A cohort study found a high risk of end-stage kidney disease associated with acromegaly

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Acromegaly is a chronic systemic disease caused by excess levels of growth hormone and insulin-like growth factor-1 and is associated with numerous complications. Significantly, there is a lack of longitudinal data on kidney complications in patients with acromegaly. As such, we investigated the risk of end-stage kidney disease (ESKD) (stage 5D, 5T) in these patients with nationwide data obtained from the National Health Information Database of the National Health Insurance Service in Republic of Korea. A retrospective cohort study was conducted of 2.187 patients with acromegaly and 10,935 age- and sex-matched (1:5) control subjects without acromegaly over a mean follow-up period of 6.51 years. The study outcomes were analyzed using Cox proportional hazards regression analysis controlling for age, sex, household income, residential area, type 2 diabetes, hypertension, dyslipidemia, urolithiasis, congestive heart failure, myocardial infarction, stroke, and atrial fibrillation. The incidence (per 1,000 person-years) ESKD was 2.00 among patients with acromegaly but only 0.46 among controls, (hazard ratio 4.35 (95% confidence interval 2.63–7.20)) implicating a significantly higher risk. After adjustment for covariates, the risk of ESKD (2.36 (1.36–4.12)) was still significantly higher in patients with acromegaly than that in controls. Among the covariates, diabetes and hypertension were significant facilitators between acromegaly and ESKD in mediation analysis. Pituitary surgery and somatostatin analogues did not significantly change these associations. Thus, acromegaly may be linked with a higher risk for ESKD both independently and through mediators such as diabetes and hypertension.

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Lay Summary

Longitudinal data on kidney complications in patients with acromegaly are lacking. We investigated the risk of end-stage kidney disease (ESKD) in patients with acromegaly ($n = 2187$) and in age- and sex-matched (1:5) controls without acromegaly ($n = 10,935$) for a mean follow-up period of 6.51 ± 3.20 years. (We define sex throughout the article as the biological characteristics that define humans as female or male according to the World Health Organization definition.) The incidence (per 1000 person-years) of ESKD was 2.00 among patients with acromegaly, and 0.46 among controls, a 4.35-fold (95% confidence interval, 2.63–7.20) difference in risk. This association was significant even after adjusting for covariates. Among covariates, diabetes and hypertension were significant mediators between acromegaly and ESKD in mediation analysis. Pituitary surgery and somatostatin analogues did not change the acromegaly–ESKD association. Acromegaly was associated with a higher risk for ESKD both independently and through mediators such as diabetes and hypertension.

Acromegaly is a chronic systemic disease caused by excess levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), and it is associated with numerous complications.[1] Compared with other acromegaly-related complications, including cardiovascular disease, osteoarthropathy, diabetes, respiratory disease, and neoplasia, few data are available on kidney complications in patients with acromegaly.[2–5] GH and IGF-1 receptors, which physiologically affect the regulation of kidney growth and function, are expressed in the kidney throughout the nephrons, including in the glomeruli and all tubular segments.[5,6] Mesangial cells are the only glomerular cells to produce IGF-1.[7,8] IGF-1 has a mitogenic effect in mesangial cells and triggers the production of extracellular matrix proteins while also suppressing apoptosis induced by high glucose levels.[9,10] Thus, mesangial cells have been accepted broadly as the key to the development of diabetic nephropathy through enhanced IGF-1 signaling.[11] Circulatory levels of GH are elevated in patients with poorly controlled type 1 diabetes mellitus.[12] According to studies on patients with type 1 diabetes mellitus, urinary GH and IGF-1 levels are

associated with the presence of microalbuminuria.[13,14] Somatostatin analog, an inhibitor of GH, improved glomerular hyperfiltration and kidney size in such patients.[15,16] A previous study reported that patients with acromegaly had a high prevalence of microalbuminuria, which was associated with disease duration, insulin sensitivity, and GH level.[17] Another cross-sectional study reported that acromegaly is characterized by significant modifications of kidney structure and function, including increased kidney size, glomerular filtration rate, microalbuminuria, and the prevalence of nephrolithiasis.[4] However, longitudinal data are lacking on kidney complications in patients with acromegaly.

The aim of this cohort study was to investigate the risk of ESKD in patients with acromegaly in a dataset from the Republic of Korea National Health Information Database (NHID), which contains longitudinal data for 97% of the Korean population.

METHODS

Study database

The data for our analysis were from the NHID, a public database including healthcare utilization data for most of the Korean population, which is linked to the national death registry, the national health screening program, and the rare incurable disease registry for the country.[18–20] Approval for the study protocol was obtained from the Institutional Review Board of Kangbuk Samsung Hospital (KBSMC 2019-09-003), which waived the need for informed consent because personal identifying information was not accessed.

Study subjects

This study was a national, retrospective, cohort study that included 13,122 subjects. We initially identified 2259 patients with acromegaly from the NHID for the years between 2006 and 2016. Of them, 14 patients were younger than 20 years, 34 had a history of ESKD, 22 developed ESKD within the first year (first-year lag period), and 2 lacked complete data and were excluded from our study. Finally, the acromegaly group was comprised of 2187 subjects. Due to the regulations of the data provider (NHID), we could not obtain data for the whole population, only data for matched controls. We enrolled age- and sex-matched subjects without acromegaly for comparison at a ratio of 1:5 (n = 10,935; Figure 1).

Definitions of acromegaly and ESKD

This study used a subset of data on rare incurable diseases taken from the Korean NHID. Acromegaly is labeled as a rare incurable disease by the Korean government, and its diagnosis is based on confirmation of suppressed growth hormone by an oral glucose tolerance test. Acromegaly was defined based on a history of outpatient care or hospitalization for both the International Classification of Diseases (ICD) 10th revision code (E22.0) and the code for financial support through the Korean National Health Insurance Service (V112). The outcome of interest in our study was newly diagnosed ESKD, defined using a combination of ICD-10 codes (N18-19, Z49, Z94.0, Z99.2) and initiation of kidney replacement therapy and/or kidney transplantation. Patients with kidney replacement therapy and/or kidney transplantation also are categorized as patients with a rare incurable disease and are reimbursed for all medical care expenses for dialysis. Kidney replacement therapy and/or kidney transplantation was defined based on rare incurable disease registry codes for hemodialysis (V001), peritoneal dialysis (V003), or kidney transplantation (V005). The study population was followed from baseline to the date of ESKD, or until December 31, 2018, whichever came first.

Comorbid metabolic diseases and acromegaly treatment

Comorbid metabolic diseases in patients with acromegaly were analyzed using data from the NHID. The presence of type 2 diabetes mellitus was defined according to ICD-10 codes E11–14 and by a prescription for antidiabetic medication. The presence of hypertension was defined according to prescription claims data for an antihypertensive medication under ICD-10 codes I10, I11, I12, I13, and I15. The presence of dyslipidemia was defined according to the presence of claims data for a prescription of antihyperlipidemic agents, under ICD-10 code E78. The presence of congestive heart failure was defined according to ICD-10 code I50 in the discharge diagnosis. The presence of urolithiasis was defined according to ICD-10 codes N20–N23. Pituitary surgery was defined according to procedure codes (P4540, S4663, S4638, S4639). Somatostatin analogues included octreotide acetate, lanreotide acetate, and pasireotide pamoate.

Data analyses

Baseline characteristics were analyzed using descriptive statistics. Categorical variables were described as frequency and percentage. Continuous variables were described as mean (±SD) for normally distributed data. We compared baseline characteristics at the time of diagnosis of patients with acromegaly and those of 1:5 age- and sex-matched controls without acromegaly. Continuous variables were compared using the independent samples t-test, and categorical variables were compared using the χ^2 test. To minimize reverse causality, we adopted a first-year lag period. The follow-up durations of the groups were obtained. The incidence rate of ESKD was estimated for each group over the total follow-up period. Incidence curves were estimated using the Kaplan–Meier method and the log rank test. Outcomes were analyzed using Cox proportional hazards regression analysis controlling for baseline covariates such as age (categorized as <40, 40–64, and ≥65 years), sex, household income, type 2 diabetes, hypertension, dyslipidemia, urolithiasis, congestive heart failure, myocardial infarction, stroke, atrial fibrillation, duration of diabetes, and duration of hypertension. Subgroup analysis by baseline covariates was performed with Cox proportional hazards regression analysis. From the mediator models, we obtained regression coefficients for the association of acromegaly with the respective mediator. From the outcome model, we obtained regression coefficients for the association of acromegaly and ESKD independent of the mediators and for independent associations between each of the mediators and ESKD. These results were expressed as hazard ratios (HRs) with 95% confidence interval (CI). The null hypothesis was rejected for values of P <0.05. Analyses were performed with SAS 9.4 (SAS Institute) and R program, version 3.4.1 (R Foundation for Statistical Computing, http://www.R-project.org).

RESULTS

Baseline characteristics of subjects

The characteristics of the patients with acromegaly (n = 2187) at the time of diagnosis and of the age- and sex-matched controls (n = 10,935) at the time of matching are summarized in Table 1. Mean age at the time of diagnosis or

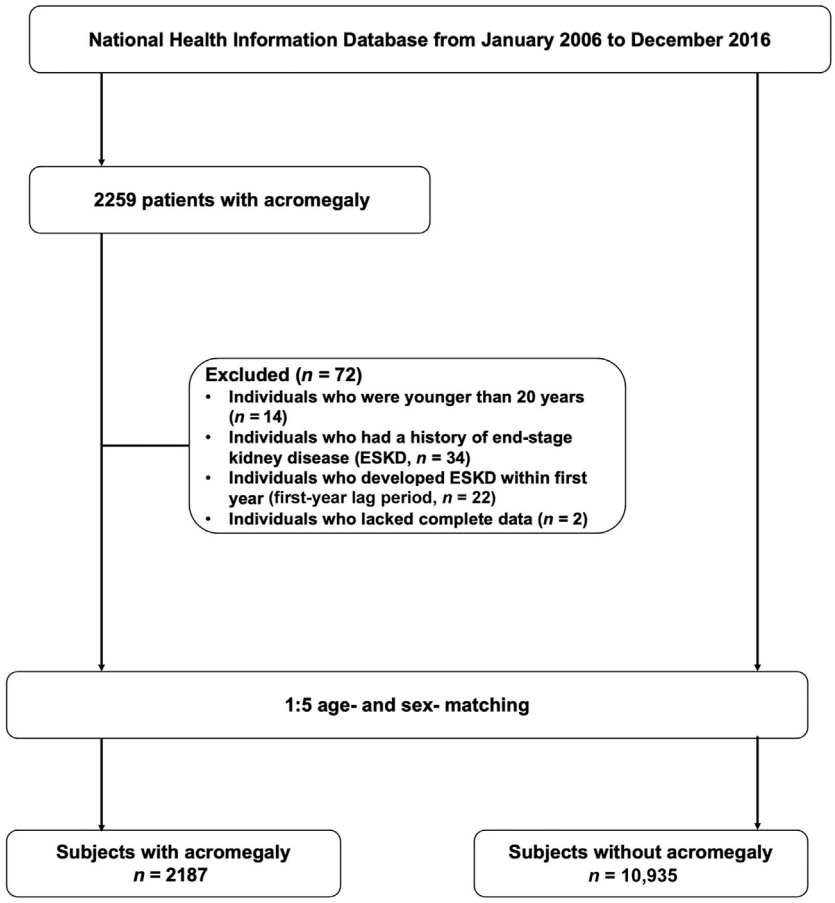

Figure 1 | Flowchart showing the selection of the study population.

Table 1 | The characteristics of the patient group with acromegaly at the time of diagnosis, and of the age- and sex-matched control group at the time of matching

Characteristic	Controls	Patients with acromegaly	
Number of subjects	10,935	2187	*P*
Age, yr	48.4 ± 12.93	48.4 ± 12.93	1
Men	4855 (44.4)	971 (44.4)	1
Urban	5047 (46.15)	1029 (47.05)	0.4429
Household income level			<0.001
Lowest	1981 (18.12)	341 (15.59)	
Medium-lowest	2246 (20.54)	383 (17.51)	
Medium-highest	2699 (24.68)	574 (26.25)	
Highest	3438 (31.44)	710 (32.46)	
Hypertension	1959 (17.91)	878 (40.15)	<0.001
Duration of hypertension	1.1 ± 2.58	2.19 ± 3.48	<0.001
Type 2 diabetes	668 (6.11)	646 (29.54)	<0.001
Duration of diabetes	0.38 ± 1.65	1.28 ± 2.86	<0.001
Dyslipidemia	1111 (10.16)	401 (18.34)	<0.001
Urolithiasis	102 (0.93)	49 (2.24)	<0.001
Congestive heart failure	91 (0.83)	65 (2.97)	<0.001
Myocardial infarction	33 (0.3)	19 (0.87)	0.001
Stroke	162 (1.48)	78 (3.57)	<0.001
Atrial fibrillation	56 (0.51)	24 (1.1)	0.001

Values are n (%) or mean ± SD, unless otherwise indicated.

matching was 48.4 ± 12.93 years, and 44.40% of the study subjects were men. Patients with acromegaly had a higher prevalence of the following: type 2 diabetes (29.54% vs. 6.11%, $P < 0.001$); hypertension (40.15% vs. 17.91%, $P < 0.001$); dyslipidemia (18.34% vs. 10.16%, $P < 0.001$); congestive heart failure (2.97% vs. 0.83%, $P < 0.001$); myocardial infarction (0.87% vs. 0.30%, $P < 0.001$); stroke (3.57% vs. 1.48%, $P = 0.001$); atrial fibrillation (1.10% vs. 0.51%, $P = 0.001$); and urolithiasis (2.24% vs. 0.93%, $P < 0.001$), compared with the control group.

Acromegaly and ESKD

The cumulative prevalence, annual incidence, and HR of outcomes in patients and the control group are shown in Table 2. ESKD occurred in 28 patients (1.28%) with acromegaly during the mean 6.39 ± 3.22 years of follow-up, and in 33 age- and sex-matched control patients (0.30%) during the mean 6.53 ± 3.2 years of follow-up. The incidence rate of ESKD was 2.00 per 1000 person-years in the patient group and 0.46 per 1000 person-years in the control group. In Kaplan–Meier survival analysis for ESKD, the incidence rate of ESKD in the patient group was significantly higher than that in the

Table 2 | Number, incidence rate, and hazard ratio of end-stage kidney disease in the patient group with acromegaly, and in the age- and sex-matched control group

Group	Patients, *n*	Events, *n*	Duration, p-y	Rate	HR (95% CI)		
					Unadjusted	Model 1	Model 2
Controls	10,935	33	71,440	0.46	1 (ref)	1 (ref)	1 (ref)
Acromegaly	2187	28	13,978	2.00	4.348 (2.628, 7.195)	4.420 (2.671, 7.314)	2.288 (1.235, 3.752)

CI, confidence interval; HR, hazard ratio; ref, reference.
Rate = events per 1000 person-years (p-y).
Model 1: adjusted by age and sex.
Model 2: adjusted by age, sex, household income, type 2 diabetes, hypertension, dyslipidemia, urolithiasis, congestive heart failure, myocardial infarction, stroke, atrial fibrillation, duration of diabetes, and duration of hypertension.

control group (log-rank, $P < 0.001$; Figure 2). In the age- and sex-adjusted model, the risk for ESKD in the patient group was 4.42-fold (95% CI 2.67–7.31; Table 2) that in the control group. In multivariable Cox proportional hazards regression modeling, after adjusting for baseline covariates such as age (categorized as <40, 40–64, and ≥65 years), sex, household income, type 2 diabetes, hypertension, dyslipidemia, urolithiasis, congestive heart failure, myocardial infarction, stroke, atrial fibrillation, duration of diabetes, and duration of hypertension, the risk for ESKD in the patient group was significantly higher than that in the control group (HR = 2.29, 95% CI 1.24–3.75; Table 2). The results for ESKD were consistent across subgroups by age, sex, concomitant type 2 diabetes, dyslipidemia, urolithiasis, and heart failure (all P for interaction > 0.050; Figure 3). However, the results for ESKD were different across subgroups by the presence of hypertension (P for interaction = 0.038; Figure 3).

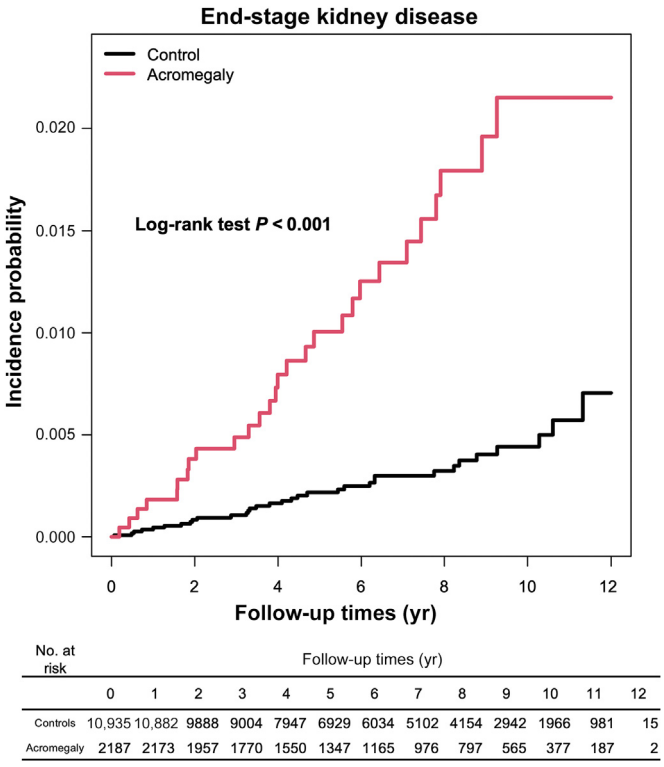

Figure 2 | The cumulative incidence of end-stage kidney disease based on Kaplan–Meier analysis. The *P*-value was calculated using the log-rank test.

Supplemental analyses

We tested the mediator role of several factors in the relationship between acromegaly and ESKD (Figure 4). Acromegaly was associated directly with ESKD (HR = 2.348, 95% CI 1.35–4.083) and associated indirectly with ESKD via diabetes and hypertension (Figure 4). We analyzed the effects of treatment for acromegaly in the association between acromegaly and ESKD. We divided patents with acromegaly into those who did versus those who did not undergo pituitary surgery within 1 year after the date of diagnosis of acromegaly and who did versus did not receive somatostatin analogues within 1 year after the date of diagnosis of acromegaly (Table 3). No significant differences in ESKD occurred based on somatostatin analogue treatment or pituitary surgery among acromegaly patients (all $P > 0.05$; Table 3).

DISCUSSION

This retrospective cohort study showed that acromegaly is associated with the risk of ESKD. During the approximate 6.4-year follow-up period, the risk for ESKD was 4.35 times higher (95% CI 2.63–7.20) in the patient group with acromegaly than in the controls without acromegaly. The association between acromegaly and ESKD was consistent even after adjusting for age, sex, household income, residential area, type 2 diabetes, hypertension, dyslipidemia, urolithiasis, congestive heart failure, myocardial infarction, stroke, atrial fibrillation, duration of diabetes, and duration of hypertension. This association was observed for all subgroups except those with hypertension. According to mediation analysis, acromegaly is both directly and indirectly associated with ESKD. Current treatments for acromegaly, such as pituitary surgery and somatostatin analogues, did not change the association between acromegaly and ESKD. Although this retrospective cohort study did have limitations, it provides new insights regarding the association of acromegaly with ESKD.

The effects of GH are induced directly or indirectly via IGF-I. GH gene overexpression in transgenic mice can lead to glomerular hypertrophy, mesangial proliferation, and

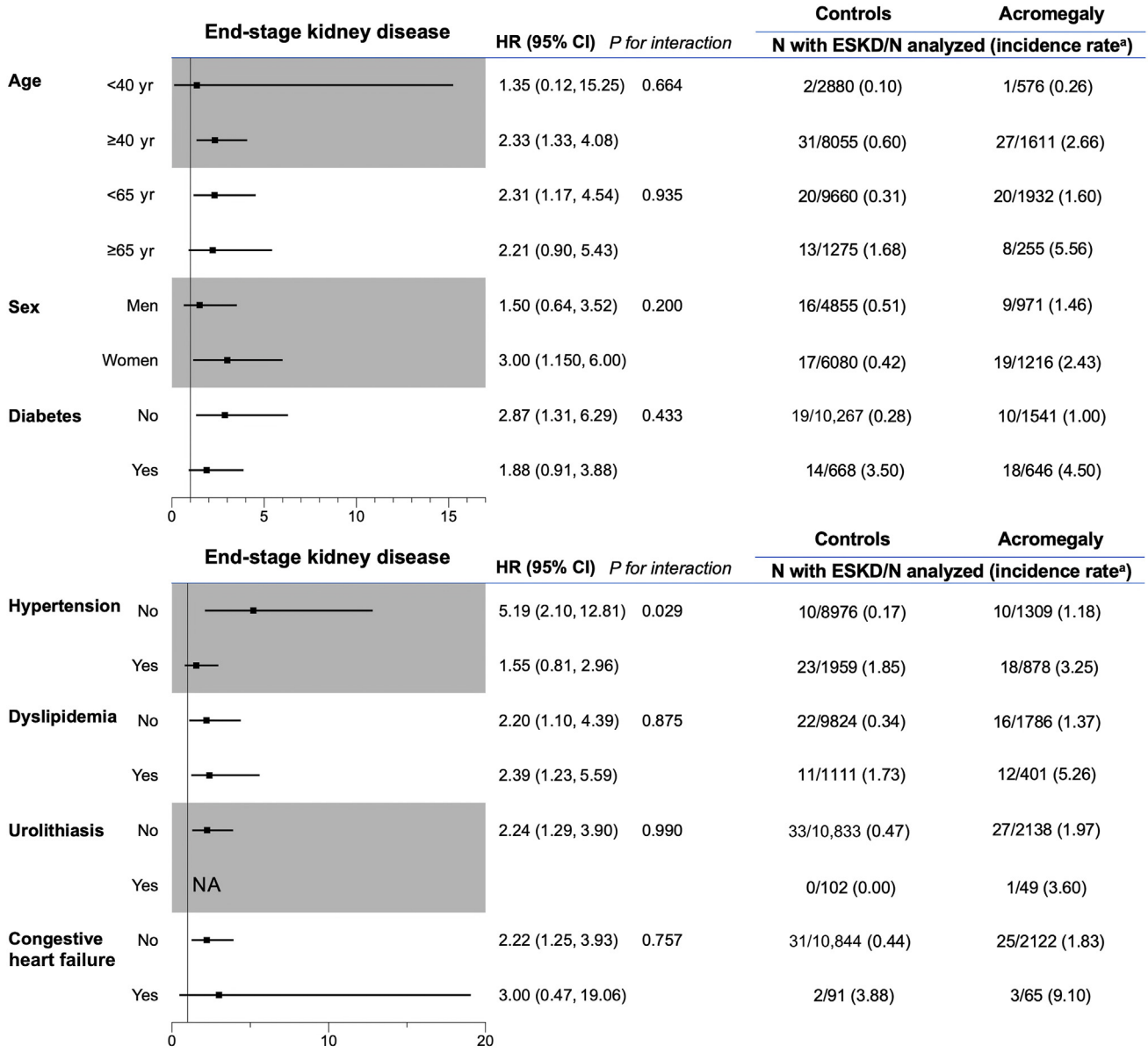

Figure 3 | The hazard ratios (HRs) for end-stage kidney disease (ESKD) between patients with acromegaly and controls in prespecified subgroups. [a]Events per 1000 person-years. CI, confidence interval; NA, not available.

matrix deposition with podocyte injury at excessive GH and IGF-1 concentrations.[21] Any or all of the preceding conditions can lead to albuminuria and progressive kidney failure with glomerulosclerosis.[22] Findings in transgenic mice and acromegalic mice must be interpreted carefully, as this model might not accurately represent human conditions. Given that acromegaly is a rare acquired endocrine disease, few studies have explored kidney function in these patients. A study of acromegaly patients (n = 30) showed an association with significant changes in kidney structure and function that were not completely resolved at 1 year after disease remission.[4] Another recent case–control study of 48 acromegalic patients showed that active acromegaly was associated with a 25% higher estimated glomerular filtration rate, and that remission of acromegaly after surgical treatment could lead to estimated glomerular filtration rate reduction 3 months postsurgery.[23] Our study of 2187 patients with acromegaly and 1:5 age- and sex-matched controls (n = 10,935) showed that acromegaly was associated with a 4.35-fold higher risk for ESKD with more than 6 years of follow-up, and the extent of difference in ESKD between acromegaly and controls did not change over these 6 years (Figure 2). Our previous studies showed that the association between acromegaly and related complications, such as cardiovascular[3] and neurologic complications,[24] was time-dependent after diagnosis and treatment of acromegaly. However, we did not observe this trend in the current study, and supplemental analysis suggested that

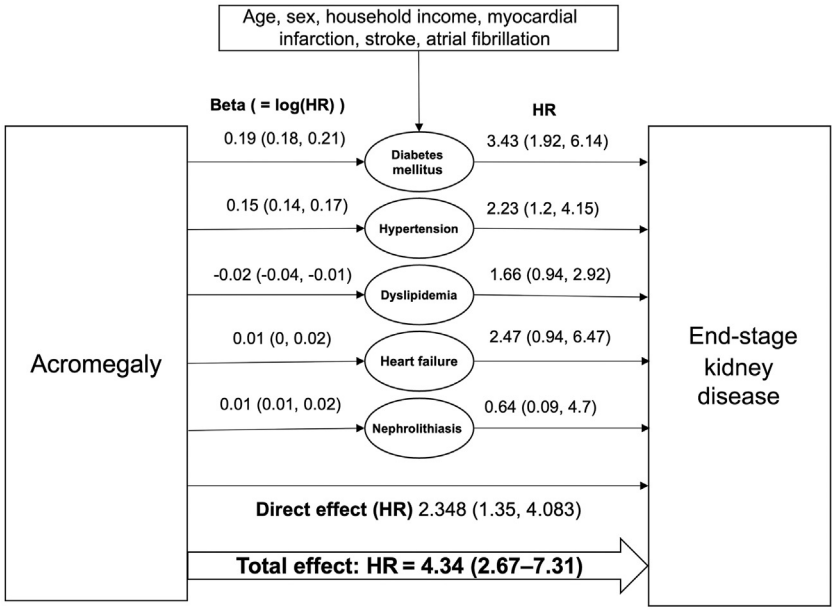

Figure 4 | Mediation analysis of diabetes and hypertension: direct and indirect effects of acromegaly on end-stage kidney disease. HR, hazard ratio.

current treatment options such as pituitary surgery and somatostatin analogues are not sufficient to prevent ESKD (Table 3).

Acromegaly is associated with a higher risk of chronic systemic complications, such as hypertension, diabetes mellitus, atrial fibrillation, congestive heart failure, and urolithiasis,[3,25] which are risk factors of ESKD.[26–29] According to mediation analysis, risk factors such as diabetes and hypertension mediated the association between acromegaly and ESKD (Figure 4). Acromegaly also is associated indirectly with ESKD via diabetes and hypertension. In all subgroup analyses, except that for hypertension, the association between acromegaly and ESKD was consistent (Figure 3). However, in patients with acromegaly, the risk of ESKD was higher in patients without hypertension than in those with hypertension, after adjusting for confounders and mediators (Figure 3). Hypertension is a critical risk factor for chronic kidney disease and progression to ESKD.[30–32] A longitudinal study of Japanese health screening data explored whether hypertension or diabetes contributed more to chronic kidney disease development in a Japanese community.[33] This study showed that the development of reduced estimated glomerular filtration rate was seen in patients with hypertension alone, and was not seen in patients with diabetes alone.[33] In our hypertensive subgroup analysis, acromegaly's direct effect on ESKD without mediator effects was seen most clearly in patients with acromegaly and without hypertension. This finding suggests that

Table 3 | Number, incidence rate, and hazard ratio of end-stage kidney disease in subgroups who received treatment within 1 year after the date of acromegaly diagnosis

Subgroup	Patients, *n*	Events, *n*	Duration, p-y	Rate	HR (95% CI)		
					Unadjusted	Model 1	Model 2
Controls	10,935	33	71,440	0.46	1 (ref)	1 (ref)	1 (ref)
Acromegaly with somatostatin analogue	1465	21	9096	2.31	5.027 (2.909, 8.689)	4.723 (2.732, 8.166)	2.594 (1.445, 4.657)
Acromegaly without somatostatin analogue	722	7	4882	1.43	3.094 (1.369, 6.994)	3.703 (1.635, 8.388)	1.659 (0.704, 3.911)
Controls	10,935	33	71,440	0.46	1 (ref)	1 (ref)	1 (ref)
Acromegaly with pituitary surgery	1261	20	8327	2.40	5.183 (2.974, 9.034)	4.764 (2.731, 8.311)	2.366 (1.303, 4.294)
Acromegaly without pituitary surgery	926	8	5651	1.42	3.098 (1.431, 6.709)	3.740 (1.720, 8.131)	2.112 (0.937, 4.759)

CI, confidence interval; HR, hazard ratio; ref, reference.
Rate = events per 1000 p-y (person-years).
Model 1: Adjusted by age and sex.
Model 2: Adjusted by age, sex, household income, type 2 diabetes, hypertension, dyslipidemia, urolithiasis, congestive heart failure, myocardial infarction, stroke, atrial fibrillation, duration of diabetes, and duration of hypertension.

hypertension is a critical mediator of the association between acromegaly and ESKD.

This study has limitations. First, the design was retrospective and observational. Although the analyses were adjusted for most available confounding factors, some unidentified parameters could have affected the results. However, acromegaly is a rare endocrine disease, so a large prospective study would be difficult. Second, this analysis was based on a small number of patients with ESKD ($n = 33$ in the acromegaly group and $n = 28$ in the control group); therefore, a small number of events within each cohort could lead to considerable variation in results. To address this problem, an external validation cohort or a larger cohort is needed, but finding such cohorts is challenging because acromegaly is so rare. Third, we did not have data for IGF-1 or GH levels, kidney size, or microscopic changes of the kidney, which are important aspects of the association between acromegaly and kidney disease. Fourth, we defined acromegaly and ESKD using claims data; this approach may not be accurate for determining the number of cases. To overcome this problem, we defined acromegaly using the national registry system for rare intractable diseases and applied the definition of ESKD that was validated in previous studies using a Korean NHIS sample cohort. Fifth, comorbidities such as diabetes, hypertension, and dyslipidemia were defined using claims data, without data on blood glucose, glycated hemoglobin, arterial blood pressure, or blood lipid levels. To minimize bias, we applied definitions of diabetes, hypertension, and dyslipidemia that were validated in previous studies.[34–36] Last, this study was not prospective, and causality could not be determined. However, to minimize the possible effects of reverse causality, subjects with preexisting conditions were excluded, and a 1-year lag period was employed.

In conclusion, this nationwide, observational, retrospective cohort study of patients with acromegaly showed that the risk of ESKD was higher in patients with acromegaly, compared with controls, after more than 6 years of follow-up. Our results suggest that timely and comprehensive treatment is needed in patients with acromegaly to reduce the risk of ESKD, including a long follow-up period; however, further research is needed on what treatment strategies can be used to reduce the risk of ESKD effectively.

DISCLOSURE

All the authors declared no competing interests.

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