Particulate Matter (Fine Particle) and Urologic Diseases

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Particulate matter (PM) has been found to damage vital body organs, including the lungs and heart, through vascular damage and oxidative stress. Recently, renal function and chronic urologic diseases have also been found to be related to PM. To investigate this, we reviewed the characteristics of PM related to renal toxicity, including recent studies on the associations of urologic diseases with PM. PM can include constituents that cause renal toxicity, such as lead, cadmium, arsenic, and crystalline silica, which result in renal tubular or interstitial damage. Since 2008, 7 studies have evaluated the renal effects of PM. Two prospective cohort studies and a quantitative study of consecutive patients showed that PM may be related to decreased renal function, as shown by the estimated glomerular filtration rate of diseased or aged participants. Two cross-sectional studies found an association between PM and chronic kidney disease. One of those studies identified the specific renal diseases of immunoglobulin A nephropathy and membranous nephropathy. Two studies that analyzed renal cancer and PM showed no evidence that renal cancer is related to PM. Nine studies were evaluated regarding the relationship of bladder and prostate cancer with PM. The evidence for an association of PM with bladder and prostate cancer is still inconclusive. Although some recently published studies have shown a significant relationship, the causal relationship is not clear. Further well-designed studies on specific renal diseases are required.

Keywords: Particulate Matter; Fine Particle; Urologic Diseases; Occupational Diseases; Environmental Exposure

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INTRODUCTION

Particulate matter (PM) has been known to be an important cause of occupational and environmental disorders since the Great Smog of London [1,2], when PM levels were ~3,000 μg/m³ (December 1952), resulting in high cardiopulmonary mortality. Since then, numerous studies regarding PM and human health have revealed that the cardiopulmonary system is particularly vulnerable to PM exposure [3-5]. Recently, the International Agency of Research on Cancer listed PM as a cause of lung cancer, based on studies showing that relatively low concentrations of PM had long-term effects on human health [6].

Since 2012, PM has increased in Korea, resulting in frequent episodes of poor air quality and increased public concern. Several studies have investigated the health consequences of this phenomenon, including ischemic heart disease, asthma, and hospital visits for Ménière disease related to PM [7-11].

The urinary system is frequently affected by occupational and environmental disorders, including acute and chronic renal failure, glomerulonephritis, tubular or interstitial nephritis, toxic nephropathy, and kidney and urinary bladder cancer due to exposure to heavy metals, organic compounds, and ionizing radiation [12-14]. Previous studies have established the toxicity of specific agents on the kidneys and/or urinary bladder. However,

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little research has been conducted on the effect of PM size [15-26].

The underlying mechanisms of how PM causes or exacerbates cardiopulmonary disorders are not yet fully understood. The major theories supported by scientific evidence are inflammation or oxidative stress in the microenvironment, and vascular endothelial damage by PM [17,27]. These cardiovascular alterations might affect the kidney, because it is a highly vascularized, multifunctional organ of the human circulatory system.

The susceptibility of the kidneys to environmental toxins can be explained by 4 factors: high blood flow, the ability of the kidney to concentrate toxic agents, the high metabolic activity of tubular cells, and the capacity of the kidney to dissociate protein-bound substances and to alter the pH of tubular fluid [12]. However, these 4 factors contributing to the susceptibility of the kidney have only been explained from a toxicological viewpoint, and the effect of particle size has not yet been considered.

According to the aerodynamic diameter, 2 categories of particles are regulated by the Environmental Protection Agency: coarse particulate matter (PM_{10}) with an aerodynamic diameter of < 10 μm, and fine particulate matter ($PM_{2.5}$) with an aerodynamic diameter of < 2.5 μm [28]. Particles < 10 μm in diameter can penetrate the nasal cavity to reach the alveoli, thus reaching the lungs and escaping into the blood stream. The smaller a particle is, the longer it will stay in the deeper sites of the lungs; furthermore, particles < 1 μm act like gas molecules and reach the circulatory system [29]. If a small particle transitions into the vascular system, the kidneys theoretically become a direct target of PM. Recent epidemiologic studies have shown that $PM_{2.5}$ [17,18] affected the decline of renal function and increased membranous nephropathy, meaning that the kidney is potentially susceptible to $PM_{2.5}$. Although some studies have reported a relationship between PM and bladder and prostate cancer, the pathophysiology has not been proposed. Because most PM contains metals, gases, and various organic chemicals [30], the effects of PM should be considered both in terms of the toxicity of its components and the size of PM. Due to the tremendous renal capacity to compensate for functional loss, an early diagnosis of renal disease is difficult. For this reason, many studies have been done on end-stage renal disease to elucidate the effects of air pollution [31].

In this study, we reviewed the effect of PM on urologic disorders based on recent research in view of PM particle size and its constituents.

PARTICULATE MATTER

The term PM refers to a mixture of solid particles and liquid droplets in the air [32]. Both PM_{10} and $PM_{2.5}$ are composed of inhalable particles of many sizes and shapes that contain hundreds of chemicals that react with each other. The main sources of PM are construction, unpaved roads, smokestacks and fires, power plants, the tire industry, and automobiles [32,33]. Naturally occurring PM comes from volcanoes, dust storms, forest fires, sea spray, and living vegetation [5].

The common chemical constituents of PM include inorganic ions (sulfates, nitrates, ammonium, sodium, calcium, and chloride), metals (cadmium, copper, nickel, vanadium, and zinc), polycyclic aromatic hydrocarbons, and microbial components. A major source of PM is traffic, due to brakes, tires, road dust, and pavement abrasion [34]. Indoor activities and sources, such as cooking, pets, carpet, aerosol cans, and office equipment, also generate PM [35].

As it is composed of particles < 10 μm in diameter, PM_{10} has the greatest effect on human health. PM with a diameter of between 5 and 10 μm is more likely to be deposited in the tracheobronchial tree, whereas PM between 1 and 5 μm can move down to the respiratory bronchioles and alveoli. PM < 1 μm in diameter can penetrate the alveoli, and can translocate into cellular tissues and the circulatory system [5].

The pathophysiology of PM toxicity in the human body is not fully understood. One hypothesis is that the mechanism involves metal-mediated processes. Metal contained in particles can mediate airway inflammation due to PM. When transitional metals are involved in this process, reactive oxygen species can be generated [36]. Several studies have reported that the elemental components of PM are associated with cell membrane disruption, a strong potential to induce proinflammatory cytokines, and tumor necrosis factor α-induced or mitochondria-induced apoptosis [37].

TOXICITY OF PARTICULATE MATTER CONSTITUENTS ON THE KIDNEY

The pathophysiology of PM depends on the size and toxicological properties of its constituents. Lead, cadmium, and arsenic are among the most common constituents of PM, and considerable research has been conducted on the renal effects of these metals [38]. All these metals can cause proximal tubular or interstitial damage and result in albuminuria or proteinuria. The

available experimental evidence indicates that reactive oxygen metabolites, which can generate intermediate metals, cause glomerular disease and tubulointerstitial damage [39]. Another environmental risk to the kidneys is crystalline silica, which is known to be related to chronic renal failure. Although the toxic effect of crystalline silica on the kidneys is not yet understood, many studies have investigated chronic kidney disease in exposed populations [40].

It is well-known that environmental lead exposure leads to renal insufficiency, resulting in the major health problems of blood pressure and renal function damage. The environmental sources of lead are the lead-based paint used in the past and leaded gasoline. The kidneys are critically affected by long-term lead exposure. Acute lead nephropathy is characterized by the tubular transport mechanism (Fancoy syndrome), which shows tubular epithelium degeneration. Chronic exposure to lead can result in tubulointerstitial changes or chronic renal failure [41].

Cadmium is another important metal related to chronic kidney disease, and is produced by fuel combustion, household waste, tobacco smoke, and sewage. Cadmium exposure induces the synthesis of metallothionein, which is a cadmium scavenger in the liver. Cadmium-induced renal damage presents as proximal tubular dysfunction, hypercalcemia, and renal stones [38].

Arsenic exposure occurs from drinking water and food in the general population, and via inhalation when the exposure is occupational [42]. Although many constituents of PM affect the renal system, no single component cannot adequately explain the overall health effect observed in epidemiologic studies, due to the scarcity of data [43]. Although studies of arsenic-induced renal disease are rare, they have generally reported a positive association of arsenic with albuminuria and proteinuria in exposed populations; some studies showed a dose-response relationship [43].

Crystalline silica dust has been studied in the context of several occupational and environmental disorders, such as lung cancer, scleroderma, systemic lupus erythematosus, rheumatoid arthritis, or antineutrophil cytoplasmic antibody-associated vasculitis. Möhner et al. [40] conducted a meta-analysis exploring the association between respirable crystalline silica and nonmalignant renal disease. A total of 23 cohort and 4 case-control studies were included in the analysis. The authors found that the cohorts exposed to silica exhibited an elevated standardized mortality ratio (SMR), without a dose-response relationship. Cohorts with silicosis showed an overall SMR of 1.28 (95% confidence interval [CI], 1.01–1.62). The combined anal-

ysis of the industry-based cohorts resulted in an SMR of 1.52 (95% CI, 1.16–1.98). Because the dose-response analysis was heterogeneous in these cohorts, the authors concluded that there were diagnostic and methodological issues related to the elevated SMR.

PARTICULATE MATTER AND RENAL FUNCTION

Previous studies on PM exposure and the circulatory system have identified renal function as an early index of cardiovascular disorders due to PM. Two prospective cohort studies and a quantitative study of consecutive patients have investigated whether decreased renal function is associated with PM exposure. The outcomes were albuminuria, microalbuminuria, and the estimated glomerular filtration rate (eGFR).

O'Neill et al. [15] conducted a prospective cohort study as part of their multiethnic study of atherosclerotic populations to investigate urinary albumin as a subclinical marker of microvascular function affected by PM (Table 1). The cohort consisted of 6,814 men and women aged 44–84 years who were free of clinical cardiovascular disease at baseline. Half of the study subjects were women, and their average age was 63 years old. The outcome of interest was creatinine-adjusted urinary albumin excretion. Subjects were classified into 4 categories of urine albumin excretion: normal, high-normal, microalbuminuria, and macroalbuminuria. Recent air pollution was assessed based on the participant's place of residence at the time of the baseline examination. Chronic exposure was estimated based on the residential history of each participant. Long-term exposure was estimated for PM_{10} and $PM_{2.5}$ using direct measurements by an Environmental Protection Agency monitoring network. The estimated association between air pollution and creatinine-adjusted urinary albumin was mostly negative. There was only weak evidence that long-term exposure was associated with changes in microalbuminuria over time. The authors concluded that urinary albumin is not a marker for the mechanism underlying the association between the cardiovascular system and air pollution. Even if albumin levels are known to be well-correlated with microvascular dysfunction, the renal system is capable enough to compensate effectively in the healthy population.

Lue et al. [16] analyzed the eGFR of acute ischemic stroke patients to elucidate the effects of PM. The authors hypothesized that the eGFR would be associated with proximity to the major roads where PM is produced, because most PM-related health outcomes are vascular diseases and due to the profound

Table 1. Summary of studies on the effects of particulate matter on the kidneys

Study	Method	Subjects	Main result
O'Neill et al. (2008) [15]	Prospective cohort	6,814 Men and women aged 44–84 years who were free of clinical cardiovascular disease at baseline	Chronic and recent PM were not associated with current urinary albumin or microalbuminuria
Lue et al. (2013) [16]	Quantitative study of consecutive patients	Confirmed acute ischemic stroke patients aged ≥21 years, residing in the Boston (MA, USA) metropolitan region between 1999 and 2004	Exposure associated with living near a major roadway contributed to reduced renal function (via the estimated glomerular filtration rate)
Mehta et al. (2016) [17]	Prospective cohort	2,280 Male volunteers from the greater Boston area aged 21–80 years	Long-term $PM_{2.5}$ exposure negatively affected renal function and increased renal function decline (via the estimated glomerular filtration rate)
Xu et al. (2016) [18]	Cross-sectional study	Renal biopsy series including 71,151 native biopsies at 938 hospitals spanning 282 cities in China between 2004 and 2014	Long-term exposure to high levels of $PM_{2.5}$ was associated with an increased risk of membranous nephropathy.
Yang et al. (2017) [19]	Cross-sectional population-based study	21,656 Adults evaluated between 2007 and 2009 in New Taipei City who were participating in the Health Screening Program	Exposure during the previous year to PM_{10} and PMCoarse, but not $PM_{2.5}$, was associated with reduced renal function and chronic kidney disease.
Raaschou-Nielsen et al. (2011) [21]	Retrospective cohort study	54,304 Participants in the Danish Diet Cancer and Health cohort	Nitrogen oxides were weakly associated with kidney cancer, without statistical significance.
Raaschou-Nielsen et al. (2017) [20]	Retrospective cohort study	European Study of Cohorts for Air Pollution Effects included 14 cohorts of 289,002 participants, with at least 20 incident kidney parenchyma cancer cases during follow-up.	An increased risk of kidney cancer was associated with PM, although not to a statistically significant extent.

PM, particulate matter.

vascularity of the kidney. The study population consisted of consecutive patients aged ≥21 years with a confirmed history of acute ischemic stroke. The results showed that living near a major roadway was associated with a lower eGFR. Patients living within 50 m of a major road had a 3.9 mL/min/1.73 m² lower eGFR (95% CI, 1.0–6.7; P=0.007) than those living within 1,000 m of a major road, and this result was not confounded or mediated by age, sex, race, history of hypertension, diabetes, or socioeconomic status. The authors explained that long-term exposure to traffic pollution leads to vascular endothelial injuries, systemic inflammation, atherosclerosis, and microvascular changes, which result in renal functional changes (Table 1).

Mehta et al. [17] concluded that $PM_{2.5}$ reduced renal function in their Veterans Administration Normative Aging Study. The study included a closed cohort of 2,280 male volunteers from the greater Boston (MA, USA) area who were 21–80 years old at study entry. The mean age of the participants was 73.5 years, and the majority were ex-smokers and used antihypertensive medications. One-year $PM_{2.5}$ exposure was associated with a lower eGFR; more specifically, a 2.1 μg/m³ interquartile

range higher 1-year $PM_{2.5}$ exposure was associated with a 1.87 mL/min/1.73 m² lower eGFR (95% CI, -2.99 to -0.76). Notably, participants using angiotensin receptor blockers showed a null association, implying that angiotensin receptor blockers might minimize the vasoconstrictive effect of PM.

The subjects analyzed by O'Neill et al. [15] were healthy, which might explain why they could not demonstrate a relationship between PM and albuminuria. By contrast, Lue et al. [16] included patients with acute ischemic stroke, and Mehta et al. [17] investigated an aged population who may have had age-related renal function changes. From these findings, the glomerular filtration rate was shown to be a possible index for measuring early renal functional changes in unhealthy, vulnerable populations who are more sensitive to the effects of PM.

CHRONIC KIDNEY DISEASE AND PARTICULATE MATTER

Two studies analyzed PM-related chronic kidney disease. One of them identified the specific renal diseases of immunoglobu-

lin A nephropathy and membranous nephropathy.

Xu et al. [18] collected 71,151 renal biopsy series over 11 years to investigate the temporal change of glomerular diseases associated with $PM_{2.5}$. The authors found that immunoglobulin A nephropathy was the most common type of glomerulopathy (28.1%), followed by membranous nephropathy (23.4%). After adjustment for age and region, the odds of membranous nephropathy increased by 13% during the 11 years of the study. An increase of 10 $\mu g/m^3$ in the $PM_{2.5}$ concentration was associated with 14% higher odds for membranous nephropathy.

Yang et al. [19] recruited 21,656 adult participants with a mean age of 53.65 years during their 2007–2009 Health Screening Program. They calculated the eGFR using the Taiwanese Chronic Kidney Disease Epidemiology Collaboration equation. Exposure was estimated via annual average concentrations of $PM_{2.5}$, PM_{10}, and PMCoarse (defined as PM_{10}–$PM_{2.5}$) at each participant's residential address. The results showed that exposure during the previous year to PM_{10} and PMCoarse, but not $PM_{2.5}$, was associated with the prevalence of chronic kidney disease and reduced renal function among Taiwanese adults. The association between PM and chronic kidney disease was stronger in females than in males for PM_{10}. The authors noted that a possible reason for the null association of $PM_{2.5}$ might be the different constituents and toxicity of PM according to diameter.

RENAL CANCER AND PARTICULATE MATTER

Almost all results showing renal cancer to be associated with environmental exposure have demonstrated a weakly increased risk related to gasoline vapors, engine exhaust, trichloroethylene, asbestos, and polycyclic aromatic hydrocarbons [44]. However, few studies have investigated PM exposure and renal cancer.

Raaschou-Nielsen et al. [21] explored the associations between traffic pollution and cancer incidence in a Danish cohort. In total, 57,053 men (48%) and women (52%) aged 50–64 years were recruited. The authors analyzed various cancers and components of air pollution. The incidence rate of kidney cancer was found to be weakly associated with nitrogen oxides, without statistical significance.

Using the European Study of Cohorts for Air Pollution Effects, Raaschou-Nielsen et al. [20] performed a multicenter cohort study to investigate the association between PM in outdoor air and kidney cancer. The participants were 14 cohorts located in 10 areas in Europe. In total, 289,002 participants were enrolled for the pooled analysis. Higher hazard ratios (HRs)

were associated with higher PM concentrations (HR, 1.57; 95% CI, 0.81–3.01 per 5 $\mu g/m^3$ of $PM_{2.5}$), although the findings were not statistically significant. The authors concluded that the small number of kidney cancer cases and misclassification of the exposure might have resulted in statistical insignificance.

BLADDER CANCER

Studies on bladder cancer and PM have only recently been conducted, meaning that insufficient evidence is available to draw conclusions on the causal relationship.

Two case-control studies, 1 ecologic study, and 3 population-based cohort studies have been conducted on the association between bladder cancer and PM (Table 2). All the results, except for 1 cohort study, showed a positive association.

Yanagi et al. [45] analyzed the association between PM_{10} and cancer incidence and mortality. They found that the incidence of some types of cancer, including bladder cancer, showed a statistically significant correlation with PM_{10}.

Case-control studies conducted by Castaño-Vinyals et al. [46] and Liu et al. [47] showed a small to moderate positive association between several indices of air pollution and bladder cancer. In the results of Castano-Vinyals et al. [46], living more than 40 years in a large city was associated with bladder cancer (odds ratio [OR], 1.30; 95% CI, 1.04–1.63). Polycyclic aromatic hydrocarbons and diesel were associated with an increased risk (OR, 1.29; 95% CI, 0.85–1.98). Liu et al. [47] found a significant association between levels of air pollution and bladder cancer mortality (OR, 1.37; 95% CI, 1.03–1.82).

The cohort studies reported uncertain correlations between bladder cancer and PM. Smith et al. [48] and Yeh et al. [22] found a positive association of air pollution and $PM_{2.5}$ with bladder cancer. However, Pedersen et al. [23] did not find any such association in their study that included 15 population-based cohorts.

PROSTATE DISEASE

Although studies on whether prostate cancer is related to PM exposure began earlier than studies of other urologic disorders, the evidence is still equivocal.

The association between prostate cancer and air pollution has been studied since Winkelstein and Kantor [24] analyzed the association of prostate cancer and air pollution in Erie County and Nashville. Because the study was conducted using

Table 2. Summary of studies on the association between particulate matter and bladder cancer

Study	Method	Subjects	Main result
Castaño-Vinyals et al. (2008) [46]	Case-control study	1,219 Incident cases and 1,271 hospital controls	Living more than 40 years in a large city was associated with bladder cancer (OR, 1.30; 95% CI, 1.04–1.63). Polycyclic aromatic hydrocarbons and diesel were associated with an increased risk (OR, 1.29; 95% CI, 0.85–1.98)
Liu et al. (2009) [47]	Matched case-control study	Deaths occurring in Taiwan from 1995 through 2005 were compared with pair matched controls.	Significant association between the levels of air pollution and bladder cancer mortality (OR, 1.37; 95% CI, 1.03–1.82). Statistically significant trend in the risk of death from bladder cancer with increasing air pollution level.
Yanagi et al. (2012) [45]	Ecological time series study	Incidence and mortality for each type of cancer in the districts with air quality monitoring were correlated with PM_{10} values.	Pearson correlation showed high incidence rates for bladder cancer with PM_{10}.
Smith et al. (2016) [48]	Population-based cohorts	National Cancer Institute age-adjusted, county-level bladder cancer mortality data from 1950 to 2007 were analyzed.	Smoking, unemployment, physically unhealthy days, air pollution ozone days, percent of houses with well water, employment in the mining industry, and urban residences were associated with increased rates of bladder cancer
Pedersen et al. (2016) [23]	Population-based cohorts	Fifteen population-based cohorts enrolled between 1985 and 2005 in eight European countries (n = 303,431; mean follow-up 14.1 years)	None of the exposures ($PM_{2.5}$, PM_{10}, and nitrogen oxides) were associated with bladder cancer.
Yeh et al. (2017) [22]	Population-based cohort	Geographically weighted regression was applied	Ambient $PM_{2.5}$ showed a positive correlation with bladder cancer mortality in males in northern Taiwan and females in most of the townships in Taiwan.

PM, particulate matter; OR, odds ratio; CI, confidence interval.

an ecologic design, the positive associations reported in this study have limited value.

Parent et al. [26] conducted a case-control study to investigate the association between air pollution and prostate cancer using ground-level nitrogen dioxide (NO_2) as a marker of traffic-related air pollution. They found that exposure to ambient concentrations of NO_2 was associated with an increased risk of prostate cancer.

Ramis et al. [25] presented research into the spatial distribution of prostate cancer mortality in an industrialized area. They used distances from each of a number of industrial facilities as an indirect measure of industrial pollution. They found a significantly elevated risk of prostate cancer (by a factor of approximately 1.4) in the immediate vicinity, decaying with distance to a value of 1.08 at 12 km.

Few studies have reported that prostatic hyperplasia was positively related with air pollution [49]; well-designed research will be necessary in the future to address this issue.

CONCLUSIONS

Too few studies on the association between PM and urologic disease have been conducted to draw conclusions regarding the causal relationship. Research on PM and human health has expanded widely from the cardiorespiratory system to include respiratory cancers and perinatal and reproductive outcomes. The most widely acknowledged mechanism through which PM affects the cardiorespiratory system is by damaging the vascular system, such as causing endothelial injuries to vessels in various organs. PM has been hypothesized to affect the kidney as a secondary effect of its damage to the respiratory or circulatory system. According to this hypothesis, PM-related vessel injury results in hypertension, which must be reflected in the renal tissue. Studies of PM exposure and the circulatory system conducted since 2008 have suggested that renal function may be an early index of cardiovascular disorders due to PM. Since then, the glomerular filtration rate has been used as a useful index to measure early renal functional changes in unhealthy, vulnerable

populations. Considering the high vascularity of this organ, more research into the direct relationship between PM and chronic renal disease has been conducted since 2016. Two studies reported a significant association between PM exposure and chronic renal disease. However, the relationship between renal cancer and PM is controversial. Although some recently published studies have shown a significant association, these findings are insufficient to demonstrate the quality and quantity of the association. The evidence regarding the potential associations between bladder and prostate cancer likewise does not allow firm conclusions to be drawn. Further well-designed studies on specific urologic diseases are required.

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