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www.bsmi.uz
https://newdaymedicine.com E:
ndmuz@mail.ru
Тел: +99890 8061882

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OVERWEIGHT AND RENAL FUNCTION

Amonov Mukhammad Komil ugli https://orcid.org/0000-0003-3021-7836

Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan, Bukhara, st. A. Navoi.1
Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Resume***

Increasing evidence accumulate to suggest that overweight increases the risk of chronic kidney disease independently of dyslipidemia, diabetes, and hypertension. This so-called overweight-related glomerulopathy is characterized at early stages by glomerular hypertrophy with or without secondary focal segmental glomerulosclerosis. Since, however, kidney biopsies are usually not performed at this phase, an early diagnosis of the disease is often difficult. Here, we review new developments in the pathophysiology of overweight-associated kidney dysfunction and discuss the potential of appropriate monitoring of glomerular filtration rate and albuminuria for early detection of the disease. We also present the benefits conferred by even moderate dietary restriction on the course of the disease.

Key words: overweight-related glomerulopathy, overweight, albuminuria, glomerular filtration rate, dietary restriction, glomerular sclerosis

ОРТИҚЧА ВАЗН ВА БУЙРАК ФУНКЦИЯСИ

Амонов Муҳаммад Комил ўғли

Абу али ибн Сино номидаги Бухоро давлат тиббиёт институти Ўзбекистон, Бухоро ш.,
А.Навоий кўчаси. 1 Тел: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Резюме***

Ортиқча вазн дислипидемия, қандли диабет ва гипертония касаллигидан қатъи назар, сурункали буйрак касаллиги хавфини ошириши ҳақида далиллар тўпланиб бормоқда. Ортиқча вазн билан боғлиқ бу гломерулопатия эрта босқичларда иккиламчи ўчоқли сегментар гломерулосклероз билан ёки унингсиз гломеруляр гипертрофия билан тавсифланади. Бироқ, буйрак биоптатлари одатда ушбу босқичда ўтказилмагани сабабли, кўпинча касалликни эрта ташхислаш қийин кечади. Бу ерда биз ортиқча вазн билан боғлиқ буйрак дисфункцияси патофизиологиясидаги янги ишланмаларни кўриб чиқамиз ва касалликни эрта аниқлаш учун коптокчалар фильтрацияси тезлиги ва албуминурияни тегишли мониторинг қилиш имкониятларини муҳокама қиламиз. Биз, шунингдек, касалликнинг кечишига ҳатто ўртача овқатланиш чекловининг афзалликларини ҳам тақдим этамиз

Калит сўзлар: ортиқча вазн билан боғлиқ гломерулопатия, ортиқча вазн, албуминурия, коптокчалар фильтрацияси тезлиги, парҳез чекланиши, коптокчалар склерози

ИЗБЫТОЧНЫЙ ВЕС И ФУНКЦИЯ ПОЧЕК

Амонов Мухаммад Комил угли

Бухарский государственный медицинский институт имени Абу Али ибн Сины, Узбекистан,
г. Бухара, ул. А. Навои. 1 Тел: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Резюме***

Растущие данные свидетельствуют о том, что избыточный вес увеличивает риск развития хронических заболеваний почек независимо от дислипидемии, сахарного диабета и артериальной гипертензии. Эта так называемая с избыточной массой тела гломерулопатия характеризуется на ранних стадиях гломерулярной гипертрофией с или без вторичного очагового сегментарного гломерулосклероза. Однако, поскольку биопсии почки обычно не выполняются на данном этапе, часто затрудняется ранняя диагностика заболевания. Здесь мы рассматриваем новые разработки в патофизиологии избыточной массы тела и дисфункции почек, а также обсуждаем потенциал соответствующего мониторинга скорости клубочковой фильтрации и альбуминурии для раннего выявления заболевания. Представляем также преимущества даже умеренного ограничения диеты в течение заболевания.

Ключевые слова: гломерулопатия, связанная с избыточным весом, избыточный вес, альбуминурия, скорость клубочковой фильтрации, ограничение диеты, гломерулосклероз

Relevance

It has been estimated that the number of people with overweight reaches 500 million worldwide and 7is continuously increasing (1). It is recognized that overweight predisposes to type 2 diabetes, hyperlipidemia and hypertension. The mechanisms underlying these disorders are complex and include insulin resistance, endothelial dysfunction, and contributions from the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) (2). Interestingly, it has recently been demonstrated that the presence of endothelial nitric oxide synthase type 3 (NOS3) gene variant T894 is associated with increased risk of hypertension in the obese (3).

While the importance of overweight in the context of metabolic syndrome is well appreciated, the effects of simple overweight are less clear. Increasing evidence suggests that overweight *per se*, i.e. without significant comorbidities, also can exert serious health effects. They include overweight-associated inflammation, endothelial cell dysfunction and altered endocrine functions of the adipose tissue (4, 5). A substantial and chronic increase in the volume of adipocytes that is unaccompanied by adequate angiogenesis leads to adverse remodelling of the adipose tissue. It is characterized by tissue hypoxia and death of the most poorly supplied adipocytes, which initiates the inflammatory response. Although of low intensity, this smouldering and chronic inflammation leads to the adipose tissue infiltration by macrophages (mainly of the pro-inflammatory phenotype M1), their activation and uncontrolled production of cytokines (monocyte chemoattractant protein-1, interleukin-1β, interleukin-6, tumor necrosis factor-α) (6). This interferes with the secretion of adipocytokines (leptin, resistin, apelin, visfatin, adiponectin and omentin) by adipose tissue, which contributes to systemic inflammation and endothelial cell dysfunction that may jeopardize kidney function (4, 7).

Materials and methods

Results of a meta-analysis clearly show that the risk of kidney disease for people with overweight is at least 40% greater than for subjects with normal body weight (8). This effect is largely independent of classic overweight-associated risk factors, such as dyslipidemia, diabetes, and hypertension. Moreover, it is characterized be a dose-response relationship, which means that the risk of kidney disease increases in parallel with increasing BMI (strictly speaking, this relationship appears to be U-shaped as underweight with low BMI may also promote kidney damage). Interestingly, the risk of kidney disease in the obese differs between the sexes and is greater for obese women. The reason for this phenomenon is not clear, but a proportionally greater amount of body fat in females seems to play a role (8).

OVERWEIGHT-RELATED GLOMERULOPATHY

The impact of overweight on renal function has been known for a long time. First reports on a possible relationship between overweight and proteinuria date back to 1970s (9). Later, many studies confirmed that overweight confers an increased risk of chronic kidney disease (CKD). They showed that patients with BMI > 30 kg/m2 suffered from renal failure more often and proportionally to the magnitude of BMI (10). Recent data indicate that structural and functional alterations in the kidney may occur even in mild overweight (BMI > 25 kg/m2) and in the absence of diabetes (11). With increased prevalence of overweight, these changes became the focus of attention and were designated as overweight-related glomerulopathy (ORG) (12). Although the clinical course of ORG appears to be less severe than that of diabetic kidney disease, yet the long-term prognosis is also negative (13).

First observations on the association between overweight and structural changes in the kidney came from autopsy studies (14). These identified glomerular hypertrophy and segmental sclerosis as the most typical lesions in the obese. The diameter of glomeruli in obese individuals was found to be approximately 1.3-fold greater compared with that of non-obese subjects. In addition, the glomerular density appeared to be reduced (15). Segmental sclerosis in ORG resembles that seen in focal segmental glomerulosclerosis (FSGS), although its intensity and frequency is usually less compared with primary FSGS. Lesions of segmental sclerosis are most often located in the perihilar region and may be associated with increased diameter of the afferent arteriole and reduced podocyte density. A decrease in podocyte density is thought to result mainly from the enlargement of glomerular volume that cannot be matched by a corresponding increase in the number of podocytes (13). Other morphological findings in ORG include tubular atrophy and interstitial fibrosis, although their severity may be minimal. Overweight-associated changes in renal histology are accompanied by changes in renal function that include an initial increase in glomerular filtration rate (GFR), followed by albuminuria and proteinuria, and a gradual decrease in GFR leading ultimately to CKD (12, 16). The prevalence of ORG is difficult to estimate. A retrospective analysis of kidney biopsies detected features of ORG in more than 2.5% of the specimens, with a clear upward trend over the past 30 years (12). These values may, however, be underestimated, because the biopsies were performed only in patients with overt symptoms suggestive of kidney disease.

The pathogenesis of ORG remains incompletely understood (12). It has been hypothesized that glomerular hyperfiltration results either from primary vasodilation of the afferent arteriole or from increased reabsorption of sodium in the proximal tubule leading to decreased exposure of the macula densa to sodium, blunted tubuloglomerular feedback and the afferent arteriole dilation (*Fig. 1*). The mechanisms that initiate these processes are unknown, however, they are likely to include activation of the renin-angiotensin-aldosterone system, increased sympathetic activity, increased leptin-to-adiponectin ratio, hypertriglyceridemia, hyperinsulinemia, and possibly a high-protein diet (17-19). An increase in the intraglomerular pressure causes glomerular stretch and enlargement, which imposes mechanical stress on podocytes leading eventually to their dysfunction and damage. In addition, persistent inflammation in the adipose tissue results in lipolysis and hyperlipidemia, which promotes lipid accumulation in mesangial cells, podocytes and proximal tubule epithelial cells. Dysfunction of these cells together with increased permeability of glomerular capillaries and albuminuria induce mediators of fibrogenesis and glomerulosclerosis (12, 20, 21).

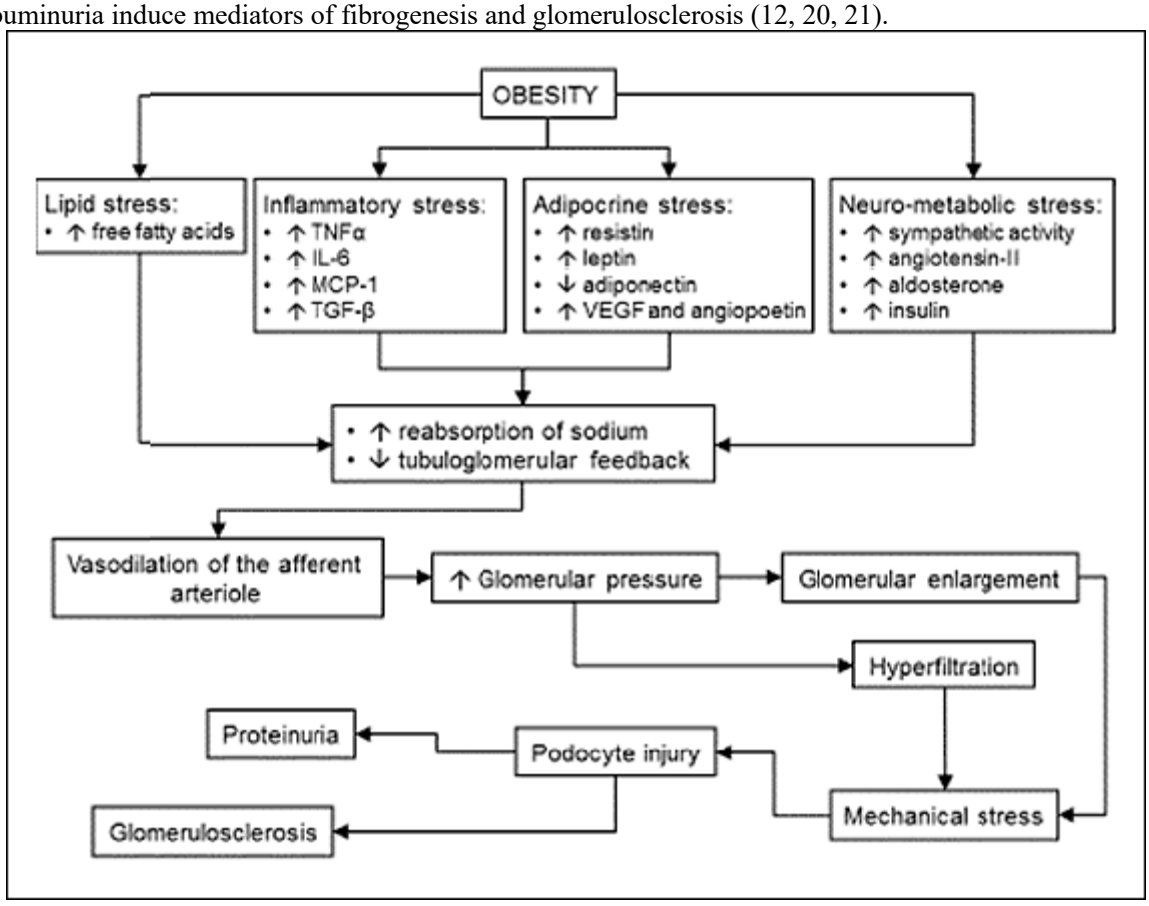

Fig. 1. Pathogenesis of overweight-related glomerulopathy.

Recent data support the importance of adipose tissue-derived endocrine signalling, pointing to a key role of adiponectin (22). Under physiological conditions adiponectin maintains podocyte integrity acting primarily through adiponectin type 1 receptor (AdipoR1) and the signalling pathway controlled by 5'AMP-activated protein kinase (AMPK) (23). Adiponectin concentration decreases when BMI increases, which makes the glomerular filtration barrier vulnerable to injury (24). Overweight can also lead to a rise in the concentration of leptin, which stimulates the expression of transforming growth factor-β (TGF-β) that acts as the main driver of extracellular matrix accumulation, mesangial cell proliferation and progressive glomerulosclerosis (12, 25). Renal changes resembling those seen in human overweight can also be detected in mice after few months on high fat diet. It has recently been demonstrated that the development of such changes in mice is related to mitochondrial dysfunction in glomerular endothelial cells, proximal tubule epithelial cells, and podocytes. Accordingly, the administration of SS-31, a mitochondrial membrane-stabilizing peptide, preserved mitochondrial structure and function, and prevented renal cell injury and subsequent glomerulosclerosis (26). It remains to be determined whether such a therapeutic approach is effective in human disease.

Prompt diagnosis of ORG is difficult, as early stages of the disease may not give overt manifestations that would justify renal biopsy. However, by carefully analysing the parameters of renal function such as GFR and albuminuria one may get a hint of what might be a developing disease.

PARAMETERS OF RENAL FUNCTION IN OVERWEIGHT-RELATED GLOMERULOPATHY

Earlier formulas for estimating GFR had some limitations when applied to obese patients (27). The Cockcroft and Gault equation may overestimate GFR in the obese (28), while a MDRD (Modification of Diet in Renal Diseases) Study equation (27) may underestimate the real GFR (29) and, thus, may be not optimal for the assessment of overweight-associated hyperfiltration (27). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (30) is more accurate, especially for GFR > 60 ml/min/1.73 m2 and appears to be currently the best option for estimating GFR in the obese (31).

Albuminuria can be the first manifestation of kidney injury in ORG (32). Since a 24-hour urine collection is inconvenient to obtain, the albumin-to-creatinine ratio (ACR) is increasingly used in clinical practice as a test of similar validity (33). The degree of correlation between ACR and albuminuria in daily urine collection can be increased by computing the logarithm for ACR (34).

THE IMPORTANCE OF WEIGHT LOSS

Some aspects of ORG can be alleviated by dietary restriction and a decrease in body fat mass (12, 35). Low-calorie diet was found to ameliorate histological alterations in the kidneys of animals with experimental overweight and diabetes (36). It is not clear, however, whether a similar effect occurs in humans. It has been observed that already few weeks of dietary regimen reduces albuminuria (37). It has been estimated that weight reduction by 1 kg decreases albuminuria by approximately 4% (38). By contrast, such a modest weight loss does not appear to produce a significant change in GFR (37, 38). However, a more substantial weight loss as a result of bariatric surgery can normalize GFR and markedly reduce albuminuria (39).

Weight loss-induced renoprotection is probably related to several factors, including dampening of systemic chronic inflammation (40) and normalization of adipocytokine profiles (12). In this respect, a significant improvement in adipocytokine levels can be achieved already with moderate dietary restriction (41), while a substantial decrease in BMI after bariatric surgery lead to a more profound decrease in serum CRP and a significant improvement in endothelial cell function (42).

OTHER TREATMENT OPTIONS

Considering the postulated role of microbiota in overweight-induced inflammation, probiotics may act to decrease inflammation and slow down the progression of ORG (43, 44). Similarly, by promoting the growth of healthy microbiota in the intestine, high-fiber diets may ameliorate partly kidney dysfunction (45). Some studies suggest that green tea polyphenols can have a positive effect on the intestinal microbiota and improve kidney function in diabetic nephropathy (46-48). Finally, the transplantation of fecal microbiota might be considered as a therapeutic option for ORG (43, 49).

While metformin can improve metabolic control in diabetes, its role in ORG not associated with diabetes is not certain (43). Data from experimental models of kidney disease suggest that metformin may display antifibrotic activity and as such may of potential benefit for patients with ORG (50).

Inhibitors of the RAAS are commonly used for treating patients with proteinuria and diabetic nephropathy. They can also decrease albuminuria and reduce the prevalence of CKD in patients with ORG (12, 43). Moreover, some data suggest that obese patients might be even more sensitive to the renoprotective activity of the RAAS blockade than patients with normal BMI (51).

Based on the observation that selective endothelin-A receptor antagonists (e.g. avosentan and antrasentan) reduce albuminuria and preserve renal function in diabetes (52), they might also be considered as a therapeutic option for ORG (53).

PERSONAL EXPERIENCE

To illustrate the problems associated with renal function in overweight, we have assessed eGFR and ACR in 57 adults (16 male and 41 female, mean age 37 ± 11 years) with simple overweight who participated in our previous study(41). These patients had no significant comorbidities and underwent a moderate 8-week dietary intervention with calorie restriction by 300 – 500 kcal/day. On average, the procedure resulted in a reduction in body weight by 5.3 ± 4.0 kg, which corresponded to a decrease in BMI by 1.84 ± 1.36 kg/m2 (*Table 1*). The GFR estimated both at the beginning and at the end of the study was formally well within normal limits. However, it tended to decrease with time. Similarly, the intervention resulted in a decrease in ACR, although absolute ACR values remained in the normal range. Thus, taking the whole clinical context into account, it is tempting to hypothesize that those decreases represented a beneficial reversal of a potentially detrimental trend towards hyperfiltration and proteinuria. Obviously, more adequately powered studies would be required to verify this hypothesis. Interestingly, this relatively modest dietary restriction resulted in a small, but consistent decrease in blood pressure (independent of any additional medication), as well as a reduction in systemic levels of TNF-α and leptin.

Table 1. Exemplary changes observed in patients with simple overweight (n = 57) undergoing an 8-week moderate dietary restriction. Values are expressed as medians and interquartile ranges.

	Before dietary restriction	**After dietary restriction**	**P-value (Wilcoxon test)**
Weight (kg)	107.4 (94.0 – 120.5)	100.4 (87.2 – 114.2)	< 0.0001
BMI (kg/m^2)	37.1 (33.0 – 41.3)	34.5 (31.6 – 0.0)	< 0.0001
Waist (cm)	113.5 (106.5 – 125.0)	110.0 (101.0 – 120.0)	< 0.0001
SBP (mmHg)	130 (121 – 137)	120 (113 – 130)	0.0006
DBP (mmHg)	80 (75 – 90)	80 (75 – 86)	0.50
Creatinine (mg/dl)	0.77 (0.67 – 0.89)	0.78 (0.71 – 0.90)	0.066
eGFR (CKD-EPI) (ml/min/1.73m^2)	104 (96 – 114)	99 (89 – 113)	0.053
eGFR (MDRD) (ml/min/1.73m^2)	97 (87 – 112)	93 (81 – 105)	0.104
ACR (mg/g)	13.4 (8.6 – 20.0)	11.0 (6.3 – 18.0)	0.061
Log [ACR (mg/g)]	1.15 (0.98 – 1.38)	1.07 (0.83 – 1.29)	0.024
TNF-α (pg/ml)	16.7 (10.7 – 21.7)	5.0 (2.4 – 11.0)	< 0.0001
Leptin (ng/ml)	51.6 (33.6 – 76.3)	34.8 (18.0 – 57.6)	< 0.0001
Adiponectin (ng/ml)	1765 (1100 – 2474)	1819 (1228 – 2642)	0.16

Results and discussions

Overweight-related glomerulopathy is characterized by the enlargement of glomeruli and secondary focal segmental glomerular sclerosis in patients with a BMI > 30 kg/m2. Since there is usually no indication for renal biopsy, other diagnostic criteria for early diagnosis of the disease are needed.

The classic criteria for ORG include (1) overweight (BMI > 30 kg/m2), (2) normal serum albumin, (3) proteinuria with or without changes in GFR. However, structural changes in the kidneys of patients with overweight develop probably much earlier than could be demonstrated by the above criteria.

Conclusion

An early diagnosis of ORG may be facilitated by monitoring GFR (according to the CKD-EPI formula) and albuminuria (as measured by ACR or log (ACR)), especially after the dietary intervention or bariatric surgery. Although at early stages of ORG these parameters may be normal, their reduction in response to weight loss could suggest that they were in fact relatively increased and reflected developing ORG.

Weight loss exerts renoprotective effects in ORG with even short-term moderate dietary restriction providing clinical benefits related mainly to a decrease in blood pressure, dampening of systemic inflammation and normalization of adipocytokine profiles.

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