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Renal Involvement in Psychological Eating Disorders

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Key Words

Chronic renal disease · Acute kidney injury · Eating disorders · Anorexia nervosa · Bulimia nervosa

Abstract

Psychological eating disorders – anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder – are an increasing public health problem with severe clinical manifestations: hypothermia, hypotension, electrolyte imbalance, endocrine disorders and kidney failure; they are of interest to nephrologists, but pathophysiological mechanisms in determining the renal involvement are still unclear. We describe pathophysiology, histological features and clinical manifestations of the most frequent psychological eating disorders: AN and BN. Regarding AN, we analyze the recent literature, and identify 3 principal pathways towards renal involvement: chronic dehydration-hypokalemia, nephrocalcinosis and chronic rhabdomyolysis. Regarding BN, we describe the correlation between obesity and many proinflammatory cytokines, chemokines, growth factors and adipokines, having potential metabolic and hemodynamic effects on the kidney and an important role in the pathogenesis of obesity-related renal injury, independently of hypertension and diabetes.

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Introduction

Eating disorders (EDs) represent a common and serious class of psychiatric disorders. According to DSM-IV [1], they include anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder and EDs not otherwise specified (EDNOS). Psychological EDs are an increasing public health problem [2] with severe clinical manifestations: hypothermia, hypotension, electrolyte imbalance, endocrine disorders and kidney failure. AN is characterized by a severely calorie-restricted diet, resulting in a body weight that is at least 85% below that expected for age and height. BN is identified by frequent fluctuations in weight and recurrent episodes of compulsive bingeing followed by self-induced vomiting, purging, fasting, laxative use and/or excessive exercise in attempts to avoid weight gain. Binge eating disorder is a more recently described syndrome characterized by repeated episodes of binge eating, similar to those of BN, in the absence of inappropriate compensatory behavior. EDNOS include behaviors such as chronic dieting, purging and binge eating, which do not meet the full criteria for a specific eating disorder; they are two to five times as common as the clinical EDs [3]. The correlation between kidney disease and EDs is of interest in common nephrological

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practice, but pathophysiological mechanisms in determining the renal involvement are still unclear. Sometimes, it is difficult to determine renal excretory function in this population: in 55 patients with AN and 44 patients with BN, Fabbian et al. [4] evaluated renal function with Cockcroft-Gault (C-G) formula for creatinine clearance calculation and glomerular filtration rate (GFR) with MAYO and MDRD equations. They determined that C-G is inaccurate when it is applied to obese or cachectic subjects, MDRD underestimates renal function in normal-high GFR, and MAYO seems to be a good alternative to the other equations leading to correct classification of patients.

About the chronic kidney failure, in 1985 Boag et al. [5] showed an improvement in creatinine clearance with weight gain in 9 of 10 patients with AN. There are no further studies in the literature about the evolution of renal function impairment in AN. We describe pathophysiology, histological features and clinical manifestations of the most frequent psychological EDs: AN and BN.

Discussion

Anorexia Nervosa

Hypokalemia is the most common laboratory finding in AN. Miller et al. [6] detected a prevalence of 19.7% of hypokalemia among 214 women with AN. Hypokalemic nephropathy is a well-known disease [7] characterized by renal hypertrophy and renal tubular cell hyperplasia involving the medullary collecting ducts and, to a lesser extent, the thick ascending limb in association with tubular atrophy, interstitial macrophage infiltration and interstitial fibrosis. Analyzing the most recent literature, we identify 3 principal pathways towards renal involvement: chronic dehydration and hypokalemia, nephrocalcinosis and chronic rhabdomyolysis (fig. 1). Chronic potassium depletion could lead to irreversible damage to the renal tubule. In vitro studies in rat models demonstrated a progressive hypokalemia-induced tubulointerstitial injury. The number of patients with AN who underwent histological evaluation is limited. Arimura et al. [8] highlighted in well-documented histological reports of AN chronic tubulointerstitial nephritis with prolonged hypokalemia. Manzato et al. [9] suggested a possible type of hypokalemic nephritis specific to AN and characterized by tubular atrophy, mononucleocyte infiltration into the interstitial spaces, interstitial fibrosis and juxtaglomerular hyperplasia. Loss of water and salts (diuretic and laxative abuse), metabolic

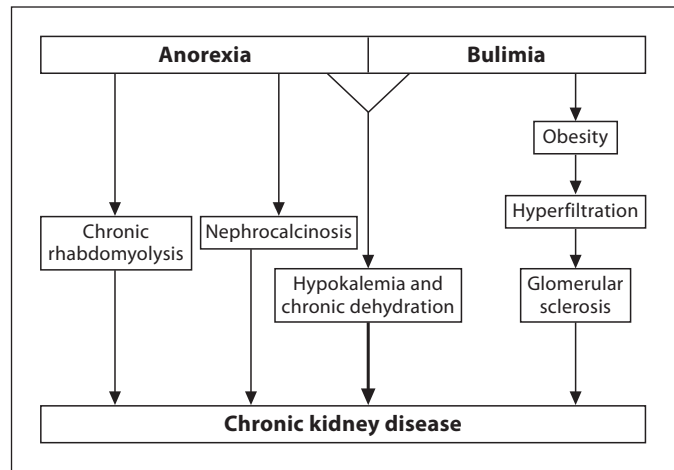


Fig. 1. Principal pathways towards renal involvement.

alkalosis (loss of acids through vomiting) and hyperaldosteronism secondary to hypovolemia in AN induced hypokalemia and chronic dehydration. It is possible to misdiagnose an eating disorder as a primary tubulopathy (e.g. Gitelman's disease) and vice versa. Three pathophysiological mechanisms may lead to renal lesions: increased ammoniogenesis, activation of vasoactive mediators and arterial hypersensitivity to Na^+ . Hypokalemia stimulates HCO_3^- reabsorption and ammoniogenesis followed by amination of C3, with consequent activation of the alternative complement pathway and deposition of proteins in the tubule. Hypokalemia causes alterations in the levels of vasoactive mediators: increase in vasoconstrictor stimuli (ACE, ET-1 and subtype B α -adrenergic receptors) and reduction in vasodilatory stimuli (EDRF-1 and PGE2). Moreover, hypokalemia is associated with increased activity of the cotransporter $\text{Na}^+\text{K}^+\text{2Cl}^-$ in the ascending limb of the loop of Henle; it may be consequent to hydrosaline retention and sometimes elevated arterial pressure. Nephrolithiasis and electrolyte disturbances (hypokalemia, hyponatremia, hypocalcemia, hypomagnesemia and hypophosphatemia) have been reported in patients with AN; they are potential risk factors that may predispose to nephrocalcinosis. Chronic diarrhea may also contribute to nephrocalcinosis by causing chronic volume depletion. Renal failure may result from tubular cell injury, tubular obstruction by calcified debris, and atrophy of nephrons. Chronic inflammation and interstitial fibrosis accompany these changes. Roberts et al. [10] described 2 cases of severe renal failure and nephrocalcinosis with histo-

logical findings, and Lim et al. [11] reported 1 case of nephrocalcinosis and senna misuse, both in anorexic patients. Hypokalemia is a known cause of rhabdomyolysis. There are some case reports of rhabdomyolysis in AN with [12] or without [13] acute renal failure. We suppose that dietary restriction and starvation, severe energetic deficit, chronic dehydration and metabolic derangement, especially hypophosphatemia and/or phosphate depletion, may induce chronic subclinical release of tissue catabolism products (CK, aldolase, AST, ALT, LDH, myoglobin) and chronic kidney injury. In AN patients, a significant alteration of the osmoregulation has been documented with an impaired urinary concentrating ability and a blunted reactivity of ADH. The potential influence of antidepressant drugs has been suggested [14]. This alteration may contribute to hydroelectrolytic imbalance and chronic renal failure.

Bulimia Nervosa

Renal function has been reported to be impaired even in the short-term by binge/purges in bulimia [15]. However, few studies have examined the extent of renal damage, especially morphologic changes, over long-term bulimic symptoms [16, 17]. Yasuhara et al. [17] described a case of a woman with longstanding BN and end-stage renal disease (ESRD). After the patient died of pneumonia and sepsis at age 52 years, autopsy of her kidney showed chronic interstitial nephritis and proximal tubular swelling. These morphologic changes were consistent with hypokalemic nephropathy. Moreover, autopsy examination of the kidneys revealed diffuse glomerular sclerosis, which may be also induced by obesity during the period of increased body weight. Indeed, a positive association between high body mass index (BMI) and risk for chronic kidney disease has been reported [17, 18]. In a large study performed in 320,252 adult volunteers, the adjusted relative risk for ESRD was 3.6 (95% CI, 3.05–4.18) for those with class I obesity (BMI, 30.0–34.9), 6.1 (95% CI, 5.0–7.5) for those with class II obesity (BMI, 35.0–39.9) and 7.1 (95% CI, 5.4–9.30) for those with morbid obesity (BMI \geq 40) compared with persons who had normal weight (BMI, 18.5–24.9) [16].

This finding persisted even after additional adjustments for baseline blood pressure level and presence or absence of diabetes mellitus [18].

Obesity

There are two major mechanisms by which obesity causes chronic kidney disease: (1) obesity may cause kidney damage directly or (2) through obesity-associated

diseases. There are several studies showing how obesity may result in functional and structural changes in the kidney. Morphologic features in obese individuals include glomerulomegaly, focal segmental glomerulosclerosis with predominance of classic perihilar lesions of sclerosis, and relatively mild foot process fusion (obesity-related glomerulopathy). Severe obesity is characterized by an increase in GFR, renal plasma flow, albumin excretion rate and fractional albumin clearance. Early stages of obesity in animal models result in increase in arterial pressure, hyperinsulinemia, activation of the renin-angiotensin system and glomerular hyperfiltration. Hormonal changes, low-grade inflammation, oxidative stress and endothelial dysfunction are the main possible pathogenic mechanisms of renal damage in obesity. During the last decade, white adipose tissue was recognized as an active endocrine organ and a source of many proinflammatory cytokines, chemokines, growth factors (angiotensin II, and transforming growth factor- β_1), complement proteins called 'adipokines' or 'adipocytokines'. These adipokines, having potential metabolic and hemodynamic effects on the kidney, seem to play an important role in the pathogenesis of obesity-related renal injury, independently of hypertension and diabetes. Patients with BN frequently exhibit fluid-electrolyte and acid-base disturbances. Routine screening detects an electrolyte abnormality in 10% of patients with BN. This is attributed to an erratic eating pattern, often accompanied by vomiting, ingestion of laxatives or diuretics, and use of enemas, frequently leading to dehydration. Dehydration can cause volume depletion that may contribute, even acutely, to impaired renal function. Although renal dysfunction in AN is often corrected after weight gain, habitual binge/purges in BN tend to be treatment resistant, which could lead to irreversible renal changes. Therefore, in patients with BN, intensive monitoring, early detection, and adequate treatment of fluid-electrolyte abnormalities and of kidney function disturbances are very important.

Disclosure Statement

The authors declare no conflicts of interest.

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Editorial Comment

M. El Nahas, Sheffield

The review by Li Cavoli et al. on renal manifestations of eating disorders reminds nephrologists of a number of electrolyte disorders associated with anorexia nervosa, including severe hypokalemia, hyponatremia and hypophosphatemia. Severe dehydration and alkalosis can also contribute to impaired kidney function as well as ammonium urate stone formation in these individuals. Therefore, careful scrutiny of fluid intake to regularly monitor serum electrolytes is important in the care of people with this eating disorder. Formulation of effective and preventive treatments can attenuate the risks of acute kidney injury. Anorexia as well as bulimia nervosa has also been associated with rhabdomyolysis and its complications. Bulimia and obesity may predispose to microalbuminuria and focal segmental glomerulosclerosis. Finally, the authors stress the difficulties of estimating renal function

(glomerular filtration rate, GFR) in people with eating disorders and extremes of weight. Cockcroft-Gault is inaccurate when applied to obese or cachectic subjects. MDRD underestimates renal function in normal-high GFR. The Mayo Clinic quadratic equation seems to be a good alternative compared to the other equations leading to a correct diagnosis and classification of subjects with eating disorders as renal insufficient [1]. Faced with an individual with a severe eating disorder, the nephrologist should be aware of the range of fluid and electrolyte disorders that can affect the kidneys acutely and chronically.

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