Obesity and Kidney Disease: A Focus on Ciliopathies

In depth review

Andrea Melluso[1], Alessandra Perna[2], Miriam Zacchia[2]

1 Nephrology and Dialysis Unit, "don Tonino Bello" Hospital, ASL Bari, Molfetta, Italy
2 Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

Corresponding author:
Andrea Melluso
E-mail: andrea.melluso@virgilio.it


Andrea Melluso

ABSTRACT

The prevalence of obesity is progressively increasing on a global scale. Among its negative health consequences, renal damage is also observed. It is due to hemodynamic, metabolic, and inflammatory alterations.

Ciliopathies are a group of disorders caused by dysfunction of the primary cilium; these include autosomal dominant polycystic kidney disease (ADPKD) as well as Alström and Bardet-Biedl syndromes. In ADPKD, obesity accelerates kidney disease progression. In Alström and Bardet-Biedl syndromes, renal disease is likely due to both local and systemic factors; in these syndromes, obesity represents one of the most common clinical manifestations, and studies are currently underway to evaluate its role in the progression of chronic kidney disease.

The management of obesity involves lifestyle interventions, medications, and surgery. Interesting new pharmacological advances are now available for both obesity in the general population and obesity associated with certain genetic disorders; the protective role of many of these drugs in the progression of chronic kidney disease – sometimes even independent of weight loss – is an observation that further highlights the intricate relationship between dysmetabolism and kidney disease.

KEYWORDS: obesity, chronic kidney disease, ciliopathies, ADPKD, Bardet-Biedl syndrome, Alström syndrome

Obesity and Renal Health. Epidemiology

Adult obesity is defined by the World Health Organization (WHO) as a body mass index (BMI) ≥ 30 kg/m², while overweight is defined as a BMI between 25 and 29.99 kg/m². In Europe, the prevalence of obesity is around 20%, with some countries exceeding 30%, and it is projected to reach 24% globally by 2035 [1, 2].

Obesity is more common among individuals with a genetic predisposition, which may be monogenic, oligogenic, or polygenic. Non-syndromic monogenic forms are rare and are typically associated with mutations in genes that regulate the interaction between the brain and adipose tissue, such as those encoding leptin, its receptor, the melanocortin 4 receptor, proconvertase 1, and proopiomelanocortin, which are involved in the leptin-melanocortin pathway. Oligogenic forms account for approximately 3% of cases, while most hereditary obesity has a polygenic basis influenced by epigenetic factors [3].

The detrimental effect of obesity on kidney function is well documented. A systematic review and meta-analysis confirmed that obesity is an independent risk factor for the development of albuminuria (relative risk 1.51, 95% CI 1.36-1.67) and chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² (relative risk 1.28, 95% CI 1.07-1.54) [4]. Furthermore, obesity is a risk factor for nephrolithiasis [5].

Epidemiological and observational studies report that 4-10% of obese patients exhibit proteinuria. However, determining the true incidence of obesity-related glomerulopathy is challenging due to variations in the biopsy protocols adopted by different centers [3].

Indices that measure central fat distribution, such as the waist-to-hip ratio, are more closely associated with the risk of end-stage kidney disease (ESKD) than BMI [6, 7]. Although BMI is the most commonly used parameter in clinical practice, it has several limitations, including its inability to differentiate body composition (which is important in the context of potential fluid retention) and fat distribution. An elevated waist-to-hip ratio (≥0.9 in men and ≥0.8 in women) is associated with a higher risk of reduced renal filtration, independent of BMI. This is because central adiposity correlates with diminished renal function even in non-obese individuals. Moreover, advanced techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) can provide more accurate measurements of metabolically active visceral fat [1, 8–10]. The distribution of adipose tissue appears to partly explain the difference in CKD risk between men and women [11].

Another promising index is the weight-adjusted waist index (WWI), calculated as waist circumference in centimeters divided by the square root of body weight in kilograms. The WWI was found to be the best indicator of obesity for predicting CKD and albuminuria compared to other parameters such as BMI, the waist-to-height ratio (WHTR), or waist circumference (WC) [12, 13].

A prospective study of 2,711 Korean participants with normal renal function and an average follow-up of 11 years reported a CKD incidence of 7%. The risk of renal disease was higher in patients with elevated BMI values and, more significantly, with higher waist-to-hip ratios. Moreover, Kaplan-Meier curves demonstrated that reducing obesity improves renal prognosis [14].

A study by Kanda et al. examined the effects of weight loss on renal function in healthy individuals, revealing significant differences based on sex, the rate of weight loss, and baseline BMI [15].

A multivariate analysis of data from the CureGN study did not find an increased risk of renal events in obese patients with glomerulopathies. However, the study had several limitations [16].

Renal damage

Renal damage associated with obesity results from both direct effects of adipose tissue on the kidneys and systemic complications related to conditions such as diabetes, metabolic syndrome,

dyslipidemia, atherosclerosis, and hypertension. These factors lead to hemodynamic, metabolic, and inflammatory alterations that underlie renal injury [3] (Figure 1).

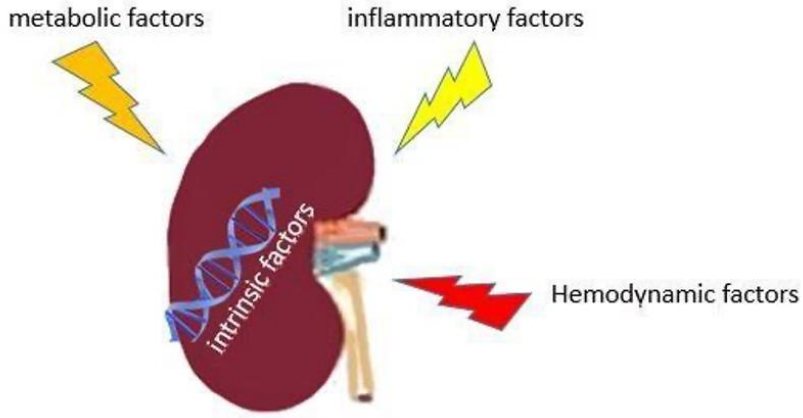

Figure 1. Obesity causes hemodynamic, inflammatory, and metabolic alterations that damage the kidney. In addition, intrinsic factors, such as genetic mutations, may compound this damage.

- **Glomerular hyperfiltration and hemodynamic alterations** [3, 4, 11, 17] In the presence of insulin resistance, sympathetic nervous system overactivity, and activation of the renin-angiotensin system (RAS), glomerular hypertension and an increased glomerular filtration rate occur.
  The dilation of the afferent arteriole coupled with efferent arteriole vasoconstriction – although initially compensatory – over time leads to glomerular hypertrophy, glomerulosclerosis, and proteinuria (generally subnephrotic, rarely nephrotic). Additionally, visceral fat may exert mechanical compression on the kidneys and vessels, further contributing to RAS activation, while adipose tissue directly produces RAS components (such as aldosterone and angiotensinogen), inducing sodium retention and volume expansion.
- **Adipose Tissue** [3, 11, 18] Perirenal fat and renal sinus fat (RSF), located near the renal arteries, compress the renal structures and secrete cytokines and angiogenic factors that influence the vascular wall. Studies have shown that an increase in RSF mass may worsen microalbuminuria, particularly during physical exercise, although available data remains limited.
  Moreover, adipose tissue releases proinflammatory cytokines that promote a state of chronic inflammation and oxidative stress while reducing the production of adiponectin, which has anti-inflammatory and insulin-sensitizing properties. Hyperleptinemia, observed in patients with CKD, exacerbates inflammation, stimulates sympathetic tone, sodium reabsorption, glomerular cell proliferation, and increases type IV collagen synthesis, promoting fibrosis and glomerulosclerosis. Mesangial cells respond to leptin by increasing glucose uptake, undergoing hypertrophy, and, as well as endothelial cells, enhancing the release of extracellular matrix components.
- **Insulin Resistance and Hyperinsulinemia**[1, 6, 11] These factors contribute to renal damage through mechanisms such as glomerular hyperfiltration, albuminuria, oxidative stress, and endothelial dysfunction. It is important to note that the predisposition to insulin resistance is not determined solely by BMI; even individuals with normal weight can be at risk for developing complications.

Therefore, adipose tissue is not merely an energy storage depot but an endocrine organ that secretes adipokines, regulating processes such as inflammation, metabolism, appetite,

cardiovascular function, and immunity. In fact, the type and amount of adipokines released by adipose tissue depend on several factors, including the type of adipocytes (white or brown), their quantity, location, and interactions with other cells.
Adipocytes are primarily divided into two categories: white adipocytes, which are most abundant in adults and store energy in the form of triglycerides, and brown adipocytes, which are less numerous and more abundant in neonates, storing energy in small lipid droplets. In addition, there is a third type, beige adipocytes – a subtype of white adipocytes – that, in response to cold exposure or specific pharmacological agents, acquire characteristics similar to brown adipocytes. The activation of the beiging process increases energy expenditure and improves carbohydrate and lipid metabolism [19].

Clinically, the earliest sign of obesity-related renal damage is a gradual increase in subnephrotic-range proteinuria [18].
Weight reduction lowers levels of obesity-related proinflammatory cytokines (e.g., TNF-α, MCP-1, and serum amyloid) [11].

Histopathological Alterations

The kidneys of obese patients tend to increase in volume [1, 6]. The diagnosis of obesity-related glomerulopathy (ORG) is based on the clinical and histopathological exclusion of other renal diseases in subjects with a BMI ≥30 kg/m². Histopathologically, ORG is characterized by glomerulomegaly, which may be accompanied by secondary focal segmental glomerulosclerosis, often localized in the perihilar glomeruli. Additionally, one may observe a reduction in podocyte density, an increase in the width of foot processes, thickening of the glomerular basement membrane, expansion of the mesangial matrix, and mesangial sclerosis.

Histological studies have also demonstrated that renal tubules can be affected, showing hypertrophy of the proximal tubular epithelial cells. Intracellular lipid vacuoles may occasionally be observed in these epithelial cells, as well as in podocytes and mesangial cells [3, 18].

An important factor in the development of ORG is the presence of predisposing conditions, such as a low nephron number at birth and renal anomalies that, when coupled with compensatory growth, may further promote glomerular hyperfiltration. Frequently associated with visceral obesity, hypertriglyceridemia is another factor that worsens renal outcomes.

Treatment of Obesity

The management of obesity includes lifestyle modifications (physical activity, nutrition, behavioral therapy), medications, and bariatric surgery.

Physical activity can reduce mortality risk even in patients with CKD, although there are currently no definitive recommendations regarding frequency, intensity, and duration; therefore, a gradual increase in activity is advised. In polycystic patients, activities that might cause trauma sufficient to rupture cysts should be avoided.

Various dietary interventions have been proposed for patients with ADPKD (e.g., caloric restriction, intermittent fasting, time-restricted feeding, and the ketogenic diet): in these patients, in addition to the benefits related to reduced visceral adiposity, an improvement in nutrient control and cellular energy status is hypothesized, which may influence the mTOR pathway that is abnormally activated in renal cysts [11, 20].

The first-line pharmacological choice for obesity-related hypertension are ACE inhibitors or ARBs because they reduce the risk of obesity-associated glomerulopathy and are associated with a lower incidence of diabetes and favorable effects on left ventricular hypertrophy [17]. Sodium restriction is also important.

When lifestyle interventions are insufficient, a broad range of medications may be used for the treatment of obesity (indicated for a BMI ≥30 kg/m² or ≥27 kg/m² in the presence of weight-related comorbidities). Approved drugs for body weight management include orlistat, extended-release naltrexone/bupropion, controlled-release phentermine/topiramate (a combination of a sympathomimetic and a carbonic anhydrase inhibitor, not approved by the EMA), setmelanotide, GLP-1 receptor agonists (liraglutide and semaglutide), and dual GLP-1/GIP agonists (tirzepatide).

Orlistat is an intestinal lipase inhibitor that reduces fatty acid absorption by up to 30%, leading to approximately 5% weight loss. The most common side effects include flatulence and malabsorption, which can result in reduced levels of vitamin D, vitamin E, and beta-carotene, making supplementation necessary.

The bupropion-naltrexone combination reduces appetite and cravings. Bupropion is a norepinephrine and dopamine reuptake inhibitor that promotes activation of the melanocortin pathway. Naltrexone, a μ-opioid receptor antagonist, mitigates the auto-inhibitory feedback triggered by bupropion on hypothalamic anorexigenic neurons. Common side effects include nausea, vomiting, headache, insomnia, and dry mouth; the potential emergence of suicidal thoughts should be monitored.

Liraglutide is a GLP-1 (glucagon-like peptide) receptor agonist that reduces appetite, slows gastric emptying, and helps balance insulin and glucagon secretion. At a dose of 3 mg/day, liraglutide can reduce body weight by 5-10% and delay the onset of diabetes in obese prediabetic individuals, while also improving glycemic control, blood pressure, and lipid profile. A dose of 1.8 mg is associated with a decreased risk of major cardiovascular events in diabetic patients. Its adverse effects are primarily gastrointestinal (nausea, vomiting, constipation, diarrhea), which can be mitigated by gradual dose escalation. It is contraindicated in patients with a history of pancreatitis, in pregnant women, and in individuals with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia (MEN).

Semaglutide, a long-acting GLP-1 agonist, is used either to reduce the risk of major adverse cardiovascular events (MACE) in adults with cardiovascular disease associated with obesity/overweight or for weight loss in obese or overweight patients with related comorbidities. It works by slowing gastric emptying and producing a central anorexigenic effect. Its main adverse effects are gastrointestinal, and similarly to liraglutide, it is contraindicated in pregnancy and in patients at risk for medullary thyroid carcinoma or MEN.

Tirzepatide is a GLP-1 and GIP receptor agonist that, when administered once weekly, reduces appetite, increases insulin sensitivity, and enhances glucose and triglyceride uptake in adipose tissue. The SURMOUNT studies have reported an average weight loss of 20%, with predominantly gastrointestinal side effects and low treatment discontinuation rates.

Setmelanotide is a melanocortin-4 receptor agonist that reduces appetite. Approved for the treatment of certain forms of monogenic obesity and for patients with Bardet-Biedl syndrome, it is administered subcutaneously once daily. The main adverse effects are local injection site reactions, hyperpigmentation, and nausea; there is a manufacturer warning regarding suicidal ideation and depression. Some drugs, although not specific for obesity management, have beneficial effects on body weight, such as metformin and SGLT-2 inhibitors.

Metformin reduces hepatic glucose production and increases insulin sensitivity. The hypothesized mechanisms for weight reduction include activation of AMPK, an increase in levels of anorexigenic hormones, and enhanced leptin sensitivity. Clinical studies indicate a long-term weight reduction of around 3%, with mainly gastrointestinal side effects and a rare risk of lactic acidosis; prolonged use may cause vitamin B12 deficiency.

SGLT-2 is the protein responsible for reabsorbing most of the glucose in the renal tubules. In patients with diabetes mellitus, SGLT-2 overexpression is often observed during the hyperfiltration phase, exacerbating hyperglycemia and renal stress. This has led to the development of SGLT-2 inhibitors, a class of drugs that block these cotransporters, increasing urinary glucose excretion. SGLT-2 inhibitors improve glycemic control, reduce blood pressure, mortality, and cardiovascular morbidity, slow CKD progression (by reducing hyperfiltration, proteinuria, oxidative stress, and inflammation), and result in an approximate weight loss of 2 kg, although this effect may also be partly due to reduced body water and offset by an increased appetite. The main adverse effects include urinary and genital infections, dehydration, and, in rare cases, diabetic ketoacidosis due to increased lipolysis and free fatty acid release [3, 11, 17, 21, 22].

Several of the aforementioned drugs are known to exert a protective effect against the progression of renal disease, particularly SGLT-2 inhibitors, GLP-1 agonists, and tirzepatide (Table 1).

Class	Main Effects
GLP-1 agonists	Reduction of proinflammatory cytokines and oxidative stress, improved glycemic and blood pressure control, decreased proteinuria and hyperfiltration (natriuresis) in DKD, weight loss, and RAAS inhibition (likely via an indirect mechanism).
Tirzepatide	Similar effects to GLP-1 agonists, with a more pronounced impact on body weight and metabolism due to its action on GIP.
SGLT-2 inhibitors (SGLT2i)	Reduction of hyperfiltration, increased natriuresis, decreased proteinuria, and cardiovascular and renal protection independent of glycemic control.

Table 1. Main effects of selected drugs with protective action on renal function.

Regarding bariatric/metabolic surgery, the National Institute for Health and Care Excellence (NICE) guidelines recommend bariatric surgery as a treatment option for individuals with a BMI ≥40 kg/m², or between 35 and 40 kg/m² in the presence of comorbidities (e.g., type 2 diabetes, hypertension) that may benefit from weight loss. Recently, new guidelines from ASMBS and IFSO have significantly expanded the indications for surgery, recommending consideration of surgery for individuals with a BMI between 30 and 35 kg/m² in the presence of metabolic diseases such as type 2 diabetes when non-surgical therapies have yielded insufficient results. In some cases, for patients of different ethnic backgrounds (e.g., Asians with a BMI >27.5 kg/m²) or as a “bridge” to subsequent treatments (such as organ transplantation), bariatric surgery may be indicated [23].

The two most common procedures are laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG). A systematic review found that, one year after the intervention, the LRYGB technique achieved a slightly higher percentage of total weight loss (%TWL) compared to LSG; however, at 5 years the differences between the two techniques were not significant, with mean values of 28.1% for LRYGB and 27.0% for LSG [24].

Weight loss reduces proteinuria and microalbuminuria in CKD patients. The proposed mechanisms include improved blood pressure control, lipid profile, insulin sensitivity, reduced leptin levels, lower activation of the RAAS, decreased glomerular hyperfiltration, and reduced inflammatory processes.

Further larger and longer-term studies will be useful to better understand the effect of weight loss on CKD progression [11].

Obesity and Ciliopathies

Cilia are microtubular structures classified, based on the architecture of their axoneme, into motile (9+2) and non-motile (9+0) types. The latter, known as primary cilia, are widely expressed throughout the body and function as sensors and transducers of cellular signals. Through receptors such as Wnt, Hedgehog, TGFβ, and PDGFR, primary cilia participate in the transduction of extracellular signals [25].
The term "ciliopathies" refers to a group of disorders caused by dysfunction of the primary cilium, such as autosomal dominant polycystic kidney disease (ADPKD), Bardet-Biedl syndrome (BBS), Alström syndrome (ALMS), and Senior-Løken syndrome.

ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) affects over 10 million people worldwide and is primarily caused by variants in the *PKD1* and *PKD2* genes, which encode polycystin 1 (PC1) and polycystin 2 (PC2), respectively. These proteins maintain primary cilium function and preserve the integrity of the renal tubules.
It is noteworthy that there is evidence for a dual ciliary function: in normal renal cells, the primary cilium inhibits cyst formation, whereas in ADPKD – when the polycystin complex is altered – it promotes cystic growth [26–29].

The accumulation of adipose tissue can exacerbate the metabolic defects associated with ADPKD by influencing various cellular signaling pathways.
In the HALT-PKD A study, a high BMI was associated with a greater increase in total kidney volume (TKV) and a more rapid decline in eGFR. In obese patients, the risk of rapid TKV progression (annual variation rate ≥7% versus <5%) was approximately four times higher, and the annual percentage increase in TKV was more than 50% greater compared to normal-weight patients.
In the TEMPO 3-4 study, the association between BMI and TKV increase was confirmed, whereas the decline in eGFR correlated with BMI only in women. To avoid bias due to the weight contribution of the cysts, in both cited studies TKV was calculated by subtracting the estimated cyst weight. Discrepancies in the results may be attributable to the lack of consideration of body fat distribution or other factors.

The TEMPO 3:4 study demonstrated that the efficacy of Tolvaptan, a drug used to slow the progression of ADPKD, was independent of BMI. However, a subsequent retrospective cohort study revealed that an increase in visceral fat more accurately predicts renal volume expansion than BMI in lean subjects, and that the drug's efficacy decreases with increasing visceral fat [11, 30–32].

Obesity affects hormone and cytokine levels, leading to increased activation of the PI3K/Akt pathway, which promotes cell survival and growth. Adiponectin – whose levels are reduced in obesity – activates AMPK, which in turn inhibits the mTOR pathway and reduces cellular proliferation. Concurrently, cytokines released from visceral fat, such as IL-6 and TNF-α, stimulate inflammation and cell proliferation, while insulin activates the PI3K-Akt, mTOR, and MAPK pathways. Moreover, saturated fatty acids bind to fetuin, an endogenous ligand for TLR2/TLR4 receptors, triggering a chronic low-grade inflammatory response.

Weight loss in obese subjects with ADPKD represents a potential therapeutic target to improve metabolic status, reduce TKV increase, and the pro-inflammatory response [11].

Syndromic ciliopathies characterized by obesity and kidney disease: Bardet-Biedl syndrome and Alström syndrome

Bardet-Biedl syndrome (BBS) and Alström syndrome (ALMS) present a clinical spectrum that includes early-onset obesity and renal dysfunction.

Bardet-Biedl syndrome is a rare autosomal recessive genetic disorder with an estimated prevalence of 1 in 120,000 to 160,000 in North America and Europe, while in some isolated communities, the frequency is significantly higher. Diagnosis, based on Beales's criteria, requires the presence of at least four primary features or three primary and two secondary features. Early diagnosis can be challenging, as clinical signs manifest progressively over time, and genetic testing can be useful for confirmation [33].

Obesity is one of the primary clinical features of BBS and manifests early: although birth weight is normal, 90% of patients experience weight gain within the first year of life, with obesity becoming evident by age three. A study by Feuillan et al. showed that BBS patients have greater visceral adiposity than BMI-matched controls, even after adjusting for covariates (age, sex, race, and total body fat percentage measured via DEXA). However, after further adjusting for age, sex, race, total body fat percentage, free testosterone, and estradiol, the difference in visceral fat adiposity becomes non-significant ($p = 0.06$). Leptin levels are higher than in controls relative to the degree of adiposity, suggesting resistance to this hormone.
In a comparison between groups with *BBS10* and *BBS1* mutations, the former showed higher BMI Z-scores and greater visceral obesity than the latter. Other genotype-phenotype studies suggest that *BBS1* mutations are linked to a milder obesity phenotype compared to other BBS genotypes (a difference that seems to diminish in adolescence), while *BBS9* and *BBS4* mutations are associated with higher BMI. Children with loss-of-function mutations have a higher risk of developing severe obesity [33–35].

The prevalence of kidney disease in BBS patients varies across studies, partly due to differing definitions. A study by Forsythe et al. on 350 patients found that 31% of children and 42% of adults had CKD at stages 2-5, while CKD stages 4-5 were present in 6% of pediatric subjects and 8% of adults. Meyer et al., analyzing 607 BBS patients from the Clinical Registry Investigation of BBS (CRIBBS), identified an end-stage renal disease (more accurately termed 'Kidney Failure') stage in 44 individuals (7.2%).

Renal abnormalities arise from both anatomical and functional causes, and the pathogenesis of kidney disease remains partially understood. The expression of BBS proteins in the kidney suggests a local contribution to renal damage. A study on 54 patients found that hyposthenuria was associated with a more rapid decline in eGFR. This reduced urine concentration capacity may indicate a tubulointerstitial disorder. Furthermore, the observation that even patients with preserved eGFR exhibit abnormalities on functional magnetic resonance imaging, particularly in the medullary region, strengthens the hypothesis of a primary tubulointerstitial disorder.

The frequent presence of factors such as obesity, diabetes, and hypertension highlights the need for in-depth analyses to quantify their contribution to kidney damage. Our recent observational study of 65 patients with BBS demonstrated that reduced eGFR correlates with hypertension and truncating mutations in any *BBS* gene; moreover, in multivariate analysis, BMI was independently associated with eGFR decline ($\beta = -2.45$; $p < 0.0001$). The presence of significant phenotypic discordance in 50% of patients with the same pathogenic variants supports the hypothesis of an interplay between intrinsic and secondary factors [33, 36, 37].

The etiopathogenic mechanisms underlying obesity in certain ciliopathies are not yet fully understood and appear to derive from multiple factors involving energy metabolism regulation at both central and peripheral levels. Neurons and glial cells also possess cilia, and the hypothalamus plays an essential role in energy homeostasis. In the hypothalamic arcuate nucleus, two neuronal populations – AgRP and POMC neurons – regulate appetite and energy expenditure: AgRP neurons activate under energy deficit conditions and are inhibited by insulin and leptin, whereas POMC

neurons activate under energy surplus conditions, reducing food intake and increasing energy expenditure [2, 38].

Studies on obesity in BBS have primarily focused on the role of BBS proteins in intracellular trafficking to the primary cilium or plasma membrane. The primary cilium is crucial for leptin signal transduction in the hypothalamus, and its alteration has also been observed in BBS patients, who exhibit higher plasma leptin levels than controls. Additionally, anomalies in the trafficking of neuropeptide Y and serotonin (5-HT2C) receptors have been proposed as potential contributors to obesity development.
Another aspect concerns adipogenesis dysfunction: during differentiation, preadipocytes express a primary cilium that hosts receptors for Wnt and Hedgehog signaling pathways, essential for proper adipocyte development. Finally, BBS1 and BBS2 proteins are indispensable for the correct trafficking of the insulin receptor to the plasma membrane [33, 39].

Regarding Alström syndrome, studies on murine models with *Alms1* gene mutations show a reduction in the percentage of ciliated hypothalamic neurons, associated with a significant decrease in energy expenditure. The molecular details of this mechanism remain unclear [2].

Alström syndrome is an autosomal recessive condition characterized by a broad range of clinical manifestations, including obesity, insulin resistance or type 2 diabetes mellitus, hypertriglyceridemia, hearing loss, cardiomyopathy, retinal dystrophy, progressive kidney, and liver disease. Its estimated prevalence ranges from 1 to 10 cases per million people. Obesity and insulin resistance typically begin to develop during the first year of life. A study by Waldman et al. on 38 patients with Alström syndrome found that among 25 observed children, only 20% had a normal weight, while 8% were overweight and 72% were obese. In the adult population (13 patients), 15% were overweight, and 85% were obese, with insulin resistance present in 100% of cases.
While BBS can be caused by mutations in over 20 genes, Alström syndrome is caused by mutations in the *ALMS1* gene [33, 40, 41]. Patients with ALMS, but not all individuals with BBS, are predisposed to type 2 diabetes, suggesting a complexity in the regulation of ciliary function, with some alterations potentially even providing protection against metabolic disorders (interestingly, the absence of *BBS12* in mice increases adipogenesis but, paradoxically, also enhances insulin sensitivity) [42, 43].

Renal function tends to deteriorate with age, as evidenced by Waldman's study and previous studies by Marshall et al.
In Waldman et al.'s study, about 20% of patients aged 20 to 38 years met the criteria for chronic kidney disease (CKD) diagnosis, with renal impairment likely linked to the absence of the ALMS1 protein, although the contribution of associated conditions such as metabolic dysfunction cannot be excluded [41].

The therapeutic approach for obesity in ciliopathies is based on lifestyle modifications, which include a hypocaloric diet and aerobic physical activity tailored to the patient's clinical condition. In addition, improving sleep hygiene and increasing sleep duration may contribute to obesity management. An optimal strategy involves the support of a multidisciplinary team composed of physicians, dietitians, psychologists and physical therapists. In high-risk obese patients, bariatric surgery may be considered, although its long-term effects remain under investigation. A review has highlighted less durable benefits in subjects with hyperphagic disorders [2, 33].

In diabetic patients, treatments that improve insulin sensitivity without causing weight gain should be prioritized (e.g., metformin, incretins, SGLT2 inhibitors) [36].

Obesity is one of the clinical features of Bardet-Biedl and Alström syndrome, for which there are promising therapeutic developments. Setmelanotide, an agonist of the melanocortin-4 receptor

(MC4R), was approved in the United States in 2020 and in Europe in 2021 for the treatment of obesity caused by mutations in *POMC*, *PCSK1*, and *LEPR* in individuals over 6 years of age [33]. In 2022, the FDA extended the therapeutic indication of setmelanotide to patients with Bardet-Biedl syndrome (BBS), based on a phase 3 study that demonstrated, after 52 weeks of treatment, that approximately 30% of participants (aged over 12 years) achieved a ≥10% reduction in body weight, with an average BMI reduction of over 9% within one year [44, 45].

A recent study investigated the efficacy of setmelanotide in children under 6 years of age and, in the BBS group, observed an average percentage reduction in BMI of 10% at week 52 [44, 46]. An abstract reporting the extension of the phase 3 study indicated sustained clinical benefits after 3 years of continuous treatment with the drug, with average weight losses of approximately 20 kg in adults and a 19.4% reduction in BMI percentiles in pediatric patients [47].

Ganawa et al. reported a case of GLP-1 agonist use in a young woman with BBS, who had childhood-onset obesity and hyperphagia. Due to weight regain upon dose reduction, it was necessary to maintain the medication. Similarly, in Alström syndrome data suggest that GLP-1 receptor agonists are not inferior in these forms of obesity compared to polygenic forms [48].

Several beneficial metabolic effects of these drugs have been observed independently of BMI reduction [48, 49].

Currently, there are no specific interventions to prevent kidney damage. Kidney transplantation is the treatment of choice for end-stage uremia. An increase in the median BMI has been reported in the cohort of transplant patients compared to non-transplanted individuals, so it is advisable to employ immunosuppressive regimens that allow for reduced steroid use and, in particular, to carefully evaluate the use of tacrolimus, considering the higher risk of post-transplant diabetes (NODAT) in obese patients [33, 36, 50].

BIBLIOGRAPHY

1. Hojs R, Ekart R, Bevc S, Vodošek Hojs N (2023) Chronic Kidney Disease and Obesity. Nephron 147:660–664. https://doi.org/10.1159/000531379.
2. Zhang Q, Huang Y, Gao S, et al (2024) Obesity-Related Ciliopathies: Focus on Advances of Biomarkers. Int J Mol Sci 25:8484. https://doi.org/10.3390/ijms25158484
3. Nawaz S, Chinnadurai R, Al-Chalabi S, et al (2023) Obesity and chronic kidney disease: A current review. Obes Sci Pract 9:61–74. https://doi.org/10.1002/osp4.629.
4. Garofalo C, Borrelli S, Minutolo R, et al (2017) A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. Kidney Int 91:1224–1235. https://doi.org/10.1016/j.kint.2016.12.013.
5. Carbone A, Al Salhi Y, Tasca A, et al (2018) Obesity and kidney stone disease: a systematic review. Minerva Urol Nefrol 70. https://doi.org/10.23736/S0393-2249.18.03113-2.
6. Kotsis V, Martinez F, Trakatelli C, Redon J (2021) Impact of Obesity in Kidney Diseases. Nutrients 13:4482. https://doi.org/10.3390/nu13124482.
7. Yun H-R, Kim H, Park JT, et al (2018) Obesity, Metabolic Abnormality, and Progression of CKD. Am J Kidney Dis 72:400–410. https://doi.org/10.1053/j.ajkd.2018.02.362.
8. Pinto-Sietsma S-J, Navis G, Janssen WMT, et al (2003) A central body fat distribution is related to renal function impairment, even in lean subjects. Am J Kidney Dis 41:733–741. https://doi.org/10.1016/S0272-6386(03)00020-9.
9. Shuster A, Patlas M, Pinthus JH, Mourtzakis M (2012) The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. Br J Radiol 85:1–10. https://doi.org/10.1259/bjr/38447238.
10. Lee MJ, Park JT, Park KS, et al (2016) Normal body mass index with central obesity has increased risk of coronary artery calcification in Korean patients with chronic kidney disease. Kidney Int 90:1368–1376. https://doi.org/10.1016/j.kint.2016.09.011.
11. Steele C, Nowak K (2022) Obesity, Weight Loss, Lifestyle Interventions, and Autosomal Dominant Polycystic Kidney Disease. Kidney Dial 2:106–122. https://doi.org/10.3390/kidneydial2010013.
12. Park Y, Kim NH, Kwon TY, Kim SG (2018). A novel adiposity index as an integrated predictor of cardiometabolic disease morbidity and mortality. Sci Rep 8:16753. https://doi.org/10.1038/s41598-018-35073-4.
13. Li X, Wang L, Zhou H, Xu H (2023) Association between weight-adjusted-waist index and chronic kidney disease: a cross-sectional study. BMC Nephrol 24:266. https://doi.org/10.1186/s12882-023-03316-w.
14. Song SH, Oh TR, Suh SH, et al (2024) Obesity is associated with incident chronic kidney disease in individuals with normal renal function. Korean J Intern Med 39:813–822. https://doi.org/10.3904/kjim.2023.491.
15. Kanda E, Muneyuki T, Suwa K, Nakajima K (2015) Effects of Weight Loss Speed on Kidney Function Differ Depending on Body Mass Index in Nondiabetic Healthy People: A Prospective Cohort. PLOS ONE 10:e0143434. https://doi.org/10.1371/journal.pone.0143434.
16. Zeitler EM, Glenn DA, Hu Y, et al (2024) Association of Obesity With Kidney and Cardiac Outcomes Among Patients With Glomerular Disease: Findings From the Cure Glomerulonephropathy Network. Am J Kidney Dis 84:306-319.e1. https://doi.org/10.1053/j.ajkd.2024.03.020.
17. García-Carro C, Vergara A, Bermejo S, et al (2021) A Nephrologist Perspective on Obesity: From Kidney Injury to Clinical Management. Front Med 8:655871. https://doi.org/10.3389/fmed.2021.655871.
18. Avgoustou E, Tzivaki I, Diamantopoulou G, et al (2025) Obesity-Related Chronic Kidney Disease: From Diagnosis to Treatment. Diagn Basel Switz 15:169. https://doi.org/10.3390/diagnostics15020169.
19. Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, et al (2023) The Role of Adipokines in Health and Disease. Biomedicines 11:1290. https://doi.org/10.3390/biomedicines11051290.
20. Kipp KR, Rezaei M, Lin L, et al (2016) A mild reduction of food intake slows disease progression in an orthologous mouse model of polycystic kidney disease. Am J Physiol-Ren Physiol 310:F726–F731. https://doi.org/10.1152/ajprenal.00551.2015.
21. Tchang BG, Aras M, Kumar RB, Aronne LJ (2000) Pharmacologic Treatment of Overweight and Obesity in Adults. In: Feingold KR, Anawalt B, Blackman MR, et al (eds) Endotext. MDText.com, Inc., South Dartmouth (MA).
22. Tsalouchos A (2023) Inibitori del cotrasportatore sodio-glucosio di tipo 2 in pazienti sottoposti a trapianto renale. G Clin Nefrol E Dialisi 35:73–81. https://doi.org/10.33393/gcnd.2023.2620.
23. Courcoulas AP, Daigle CR, Arterburn DE (2023) Long term outcomes of metabolic/bariatric surgery in adults. BMJ e071027. https://doi.org/10.1136/bmj-2022-071027.
24. Van Rijswijk A-S, Van Olst N, Schats W, et al (2021) What Is Weight Loss After Bariatric Surgery Expressed in Percentage Total Weight Loss (%TWL)? A Systematic Review. Obes Surg 31:3833–3847. https://doi.org/10.1007/s11695-021-05394-x.

25. McConnachie DJ, Stow JL, Mallett AJ (2021) Ciliopathies and the Kidney: A Review. Am J Kidney Dis 77:410–419. https://doi.org/10.1053/j.ajkd.2020.08.012.
26. Ma M (2021) Cilia and polycystic kidney disease. Semin Cell Dev Biol 110:139–148. https://doi.org/10.1016/j.semcdb.2020.05.003.
27. H. Kathem S, M. Mohieldin A, M. Nauli S, 1 College of Pharmacy and Pharmaceutical Sciences, University of Toledo, Toledo, Ohio; (2013) The Roles of Primary cilia in Polycystic Kidney Disease. AIMS Mol Sci 1:27–46. https://doi.org/10.3934/molsci.2013.1.27.
28. Boletta A (2009) Emerging evidence of a link between the polycystins and the mTOR pathways. PathoGenetics 2:6. https://doi.org/10.1186/1755-8417-2-6.
29. Reiterová J, Tesař V (2022) Autosomal Dominant Polycystic Kidney Disease: From Pathophysiology of Cystogenesis to Advances in the Treatment. Int J Mol Sci 23:3317. https://doi.org/10.3390/ijms23063317.
30. Nowak KL, Moretti F, Bussola N, et al (2024) Visceral Adiposity and Progression of ADPKD: A Cohort Study of Patients From the TEMPO 3:4 Trial. Am J Kidney Dis 84:275-285.e1. https://doi.org/10.1053/j.ajkd.2024.02.014.
31. Nowak KL, Steele C, Gitomer B, et al (2021) Overweight and Obesity and Progression of ADPKD. Clin J Am Soc Nephrol 16:908–915. https://doi.org/10.2215/CJN.16871020.
32. Torres VE, Chapman AB, Perrone RD, et al (2012) Analysis of baseline parameters in the HALT polycystic kidney disease trials. Kidney Int 81:577–585. https://doi.org/10.1038/ki.2011.411.
33. Melluso A, Secondulfo F, Capolongo G, et al (2023) Bardet-Biedl Syndrome: Current Perspectives and Clinical Outlook. Ther Clin Risk Manag Volume 19:115–132. https://doi.org/10.2147/TCRM.S338653.
34. Feuillan PP, Ng D, Han JC, et al (2011) Patients with Bardet-Biedl syndrome have hyperleptinemia suggestive of leptin resistance. J Clin Endocrinol Metab 96:E528-535. https://doi.org/10.1210/jc.2010-2290.
35. Pomeroy J, Krentz AD, Richardson JG, et al (2021) Bardet-Biedl syndrome: Weight patterns and genetics in a rare obesity syndrome. Pediatr Obes 16:e12703. https://doi.org/10.1111/ijpo.12703.
36. Dollfus H, Lilien MR, Maffei P, et al (2024) Bardet-Biedl syndrome improved diagnosis criteria and management: Inter European Reference Networks consensus statement and recommendations. Eur J Hum Genet 32:1347–1360. https://doi.org/10.1038/s41431-024-01634-7.
37. Zacchia M, Secondulfo F, Melluso A, et al (2024) CKD in Bardet-Biedl Syndrome: Evidence Supporting Multifactorial Etiology. Kidney Int Rep S2468024924019983. https://doi.org/10.1016/j.ekir.2024.10.030.
38. Brüning JC, Fenselau H (2023) Integrative neurocircuits that control metabolism and food intake. Science 381:eabl7398. https://doi.org/10.1126/science.abl7398.
39. Zhong B, Nie N, Dong M (2024) Molecular mechanisms of the obesity associated with Bardet-Biedl syndrome: An update. Obes Rev e13859. https://doi.org/10.1111/obr.13859.
40. Vaisse C, Reiter JF, Berbari NF (2017) Cilia and Obesity. Cold Spring Harb Perspect Biol 9:a028217. https://doi.org/10.1101/cshperspect.a028217.
41. Waldman M, Han JC, Reyes-Capo DP, et al (2018) Alström syndrome: Renal findings in correlation with obesity, insulin resistance, dyslipidemia and cardiomyopathy in 38 patients prospectively evaluated at the NIH clinical center. Mol Genet Metab 125:181–191. https://doi.org/10.1016/j.ymgme.2018.07.010.
42. Zhang Y, Hao J, Tarrago MG, et al (2021) FBF1 deficiency promotes beiging and healthy expansion of white adipose tissue. Cell Rep 36:109481. https://doi.org/10.1016/j.celrep.2021.109481.
43. Marion V, Mockel A, De Melo C, et al (2012) BBS-Induced Ciliary Defect Enhances Adipogenesis, Causing Paradoxical Higher-Insulin Sensitivity, Glucose Usage, and Decreased Inflammatory Response. Cell Metab 16:363–377. https://doi.org/10.1016/j.cmet.2012.08.005.
44. Haqq AM, Chung WK, Dollfus H, et al (2022) Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. Lancet Diabetes Endocrinol 10:859–868. https://doi.org/10.1016/S2213-8587(22)00277-7.
45. Forsythe E, Haws RM, Argente J, et al (2023) Quality of life improvements following one year of setmelanotide in children and adult patients with Bardet–Biedl syndrome: phase 3 trial results. Orphanet J Rare Dis 18:12. https://doi.org/10.1186/s13023-022-02602-4.
46. Argente J, Verge CF, Okorie U, et al (2024) Setmelanotide in patients aged 2–5 years with rare MC4R pathway-associated obesity (VENTURE): a 1 year, open-label, multicenter, phase 3 trial. Lancet Diabetes Endocrinol S2213858724002730. https://doi.org/10.1016/S2213-8587(24)00273-0.
47. Yanovski J, Angel M-MG, Malhotra S, et al (2024) 3-year setmelanotide weight outcomes in patients with bardet-biedl syndrome and obesity. Endocr Abstr. https://doi.org/10.1530/endoabs.99.EP23.
48. Ali S, Baig S, Wanninayake S, et al (2024) G lucagon-like peptide-1 analogues in monogenic syndromic obesity: Real-world data from a large cohort of Alström syndrome patients. Diabetes

Obes Metab 26:989–996. https://doi.org/10.1111/dom.15398.
49. Haqq AM, Poitou C, Chung WK, et al (2025) Impact of Setmelanotide on Metabolic Syndrome Risk in Patients With Bardet-Biedl Syndrome. J Clin Endocrinol Metab dgaf079. https://doi.org/10.1210/clinem/dgaf079.
50. Haws RM, Joshi A, Shah SA, et al (2016) Renal transplantation in Bardet–Biedl Syndrome. Pediatr Nephrol 31:2153–2161. https://doi.org/10.1007/s00467-016-3415-4.