Taken collectively, when dual anti-RAAS therapy in NS is considered, it must continue to be individualized and exercised with great caution by a vigilant nephrologist. Nevertheless, despite this warning, the superior solution for combination, antiproteinuric therapy is an ACEI or ARB plus spironolactone. The combination of lisinopril plus spironolactone at 25 mg daily was clearly superior to that of lisinopril at 80 mg daily plus losartan at 100 mg daily in a double-blinded, placebo-controlled trial of 81 diabetics with hypertension and albuminuria of at least 300 mg/g creatinine.[18] However, serum K concentrations must be monitored closely with this approach.

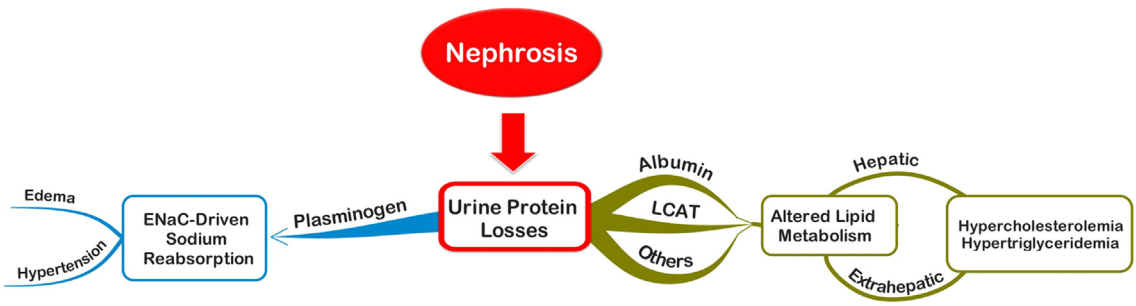

Figure 1. Dyslipidemia of nephrotic syndrome. A glomerular disorder leads to excessive proteinuria with urinary protein losses. Urinary plasminogen losses induce ENaC sodium reabsorption, leading to edema and hypertension. Urinary losses of albumin, LCAT, and potentially other proteins lead to hepatic and extrahepatic biochemical alterations that produce elevations of CHOL and TG. Abbreviations: CHOL, cholesterol; ENaC, epithelial sodium channel; LCAT, lecithin cholesterol acyl transferase; TG, triglycerides. Diagram by Pablo Buitron de la Vega and Jerry Yee (iMindmap v. 6.0, ThinkBuzan, Cardiff).

The dimethylxanthine, pentoxifylline, an agent that reduces inflammatory cytokine release, leukocyte activation, and platelet aggregation at the microcirculatory level, has been more recently touted as antiproteinuric and disease-modifying via reductions in urinary cytokines, tumor necrosis factor-α, and monocyte chemoattractant protein-1.[19] A recent clinical trial affirms this effect in non-nephrotic individuals, even at a low dose of 400 mg per day.[20] This dose added to ACEI therapy reduced proteinuria from 617 to 378 mg at 3 months and 192 mg after 6 months. Importantly, pentoxifylline should only be considered as additive to other antiproteinuric strategies. Clinical trials that will evaluate the long-term patient-centered benefits with pentoxifylline treatment are in progress.

Proteinuria (and edema) is aggravated by sodium loading, and this was demonstrably evident from the Ramipril Efficacy in Nephropathy-2 trial.[21] The institution of lower sodium diets during treatment with ACEI, lisinopril, significantly reduced proteinuria. Given the high average sodium intake of many CKD patients, the possibility that dietary sodium proscription will circumvent antiproteinuric therapy by anti-RAAS therapy is likely. The solution in this case is first an engaged kidney nutritionist. The second solution is diuretic therapy.[22] Diuretics nullify the hyperavid sodium reabsorption of nephrosis, the consequence of conversion of excessively filtered plasminogen to plasmin through a too-permeable glomerular barrier by tubular urokinase-type plasminogen activator. Plasmin cleavage of the ectodomain of the epithelial sodium channel, expressed at the apical collecting duct, enhances sodium reclamation by perturbing the balance between endogenous proteolytic-activating and antiproteolytic-inhibitory regulators[23] (Fig 1). Reducing plasminogenuria will thereby reduce edema formation. Because the locus of epithelial sodium channel action is in the distal nephron, diuretic therapy with a loop agent along with amiloride, spironolactone, or epleronone may be salutary.

Other nonspecific therapies for the NS include ministrations of nutritional vitamin D, either ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3), and anticoagulants. Although vitamin D levels are frequently low in NS, the free hormonal level of vitamin D is buffered by reservoirs of protein-bound hormone, specifically albumin to a minor extent and vitamin D-binding protein (DBP) to a major extent.[24] Commercial assays calculate vitamin D levels using a formula that is based on VDBP and albumin levels; a specific, commercial assay of free vitamin D levels is not currently available. Thus, vitamin D deficiency may be errantly reported in NS because of DBP- and albumin-associated urinary losses. As a result, high-dose vitamin D therapy may be initiated to correct a depressed "commercial" vitamin D level. A recent study described a genetic polymorphism of African Americans that resulted in a phenotype with normal free circulating vitamin D levels and relatively lower levels of DBP-bound vitamin D.[24] This phenotype is portrayed as vitamin D deficient but does not require any vitamin D treatment. Overall, vitamin D therapy in NS at conventional doses is likely of minimal harm because of human tolerance of very high doses. However, massive or submassive vitamin D therapy is clearly irrational and not supported by any evidence.

Regarding anticoagulation, the timeliness of warfarin or aspirin therapy during the NS has been much debated. Most clinicians are loathe to initiate coumarin therapy despite the high benefit-to-risk ratio. Several disorders have a greater propensity for clinical thromboembolism: membranous nephropathy (primary and secondary), membranoproliferative glomerulonephritis, minimal change disease, and possibly renal amyloidosis.[25] The observation that venous thromboembolism occurred at more severe levels of albuminuria and hypoalbuminemia has led to a host of recommendations as to the appropriateness and duration of anticoagulation. A recent analysis yielded a threshold serum albumin level of less than 2.8 g/dL as the point at which to begin anticoagulation.[26] However, an even more recent, European strategy reconsidered the albumin threshold and agent (aspirin vs warfarin) for commencement of anticoagulation, based in part on the serum albumin level and with a Markov Decision Model.[27,28] There is now more science than art for initiating warfarin therapy in NS, but one cannot dismiss the importance balancing the clinical benefits and risks of anticoagulation against those of no anticoagulation. In summary, anticoagulation should be judiciously considered, particularly in the severely hypoalbuminemic patient with membranous nephropathy.[28]

With regard to the latter, an unanticipated serum creatinine increase of 0.3 mg/dL within 1 week in a patient who experiences an elevation of the international normalized ratio to greater than 3 warrants suspicion for warfarin-related nephropathy (WRN).[29] This newly described entity is characterized by intraglomerular hemorrhage with tubular obstruction by erythrocyte casts in the absence of overt clinical hemorrhage. WRN was established in a substantial proportion of over-anticoagulated patients with and without CKD. It is important to note that the risk of WRN doubled in those with CKD. Furthermore, WRN is just part of the broader spectrum of anticoagulation-related nephropathy because an identical clinical picture has arisen in the face of dabigatran therapy, with heme-associated AKI.[30,31]

In retrospect, much of our treatment of NS has been largely correct, despite the absence of robust supporting clinical trials evidence. Therapy was antecedent to today's more sophisticated understanding of pathophysiology, and consequently, it was not always of the best rationale. Treatment was primarily that of function following form. Actions were contingent on what was clinically encountered, and this was no fault. However, contemporaneous therapy can be applied more scientifically and wisely and form may now follow function, liberating us from any dotard vanity. Function is

represented by the degree of albuminuria, and the form of treatment is now 2-fold: use the most etiospecific therapy and implement the optimal combination of nonspecific therapies that decrease albuminuria. To sum up, we should evoke the words of the late, eminent glomerulologist, J.S. Cameron: "Contrary to beliefs held 20 years ago, we do not possess a unique satisfying explanation for the induction, maintenance, and resolution of nephrotic edema, and many concepts firmly established as 'classic' are now being revised or reconsidered."[32]

Acknowledgments

The author expresses his gratitude to Richard J. Glassock for his insightful comments regarding hyperlipidemia therapy in nephrotic syndrome and to Holly Kramer, Kevin Ho, and Donald Molony for their critical readings of the manuscript.

Jerry Yee, MD
Editor-in-Chief

References

1. Definition from the UK National Institute for Clinical Effectiveness (NICE). 2004. Citizen Council Report on Ultra-Orphan Drugs. Available at: http://tinyurl.com/b3qurp3 and as defined in the following documents: Wales Medicines Strategy Group (AWMSG); Recommendations for a Belgian Plan for Rare Diseases; the EMINET Report commissioned by the European Commission's Directorate General Enterprise and Industry, the European Union Committee of Experts on Rare Diseases' (EUCERD). Accessed January 5, 2014.
2. Smith RJH, Alexander J, Barlow PN, et al. for the Dense Deposit Disease Focus Group. New approaches to the treatment of dense deposit disease. *J Am Soc Nephrol.* 2007;18(9):2447-2456.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for glomerulonephritis. *Kidney Int Suppl.* 2012;2:139-274.
4. Linden E, Cai W, He JC, et al. Endothelial dysfunction in patients with chronic kidney disease results from advanced glycation end products (AGE)-mediated inhibition of endothelial nitric oxide synthase through rage activation. *Clin J Am Soc Nephrol.* 2008;3(3):691-698.
5. Bonsib SM. Glomerular basement membrane discontinuities. Scanning electron microscopic study of acellular glomeruli. *Am J Pathol.* 1985;119(3):357-360.
6. Faul C, Donnelly M, Merscher-Gomez S, et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med.* 2008;14:931-938.
7. Welsh GI, Saleem MA. The podocyte cytoskeleton—key to a functioning glomerulus in health and disease. *Nat Rev Nephrol.* 2012;8(1):1759-5061.
8. Kaysen GA, Gambertoglio J, Felts J, Hutchison FN. Albumin synthesis, albuminuria and hyperlipemia in nephrotic patients. *Kidney Int.* 1987;31(6):1368-1376.
9. Vaziri D. Nephrology forum: molecular mechanisms of lipid disorders in nephrotic syndrome. *Kidney Int.* 2003;63:1964-1976.
10. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med.* 1994;330(13):877-884.
11. Barness LA, Moll GH, Janeway CA. Nephrotic syndrome. I: natural history of the disease. *Pediatrics.* 1950;5(3):486-503.
12. Ogi M, Yokoyama H, Tomosugi N, et al. Risk factors for infection and immunoglobulin replacement therapy in adult nephrotic syndrome. *Am J Kidney Dis.* 1994;24(3):427-436.
13. Kroger AT, Sumaya CV, Pickering LK, Atkinson WL. General recommendations on immunization: recommendations of the advisory committee on immunization practices (ACIP). Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for lipid management in chronic kidney disease. *Kidney Int Suppl.* 2013;3:259-305.
14. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. *Kidney Inter Suppl.* 2013;3:259-305.
15. Navaneethan SD, Pansini F, Perkovic V, et al. HMGCoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev.* 2009;(2):CD007784.
16. Remuzzi G, Perico N, Macia M, Ruggenenti P. The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. *Kidney Int Suppl.* 2005;99:S57-S65.
17. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med.* 2013;369(20):1892-1903.
18. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol.* 2009;20(12):2641-2650.
19. Chen YM, Ng YY, Lin SK, et al. Pentoxifylline suppresses renal tumour necrosis factor-alpha and ameliorates experimental crescentic glomerulonephritis in rats. *Nephrol Dial Transplant.* 2004;19(5):1106-1115.
20. Ghorbani A, Omidvar B, Beladi-Mousavi SS, Lak E, Vaziri S. The effect of pentoxifylline on reduction of proteinuria among patients with type 2 diabetes under blockade of angiotensin system: a double blind and randomized clinical trial. *Nefrologia.* 2012;32(6):790-796.
21. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol.* 2012;23(1):165-173.
22. Buter H, Hemmelder MC, Navis G. The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide. *Nephrol Dial Transplant.* 1998;13:1682-1685.
23. Svenningsen P, Bistrup C, Friis UG, et al. Plasmin in nephrotic urine activates the epithelial sodium channel. *J Am Soc Nephrol.* 2009;20(2):299-310.
24. Powe CE, Evans MK, Wenger J, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med.* 2013;369(21):1991-2000.
25. Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. *J Am Soc Nephrol.* 2007;18(8):2221-2225.
26. Lionaki S, Derebail VK, Hogan SL, et al. Venous thromboembolism in patients with membranous nephropathy. *Clin J Am Soc Nephrol.* 2012;7(1):43-51.
27. Medjeral-Thomas N, Ziaj S, Condon M, et al. Retrospective analysis of a novel regimen for the prevention of venous thromboembolism in nephrotic syndrome. *Clin J Am Soc Nephrol.*, http://dx.doi.org/10.2215/CJN.07190713.
28. Lee T, Biddle AK, Lionaki S, et al. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. *Kidney Int.*, http://dx.doi.org/10.1038/ki.2013.476.
29. Brodsky SV, Nadasdy T, Rovin BH, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int.* 2011;80(2):181-189.
30. Ryan M, Ware K, Qamri Z, et al. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. *Nephrol Dial Transplant.*, http://dx.doi.org/10.1093/ndt/gft380.
31. Moekel GW, Luciano RL, Brewster UC. Warfarin-related nephropathy in a patient with mild IgA nephropathyon dabigatran and aspirin. *Clin Kidney J.* 2013;6:507-509.
32. Cameron JS. The nephrotic syndrome and its complications. *Am J Kidney Dis.* 1987;10(3):157-171.