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CASE STUDY

Proteinuria as a Mortality Risk

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This case report examines the factors involved in the mortality risk of low-grade proteinuria. Proteinuria and microalbuminuria are defined and the use of the protein-creatinine ratio is discussed. Studies from the medical literature suggest that albuminuria complements risk selection in diabetics and nondiabetics and may parallel or adversely modify other cardiovascular risk factors.

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A 47-year-old male, one of your agents, applies for life insurance. He takes a calcium-channel blocker for mild hypertension and is otherwise in good health. He is 5'11'' tall and weighs 246 lbs. His blood pressure was 132/88. His screening laboratory tests show the following results:

Glucose	81 mg/dL
BUN	15 mg/dL
Creatinine	1.2 mg/dL
Protein	7.4 g/dL
Albumin	4.3 g/dL
Cholesterol	253 mg/dL
HDL	37 g/dL
LDL	148 mg/dL
Trig	362 mg/dL
HIV	negative

Table 1 summarizes urinalysis findings. The applicant demonstrates constant proteinuria. The underwriter wants to rate the applicant substandard, and the agent is questioning the action. How would you rate this applicant?

The purpose of this article is to review the etiology and long-term mortality considerations of mild constant proteinuria with normal renal function.

ETIOLOGY OF PROTEINURIA

What Allows Proteinuria to Occur?

As blood flows through the nephron, the integrity of the glomerular capillary wall prevents macromolecules and cellular elements from passing into the filtrate. Disruptions in this wall allow various degrees of proteinuria and hematuria to occur. The wall has 3 components, including the fenestrated endothelial cells, the glomerular basement membrane and the epithelial cell foot processes. Disruptions in these components can include actual gaps in the membrane (size selectivity), as well as ionic charge abnormalities (charge selectivity). Albumin is both a large molecule and an anion and is blocked from filtration by a concerted action of the glomerular capillary wall elements.

Table 1. Urinalysis Results for Applicant

Urinalyses:	Application	First Repeat	Second Repeat	Normal Ranges
Glucose screen	negative	—	—	negative
Protein (mg/dL)	87	58	63	0–30
Reflex microalbumin (mg/dL)	69.3	—	—	<3
WBCs (per hpf)	0	0	0	0–9
RBCs (per hpf)	0	0	0	0–4
Urine creatinine (mg/dL)	186	193	164	27–260
Protein/creatinine ratio	0.47	0.30	0.38	0–0.20

How is Urine Protein Measured?

Urinary dipsticks measure albumin but are relatively insensitive and inaccurate. They generally detect levels of protein in the range of 300–500 mg albumin/24 hours and up, with only gross gradations in the amount of protein measured. Reference labs used in insurance medicine perform colorimetric testing of urine samples to determine protein levels. In this test, albumin is the primary protein detected, but other proteins can also be found. These primarily include proteins from cellular elements in the genitourinary tract. A more exact test for albumin alone can be performed and is referred to as a microalbumin test, since it is precise enough to measure small amounts of albumin.

The amount of protein excreted per day is important, and the most accurate way to determine the amount is by 24-hour urine collection. This dampens the effect of diurnal variation and differences in urine concentration. Since this is impractical for insurance testing, the urine protein/creatinine ratio is used to estimate a comparable figure.[1] The use of the protein/creatinine ratio has been validated in clinical studies. A fairly accurate estimate of 24-hour protein excretion can be made using the protein/creatinine ratio and is expressed directly, eg, a ratio of 2.1 (for instance, 96 mg/dL protein with a urine creatinine of 46 mg/dL) represents approximately 2.1 grams (2100 mg) of protein/ $1.73m^2$ body surface area in 24 hours. The ratio has some broad limitations, such as being underestimated in very muscular individuals (more creatinine excreted than normals) and overestimated in very thin or cachectic individuals (less creatinine excreted). Normal individuals excrete less than 20 mg of albumin per day. Levels of albumin excretion in the range of 30 to 300 mg/24 hours are referred to as microalbuminuria, and a level over 300 mg/day constitutes gross albuminuria. Microalbuminuria implies early risks of renal damage and cardiovascular disease especially in the presence of diabetes or hyperinsulinemia, while gross albuminuria implies frank glomerular damage.

Confounders of proteinuria include excess protein excretion during fever or heavy exercise in normal subjects and orthostatic proteinuria primarily in adolescents. These can be mitigated by repeat urine studies performed in the morning, which would be normal after periods without fever, exercise or the upright position, respectively.

CAUSES OF PROTEINURIA

Frequent causes of proteinuria are listed in Table 2. Various studies have evaluated the outcomes and causes of proteinuria, ranging from the prevalence of glomerulopathies to determinants of glomerular blood flow (effects of angiotensin and norepinephrine). In cases of mild proteinuria, cases of IgA nephropathy or focal or membranous glomerulosclerosis were found in about half of children taken to biopsy in a study of isolated mild proteinuria.[2] Similarly in adults biopsied for moderate proteinuria, IgA nephropathy was found in 68%, and other forms of glomerulopathy or minimal change disease

Table 2. Frequent Causes of Proteinuria

- IgA nephropathy (usually with red cells in urine)
- Postural proteinuria (associated with postural release of angiotensin II/norepinephrine and with left renal vein entrapment, an anatomic variant)
- Hypertensive nephrosclerosis
- Diabetic nephropathy
- Primary renal disease (glomerulonephritis)
- Vascular endothelial damage
- Chronic pyelonephritis
- Ureteral reflux
- Polycystic kidney disease
- Congestive heart failure (mediated by excess angiotensin II and norepinephrine)

were found in 26%.[3] One must keep in mind that no studies have reviewed biopsies performed on subjects with microalbumin range proteinuria. The vast majority of those presenting with proteinuria had good renal outcomes over a long follow-up period.

Other states affect blood flow within the nephron, allowing protein to escape the glomerulus. For instance, in heart failure, postural changes or vigorous exercise, the release of angiotensin II, and norepinephrine change the permeability of the glomerulus and allow albumin to be excreted. Other causes include abnormalities in glomerular dynamics from reflux nephropathy and polycystic kidney disease.

Finally, endothelial damage affects the permeability of the glomerulus, and it is this endothelial damage that associates various levels of albuminuria with cardiovascular diseases, such as myocardial infarction and stroke. This is one of the most intriguing aspects of proteinuria and may be one of the primary reasons for rating a person who has persistent proteinuria but no history of diabetes or hypertension. An approach to the differential diagnosis of proteinuria is outlined in Table 3.

Two studies illustrate the value of urinary protein measurement in cardiovascular risk assessment, the HOPE trial and the LIFE study. In the HOPE (Heart Outcomes Prevention Evaluation) trial with a median 4.5 year follow-up, 9000 subjects with other cardiovascular risks were screened for microalbuminuria. Microalbuminuria was associated with an increased risk of myocardial infarction, stroke or cardiovascular death, with a 1.97 relative risk ratio in diabetics and a 1.61 relative risk ratio in nondiabetics. The risk increased with increasing amounts of microalbuminuria.[4] Similarly, the LIFE (Losartan Intervention for Endpoint Reduction) study used the albumin/creatinine ratio to evaluate over 7000 hypertensive subjects without diabetes and found that for every 10-fold increase in ratio there was an increase in hazard ratio for cardiovascular death of 97%.[5]

More applicable to the life insurance industry, a cohort of healthy post-menopausal women aged 52–67 revealed that women in the highest quintile of urinary albumin levels sustained an approximate 4-fold increase in cardiovascular death compared to those with no albuminuria.[6] In hypertensive nondiabetic patients with microalbuminuria, the level of microalbuminuria correlated individually with levels of von Willebrand Factor (vWF) antigen.[7] vWF is associated with vascular thrombosis, so the thought here is that the microalbuminuria is a signal from the kidney of increased cardiac risk. It may also be considered a surrogate for the presence of other cardiovascular risk factors, as microalbuminuria correlates in hypertensive nondiabetics with higher blood pressures, lower HDL, and higher total cholesterol levels. Yet, another study linked hyperhomocysteinemia with microalbuminuria. [8]

Thus, microalbuminuria may be considered to be a nonspecific message via the kidney that vascular function is impaired and similarly that increased cardiovascular risk is present.

HYPERINSULINEMIA AND DIABETES

In a population of elderly nondiabetics, the presence of microalbuminuria with hyperinsulinemia combined to result in a dramatic coronary event and mortality risk, much greater than either component alone.[9] A sub-

Table 3. Major Causes of and Approach to Nonnephretic Proteinuria

Type	Frequency in Office Practice	Pathophysiology
Exclude first: Transient proteinuria secondary to stress such as fever or heavy exercise	4% of men 7% of women	Possibly transient angiotensin II or norepinephrine-mediated alterations in glomerular permeability
Orthostatic proteinuria	2% to 5% of adolescents Uncommon over age 30	Not clear. Possibly neurohumoral or altered glomerular hemodynamics
Hemodynamic causes:		
Congestive heart failure; renovascular hypertension		Possibly angiotensin II and, in heart failure, norepinephrine-mediated increase in glomerular permeability
Glomerular proteinuria:		
	Major cause when above disorders excluded; responsible for all causes of nephrotic syndrome	Abnormalities in glomerular capillary wall
Glomerular diseases, Diabetic nephropathy	Increasing frequency with prolonged duration of diabetes	
Reflux nephropathy and other tubulointerstitial diseases		Secondary glomerular injury due to hemodynamic and structural changes resulting from nephron loss.
Overflow proteinuria:		
Multiple myeloma with cast nephropathy	Uncommon	Overproduction of light chains, leading to tubular obstruction; suspect if acute renal failure, bland urine sediment, negative dipstick for protein, and positive sulfosalicylic acid test, indicating nonalbumin proteinuria

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set evaluation of the DCCT (Diabetes Control and Complications Trial) correlated microalbuminuria with high-risk lipoprotein particles, and yet another study linked microalbuminuria with elevated homocysteine levels.[10]

Some association in diabetics has also been made between microalbuminuria and endothelial lipid deposition from hyperglycemia-induced changes in the extracellular matrix. Diabetics with microalbuminuria within 10 years of diagnosis are more likely to progress to frank nephropathy. Other associations in diabetics with microalbuminuria include:

- Higher HbA1c, especially prominent in levels >8%
- Higher blood pressures
- Once microalbuminuria presents, a large percentage of diabetics will progress to gross proteinuria within 4–5 years

TREATMENT EFFECTS OF PROTEINURIA

Regression of proteinuria can be achieved with lowering of HbA1c levels, reduction in cholesterol or triglyceride levels and reduction in blood pressure with or without angiotensin II converting enzyme (ACE) inhibitors. Special emphasis is being made with the use of ACE inhibitors in the treatment of diabetics with albuminuria or hypertension, due to

renal protective attributes of ACE inhibitors. Extrapolation of this policy is being extended to angiotensin receptor blockers (ARBs) due to their similar mode of action.

The mortality effect of ACE inhibition is not known, but proteinuria can be reduced and renal function can be preserved. One study assessing cardiovascular mortality in patients with proteinuria showed benefit with an ACE inhibitor, but it was not controlled for hypertension since the control group received a placebo, not another antihypertensive. Treatment of diabetics with hypertension or microalbuminuria with ACE inhibition has become standard practice in North America. Angiotensin receptor blockers (ARBs) are thought to reduce proteinuria, and other antihypertensives including diltiazem and verapamil have been shown to reduce it.[11]

CONCLUSION

Let's look at the objective data presented in this case. The applicant is overweight and demonstrates mildly elevated blood pressure, elevated cholesterol and low HDL, suggesting the metabolic syndrome. In addition, he has mild constant proteinuria confirmed to be microalbuminuria by reflex testing. His estimated 24-hour urine protein excretion averages to approximately 380 mg/24 hours. He is at increased mortality risk, primarily due to increased cardiovascular risk. As noted above, the kidney is signaling a vascular abnormality, accentuating the risk from the metabolic syndrome, a hyperinsulinemic state. While exact mortality figures are not available for this risk pool, mortality would be expected to be slightly greater than expected compared to the insured select population.

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