Medical Care Costs Associated With Progression of Diabetic Nephropathy

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OBJECTIVE—To estimate the direct medical costs of hypertensive patients with type 2 diabetes by the level of proteinuria and to evaluate the differences between patients whose nephropathy did and did not progress.

RESEARCH DESIGN AND METHODS—We identified 7,758 patients with diabetes and hypertension who had a urine albumin-to-creatinine ratio (UACR) during 2001–2003 and at least one follow-up UACR 3–5 years later. Patients were followed for up to 8 years for progression of nephropathy, which was defined by increasing levels of proteinuria: normoalbuminuria (UACR <30 mg/g), microalbuminuria (30–299 mg/g), macroalbuminuria (≥300 mg/g), and end-stage renal disease (dialysis or transplant). We calculated annualized inpatient, outpatient, pharmaceutical, and total medical costs incurred by patients after the baseline measure through 2008, comparing patients who did and did not progress to a higher nephropathy stage. We also compared pre- and postprogression costs among those whose nephropathy progressed.

RESULTS—Patients with normoalbuminuria who progressed to microalbuminuria experienced an annualized change in baseline costs that was $396 higher ($P < 0.001$) than those who maintained normal albuminuria ($902 vs. $506). Among those with microalbuminuria, progression was significantly associated with a $747 difference ($P < 0.001$) in annualized change in outpatient costs compared with no progression ($1,056 vs. $309). Among patients who progressed, costs were 37% higher following progression from normoalbuminuria to microalbuminuria ($10,188 vs. $7,424; $P < 0.001$), and 41% higher following progression from microalbuminuria to macroalbuminuria ($12,371 vs. $8,753; $P < 0.001$).

CONCLUSIONS—Progression of nephropathy was strongly associated with higher subsequent medical care costs in hypertensive patients with diabetes. Greater prevention efforts may reduce the substantial economic burden of diabetic nephropathy.

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Complications add greatly to the already substantial costs of medical care for patients with type 2 diabetes, the majority of whom are hypertensive (1). As the leading cause of end-stage renal disease (ESRD), which ultimately requires kidney dialysis or transplant, late-stage diabetic nephropathy is the single largest contributor to these additional costs (2,3). Clearly, avoidance of ESRD would have enormous cost-savings implications. Using a mathematical model and data from the U.S. Renal Data System, Trivedi et al. (4) estimated that slowing the progression of chronic renal failure by 20% would save approximately $39 billion over 10 years. On an individual basis, the Reduction of End Points in Type 2 Diabetes With Angiotensin II Antagonist Losartan (RENAAL) study showed that treatment with losartan reduced the number of ESRD days by 33.6 per patient over 3.5 years, resulting in a net savings of $3,522 per patient (5). Although the RENAAL study observed reduced costs over all levels of baseline albuminuria (6), macroalbuminuria (urinary albumin-to-creatinine ratio [UACR] ≥300 mg/g) was a study entry criterion, and the basis for the cost reductions was estimated as a function of ESRD-free days. To our knowledge, no study to date has estimated the medical costs associated with earlier stages of diabetic nephropathy or the progression from normoalbuminuria to microalbuminuria to macroalbuminuria. Therefore, we undertook the current study to estimate, in a population-based sample of managed care members, the medical costs associated with baseline stages of diabetic nephropathy, and to compare medical costs of patients who did and did not progress from normoalbuminuria, microalbuminuria, or macroalbuminuria to a more severe stage of nephropathy.

RESEARCH DESIGN AND METHODS

Kaiser Permanente Northwest (KPNW) is a health maintenance organization that provides comprehensive medical care to approximately 475,000 individuals in the 75-mile radius around Portland, Oregon. KPNW maintains complete electronic medical records that include clinician-coded diagnoses, laboratory results, and pharmacy dispensing data. An electronic diabetes registry with entrance criteria including an inpatient or outpatient diagnosis of diabetes, receipt of an antihyperglycemic drug, or a fasting glucose value >125 mg/dl, assists clinicians to provide guideline-consistent medical care.

For this study, we identified all diabetes registrants with hypertension (chart diagnosis, use of antihypertensive medication, or systolic blood pressure >130 mmHg) who had a baseline UACR measured in the calendar years 2001–2003, were health plan members at least 6 months prior to the baseline UACR measure, and who had at least one subsequent UACR 3–5 years later (n = 7,758). Consistent with American Diabetes Association (ADA) guidelines, KPNW guidelines recommend annual assessment of urine albumin excretion for patients with type 2 diabetes (7). We classified patients into three baseline stages of diabetic nephropathy:

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normoalbuminuria (<30 mg/g), microalbuminuria (30–299 mg/g), and macroalbuminuria (≥300 mg/g). We examined all subsequent UACR test results for evidence of progression to a higher stage of nephropathy and also examined the electronic medical records for evidence of ESRD (dialysis or transplant). Documented progression was defined as having occurred on the date that the first UACR in a higher stage was recorded. Patients were censored if they *1*) died, *2*) left the health plan, or *3*) reached the end of the study observation period on 31 December 2008—whichever came first. We independently analyzed each patient cohort defined by baseline stage of nephropathy.

The main outcome of interest was total direct medical care costs incurred over the entire follow-up period. We calculated inpatient, outpatient, pharmacy, and total direct medical costs incurred over each patient's entire follow-up period. To account for differential follow-up times, we annualized the costs by summing them, dividing by individual months of health plan eligibility, and multiplying by 12 (months).

We examined the costs associated with progression of diabetic nephropathy in two ways. First, we subtracted adjusted baseline costs from adjusted annualized follow-up costs and compared the results for individuals who progressed from their baseline nephropathy stage to a higher stage with those who did not progress. Second, we further examined annualized costs among only those patients who progressed, comparing costs prior to progression with costs incurred following progression.

Costing methods

We based our costing method for this study on procedures developed and validated for research and risk adjustment purposes by the Kaiser Permanente Center for Health Research (8). For outpatient costs, this method creates standard costs for office visits by specialty/department and type of clinician (medical doctor vs. physician assistant/nurse practitioner). The number of visits per department per clinician type was then multiplied by the appropriate unit cost. Pharmaceutical costs were calculated based on retail prices. Inpatient costs were based on assigned diagnosis-related group codes for the primary reason for hospitalization. The average daily cost per diagnosis-related group was then multiplied by the length of stay. Costs for medical services incurred at facilities not owned by KPNW were based on the amount paid by KPNW to the nonplan provider. These methods ensure that while the costs reported herein may be specific to KPNW, they approximate the charges a nonmember would be billed if these same services were purchased from KPNW. All costs were adjusted to 2009 U.S. dollars using the medical or pharmaceutical component of the Consumer Price Index.

Statistical analyses

Medical costs are not normally distributed. Although log transformation can be used to normalize the data, we chose to use simple ordinary least squares regression to estimate the independent contribution of nephropathy progression on untransformed annualized costs. Prior research in this setting demonstrated that ordinary least squares regression predicts costs at least as well as more sophisticated techniques (2), and others have argued that the sample mean performs well and is unlikely to lead to inappropriate conclusions (9). Therefore, for ease of interpretation, we calculated the difference in adjusted mean baseline and adjusted mean annualized follow-up costs. We made the adjustments for age; sex; African American race; duration of diabetes; BMI; blood pressure; A1C; LDL cholesterol; presence of comorbidities including cardiovascular disease, stroke, heart failure, neuropathy, retinopathy, and depression; and use of ACE inhibitors, angiotensin receptor blockers (ARBs), other antihypertensive agents, metformin, sulfonylureas, insulin, or statins with the LSMEANS options in PROC GLM (SAS version 8.2; SAS Institute, Cary, NC).

RESULTS—Of the 7,758 study subjects, 67.3% (n = 5,223) had normoalbuminuria, 27.5% (n = 2,136) had microalbuminuria, and 5.2% (n = 399) had macroalbuminuria at baseline (Table 1). The groups were statistically significantly different across a number of demographic and clinical characteristics, comorbidities, and pharmaceutical use. Unadjusted baseline costs for the three patient cohorts are shown in Table 2. Patients with normoalbuminuria had significantly lower outpatient and total costs than those with micro- or macroalbuminuria ($P < 0.001$). Additional detail comparing baseline demographic and clinical characteristics, comorbidities, and pharmaceutical use at baseline among patients in each cohort who did and did not progress is displayed in Supplementary Table 1, and comorbidities and pharmaceutical use at follow-up are shown in Supplementary Table 2.

Over a mean follow-up of 4.9 ± 2.2 years, 51.2% (n = 2,676) of patients with normoalbuminuria at baseline progressed to a higher stage of nephropathy. As shown in Table 3, these patients had mean adjusted baseline costs that were $788 higher than those who did not progress ($P < 0.001$). Although adjusted annualized costs incurred during follow-up increase from baseline for those with normoalbuminuria who progressed ($902) as well as for those who did not progress ($506), the change was $396 greater ($P < 0.001$) among those who progressed. Among those with microalbuminuria at baseline, 30.9% (n = 659) progressed to macroalbuminuria over a mean follow-up of 5.7 ± 2.0 years. Mean adjusted total costs for those who progressed were not significantly different at baseline, nor was change in adjusted total costs at follow-up. However, change in outpatient cost from baseline to follow-up was $747 ($P < 0.001$) greater among those who progressed to macroalbuminuria. Only 5.0% (n = 20) of patients with macroalbuminuria progressed to ESRD over a mean follow-up of 6.5 ± 1.1 years. Baseline costs were not statistically significantly different, but change in costs during follow-up was much greater among those who progressed ($23,798; $P < 0.001$). Much of this was due to higher outpatient costs resulting from dialysis ($17,085; $P < 0.001$), but change in inpatient costs were also significantly greater ($5,356; $P < 0.001$).

Table 4 shows the medical costs for patients who progressed to higher stages of nephropathy prior to and following progression. Among patients with baseline normoalbuminuria who progressed, annualized total costs were $2,764 higher after progression than before ($P < 0.001$). Total annualized costs were $3,618 higher after progression among those with microalbuminuria ($P < 0.001$), and $56,745 higher after progression among patients with macroalbuminuria ($P < 0.001$).

CONCLUSIONS—The growing economic burden of hypertension, type 2 diabetes, and ESRD has been well documented. Although prior studies acknowledge chronic kidney disease as one of the major contributors to that burden, the definitions of renal disease are typically ill defined (1,3,10). In this retrospective cohort study of 7,758 patients with diabetes and hypertension, we used the stages of diabetic nephropathy defined by the ADA to benchmark medical care

Table 1—*Baseline demographic and clinical characteristics of study sample by baseline stage of diabetic nephropathy*

	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
n	5,223	2,136	399
Age (years)	60.6 (11.0)	60.7 (11.9)	61.7 (11.8)
Men (%)*	49.1	54.0	49.9
Current smoker (%)*	9.5	13.5	13.8
African American (%)	3.0	2.7	3.5
Diabetes duration*†‡	4.3 (4.0)	5.1 (4.3)	6.1 (4.9)
BMI	34.5 (7.2)	34.5 (7.3)	34.6 (7.5)
Systolic BP*†‡	137 (13)	140 (14)	146 (17)
Diastolic BP*†	79 (8)	80 (9)	81 (9)
A1C*†	7.6% (1.6)	8.2% (1.9)	8.3% (1.9)
LDL cholesterol	111 (31)	110 (35)	110 (38)
eGFR	89 (26)	89 (34)	86 (47)
Cardiovascular disease (%)*†	19.4	22.9	27.3
Stroke (%)*†	6.2	9.6	13.0
Heart failure (%)*†‡	6.0	10.3	15.5
Neuropathy (%)*†	17.3	21.2	25.1
Retinopathy (%)*†‡	5.8	10.7	23.1
Depression (%)	23.1	20.9	24.1
ACEI or ARB (%)*†‡	50.5	65.7	75.4
Other antihtn Rx (%)*†	49.5	52.9	63.9
Metformin (%)*	35.6	42.0	40.6
Sulfonylurea (%)*†	44.2	51.4	52.9
Insulin (%)*†	10.9	17.4	22.1
Statin (%)	32.0	33.0	31.6

Data are means (SD) or percentages. ACEI, ACE inhibitor; antihtn Rx, other antihypertensives including diuretics, β-blockers, calcium channel blockers, and vasodilators; BP, blood pressure; eGFR, estimated glomerular filtration rate. *Normoalbuminuria differs from microalbuminuria, $P < 0.001$. †Normoalbuminuria differs from macroalbuminuria, $P < 0.001$. ‡Microalbuminuria differs from macroalbuminuria, $P < 0.001$.

costs of hypertensive diabetic patients and quantified the increasingly higher costs observed across these stages. In addition, whereas previous studies have estimated costs of *prevalent* nephropathy (2,3), we used our longitudinal data to demonstrate that the medical costs associated with the *progression* of diabetic nephropathy are substantial even among patients progressing from normoalbuminuria to microalbuminuria, one of the earliest indicators of kidney damage. To our knowledge, ours is the first study to evaluate costs of progression of nephropathy and suggests that preventing progression may result in significant cost savings.

The higher medical costs associated with progression of diabetic nephropathy that we report were present for all aspects of health care (inpatient and outpatient services as well as pharmaceuticals). Thus, it is unlikely that the elevated costs can be attributed to a single event. Albuminuria is known to increase the risk of cardiovascular disease (11), heart failure (12), and retinopathy (13), all of which can significantly contribute to medical costs. We controlled for the presence of these and other comorbidities observed at baseline as well as a large number of other demographic and clinical characteristics, but doing so had very little effect on the cost estimates and no effect on the relative cost differences between patients who did and did not progress. Nevertheless, the greater incidence of other diabetes complications documented during follow-up could explain some of the cost increases we attribute to progression of nephropathy. Progression of diabetic nephropathy is unlikely to occur in isolation and, in fact, is associated with other complications of diabetes. Thus, attempts to isolate the cost of progression from other complications of diabetes and hypertension could result in unrealistic estimates.

In comparing change in costs over time incurred by patients who did and did not progress (Table 3), the annualized follow-up costs among those who progressed comingles costs that occurred prior to progression with those that occurred following progression. Thus, the costs associated with progression in that comparison may underestimate the true costs of progression. Consistent with that hypothesis, our second analysis comparing costs before and after progression only among those who progressed (Table 4) demonstrates that costs associated with progression were higher than the comparison of those who did and did not progress would suggest. For example, among patients with normoalbuminuria at baseline, costs associated with progression were $396 higher when comparing those who did and did not progress, but $2,764 higher when comparing costs pre- and postprogression. Similarly, among patients with baseline microalbuminuria, costs were $282 greater when comparing those who did and did not progress, but $3,618 greater when comparing costs pre- and postprogression. These larger differences in the second analyses were found despite the fact that follow-up costs incurred prior to progression among those who progressed were approximately $500 to $700 higher than costs incurred by those who did not progress. It appears, therefore, that some of the morbidity that drives costs associated with progression was already present in patients who were destined to progress. Indeed, baseline costs were significantly higher ($788) among patients with normal albuminuria who later progressed compared with those who did not progress, with a similar albeit not statistically significant differential between patients with microalbuminuria who did and did not progress ($736). Costs associated with progression from macroalbuminuria to ESRD were substantial, but should be interpreted with caution given the small number of patients who developed ESRD ($n = 20$) in our study.

Current guidelines recommend optimizing glucose and blood pressure control to reduce the risk or slow the progression of diabetic nephropathy (7). More specifically, clinical trials have shown that treatment with renin-angiotensin-aldosterone system inhibitors such as angiotensin-converting enzyme inhibitors and ARBs can delay progression of renal disease in hypertensive patients with type 2 diabetes (14–16). Renoprotective effects of direct renin inhibitors have also been reported (17). Unfortunately, use of these medications in the current study was suboptimal as only 51, 66 and 75% of those with normoalbuminuria, microalbuminuria and macroalbuminuria were taking them at baseline. In addition, recent findings from the ACCORD and ADVANCE studies have shown that intensive glycemic control can delay the onset of albuminuria

Table 2—*Unadjusted baseline costs by stage of diabetic nephropathy*

	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
n	5,223	2,136	399
Inpatient			
Mean	$1,201	$1,558	$1,428
SD	$5,069	$7,016	$4,841
Median	$0	$0	$0
Interquartile range	$0	$0	$0
% with cost	11.7	12.6	15.5
Outpatient			
Mean*†	$2,921	$3,331	$3,878
SD	$3,116	$3,823	$3,927
Median	$1,993	$2,280	$2,805
Interquartile range	$1,107–3,626	$1,224–4,083	$1,603–5,197
% with cost	99.8	99.9	99.8
Pharmacy			
Mean†	$2,333	$2,510	$2,781
SD	$2,658	$2,515	$2,163
Median	$1,711	$1,979	$2,296
Interquartile range	$823–3,014	$997–3,282	$1,223–3,843
% with cost	99.0	99.2	98.3
Total			
Mean*†	$6,455	$7,398	$8,087
SD	$7,754	$9,736	$8,048
Median	$4,057	$4,605	$5,355
Interquartile range	$2,427–7,268	$2,813–8,156	$3,334–9,842
% with cost	100.0	100.0	100.0

*Normoalbuminuria differs from microalbuminuria, $P < 0.001$. †Normoalbuminuria differs from macroalbuminuria, $P < 0.001$.

(18,19). Because we found that progression of diabetic nephropathy was associated with substantially higher medical costs, it is likely that intensifying antihypertensive and antihyperglycemic therapies that prevent progression would result in cost savings.

As an observational study, our main limitation is that while we can report strong and significant associations between the progression of diabetic nephropathy and higher medical care costs, we cannot conclude that the association is causal. Another important limitation is that we did not attempt to confirm progression to higher stages of nephropathy beyond a single higher UACR measure. This may have resulted in misclassifying some patients as having progressed despite having a single transient elevated UACR. However, because of the strong association between progression and subsequent costs observed in this study, any misclassifications would have likely diluted the association, resulting in conservative estimates. Our study sample was limited to patients with type 2 diabetes and hypertension who had UACR tests on multiple occasions, which may limit the generalizability. Although KPNW guidelines recommend annual urine albumin testing for patients with type 2 diabetes, it is possible that those who are less healthy and more frequently access medical services were over-represented in our sample. This could lead to a systematic overestimation of costs. On the other hand, if healthier patients who were less likely to progress were under-represented among those who did not progress, then the cost differences we report could be underestimated. Finally, our findings may not generalize to uninsured populations.

In conclusion, we found that medical costs associated with diabetic nephropathy increased with the severity of the baseline stage of nephropathy. Further,

Table 3—*Adjusted baseline costs and change from baseline in adjusted annual costs incurred during follow-up by baseline stage of diabetic nephropathy and progression of diabetic nephropathy*

		Mean adjusted baseline	Increase (decrease) from baseline in mean adjusted annual follow-up medical costs			
	n	total costs	Total	Inpatient	Outpatient	Pharmaceuticals
Normoalbuminuria						
Progressed	2,676	$7,134	$902	$59	$761	$82
Did not progress	2,547	$6,346	$506	$209	$266	$31
Mean cost differential		$788	$396	($149)	$495	$51
P value		<0.001	<0.001	<0.001	<0.001	0.095
Microalbuminuria						
Progressed	2,676	$8,275	$1,138	$331	$1,056	($249)
Did not progress	2,547	$7,539	$856	$515	$309	$31
Mean cost differential		$736	$282	($184)	$747	($280)
P value		0.148	0.16	0.071	<0.001	<0.001
Macroalbuminuria						
Progressed	2,676	$7,085	$26,302	$6,181	$18,531	$1,590
Did not progress	2,547	$8,575	$2,504	$825	$1,446	$233
Mean cost differential		($1,490)	$23,798	$5,356	$17,085	$1,357
P value		0.456	<0.001	<0.001	<0.001	<0.001

Note: Baseline and follow-up costs are adjusted for the demographic and clinical characteristics displayed in Table 1.

Table 4—*Follow-up costs incurred prior to and following progression of diabetic nephropathy among patients who progressed*

	Years of observation	Mean annualized follow-up medical costs			
		Inpatient	Outpatient	Pharmaceuticals	Total
Normoalbuminuria (n = 2,676)					
Prior to progression	3.4 ± 1.9	$1,441	$3,340	$2,643	$7,424
After progression	3.3 ± 2.0	$2,674	$4,628	$2,886	$10,188
Cost of progression	—	$1,233	$1,288	$243	$2,764
P value	0.893	<0.001	<0.001	<0.001	<0.001
Microalbuminuria (n = 659)					
Prior to progression	3.5 ± 2.0	$1,901	$4,200	$2,652	$8,753
After progression	3.3 ± 2.1	$3,687	$5,902	$2,782	$12,371
Cost of progression	—	$1,786	$1,702	$130	$3,618
P value	0.168	0.064	<0.001	0.003	<0.001
Macroalbuminuria (n = 20)					
Prior to progression	5.6 ± 1.7	$6,564	$15,120	$4,067	$25,751
After progression	1.3 ± 1.4	$12,994	$65,152	$4,350	$82,496
Cost of progression	—	$6,430	$50,032	$283	$56,745
P value	<0.001	0.008	<0.001	0.351	<0.001

the progression of diabetic nephropathy from all baseline stages to a more severe stage was strongly associated with higher medical care costs. While there is little doubt that preventing kidney failure will reduce medical costs, our study also suggests that preventing progression from normo- to microalbuminuria and micro- to macroalbuminuria may reduce the economic burden of diabetic nephropathy patients with hypertension and type 2 diabetes.

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G.A.N., S.V., and H.L. contributed to the study conception, design, and interpretation of results. G.A.N. researched the data and developed the first draft of the manuscript. S.V. and H.L. contributed to the discussion and reviewed and edited the manuscript. The final draft for submission was approved by all authors.

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