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Review

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Smoking and Chronic Kidney Disease

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Abstract

Smoking is the leading preventable cause of death worldwide. Smoking affects all systems of the organism. Smoking stimulates the sympathetic nervous system, increases blood pressure and albuminuria, and decreases renal function. Smoking increases renal functional loss in patients with chronic kidney disease. Moreover, smoking accelerates the course of atherosclerosis, causing cardiovascular complications and premature death. Smoking decreases graft survival in kidney transplant patients. As a result, all physicians and health care providers should acknowledge all patients who smoke about the deleterious effects of smoking and continuously motivate them to stop smoking.

Keywords: Chronic kidney disease, diabetes, hypertension, smoking

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INTRODUCTION

Smoking is one of the leading and preventable causes of death. It has a large number of harmful effects on all systems in the organism. It has a negative impact on the cardiovascular system and respiratory system in the foreground. As a result, it is well known that it may lead to cardiovascular diseases, chronic obstructive pulmonary diseases, and lung carcinomas. It also has carcinogenic effects on the urinary tract. It shows a facilitating effect on the development of kidney, kidney pelvis, ureter, and bladder carcinomas. In addition, it has been found that smoking has negative effects on kidney function and may accelerate the development of renal failure in renal patients (1, 2).

Effects of Smoking on The Kidney in The General Population

Smoking activates the sympathetic nervous system, causing increased blood pressure and tachycardia. As a result, vasoconstriction may occur in certain areas, such as coronary circulation. Smoking causes acute and chronic changes in the kidney even in normal individuals. In a study conducted with 15 volunteers with normal blood pressure, Ritz et al. (3) investigated renal hemodynamic changes developing after smoking a single cigarette. In their study, it was noted that the mean arterial pressure and pulse rate increase significantly after smoking. In addition, it was observed that plasma adrenaline concentration and arginine vasopressin concentration increase significantly. In the same study, it was found that renovascular resistance increases by 11% along with cigarette smoking, glomerular filtration rate (GFR) decreases by 15%, and filtration fraction decreases by 18%. These acute effects of smoking on the cardiovascular system are probably due to nicotine because similar findings may also develop with nicotine chewing (3). In addition, Gambaro et al. (4) found in their cross-sectional study that renal plasma flow is lower in smokers than in non-smokers. Furthermore, plasma endothelin concentration was found to be increased in these individuals.

In the Prevention of Renal and Vascular End-stage Disease study that was conducted in the Netherlands and in which albuminuria was investigated in 40,856 people aged between 28 and 75 years in the general population, smoking was shown to increase albuminuria (5, 6). Additionally, this study reported a close relationship between the number of cigarettes smoked and an increase in albuminuria and a decrease in GFR (7).

In a cross-sectional study in which 28,409 volunteers in the general population were included, it was shown that smoking could irreversibly lead to proteinuria (8).

In Australia, a total of 11,247 adults from the normal population were included in the Australian Diabetes, Obesity and Lifestyle study, and a significant relationship was found between smoking and proteinuria and renal dysfunction (9). Similarly, in a study in which the data of 4142 individuals without diabetes aged ≥65 years in the Cardiovascular Health Study cohort were evaluated retrospectively, it was shown that there was a parallelism between the number of cigarettes smoked and the increase in serum creatinine level (10).

In a prospective study conducted by Maeda et al. (11), 10,118 Japanese men who were aged between 40 and 55 years and who did not have proteinuria and renal dysfunction were followed up for a total of 6 years. At the end of this period, the risk of glomerular hyperfiltration development was found to be 1.32 times higher in smokers than in non-smokers. In addition, the risk of proteinuria development was found to be 1.51 times higher in smokers than in non-smokers. Hyperfiltration and proteinuria caused by smoking may result in long-term glomerular damage.

In a case-control study conducted in the general population by Ejerblad et al. (12), 926 patients who were aged between 18 and 74 years and had a serum creatinine level >3.4 mg/dL (in men) or 2.8 mg/dL (in women) were examined in Sweden. It was noted that in renal diseases, nephrosclerosis had the strongest relationship with smoking. There was also a significant relationship between smoking and chronic glomerulonephritis.

For a median of 10.3 years, Hallan and Orth (13) examined the data of the second Nord-Trøndelag Health study in which 65,589 people in the general population were included in the study. As a result of the study, they reported that the risks of renal failure development are 3.32 and 4.01, respectively, times higher in those who had previously smoked or were still smoking than in those who had never smoked.

Xia et al. (14) published a meta-analysis that examined 65,064 patients newly determined to have chronic kidney disease in 15 prospective cohort studies in order to investigate the relationship between smoking and chronic kidney disease in the general population. In this meta-analysis, it was noteworthy that there was a statistically significant relationship between smoking and an increased risk of chronic kidney disease in the general population. This relationship was independent of age, hypertension, diabetes, and body mass index, which are risk factors for chronic kidney disease. This risk, which was high for the development of chronic kidney disease, was markedly decreased, though it continued for years after smoking cessation.

Effects of Smoking on The Kidneys in Patients with Hypertension

Smoking makes it difficult to control blood pressure in patients with hypertension. In addition, it increases the risk of target organ damage in patients with hypertension. The prevalence of microalbuminuria is approximately two-fold higher in patients who smoked with primary hypertension than in patients who had never smoked with hypertension (15). Smoking has been found to be an independent predictor of albuminuria development in the Heart Outcome Prevention Evaluation study in which patients with diabetes and without diabetes with high cardiovascular risk were included (16). In addition, in the analysis of the Losartan Intervention for Endpoint Reduction in Hypertension study, which included patients with hypertension with left ventricular hypertrophy, it was reported that the prevalence of microalbuminuria was 1.6 times higher in patients who smoked >20 cigarettes/day than in non-smokers, and the prevalence of macroalbuminuria was 3.7 times higher (17).

In a prospective study conducted in 51 patients with primary hypertension, it was found that smoking was the strongest determinant in the development of renal insufficiency even if blood pressure was controlled (18).

Effects of Smoking on The Kidney in Patients with Chronic Renal Disease

The first studies showing the negative effects of smoking on kidney patients were conducted in patients with type 1 diabetes mellitus (19-21). It has been found in studies that the risk of nephropathy is higher in patients who smoked with type 1 diabetes mellitus than in non-smokers. Smoking significantly increases the risk of microalbuminuria development in patients with type 1 diabetes mellitus (19). It also accelerates the transition from microalbuminuria to macroalbuminuria (21).

In a prospective study conducted in 794 patients with type 2 diabetes, the risk of transition from microalbuminuria to macroalbuminuria was found to be 2-2.5 times higher in smokers than in non-smokers (22).

In a study conducted by Sawicki et al. (23), it was reported that the rate of decrease in glomerular filtration was significantly lower in patients with type 1 diabetes mellitus who quit smoking and whose blood pressure and blood sugar were well controlled than in those who continued to smoke. This finding is important in terms of demonstrating that patients can benefit from smoking cessation even after the development of diabetic nephropathy.

In a study conducted in 33 patients with type 2 diabetes nephropathy, although good blood pressure control and good glucose control were provided with antihypertensive treatment including angiotensin-converting enzyme inhibitor in all patients, it was noted after a 5-year follow-up that renal function was impaired faster in smokers than in non-smokers (24).

Smoking is also known to have negative effects on other kidney diseases other than diabetic nephropathy. In the Multiple Risk Factor Intervention Trial, a large epidemiological study, it was found that the risk of end-stage renal disease was higher in smokers than in non-smokers (25). The risk-increasing effect of smoking on renal failure development has also been shown in other chronic renal diseases, such as chronic glomerulonephritis, polycystic kidney disease, and lupus nephritis (26-29).

Data of a total of 582 patients from 9 centers in Germany, Italy, and Austria were analyzed in a retrospective and multicenter case–control study conducted by Orth et al. (30). The patients had IgA nephropathy or autosomal dominant polycystic kidney disease. A significant relationship between smoking and end-stage renal failure was found in 144 male patients included in this study.

Smoking and Atherosclerotic Renal Artery Stenosis

The prevalence of atherosclerotic renal artery stenosis is increasing in the aging population (31). Renal artery stenosis is more common in patients with peripheral vascular disease (32). Smoking may accelerate the development of renal artery stenosis and ischemic nephropathy by facilitating atherosclerosis in the renal arteries and branches (33, 34). In addition, smoking is a risk factor for the development of cholesterol microemboli (35).

In a study conducted with 89 elderly patients without diabetes and with normal blood pressure, renal plasma flow was observed to decrease in parallel with the severity of peripheral atherosclerosis (36). In this study, cigarette smoking and serum low-density lipoprotein cholesterol levels were found to be the most related factors with the decrease in renal plasma flow.

Drummond et al. (37) analyzed the data of patients included in the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study in order to investigate the relationship between smoking and cardiorenal endpoints in patients with atherosclerotic renal artery stenosis. In the CORAL study, 931 patients with atherosclerotic renal artery stenosis were randomized to the medical treatment or stent treatment group and prospectively followed up. Of the 931 patients included in the study, 277 were active smokers and were significantly younger than non-smokers. In addition, cardiorenal endpoints, such as stroke, cardiovascular or renal death, myocardial infarction, hospitalization due to congestive heart failure, need for renal replacement therapy, and progressive renal failure, in these patients were significantly higher than those in non-smokers.

Effects of Smoking on Dialysis Patients

Patients in whom dialysis treatment has been started due to end-stage renal failure should also be encouraged to make an effort to quit smoking. In dialysis patients, in whom the most common cause of death is cardiovascular diseases, smoking can significantly increase morbidity and mortality (38, 39). In the United States Renal Data System Wave 2 study, which was conducted by Foley et al. (38) and in which the data of patients receiving dialysis treatment in the United States were analyzed, the effects of smoking on cardiovascular endpoints in dialysis patients were investigated. In this study, a significant relationship was found between smoking in dialysis patients and development of congestive heart failure, development of peripheral artery disease, and mortality.

In a systematic review and meta-analysis conducted by Liebman et al. (40), 10 studies (n=6538) in which the relationship between smoking and mortality was investigated in dialysis patients were examined. It has been found that smoking significantly increases mortality in dialysis patients.

Effects of Smoking on Kidney Transplant Recipients

Smoking has negative effects on the transplanted kidney in renal transplantation patients (41). In a study conducted on 645 patients with renal transplantation, it was observed that smoking had a negative effect on graft prognosis (42). The duration of graft survival in smokers is significantly lower in the period before transplantation than that in non-smokers. The risk of graft loss was found to be 2.3 times higher in these patients than in non-smokers. In addition, smoking increases the risk of cardiovascular disease, which is a frequent cause of morbidity and mortality in renal transplantation patients. For this reason, patients who are prepared for transplantation should be warned not to smoke.

In a study conducted by Ponticelli et al. (43), the factors affecting long-term patient and graft survival were investigated in 864 kidney transplantation patients with graft function in the first year after transplantation. In this study, in which the half-life of the graft was found to be 20 years, it was understood that the leading cause of death was cardiovascular diseases, and the leading cause of graft loss was chronic allograft nephropathy. In a multivariate analysis, the risk for cardiovascular events was found to be higher in patients with cardiovascular disease, elderly patients, those with pretransplant hypertension, smokers, and those with long dialysis duration in the first year after transplantation.

In a study conducted by Zitt et al. (44), the relationship between smoking and renal biopsy findings was investigated in 76 patients with renal transplantation. In this study, it was noted that vascular intimal fibrosis was significantly higher in smokers than in non-smokers.

Smoking of even the kidney donor may have negative effects in patients undergoing renal transplantation. Heldt et al. (45)

followed up 100 live kidney donors and recipients for an average of 38 months. In this study, the GFR of the kidneys obtained from smoking donors was significantly lower than that from non-smoking donors (37.0 mL/min/1.73 m^2 and 53.0 mL/min/1.73 m^2, p<0.001).

Factors Playing A Role in The Development of Kidney Damage Due to Smoking

Several factors related to smoking are known to play a role in the damage of both kidney and other organs (1, 46). These factors can be grouped as hemodynamic and non-hemodynamic. Smoking causes acute stimulation of the sympathetic nervous system. As a result of sympathetic activation due to the effect of nicotine, an increase occurs in blood pressure and heart rate. Nicotine increases the release of catecholamine from the peripheral sympathetic nerve endings and adrenal medulla. An increased sympathetic activity accelerates the progression of kidney disease independent of blood pressure (47).

Smoking causes a change in diurnal rhythm in blood pressure. Hansen et al. (48) reported that the day/night rates of systolic and diastolic blood pressures are lower in healthy smokers than in non-smokers. This finding indicates that the physiological decline in blood pressure values at night, which is also called as "dipping", decreases in smokers. In addition, smoking increases renal vascular resistance, leading to a reduction in GFR and renal plasma flow.

It has been reported that smoking causes insulin resistance and increases the risk of type 2 diabetes development (49). It is also known that smoking-induced insulin resistance may lead to glomerular hyperfiltration. Indeed, the mechanism of renal injury that may be associated with smoking is similar to the mechanisms of diabetic nephropathy or obesity-associated nephropathy (1, 2). In chronic smokers, a histopathological appearance, also called as "idiopathic nodular glomerulopathy," has been described (50). Here, nodular mesangial sclerosis is observed without immune storage along with the thickening of the basal membrane.

Smoking accelerates the proliferation of endothelin-1 and angiotensin-II in vascular smooth muscle cells, endothelial cells, and mesangial cells. In addition, it leads to endothelial cell dysfunction and oxidative stress (51, 52). Smoking may also impair the tubular function by showing toxic effects on renal tubular cells (53). In vivo studies have shown that nicotine causes mesangial cell proliferation and leads to an increase in extracellular matrix (51). In addition, it is known that glycotoxins in cigarette smoke increase vascular permeability (53, 54) by inducing the formation of advanced glycation end products in in vivo and in vitro environments and lead to pathological vascular changes (54).

CONCLUSION

In addition to the negative effects of smoking on the respiratory system and cardiovascular system, it also has harmful effects on kidney function. Smoking accelerates the development of renal failure in patients with chronic kidney disease. It also increases the risk of the development of cardiovascular diseases, which are the most common cause of morbidity and mortality in these patients. Therefore, physicians have a great responsibility for encouraging patients to quit smoking. Physicians should question smoking in every patient and educate patients on the negative effects of smoking.

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