Aging Promotes Progression of IgA Nephropathy: A Systematic Review and Meta-Analysis

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Key Words

Aging · IgA nephropathy · End-stage renal disease · Meta-analysis

Abstract

Background: There has been considerable interest in whether old age is associated with IgA nephropathy (IgAN) progression, which is still controversial. **Methods:** We searched multiple databases for studies published from 1980 to 2012. The inclusion criteria were case-control, cohort studies published in any language. The included studies needed to have an older group. IgAN was proven by biopsy. **Results:** We included 9 studies with a total of 6,543 patients. The meta-analyses of other risk factors between the older group (>50 years old) and the non-older group (15–50 years old) found significant differences in the presence of hypertension, proteinuria, serum cholesterol levels and baseline renal function. In the overall analysis, compared to the non-older group, older age significantly increased the incidence of developing end-stage renal disease [ESRD; relative risk (RR) random model 1.95; 95% CI: 1.27–3.01]. In the subgroup analyses, we found the age limit and traditional risk factors of IgAN may be the sources of heterogeneity between studies. Moreover, the RR (2.56) of the Asian countries was much higher than the RR (1.11) of the European countries. **Conclusions:**

This comprehensive review revealed that old age is a real risk factor for IgAN progression to ESRD. The incidence of ESRD in the older IgAN patients was 1.95 times higher than that in the non-older IgAN patients. Moreover, the risk of IgAN progression to ESRD of the older patients in Asia was higher than that of the older patients in Europe. © 2013 S. Karger AG, Basel

Introduction

IgA nephropathy (IgAN) was first reported by Berger and Hinglais in France in 1968 [1]. Today, IgAN has become the most common primary glomerulonephritis worldwide [2], especially in Southeast Asia. Approximately 30–40% of IgAN patients progress to end-stage renal disease (ESRD) within 20 years [3]. In Italy, and Europe as a whole, approximately 24% of histologically examined patients have IgAN as the cause of ESRD [4]. In the assessment of most of the IgAN clinical trials, we previously concluded that IgAN was the most common cause of ESRD in China [5]. IgAN generally affects young people <30 years of age. In the literature from the 1990s, patients older than 50 years accounted for only 2.3% of all the patients [6], but this proportion has risen to 18.3% recently [7]. This change may be caused by an increased

human life expectancy, increasing the proportion of elderly patients.

The world is likely to have one billion people older than 65 years by 2030, accounting for 13% of the total population [8]. With life expectancy increasing and medical conditions progressing, the age of the population in developed countries is accelerating [9–11]. We found few reports of the impact of aging on IgAN [6, 7, 12, 13], and the existing studies did not reveal the impact of aging on long-term kidney survival in IgAN patients. Some studies found that aging would increase the risk of IgAN progressing to ESRD [7, 12]. However, other studies showed that aging was a protective factor against developing ESRD [6]. To clarify the impact of aging on IgAN progression to ESRD, we conducted the following meta-analysis.

Methods

Search Strategy

We used the following terms for standard medical subject headings and free-text words: IgA glomerulonephritis, IgA nephropathy, Berger disease, immunoglobulin A nephropathy, prognosis, long-term, outcome, and predict. We only made slight modifications to the basic search template to optimize the search strategy in the individual electronic databases. We also reviewed the references cited in all of the studies selected for review. The investigators who had published any study on the relationship between aging and IgAN were also contacted.

From April 1, 2012, to June 1, 2012, we screened eight electronic databases: PubMed/MEDLINE, EMBASE, Science Citation Index, OVID evidence-based medicine, Chinese Biomedical Literature and Chinese science and technology periodicals (CNKI, VIP, and Wan Fang). All of the relevant studies were published from January 1980 to May 2012. Two searchers conducted the search independently. If one of the searchers thought that the article was appropriate, the study was selected. The search was repeated in September 2012, using PubMed/MEDLINE to capture any articles that were published after the original search date.

Study Selection

The inclusion criteria were case-control, cohort studies published in any language. Cross-sectional studies were excluded because they cannot clearly identify the causal relationship between observed indicators and diseases. The included studies needed to have an older group. IgAN was proven by biopsy. We excluded patients with secondary IgAN. The end point was progression to ESRD, chronic kidney disease stage 5, CRF or the need for renal replacement therapy, and the follow-up period was longer than 12 months. The exclusion criteria were the following: not having an older group (older than 50 years of age), no matched outcomes, lack of raw data and data duplication.

Quality Assessment

We used the US preventive task force methodology to critically assess the quality of the studies included in this review [14].

Fig. 1. Study selection process.

The evaluation criteria for the cohort studies were the following: (1) initial assembly of the cohort; (2) maintenance of comparable groups; (3) attrition; (4) clear definitions of exposure; (5) assessment of measurements; (6) adjustment for important potential confounders, and (7) inclusion of all important results [15]. Instead of scores, we used ‘good’, ‘fair’, and ‘fail’ to judge the overall quality of the included studies. When both reviewers judged a study to be ‘fair’, the study was evaluated in the final round. If the results of the two reviewers were significantly different, i.e. one judged a study as ‘good’ and another as ‘fail’, the committee conducted a collective discussion to arrive at a final opinion.

Data Extraction and Statistical Analysis

Data on trial design, sample size, nationality, males, age, exposure definition, outcome definition, follow-up time, renal function, hypertension, events were extracted. Relative risk (RR) and 95% confidence intervals were used to analyze the dichotomous data. The random effects model was weighted using the DerSimonian and Laird methods [16]. A random effects model was chosen a priori because of the belief that variation in the study populations and underlying diseases between the groups (older and younger groups) would result in inter-study heterogeneity beyond sampling variability. Heterogeneity between studies was tested using the χ^2 test. When the heterogeneity results showed a $p < 0.10$, heterogeneity was considered to be present. The size of heterogeneity in the included studies was assessed using I^2 [17]. All of the analyses were performed using Review Manager 5.1 (The Nordic Cochrane Centre, Rigshospitalet 2008).

Table 1. Main characteristics of the included studies

Study	Design	Sample size	Nationality	Males, %	Age, years	Exposure definition ¹ , years of age	Outcome definition	Events	Follow-up
Goto [7]	cohort study	2,283	Japanese	48.7	31.2	≥60	ESRD: beginning of chronic hemodialysis	252	87 months
Kuhara [18]	cohort study	291	Japanese	45.4	54.6±2.8	≥50	CRF	24	older group: 4.9±2.9 years
Takeda [20]	cohort study	117	Japanese	57.3	NS	≥50	CRF	16	3.8 years
Frimat [13]	cohort study	129	French	81.4	38.4	≥50	ESRD, required dialysis or kidney transplantation	22	41 months
Soleymanian [12]	cohort study	70	Iranian	35.7	39±12.1	≥50	ESRD, need for renal replacement	10	23.5 months
Yang [21]	cohort study	152	Chinese	56.6	older group: 65.2±4.7 control group: 34.2±9.4	≥60	ESRD	5	34.6±33.3 months
Ferro [22]	cohort study	392	Italian	58.2	53	≥65	CRF	10	NS
Rivera [23]	cohort study	total: 9,378	Spanish	60.4	NS	≥65	CRF	148	NS
Yokoyama [24]	cohort study	total: 3,109	Japanese	50.1	NS	≥65	CKD stage 5	48	NS

CKD = Chronic kidney disease; CRF = chronic renal failure; NS = without giving specific figure.

¹ Old age designated as older than 50 years.

Table 2. Quality assessment of the reviewed cohort studies

Reference	Initial assembly of the cohort	Maintenance of comparable groups	Attrition	Clear definitions of exposure	Assessment of measurements	Adjustment for important potential confounders	Inclusion of all important results	Overall quality
Goto [7]	yes	yes	yes	yes	yes	yes	no	good/fair
Kuhara [18]	yes	yes	yes	yes	yes	yes	yes	good/good
Takeda [20]	yes	yes	yes	yes	yes	yes	yes	good/good
Frimat [13]	yes	yes	yes	yes	yes	yes	yes	good/good
Soleymanian [12]	yes	no	yes	yes	yes	no	no	fair/fair
Yang [21]	yes	yes	yes	yes	yes	yes	yes	good/good
Ferro [22]	yes	yes	yes	yes	yes	yes	no	good/good
Rivera [23]	yes	yes	yes	yes	yes	yes	yes	good/good
Yokoyama [24]	yes	yes	yes	yes	yes	yes	yes	good/good

Results

Identification of Studies and Their Evaluation

Nine studies published before September 30, 2012, were identified as eligible for inclusion (fig. 1) [7, 12, 13, 18, 20–24]. One cross-sectional study and 2 duplicated trials were excluded [19, 25, 26]. The main features of these studies are shown in table 1. The quality assessment of the studies varied from two ‘fair’ to two ‘good’. All 9

cohort studies documented the initial assembly of the cohort, attrition, clear definitions of exposure and assessment of measurements (table 2).

Study Characteristics

Nine studies, 4 of them from Japan, one from France, one from Iran, one from Italy, one from Spain, and one from China, containing a total of 6,543 patients (all of the included patients were older than 15), were selected

Table 3. Basic clinical indicators for the included study populations

Study	Proteinuria	Hematuria	Serum IgA	Renal function	Hypertension
Goto [7]	[+]: 23.1% [++]: 21.4% [+++]: 14.6% Total: 59.1%	70.5%	NS	CKD ≥ 3 : 31.6%	13.1%
Kuhara [18]	20–29 years: 1.8 ± 0.9 g 30–39 years: 2.0 ± 0.9 g 40–49 years: 2.2 ± 0.9 g 50–60 years: 2.0 ± 0.9 g	8.1% (macro-hematuria)	41.0% (≥ 2 SD)	CRF: 61.5%	13.9%
Takeda [20]	0–10 years: 780 ± 280 mg/m ² /day 10–20 years: 220 ± 70 mg/m ² /day 20–30 years: 440 ± 80 mg/m ² /day 30–40 years: 410 ± 90 mg/m ² /day 40–50 years: $1,110 \pm 290$ mg/m ² /day ≥ 50 years: 680 ± 220 mg/m ² /day	25%	38.5%	Ccr: 0–10 years: 112 ± 14 ml/min/1.73 m ² 10–20 years: 114 ± 5 ml/min/1.73 m ² 20–30 years: 100 ± 8 ml/min/1.73 m ² 30–40 years: 90 ± 11 ml/min/1.73 m ² 40–50 years: 64 ± 10 ml/min/1.73 m ² ≥ 50 years: 79 ± 3 ml/min/1.73 m ²	13.7%
Frimat [13]	79.8%	40.3%	<50 years: 3.42 ± 0.1 ≥ 50 years: 4.56 ± 0.4	Ccr: <50 years: 89.0 ± 5.9 ml/min ≥ 50 years: 39.9 ± 6.1 ml/min Scr: <50 years: 148.2 ± 19 μ mol/l ≥ 50 years: 192.4 ± 25 μ mol/l	19.4%
Soleymanian [12]	1,829 (IQR)	NS	NS	Scr: 1.6 mg/dl (median), 1–2.1 mg/dl (IQR)	35.7%
Yang [21]	Older group: 3.4 ± 2.9 g Younger group: 1.8 ± 2.0 g	NS	NS	CKD stage: 3–5: 34.9%	43.4%
Ferro [22]	Mean: 4 ± 4.3 g/day	NS	NS	Average serum creatinine: 2.9 ± 2.8 mg/dl	NS
Rivera [23]	20.7%	NS	NS	CRF: 26.8%	3.1%
Yokoyama [24]	Elderly 1.7 ± 2 g/day Control: 1.1 ± 1.4 g/day	86.4%	NS	Serum creatinine: elderly: 1.40 ± 1.10 mg/dl control: 1.00 ± 0.80 mg/dl Estimated GFR: elderly: 51.4 ± 25.3 ml/min/1.73 m ² Control: 81.1 ± 34.9 ml/min/1.73 m ²	NS

Ccr = Creatinine clearance; GFR = glomerular filtration rate; IQR = interquartile range; NS = without giving specific figures; Scr = serum creatinine; SD = standard deviation.

for the meta-analysis, and there were 6 studies that were conducted using an Asian population. One reason was that the incidence of IgAN in Asia was higher compared with other continents [27]. The longest mean follow-up time was 4.9 years, and the shortest was 23.5 months. Four studies were multi-center studies [7, 13, 23, 24]. The age limit for the older group in the 4 studies was 50 years old [12, 13, 18, 20]. Table 3 lists the basic clinical indicators measured in the included study populations.

Different Characteristics between the Groups in the Included Studies

Many studies showed that hypertension, hematuria, proteinuria, serum IgA level, baseline renal function and serum cholesterol level could impact the prognosis of

IgAN [28, 29]. Therefore, we decided to conduct meta-analyses of other risk factors between the groups (table 4). The incidence of hypertension in the older group was significantly higher than in the younger group. In the incidence data, proteinuria was significantly different between the groups [13, 24]. Moreover, other studies also found proteinuria was significantly different between the groups [18, 20, 21]. The incidence of an elevated serum IgA level was significantly different between the groups, with the older group having a higher level [13, 18, 20]. Moreover, we found that serum cholesterol levels between the groups were significantly different.

Because of the lack of information in the original studies, other factors, such as treatment, blood glucose level, pathological grade and uric acid, were not analyzed here.

Fig. 2. Comparison between old and young IgAN patients in terms of ESRD incidence.

Fig. 3. Age limit used in subgroup analysis.

Fig. 4. Hypertension with or without significant differences used in subgroup analysis.

Table 4. Meta-analyses of hypertension, gross hematuria, proteinuria and serum IgA levels between older group and non-older group

Old vs. young	Studies	p for heterogeneity ¹	Pooled estimate ²	95% CI	p for overall effect
Hypertension	4	0.51	2.24	1.76–2.86	<0.00001
Hematuria	5	0.03	0.86	0.65–1.15	0.31
Proteinuria	2	0.88	1.06	1.01–1.11	0.01
Serum IgA levels	2	0.87	1.60	1.18–2.19	0.003

¹ From χ^2 test.

² Using risk ratio and random effects model.

Three studies found baseline renal function of the older groups was generally worse than that of the younger groups [13, 21, 24], but the time between disease onset and diagnosis in the older group and the younger group was not significantly different, which proves that aging

itself can damage renal function in IgAN patients and adversely impact IgAN prognosis.

Based on the results above, the older and younger groups were significantly different in the incidence of hypertension, proteinuria, serum IgA level, serum cholesterol level and baseline renal function, but the incidence of gross hematuria was not significantly different.

Effect of Aging on IgAN Prognosis

Pooled analyses found that the incidence of ESRD in the older IgAN patients was 1.95 times higher than that in the non-older IgAN patients [RR random effects model 1.95 (1.27–3.01)]. The combined results showed heterogeneity ($p = 0.007$, $I^2 = 62\%$; fig. 2). So, we used a fixed effects model instead of a random effects model, which did not change our initial result. Sensitivity analysis excluding each individual study at a time was similar in the direction and magnitude of the overall estimates. Additionally, the sources of heterogeneity were investigated using subgroup analysis. The age limit of the older group

Fig. 5. Proteinuria with or without statistical significance used in subgroup analysis.

ranged from 50 to 65 years. In the subgroup analysis, we found that the RR of the ‘60- and 65-year-old group’ was 1.80 (95% CI: 1.15–2.83; fig. 3). The RR of the ‘50-year-old group’ subgroup was 2.06 (95% CI: 0.77–5.50), and did not have statistical significance (fig. 3). In the hypertension, proteinuria, serum cholesterol level, baseline renal function and serum IgA level subgroup analyses, none of the RR of ‘significant differences in hypertension (or proteinuria, serum cholesterol level, baseline renal function, serum IgA level) between older group and non-older group’ subgroups had statistical significance. But the RR of the ‘no mention or no significant differences’ subgroups ranged from 1.70 to 2.27 (fig. 4–8). This may indicate that the age limit and those traditional risk factors of IgAN were the sources of heterogeneity between studies. Controlling for those factors when comparing the groups may be good for exposing the true impact of aging on IgAN. In addition, we conducted a funnel plot analysis for the included studies (fig. 9).

In the study location subgroup analysis, the RR (2.56) of the Asian countries was much higher than the RR (1.11) of the European countries. The p value for subgroup differences was 0.02 ($p < 0.10$; fig. 10).

Discussion

IgAN often occurs in young people, but there is still controversy whether aging could increase the risk of IgAN progressing to ESRD. To ascertain the true impact of aging on the incidence of IgAN patients developing ESRD, we conducted a systematic review and meta-analysis. We found that aging could significantly increase the incidence of IgAN patients developing ESRD, and traditional risk factors (hypertension, proteinuria, serum cholesterol, serum IgA level and baseline renal function) of IgAN did not change the results.

The older people had a higher incidence of underlying diseases and more severe symptoms of IgAN, and these

Fig. 6. Serum cholesterol with or without statistical significance used in subgroup analysis.

underlying diseases and symptoms were often the risk factors of IgAN. To confirm these confounding factors, we conducted a cross-sectional analysis. The results showed that there were significant differences between the groups for hypertension, proteinuria, serum IgA level, serum cholesterol level, baseline renal function, and the older group was generally worse than the younger group.

Then, we conducted a longitudinal meta-analysis. Pooled analyses of all of the studies found that the incidence of ESRD in the older IgAN patients was 1.95 times higher than in the non-older IgAN patients. The results showed heterogeneity. In the subgroup analyses, we found that the age limit and hypertension, proteinuria, serum IgA level, serum cholesterol level, baseline renal function may be the sources of heterogeneity between studies. In those subgroup analyses, the ‘no mention or no significant difference’ subgroups, due to the relative elimination of the impact of those factors, revealed the real role of aging itself (RR ranged from 1.70 to 2.27).

There were 4 studies that found a positive, significant correlation between aging and the incidence of ESRD among the IgAN patients. All of them were from Asian countries. And our subgroup analysis of the study location found that the RR (2.56) of the Asian countries was much higher than the RR (1.11) of the European countries. So, we could conclude that the risk of IgAN progression to ESRD of the older patients in Asia was higher than that of the older patients in Europe.

The reason may be due to genetic differences between races. It has been reported that, consistent with the higher prevalence of IgAN in Asians, the frequency of protective alleles was significantly lower in the Chinese cohort compared with the European group [30]. The frequency of the risk alleles was highest in East Asians, intermediate in Europeans and lowest in African-Americans [30, 31]. They also examined global geographic variation in the genetic risk for IgAN by applying the newly refined IgAN risk score in 6,319 healthy individuals across 85 worldwide populations. The result showed

Fig. 7. Baseline renal function with or without statistical significance used in subgroup analysis.

that the mean standardized risk score was lowest for Africans, intermediate for Middle Easterners and Europeans, and highest for East Asians and Native Americans [31]. The analysis of the United States Renal Data System dataset confirmed that the percentage of ESRD attributable to IgAN was 5-fold greater for Caucasian and 15-fold greater for Asian Americans compared to African-Americans [31].

The major mechanism is the impact of aging itself, which includes functional and structural changes, such as a decline in renal blood flow, age-related nephrosclerosis, systemic and local renal inflammation, and diminished renal adaptive capacity. With increasing age, renal blood flow progressively decreases and renal vascular resistance increases [32–34]. Decreased renal blood flow, renal vascular resistance and narrowing in the arteries and arterioles all result in nephrosclerosis. Nephrosclerosis is known to occur with aging based on autopsy series [35]. The incidence of glomerular sclerosis was <5% in those under the age of 40; however, by age 80, the incidence increased to 30% [34, 36]. Our includ-

ed studies [7, 21] clearly showed that the incidence of glomerulosclerosis in the older group was significantly higher than in the younger group. Three studies also confirmed that the incidence of tubulointerstitial fibrosis in the older group was significantly higher than in the younger group [18, 20, 21]. The same trend was seen for arteriolosclerosis [20, 21]. Glomerulosclerosis, tubular atrophy, interstitial inflammation and hyaline arteriosclerosis correlated with progression in all IgAN patients and also in IgAN patients with a normal initial serum creatinine [37]. Physiological aging is associated with a chronic subclinical systemic inflammation state, termed inflammaging [38]. Interestingly, Frimat et al. [13] found that only endarteritis was significantly more common in the older patients. During inflammaging, inflammatory markers increase [39], and inflammaging may be associated with accelerated age-related loss of renal function and IgAN progression [39, 40]. Meanwhile, with the nephrosclerosis incidence increasing and the reduction in renal autacoid modulatory capacity, particularly at the vasodilating prostaglandin level, in

Fig. 8. Serum IgA with or without statistical significance used in subgroup analysis.

Fig. 9. Funnel plot of 9 trials on the effect of aging on the progression of IgAN to ESRD.

aging kidneys, the functional reserve of the aging nephron decreases.

One of the advantages of this meta-analysis is an adequate follow-up time for the included studies, and the average follow-up time was greater than or almost 2 years (24 months). The first limitation is that we may not thoroughly separate the independent effects of covariates from aging without getting raw data. The second limitation is that there is heterogeneity. There was heterogeneity in the source populations, sample sizes and underlying diseases between the groups (older and younger groups). Specifically, the underlying diseases were quite different. However, the overall validity of our conclusion was supported by the highly significant association between aging and a high risk of IgAN progressing to ESRD. Seven of the nine correlation coefficients were positive in the direction of progressing to ESRD in the older groups. Both the random effects and fixed effects models confirmed the validity of the results. Sensitivity analysis excluding each indi-

Fig. 10. Study location used in subgroup analysis.

vidual study at a time was similar in the direction and magnitude of the overall estimates.

In summary, our meta-analysis found that old age is a real risk factor for IgAN progression to ESRD. Future studies need to examine the strength of the effect of aging leading the progression to ESRD in IgAN patients and control for other relevant factors to further clarify the impact of aging. Because a randomized trial is impossible, a cohort study design is best and will allow for the identification of incident cases, establishment of temporality, and the ability to make powerful, etiologic inferences.

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Disclosure Statement

There are no conflicts of interest to declare.

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