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Proteinuria

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Continuing Education Activity

Proteinuria is a very common finding in outpatient as well as inpatient settings. Any such results warrant further investigation, especially in the setting of comorbidity. Given the rising trends of diabetes, proteinuria prevalence is on the rise. This activity reviews the evaluation and management of proteinuria and explains the role of the interprofessional team in improving care for patients with this condition.

Objectives:

- Identify the etiology of proteinuria.
- Explain the evaluation of proteinuria.
- List the management options available for proteinuria.
- Summarize interprofessional team strategies for improving care coordination and communication in patients with proteinuria and improve outcomes.

Access free multiple choice questions on this topic.

Introduction

Proteinuria is a broad term used to describe protein in the urine. It is a general term for the presence of proteins, including albumin, globulin, Bence-Jones protein, and mucoprotein in the urine.[1] Almost half of the protein lost in the normal urine is derived from the distal tubule, known as Tamm-Horsfall glycoprotein (THG).[2][3] Persistent proteinuria is a marker of kidney damage. It also helps with the diagnosis, prognosis, and therapy.[4][5]

The major etiology of proteinuria is the disturbance in the kidney filter. In addition to its association with early renal disease, it is also seen in benign conditions.[6][7] Proteinuria has now also been used along with the estimated glomerular filtration rate (eGFR) in the classification of chronic kidney disease (CKD).[8] Proteinuria can serve as an indicator of early renal disease. It marks an increased risk of renal damage secondary to hypertension and cardiovascular disease.[9] The degree of proteinuria correlates with disease progression.[10]

According to the UK chronic kidney disease guidelines, proteinuria is defined as urine protein creatinine ratio (UPCR) more than 45 mg/mmol, but this does not warrant further evaluation in the absence of hematuria unless the UPCR is more than 100 mg/mmol.[3]

According to the NICE guidelines, proteinuria is defined as a UPCR of more than 50 mg/mmol or a urine albumin creatinine ratio (UACR) of more than 30 mg/mmol.[3][11]

Etiology

Proteinuria can be classified as transient and persistent.

Transient Proteinuria[9]

- Urinary tract infection
- Orthostatic proteinuria (occurs after the patient has been upright for a prolonged period, absent in early morning urine). Rare in more than 30 years of age
- Fever
- Heavy exercise
- Vaginal mucus
- Pregnancy

Persistent Proteinuria[9]

- Primary renal disease
    - Glomerular (such as glomerulonephritis)
    - Tubular
- Secondary renal disease
    - Diabetes mellitus
    - Connective tissue diseases
    - Vasculitis
    - Amyloidosis
    - Myeloma
    - Congestive cardiac failure
    - Hypertension

Benign Causes of Proteinuria

- Fever
- Acute illness
- Exercise/ Intense physical activity
- Orthostatic proteinuria[8]
- Dehydration
- Emotional stress
- Hear injury
- Inflammatory process[5]

The benign causes of proteinuria do not increase morbidity or mortality otherwise. These conditions are highly variable and usually reversible as the precipitating factor is addressed. Proteinuria is not a part of normal aging.[5]

Epidemiology

In the general population, the prevalence of proteinuria lies between 8% to 33%. The broad range is due to the variety of methods used to report proteinuria.[12][13][14] Due to its high prevalence, Japan has a screening program for proteinuria.[15][16] One of the major causes of renal disease and resultant proteinuria is the growing prevalence of type 2 diabetes mellitus. The prevalence of persistent proteinuria in affected individuals has been reported to be 15.3 per 1000 person-years. Less than 2% of patients with positive urine dipstick have a serious underlying etiology or urinary tract infection.[5]

Race

In a survey, it was found that the prevalence of microalbuminuria is greater in non-Hispanic Blacks and Mexican Americans compared with non-Hispanic Whites.[17]

Sex

Most primary and secondary renal diseases are more common in males than in females. Persistent proteinuria is twice as common in males as in females.

Age

Due to the increase in the incidence of hypertension and diabetes with age persistent proteinuria and microalbuminuria also increases with age.

Pathophysiology

Proteinuria is a result of three different pathways, including

1. Glomerular dysfunction
2. Tubulointerstitial disease
3. Overflow proteinuria

Glomerular Dysfunction

This is the most common cause of proteinuria. Glomerular dysfunction alters the permeability of the glomerular basement membrane leading to albuminuria and immunoglobinuria. Glomerular dysfunction causes urinary protein excretion of more than 2 g/24-hour.[5]

The glomerular filtration barrier is a three-layer membrane structure with the following layers (inner to outer):

1. Fenestrated glomerular endothelium
2. Glomerular basement membrane
3. Podocyte[18]

The basement membrane of the glomerular capillary wall is responsible for restricting protein filtration owing to the presence of type 4 collagen. This filtration restriction is weight and size-based. As a result, larger and heavier proteins like albumin (molecular weight of 69000 D) are not seen in the urine under normal circumstances. In addition to the size and weight barrier, the negative charge on the glomerular capillary wall prevents the passage of negative charges proteins like albumin.[1]

Glomerular proteinuria is a result of a damaged glomerular filtration barrier or increased hydrostatic pressure. Dysfunction of the charge barrier that consists of collagen and laminin leads to a loss of the negative charge, which manifests with the appearance of negatively charged proteins in the urine. In addition to all these, mesangial cell

growth in the glomerulus, extracellular matrix production, and infiltration with inflammatory cells can also lead to proteinuria. Podocytes are an important barrier to proteinuria, and molecular dysfunction of nephrin and podocin at the level of podocytes can lead to the development of proteinuria. Transient receptor potential cation (TRPC) is a protein involved in calcium influx and has been shown to be associated with podocyte injury through an NFAT-mediated signaling pathway. The kidney also produces a membrane protein known as Klotho. In a recent study, klotho has been shown to suppress TRPC and hence may offer a therapeutic benefit for proteinuria in the future.[18]

Causes of glomerular dysfunction include:

- Diabetic nephropathy (most common)
- Drug-induced nephropathy (NSAIDs, lithium, heavy metals, heroin)
- Lymphoma
- Infections (HIV, hepatitis B, and C)
- Primary glomerulonephropathies
- Amyloidosis
- Malignancies[5]
- Dyslipidemia
- Reactive oxygen species
- Inflammatory cytokines
- Activation of the renin-angiotensin system (RAS)[18]
- Connective tissue diseases such as SLE

Chronic proteinuric glomerulopathy is defined as a sustained or permanent loss of protein filtration selectivity of the glomerulus.[18]

Tubulointerstitial Dysfunction

This is due to the dysfunction at the proximal tubule resulting in the impairment of the uptake of filtered proteins. Tubulointerstitial dysfunction usually leads to less severe proteinuria as compared to glomerular dysfunction, with 24-hour urine protein levels less than 2 grams.[5]

Smaller and positively charged proteins that are usually filtered through the glomerular capillary are absent in the urine owing to the nearly complete reabsorption by the tubular epithelial cells. Most of the protein reabsorption occurs in the proximal convoluted tubules. This reabsorption in the proximal convoluted tubules has a transport maximum which, when reached can result in proteinuria.[1]

Causes of tubular dysfunction include:

- Hypertensive nephrosclerosis
- NSAIDs induced nephropathy[5]
- Nephrotoxins
- Chronic tubulointerstitial disease[1]

Overflow Proteinuria

Increased production of proteins can saturate the reabsorptive channels in the proximal convoluted tubules leading to proteinuria.

Causes of overflow proteinuria include:

- Multiple myeloma
- Myoglobinuria
- Amyloidosis[5]

History and Physical

Proteinuria may be asymptomatic, many patients do not report any symptoms, and proteinuria is detected on routine laboratory examination. A thorough history should be obtained from the patient particularly asking about the symptoms of renal failure, including leg swelling, weight changes, as well as symptoms for connective tissue diseases including arthralgias, skin rashes, and mouth ulcers. Patients should be asked about loin pain, abdominal pain, shortness of breath, pleuritic chest pain, or rigors. History about changes in the urine's appearance (red/smoky, frothy) and its relation to an upper respiratory tract infection should also be obtained. In addition to these, a detailed history regarding comorbid conditions including hypertension, diabetes mellitus, heart failure, etc. is required.

Thorough drug history is essential to rule out any nephrotoxic drug currently being used or used in the past as a possible cause of proteinuria. These drugs include but are not limited to non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensive drugs including angiotensin-converting enzyme (ACE) inhibitors, and loop diuretics, and a variety of antibiotics, especially penicillamine, aminoglycosides, and over the counter herbal medicines. Detailed family history is essential to rule out any familial renal disease and connective tissue diseases. The physical examination should focus on edema, muscle wasting, rashes, abdominal bruits, and splinter hemorrhages. On examination, there may be signs of systemic disease e.g., retinopathy, joint swelling or deformity, stigmata of chronic liver disease, cardiac murmurs, organomegaly, and lymphadenopathy. Measurement of blood pressure can also help in making a diagnosis.[9]

Evaluation

Evaluation of a patient with proteinuria should begin with excluding urinary tract infection and the presence of diabetes mellitus.

Urine dipsticks are the first screening tests for proteinuria that can be performed in an office. This is a semiquantitative test in addition to being a qualitative test. The reading of proteinuria on a urine dipstick should be interpreted, taking into consideration the concentration of the urine that is reflected by the specific gravity. For instance, a urine dipstick value of 11 in a well-hydrated patient producing large quantities of dilute urine represents far more severe proteinuria than a dehydrated patient with similar values on a dipstick. The urine dipstick is semi-quantitative because of the fact that although a reading of 11 on a dipstick shows proteinuria greater than 1 g/24 hour, it does not signify how much the value is greater than 1 g/24 hour.[8] The urine dipstick diagnostic pad usually contains tetra bromophenol blue and citrate buffers. Several other dyes are also available that are more specific to albumin.[8][19][20] The pad detects the protein due to its electronegativity by a color change from yellow to blue. The mechanism used for protein detection by dipsticks should be considered due to the fact that few proteins have a positive charge, like immunoglobulins. As a result, they are not detected on a urine dipstick. This problem can be solved by using sulfosalicylic acid (SSA) that can detect immunoglobulins by flocculating. Similarly, alkaline urine will also change the color of the dipstick, giving a false positive.[20] Any positive results on dipstick and SSA should be further evaluated promptly.

Urine Dipstick Readings

False Positive

- Dehydration
- UTI
- Hematuria
- Alkaline urine pH more than 8
- Recent exercise

False Negative

- Overhydration
- Positively charged proteins (light chains)[8]

In order to quantify the degree of proteinuria, a 24-hour urine collection is quite accurate but cumbersome to calculate the 24-hour urinary protein excretion in mg per 24 hours. Any value greater than 150 mg/24 hours is considered abnormal and should be further evaluated for underlying reasons.[9] The 24-hour urine collection is quite susceptible to an error with overcollection or under-collection.[8]

An easier and reliable alternative is the spot urine protein to creatinine ratio (UPCR) from a single specimen that should preferably be the early morning urine sample. [(mg/l protein)/(mmol/l creatinine)*10]. A UPCR value greater than 15 mg/mmol should raise suspicion and warrant further investigation.[9]

In addition to the protein levels, serum electrolytes, urea, and creatinine should be checked.[9] For a nephrotic range of proteinuria with more than 3.5 g/24-hours or a UPCR of more than 350 mg/mmol, the serum albumin levels, and cholesterol concentrations should be checked. The value of proteinuria should be correlated with renal function tests. For example, in a patient with UPCR values in normal limits with abnormal renal function tests, hematuria, and comorbidities should be evaluated.

Creatinine clearance is more helpful in the evaluation of renal function than creatinine levels. This can be calculated using the Cockcroft-Gault formula.

Creatinine clearance (ml/min) = [(140-age) X weight (kgs) X C] / Serum creatinine (mol/l);

where C is 1.23 in males and 1.04 in females.

For a healthy young adult, normal creatinine clearance is more than 90 ml/min. It changes as the muscle mass changes in elderly patients and bodybuilders.[9] With aging, there is a decrease in creatinine clearance by 0.75 ml/min/year.[5][21] As a result, age and muscle mass should be taken into consideration with these values.[9] For healthy adult males, the creatinine excretion ranges from 20 to 25 mg/kg/24 hours, whereas females excrete about 15- 20 mg/kg/24 hours. A healthy adult male of 70 kg will have 1400 to1850 mg of creatinine excretion in a day.[8]

Imaging (particularly renal ultrasonography), immunology screen (ANA, ANCA), and viral screen (hepatitis B and C) are also helpful in diagnosing the underlying cause.[9]

Degrees of Proteinuria

- Normal: Less than 150 mg/24 hour or 15 mg/mmol
- Nephritic: 150-3000 mg/24 hour or 12-300 mg/mmol
- Nephrotic: More than 3500 mg/24 hour or more than 350 mg/mmol

The type of protein constituting the proteinuria can be determined by immunoelectrophoresis.

Albuminuria (mg/d)

- Normal: Less than 30
- Microalbuminuria: 30-300
- Macroalbuminuria: More than 300[8]

Other Tests

- Autoantibody determinations - including antistreptolysin O titers, antinuclear antibodies (ANAs), anti-DNA antibodies, complement levels (C3 and C4), anti-phospholipase A1 receptor autoantibody, and cryoglobulins
- Hepatitis B and C, and HIV serologies
- Urine and plasma protein electrophoresis for light chains
- Anti–glomerular basement membrane (anti-GBM) antibodies and antineutrophil cytoplasmic antibodies (ANCA)

Imaging Studies

- Renal ultrasonography is being considered to review the size and echogenicity of the kidneys
- Chest radiography or computed tomography may also be indicated

Renal Biopsy

Renal biopsy should be considered in patients with proteinuria above 1 g per day because it can guide the choice of a specific therapy.

Treatment / Management

The treatment of proteinuria is mainly focused on treating the specific underlying cause. In addition, most of the treatment modalities are focused on reducing the degree of proteinuria, particularly albuminuria. These include drugs acting on the renin-angiotensin-aldosterone system. The 2013 Kidney Disease Improving Global Outcomes (KDIGO) guideline strongly recommend the use of ACE inhibitor or angiotensin receptor antagonist (ARB) in adults with persistent proteinuria more than 300 mg/24 hour. The Chronic Kidney Disease Management publication by the Kidney Health Australia in 2015 set the target of treatment as a 50% reduction in albuminuria.[22]

Data obtained from multiple efficacy trials have shown the effectiveness of ACE inhibitors in reducing proteinuria in diabetic as well as nondiabetic patients. In addition to their effect on proteinuria, they have been effective in reducing the risks of renal disease progression and hence, the requirement for renal replacement therapy.[23][24] As advised by Kidney Health Australia, the target of reducing proteinuria by 50% in the first six months to a year is associated with a similar decrease in the risk of renal disease progression.[22][25]

A study has shown that the efficacy of ACE inhibitors in halting the progression of proteinuria is greater in patients with higher quantities of proteinuria as compared to those with lower amounts of protein in the urine.[5][26] The initiation of therapy with ACE inhibitors requires a close check on creatinine as well as potassium levels. The current data does not show any significant difference between the efficacy and side effect profile of both ACE inhibitors and ARBs. Hence the decision should be guided by the patient's individual response as well as the provider's experience.[22]

Combination therapies of ACE inhibitors with ARBs and direct renin inhibitors have been trialed in multiple studies that have shown an increased risk of adverse effects, including hyperkalemia, hypotension, renal impairment, and syncope.[27] Data is insufficient to recommend a combination of ACE and ARB in order to prevent any progression of renal disease. The Kidney Health Australia, as well as the NICE guidelines in the UK, do not recommend

combination therapy for progression prevention in proteinuria.[22]

Diuretics

Patients with moderate to severe proteinuria have fluid overload and require diuretic therapy along with dietary salt restriction. Aldosterone antagonists have also shown an advantage with their efficacy for proteinuria.[22] Combination therapy of ACE inhibitors with aldosterone antagonists is associated with an increased risk of hyperkalemia and gynecomastia. However, this combination has shown significant mortality benefits in patients with heart failure.[22][28]

Calcium Channel Blockers

Non-dihydropyridine calcium channel blockers (NDCCBs), diltiazem, and verapamil decrease proteinuria greater than dihydropyridine calcium channel blockers (DCCBs). The newer NDCCBs such as efonidipine and benedipine used in combination with ARBs, have been shown to reduce proteinuria.[29][30][29]

Differential Diagnosis

The presence of proteinuria in a patient requires a thorough evaluation and appropriate management in order to avoid the development of any complications. The following differential diagnosis should be considered in a patient with proteinuria.[1][5][8][9][31][32]

- Diabetic nephropathy
- Orthostatic proteinuria
- Nephrotoxins, drug-induced nephropathy (NSAIDs, lithium, heavy metals, heroin)
- Infections (urinary tract infection, HIV, hepatitis B, and C)
- Primary glomerulonephropathies, chronic tubulointerstitial disease
- Amyloidosis
- Post renal transplant
- Preeclampsia
- Malignancies (myeloma, lymphoma)
- Dyslipidemia
- Connective tissue diseases
- Vasculitis
- Congestive cardiac failure
- Hypertension
- Dehydration
- Exercise/intense physical activity
- Emotional stress

Prognosis

Studies have suggested that early recognition and management play a key role in the prognosis of patients with proteinuria.[5] Proteinuria is used to assess the prognosis of many diseases. Proteinuria in IgA nephropathy is

associated with a worse patient outcome.[33]

Similarly, in patients with chronic kidney disease, higher proteinuria is correlated with a poor prognosis.[34] In idiopathic membranous nephropathy, the presence of proteinuria also reflects a poor prognosis.[35] Post renal transplantation proteinuria is associated with higher mortality and reduced graft survival.[32] In a patient with preeclampsia, proteinuria reflects worse outcomes for both the mother and the fetus.[31]

Complications

Proteinuria is associated with significant complications, including increased risks of

- Coronary heart disease
- Cerebrovascular disease[36][37]
- Gastrointestinal hemorrhage[38]
- Progression of kidney disease[39]
- Hypercoagulability, Venous thromboembolism[40]
- Pulmonary edema due to fluid overload
- Bacterial infections
- Renal replacement therapy including dialysis and transplant
- Death[5][22][41]

Studies have shown that microalbuminuria increases the risk of coronary artery disease by 50%, whereas the risk of cerebrovascular disease is increased by 70%. Macro-albuminuria is associated with doubling the risk for both.[22]

Consultations

In addition to thorough evaluation and referral to a nephrologist, any patient with proteinuria should be assessed periodically, preferably every six months, while managing hypertension, diabetes, and any other comorbidity.[9] A patient with proteinuria may require the following consultations during the course of his/her diagnostic workup and management of the underlying factors and their complications.

- Nephrologist
- Immunologist
- Endocrinologist
- Cardiologist
- Neurologist
- Gastroenterologist
- Transplant team (transplant nephrologist, transplant surgeon, nursing, social worker, psychiatrist)

Deterrence and Patient Education

The urine collection over a 24-hour period requires that the urine collection process be educated to the patient clearly with clear written instructions.[8] The patient should be warned about the likely adverse effects of ACE inhibitors and angiotensin receptor blockers, including angioedema, dizziness, cough, syncope, hypotension, hyperkalemia, and a slightly increased risk of lung cancer.[22] Patients who have moderate to severe proteinuria are in a fluid overload

state so the salt restriction is also advised.

Enhancing Healthcare Team Outcomes

Proteinuria has no traditionally set cut-off values and it varies from 150 to 300 mg/24 hours depending upon the laboratory.[3]

Any potential nephrotoxic drug should be preferably replaced if possible or dosage adjustments are made.

In a patient with coexistent hypertension or heart failure, angiotensin-converting enzyme or angiotensin 2 receptor blockers should be the first line of management.[9]

An approach that is likely to benefit the patients is the gradual titration of ACE inhibitor or ARB dosages by increments taking into consideration the patient's individual response with drug tolerance and adverse effects.[22] Management of a patient with proteinuria requires a multidisciplinary team consisting of providers, nursing staff. laboratory technicians, and pharmacists.

Screening:

It is recommended to screen adults with one or more of the following risk factors.

- Chronic kidney disease
- Diabetes
- Hypertension
- Obesity
- Current smoking
- Cardiovascular disease
- Family history of chronic kidney disease
- Aboriginal or Torres Strait Islander people[22]

Screening is recommended due to the fact that early recognition and management are associated with better outcomes in terms of reduced morbidity and mortality.

Review Questions

- Access free multiple choice questions on this topic.
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