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PROTEINURIA – RENAL FUNCTION EVALUATION IN CLINICAL PRACTICE

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ABSTRACT

Patients suffering from various kidney diseases have very few clinical symptoms and signs pointing towards renal involvement. Renal functions can be assessed by microscopic and biochemical examination of urine, biochemical determinations on plasma samples and by procedures involving administration of test substances. In this article a review on proteinuria is done which is useful in day to day clinical practice.

Keywords: Albumin, Globulin, Glomerular diseases, Proteinuria, Renal function

INTRODUCTION

A normal barrier to protein filtration begins in the glomerulus. The normal glomerular endothelial cells form a barrier and hold back cells and other particles. They are penetrated by large pores of 100nm called fenestrae that can be easily traversed by proteins. The glomerular basement traps most large proteins (>100Kda), while the foot process of epithelial cells (podocytes) cover the urinary side of the glomerular basement membrane and produce a series of narrow channels (slit diaphragm) to allow passage of small solutes and water. These slit diaphragm bridges the slits between the foot processes of the glomerular basement membrane [1]. The visceral epithelial cells are covered with negatively charged heparan sulfate proteoglycans [2]. This negative charge and size selectivity of glomerular basement membrane impedes the passage of anion molecules such as albumin, globulin and large molecular weight protein across the glomerular wall. The smaller proteins that are filtered across the glomerular basement membrane are largely reabsorbed at the proximal tubule and only small amount are excreted.

PATHOPHYSIOLOGICAL CLASSIFICATION OF PROTEINURIA

A) BENIGN

1. Postural Orthostatic proteinuria 2. Functional 3. Transient 4. Intermittent

B) PATHOLOGICAL

1. Glomerular 2. Tubular 3. Overflow 4. Secretory

A) BENIGN PROTEINURIA

This is a transient proteinuria that occurs with normal renal function, bland urinary sediment, and normal blood pressure and without any significant oedema. 24 hour urine albumin is usually less than one gram. They do not indicate any significant renal disease and disappears on repeated testing.

1) Postural /Orthostatic Proteinuria

This is seen in 3 to 5% of adolescents, especially in young males. It is characterized by increased protein excretion in the upright position and normal protein excretion during recumbency [3]. It is diagnosed by split urine protein excretion examination. In orthostatic proteinuria, the day time specimen typically has an increased concentration of protein, with night time specimen having a normal concentration usually less than 50 mg over eight hours [4]. In true glomerular disease there is reduced protein excretion in the supine position but it will not return to normal as with orthostatic proteinuria. Springberg found that long term prognosis of orthostatic proteinuria is benign in virtually all cases over many decades [5]. Data on renal biopsies on orthostatic proteinuria are confusing. Some showed minor glomerular changes [6] .Posture affects urinary protein excretion, probably via an increase in glomerular capillary hydrostatic pressure and for change in permeability of the glomerular capillary walls [7]. An alternate explanation is entrapment of renal veins [8, 9].

2) Functional Proteinuria

It is a benign proteinuria due to changes in glomerular ultra filtration pressure and/or membrane permeability. It is seen in fever, exercise, cardiac failure, emotional stress and acute illness. Functional Proteinuria is usually less than 0.5 gm/day but may be as heavy as 5.0 gm/day (following marathon running). It disappears with the resolution of causative disorder [10].

Kallmeyer et al found that recent exercise can induce several gram of protein per litre of urine, sometimes together with haematuria and even casts so called jogger's nephritis [11]. Post exercise proteinuria is about 15 to 20 times the resting range of proteinuria and requires about 4 hours to regain resting value in the recovery period [12]. Poortmans et al found that proteinuria was influenced mostly by the intensity of exercise rather than its duration [13].

3) Idiopathic Proteinuria

This is seen in young healthy adults. This dipstick positive proteinuria disappears spontaneously by next clinical visit.

4) Intermittent Proteinuria

This benign proteinuria is found in half of their different urine samples in absence of other renal or systemic abnormalities.

B) PATHOLOGICAL PROTEINURIA

This is persistent proteinuria that is detected on multiple ambulatory clinical visits. This is seen in both recumbent and upright position and usually signals a structural renal disease.

1) Glomerular Proteinuria

It is the most common cause of proteinuria in clinical practice. It is characterized by a disproportionate amount of albumin in urine [14]. Due to preservation of selectivity and large concentration of albumin in blood glomerular proteinuria is 85 to 90 % albumin, accompanied by pre-albumin, transferrin and relatively low molecular weight proteins since it contains mostly albumin. They are readily detected by stick or turbidometric methods. Glomerular proteinuria ranges from few hundred mg per 24 hours to 100 gms per 24 hours. McConnell et al on evaluation of proteinuria found that urinary excretion of more than 2 gm per 24 hours is usually a result of glomerular disease [15]. In glomerular proteinuria there is increased glomerular capillary permeability to high molecular weight anionic plasma proteins. How the glomerular barrier is damaged so that it leaks more than normal remains unclear [16]. This may be due to:

-Loss of fixed anionic charge (Congenital nephrotic syndrome, minimal change nephropathy)

- Detachment of epithelial podocytes from basement membrane [17].

- Immune aggregation.

- Increase in glomerular capillary pressure.

The filtered protein, that reach the tubules overwhelm the limited capacity of tubular reabsorption and cause these proteins to appear in urine. Glomerular disease is classified as primary when the pathology is confined to the kidney and secondary when it is a part of multi system disorder.

Glomerular proteinuria is of two types:

a) Selective Proteinuria

b) Non-selective Proteinuria

In selective proteinuria the clearance ratio of immunoglobulin to albumin or transferrin is less than 0.10(<10%).In non-selective proteinuria the clearance ratio of immunoglobulin to albumin or transferrin is more than 0.50(>50%).

GLOMERULAR PROTEINURIA -CAUSES

Primary Glomerulonephropathy:

- Minimal change disease
- Focal segmental glomerulonephritis
- Idiopathic membranous glomerulonephritis
- Membranoproliferative glomerulonephritis
- IgA nephropathy

Secondary Glomerulonephropathy:

- Diabetes Mellitus - Amyloidosis - Collagen vascular disease (Eg-Lupus nephritis)
- Infections - HIV - Hepatitis B and C infection - Post streptococcal - Syphilis
- Malaria - Infective Endocarditis - Drugs - NSAIDS - Penicillamine - Lithium
- Heroin - Heavy metals - Gastrointestinal and lung cancers - Lymphoma

2) TUBULAR PROTEINURIA

Proteinuria results from the damage of proximal tubule so that normally reabsorbed protein, principally of low molecular weight pass into the urine .This usually occurs as part of the Fanconi syndrome of proximal tubular dysfunction. Tubular proteinuria usually does not exceed 2 gm per day [18, 19]. Beta 2-microglobulin is one of the many micro globulin which make up tubular proteinuria. Normal level of Beta 2-microglobulin in urine is less than 0.4 mcg/L. It can be assessed by RIA or ELISA. The urinary albumin and Beta 2-microglobulins ratio of 10 to 1 suggests the presence of Beta 2-microglobulin. Further measurement of Beta 2 lysozyme may help in distinguishing type of urinary tract infection besides diagnosis of heavy metal poisoning [20, 21] .Urinary protein electrophoresis and/or immuno electrophoresis may aid in distinguishing tubular and glomerular proteinuria.

TUBULAR PROTEINURIA – CAUSES

-Hypertensive nephrosclerosis -Tubulo interstial diseases -Fanconi syndrome

-Heavy metals -Uric acid nephropathy -Acute hypersensitivity -Interstitial nephritis

-Sickle cell disease -Drugs (NSAID, antibiotics)

3) OVERFLOW PROTEINURIA

It is due to filtration by normal glomerulus of an abnormally large amount of low molecular weight proteins, which exceeds the capacity of the normal tubules for reabsorption. It is characterized by the presence of abnormal peak or spike on urinary electrophoresis. Most often, this is a result of the immunoglobulin over production that occurs in multiple myeloma. The resultant light change immunoglobulin fragments (Bench Jones proteins) produce a monoclonal spike in the urine electrophoresis [22, 23] .

OVERFLOW PROTEINURIA – CAUSES

-Multiple myeloma -Myoglobinuria -Rhabdomyolysis -Lymphoproliferative disorders

4) SECRETORY PROTEINURIA

It occurs due to secretion of proteins into the urine after glomerular filtration. About 20 to 30 mg/24 hours of non plasma protein is contributed by renal tubules and lower urinary tract. Mostly they are formed by Tomm-Horsfall proteins . Some secretary IgA is added by lower urinary track including the urethral glands together with trace quantity of protein of prostatic or seminal vesicular organ [24, 25]. Tomm-Horsfall protein is secreted by the

ascending thick limb and early distal convoluted tubule into the tubular fluid. It is an easily polymerized glycoprotein. They form the major constituent of renal tubular casts [26], along with albumin and traces of many plasma proteins, including immunoglobulins [27]. In myeloma, casts contain paraproteins polymerized with Tomm-Horsfall protein, and may show a micro fibrillar structure that will stain positive with Congo red, even though no amyloid is present in renal tissue.

Thus, the normal 24 hours urine protein excretion does not exceed 150 mg/dl in adults and 140 mg/m^2 in children and generally this corresponds to approximately 10 mg/dl. Microalbuminuria refers to elevated urinary albumin excretion with normal total urine proteins. This corresponds to albumin excretion rates in the range of 20 to 200 µg/min. It has been found a useful early marker of development of diabetic nephropathy. It is detected by RIA or ELISA technique.

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