The Relationship of Cigarette Smoking to End-Stage Renal Disease

By Donald E. Wesson

Cigarette smoking (CS) has been associated with augmented progression of nephropathies responsible for the 4 major causes of end-stage renal disease (ESRD) in the United States. CS has well-described ways by which it causes tissue injury in other organ systems and the mechanisms by which it adversely affects nephropathy progression might be similar. Therefore, exploring the mechanisms for CS-induced nephropathy or progression thereof might yield important insights into the general mechanisms by which some or most nephropathies progress to ESRD. In addition, CS can be discontinued and so is a potentially correctable risk factor for ESRD, a syndrome whose incidence continues to increase. Therefore, the mechanism(s) by which CS induces nephropathy progression is an important area of investigation.

CIGARETTE SMOKING (CS) is associated with progression of some types of kidney diseases or nephropathies,[1] making it a potentially correctable risk factor to target in the effort to reduce the growing incidence of end-stage renal disease (ESRD).[2] The mechanism(s) by which CS contributes to nephropathy progression are unknown but insights as to the mechanisms by which it mediates other cigarette-related diseases might shed light on the mechanisms for progression of renal disease to ESRD. Although CS itself might cause nephropathy, current data are more supportive that CS exacerbates progression of pre-existing nephropathy rather than causing nephropathy de novo in an otherwise healthy individual. Although there are data to support that CS augments progression of each of the 4 main causes of ESRD in the United States (diabetes, hypertension, glomerulonephritis, and polycystic kidney disease), current data most convincingly support an exacerbating role for CS in progression of diabetic nephropathy.

CS AS A CAUSE OF DE NOVO RENAL DISEASE

Renal function typically is quantified by measuring the glomerular filtration rate (GFR) or some surrogate thereof such as creatinine clearance. More commonly, but less accurately, clinicians assess the level of remaining GFR by following changes in the concentration of plasma creatinine levels with increases in this parameter indicating decreases in GFR. Because of a large nephron reserve, humans can lose as much as 50% of baseline nephron mass before plasma creatinine concentration increases. Consequently, clinicians and researchers have looked for markers that indicate early renal parenchymal injury before GFR measurably declines. One such commonly accepted parameter that is easily available to both clinicians and researchers is urine albumin excretion (UAE). More recent methods allow small urine concentrations of albumin to be measured rapidly and accurately. Consequently, it is now recognized that even small increases in this parameter greater than the normal value of less than 30 mg/d are indicative of renal parenchymal injury.[3] UAE reflected by 1+ or greater reading on the conventional urine dipstick is greater than 300 mg/d and is called *macroalbuminuria*.[4] Levels less than macroalbuminuria but more than normal (30–300 mg/d) are called *microalbuminuria*.[4] Higher UAE indicates greater renal injury.[3]

Chronic cigarette smokers who are otherwise healthy have a normal GFR but have a decreased renal plasma flow, consistent with chronic vascular injury.[5] This finding might be mediated by the well-described damage to renal arterioles associated with CS.[6,7] Additionally, acute CS decreases GFR and filtration fraction and increases renal vascular resistance,[8] consistent with acute vascular changes. These CS-induced renal changes, however, reversed on discontinuation of smoking.[8] CS-induced direct vascular endothelial injury[9] might mediate both the chronic and acute vascular changes. Longer-term studies show that smoking increases the risk for renal failure in the general male population,[10] and studies in abstract form

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show that this risk is dose related in a large population of men and women.[11] In addition, CS accelerates the age-related GFR decline in 2 population-based surveys.[12,13]

Although CS is associated uncommonly with a chronically decreased GFR in otherwise healthy individuals, many studies associate CS with an increased UAE, an index of renal injury as discussed. Albuminuria by urine dipstick was more common in smokers than nonsmokers who underwent multiple health care check-ups in a large managed care organization with heavier smokers having even greater risk.[14] Other population studies in nondiabetics showed a strong association between CS and microalbuminuria.[15,16] Thus, smoking is associated frequently with increased UAE, an index of renal injury, but is associated infrequently with frankly decreased GFR in otherwise healthy individuals. This renal injury might eventually progress to the degree necessary to cause a measurable decrease in GFR. On the other hand, CS-related renal injury might lead to progressive renal injury that more likely reduces GFR when it is combined with an additional renal insult.

CS ENHANCES PROGRESSION OF EXISTING RENAL DISEASE

Diabetic Nephropathy

Retrospective studies show that smoking compared with nonsmoking type I diabetics had increased renal failure risk.[17,18] Cross-sectional studies showed a greater proportion of smokers compared with nonsmokers with increased UAE among type 1[19,20] and type 2[21,22] diabetics. Prospective studies showed that CS is associated with augmented progression to higher levels of UAE in both type 1[23,24] and type 2[25,26] diabetes. Importantly, prospective studies show that smoking cessation is associated with amelioration of UAE in type 1,[19] and preliminary observations show that smoking cessation ameliorates renal injury in microalbuminuric type 2, diabetes.[27] Furthermore, prospective studies showed that CS in diabetics is associated with a higher risk for progression to renal failure in both type 1[28,29] and type 2[25,29-31] diabetes. Whether smoking cessation reduces the risk for diabetic nephropathy to progress to ESRD as suggested by its effect to reduce UAE is not known. These studies show that CS is a risk factor for the appearance of nephropathy in diabetes and for its progression to more advanced stages, including renal failure. The data also show that smoking cessation ameliorates diabetic nephropathy as measured by increased UAE, at least in its early stages.

Hypertension-Associated Nephropathy

Population studies in patients with primary (essential) hypertension show that microalbuminuria is more frequent in smokers compared with nonsmokers[32] and independently predicts microalbuminuria in such patients,[33] particularly those with a high cardiovascular risk profile.[34] Furthermore, smokers with primary hypertension had a greater prevalence of macroalbuminuria.[35] A prospective study of patients with severe hypertension showed that smoking was the only examined parameter that predicted a subsequent decrease in calculated GFR during follow-up.[36] By contrast, a retrospective analysis performed during this study showed that CS did not predict calculated GFR decline in patients with mild hypertension (unpublished observations). To date, there are no published studies that examine the effects of smoking cessation on indices of renal injury in hypertension-associated nephropathy (HAN). Together, published data suggest that CS is a risk factor for the appearance of nephropathy in essential hypertension and might contribute to its progression in those with severe hypertension but more confirmatory studies are needed.

Glomerulonephritis

The few studies that have examined CS as a potential risk factor for the appearance of glomerulonephritis have not shown a connection.[37-40] Nevertheless, some studies support that CS contributes to progression of existing glomerulonephritis. In a post hoc analysis of a prospective study of patients with chronic glomerulonephritis, CS predicted subsequent GFR decline during follow-up evaluation.[41] In addition, CS was an independent risk factor for faster GFR decline toward ESRD in patients with lupus nephritis,[42] but this finding was not confirmed in a more recent study.[43] Further studies are necessary to establish if CS is a risk factor for the appearance and/or progression of glomerulonephritis.

Autosomal-Dominant Polycystic Kidney Disease

In a cross-sectional analysis, autosomal-dominant polycystic kidney disease (ADPKD) patients with urine protein excretion greater than 300 mg/d had a greater pack-year smoking history than those with less proteinuria.[44] In addition, a retrospective, matched, case-control study of a population of patients with ADPKD and IgA nephropathy (there was no strata inhomogeneity between diseases) showed a dose-dependent increased risk for ESRD in smokers compared with nonsmokers.[45] These data suggest that CS increases the risk for proteinuria in established ADPKD and might increase the risk for its progression. Nevertheless, much more work needs to be performed in this area before any further conclusions can be drawn.

POTENTIAL MECHANISMS FOR SMOKING-INDUCED RENAL INJURY

Smoking-Induced Hypertension

Poor hypertension control exacerbates nephropathy progression in diabetic nephropathy[46] and in HAN.[47] Hypertensives with poor compared with good blood pressure (BP) control more likely progress to ESRD[10] and CS is associated with higher BP in hypertensives.[48-50] CS induces sympathetic activation[51] and so might mediate CS-induced increases in BP. Nevertheless, CS was associated with nephropathy progression in both diabetic nephropathy[26] and HAN[36] despite improved BP control. Consequently, although CS might contribute to progression of established renal disease through increased BP, additional mechanisms appear to mediate the progressive renal function in patients with established renal parenchymal disease, most notably the nephropathy of diabetes and hypertension.

Smoking-Induced Vasculopathy

CS increases intimal thickening in renal and myocardial arterioles[6,7] and this finding was less evident in other tissues.[7] Because HAN is mediated predominantly by nephrosclerosis,[52] an arteriolar vasculopathy,[53] and because smoking damages arterioles,[6,7] progressive vascular injury is a likely contributor to the renal function decline attributable to HAN. Interestingly, renal pathologic studies show that CS in patients with hypertension is associated more with arteriole myointimal hyperplasia than with glomerulosclerosis.[54] In support of the hypothesis of a CS-induced vasculopathy, chronic cigarette smokers with a normal GFR nevertheless have decreased renal plasma flow, consistent with chronic vascular injury.[5] Additionally, acute CS decreases GFR and filtration fraction and increases renal vascular resistance,[55] consistent with acute vascular changes. Direct vascular endothelial injury[56] might mediate both the chronic and acute vascular changes induced by CS.

Although the best evidence for a contributing role of CS-induced vasculopathy in nephropathy progression is with renal microvasculature, CS also is associated with the presence[57] and progression[58] of atherosclerotic disease–mediated renal artery stenosis as well as with the progression of renal artery stenosis mediated by fibromuscular dysplasia.[59] Because CS contributes to atherosclerosis[60] and atherosclerosis is associated strongly with HAN,[61,62] HAN might be mediated by mechanisms common to atherosclerosis[63] and CS might exacerbate these mechanisms. CS-induced macrovasculopathy might also contribute to progression of other nephropathies.

Increased Cytokines

CS smoking increases plasma and tissue levels of cytokines purported to mediate nephropathy progression including transforming growth factor β[64] and endothelin.[65] Transforming growth factor β[66] and endothelins[67] are implicated in the progression of diabetic nephropathy and CS might augment its progression through these and possibly other mechanisms. Furthermore, endothelin-1 gene expression is up-regulated in renal microvessels of animal models of hypertensive nephrosclerosis[68] and endothelin-1 increases synthesis of collagen types I and III,[69] the latter being important components of glomerulosclerosis.[61] Transforming growth factor β facilitates matrix production,[70] causes fibrinogenesis,[70] and its circulating level is higher in hypertensive African Americans[71] who are at higher risk than other US population groups for HAN ESRD.[2] These and other cytokines might play an important role in the progression of the glomerular and tubulointerstitial disease that characterize diabetic nephropathy[72,73] and HAN.[74]

Oxidant Stress

CS increases oxidative stress,[75] a phenomenon that has been implicated in the progression of experimental models of diabetic nephropathy.[76]

Oxidant stress also mediates the vascular pathology of humans with essential hypertension,[77] thought to play a role in HAN as discussed earlier. Human diabetes is characterized by oxidative stress[78] and anti-oxidants ameliorate disturbed vascular function in diabetes.[79] Consequently, exacerbation of oxidative stress in diabetes might mediate the CS-induced faster progression of human diabetic nephropathy.[26] Human hypertension also is characterized by oxidative stress[77] and oxidative stress mediates the hypertension and vascular endothelial dysfunction of experimental models of chronic renal failure.[80] Likewise, CS-induced increases in oxidative stress in essential hypertension might mediate faster progression of HAN.[36]

Increased Sympathetic Tone

CS increases sympathetic outflow in humans,[51] increasing BP,[81] and thereby exacerbating nephropathy progression as discussed earlier. CS-induced increased sympathetic tone is not ameliorated by angiotensin-converting enzyme inhibition,[82] suggesting that this phenomenon is not mediated by angiotensin II. Furthermore, increased sympathetic activity accelerates progression of experimental models of chronic renal failure independent of its effects on BP.[83] Thus, the untoward effects of CS on nephropathy progression might be mediated, at least in part, through increased sympathetic tone that is not decreased by angiotensin-converting enzyme inhibition, a common renoprotection strategy.

CONCLUSION

CS is associated with faster progression of existing nephropathies and the case is strongest for that caused by diabetes, types 1 and 2. Although current data are not strongly supportive, the association of CS with indices of renal injury in otherwise normal individuals raises the possibility that CS might cause be a cause of de novo nephropathy. Exploring the mechanisms by which CS adversely affects nephropathy progression might shed light on general mechanisms for nephropathy progression. More studies are warranted to determine if its cessation reduces the risk for nephropathy progression to ESRD.

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