Gender Difference in the Mean Age at the Induction of Hemodialysis in Patients With Autosomal Dominant Polycystic Kidney Disease

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• **Male patients with autosomal dominant polycystic kidney disease (ADPKD) begin hemodialysis earlier than female patients. The rate of progression of many other renal diseases is also faster in men than women. In this study, gender difference in ADPKD was compared with that in other diseases, such as chronic glomerulonephritis, diabetic nephropathy, and nephrosclerosis, using the data obtained from an annual statistical survey of the Japanese Society for Dialysis Therapy. The male-female ratio in ADPKD (n = 8,176) was 1.17:1 and closer to 1.0:1 than the other diseases. Men with ADPKD started hemodialysis therapy 1.3 years earlier than women (male age, 55.9 ± 12.4 years versus female age, 57.2 ± 11.5 years), and the age difference was less than that in other diseases. These results suggest that the prognosis in women with ADPKD is relatively worse than that in men with ADPKD or that women are not well protected against the progression of this disease compared with other renal diseases. In conclusion, men with ADPKD are introduced to hemodialysis therapy earlier than women; however, the age difference was small compared with other common renal diseases.**

INDEX WORDS: Autosomal dominant polycystic kidney disease (ADPKD); diabetic nephropathy; gender; glomerulonephritis; hemodialysis (HD).

MALE PATIENTS WITH autosomal dominant polycystic kidney disease (ADPKD) undergo hemodialysis earlier than female patients with ADPKD.[1-4] Although many other chronic renal diseases also show this tendency, ie, the rate of progression of chronic renal disease is faster in men than women,[5-7] we studied gender differences concerning the prognosis of renal diseases using accumulated data in Japan.

This study was performed to determine whether men with ADPKD are more disadvantaged concerning the start and prevalence of dialysis therapy than women with ADPKD compared with other renal diseases.

MATERIALS AND METHODS

Data were obtained from an annual statistical survey of the Japanese Society for Dialysis Therapy between 1983 and 1997,[8] and permission for use was obtained by the Patient Registration Committee of the Japanese Society for Dialysis Therapy. The registration procedure has been described previously.[8] This is a retrospective study using combined multicenter data for each year.

The timing and indications for starting hemodialysis therapy were the same for men and women during these time periods, and there was no exclusion or refusal of treatment, as a general rule in Japan. The indication and timing of the start of hemodialysis was the same for chronic glomerulonephritis, ADPKD, and nephrosclerosis, although patients with diabetic nephropathy tended to be introduced to hemodialysis earlier than other diseases. The male-female ratio was calculated to determine the influence of gender on the prevalence of renal disease. Gender differences in mean age distribution at the introduction of dialysis were compared among various diseases. There was no distinction made between PKD1 or PKD2 in patients with ADPKD, and specific features of the ADPKD population were not analyzed because these data were not available from the registry.

Data are expressed as mean ± SD. Statistical treatment of the data included testing for significant differences between means by non-paired Student's *t*-test.

RESULTS

The male-female ratios at the start of dialysis for chronic glomerulonephritis (n = 134,202), diabetic nephropathy (n = 82,163), nephrosclerosis (n = 15,614), and ADPKD (n = 8,176) were 1.51:1, 1.75:1, 1.67:1, and 1.17:1, respectively (Fig 1). The male-female ratio was the lowest in ADPKD and highest in diabetic nephropathy.

Figure 1 shows that for every disease, men started dialysis at an earlier age than women. Men with chronic glomerulonephritis began dialysis 1.9 years earlier than women (male age, 55.9 ± 15.7 versus female age, 57.8 ± 15.7 years; $P < 0.0001$). Men with diabetic nephropathy started dialysis therapy 1.8 years earlier than women (male age, 60.3 ± 10.5 versus female age, 62.1 ± 11.9 years; $P < 0.0001$). Men with nephrosclerosis started on dialysis therapy 2.2 years earlier than women (male age, 69.9 ± 11.6

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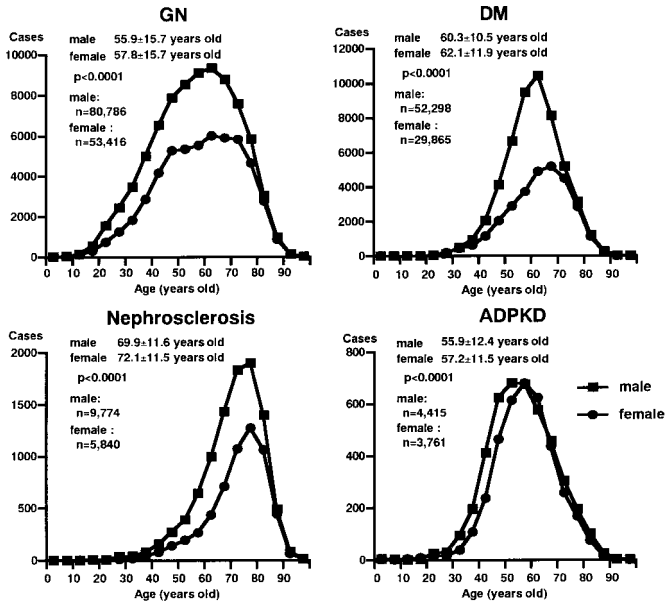

Fig 1. Gender differences of age distribution when starting hemodialysis in patients with glomerulonephritis (GN), diabetic nephropathy (DM), ADPKD, and nephrosclerosis. The prevalence of females was the greatest in ADPKD and the least in DM, and the difference in mean age was the least in ADPKD and the greatest in nephrosclerosis.

versus female age, 72.1 ± 11.5 years; $P <$ 0.0001). In men with ADPKD, dialysis began 1.3 years earlier than for women (male age, 55.9 ± 12.4 versus female age, 57.2 ± 11.5 years; $P <$ 0.0001). In ADPKD, the mean age of women at the start of dialysis therapy was slightly younger than that for other diseases.

The ages of both men and women in all diseases showed normal distribution curves, except for women with chronic glomerulonephritis, which showed a bumpy curve (Fig 1).

DISCUSSION

The overall prevalence of end-stage renal disease (ESRD) is greater in men than women. A greater incidence of ESRD in men was described in glomerulonephritis,[9] and a greater incidence of ESRD was detected in white men, but not in black men, with diabetic nephropathy. The male-female ratio was 1.6:1 for ESRD caused by glomerulonephritis and 2.2:1 for immunoglobulin A nephropathy.[10] In this study, the male-female ratio was 1.17:1 for ADPKD. This ratio was closer to 1:1 compared with the male-female ratio at the start of dialysis; 1.51:1 for chronic glomerulonephritis, 1.75:1 for diabetic nephropathy, and 1.67:1 for nephrosclerosis. The male-female prevalence of ADPKD was almost equal, showing that women with ADPKD were not strongly protected against this disease.

The progression of chronic renal disease is faster in men than women, and men begin hemodialysis therapy at an earlier age than women for conditions such as immunoglobulin A nephropathy, chronic glomerulonephritis, diabetic nephropathy, and nephrosclerosis. Men with ESRD showed a standardized mortality rate twice that of women.[11] Men had a 22% greater risk for death than women, attributable to a greater risk for death from acute myocardial infarction, cardiac complications, and malignancy.[12]

With one exception,[13] all studies reported that the rate at which renal failure progresses is faster in men than women with ADPKD.[1-4,13] Survival analysis of age at renal death showed a significant gender difference: median age at renal death was 53.5 years in men and 58.0 years in women,[1] and the mean age at ESRD was 50.6 years in men and 55.1 years in women.[4] However, in this study, the mean age was 55.9 years in men and 57.2 years in women. The difference in age was 1.3 years, in contrast to 4.5 years.[1,4]

One study,[3] a nationwide registration, showed that more men than women with ADPKD (630 men, 527 women) enter ESRD programs between the ages of 25 and 44 years and 65 and 74 years, respectively, although the prevalence in both sexes was similar for the ages of 45 to 64 years. In our study, the male-female ratios at the start of dialysis for the ages of 25 and 44 years (n = 1,127), 45 and 64 years (n= 4,936), and 65 and 74 years (n= 1,453) were 1.84:1, 1.07:1, and

1.10:1, respectively, suggesting that more men than women with ADPKD had entered ESRD programs only between the ages of 25 and 44 years. Unfortunately, our study only indicates age at onset of ESRD and does not give information on the rate of progression of the disease.

Female gender did not show protection against the progression of ADPKD compared with other renal diseases in this study. The precise mechanisms underlying gender differences in the progression of chronic diseases remain to be elucidated. Deterioration of renal function in patients with chronic renal disease is faster in men than women[14,15] independent of the presence of hypertension or hyperlipidemia. However, many mechanisms of renal injury have been proposed by using animal experiments related to the progression of chronic renal disease. One mechanism involves genetic changes in structure and function between men and women. Sex hormones[16] may be related to mesangial proliferation and extracellular matrix formation through the release of cytokines, vasoactive agents, and growth factors. Recently, Torres et al[17] reported that female Han:Sprague-Dawley rats had greater renal concentrations of α-tocopherol and less severe renal cystic disease. Estrogens show potent antioxidant activity, unlike testosterone. Men ingest more protein and phosphate than women, resulting in hyperfiltration in glomerular filtration.[18] Therefore, sex hormones may be the main cause for this gender difference and poorer outcomes in men.

However, sex hormones and acquired environmental factors that prevent the progression of renal diseases in women may be less effective in ADPKD. Although ADPKD is an autosomal dominant disease, hereditary factors equally disadvantageous to both genders may be more important for the progression of ADPKD than acquired aggravating environmental factors. This theory suggests that the prognosis in women with ADPKD is worse than that in men with ADPKD if ADPKD is compared with other renal diseases.

Significant gender differences were observed in terms of more pronounced progression in women with autosomal recessive polycystic kidney disease[19] and in terms of a greater incidence of renal cell carcinoma in male dialysis patients.[20] No gender difference was found for age at renal death in prepubertal patients with cystinosis or nephronophthisis,[1] and only a slight male dominance was observed in patients with ADPKD.

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