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REVIEW

Cigarette smoking and chronic kidney diseases

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Observational studies have suggested that different chronic kidney diseases (CKDs) have differing relationships to smoking, but no randomized controlled trial has been conducted to examine this topic. In this article, we review available evidence concerning the relationship between smoking and each type of CKD in the general population as well as in patients with diabetes mellitus (DM), hypertension (HT), primary glomerulonephritis and kidney transplants. There is good evidence of a relationship between smoking and CKD in patients with IgA nephropathy and kidney transplant recipients, but not in patients with DM or HT. Interestingly, it has been reported that the effect of smoking on CKD progression varies depending on the CKD stage. This variation might indicate a cumulative effect of smoking, possibly through oxidative stress. A better understanding of the relationship between smoking and CKD would be useful for nephrologists.
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INTRODUCTION

Many observational studies have suggested a relationship between smoking and chronic kidney disease (CKD). However, no randomized controlled trial has examined whether cessation of smoking could inhibit the onset or progression of CKD because no broadly reliable method for smoking cessation exists. For example, new drugs for smoking cessation have produced mixed results.[1,2] In addition, a long observation period would be required because CKD may develop over an extended period of time. Therefore, the best evidence for a relationship between smoking and CKD comes from observational cohort studies and case-controlled studies. The relationship between smoking and metabolic syndrome should also be considered.[3] Analyses should also account for many confounding factors, such as sex, age, blood pressure, proteinuria, estimated glomerular filtration rate, glucose tolerance and dyslipidemia.

In this article, we review available evidence concerning the relationship between smoking and each type of CKD in the general population as well as in patients with diabetes mellitus (DM), hypertension (HT), primary glomerulonephritis and kidney transplants.

SMOKING AND CKD IN THE GENERAL POPULATION

Bleyer *et al.*[4] first reported the relationship between CKD and smoking in a population-based, observational, large-cohort study, the Cardiovascular Health Study, whose subjects were >65 years of age and lived in the United States. In this study, which included 4142 subjects (mean age ± s.d. was 73.4 ± 5.8 years for men and 72.4 ± 5.4 for women), 2.8% of patients demonstrated a $>0.3\,mg\,dl^{-1}$ elevation of creatinine during the 3- to 4-year observation period. A multiple logistic regression analysis identified smoking as a factor related to CKD progression. Other factors included body weight, age, baseline creatinine level, intimal thickening in the internal carotid artery and systolic blood pressure. This report also demonstrated a dose-dependency between the number of cigarettes smoked and CKD progression. However, this study had several limitations. Proteinuria, which is a well-known risk factor for CKD progression, was not included as an independent variable. In addition, the observation period was relatively short. Given that subjects were >65 years of age, it is unclear whether these results are applicable to younger patients.

Subsequently, many observational studies have confirmed the relationship between smoking and CKD onset and progression (Table 1). Of these studies, the largest cohort, which consisted of 123 764 subjects >40 years of age in the residential health system in Japan's Ibaragi prefecture, was reported by Yamagata *et al.*[5] During the 10-year observational period of this study, 4307 subjects had new-onset CKD stage 1 or 2 and 19 411 subjects had new-onset CKD stage 3–5. When new-onset CKD stage 1 or 2 was treated as the outcome of interest, multiple logistic regression analyses identified current smoking *vs.* never smoking as a significant risk factor (hazard ratio, 1.26; 95% confidence interval (CI), 1.14–141 for men; hazard ratio, 1.40; 95% CI, 1.16–169 for women). When new-onset CKD stage 3–5 was treated as the outcome of interest, the results were similar. This study did not analyze the relationship between a dose-dependency of smoking and CKD.

A systematic meta-analysis based primarily on community-based cohort studies[6–10] (shown in Table 1) confirmed the effect of smoking on CKD development.[11] The increased risk of developing CKD among smokers *vs.* non-smokers was reported to be associated with smoking >20 cigarettes per day (odds ratio, 1.51; 95% CI, 1.06–2.15), male (odds ratio, 2.4; 95% CI, 1.2–4.5) and smoking for over 40 years (odds ratio, 2.3; 95% CI, 1.2–4.3).[11] However, this meta-analysis included

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Table 1 Large observational cohort studies of the relationship between smoking and the incidence or progression of CKD

Year	*Authors*	*Nation*	*Subjects*	*Period (year)*	*Outcome*	*Reference*
2000	Bleyer AJ	USA	4142 Non-DM cases over 65 years old (CHS)	3–4	Increase of serum creatinine $\geqq 0.3\,mg\,dl^{-1}$	4
2002	Tozawa M	Japan	5403 Cases with negative proteinuria, Cr$\leqq 1.2\,mg\,dl^{-1}$ (male), $\leqq 1.0\,mg\,dl^{-1}$ (female)	2	Proteinuria $\geqq$(1+)	9
2003	Haroun MK	USA	2353 General adult population (CLUE)	20	ESRD, death related with CKD	7
2003	Stengel B	Japan	9082 Cases 30–74 years old (NHANES II)	12–16	ESR, death related with CKD	8
2004	Fox CS	USA	2585 Non-CKD (Framingham Offspring Study)	16–22	Incidence of CKD 3–5	6
2005	Baggio B	Italy	1906 Non-CKD 65–84 years old (ILSA)	Average 3.6	Increase of serum creatinine $\geqq 0.3\,mg\,dl^{-1}$	42
2006	Shankar A	USA	3392 Non-CKD 43–84 years old	5	Incidence of CKD 3–5	43
2006	Ishani A	USA	23 866 Male patients with high coronary risk, along with Cr$\leqq 2\,mg\,dl^{-1}$ (MRFIT)	25	ESRD, death related with CKD	44
2007	Yamagata K	Japan	123 764 Non-CKD >40 years old	10	Incidence of CKD 1, 2, 3–5	5
2010	Yamamoto R	Japan	971 Adult IgA nephropathy patients	2.6–10.2	50% increase in creatinine	21
2010	Nougueira-JM	USA	997 Kidney transplantation patients	Average 3.5	Transplant survival	27

CHS, Cardiovascular Health Study; CKD, chronic kidney disease; ESRD, end-stage renal disease; ILSA, Italian Longitudinal Study on Aging; MRFIT, Multiple Risk Factor Intervention Trial; NHANES II, The Second National Health And Nutritional Examination Survey.

only five articles analyzing the dose-dependency between the number of cigarettes smoked and CKD, and no significant relationship was found between CKD incidence and smoking fewer than 20 cigarettes per day.

Based on the literature discussed so far, the relationship between smoking and CKD has been established. However, the relationship between cigarette smoking and different types of CKDs remained unclear. In a report from the Swedish Population Registry, 926 patients with chronic renal failure (creatinine level $>3.4\,mg\,dl^{-1}$ for men and $>2.8\,mg\,dl^{-1}$ for women) were compared with age- and sex-matched controls.[12] This report demonstrated a relationship between smoking and CKD that was statistically significant for renal sclerosis (286 cases) and marginally significant for glomerulonephritis (222 cases). There was no significant relationship between smoking and diabetic nephropathy (286 cases), genetic nephropathy (98 cases), vasculitic nephritis (82 cases) or other nephropathies (99 cases). Because of the differences in the numbers of cases, comparisons among the different types of CKDs were difficult. However, it is still interesting to note differences in the relationship between cigarette smoking and diabetic nephropathy, glomerulonephritis and renal sclerosis. CKD in different clinical conditions is discussed below.

SMOKING AND CKD IN PATIENTS WITH DM

Many observational cohort studies have investigated the relationship between smoking and CKD onset, and progression in patients with DM. However, these studies had limitations, such as low patient numbers or study design concerns, resulting in controversial conclusions. For example, two studies that prospectively observed the relationship between microalbuminuria onset and smoking in ~1000 patients with type I DM showed opposing results.[13,14] During the 4-year observational period, 109 of 943 type I DM patients followed by the Joslin diabetic clinic displayed the onset of microalbuminuria. The multivariate adjustment odds ratio for albuminuria onset in current smokers *vs.* those who never smoked was 3.1 (95% CI, 1.9–5.1). Based on these data, the authors concluded that smoking was an independent predictor of albuminuria onset in diabetic patients.[13]

Conversely, the Epidemiology of Diabetes Interventions and Complications Trial, which followed participants of the Diabetes Control and Complication Trial, demonstrated that intensive insulin therapy improved the prognosis of patients with type I DM and showed that 93 of 1105 type I DM patients presented microalbuminuria onset during the 8-year observational period.[14] Multivariate Cox proportional hazards model analyses identified several factors, including waist circumference, age, HbA1c level and degree of albuminuria, as independent predictors of microalbuminuria. However, the multivariate adjusted hazard ratio for the effect of active smoking on microalbuminuria onset was 1.48 (95% CI, 0.91–2.40), which was not statistically significant.

These two studies included similar numbers of patients, including those with microalbuminuria, resulting in similar levels of statistical power. Several factors might explain why these two reports suggested different conclusions, such as patient demographics and adjusted confounding factors. The available literature offers no conclusive evidence concerning the relationship between smoking in diabetic patients and onset or progression of diabetic nephropathy.

SMOKING AND CKD IN PATIENTS WITH HT

Many longitudinal observational studies have suggested a relationship between smoking and CKD onset and progression in patients with HT, but these studies had several limitations, such as small sample sizes and study design concerns. At the time of this writing, the study with the largest sample size and longest observational period was the Hypertension Screening Treatment Program, which included 11 912 male retired military officers and had an observation period of at least 13.9 years.[15] A total of 245 subjects developed end-stage renal disease (ESRD) during the study period. Cox proportional hazards model analysis revealed that there was no relationship between smoking and ESRD incidence. As compared with non-smokers, those smoking 1–9 cigarettes per day, 10–20 cigarettes per day and >20 cigarettes per day had univariate hazard ratio's of 1.11 (95% CI, 0.63–1.42), 1.41 (95% CI, 0.98–2.03) and 1.17 (95% CI, 0.86–1.60), respectively. During the observation period, 5337 subjects (44.8%) died and 245 subjects developed ESRD. Because many reports suggest that CKD patients die before ESRD onset,[16,17] especially among older patients,[18] this study might have underestimated the effect of smoking on CKD because ESRD was the study outcome. The relationship between smoking and CKD onset and progression in hypertensive patients has not been established, and further studies are required.

SMOKING AND CKD IN PATIENTS WITH PRIMARY GLOMERULONEPHRITIS

Among studies investigating the relationship between smoking and CKD in patients with primary glomerulonephritis, the report by Orth *et al.*[19] is the most well-known and one of the earliest. In this study, 54 patients with IgA nephropathy and 48 patients with autosomal dominant polycystic kidney disease were compared with 102 control cases, whose creatinine level stayed under 3 mg dl^{-1} during the observation period, matched by original kidney disease, sex, age and residence. In this case-match study, smoking was identified as a risk factor for ESRD in a dose-dependent manner only in male patients. However, this study did not include baseline proteinuria or kidney function as independent variables, which could lead to confounding. Another observational study that followed up 160 patients with lupus nephritis for 6.4 years concluded that smoking was a risk factor for ESRD.[20] Like the previous study, this study did not include baseline proteinuria or kidney function as independent variables at study entry.

Recently, we reported that smoking was identified as the key prognostic factor and was dose-dependent in 971 patients with IgA nephropathy.[21] In that paper, we adjusted for confounding factors using propensity scoring to avoid the effects of metabolic syndrome. Smoking was identified as an independent risk factor for CKD progression. We also found an interesting interaction between CKD stage and the effect of smoking on deterioration of kidney function (Figure 1). The present analysis used the same patients as those in our published report,[21] but this figure is unique to the current paper. According to our analysis, the association of current smoking with adverse outcomes was stronger in patients with lower glomerular filtration rate compared with higher estimated glomerular filtration rate.

There are two potential explanations for this association. One is specific to IgA nephropathy. IgA nephropathy patients often develop macroscopic hematuria during upper respiratory infections, such as tonsillitis. Differences in gene expression in the tonsils between patients with IgA nephropathy and controls has been reported,[22] as have structural differences.[23] These changes may be because of continuous immune stimulation from smoking. According to this theory, the association between CKD and smoking should be observed only in IgA nephropathy patients, not in patients with other kidney diseases. The other potential explanation is a common mechanism in many CKD-related diseases, such as oxidative stress (Figure 2). This is discussed further below.

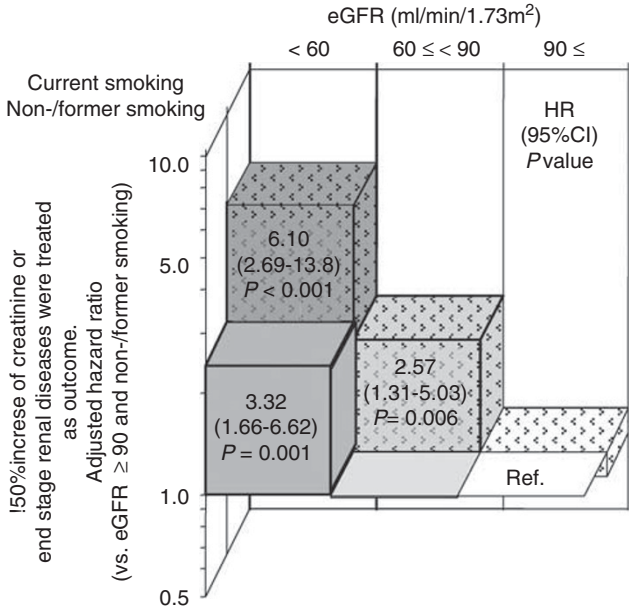

Figure 1 Effect modification between smoking status and the renal function in a categorization analysis. Patients with estimated glomerular filtration rate (eGFR) ⩾90 and non-/former smokers are used as a reference for all other columns. The results are adjusted for facility, age, sex, body mass index, systolic blood pressure, urinary protein, total cholesterol, uric acid, use of renin–angiotensin–aldosterone system (RAAS) blockers and use of other hypertensives at the time of diagnosis.

SMOKING AND CKD IN PATIENTS WITH RENAL TRANSPLANTS

Several reports are available concerning the relationship between smoking and CKD in patients with renal transplants because changes in kidney function tend to be discovered earlier in CKD than in other conditions or in the normal population. These reports suggest that active smoking is a potential risk factor for graft loss[24–27] and mortality.[25,28]

A retrospective cohort study comprising 1334 renal transplant recipients at the Henepin County Medical Center in the United States found that a smoking history of >25 pack-years was significantly associated with a 30% increase in risk of graft failure, whereas a history of <25 pack-years did not affect graft survival.[25] This study also suggested that the higher rate of graft loss in recipients with a history of heavy smoking was caused by higher mortality as compared with non-smokers. Another cohort study, of 645 kidney transplant recipients, identified pre-transplant smoking as a significant risk factor for graft loss (adjusted relative risk, 2.3; $P<0.005$).[26] In contrast to the previous study, there were no significant differences in patient survival between smokers and non-smokers, which might suggest that risk factors other than smoking were related to mortality. This study also found no difference in risk of acute rejection between smokers and non-smokers.

Recently, a cohort study of 997 living-donor kidney transplant recipients from tertiary-care transplant centers confirmed the effect of smoking on graft loss (adjusted relative risk, 1.47; 95% CI, 1.08–1.99; P=0.01).[27] This report also confirmed the effect of smoking on patient mortality (adjusted relative risk, 1.60; 95% CI, 1.06–2.41; P=0.02). With respect to rejection, this study found that first-year rejection-free survival was significantly worse (adjusted relative risk, 1.46; 95% CI, 1.05–2.03; P=0.03) and that the risk of rejection on or before

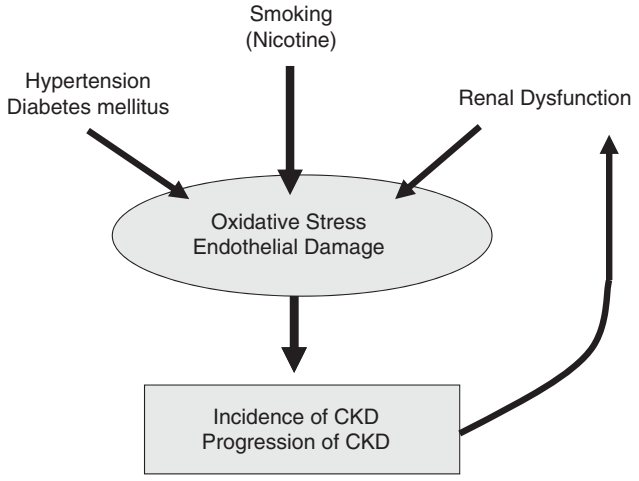

Figure 2 Considered mechanisms of the relationship between CKD and smoking.

post-transplant day 10 was significantly higher (adjusted relative risk, 1.8; 95% CI, 1.10–2.94; P=0.02) in those who had smoked *vs*. those who had never smoked. Although this report did not include a measure of the number of cigarettes smoked, it confirmed the effect of smoking on kidney-recipient graft loss and patient mortality.

POTENTIAL MECHANISMS OF THE RELATIONSHIP BETWEEN SMOKING AND CKD

There are two mechanisms that might explain the relationship between smoking and CKD onset and progression. The first is related to conditions that predispose for CKD, such as DM, HT and IgA nephropathy. We previously discussed a potential mechanism regarding IgA nephropathy. Endothelial damage is associated with both HT and DM. Smoking can cause further endothelial damage in patients with HT or DM, resulting in CKD onset or progression. The second category is a shared feature of smoking and CKD, specifically, oxidative stress. Oxidative stress is already increased during the early stages of CKD as a result of enhanced oxidant production and a compromised antioxidant mechanism.[29] Patients with DM suffer from oxidative stress[30–32] and hypertensive patients have been recognized to experience hyper-oxidative stress.[33,34] Oxidative stress induced by smoking, overlaid on increased oxidative stress in patients with HT, DM or CKD, may have an important role in CKD onset and progression, although the precise nature of the nephrotoxic effect of cigarette smoking is not well understood (Figure 2). Interestingly, the effect of smoking on CKD progression varied depending on CKD stage (Figure 1). This might indicate that the factors associated with CKD progression, for example, oxidative stress, have a cumulative effect, possibly mediated through ongoing endothelial damage.

Although the harmful effects of smoking may be because of many components of cigarettes, one of the more likely causative agents is nicotine.[35] In the brain, nicotine leads to habitual use through the nicotine receptor, and in the kidney, nicotine induces oxidative stress because nicotine is excreted by glomerular filtration and tubular secretion.[35] It has been reported that chronic exposure to nicotine increases oxidative stress levels in the kidney,[36,37] cultured proximal tubule,[38] and mesangial cells.[39] Chronic exposure to nicotine exacerbates the acute renal ischemic injury.[40] These reports strongly suggest that the causative agent for CKD in cigarettes is nicotine (Figure 2).

CONCLUSION

According to the available evidence, it can be concluded that smoking is a risk factor for the onset and progression of CKD in the general population. At this time, there is an adequate evidence for a relationship between smoking and CKD in patients with IgA nephropathy and in kidney transplant recipients, but there is inadequate evidence for patients with DM and HT. The drugs which assist smoking cessation are now available.[1,2,41] These drugs should be targeted to CKD patients. Further studies are needed to better clarify the relationship between smoking and CKD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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