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Valoración de la función renal en niños con sobrepeso y obesidad con las moléculas NGAL y KIM-1

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ABSTRACT

Aim and background: the incidence of obesity has increased among children, and obesity has been considered an independent risk factor for chronic kidney disease. We aimed to determine the degree of kidney function impairment by evaluating urine neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) levels.

Materials and methods: in total, 15 obese, 26 overweight, and 26 control adolescents aged 10 to 16 years were enrolled into the study. Urine samples were evaluated for NGAL and KIM-1 levels using enzyme-linked immunosorbent assay kits. We investigated the association between obesity and related comorbidities with urinary NGAL and KIM-1 excretion.

Results: no significant differences were noted between the obese, overweight, and control groups in urinary NGAL and KIM-1 excretion (p = 0.327 and p = 0.917, respectively). In the obese and overweight groups urinary NGAL levels were 50.39 [30.88-74.22] in females and 26.67 [23.24-45.59] in males (p = 0.013). Also, urinary NGAL levels were increased in obese and overweight adolescents with LDL dyslipidemia at 64.12 [30.98-114.32] as compared to those without LDL dyslipidemia: 39.51 [25.59.56.37] (p = 0.024). Furthermore, a correlation was observed between insulin and homeostasis model assessment of insulin resistance levels with the NGAL/creatinine ratio in the overweight group (r = 0.515; p = 0.008, and r = 0.483; p = 0.014, respectively). Such correlation was not found in the obese group.

Conclusion: the effect of obesity on renal function could not be determined in children. A longer exposure may be required for obesity-induced disruption

of renal function in children. Renal function may be disrupted by dyslipidemia in obese adolescents. Furthermore, obesity impaired renal function in female adolescents. The normalization of these urinary markers as related to urine creatinine should be discussed.

RESUMEN

Introducción: la incidencia de la obesidad en la edad infantil ha aumentado. Se considera la obesidad como un factor de riesgo independiente para el desarrollo de la enfermedad renal crónica. El objetivo de este estudio fue valorar el grado de alteración de la función renal evaluando los niveles urinarios de NGAL y KIM-1.

Material y métodos: el estudio incluyó a 15 adolescentes con obesidad, 26 con sobrepeso y 26 controles sanos. Las edades de los participantes estaban entre los 10 y los 16 años. Los niveles de NGAL y KIM-1 en orina se determinaron mediante un kit ELISA. Se investigó la asociación entre la obesidad y su comorbilidad con la excreción urinaria de NGAL y KIM-1.

Resultados: no se encontraron diferencias significativas en la excreción urinaria de NGAL y KIM-1 entre los sujetos con obesidad, los sujetos con sobrepeso y los controles sanos (p = 0,327 y 0,917, respectivamente). En el grupo con sobrepeso y obesidad, los niveles de NGAL en las niñas fueron de 50,39 (30,88-74,22), mientras que en los niños fueron de 26,67 (23,24-45,59) (p = 0,013). Para los sujetos con dislipemia de LDL, el nivel de NGAL fue de 64,12 (30,98-114,32) frente a 39,5 (25,59-56,37) entre los que no la tenían (p = 0,024). Se encontró correlación entre los nivles de insulina, el HOMA-IR y la ratio NGAL/creatinina en el grupo con sobrepeso (r = 0,515; p = 0,008, y r = 0,483; p = 0,014, respectivamente). En el grupo con obesidad no se encontró dicha correlación.

Conclusiones: se precisa una duración más prolongada para encontrar alterada la función renal en los niños con exceso de peso. La función renal puede alterase por la dislipemia en el caso de los adolescentes con obesidad. La función renal se afecta más en las adolescentes femeninas. En el artículo se discute la normalización de estos marcadores urinarios con la creatinina en orina.

Palabras clave: Obesidad infantil. Síndrome metabólico. NGLA. KIM-1. Daño renal.

INTRODUCTION

The incidence of obesity has increased among children and adolescents, and obesity has been considered one of the most serious public health problems in recent years (1). Childhood obesity, similar to that in adults, also carries risk factors for atherosclerosis and cardiovascular diseases, such as hypertension, dyslipidemia, low HDL cholesterol, and impaired glucose metabolism (2). The effect of obesity on metabolic disease has been previously demonstrated (2). Obesity has been considered an independent risk factor for chronic kidney disease (CKD). Therefore, concurrent with a dramatic increase in the frequency of end-stage renal disease (ESRD), many studies have been conducted on obesity as a risk factor for CKD. Moreover, body mass index has been reported as an independent predictor of CKD progression (3,4).

The significant increase in childhood obesity has in turn increased the number of kidney disease patients (5). Early detection of impairment in kidney function before a significant decline in glomerular filtration rate (GFR) is crucial. Blood urea nitrogen (BUN) and serum creatinine levels do not help in the recognition of early renal damage because detectable increases in these levels can be seen only after substantial kidney injury (6). Hence, early biomarkers of renal dysfunction such as cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and N acetyl-beta-D-glucosaminidase (NAG) were evaluated in several studies. These biomarkers were suggested to determine early renal damage and its location (7,8).

Urinary NGAL levels increase particularly in patients with acute kidney injury. NGAL is readily excreted and detected in the urine. Kidney tubular epithelial cells release NGAL in response to inflammation and other tissue insults (9). Furthermore, NGAL is a sensitive biomarker of tubular damage (10).

Kidney injury molecule 1 (KIM-1) is a type-1 transmembrane glycoprotein expressed in the glomerular and tubular epithelial cells of a damaged kidney. KIM-1 is untraceable in the normal kidney, but its level increases significantly

in damaged kidneys (9). KIM-1 can be used to detect early renal damage in obese children (8).

Considering that the onset of obesity-associated renal disease is insidious and asymptomatic, we proposed early biomarkers to detect impaired renal function in obese adolescents. We aimed to determine the degree of impairment of kidney function by evaluating urine NGAL and KIM-1 levels in obese adolescents with normal serum creatinine (sCre) and BUN levels.

MATERIALS AND METHODS

Participants and study area

In total, 59 obese, 37 overweight, and 28 control adolescents were enrolled from the outpatient department at the Tokat Gaziosmanpasa University School of Medicine Hospital, Tokat, Turkey. Subjects were classified based on the body mass index (BMI) reference curve adjusted for Turkish children according to age and sex. Adolescents with a BMI above the 95th percentile were accepted as obese, those with a BMI between the 85th and 94th percentile were accepted as overweight, and those with a BMI within the 5-84th percentile were accepted as normal (11). Waist circumference was measured midway between the lowest rib and the iliac crest with a flexible anthropometric tape (12).

We excluded nine obese (three with familial Mediterranean fever, two with Hashimoto thyroiditis, and four aged < 10 years), 11 overweight (two with urinary tract infection; two with < 75% of estimated GFR (eGFR), which was calculated according to the Schwartz formula, and seven aged < 10 years), and two control (one with urinary tract infection and one with familial Mediterranean fever) subjects. Finally, 50 obese, 26 overweight, and 26 control adolescents aged 10-16 years were enrolled. Figure 1 displays the flowchart depicting the study population.

Subjects' demographic and clinical data, basic demographic information (age and sex), and physical data (height, weight, BMI, and systolic and diastolic blood pressure) were recorded. Weights were measured using a digital scale

(Seca Corp., Chino, California, USA) with the patients being barefoot and wearing light clothing. Height was measured using a portable stadiometer (Seca) together with weight. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). The demographic data and characteristics of the study group are shown in table I.

Laboratory tests

Laboratory tests, including complete blood count, glucose, BUN, sCre, aspartate transaminase (AST), and alanine transaminase (ALT), were derived from fasting blood samples drawn from all participants, whereas insulin levels, lipid profiles, and thyroid function tests were only conducted on obese and overweight participants. Urinary creatinine and protein were determined from urine samples.

Serum fasting glucose, insulin, triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C) were detected using reagent kits from Roche Diagnostics adapted to the COBAS 6000 Autoanalyzer (Roche Diagnostics, Indianapolis, IN, USA). GFR was calculated using the Schwartz formula ([k × height]/sCre) in units of GFR mL/min/1.73 m^2 (k constant, child or female adolescent: 0.55, male adolescent: 0.70).

Urine specimens were taken of 10 mL as spot urine, and centrifuged at 1,500 rpm for 5 min. The supernatant was removed and stored at -80 °C. Urinary NGAL (Affymetrix eBioscience Human NGAL Platinum ELISA, Austria) and KIM-1 levels (Elabscience Biotechnology Co., Ltd, China) were measured using an enzyme-linked immunosorbent assay kit. Urinary NGAL and KIM-1 levels were expressed related to urine creatinine as pg/mL/creatinine for NGAL and ng/mL/creatinine for KIM-1.

Definition of hypertension, insulin resistance, dyslipidemia, and metabolic syndrome

Blood pressure was measured using a digital sphygmomanometer (OMRON 705IT, Omron Healthcare Co., Kyoto, Japan). Hypertension was defined as blood pressure ≥ 95th percentile according to age, sex, and height (13).

The homeostasis model assessment of insulin resistance (HOMA-IR) level was calculated using the following equation: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mg/dL)/405. The HOMA cutoff for insulin resistance diagnosis was 5.22 for male and 3.82 for female adolescents (14). Dyslipidemia was defined as the existence of any of these criteria: TGs > 136 mg/dL in children ≥ 10 years of age, and HDL-C < 35 mg/dL (15). We determined proteinuria with the urine protein/creatinine ratio in spot urine samples as ≥ 0.20 mg/mg (16).

Current definitions of metabolic syndrome (MetS) include the following key characteristics: hyperinsulinemia or insulin resistance, dyslipidemia, hypertension, and obesity, with a particular emphasis on central adiposity height (17,18).

Statistical analyses

Quantitative data are expressed as arithmetic mean and standard deviation. Categorical variables are demonstrated as number and percentage. An independent sample t-test or one-way analysis of variance was used to compare continuous normal data between groups. For multiple comparisons, Tukey's HSD test was used. Chi-square tests or Kruskal–Wallis tests were used for categorical data analysis or non-normal data comparisons between groups. For examining the relationships between variables a simple correlation analysis and Pearson's correlation coefficient were used. A value of $p < 0.05$ was considered statistically significant. The statistical analysis of the data was performed using the SPSS 19 (IBM SPSS Statistics 19, SPSS Inc., Somers, NY, USA).

RESULTS

NGAL and KIM-1 levels were studied in urine samples from 102 subjects. NGAL and KIM-1 levels were expressed as a ratio to urine creatinine levels. The results obtained according to each study group are summarized in table II. The nonparametric results of urinary NGAL and KIM-1 levels were shown using median values because their distribution was not homogeneous.

In addition, obese and overweight adolescents were grouped according to sex, proteinuria, MetS, hypertension, dyslipidemia, and insulin resistance, and statistical analyses were performed for NGAL and KIM-1 levels. In the obese and overweight group, urinary NGAL levels were higher in females than in males ($p = 0.013$) (Table III). Additionally, urinary NGAL levels were increased in obese and overweight adolescents with LDL dyslipidemia as compared with those without LDL dyslipidemia ($p = 0.024$) (Table III). Table III summarizes the obtained NGAL and KIM-1 levels according to these variables in the obese and overweight group. In the group with high triglyceridemia, urinary NGAL and NGAL/Cre levels were higher than in those outside this group ($p = 0.032$ and 0.020, respectively; Table III).

The KIM-1/Cre ratio was higher in overweight adolescents with abdominal obesity than in those without abdominal obesity (52.89 [28.55-55.69] and 93.22 [63.48-133.04], respectively, $p = 0.007$). This significant difference was not determined in the obese group (65.75 [41.73-101.36] and 80.09 [30.23-129.95], respectively, $p = 0.978$).

We determined a correlation between insulin and HOMA-IR levels with the NGAL/Cre ratio in the overweight group ($r = 0.515$; $p = 0.008$, and $r = 0.483$; $p = 0.014$, respectively). No correlation was found between insulin and HOMA-IR levels with NGAL/Cre ratio in the obese group ($r = -0.151$; $p = 0.296$, and $r = -0.149$; $p = 0.300$, respectively). In the obese group, insulin and HOMA-IR levels were correlated with ALT levels ($r = 0.388$; $p = 0.006$, and $r = 0.398$; $p = 0.005$, respectively).

DISCUSSION

Obesity is suggested to contribute to renal disease (19). Early renal markers (NGAL, cystatin C, NAG, and KIM-1) have been used in studies to evaluate renal function because of the late presentation of obesity-related kidney disorders. NGAL and KIM-1 as tubular damage markers have been used to assess proteinuric, toxic, and ischemic kidney diseases (20,21). If metabolic disturbances are not considered, we determined that renal function is not yet affected in obese adolescents as compared to controls and overweight participants. We observed that the renal function of obese female adolescents may have been impaired when compared with that of male adolescents.

The mechanisms by which obesity may initiate and exacerbate CKD remain unclear. Deterioration in renal hemodynamics is very likely the main factor; however, a contribution of inflammatory and metabolic mechanisms may be considered. The time at which the harmful effects of obesity on the kidney can be determined has not been established yet. Savino et al. suggested that a longer exposure to obesity is probably needed before renal function impairment develops (22). Han et al. showed that KIM-1 can be excreted in the urine within 12 h after an initial ischemic renal insult, before regeneration of the epithelium, and then persists over time (23).

Hypertension, DM, and hyperlipidemia, all of which increase the risk of ESRD, are more prevalent in the obese population. Obesity is linked with glomerular hyperfiltration and hypertension (3). Hypertension and hyperfiltration may contribute to glomerulosclerosis (24). Consistent with Goknar et al. (8), we found that hypertension was not associated with kidney injury in obese adolescents. In the present study, no significant differences in eGFR were found between the obese, overweight, and control groups. However, Duzova et al. found that eGFR was lower in patients with higher BMI; hence, obese children had the lowest eGFR (25). We thought that these different findings would depend on our small sample size. Conversely, Duzova et al. reported that there was no significant difference between the groups in terms of frequency of subjects with eGFR < 75 mL/min/1.73 m^2 (25). Also, Salman et

al. reported that eGFR as calculated from sCre was higher in obese patients without MetS than in nonobese controls. They interpreted this as a symptom of hyperfiltration, which is the first stage of progression to renal dysfunction (26). Metabolic effects, including inflammation, insulin resistance, and adipokine dysregulation, may directly or indirectly affect renal structure and function (27). Conversely, inflammatory risk factors and lipid byproducts play a key role in the progression of renal dysfunction in obese adult patients (28). As mentioned above, consistent with the concept of a causal relationship between dyslipidemia and renal dysfunction, we found that the high LDL-c group had higher KIM1/Cre levels than the normal group. In the present study a statistically significant difference was found in the urinary excretion of NGAL between those with and without hypertriglyceridemia in the obese and overweight group. Intracellular accumulation of free fatty acids and triglycerides in renal glomerular and tubulo-interstitial cells may lead to renal lipotoxicity (29). Taken together, in agreement with the present study, abdominal obesity was reported to be an important risk factor for CKD (30).

In chronic hyperglycemia, especially in diabetes, the renin-angiotensin system and the endothelin system may induce hemodynamic effects, which lead to microvascular complications, and non-hemodynamic effects through an autocrine or paracrine action, which may contribute to the proliferation of kidney cells and the expression of growth factors or cytokines, leading to changes in renal function (31,32). Insulin resistance may be one of the real culprits in the development of glomerulosclerosis (33). Despite these mechanisms, consistent with the present study, Goknar et al. found that urinary injury markers did not differ among patients with insulin resistance and impaired glucose tolerance. These values have not correlated with fasting and postprandial glucose values (8). Conversely, urine samples from patients with diabetic nephropathy and SLE nephropathy, who had significant proteinuria (3 g/day) but no evidence of tubule necrosis on urine sediments, had no elevated KIM-1 protein levels (23). Furthermore, we found a positive correlation between insulin and HOMA-IR values with NGAL/Cre values in

overweight subjects, but not in obese subjects. A study from the EGIR-RISC cohort reports that improving insulin sensitivity might also reduce or prevent albuminuria, in particular at very early stages (34). Based on these findings, renal function was correlated with insulin and HOMA-IR levels in the early stages of excess weight gain. However, in the later stages of obesity we thought that NGAL excretion could be disproportionate with further deterioration of tubular function. We judged that excretion of NGAL in urine might be unstable when tubular disorder progresses.

The aforementioned mechanisms have been suggested to explain the impact of obesity on renal function. However, a meta-analysis suggested that a high body mass index acts as an independent predictor of new-onset CKD, which remains currently undefined (35). In a cohort study, central adiposity and metabolic disturbances may lie in the causal pathway between obesity and CKD (30). Therefore, renal function is not affected by obesity as compared with the control group according to the results of the present study. Otherwise, based on systematic review findings from cohort studies, Wang et al. suggested that obesity increased the risk for kidney disease, including CKD, ESRD, kidney stones, kidney cancer, and RCC (3). So, in light of these opinions, the finding might suggest that debates on the timing of kidney injury by obesity will continue. After an average follow-up of > 6 years, obesity increased the risk of low eGFR and albuminuria by 28% and 51%, respectively (35).

Physiological differences in the kidneys of men and women may be driven by the kidney's sex hormone receptors (36). Hill et al. reported a higher prevalence of CKD in women compared with men in a meta-analysis (37). Likewise, in our cohort, female obese adolescents excreted higher urinary NGAL levels than male obese adolescents. Hsu et al. suggested a higher risk for CKD in obese women when compared to obese men. This finding is due to a higher percentage of adipose tissue in obese women than in obese men (3). Differences in diet habits may also contribute to differences between genders.

Given that renal injury markers should be investigated in long-term, prospective, observational studies, the present study had a cross-sectional design and small sample size, which is a limitation of our study. By designing a longitudinal study, the effect of obesity on kidney function may be determined more accurately. The unsteady creatinine volume output will influence the data considerably. As such, the normalization of urinary markers as related to urine creatinine concentration poses a limitation. The strength of this study is that we chose to prospectively assess obese and overweight adolescents to evaluate kidney function. In the present study we also investigated the effects of all obesity-related comorbidities, i.e., hypertension, dyslipidemia, insulin resistance, and proteinuria, on kidney function in obese adolescents.

Further, comprehensive studies are needed to prove that obesity disrupts renal function in adolescents. In the present study we observed that obese and overweight adolescents had no notable renal dysfunction when compared with control adolescents. However, dyslipidemia in obesity affects kidney function. In addition, obesity impaired renal function in female adolescents as compared with male adolescents. Excretion of NGAL in urine might be unsteady when tubular disorder progresses. We suggest that the use of normalization of the urinary marker to urine creatinine ratio should be discussed.

REFERENCES

1. Gungor NK. Overweight and obesity in children and adolescents. Journal of clinical research in pediatric endocrinology 2014;6(3):129-43. DOI: 10.4274/jcrpe.1471

2. Han JC, Lawlor DA, Kimm SY. Childhood obesity. Lancet (London, England) 2010;375(9727):1737-48. DOI: 10.1016/S0140-6736(10)60171-7

3. Wang Y, Chen X, Song Y, Caballero B, Cheskin L. Association between obesity and kidney disease: a systematic review and meta-analysis. Kidney Int 2008;73(1):19-33. DOI: 10.1038/sj.ki.5002586

4. Hsu C-y, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Annals of internal medicine 2006;144(1):21-8. DOI: 10.7326/0003-4819-144-1-200601030-00006

5. Ross WR, McGill JB. Epidemiology of obesity and chronic kidney disease. Advances in chronic kidney disease 2006;13(4):325-35. DOI: 10.1053/j.ackd.2006.07.012

6. Hewitt SM, Dear J, Star RA. Discovery of protein biomarkers for renal diseases. Journal of the American Society of Nephrology 2004;15(7):1677-89. DOI: 10.1097/01.ASN.0000129114.92265.32

7. Ding W, Mak RH. Early markers of obesity-related renal injury in childhood. Pediatr Nephrol 2015;30(1):1-4. DOI: 10.1007/s00467-014-2976-3

8. Goknar N, Oktem F, Ozgen IT, Torun E, Kucukkoc M, Demir AD, et al. Determination of early urinary renal injury markers in obese children. Pediatr Nephrol 2015;30(1):139-44. DOI: 10.1007/s00467-014-2829-0

9. Thakur V, Chattopadhyay M. Early Urinary Markers for Diabetic and Other Kidney Diseases. Current drug targets 2018;19(7):825-31. DOI: 10.2174/1389450119666180319124639

10. Xu SY, Venge P. Lipocalins as biochemical markers of disease. Bba-Protein Struct M. 2000;1482(1-2):298-307. DOI: 10.1016/S0167-4838(00)00163-1

11. Ozturk A, Mazicioglu MM, Hatipoglu N, Budak N, Keskin G, Yazlak Z, et al. Reference body mass index curves for Turkish children 6 to 18 years of age. Journal of pediatric endocrinology & metabolism 2008;21(9):827-36. DOI: 10.1515/JPEM.2008.21.9.827

12. Lear S, James P, Ko G, Kumanyika S. Appropriateness of waist circumference and waist-to-hip ratio cutoffs for different ethnic groups. European Journal of Clinical Nutrition 2010;64(1):42-61. DOI: 10.1038/ejcn.2009.70

13. Tümer N, Yalcinkaya F, Ince E, Ekim M, Köse K, Cakar N, et al. Blood pressure nomograms for children and adolescents in Turkey. Pediatric nephrology 1999;13(5):438-43. DOI: 10.1007/s004670050636

14. Kurtoglu S, Hatipoglu N, Mazicioglu M, Kendirici M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. Journal of clinical research in pediatric endocrinology 2010;2(3):100-6. DOI: 10.4274/jcrpe.v2i3.100

15. Sangun Ö, Dündar B, Köşker M, Pirgon Ö, Dündar N. Prevalence of metabolic syndrome in obese children and adolescents using three different criteria and evaluation of risk factors. Journal of clinical research in pediatric endocrinology 2011;3(2):70-6. DOI: 10.4274/jcrpe.v3i2.15

16. Houser MT, Jahn MF, Kobayashi A, Walburn J. Assessment of urinary protein excretion in the adolescent: effect of body position and exercise. The Journal of pediatrics 1986;109(3):556-61. DOI: 10.1016/S0022-3476(86)80143-3

17. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents. The Lancet 2007;369(9579):2059-61. DOI: 10.1016/S0140-6736(07)60958-1

18. Güngör NK. Overweight and obesity in children and adolescents. Journal of clinical research in pediatric endocrinology 2014;6(3):129. DOI: 10.4274/jcrpe.1471

19. Vivante A, Golan E, Tzur D, Leiba A, Tirosh A, Skorecki K, et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. Archives of internal medicine 2012;172(21):1644-50. DOI: 10.1001/2013.jamainternmed.85

20. Mohammadi-Karakani A, Asgharzadeh-Haghighi S, Ghazi-Khansari M, Hosseini R. Determination of urinary enzymes as a marker of early renal damage in diabetic patients. Journal of clinical laboratory analysis 2007;21(6):413-7. DOI: 10.1002/jcla.20212

21. Nielsen SE, Schjoedt KJ, Astrup AS, Tarnow L, Lajer M, Hansen PR, et al. Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Kidney Injury Molecule 1 (KIM1) in patients with diabetic nephropathy: a cross-sectional study and the effects of lisinopril. Diabetic medicine : a journal of the British Diabetic Association 2010;27(10):1144-50. DOI: 10.1111/j.1464-5491.2010.03083.x

22. Savino A, Pelliccia P, Giannini C, de Giorgis T, Cataldo I, Chiarelli F, et al. Implications for kidney disease in obese children and adolescents. Pediatric Nephrology 2011;26(5):749-58. DOI: 10.1007/s00467-010-1659-y

23. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int 2002;62(1):237-44. DOI: 10.1046/j.1523-1755.2002.00433.x

24. Praga M. Synergy of low nephron number and obesity: a new focus on hyperfiltration nephropathy. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2005;20(12):2594-7. DOI: 10.1093/ndt/gfi201

25. Duzova A, Yalcinkaya F, Baskin E, Bakkaloglu A, Soylemezoglu O. Prevalence of hypertension and decreased glomerular filtration rate in obese children: results of a population-based field study. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 2013;28 Suppl 4:iv166-71. DOI: 10.1093/ndt/gft317

26. Salman DÖ, Şıklar Z, İlarslan ENÇ, Özçakar ZB, Kocaay P, Berberoğlu M. Evaluation of Renal Function in Obese Children and Adolescents Using Serum Cystatin C Levels, Estimated Glomerular Filtration Rate Formulae and Proteinuria: Which is most Useful? Journal of clinical research in pediatric endocrinology 2019;11(1):46. DOI: 10.4274/jcrpe.galenos.2018.2018.0046

27. Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. Clinical journal of the American Society of Nephrology 2007;2(3):550-62. DOI: 10.2215/CJN.04071206

28. Ramkumar N, Cheung AK, Pappas LM, Roberts WL, Beddhu S. Association of obesity with inflammation in chronic kidney disease: a cross-sectional study. Journal of Renal Nutrition 2004;14(4):201-7. DOI: 10.1016/S1051-2276(04)00133-5

29. Bobulescu IA. Renal lipid metabolism and lipotoxicity. Current opinion in nephrology and hypertension 2010;19(4):393. DOI: 10.1097/MNH.0b013e32833aa4ac

30. Kramer H, Gutierrez OM, Judd SE, Muntner P, Warnock DG, Tanner RM, et al. Waist Circumference, Body Mass Index, and ESRD in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. American journal of kidney diseases : the official journal of the National Kidney Foundation 2016;67(1):62-9. DOI: 10.1053/j.ajkd.2015.05.023

31. Gross ML, Dikow R, Ritz E. Diabetic nephropathy: recent insights into the pathophysiology and the progression of diabetic nephropathy.

Kidney international Supplement 2005(94):S50-3. DOI: 10.1111/j.1523-1755.2005.09412.x

32. Hale LJ, Hurcombe J, Lay A, Santamaria B, Valverde AM, Saleem MA, et al. Insulin directly stimulates VEGF-A production in the glomerular podocyte. American journal of physiology - Renal physiology 2013;305(2):F182-8. DOI: 10.1152/ajprenal.00548.2012

33. Kincaid-Smith P. Hypothesis: obesity and the insulin resistance syndrome play a major role in end-stage renal failure attributed to hypertension and labelled 'hypertensive nephrosclerosis'. Journal of hypertension 2004;22(6):1051-5. DOI: 10.1097/00004872-200406000-00001

34. Pilz S, Rutters F, Nijpels G, Stehouwer CD, Højlund K, Nolan JJ, et al. Insulin sensitivity and albuminuria: the RISC study. Diabetes Care 2014;37(6):1597-603. DOI: 10.2337/dc13-2573

35. Garofalo C, Borrelli S, Minutolo R, Chiodini P, De Nicola L, Conte G. A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. Kidney international 2017;91(5):1224-35. DOI: 10.1016/j.kint.2016.12.013

36. Jelinsky SA, Harris HA, Brown EL, Flanagan K, Zhang X, Tunkey C, et al. Global transcription profiling of estrogen activity: estrogen receptor α regulates gene expression in the kidney. Endocrinology 2003;144(2):701-10. DOI: 10.1210/en.2002-220728

37. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease–a systematic review and meta-analysis. PloS one 2016;11(7):e0158765. DOI: 10.1371/journal.pone.0158765
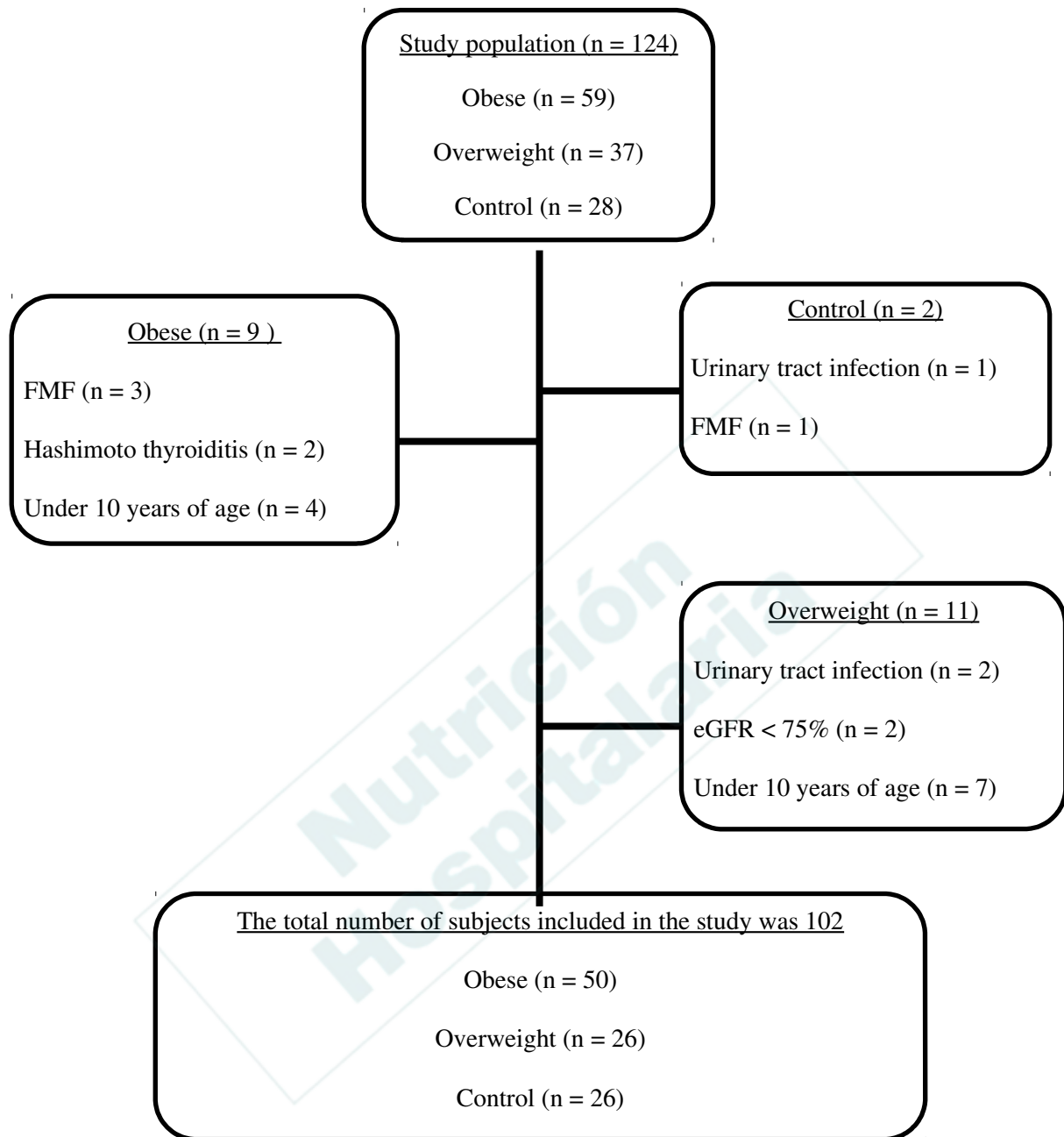
Fig. 1. Flowchart diagram of the study population. FMF: familial Mediterranean fever; eGFR: estimated glomerular filtration rate.

Table I. Demographic data and subject characteristics according to groups

	Total	Group Obese (n = 50)	Overweight (n = 26)	Control (n = 26)	p
Age	13.14 ± 2.17	13.46 ± 2.13	11.56 ± 1.81	14.12 ± 1.73	< 0.001
Gender F	65 (63.7)	33 (66)	13 (50)	19 (73.1)	0.200
M	37 (36.3)	17 (34)	13 (50)	7 (26.9)	
Weight (kg)	62.85 ± 19.97	77.64 ± 15.81 (a)	51.18 ± 12.49 (b)	46.09 ± 9.72 (b)	< 0.001
Height (cm)	155.43 ± 10.46	158.9 ± 8.84 (a)	148.29 ± 11.25 (b)	155.92 ± 9.22 (a)	< 0.001
BMI (kg/m^2)	25.56 ± 6.25	30.5 ± 4.56 (a)	22.86 ± 2.53 (b)	18.75 ± 2.4 (c)	< 0.001
Z score (BMI)	1.71 ± 1.44	2.74 ± 0.54 (a)	1.75 ± 0.49 (b)	-0.33 ± 1.06 (c)	< 0.001
BPs (mmHg)	107.56 ± 11.14	111.39 ± 10.39 (a)	102.77 ± 11.01 (b)	105.15 ± 10.46 (ab)	0.006
BPd (mmHg)	75.2 ± 8.81	78.31 ± 7.51 (a)	74.23 ± 10.34 (ab)	70.31 ± 7.13 (b)	< 0.001
BUN (mg/dL)	9.7 ± 2.46	9.64 ± 2.18	9.87 ± 3.19	9.65 ± 2.2	0.761
sCre (mg/dL)	0.57 ± 0.1	0.59 ± 0.09 (a)	0.53 ± 0.09 (b)	0.57 ± 0.11 (ab)	0.223
eGFR (ml/min/1.73m^2)	169.3 ± 33.83	165.76 ± 31.67	179.14 ± 38.44	166.12 ± 32.25	0.724
Glucose (mg/dL)	87.94 ± 7.26	87.76 ± 6.77	88.9 ± 9.22	87.06 ± 5.38	0.848
Insulin (uIU/mL)	22 ± 13.9	25.59 ± 14.15	15.08 ± 10.8		-
HOMA-IR	4.88 ± 3.31	5.61 ± 3.33	3.46 ± 2.9		-
TSH (IU/mL)	2.65 ± 1.14	2.75 ± 1.14	2.31 ± 1.05	3.32 ± 1.,22	-
sT4 (IU/mL)	1.24 ± 0.18	1.23 ± 0.17	1.25 ± 0.2	1.27 ± 0.1	0.850
TG (mg/dL)	117.5 ± 52.13	128.13 ± 52.34	97.95 ± 47.61		-

LDL-c (mg/dL)	108.86 ± 31.33	118.42 ± 30.34	90.3 ± 24.87		-
Cholesterol (mg/dL)	162.53 ± 34.15	171.21 ± 35.18	145.77 ± 25.95		-
HDL-c (mg/dL)	46.38 ± 11.02	44.88 ± 9.26	49.05 ± 13.69		-
UProt/Cre	0.18 ± 0.31	0.18 ± 0.43	0.18 ± 0.11	0.18 ± 0.11	0.793
AST	22.21 ± 14.5	23.55 ± 18.96	23.3 ± 9.21	18.48 ± 5.96	0.378
ALT	19.89 ± 17.96	24.52 ± 21.6 (a)	16.15 ± 7.92 (ab)	14.53 ± 15.28 (b)	**0.026**

F: female; M: male; BPs: systolic blood pressure; BPd: diastolic blood pressure; BUN: blood urea nitrogen; sCre: serum creatinine; eGFR: estimated glomerular filtration rate; HOMA-IR: Homeostasis Assessment Model-Insulin Resistance; TSH: thyroid stimulating hormone; fT4: free T4; TG: triglycerides; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol. Data are presented as number-percentage, mean ± standard deviation, using [Q1-Q3] for median. Chi-square and one-way ANOVA tests were used to compare groups. (ab): the common letter in a line means statistical insignificance. Statistically significant differences are shown in bold type. Age correction was applied for quantitative variables.

Table II. Urinary NGAL and KIM-1 levels according to groups

	Total		Group						p
			Obese (n = 50)		Overweight (n = 26)		Control (n = 26)		
NGAL	40.59	[26.37-62.84]	45.88	[25.98-71.08]	35.98	[25.59-49.12]	40.39	[28.53-56.96]	0.327
KIM1	85.88	[75.41-98.45]	89.03	[77.5-98.45]	80.65	[75.41-98.45]	84.84	[77.5-96.36]	0.917
NGAL/Cre	31.99	[19.58-53.37]	34.25	[20.54-56.65]	32.27	[19.58-45.62]	28.45	[16.65-49.88]	0.848
KIM-1/Cre	65.49	[48.26-108.21]	65.2	[41.73-101.36]	73.33	[55.69-126.26]	63.09	[44.72-100.47]	0.877

NGAL: ng/mL in urine; KIM-1: pg/mL in urine; NGAL/Cre: ng/mg; KIM-1/Cre: pg/mg. Data are presented using [Q1-Q3] for median. Chi-square, one-way ANOVA, and Kruskal-Wallis tests were used to compare groups. Age correction was applied for quantitative variables.

Table III. Urinary NGAL, NGAL/Cre, KIM-1, and KIM-1/Cre levels in the obese and overweight group according to gender and clinical disturbances

		n	NGAL (ng/mL)		NGAL/Cre (ng/mg)		KIM-1 (pg/mL)		KIM-1/Cre (pg/mg)	
Gender	Female	46	50.39	[30.88-74.22]	36.38	[22.27-58.72]	89.03	[79.6-100.54]	63.13	[43.95-111.27]
	Male	30	26.67	[23.24-45.59]	24.73	[18.56-45.62]	82.74	[75.41-94.26]	85.52	[54.47-108.21]
p			**0.013**		0.099		0.917		0.515	
HT	Yes	59	41.08	[26.37-62.84]	31.37	[20.54-52.59]	85.88	[75.41-98.45]	68.46	[50.95-123.07]
	No	16	42.55	[25.79-80.69]	39.69	[20.93-64.82]	86.93	[76.46-94.26]	57.21	[44.3-102.95]
p			0.142		0.909		0.358		0.351	
Insulin Resistance	No	42	42.85	[27.35-66.57]	33.52	[20.54-61.48]	85.88	[75.41-98.45]	67.37	[52.89-123.07]
	Yes	33	35	[24.02-53.63]	31.14	[18.87-45.62]	90.07	[77.5-98.45]	64.66	[43.95-101.36]
p			0.687		0.460		0.277		0.324	
High TG	No	58	39.51	[25-62.84]	31.09	[19.06-53.37]	85.88	[75.41-96.36]	67.1	[51.61-104.55]
	Yes	17	45.98	[35-83.04]	41.93	[31.03-62.46]	90.07	[79.6-100.54]	66.85	[50.95-133.04]
p			**0.032**		**0.020**		0.822		0.482	
High LDL-c	No	58	39.51	[25.59-56.37]	30.83	[19.36-52.59]	84.84	[75.41-94.26]	65.17	[51.81-108.21]
	Yes	16	64.12	[30.98-114.32]	40.13	[31.03-61.97]	93.22	[81.69-119.4]	75	[42.63-104.07]
p			**0.024**		0.849		0.128		0.521	
Low HDL-c	No	65	42.25	[25.59-62.84]	34.44	[20.54-56.65]	85.88	[75.41-98.45]	68.46	[51.61-105.61]
	Yes	10	40.3	[30.88-65.2]	31.2	[22.16-51.83]	92.16	[83.79-98.45]	62.69	[40.57-129.95]
p			0.801		0.934		0.628		0.638	
Proteinuria	No	67	39.51	[25.98-62.06]	32.61	[20.54-51.83]	85.88	[75.41-96.36]	64.66	[50.95-105.61]
	Yes	9	60.1	[39.51-186.76]	62.46	[16.38-225.89]	94.26	[90.07-108.92]	93.22	[54.47-152.77]
	p		**0.001**		**< 0.001**		**0.017**		**0.013**	
Metabolic syndrome	No	59	40.29	[25.59-65.2]	32.61	[19.06-61.48]	87.98	[75.41-102.64]	68.46	[51.47-123.07]
	Yes	17	41.08	[30.29-47.35]	33.16	[22.83-48.29]	85.88	[79.6-92.17]	60.79	[42.86-104.55]
	p		0.253		0.723		0.371		0.294	

HT: hypertension; Cre: creatinine; TG: triglycerides; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol. Data are presented using [Q1-Q3] for median. Kruskal-Wallis tests were used to compare groups. Age correction was applied.