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Albuminuria and Cardiovascular Mortality: Rationale for Screening All Applicants for Microalbuminuria

Albuminuria is a strong and independent indicator of cardiovascular risk (CV). Absence of or very low urinary albumin levels is associated with low CV risk, whereas the CV risk increases markedly with increasing urinary albumin levels.

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The predictive power of urinary albumin levels for CV risk is independent of other CV risk factors in individuals with diabetes, hypertension and even those who are apparently healthy. Treatments that lower

albuminuria are associated with CV protection in patients with diabetes as well as in patients with hypertension. There is recent evidence that this is so even in those without diabetes and hypertension.

A small amount of protein is excreted in the urine in healthy individuals and consists of albumin, Tamm-Horsfall mucoprotein secreted by renal tubules, and immunoglobulins. Protein excretion less than 150 mg/day is considered normal and any value above this range is considered proteinuria.

For decades, it has been standard clinical practice to screen for proteinuria as an indicator of future kidney disease. The discovery that albumin excretion is a more accurate predictor of progression to end stage renal disease in diabetics led to screening all diabetics for microalbumin. This is because the traditional screening test for proteinuria does not have the sensitivity to detect small increases in albumin excretion that are significant.

Albuminuria is a general term and refers to presence of abnormal amounts of albumin in the urine. Microalbuminuria is more specific and refers to the excretion of 30 to 300 mg of albumin per

24 hours and requires a special test for detection. Excretion of greater than 300 mg of albumin per 24 hours is referred to as macroalbuminuria or clinical proteinuria and is easily detected by the customary tests for proteinuria.

The preferred method for measuring albuminuria is by collecting a 24 hour urine sample or a time urine sample. Both techniques are only accurate when closely monitored by professionals. For practical reasons, in insurance and even in clinical practice, testing is performed on a random urine sample. One of the main drawbacks when measuring albumin in a random sample is that the concentration of the urine influences the result. Specifically, for a given level of albuminuria, the result would be higher in concentrated urine and lower in dilute urine. Therefore it is essential to adjust the measured level of albuminuria for the concentration of urine.

The measured level adjustment is done by dividing the albumin level in the urine by the creatinine level in the urine, as the urine creatinine is a good measure of urine concentration. This adjusted value is referred to as the albumin creatinine ratio (ACR). ACR is widely used in clinical practice. A single elevated ACR value may or may not be significant as albumin excretion varies daily. Consequently when ACR is elevated, a total of three samples should be obtained; two out of three samples should have elevated ACR to be considered abnormal.

The ideal methods of expressing the urinary albumin excretion are either as the amount excreted per 24-hour period (mg/24 h) or as micrograms per minute (mcg/min). When using a random sample it is customary to express ACR as milligrams of albumin per gram of creatinine (mg/gram) or milligrams per millimole of creatinine (mg/mmol). The various units of measurement and their equivalents are summarized in Table 1 (see page 2).

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Albuminuria is highly prevalent in diabetes. A recent study of primary care diabetic patients in a large regional health maintenance organization (J Am Soc Nephrol 2005; 16: 219–28) found that 24.6 percent had microalbuminuria and 6.3 percent had macroalbuminuria. The prevalence of microalbuminuria in nondiabetic hypertensive patients is 8 to 23 percent and is 5 to 7 percent in apparently healthy individuals without diabetes or hypertension. (J Am Soc Nephrol 17: 2100–05, 2006)

A community-based sample of 1,568 middle-aged (average age 55 ± 9) nonhypertensive nondiabetic individuals free of CV disease were examined for urinary albumin excretion in The Framingham Heart Study. (Circulation 2005; 112:969-75) They were followed for median of six years. The median value of sex-specific ACR was 3.9 mg/g for males and 7.5 mg/g for females. Those above the median experienced a three-fold risk of CV disease and borderline significantly increased risk

of death. One standard deviation increase of ACR was associated with 55 percent higher mortality risk after adjustment for established CV risk factors. This increased mortality was noted even in those with the lowest Framingham Risk Scores. Compared with the lowest tertile (less than 2.4 mg/g for males and 4.3 mg/g for females) the highest tertile (greater than 5.5 mg/g for males and 11.9 mg/g for females) had a greater than two-fold increased risk for total mortality.

The inhabitants of the city Groningen in the Netherlands, aged between 28 and 75, participated in a large (N=40,548) study evaluating the relationship between increased urinary albumin excretion and all cause mortality in the general population.

(Circulation 2002; 106:1777-82) Urine albumin was measured on an early-morning urine sample at baseline. The prevalence of microalbuminuria was 7.2 percent. The study subjects were then followed for an average of 961 days. The results of this study supported the finding of the Framingham Heart Study. Investigators found that urinary albumin excretion is a predictor of all cause mortality in the general population. The excess mortality risk was mostly due to CV causes, was independent of other CV risk factors, and was apparent even at levels of albuminuria currently considered normal.

Rationale for Screening All Applicants

The evidence for albuminuria as a powerful independent risk factor for CV disease in diabetes, hypertension and even apparently healthy nondiabetic nonhypertensive individuals is very credible. The Framingham study suggests that the risk of increased CV mortality is even noted in those who would be considered low risk based on other CV risk factors.

According to the Centers for Disease Control estimates in 2005, 9.6 percent of the United States population age 20 and older has diabetes; a third of them are undiagnosed. The prevalence of hypertension in the United States is 25 percent based on an article in the Journal of the American Medical Association (JAMA 289: 2363–2369, 2003). Thus 35 percent of the US population is at significant risk of for albuminuria. In addition, among the balance, nonhypertensive nondiabetics, 5 to 7 percent have proteinuria. These facts justify screening all applicants.

Risk Selection

Guidelines for handling increased albumin excretion should

Table 1. Classification of Abnormal Urinary Albumin Excretion

	24-H Urine Albumin (mg/24 h)	Overnight Urine Albumin (mcg/min)	Spot Urine			
			Albumin (mg/L)	Albumin/Creatinine Ratio		
				Gender	mg/mmol	mg/g*
Normal	<15	<10	<10	M	< 1.25	< 10
				F	< 1.75	< 15
High Normal	15 to <30	10 to <20	10 to <20	M	1.25 to < 2.5	10 to < 20
				F	1.75 to < 3.5	10 to < 30
Microalbuminuria	30 to <300	20 to <200	20 to <200	M	2.5 < 25	20 to < 200
				F	3.5 < 35	30 to < 300
Macroalbuminuria	> 300	> 200	> 200	M	> 25	> 200
				F	> 35	> 300

Mg/g is the preferred method reporting; the corresponding mg/mg value is obtained by dividing the above value by 1000. Thus ACR of 10mg/g = 0.01 mg/mg.

Source: J Am Soc Nephrol 17: 2120–2126, 2006.

Cardiovascular Risk

Microalbuminuria testing was initially performed on diabetics to detect incipient diabetic nephropathy. Studies done during the last two decades have shown that it is also a powerful marker for CV morbidity and mortality in diabetics and hypertensives and also those without either impairment. Even among those with diabetic nephropathy, two thirds die of CV causes long before they are likely to develop end stage renal disease.

A systematic review of the literature (Arch Intern Med 157: 1413–1418, 1999) found microalbuminuria is a strong predictor of total and CV morbidity and mortality in patients with type-2 diabetes. The overall odds ratio for death was 2.4 (95% confidence interval, 1.8-3.1) and for CV morbidity or mortality, 2.0 (95% confidence interval, 1.4-2.7) when compared with diabetics whose urine albumin is in the currently accepted normal range.

The Heart Outcomes Prevention Evaluation study (JAMA 2001; 286:421-26) evaluated the impact of microalbuminuria on CV risk in 3,495 persons 55 and older with a history of CV disease or diabetes and one or more CV risk factors. The study was conducted between 1994 and 1999. Those dipstick positive for proteinuria or with a diagnosis of diabetic nephropathy were excluded. Microalbuminuria was detected in 32.6 percent of the participants with diabetes and 14.8 percent of those without diabetes at baseline. There was a graded relationship between ACR and all cause mortality. The relative risk for all cause mortality increased with each quartile of albuminuria and increased mortality was noted in both diabetics and nondiabetics. This increased mortality was noted even below currently established cutoffs for normal range for microalbuminuria.

take into consideration the fact that microalbuminuria is a powerful CV risk factor, in addition to the already well recognized ones in current use. Therefore a redesign of guidelines for all CV risk factors may be appropriate to make the overall assessment match the risk. Further, the relationship between albumin excretion and mortality is linear and increased mortality is present even in those with high normal ranges of albumin excretion. ♦

Myasthenia Gravis

“The goal of therapy in MG is to induce a sustained remission.”

Myasthenia gravis (MG) is a potentially life threatening but treatable autoimmune disorder characterized by weakness and fatigability of the voluntary muscles. It is caused by auto-antibodies directed against the acetylcholine receptor (AChR) located on the endplate in the neuromuscular

junction. In the United States, the prevalence of MG is estimated at 14 to 20 per 100,000 population. However, it is under diagnosed and the real prevalence is likely higher. The most common age at onset is the second and third decades in women and the seventh and eighth decades in men. (Myasthenia Gravis Foundation of America: <http://www.myasthenia.org>)

Patients with MG present with specific muscle weakness that improves after rest. The severity of weakness fluctuates during the day, usually being least severe in the morning and getting worse as the day progresses. This weakness affects the eye muscles and diplopia or ptosis is the presenting symptom in two thirds of the cases. One sixth of the cases present with oropharyngeal muscle weakness, difficulty chewing, swallowing or talking; ten percent of cases present with limb weakness.

The course of disease is usually progressive. Weakness remains restricted to the ocular muscles in only about 10 to 40 percent of the cases; these cases are referred to as ocular myasthenia gravis (oMG). Generalized myasthenia gravis (gMG) describes the medical condition of the balance; those who develop progressive weakness affecting other muscles during the initial two years after diagnosis. This progression usually occurs in a craniocaudal direction, spreading from the eye muscles to the facial muscles, to the oropharyngeal muscles and ultimately the muscles of the lower limbs.

Factors that worsen myasthenic symptoms are emotional upset, systemic illness (especially viral respiratory infections), hypothyroidism or hyperthyroidism, pregnancy, the menstrual cycle, drugs affecting neuromuscular transmission (e.g. gentamicin, doxycycline, beta blockers) and increases in body temperature.

Diagnosis

The diagnosis of MG in many cases may be made based on clinical presentation alone. However it is important to confirm the diagnosis before beginning therapy. The diagnostic tools available include intravenous edrophonium chloride, serum antibody assays and electrodiagnostic tests.

The Edrophonium Chloride (Tensilon) Test is familiar to most underwriters. Intravenous administration of this drug improves muscle function within thirty seconds and its effect lasts a few minutes. This test is diagnostic in patients with ptosis or weakness of the extraocular muscles but the response is difficult to measure and may be inconclusive when other muscles are affected.

Table 2. Autoantibodies in Myasthenia Gravis

Tests	Sensitivity	Comments
Anti-AChR Ab	80–90% of gMG and 30–50% of oMG patients	Highly specific diagnostic “gold standard”
Anti-MuSK AB	30 to 40% of anti-AChR Ab-negative patients	Useful in those who are Anti-AChR Ab-negative
Anti-Str Ab	80% MG with thymoma 30% of MG without thymoma	More common in older patients – has poor specificity, not diagnostic

Source: J. Clin. Invest.2006; 116:2843–2854

Several antibody assays are utilized in establishing diagnosis (Table 2) of MG. Of these, the serum AChR antibody assay is highly specific for the diagnosis of MG; but it has a low sensitivity in oMG. The actual antibody titre, however, does not correspond to the severity of disease. Other antibody assays may be of use

Myasthenia Gravis Terminology

Neuromuscular junction (NMJ) is a location where chemical communication between the nerve ending and muscle takes place. The motor nerve fiber that supplies the muscle divides into many terminal branches; each terminal branch ends on a region of muscle fiber called the endplate. The communication between the terminal branches of the nerve fiber and the end plate is mediated through chemicals called neurotransmitters.

Neurotransmitters are the chemicals which transmit signals from one neuron to the next neuron or to muscle at the NMJ.

Acetylcholine (ACh) is a neurotransmitter. Transmission of signals across the neuromuscular junction is one of its many functions. When an impulse reaches the nerve ending, ACh is released at the NMJ and it binds to receptors (AChR) in the endplate (located on the muscle fiber) transmitting the nerve impulse to the muscle, initiating muscle contraction. Afterwards it is broken down into its components by the enzyme **cholinesterase (AChE)**.

Anti-AChR antibody is directed against the acetylcholine receptor.

Anti-MuSK antibody is directed against the muscle specific tyrosine kinase (MuSK), a surface membrane enzyme.

Anti-Str antibody reacts with the contractile elements of skeletal muscle.

in making a diagnosis in those who are AChR antibody negative. Repetitive nerve stimulation and single fiber electromyography are useful adjuncts to the other tests in diagnosing MG. Both tests are sensitive but lack specificity. A normal finding in these tests excludes the diagnosis of MG.

The foremost indication for thymectomy in MG is thymoma. Thymoma is present in ten percent of cases; there is increased incidence of thymoma with late onset MG. Surgery is the treatment of choice in thymoma and removal of the thymus is essential to determine prognosis.

Table 3. Clinical Classification (Myasthenia Gravis Foundation of America)

Class	Description
I	Any ocular muscle weakness, all other muscle strength is normal
II*	Mild weakness affecting muscles other than ocular muscles, may have ocular muscle involvement
III*	Moderate weakness affecting muscles other than ocular muscles, may have ocular muscle involvement
IV*	Severe weakness affecting muscles other than ocular muscles, may have ocular muscle involvement
V	Intubation with or without mechanical ventilation except when employed in routine postoperative management

Class II, III and IV are further subdivided into subclass (a) predominantly affecting limb and axial muscles and (b) predominantly affecting oropharyngeal and or respiratory muscles. The use of feeding tube without intubation places the patient in class IVb.

Source: Neurology 2000; 55:16-23

Therapy

The goal of therapy in MG is to induce a sustained remission. The modalities available include anticholinesterase inhibitors, immunosuppression, thymectomy, plasmapheresis and administration of intravenous immunoglobulins. Acetylcholinesterase inhibitors (AChEI) act by inhibiting acetylcholinesterase and by increasing the amount of acetylcholine available to act on the ACh receptors. Pyridostigmine bromide (Mestinon) is the most frequently prescribed drug in this class. It takes effect rapidly, within 30 minutes, and improves myasthenic symptoms in nearly all patients, but results in full relief of symptoms in only a few. It does not modify the course of the disease.

Since MG is an autoimmune disorder, immunosuppressive therapy is the mainstay of treatment. Corticosteroid therapy is required in most patients with moderate to severe MG and mild cases not responding to AChEI therapy. The vast majority of patients improve within a few weeks of the onset of steroid therapy. Once the maximum benefit is realized, the dose is reduced and maintained at the minimum effective dosage long-term. Other immuno suppressive drugs such as azathioprine (Imuran), cyclophosphamide, and cyclosporine and mycophenolate mofetil are frequently used in combination with corticosteroids.

Plasmapheresis involves replacing 1–1.5 times the plasma volume with saline, albumin or plasma protein fraction. The intent is to reduce the amount of circulating serum AChR antibodies and obtain rapid, temporary improvement of symptoms. This therapy is utilized to stabilize patients prior to surgery or for the immediate control of symptoms in severe cases of MG. The improvement lasts for a few weeks and buys time to institute effective long-term treatment.

Intravenous immunoglobulin is also used in severe cases to obtain immediate response in an acute situation. It is easier to administer than plasmapheresis.

Thymectomy as a treatment of MG, in the absence of thymoma, has been the standard practice for decades. It is generally agreed that patients with gMG who are between the ages of adolescence and 60 years should be offered thymectomy, as nearly 80 to 85 percent of patients eventually experience improvement in their MG after thymectomy. The benefits of thymectomy usually appear months or years after the operation.

Complications of MG are related to MG itself or due to superimposition of other medical conditions. As expected long-term corticosteroid therapy or immunosuppression may also result in complications. Respiratory failure due to severe respiratory muscle weakness, aspiration pneumonia or infection is among the most serious complications of MG. This requires urgent respiratory support and aggressive therapy which may include plasmapheresis or intravenous immunoglobulin. Pregnancy leads to worsening of myasthenia in a third of the cases. (Postgrad. Med. J. 2004; 80; 690-700)

Prognosis

Untreated MG has a 10 year mortality of 20 to 30 percent. However, with treatments available today, the prognosis is excellent. Most patients are able to live normal lives, though will require immunosuppressant drugs for life. Myasthenia gravis associated with thymoma, particularly in older patients, carries a poor prognosis.

A Danish study of 290 patients found the survival was shorter for cases of MG when compared to a matched healthy Danish population. Mortality was low for those with MG under the age of 50. Older age, more severe disease and presence of thymoma are indicators of unfavorable prognosis. The overall three, five, 10 and 20 year survival rates were 85 percent, 81 percent, 69 percent and 63 percent respectively. (J Neurol Neurosurg Psychiatry 1998; 64:78–83)

Risk Selection

When assessing a case of MG, age, the severity of disease, duration of remission, the number and severity of the relapses, and the dose of corticosteroids and immunosuppressants required to maintain remission should be considered. Since progression of disease occurs in the first two years after diagnosis, cases should be assessed conservatively during this period. When muscles that perform vital functions are affected, such as oropharyngeal or respiratory muscles, serious complications are possible; these cases may be higher risk. Lastly, when thymoma is associated with MG, the stage and histology should be carefully assessed as this may determine the final action on the case. ♦

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