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Acanthosis nigricans: a warning sign of lower urinary tract dysfunction in obese children?

B. ÖZHAN[1], H. ASILTÜRK[2], S. YÜKSEL[3]

[1]Division of Pediatric Endocrinology, Pamukkale University, School of Medicine, Denizli, Turkey
[2]Division of Pediatrics, Pamukkale University, School of Medicine, Denizli, Turkey
[3]Division of Pediatric Nephrology and Rheumatology, Pamukkale University, School of Medicine, Denizli, Turkey

Abstract. – OBJECTIVE: There have been very few studies on the relationship between lower urinary tract dysfunction (LUTD) and obesity-related metabolic disorders in the pediatric age group. This study investigated the relationship between LUTD and metabolic disturbances in obese children.

PATIENTS AND METHODS: Four-hundred obese children (body mass index ≥ 95th percentile) were included in the present study. Anthropometric, clinical, and biochemical parameters were evaluated. The Dysfunctional Voiding and Incontinence Scoring System (DVISS) questionnaire was administered and scores over 8.5 were considered to be reflective of LUTD. Subjects were stratified into two groups based on DVISS symptom scores – obese children with and without LUTD. The homeostasis assessment model was used to evaluate insulin resistance and the International Diabetes Federation criteria to identify metabolic syndrome.

RESULTS: Lower urinary tract dysfunction was detected in 19% of the study population. There were no significant differences between the two groups in terms of laboratory results. No statistically significant relationship was found between LUTD and the presence of metabolic syndrome or insulin resistance; however, a significant association was observed between LUTD and acanthosis nigricans. Regression analysis revealed that only the presence of acanthosis nigricans significantly increased the risk of lower urinary tract dysfunction by 1.75-fold ($p < 0.05$).

CONCLUSIONS: The presence of acanthosis nigricans in obese children may suggest the concurrent occurrence of lower urinary tract dysfunction and should be investigated accordingly.

Key Words:
Obesity, Lower urinary tract dysfunction, Insulin resistance, Acanthosis nigricans, Children, Adolescents.

Introduction

Lower urinary tract dysfunction (LUTD) is a common childhood condition characterized by abnormalities in either the filling and/or emptying of the bladder. The symptoms of LUTD include urgency, incontinence, holding maneuvers, increased urination frequency, and straining[1]. The reported prevalence rates range from 17% to 22[2]. Bladder control, the ability to consciously suppress the sensation of bladder fullness, contract the detrusor muscle, and control the external sphincter, develops gradually along with the central nervous system and medulla spinalis myelination. Daytime urinary control is usually acquired by the age of four, while nocturnal control is usually achieved between five and seven years old. The inability to achieve daytime urine control, particularly in school-age children, can create anxiety and lower self-esteem. Given that school-age children are affected by high rates of LUTD, the ability to identify and intervene promptly is crucial.

Diagnosis is easy in children who present with the more common LUTD-related issues such as incontinence, urgency, etc. However, LUTD is often overlooked if its symptoms are not investigated in conditions that may be comorbid with LUTD, such as obesity, attention deficit hyperactivity disorder, constipation and fecal incontinence, neuropsychiatric conditions, intellectual disabilities, sleep apneas, and parasomnias[3].

Obesity is a major health problem that is growing rapidly in both resource-rich and resource-poor countries with a sharp increase in global prevalence in recent decades. Over 30% of children and adolescents in the United States of America and many European countries are obese or overweight[4]. Considering that 60% of these

Corresponding Author: Bayram Ozhan, MD; e-mail: bayramozhan@yahoo.com

children will be obese in adulthood, an increase in the prevalence of obesity-related comorbidities such as hypertension, insulin resistance, and dyslipidemia seems inevitable[5].

The adverse effect of obesity on voiding function has recently become a subject of growing interest. Studies have shown that obesity increases the prevalence of LUTD in both childhood and adulthood[6]. Obesity-related metabolic disturbances are associated with the risk of lower urinary tract symptoms[7]. The pathophysiology involved in this relationship is poorly elucidated and requires further investigation.

The main purpose of this study was to determine the frequency of LUTD in obese children and adolescents and to evaluate the relationship between clinical and metabolic variables of obesity and LUTD.

Patients and Methods

This cross-sectional study involved children and adolescents aged between six and 18 years-old presenting to the Pamukkale University Hospital Pediatric Outpatient Clinic, Denizli/Turkey, between November 2016 and November 2017 with obesity as their chief complaint. Written informed consent was obtained from all patients or their parents prior to their participation in the study. The current study was approved by the Pamukkale University Local Ethics Committee (Protocol No. 01.11.2016/19) and was performed in accordance with the Helsinki Declaration. Patients with a history of urinary tract infection, diabetes mellitus, neurological disease, psychiatric disease, or pelvic and vertebral surgery were excluded. Physical examination was performed in all cases. Puberty grading was performed based on the Tanner-Marshall classification system. Blood pressure, body height, weight, and waist circumference were measured using standard techniques. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Children with a BMI $\geq$ 95th percentile for their age and sex were regarded as obese[8]. Acanthosis nigricans was diagnosed clinically. It is characterized by symmetric, velvety, dark brown hyperpigmented plaques, particularly on the intertriginous regions of the axilla, groin, and posterior neck[9]. All obese patients underwent urinalysis, urine culture, serum creatinine measurement, and urinary tract ultrasonography. Patients with real-time urinary tract infections were excluded from the study. Blood samples were collected for biochemical analysis following an overnight fast of at least 8 h. Fasting glucose, insulin, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol were measured using standard laboratory methods by certified laboratory staff and the cobas 8000 c702 analyzer (Roche Diagnostics, Mannheim, Germany) was used for chemistry analyses. The Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated[10]. HOMA-IR values > 2.22 in prepubertal girls and > 2.67 in prepubertal boys, and > 3.82 in pubertal girls and > 5.22 in pubertal boys were regarded as indicative of insulin resistance[11]. Metabolic syndrome (MS) was diagnosed based on the International Diabetes Federation (IDF) criteria in obese patients[12]. LUTD was diagnosed using the Dysfunctional Voiding and Incontinence Scoring System (DVISS) questionnaire, validated for Turkish children by Akbal et al[13] with 90% sensitivity and 90% specificity. Children with scores of 8.5 or higher were regarded as having LUTD.

Statistical Analysis

Mean values were expressed as mean ± standard deviation (SD). Data distribution was analyzed using the Kolmogorov-Smirnov test. Subjects were stratified into two groups based on DVISS symptom scores – obese children with and without LUTD, and potential associations between LUTD and the categorical variables (metabolic syndrome, insulin resistance (IR), and acanthosis nigricans). The Mann-Whitney *U* test, *t*-test, and chi-square test were used to compare variables. Logistic regression analysis was applied to test the joint effects of different variables on LUTD. p-values $\leq$ 0.05 were considered statistically significant for all analyses. All analyses were performed using SPSS (Statistical Packard for Social Sciences) for Windows version 21.0 (IBM, Armonk, NY, USA).

Results

We aimed to recruit consecutive obese patients for one-year study. Among 445 consecutive patients who were referred to the outpatient clinic, 45 patients were excluded, including five individuals with new-onset type 2 diabetes mellitus, seven obese children with a documented urinary tract infection, and the remaining 33 patients

Table I. The demographic features of obese patients with/without lower urinary tract dysfunction.

	Obese subjects without LUTD (n = 324)	Obese subjects with LUTD (n = 76)	*p*-value
Age mean ± SD	11.1 ± 2.9	10.2 ± 2.8	**0.03**
DVISS, score	2.3 ± 2.1	13.1 ± 4.4	**0.00**
Nocturnal enuresis, n (%)	53 (13.3)	347 (86.8)	**0.01**
Urgency, n (%)	51 (12.7)	349 (87.3)	**0.01**
Bladder holding maneuver, n (%)	165 (41.2)	235 (58.8)	**0.02**
Overactive bladder, n (%)	170 (42.5)	230 (57.5)	**0.02**

Data presented as mean ± SD or n (%). LUTD Lower urinary tract dysfunction, DVISS: The Dysfunctional Voiding and Incontinence Scoring System.

had a history of psychiatric disease. Data were collected from 400 consecutive obese children and adolescents (165 boys and 235 girls). Patients' mean age was 10.9±2.9 years. LUTD was detected in 19% (n = 76) of the sample population. The characteristics of LUTD and non-LUTD children are given in Table I. The mean age of the group with LUTD was 10.2±2.8 years, significantly lower than the non-LUTD group, which was 11.1±2.9 years (p=0.03) (Table II). Mean systolic blood pressure was 111.5±18.6 mmHg in the group with LUTD and 116.1±14.9 mmHg in the group without LUTD. There were no significant differences between the two groups in terms of laboratory results (Table III). HOMA-IR was not statistically different in both pubertal obese adolescents and prepubertal children (5.85±4.15 *vs.* 5.51±3.32, p=0.637 / 3.60±2.12 *vs.* 5.28±5.85, p=0.092). Of the 175 prepubertal obese children, 68.5% (120 of 175) had IR, 14.8% (26 of 175) had MS, 27.4% (48 of 175) had acanthosis nigricans. Of the 225 pubertal obese children, 58.6% (132 of 225) had IR, 22.6% (51 of 225) had MS, 35.1% (79 of 225) had acanthosis nigricans. No significant relationship was found between LUTD and the presence of metabolic syndrome or insulin resistance, although, a significant association was observed between LUTD and acanthosis nigricans (p=0.031) (Table IV). Multiple linear regression analysis was performed to assess the joint effects of different variables such as TG, HDL, glucose, insulin, Homa-IR, BMI, metabolic syndrome, insulin resistance, and acanthosis nigricans on the risk of LUTD, and it demonstrated that only acanthosis nigricans increased the risk of LUTD in obese children (OR: 1.75; 95% CI: 1.048-2.932; p=0.032) (Table V).

Discussion

The purpose of this study was to determine the prevalence of and relationship between metabolic

Table II. Anthropometric characteristics of obese patients with/without lower urinary tract dysfunction.

Anthropometric characteristics	Obese subjects without LUTD (n = 324)	Obese subjects with LUTD (n = 76)	*p*-value
Gender (female:male), n	187:137	48:28	0.386
Prepubertal, pubertal, n	137/187	38)/38	0.22
Weight, kg	67.4 ± 22.0	64.0 ± 21.5	0.185
Weight, SDS	2.6 ± 0.9	2.7 ± 0.9	0.506
Height, cm	150.1 ± 15.0	146.8 ± 14.4	0.086
Height, SDS	0.6 ± 1.3	0.7 ± 1.1	0.327
BMI, SDS	2.5 ± 0.6	2.6 ± 0.6	0.555
Waist circumference, cm	92.8 ± 13.8	90.8 ± 13.9	0.137
Systolic blood pressure, mmHg	116.0 ± 14.9	111.5 ± 18.6	**0.027***
Systolic blood pressure, SDS	0.9 ± 1.04	0.8 ± 0.9	0.420
Diastolic blood pressure, mmHg	72.8 ± 10.8	70.3 ±10.9	0.054
Diastolic blood pressure, SDS	1.0 ± 0.8	0.8 ± 0.8	0.180

Data presented as mean ± SD or n (%). SDS: standard deviation scores, MI: Body mass index, LUTD Lower urinary tract dysfunction, p-values <0.05 were considered statistically significant*.

Table III. Metabolic variables of obese patients with/without lower urinary tract dysfunction.

	Obese subjects without LUTD (n = 324)	Obese subjects with LUTD (n = 76)	*p*-value
FBG, mg/dL	92.2 ± 7.4	91.2 ± 7.0	0.286
Insulin, mIU/mL	21.2 ± 14.1	23.4 ± 19.1	0.907
HDL, mg/dL	47.8 ± 11.6	49.8 ± 12.7	0.238
LDL, mg/dL	88.9 ± 24.6	90.4 ± 22.1	0.639
TG, mg/dL	114.7 ± 58.6	117.2 ± 49.0	0.368
Total cholesterol, mg/dL	159.7 ± 29.7	163.6 ± 26.6	0.099
HOMA-IR	4.9 ± 3.6	5.4 ± 4.7	0.826

FBG: fasting blood glucose, HDL: high density lipoprotein, LDL: low density lipoprotein. TG: triglyceride. HOMA-IR: homeostasis model assessment for insulin resistance., LUTD Lower urinary tract dysfunction. *p*-values <0.05 were considered statistically significant*.

Table IV. Associations of lower urinary tract dysfunction with metabolic syndrome, insulin resistance and acanthosis nigricans.

	Obese subjects without LUTD (n = 324)	Obese subjects with LUTD (n = 76)	Total	*p*-value
Metabolic syndrome, n (%)	63 (19.4)	14 (18.4)	77 (19.2)	0.839
Insulin resistance, n (%)	206 (63.5)	46 (60.5)	252 (63)	0.620
Acanthosis nigricans, n (%)	95 (29.3)	32 (42.1)	127 (31.7)	**0.031***

Data presented as n (%). *Chi-square test. *p*-values <0.05 were considered statistically significant*. LUTD: Lower Urinary Tract Dysfunction.

variables and LUTD, and to identify which metabolic variables would be predictive or associated with LUTD in obese children and adolescents. The prevalence of LUTD was 19%, and acanthosis nigricans, which is a cutaneous condition that can be commonly detected in obese patients with insulin resistance, might be a reliable marker of concomitant LUTD comorbidity. To the best of our knowledge, the association between acanthosis nigricans and LUTD has not been previously described in the literature and the presence of acanthosis nigricans increased the risk of LUTD 1.75-fold in obese children and adolescents.

Clinical studies[14,15] on the relationship between LUTD and obesity in children are prevalence studies, and the association between obesity-related-metabolic disturbances and LUTD has not been investigated. The reported prevalence of LUTD changes according to the study population, which largely depends on the definition of dysfunction. The urodynamic study is the gold standard methodology to investigate LUTD, but this urological investigation is not frequently used because it does have a little effect on treatment planning, it is also invasive, time-consuming, costly, and difficult to interpret[12]. Therefore, a variety of questionnaires, which are easy to use and highly sensitive and specific, were used to determine the prevalence of LUTD[16]. The first study that was conducted in children to identify an association between voiding dysfunction and obesity found that most of the children with void-

Table V. Odds ratios of lower urinary tract dysfunction and corresponding 95% confidence intervals as derived from the best stepwise multiple logistic regression model.

Variables	Odds ratio	95% CI	*p*-value
Insulin resistance	0.87	(0.52-1.46)	0.620
Metabolic syndrome	2.18	(0.94-5.08)	0.068
Acanthosis nigricans	1.75	(1.04-2.93)	**0.032***

CI: Confidence Interval, *p*-values <0.05 were considered statistically significant*.

ing dysfunction were also obese and the rate of voiding dysfunction was almost double in obese patients compared to the normal population[17]. Subsequent studies revealed that obesity was an independent risk factor for overactive bladder (OAB) in children and these studies showed that obese children had higher mean scores for lower urinary tract symptoms[14,18]. The present study used the DVISS questionnaire and the prevalence of LUTD was found to be 19%. DVISS is 81% sensitive, 97.6% specific, and 89% accurate to diagnose LUTD, and it was also used in another study from the same region that reported a LUTD prevalence of 9.3%[19,20]. LUTD and obesity are common clinical health problems that adversely affect individuals' quality of life, and self-esteem in childhood and adulthood. They are risk factors for future obesity and OAB symptoms in adulthood. Consequently, timely diagnosis and treatment in childhood are very important to decrease the prevalence of adult obesity-related-disorders[21,22]. Evidence from numerous adult studies support the association between LUTD and obesity, the metabolic syndrome diagnostic criteria of low HDL, impaired glucose tolerance, hypertriglyceridemia, increased BMI, the number of births among women, and increased waist circumference in men[23,24].

Various mechanisms were suggested to explain the pathogenesis in this association. The most widely proposed mechanism was elevated intra-abdominal and intra-vesical pressure that could contribute to the development of stress incontinence by increasing pelvic floor stress and compromising functional bladder capacity in obese patients[25]. Besides, comorbid constipation which occurs as a result of dietary habits, autonomic dysfunction, hormonal effects, and diminished activity in obese patients is another contributing mechanism to the pathogenesis[26]. Finally, experimental animal studies have shown that OAB and urodynamic alterations were resolved by treating insulin resistance in experimentally induced diabetic rats, and insulin participates in bladder relaxation through mucosal the phosphoinositide 3-kinase/protein kinase Akt pathway activation[27,28].

A reduced biological response to the insulin molecule at a normal insulin concentration is considered to be insulin resistance. Surrogate markers of insulin resistance indices such as HOMA-IR could be useful to quantify insulin resistance, but these indices may be imprecise and there is currently no acceptable test for measuring insulin resistance in a clinical setting. The insulin-resistant state frequently manifests clinically in association with obesity and the diagnosis should be based upon clinical findings and presentations such as impaired glucose tolerance, metabolic syndrome, polycystic ovary syndrome, non-alcoholic fatty liver disease, and acanthosis nigricans[29]. Under physiological conditions, insulin relaxes the urinary bladder via nitric oxide released from the urothelium. In the presence insulin resistance, this mechanism would also be impaired in addition to the abovementioned clinical manifestations of insulin resistance.

Acanthosis nigricans is a dermatological manifestation of both insulin resistance and some other systemic disorders. The insulin resistance-related form is commonly seen in clinical practice and increasing insulin levels are implicated in insulin-like growth factor receptor-1-mediated keratinocyte and dermal fibroblast proliferation[30]. In the present study, acanthosis nigricans was significantly more prevalent in obese patients with LUTD.

The present study has some limitations. First, control subjects who were lean and healthy were not evaluated for LUTD and metabolic variables. Second, we did not follow-up obese children and adolescents with LUTD to observe the disappearance of acanthosis nigricans and resolution of symptoms with obesity treatment. However, the main benefit of the study is that, because of the survey, these obese children with LUTD were recognized and received medical attention that they may not have otherwise received.

Conclusions

This is the first study investigating the relationship between LUTD and obesity-related-metabolic disturbances and it showed that the presence of acanthosis nigricans in obese children may suggest concurrent LUTD, which should be investigated accordingly.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

B.O, H.N.A, and S.Y. were involved in the design and performance of the study. B.O, H.N.A, and S.Y. collected and

analyzed the data. S.Y was involved in data interpretation. B.O. and H.N.A. wrote the manuscript. H.N.A. wrote the first draft. All authors contributed significantly to the development and improvement of the manuscript and have approved the final content of this manuscript.

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