

Protein

Normal Physiology

Normally, large quantities of high-molecular-weight (HMW) plasma proteins traverse the glomerular capillaries, mesangium, or both without entering the urinary space. Both charge- and size-selective properties of the capillary wall prevent all but a tiny fraction of albumin, globulin, and other large plasma proteins from crossing.^{[353] [354]} Smaller proteins (<20,000 D) pass readily across the capillary wall.^{[355] [356]} However, because the plasma concentration of these proteins is much lower than that of albumin and globulins, the filtered load is small. Moreover, LMW proteins are normally reabsorbed by the proximal tubule. Thus, proteins such as α_2 -microglobulin, apoproteins, enzymes, and peptide hormones are normally excreted in only very small amounts in the urine.^{[355] [356]} Most healthy individuals excrete between 30 and 130 mg/day of protein, and the upper limit of normal total urine protein excretion is generally given as 150 to 200 mg/day for adults.^{[357] [358] [359]} The upper limit of normal albumin excretion is usually given as 30 mg/day.^[359]

The very small amount of protein that normally appears in the urine is the result of normal tubular secretion. Tamm-Horsfall protein is an HMW glycoprotein (23×10^6 D) that is formed on the epithelial surface of the thick ascending limb of the loop of Henle and early distal convoluted tubule.^{[360] [361]} Tamm-Horsfall protein, also known as uromodulin, binds and inactivates the cytokines interleukin-1 and tumor necrosis factor.^{[362] [363]} Immunoglobulin A (IgA) and urokinase are also secreted by the renal tubule and appear in the urine in small amounts.^[364]

From a consideration of normal physiology, it is apparent that abnormal amounts of protein may appear in the urine as the result of three mechanisms. First, a disruption of the capillary wall barrier may lead to a large amount of HMW plasma proteins that overwhelm the limited capacity of tubular reabsorption and cause protein to appear in the urine. The resulting proteinuria can be classified as glomerular in origin. Second, tubular damage or dysfunction can inhibit the normal resorptive capacity of the proximal tubule, resulting in increased amounts of mostly LMW protein to appear in the urine. Such proteinuria can be classified as tubular proteinuria. Third, increased production of normal or abnormal plasma proteins produced can be filtered at the glomerulus and overwhelm the resorptive capacity of the proximal tubule. These filtered proteins can be especially numerous if they are small or positively charged. Finally, although greater urine protein excretion can also result from increased tubular production of protein, this is rarely the case.