

# Orthostatic proteinuria: a harmless variant of protein loss?

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## ABSTRACT

A 28-year-old young woman was referred to our department of Internal Medicine for analysis of unintentional weight loss. At initial analysis, a persistent proteinuria was found with no evident relation to her weight loss. Anamnestic as well as additional studies showed no evidence of a primary kidney disease. After this exclusion, orthostatic proteinuria was confirmed by simple urine analysis. Since the weight loss had not yet been explained, an analysis followed at the Department of Gastrointestinal and Liver Diseases where inflammatory bowel disease (IBD) was found. Literature study shows that proteinuria may be associated with IBD. This concerns mainly selective tubular protein loss, without a distinctive change in protein loss with a change in position. Orthostatic proteinuria, therefore, remained the most likely diagnosis. In this case, the patient was advised to check both urine and kidney function annually.

## KEYWORDS

Orthostatic proteinuria, kidney function, proteinuria, inflammatory bowel disease

## INTRODUCTION

In recent years, there has been much attention for proteinuria, focusing mainly on its pathological significance in the context of renal diseases, progression of this disease, and for proteinuria as a marker of secondary injury of other causative diseases such as arteriosclerosis or diabetes. In addition, protein loss itself could cause damage to glomeruli and tubules which could deliver further deterioration of renal function. However, proteinuria is not always a harbinger of renal damage and loss of renal function. This case shows that isolated proteinuria without

renal disease or renal damage may occur and may have an innocent origin.

## CASE REPORT

A 28-year-old, previously healthy athletic young woman was referred to the Internal Medicine clinic in relation to unintentional weight loss. In a period of five months, she had lost about 12 kilos reducing her weight to 65 kilos (body mass index 18.6). She had had no fever. She denied gastrointestinal complaints and had a normal eating pattern and unchanged defecation. Also diuresis was normal. There were no joint or skin disorders, nor cardiopulmonary symptoms.

She did not smoke, alcohol consumption was limited and she took no medications or vitamins. Her family history was negative for kidney disease and diabetes.

On physical examination no abnormalities were found except the slender habit. Blood pressure was normal, 110/65 mmHg RR.

Laboratory showed no abnormalities; in particular kidney and liver function tests were normal. No inflammatory markers were found and thyroid functions were also normal. Determination of anti-TTG (tissue transglutaminase) was repeatedly negative. Serology revealed no evidence of parasitic infections; a triple faeces test was also negative. Stool examination was negative for elastase and lipase. A chest X-ray revealed no abnormalities; an ultrasound found normal kidneys, in size as well as the aspect of the parenchyma and cortex.

The urine screen tested repeatedly positive for protein, without erythrocyturia, leucocyturia or glucosuria. Quantitative research showed a 24-hour protein excretion of 0.30 g/24 hours (2.10 litre volume, creatinine excretion 13.9 mmol /24 hrs) and a micro-albumin excretion of 127 mg/24 hrs (9.1 micro-albumin/creatinine ratio mg/mmol).

In summary, neither anamnestic nor additional studies were indicative of IgA nephropathy, post-infectious or other primary or secondary renal disorders. Because we suspected orthostatic proteinuria, we asked the patient to collect a single morning urine sample immediately after rising in the morning and a second sample on the same day at normal work and effort patterns.

The morning urine was completely free of protein, the second sample of urine showed a marked proteinuria with a protein/creatinine ratio of 30.2 mg/mmol and 17.1 mg of micro-albumin/creatinine ratio/mmol. Because of this finding, we concluded the proteinuria to be orthostatic proteinuria. The patient refused to start ACE inhibition, partly because of the predominantly good prognosis of this illness and her low-normal blood pressure.

Because we could not explain the substantial weight loss over 12 kilos, she was referred for further analysis. At gastroduodenoscopy, a normal surface of gastric and duodenal mucosa was found and the biopsies were negative for coeliac disease. Colonoscopy, however, yielded an image of a mild sigmoiditis which, on microscopic examination, was suspicious for Crohn's disease. Literature studies found an association with inflammatory bowel diseases and slight to moderate proteinuria without loss of renal function. However, this could not explain the postural aspect of the proteinuria; therefore we did not doubt the existence of orthostatic proteinuria. Regarding this sigmoiditis, the patient remained for therapy on the Gastrointestinal and Liver Diseases ward.

## DISCUSSION

Isolated asymptomatic proteinuria is frequently encountered in daily practice.<sup>1</sup> It is easy to detect, and an estimated quantification by using the dipstick is easy to make, based on coloration of the strip. When finding proteinuria, one should always consider further analysis because proteinuria may be a symptom of a primary renal disease or a complication of another disease such as diabetes, hypertension or systemic disease

In recent years, random screening for proteinuria has increased, partly because of the 'kidney screening' introduced by the Kidney Foundation in the Netherlands. This campaign has now been discontinued because its goal was achieved: attention to and highlighting of early symptoms and the silent course of renal disease and thus to emphasise the importance of screening for proteinuria in risk groups, such as diabetics or patients with hypertension.<sup>2</sup> Early detection of proteinuria could lead to earlier diagnosis and treatment of kidney diseases as well as slowing down the progression of complications of diseases such as diabetes or hypertension.<sup>1,2</sup>

Nevertheless, the existence of isolated asymptomatic proteinuria should not always raise suspicion of a primary renal disease or complication of other diseases. It is therefore essential to make a distinction between innocent causes of transient proteinuria and pathological causes which need treatment in short notice.<sup>1</sup>

## ORTHOSTATIC PROTEINURIA

Orthostatic proteinuria was first reported in the *Lancet* by Pavy in 1885, who described a proteinuria with a cyclic character which consisted of protein-free urine in the morning and at night, but proteinuria at daytime. In 1887, Striling found a relation with position and called it postural proteinuria. Soon, it became known that this cyclic proteinuria was present in 15 to 30% of children and was related to physical disturbances such as headache, dizziness, paleness and collapse. Causal explanations were numerous: anatomical changes, metabolic disorders, glomerular disorders, some kind of infectious or septic kidney disruption, cardiovascular disorder or just a weak constitution were all thought to be possible causes. Nevertheless, it was mostly believed to be a mechanical disorder caused by a hyperlordosis in the lumbar spine, which caused an extension of the renal vein while standing that disappeared while lying down, thus causing hydronephrosis and proteinuria with a variability in protein loss between day and night. As the muscles of the lumbar spines strengthen while growing up and the hyperlordosis disappears, this would explain why this disorder particularly exists in children.

When only orthostatic proteinuria is present, it was believed to be a benign disorder with benign causes, which would probably disappear over time. Urine was checked once in a while for the amount of protein loss. However, when urine samples also showed significant haematuria or cylinders, a renal disorder was suspected.

The first thesis about orthostatic proteinuria in our country dates from 1918 and was written by P.H. Kramer. He tested urine samples from soldiers for protein and found orthostatic proteinuria in 8% of healthy individuals, especially after hard work and effort or long periods of standing. This thesis again emphasised the mechanical anatomical explanation, but also found a relation with a weak cardiovascular system, both of which were supposed to cause congestion of the kidneys.<sup>3</sup>

Nowadays, orthostatic proteinuria can still be defined as isolated proteinuria that occurs in the upright position and disappears in a supine position. This distinguishes orthostatic proteinuria from other benign causes of proteinuria, such as some types of proteinuria during pregnancy, hyperthermia, but also exercise-induced, cold-induced, and orthostatic proteinuria.<sup>2,4</sup> There is a

fixed, reproducible form and a transient form, but the latter could possibly be regarded as a different kind of proteinuria.<sup>2,5</sup> Orthostatic proteinuria is the most common cause of protein loss in children (60%) and adolescents (75%), but its prevalence decreases during ageing and is rare in adults over 30 years.<sup>2,6</sup> The severity of proteinuria can not be used diagnostically, nor for prognostic purposes: proteinuria could even be found in the nephrotic range.<sup>5</sup> While this form of proteinuria has long been known and has been described in many textbooks, maybe the pathophysiology is still not complete or perhaps misunderstood. Several mechanisms may be responsible for the development of proteinuria, including changes in glomerular permeability or inadequate tubular dysfunction, but permanent renal damage is not necessary for proteinuria to occur.<sup>2</sup>

### HAEMODYNAMIC MECHANISM

A number of interesting hypotheses attribute proteinuria to altered renal haemodynamics and associated changes in glomerular filtration. Generally, the degree of protein loss in a standing position is greater than in the supine position, even in normal physiology and a healthy kidney.<sup>5,7</sup> Up to 20% of healthy volunteers would lose more protein in a standing than in lying position, while total proteinuria loss does not exceed 150 mg/day.<sup>6</sup> This can be explained by the increase of angiotensin II and noradrenaline in the standing position, which causes renal efferent vasoconstriction and arteriolar resistance, increases the glomerular filtration pressure and glomerular filtration rate and thus causes an increase of proteinuria.<sup>5,7</sup> It could therefore be assumed that orthostatic proteinuria is an 'exaggerated' response to angiotensin and is thus a variant of a normal response.<sup>5,6</sup> Moreover, it is shown that this increase in protein loss is a selective proteinuria, which supports this hypothesis.<sup>6</sup> In many other forms of proteinuria, such as in pathological glomerulonephritis, also an increase in non-selective protein loss is seen in an upright position. The local glomerular haemodynamics may also change in the standing position, again caused by angiotensin II. By increasing the glomerular filtration pressure and filtration fraction in local efferent vasoconstriction, the intrinsic size selectivity of the basement membrane changes, increasing filtration of large proteins.<sup>9</sup> Damage to the glomerular basement membrane by continued elevated pressures and increased proteinuria could be a logical result.<sup>9</sup> Other studies suggest that non-haemodynamic effects of angiotensin II, which acts as a local endogenous hormone, cause increased production of free oxygen-radicals, upregulation of cytokines and leukotrienes, profibrotic growth factors and, eventually, an increased production of extracellular metalloproteins,<sup>7,9</sup> resulting in proteinuria.

### NUTCRACKER PHENOMENON: OBSTRUCTION MECHANISM

Especially in paediatric literature, much attention is paid to the so-called nutcracker phenomenon as an explanation for orthostatic proteinuria. This phenomenon was first described in 1972. It is thought to be caused by a transient partial obstruction of the left renal vein because of its anatomical location between the abdominal aorta and the superior mesenteric artery.<sup>9,10-12</sup> Although rare, the nutcracker phenomenon causes a variety of symptoms of (left-sided) microscopic and macroscopic haematuria, ureter and parapelvic varices and unexplained flank pain. Also an association was found with chronic fatigue in children.<sup>12,13</sup> This obstruction, which occurs especially in the standing position, also leads to stimulation of angiotensin II by the decreased renal blood flow.<sup>10</sup> Proteinuria may occur or increase in the same way as described above.<sup>5,7,9</sup>

The nutcracker obstruction can be visualised with Doppler ultrasound and MRI, but the gold standard is renal angiography or retrograde renography.<sup>10-13</sup> However, using imaging techniques to show obstruction does not give reliable answers to the haemodynamic significance of this obstruction, so the nutcracker syndrome should solely be a clinical diagnosis.<sup>12</sup> A surgical approach may be chosen if the nutcracker syndrome causes severe symptoms such as massive haematuria causing refractory anaemia or persistent flank pain. For asymptomatic proteinuria, however, surgical intervention is not indicated. ACE inhibition may be considered, with significant reduction or even disappearance of the protein loss.<sup>8,9</sup> However, after cessation of treatment, proteinuria usually reappears. Because of the presumed benign course, it remains unclear whether medical therapy or conservative management should be chosen.<sup>8,9</sup>

### IMMUNOLOGICAL MECHANISM

Still unclear and maybe even controversial remains the significance of subtle but pathological changes found on renal biopsy. These changes are seen in the glomerular basement membrane, best shown by immunofluorescence. There seems to be a possible relationship to complement activation (especially C3 and C4 activation, found in basement membrane in orthostatic proteinuria).<sup>5,6</sup> To increase the knowledge base in this area, further study and research is required, in order that clearer statements can be delivered.

### DIAGNOSTICS

The diagnostics of orthostatic proteinuria are easy to determine in different ways. The most reliable, but less

practical method consists of a 24-hour urine collection, which is separated into a 16-hour collection during the day and an 8-hour collection during the night. The supine position should be taken two hours before finishing the 16-hour day collection, to avoid contamination of the following 8-hour collection of urine.

An easier alternative is calculating a micro-albumin/creatinine ratio in two different urine samples: one first morning urine sample and a sample during the day. The normal value is <0.5 mg/mmol. When the second sample is both dipstick positive for protein and shows an increased micro-albumin/creatinine ratio, orthostatic proteinuria can be strongly suspected.<sup>7,9,14</sup>

## COURSE AND PROGNOSIS

Although it is generally accepted that proteinuria itself could be harmful to the kidney, deterioration of renal function is uncommon and progression to end-stage renal disease has not been described; proteinuria usually decreases and disappears over the years.<sup>1,2,5-7,14,15</sup> To our knowledge, the period during which renal function and proteinuria should be monitored is not explicitly stated. Also, the frequency at which urine samples and kidney function should be checked has not been specified, but annual monitoring seems to be sufficient and reasonable. When renal function deteriorates and with a persistently increasing proteinuria, one should consider other kidney diseases and refer the patient to a nephrologist.<sup>1,2,14,15</sup>

## RELATIONSHIP BETWEEN PROTEINURIA AND IBD?

As described earlier, proteinuria is frequently noted as a secondary phenomenon in disorders other than renal diseases, and can also occur secondary to inflammatory bowel diseases (IBD).<sup>16-18</sup> Proteinuria in inflammatory bowel disease is variable in nature, but seems partly correlated with histopathological staging of the disease and disease activity.<sup>16-18</sup> Some authors even suggest that the degree of proteinuria can be used as a marker for the degree of disease activity.<sup>16,17</sup> This relationship especially seems to exist for the loss of tubular proteins (e.g. microglobulin).<sup>17</sup> The suggestion that proteinuria could be caused by treatment of inflammatory bowel disease can be ignored in our case, since at the time of the analysis and diagnosis, the patient was not taking any medication.<sup>13,16</sup> To our knowledge, only accidental relationships but no causal ones between orthostatic proteinuria and inflammatory bowel disease have been described in literature.

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