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The Effects of Obesity on Bladder Capacity in Children with and without Lower Urinary Tract Symptoms

THESIS

Submitted in partial satisfaction of the requirements

for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Crystal Dorgalli

Thesis Committee:
Professor Antoine. E Khoury, Chair
Professor Sherrie H. Kaplan
Assistant Adjunct Professor John Billimek

2016

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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Finally, I must express my profound gratitude to my family, especially my parents, and friends. Thank you for providing me with continuous encouragement and support throughout my academic career and throughout the process of conducting research and writing this thesis. I would not have been able to accomplish this without you. Thank you.

ABSTRACT OF THESIS

The Effects of Obesity on Bladder Capacity in Children with and without Lower Urinary Tract Symptoms

By

Crystal Dorgalli,

Master of Science in Biomedical and Translational Science

University of California Irvine, 2016

Professor Antoine Khoury, Chair

Objectives: Functional bladder capacity is an important factor in the diagnosis of lower urinary tract symptoms (LUTS) in children. LUTS are highly prevalent in children and this prevalence increases in obese children. However, the effects of obesity on bladder capacity are unknown. This study examines the relationship of obesity on functional bladder capacity and LUTS. This study also examines the differences in expected values based on the Koff formula between obese versus non-obese children.

Methods: Demographic data and voiding diary measurements were prospectively collected, after informed consent, for children without LUTS. The same data set was compared to data collected retrospectively for children with LUTS managed at the CHOC Children's Pediatric Urology Center after ethics approval from the institution. Obesity was defined as children who were above the 95th percentile in gender specific weight by age.

Expected bladder capacity was calculated using the Koff formula. Statistical comparison was performed using the Student t-test, where significance was set at $p<0.05$.

Results: We prospectively screened 110 children without LUTS and enrolled 35 and retrospectively identified 35 children with LUTS. Eighteen of the children without LUTS (25.7%) were non-obese while 17 (24.3%) were obese. In the LUTS group, 19 (27.1%) were non-obese and 16 (22.9%) were obese. Among patients with LUTS, AVV, MVV, and MMVV were not significantly different in obese versus non-obese children ($p=0.154$, $p=0.587$, $p=0.378$, respectively). There was no difference in prevalence of LUTS between healthy weight and obese children ($p=1.000$). Furthermore, bladder capacity expressed as a percentage of expected bladder capacity (as calculated by the Koff formula) was significantly different between non-obese and obese patients without LUTS ($p=0.040$).

Conclusion: Although this study has low statistical power due to a small sample size, trends show a lower functional bladder capacity in obese children compared to non-obese children with LUTS. Therefore weight counseling should be included in the management of these children. Additionally, LUTS does not have a higher prevalence in obese children when compared to healthy weight children in this study population. Furthermore, the Koff formula underestimates bladder capacity in obese, non-symptomatic children.

SECTION 1: INTRODUCTION

Serving as a reservoir, the urinary bladder's primary function is to store and empty urine while maintaining low internal pressure. To ensure this task is carried out correctly, a reciprocal relationship between the bladder and the lower urinary tract outlet is preserved by a network of neural connections. Several studies have tried to determined bladder capacity in healthy children. These studies used maximum capacities as measured on urodynamic studies (Berger et al 1983, Treves et al 1996; Kaefer et al 1997) and were conducted by insertion of a catheter to fill the bladder while simultaneously recording pressures. The maximum capacity was determined if leakage around the catheter occurred or the child expressed significant discomfort with the volume instilled into his/her bladder. In a similar study, patients were under anesthesia during the artificial filling of their bladders and could not express their need to void (Koff 1983). These four studies concluded with various formulas that allow physicians to calculate the expected or maximal bladder capacity. The techniques used in these studies may have caused the current formulas used in urology practice to be clinically flawed, as they were not based on a child's natural urge and signals to void. Also, the bladder capacity was determined in a non-physiologic way using an invasive method of introducing a catheter into the bladder and rapidly filling it with room-temperature fluid. Regardless of the technique used to derive the formula, the "Koff" formula is widely used and is currently the gold standard.

Several clinical conditions can lead to a reduction in functional bladder capacity, and cause the child to experience lower urinary tract symptoms (LUTS). The symptoms can either be related to abnormal bladder storage (frequency of urination, incontinence, urgency, and nocturia) or voiding symptoms (hesitancy, straining, weak or intermittent stream, and dysuria). Epidemiological studies report the incidence of LUTS is as high as 25% among school-aged children, making up about 40% of referrals to pediatric urologists (Vaz et al 2012; Beksac et al 2016). Although the majority of LUTS are treatable, there can be a group of patients who suffer from persistent symptoms that can have comorbidities (Vaz et al 2012; von Gontard et al 2015).

Some examples of the tools used for diagnosing LUTS include invasive urodynamic studies involving catheterization of the bladder to observe filling and emptying, uroflow studies to measure rate, volume, time and pattern of urination, and voiding diaries to measure the volume of urine voided throughout the day for 48-hours.

Evaluating functional bladder capacity in the pediatric population is especially important for recognizing bladder dysfunction in children who complain of LUTS. These children tend to have a smaller bladder capacity that causes them to void more urgently and frequently or to overflow their bladders and have urine incontinence (Starfield 1997; Bower et al 1997; Mahler et al 2007; Kwak & Park 2008). Functional bladder capacity is defined as the volume at which a child will feel the urge to void (Hamamo et al 1999). Having an accurate estimation of the normal average bladder capacity for pediatric patients is helpful in the diagnosis and treatment of many urological conditions. By predicting the size of a healthy pediatric patient's bladder, urologists are more easily able to diagnosis and treat bladder dysfunction and other conditions. However, the true functional bladder capacity in children is unknown as many studies are inconclusive about the range of normal findings. Although there are multiple formulas used to estimate the expected bladder capacity, to date no standard formulas are commonly in use in clinical settings to predict functional bladder capacity.

Obesity is a growing epidemic that has doubled in prevalence in the United States alone over the past few decades (Erdem et al 2006). It is prevalent in 33.6% of children and adolescents ages 2 to 19 years old (Guven et al 2007). Obesity has many associated comorbidities such as increased risk of type 2 diabetes, cardiovascular disease, gallbladder disease, etc. (Guven et al 2007). There is a high correlation between obese children and the experience of any LUTS but the reason for this is unknown. Few studies have documented a significant difference between healthy weight children and obese children with LUTS; however, questionnaires (vs. actual bladder capacity determination) were used to screen for LUTS (Schwartz et al 2009; Chang et al 2015). Through the use of uroflowmetry, two studies concluded that there is a significant effect of bladder surface area on average and maximum flow rates (Wese et al 1988; Segura et al 1997). However, the reason behind this is unknown and these studies do not focus on bladder capacity, an important factor in diagnosing a child with LUTS.

Using a two-day voiding diary, requiring the patient or caregiver measure and record volume and time of voids, this study aims to determine whether there is a significant difference between the bladder capacities and obesity status. This study also aims to determine if there is an association between obesity and LUTS. Furthermore, we plan to use a child's natural home environment and natural urges to urinate to determine if there is a difference between the expected bladder capacity as determined by the Koff formula between obese and non-obese children.

SECTION 2: BACKGROUND

2.1 Anatomy & Function of the Bladder

The urinary bladder and the urethra make up the lower urinary tract (LUT) (Figure 1). The outlet of the LUT is made up of the urethra, the bladder neck, and the urethral sphincter and the bladder serves as the storage tank (de Groat 1998). The urethral sphincter is broken down into two components: the internal sphincter and the external sphincter. The internal sphincter delineates the area of the bladder neck and proximal urethra, whereas the external sphincter is more obvious anteriorly and either diminished or completely absent posteriorly (Agarwal & Bagli 1997; Yeung & Sihoe, 2012). Although the internal sphincter has not been precisely depicted anatomically, it has been accepted that it is made up of smooth muscle fibers that extend from the bladder base and trigone to the proximal urethra (Yeung & Sihoe, 2012). It helps in retaining continence by closing the bladder neck and proximal urethra and the external sphincter is critical for voluntary terminating urine flow and preventing incontinence under stressful circumstances (Agarwal & Bagli 1997). The external sphincter has both an inner layer of smooth muscle and outer layer of striated muscle and is more developed in males than it is in females (Yeung & Sihoe, 2012).

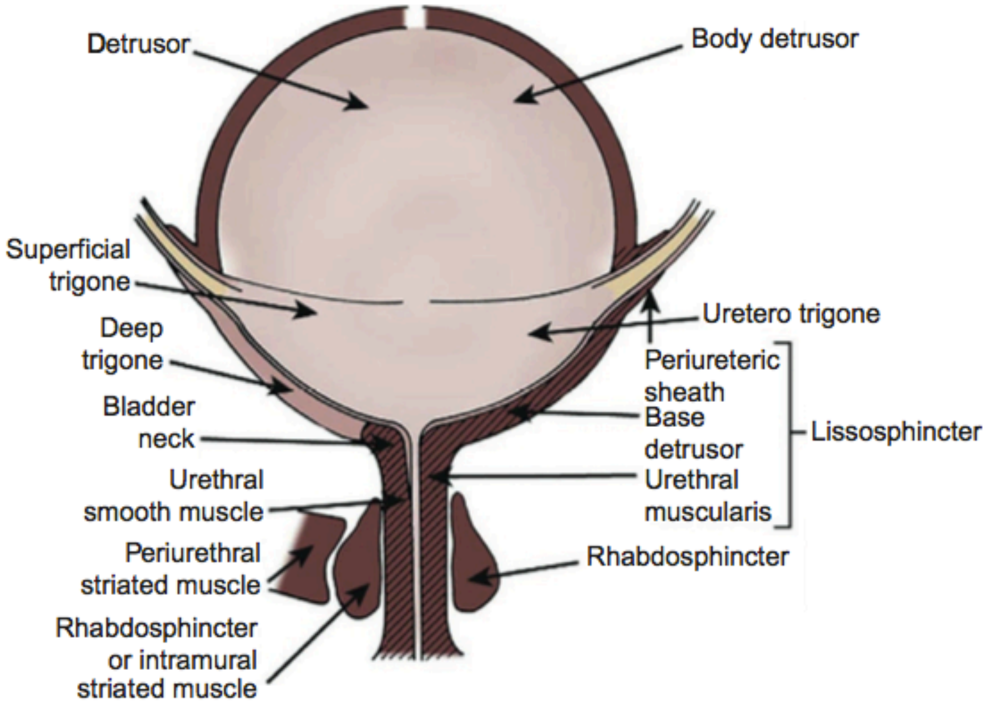

Figure 1: Anatomy of the Bladder

(De Groat & Yoshimura 2015).

The bladder body is located above the ureteral orifices and the bladder base consists of the trigone, urethrovesical junction, deep detrusor, and the anterior bladder wall (Andersson & Arner 2004). The bladder wall is made up of primarily three layers: mucosa, detrusor muscle, and adventitia. The mucosa serves as a barrier between urine and underlying tissues and as a sensor for bladder filling, and also has the ability to apply control over detrusor contractile activity (Fry & Vahabi 2016). The detrusor consists of smooth muscle fibers that work as a single functioning unit and can generate maximum active tension over various lengths, allowing the bladder to distend and fill with urine while maintain low pressure (Yeung & Sihoe, 2012). Lastly, the adventitia, which is primarily made up of adipocytes, is a loose connective tissue that covers the bladder and connects it to surrounding tissues.

The storage and emptying of urine involves a reciprocal relationship between the urinary bladder and the outlet of the LUT that is maintained by a complex neural control system. Storage reflexes are activated in the spinal cord as the bladder is filling, while voiding reflexes are carried out in the brain (Fowler et al 2008). To prevent involuntary emptying of the bladder, parasympathetic innervation of the detrusor is inhibited and the smooth and striated parts of the urethral sphincter are activated. When distension of the bladder reaches a certain level, which is sensed by tension receptors (afferent activity), the parasympathetic efferent pathway switches to maximal activity (Fowler et al 2008). This then allows one to plan to void at a socially acceptable time and place, combining factors including one's emotional state, social environment, and the sensory signals arising from the bladder when making the decision to void (Fowler et al 2008). The periaqueductal grey (PAG) has a critical role in the voluntary control of both the bladder and the urethra as it receives and passes signals responsible for conscious sensation. It also controls the primary input to the pontine micturition centre (PMC), allowing it to suppress the excitatory signal to the PMC and prevent voiding when not desired or release the excitatory signal to the PMC for desired voiding (Fowler et al 2008). Excitation of the PMC causes these events to follow: bladder contraction, an increase in intravesical pressure, and the flow of urine (Fowler et al 2008).

In summary, the detrusor stays relaxed as the bladder fills with a large volume of urine without increasing in pressure, and the urethral sphincter is contracted to hold the urethra closed. The urethral sphincter then relaxes and the detrusor contracts to allow voiding and the emptying of the bladder (Griffiths et al 1986)(Figure 2). For proper and voluntary function, these events require a complex neural control system and the structures involved to work together and respond correctly to signals.

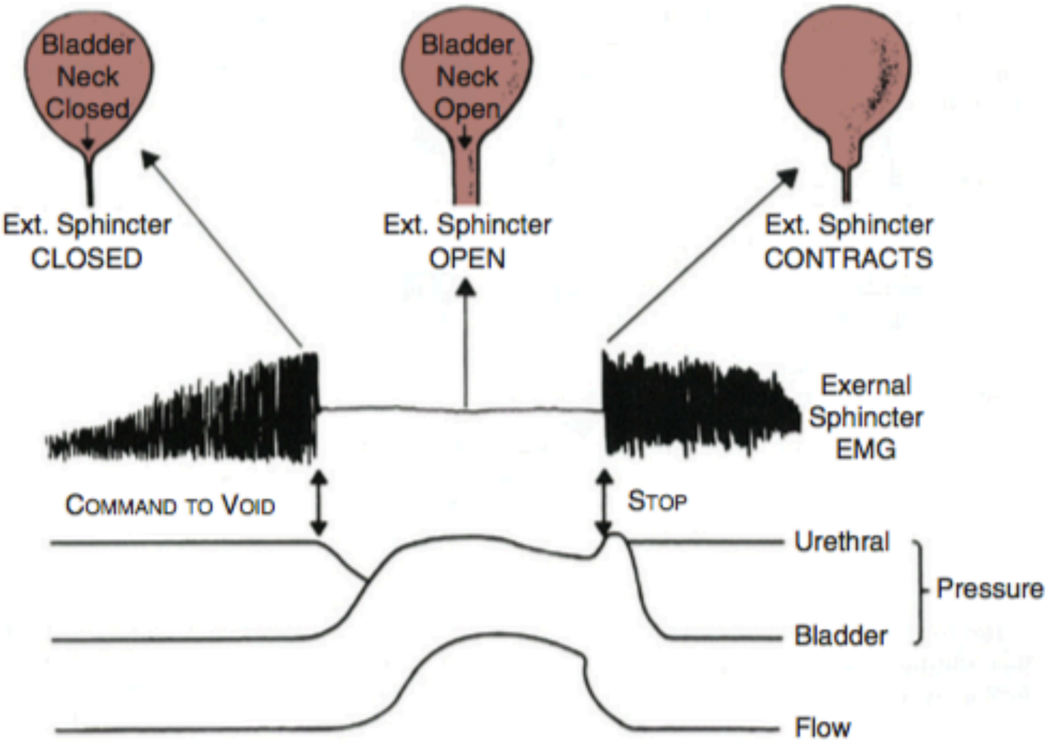

Figure 2: Physiology Schematic of Voiding

(Nitti 2012).

2.1a Expected versus Functional Bladder Capacity of a Normal Bladder

Functional bladder capacity (FBC) is different from maximal cystometric capacity or expected bladder capacity (EBC) in that FBC can be measured using a voiding diary in order to represent natural filling of the bladder whereas EBC is measured through artificial filling of the bladder. Four different studies were completed with a specific aim of determining the EBC, introducing formulas factoring age into the equation (Koff 1983; Berger et al 1983; Treves et al 1996; Kaefer et al 1997). While children were under anesthesia for urological surgeries unrelated to the bladder, Koff used VUDS to artificially fill the bladder until the pressure per unit volume increased in a linear fashion and there was an abrupt change in the slope of the cystometric curve. The volume of fluid used to get to that point was defined as the actual bladder capacity and the formula derived from this study is bladder capacity (ounces) = age (years) + 2 (Koff 1983). Similarly to Koff, Berger et al. used radionuclide cystoscopy and confirmed Koff's formula with 132 children and then tested the formula with 68 children with LUTS, stating that those with infrequent voiding have larger bladder capacities and those with frequency or incontinence have smaller bladder capacities than non-symptomatic children (Berger et al 1983). Also using radionuclide cystography, Treves et al. and Kaefer et al. both enrolled a high number of patients but concluded with different formulas. Treves et al. concluded his formula in ounces (54 * ((10 x age)+1)^0.4) be used for children ages 0-14 (Treves et al. 1996), while Kaefer et al. have one formula in ounces (2 x age + 2) for children less than two years of age and another formula in ounces as well (age/2 + 6) for patients greater than two years of age (Kaefer et al. 1997). Fairhurst et al. also conducted a similar study using a VCUG in infants giving a formula that is used for those less than one year of age making this formula not applicable to children in the reviewed literature (Fairhurst et al 1991).

Although there are multiple formulae in the literature, the formula produced by Koff and Berger et al., more commonly referred to as the "Koff formula", has been considered the gold standard for predicting expected bladder capacity for many years (Hamano et al 1999). This formula has been recently validated by Rittig et al. in Danish children by using VDs and is included in the guidelines put forth by the ICCS for a reference. The International Children's Continence Society (ICCS) recommends that the Koff formula is applicable for children and defines an abnormal bladder as one that has a MVV of less than 65% or greater than 150% of the EBC (Austin et al 2014). Many studies argue that having a value for EBC for each age to compare to FBC is very useful but children of the same age can have varying body parameters and therefore these values cannot be standardized (Bower et al 1997; Chrzan et al 2006).

2.2 Lower Urinary Tract Symptoms

Studies report that about 40% of referrals to pediatric urologists are due to LUTS as these symptoms have an incidence as high as 25% among school-aged (Vaz et al 2012; Beksac et al 2016). LUTS can be subcategorized into storage symptoms and voiding symptoms as defined by the International Children's Continence Society (ICCS)[1] The ICCS lists the following as storage symptoms: increased or decreased voiding frequency, incontinence, urgency and nocturia, whereas voiding symptoms include: hesitancy, straining, weak stream, intermittency, and dysuria (Austin et al 2014). . The following definitions are adapted from "The Standardization of Terminology of Lower Urinary Tract

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[1] The ICCS is an organization with members from multiple disciplines and specialties around the world dedicated to provide guidance for the standardization of terminology for bowel and bladder dysfunction in children

Function in Children and Adolescents: Update Report from the Standardization Committee of the ICCS" in the *Journal of Urology* (Austin et al 2014):

Storage Symptoms -

- *Increased or decreased daytime voiding frequency*: Children who void ≥ 8 times per day (increased) and children who void ≤ 3 times per day (decreased).
- *Incontinence*: Involuntary leakage of urine. For incontinence subtypes, *see Figure 3*. Nocturnal enuresis is defined as intermittent incontinence that occurs during sleeping periods.
- *Urgency*: Experiences of sudden and unexpected urges to void. Often a sign of bladder overactivity.
- *Nocturia*: When the child needs to wake up at night to void.

Voiding Symptoms -

- *Hesitancy*: Difficulty in initiating voiding.
- *Straining*: Needing an intense effort to initiate and maintain voiding
- *Weak Stream*: When stream or uroflow is observed to be weak
- *Intermittency*: Voiding that is not continuous
- *Dysuria*: Burning or discomfort

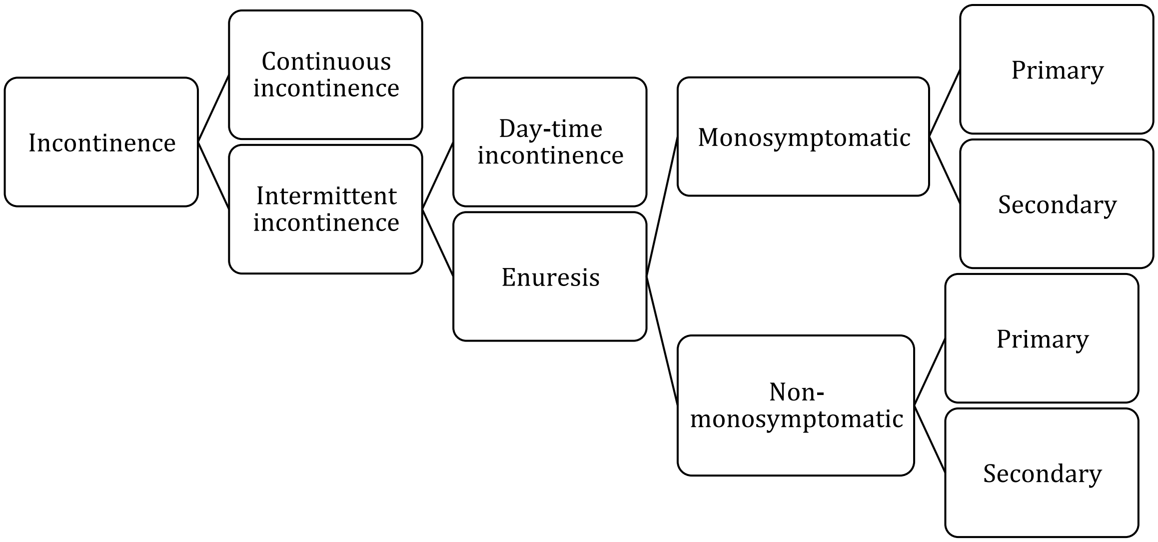

Figure 3: Incontinence Subtypes

(Austin et al 2014).

There are many invasive and non-invasive tools of investigation to diagnose children with LUTS. Invasive urodynamic studies include VUDS, which use the catheterization of the bladder for filling and emptying observations, and voiding cystometry, which is also known as pressure flow studies. Non-invasive studies include diaries, questionnaires, psychological screening, uroflow studies (measures rate, volume voided, voiding time, and pattern during urination), and pelvic ultrasound (Austin et al 2014).

Bladder capacity is a very important factor to consider when diagnosing a child who is experiencing LUTS (Starfield 1967; Hamano et al 1999; Maternik et al 2016). Many studies report that there is a significant difference in bladder capacities between healthy children and those with LUTS, concluding that healthy children have higher bladder capacities (Starfield 1967; Bower et al 1997; Mahler et al 2007; Kwak & Park 2008). In order to measure and compare bladder capacities of children with enuresis and their nonenuretic siblings, Starfield had study participants drink 30 ml of water per kilogram of body weight and only void once the participant can no longer "hold it", for a total of two voids. She concluded that children with reported enuresis have smaller bladder capacities than their siblings (Starfield 1967). By using voiding diaries to record the frequency and volumes of voids, Bower et al aimed to establish mean maximum voided volumes (MVV) in three types of incontinence in children. It was concluded that the MVV did not differ significantly in children with enuresis, daytime incontinence, or combined day-night incontinence (Bower et al 1997). This data was compared to a previously published study with voiding diaries obtained from healthy schoolchildren (Mattsson 1994) and it was found that the incontinent children had smaller bladder capacities. However, Bowler explained that this difference could be due to the fact that he excluded the first morning void from his analysis as these voids are not representative of functional bladder capacities because of overnight voids (Bower et al 1997).

2.2a Videourodynamic Studies versus Voiding Diaries

Videourodynamic studies measure bladder capacity, contractility, compliance, emptying ability and the degree of continence in patients through the use of catheterization and filling of the bladder until the child voids (Drzewiecki et al 2011)(Figure 4). VUDS are considered the gold standard to assess persistent LUTS as they are the most reliable way to obtain useful information about the bladder dynamics in a patient and can identify the cause of the LUTS, allowing providers to tailor therapy for patients (Agarwal & Bagli 1997; Hjalmas et al 2000; Parekh et al 2001; Leitner et al 2016). Voiding diaries (VD), however, are routinely used by providers to initially evaluate patients with LUTS. VDs vary but generally include a log of time and volume of fluid intake, time and volume of each urination, a yes/no question on presence of bowel movement at the time of urination, a yes/no question on urgency, and a rating for wetness (Lopes et al 2015) (Appendix 2.1). This is completed using a hat-style urine collector that sits in the toilet (Appendix 2.2). Although VDs do not provide information regarding bladder dynamics such as compliance and contractility, many studies report that VDs have an advantage over other methods as they reflect daily voids more realistically and are a valuable component to add to a patient's history for evaluation of LUTS (Mattsson 1994; Hagstroem et al 2006; Hoeck et al 2006; Lopes et al 2015; Maternik et al 2016).

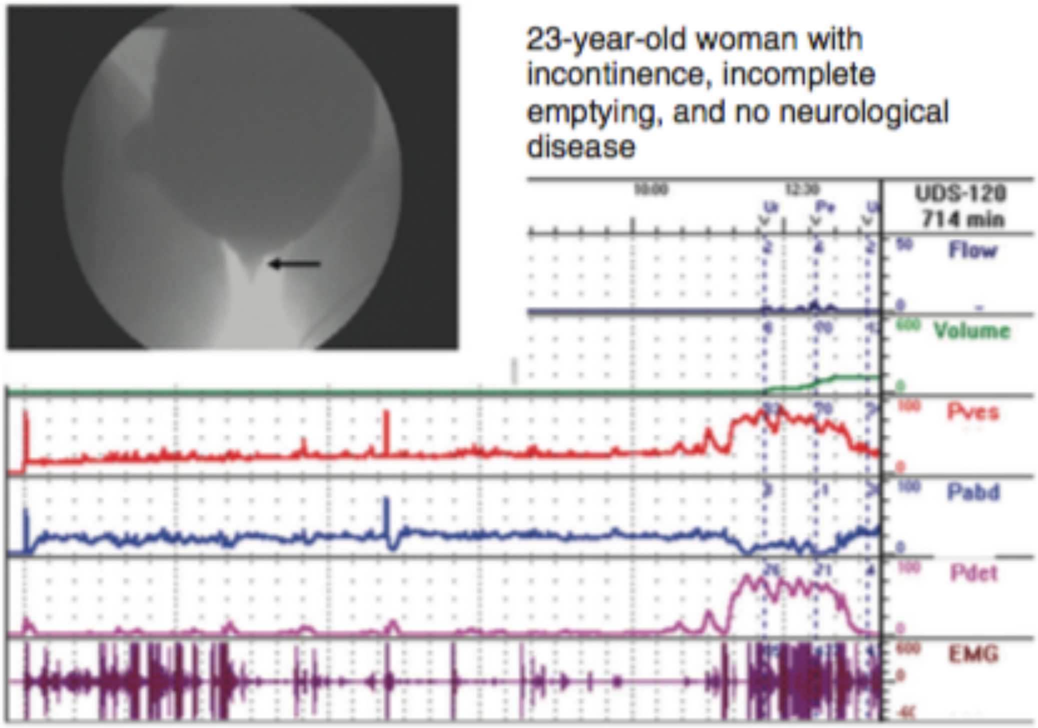

Figure 4: Results from VUDS

> *"Dysfunctional voiding—a urodynamics study of a 23-year-old woman with urgency incontinence, incomplete emptying, and no neurologic disease. Just before voiding there is an involuntary detrusor contraction. With voiding there is increased electromyography activity. The fluoroscopic picture taken during voiding shows a characteristic "spinning top urethra" with the level of obstruction at the external sphincter. The high-pressure– low-flow voiding is also characteristic of obstruction."*
>
> (Nitti 2012).

2.3 Obesity and LUTS

Obesity is a common problem worldwide that continues to grow. In the past few decades, childhood obesity has doubled in prevalence in the United States alone (Erdem et al 2006). There are a few published studies that investigate the prevalence of obesity in children experiencing LUTS, however, there are less studies on the role of obesity on expected bladder capacity and none looking at functional bladder capacity. There is a significant association between obesity and an increased rate of voiding problems in children (Guven et al. 2007). Those with normal body mass index (BMI) are more likely to respond to treatment of LUTS (Guven et al. 2007). Obesity is an independent risk factor for LUTS and it is important for providers who care for obese children to screen for these symptoms (Subak et al 2009; Schwartz et al 2009; Chang et al 2016). Through the use of uroflow studies, Wese et al. analyzed 511 normal pediatric patients and concluded that body surface area and weight more reliable criteria than age when establishing nomograms to help define normal and abnormal (Wese et al 1988). Also using uroflowmetry, another study was done analyzing voided volumes and flow rates in healthy children finding that maximum and average flow rates increase with body surface area (Segura et al 1997). These studies suggest that there is a correlation between children experiencing LUTS and obesity, however the underlying causes for this association are unknown (Erdem et al 2006). Because bladder capacities are an important factor in diagnosing a child with LUTS, it is important that the effects of obesity on bladder capacity are investigated.

2.4 Specific Aims of this Study

In summary, LUTS are highly prevalent in school-aged children and depending on the degree of the symptoms, LUTS can affect the quality of life of these children. Obesity is also prevalent in children; however, one aspect that is unclear in the literature is the growing epidemic of obesity and its association with LUTS. In order to investigate the degree of this association, we aim to answer the following questions using two-day voiding diaries:

1. Is there a significant difference in bladder capacities between obese and non-obese children?
2. Is there an association between obesity and LUTS?
3. Are there differences in expected bladder capacity based on the Koff formula between obese versus non-obese children?

SECTION 3: METHODS

3.1 Study Design

The study was conducted at the Children's Hospital of Orange County (CHOC) Primary Care Clinic and at CHOC/University of California, Irvine (UCI) Pediatric Urology Division in Orange, California. After obtaining Institutional Review Board approval, we enrolled patients into a prospective study to obtain data on non-symptomatic children (controls). Upon completion of patient enrollment for the prospective study, we began a retrospective review of patient medical records to find patients with completed voiding diaries (VD) who were seen for lower urinary tract symptoms (LUTS) at the time of diary completion. The controls and symptomatic patients were further divided into the following subgroups: non-symptomatic healthy weight, non-symptomatic obese, LUTS healthy weight, LUTS obese. By using VDs from non-symptomatic patients from the prospective portion of the study and LUTS symptomatic children from the retrospective study, we analyzed non-obese and obese children with and without LUTS to determine if there is a significant difference in bladder capacity between obese and non-obese. We also analyzed non-obese and obese children with LUTS to determine if there is an association between obesity and LUTS. By observing non-obese and obese children without LUTS, we aimed to determine if there is a significant difference in the expected bladder capacity as determined using the Koff formula between them.

3.2 Patient Selection

3.2a Prospective Cohort Study

To be eligible for enrollment in the prospective study, patients needed to be between 5-18 years of age and English or Spanish speaking (child and family). Patient must have normal urologic and neurologic anatomy and functions. Patients were excluded from the study if they meet any of the following exclusion criteria: developmental delays or special needs, congenital or acquired anomalies of the genitourinary tract or nervous system, psychological or neurological disorders with impact on bladder function including neurogenic bladders, daytime incontinence, recurrent urinary tract infections (greater than 3 within the past 6 months), or significant constipation.

3.2b Retrospective Case-Control Study

To be eligible for enrollment in the retrospective study, patients needed to be between the ages of 5-18 years old and English or Spanish speaking (child and family). Patient must have had normal urologic and neurologic anatomy and functions. The retrospective cohort consists of patients who sought care at CHOC/UCI Pediatric Urology Department for LUTS, which may include day or night incontinence, urgency or frequency of urination, with or without constipation since January 2010. Patients are excluded from the study if they meet any of the following exclusion criteria: developmental delays or special needs, congenital or acquired anomalies of the genitourinary tract or nervous system, psychological or neurological disorders with impact on bladder function including neurogenic bladders.

3.3 Data Collection Procedure

3.3a Prospective Patient Recruitment & Data Collection

At a regularly scheduled visit from January 2014-December 2014, per standard of care, the patient's history was taken by clinical practitioner. The investigator reviewed the medical record to capture data points as outlined in a data collection spreadsheet and ensured that the child did not have any dysfunctional voiding patterns such as any LUTS that may skew the results.

Once a child was confirmed to not have symptoms of dysfunctional voiding and fit the inclusion and exclusion criteria, a member of the study team explained the study protocol to the family and allowed them to review the IRB-approved consent form. The investigators were available to answer any questions the family may have had about the study and participation. A signed IRB-approved consent form was obtained from the parent or legal guardian who opted for their child to participate in the study.

Children enrolled in the study were asked to complete a voiding diary for two days. In completing the VD they (with the help of their parent/guardian/caregiver) were told to record the time they used the restroom to void and the total volume voided. They were given a hat-style urine collector to collect and measure the volumes voided during the study from our office, a VD, and a prepaid envelope for returning the diary. Families were asked to allow the child to void via their regular pattern and urges, and not to encourage the child to use the restroom unnecessarily. Families then mailed the completed diary and questionnaires to our office. Families whose data we received were compensated $20.00 for their time and effort.

3.3b Retrospective Data Collection

We planned to collect data on up to 150 patients; however, we collected data on 35 eligible previous patients from the CHOC/UCI Pediatric Urology Division from January 2010 to June 30, 2014 in order to match the number of symptomatic patients to the healthy controls. We extracted their completed voiding diaries, which should have been carried out for at least 2 days prior to their office visit. We also collected demographic data, weight, household status, number of siblings, history of urinary tract infections and payer information.

3.3c Data Protection Measures

All research documents were stored in locked file cabinets in our locked research office at 505 S. Main Street, Suite 100, Orange, CA 92868. Only research team members had access to the files. Only authorized personnel had access to the research database. Potential subjects were reassured that their study participation is totally voluntary and their refusal will not affect their current or future medical and health care. Subjects were able to decide if they do not want to participate or complete the study at any time. They could be dropped from the study and their questionnaires destroyed at their request.

3.4 Statistical Analysis

A power analysis for a study such as this one is difficult to conduct due to the extent of variability in the sample sizes and results from similar studies. This was a pilot study and we plan to reach our target enrollment of 150 patients to reassess the number required according to the results from 150 patients. A sample of this size would be adequate to detect a group difference as small as 46% of one standard deviation for the primary outcome with $\alpha = 0.05$ and Power $(1 - \beta) = 0.8$. We enrolled a total of 70 patients: 35 non-symptomatic controls and 35 patients with LUTS (Figure 5).

In order to calculate the percent of the expected bladder capacity, we used the following formulas:

1. The Koff formula: (Age in years + 2) * 30 = EBC in mL
2. The Treves formula: 54 * ((10 x age)+1)^0.4 = EBC in mL
3. The Kaefer formula: ((Age/2) + 6) * 30 = EBC in mL

We then took the actual values for AVV and divided them by the EBC for each formula and multiplied by 100% to get the percentage. The percent of EBC values were used to compare non-obese and obese patients without LUTS.

Using the Obesity Action Coalition's (OAC) definition of obesity, a child was considered obese if they were at or above the 95th percentile for children and teens of the same age and sex using gender specific weight-for-age percentile charts (www.obesityaction.org). Patients' weights were coded as a dichotomous variable where "0" means the child is of normal weight and "1" signifies the child is obese.

Statistics were completed using Statistical Product and Service Solutions (SPSS version 21.0, IBM Corporation, Armonk, NY, USA). Independent samples t-tests were performed to explore age and weight, as they are continuous variables, whereas Fisher's exact tests were performed for patient characteristics involving dichotomous variables. For dichotomous variables with more than two categories, Pearson's chi-squared tests were run. Independent samples t-tests were performed to determine if there were significant group differences in average voided volume (AVV), maximum voided volume (MVV), maximum morning voided volume (MMVV), and number of voids per day for obese and non-obese patients (irrespective of LUTS status), and for patients with and without LUTS (irrespective of obesity status). We also used t-tests to examine differences in these indicators by obesity status for the subgroup of children with LUTS, and again for the subgroup of children without LUTS. To compare patients' MVV to the percent of the expected bladder capacity for each of the three formulas, independent samples t-tests were also performed. A p-value of <0.05 was considered statistically significant.

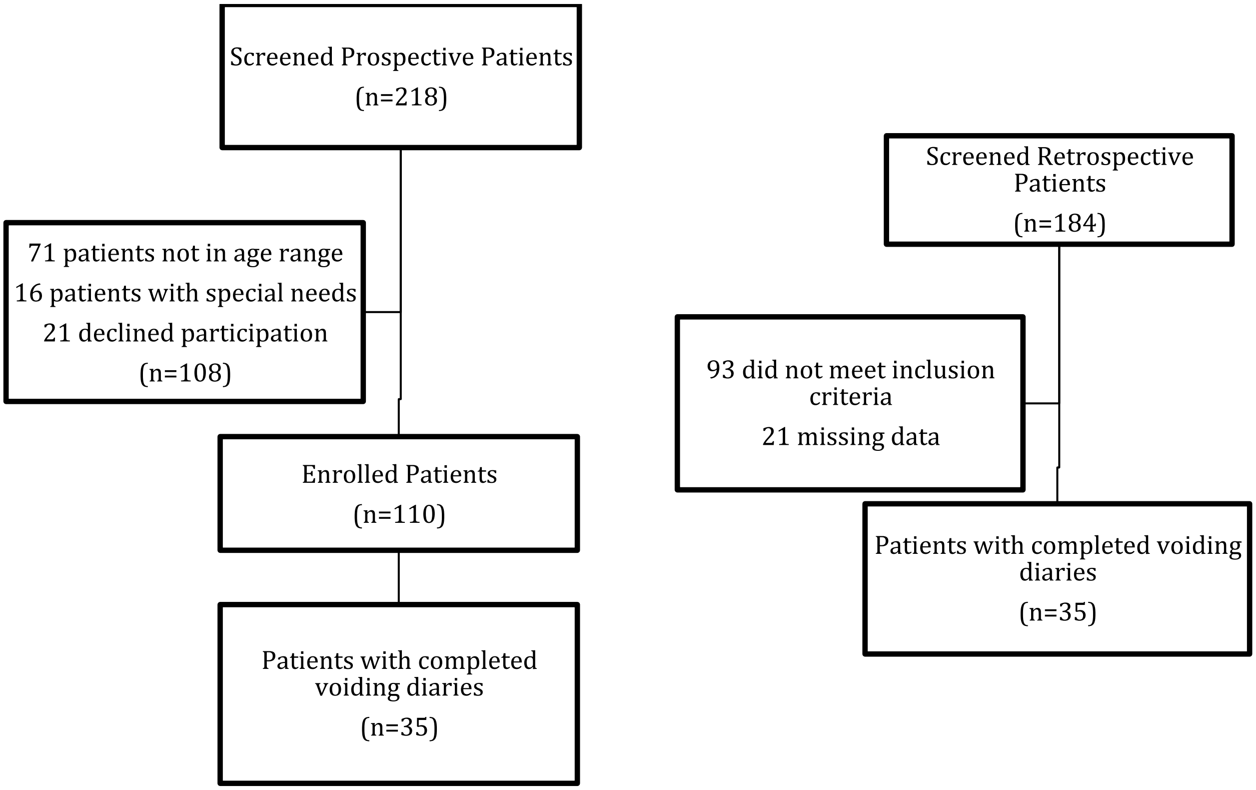

Figure 5. Consort diagram of prospective and retrospective patient enrollment.

SECTION 4: RESULTS

Of the 110 consented patients during the period of this study, 35 patients returned completed voiding diaries (VD) (31.8%). Among the total of 70 patients in the study ranging between the age of 5 and 17 (mean age of 9), 40 patients (57.1%) were female and 30 (42.9%) were male (Table 1). Figure 6 summarizes the number of patients per year of age. The patients' weights ranged from 15.7 to 91.0 kilograms, with the majority of the patients in the non-obese group. The majority of patients were also English speaking (74.3%), come from two-parent households (75.7%) with at least one sibling (72.9%). A large number of patients were Medi-Cal patients (62.9%). Five of the patients (7.1%) in the sample had a history of urinary tract infections. Overall, the patient characteristics did not significantly differ between the two groups. This information is summarized in Table 1. Table 2 shows the patient characteristics for the controls (non-symptomatic patients) and the LUTS symptomatic patients. The subgroups consisted of the following: eighteen of the children without LUTS (25.7%) were non-obese while 17 (24.3%) were obese; in the LUTS group, 19 (27.1%) were non-obese and 16 (22.9%) were obese.

Table 1. Patient Characteristics Based on Obesity Status

Characteristics	Non-Obese Patients (N=37)	Obese Patients (N=33)	p-value
Age—years*	9.8 ± 3.6	8.3 ± 2.5	0.053
Gender †			0.090
Female	25 (67.6)	15 (45.5)	
Male	12 (32.4)	18 (54.5)	
Race ❖			0.177
White	6 (16.2)	5 (15.2)	
Hispanic	16 (43.2)	21 (63.6)	
Other/Unknown	15 (40.5)	7 (21.2)	
Language Spoken †			0.427
English	29 (78.4)	23 (69.7)	
Spanish	8 (21.6)	10 (30.3)	
Weight—kg*	31.5 ± 13.2	40.0 ± 18.4	0.029
Household Status ❖			0.245
Two-Parent	30 (81.1)	23 (69.7)	
Single-Parent	5 (13.5)	4 (12.1)	
Other/Unknown	2 (5.4)	6 (18.2)	
Number of Siblings ❖			0.480
Only Child	3 (8.1)	6 (18.2)	
1 sibling	10 (27.0)	10 (30.3)	
2 siblings	10 (27.0)	9 (27.3)	
3+ siblings	8 (21.6)	4 (12.1)	
Unknown	6 (16.2)	4 (12.1)	
Payer Information ❖			0.133
Medi-Cal	21 (56.8)	23 (69.7)	
HMO	6 (16.2)	4 (12.1)	
PPO	10 (27.0)	3 (9.1)	
Self-Pay	0	2 (6.1)	
Unknown	0	1 (3.0)	
History of UTI †			0.361
Yes	4 (10.8)	1 (3.0)	
No	33 (89.2)	32 (97.0)	

* Independent samples t-test was preformed; Values reported are mean ± standard deviation

† Fisher's exact test was performed; Values reported as number (%)

❖ Pearson's chi-squared test was performed; Values reported as number (%)
P-value of <0.05 is considered statistically significant

Table 2. Patient Characteristics for Controls and Symptomatic Patients

Characteristics	Nonsymptomatic Patients (N=35)	LUTS Patients (N=35)	p-value
Age—years*	8.9 ± 3.0	9.3 ± 3.4	.631
Gender †			.469
Female	18 (51.4)	22 (62.9)	
Male	17 (48.6)	13 (37.1)	
Race ❖			<0.001
White	3 (8.6)	8 (22.9)	
Hispanic	31 (88.6)	6 (17.1)	
Other/Unknown	1 (2.9)	21 (60)	
Language Spoken †			0.013
English	21 (60)	31 (88.6)	
Spanish	14 (40)	4 (11.4)	
Weight—kg*	34.9 ± 16.3	36.1 ± 16.4	0.769
Household Status ❖			0.043
Two-Parent	22 (62.9)	31 (88.6)	
Single-Parent	7 (20.0)	2 (5.7)	
Other/Unknown	6 (17.1)	2 (5.7)	
Number of Siblings ❖			0.188
Only Child	6 (17.1)	3 (8.6)	
1 sibling	8 (22.9)	12 (34.3)	
2 siblings	11 (31.4)	8 (22.9)	
3+ siblings	6 (17.1)	6 (17.1)	
Unknown	4 (11.4)	6 (17.1)	
Payer Information ❖			<0.001
Medi-Cal	32 (91.4)	12 (34.3)	
HMO	0	10 (28.6)	
PPO	0	13 (37.1)	
Self-Pay	2 (5.7)	0	
Unknown	1 (2.9)	0	
History of UTI †			0.054
Yes	0	5 (14.3)	
No	35 (100)	30 (85.7)	

* Independent samples t-test was preformed; Values reported are mean ± standard deviation

† Fisher's exact test was performed; Values reported as number (%)

❖ Pearson's chi-squared test was performed; Values reported as number (%)

P-value of <0.05 is considered statistically significant

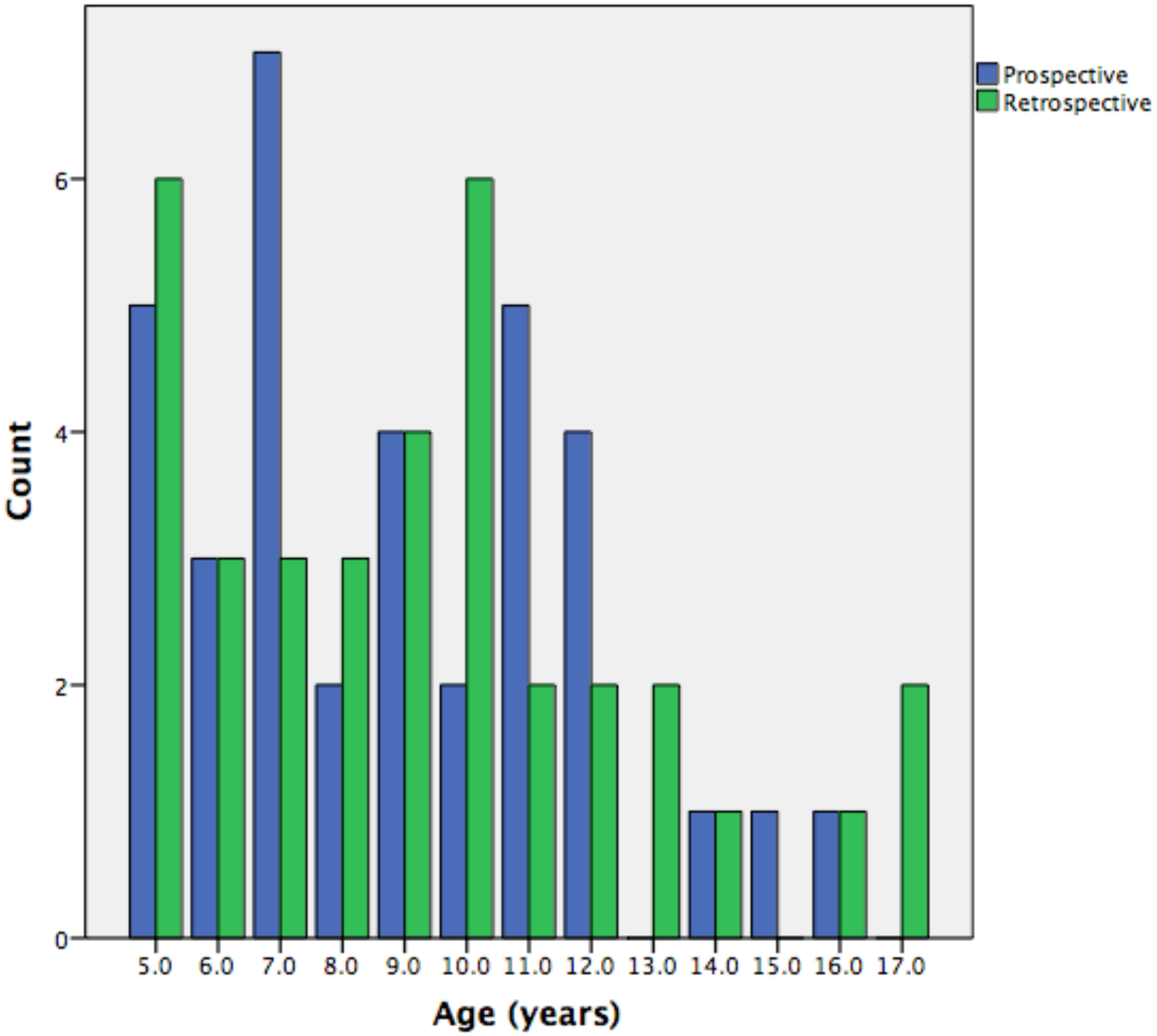

Figure 6. Number of patients per year of age for prospective and retrospective groups

Bladder Capacities and Obesity Status:

Healthy weight and obese children, irrespective of the presence or absence of LUTS did not differ in average voided volume (AVV), maximum voided volume (MVV), maximum morning voided volume (MMVV) and number of voids per day (p=0.703, p=0.462, p=0.310 and p=0.798, respectively)(Table 3).

Looking solely at children without LUTS, no significant differences were observed in AVV and MVV between healthy weight and obese patients (p=0.099 and p=0.087, respectively); however, MMVV is greater in obese children (p=0.036) (Figure 7).

Among patients with LUTS, AVV, MVV, and MMVV were not significantly different in obese versus non-obese children (p=0.154, p=0.587, p=0.378, respectively) (Figure 8).

Bladder Capacities and LUTS

Non-symptomatic versus symptomatic patients differed significantly in AVV, MMVV and average number of voids/day over the two-day period, irrespective of obesity status (p=0.003, p=0.002, and p=0.020, respectively)(Table 4).

LUTS and Obesity Status:

There was no difference between non-obese and obese patients with and without the presence of LUTS in this study population (p=1.000). In this study population, LUTS is present in 51.4% in non-obese versus 48.5% in obese children (Table 5). The average number of voids over the two-day period of the study also did not differ between the two groups with a mean ± standard deviation of 5.2 ± 2.3 in the healthy weight patients and 5.7 ± 2.2 in the obese patients (p=0.798).

Expected Bladder Capacities and Obesity Status without LUTS:

The expected bladder capacities as calculated by the Koff, Treves, and Kaefer formulas were compared for obese and non-obese patients. There was a significant difference in non-obese and obese patients and the percent of expected bladder capacity as calculated by the Koff formula (p=0.040). Obese patients had a significantly greater percent expected than non-obese patients (121% versus 81%) (Table 6). The percentages of expected bladder capacity as calculated by the Treves and Kaefer formulas are also significantly different between the two groups with the values exceeding 115% with both formulas (p=0.043 and p=0.038, respectively). The difference between healthy weight and obese patients and the percentages of expected bladder capacity as calculated by all three formulas are not observed when grouping patients by obesity status alone, not considering the presence or absence of LUTS (Table 3). However, significant differences are seen between all three formulas and the presence or absence of symptoms, without considering obesity (Table 7).

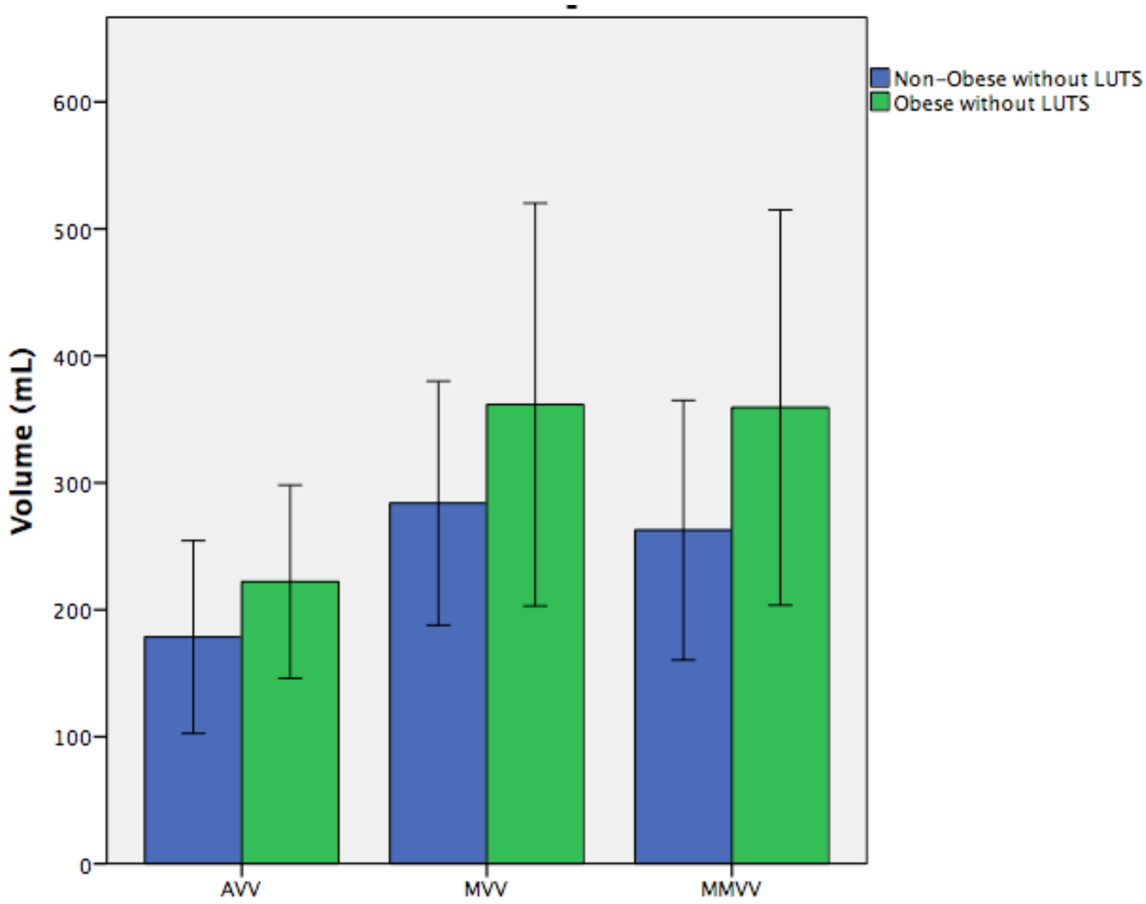

Figure 7. Bladder capacities by obesity status in children without LUTS

Error bars represent standard deviation of the mean

*P value of 0.05 is considered statistically significant

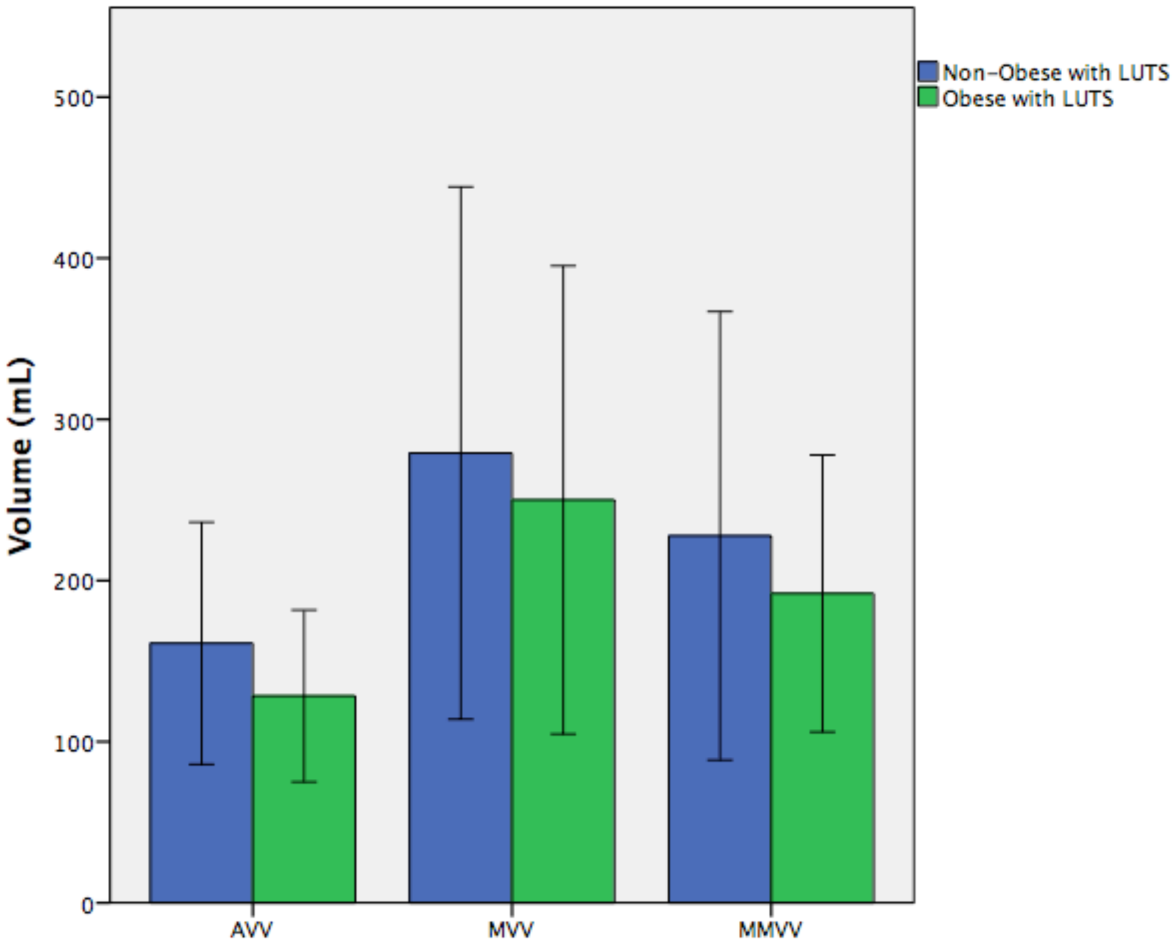

Figure 8. Bladder capacities by obesity status in children with LUTS

Error bars represent standard deviation of the mean

*P value of 0.05 is considered statistically significant

Table 3: Voided Volumes and Percentage of Expected Bladder Capacity According to Obesity Status, Irrespective of LUTS

Volumes	Healthy Weight Patients (N=37)	Obese Patients (N=33)	Mean difference (95% Confidence Interval)	p-value
AVV	169.6 ± 75.0	176.7 ± 80.6	7.1 (-44.2, 30.0)	0.703
MVV	281.5 ± 134.2	307.5 ± 160.2	26 (-96.3, 44.2)	0.462
MMVV	244.7 ± 122.2	278.1 ± 151.0	33.4 (-98.6, 31.8)	0.310
Number of voids/day	5.2 ± 2.3	5.7 ± 2.2	0.5 (-1.2, 0.9)	0.798
% Expected (Koff)	85.0 ± 40.2	100.7 ± 49.4	15.7 (-37.0, 5.7)	0.149
% Expected (Treves)	85.1 ± 37.9	97.0 ± 47.4	11.9 (-32.2, 8.5)	0.249
% Expected (Kaefer)	87.2 ± 38.9	100.2 ± 49.0	13.0 (-34.0, 8.0)	0.220

* Independent samples t-test was preformed
Values are presented as mean ± standard deviation
95% confidence intervals of the mean difference reported
P-value of <0.05 is considered statistically significant

Table 4: Voided Volumes and Percentage of Expected Bladder Capacity According to Presence or Absence of LUTS, Irrespective of Obesity Status

Volumes	Nonsymptomatic Patients (N=35)	LUTS Patients (N=35)	Mean difference (95% Confidence Interval)	p-value
AVV	199.7 ± 78.1	146.1 ± 67.2	53.6 (18.8, 88.3)	0.003
MVV	321.7 ± 134.2	265.8 ± 154.8	55.9 (-13.2, 125.0)	0.111
MMVV	309.6 ± 138.0	211.4 ± 117.6	98.2 (37.1, 159.4)	0.002
Number of voids/day	5.0 ± 2.2	6.2 ± 2.3	1.2 (-2.3, -0.2)	0.020
% Expected (Koff)	104.2 ± 48.9	80.6 ± 39.0	23.6 (2.7, 44.5)	0.028
% Expected (Treves)	100.8 ± 42.0	80.6 ± 41.7	20.2 (0.2, 40.1)	0.048
% Expected (Kaefer)	103.8 ± 43.5	82.9 ± 42.8	20.9 (0.4, 41.5)	0.046

* Independent samples t-test was preformed
Values are presented as mean ± standard deviation
95% confidence intervals of the mean difference reported
P-value of <0.05 is considered statistically significant

Table 5: Presence of LUTS and Obesity Status

Volumes	Non-Obese Patients (N=37)	Obese Patients (N=33)	p-value
LUTS †			1.000
Absent	18 (48.6)	17 (51.5)	
Present	19 (51.4)	16(48.5)	

† Fisher's exact test was performed; Values reported as number (%)
P-value of <0.05 is considered statistically significant

Table 6: Percentage of Expected Bladder Capacity According to Obesity Status Without LUTS

Volumes	Non-Obese Patients without LUTS (N=18)	Obese Patients without LUTS (N=17)	Mean difference (95% Confidence Interval)	p-value
% Expected (Koff)	88.1 ± 35.0	121.2 ± 55.1	33.1 (-64.6, -1.5)	0.040
% Expected (Treves)	87.0 ± 28.1	115.4 ± 49.6	28.4 (-56.0, -0.9)	0.043
% Expected (Kaefer)	89.1 ± 28.5	119.3 ± 51.5	30.2 (-58.6, -1.8)	0.038

* Independent samples t-test was preformed
Values are presented as mean ± standard deviation
95% confidence intervals of the mean difference reported
P-value of <0.05 is considered statistically significant

Table 7: Voided Volumes and Percentage of Expected Bladder Capacity According to Presence or Absence of LUTS, Irrespective of Obesity Status

Volumes	Nonsymptomatic Patients (N=35)	LUTS Patients (N=35)	Mean difference (95% Confidence Interval)	p-value
AVV	199.7 ± 78.1	146.1 ± 67.2	53.6 (18.8, 88.3)	0.003
MVV	321.7 ± 134.2	265.8 ± 154.8	55.9 (-13.2, 125.0)	0.111
MMVV	309.6 ± 138.0	211.4 ± 117.6	98.2 (37.1, 159.4)	0.002
Number of voids/day	5.0 ± 2.2	6.2 ± 2.3	1.2 (-2.3, -0.2)	0.020
% Expected (Koff)	104.2 ± 48.9	80.6 ± 39.0	23.6 (2.7, 44.5)	0.028
% Expected (Treves)	100.8 ± 42.0	80.6 ± 41.7	20.2 (0.2, 40.1)	0.048
% Expected (Kaefer)	103.8 ± 43.5	82.9 ± 42.8	20.9 (0.4, 41.5)	0.046

* Independent samples t-test was preformed
Values are presented as mean ± standard deviation
95% confidence intervals of the mean difference reported
P-value of <0.05 is considered statistically significant

SECTION 5: DISCUSSION

5.1 Discussion

This study aimed to analyze the difference in functional bladder capacity between non-obese and obese children using a two-day voiding diary. We also used prospective and retrospective data to determine if there is an association between obesity and the presence of lower urinary tract symptoms (LUTS). Finally, by using a two-day voiding diary, we aimed to determine whether there is a difference in expected bladder capacity as determined by the Koff formula between obese and non-obese children.

The present study indicates that average voided volume (AVV), maximum voided volume (MVV), and maximum morning voided volume (MMVV) were not statistically different between the healthy weight and the obese groups. Segura et al. used uroflowmetry to obtain voided volumes and flow rates to correlate with body surface area and found that volumes voided and flow rates increased with increasing body surface area (Segura et al 1997). Although our data shows that the obese group had higher averages for the three variables analyzed, the bladder capacities were not significantly different from each other. A difference is observed, however, when dividing the groups into the following subgroups: non-obese and obese with and without LUTS. Obese patients without LUTS show a higher MMVV than non-obese patients without LUTS, while obese patients with LUTS do not a show a statistical difference in AVV, MVV and MMVV than non-obese patients with LUTS. However, all three values of AVV, MVV and MMVV are lower in the obese patients than the non-obese patients with LUTS. Although there is low statistical power due to a small sample size, the lower AVV, MVV and MMVV in the obese group with LUTS are consistent with the study hypothesis that the functional bladder capacity in children with LUTS is less than those without LUTS (Starfield 1967; Bower et al 1997; Mahler et al 2007; Kwak & Park 2008). However, the effect of obesity on bladder capacity is uncertain. This study shows that functional bladder capacity tends to be lower in obese children than non-obese children with LUTS. To our knowledge, a relationship between functional bladder capacity and obesity status with the presence or absence of LUTS has not been previously analyzed, but may be significant as it can affect the management of these children.

By using voiding cystourethrogram, Fairhurst et al. proposed a formula for expected bladder capacity in infants that includes weight, and concluded that that weight is a better parameter for such formulas than age (Fairhurst et al 1991). Our results show that there is no difference in bladder capacities between obese and healthy weight patients, irrespective of the presence of LUTS; however, we did not utilize the artificial filling of the bladder to obtain the voided volumes. Also, we grouped our patients according to weight-to-age percentiles rather than using a continuous weight variable. The numbers in our pilot study are too low to be able to correlate the effect of weight on bladder capacities. Future studies with increased samples are needed to effectively address this relationship.

The AVV and MMVV were significantly higher in the non-symptomatic, healthy children; however, the average number of voids per day was higher than the LUTS patients. This is consistent with the study hypotheses and clinical expectation, as having a lower bladder capacity causes the patient to feel the urge to urinate more often. These results are also consistent with a study that was conducted a study comparing voiding diaries from children with only complaints of enuresis and children with complaints of enuresis and additional LUTS. That study found that MVV and average voided volume (AVV) were significantly higher in children without additional LUTS. The authors also commented that children with LUTS are more likely to show signs of needing to void and daytime wetting because of their smaller bladder capacities (Kwak & Park 2008). Kwak and Park's study did not analyze MMVV. There is high variation in voided volume in both groups and this is consistent with other studies (Mattsson 2003; Hoeck et al 2006).

The prevalence of LUTS in the obese population of this study is similar to that of the non-obese population. This is inconsistent with the findings of studies in the literature (Schwartz et al 2009; Chang et al 2015). However, these studies used questionnaires to screen school-aged children for LUTS, whereas the data used in this study was from clinical diagnoses of LUTS. To further investigate the association between LUTS and obesity status, a study with a larger sample size is needed.

As our third outcome, we used the "gold standard" formula for estimating expected bladder capacity (the Koff formula) and calculated the percentage expected to see if these values are different between non-obese and obese patients without LUTS. We also divided the groups based on obesity status including both non-symptomatic and symptomatic patients. To estimate the expected bladder capacity for non-obese and obese patients, we also used the formulas derived by Treves et al. and Kaefer et al. as these formulas pertain to our study population age. The non-obese and obese patients without LUTS show significant differences among the expected bladder capacities as calculated by all three formulas. Obese patients have larger bladder capacities than expected according to the

Koff, Treves, and Kaefer formulas, whereas the non-obese, non-symptomatic patients have about 90% of the expected capacities. Rittig et al. used voiding diaries from 148 healthy children and concluded that the Koff formula was valid in the Danish population used for the study (Rittig et al 2010). These findings parallel those from our study in that the Koff formula is a good predictor of bladder capacity for our population of non-obese children, however Rittig et al. did not compare healthy weight children to obese children. Martinez Garcia et al. performed a systematic review of the formulas and concluded that all the formulae were too inaccurate for estimating bladder capacities due to the wide variation between them (Martinez Garcia et al 2014). The ICCS defines an abnormal bladder as one with a capacity that is either <65% of the EBC (too small) or >150% of the EBC (too large), when deriving EBC from the Koff formula. However, our data shows that LUTS patients have an average of 81% of the EBC, and therefore the ICCS guidelines may be an overestimation when defining an abnormal bladder.

The association of constipation and LUTS has been established and is well recognized in the literature (Erdem et al 2006). There are theories to help explain the pathophysiology for impact of constipation on LUTS. The urinary bladder is very close to the rectum and sigmoid colon; therefore, compression on the bladder and pelvic floor may impair the bladder emptying and efficiency, resulting in dysfunctional voiding (Chang et al. 2012). Constipation is also more prevalent in obese children (Fishman et al 2004). The etiology of constipation in obese children is unknown, however, this may be due to poor diet and learned holding type of behavior (Erdem et al 2006). It remains important to inquire about the relationship between constipation, obesity, and LUTS.

Increased body fat is the primary factor that contributes to diabetes and cardiovascular disease in children and adolescence (Goran et al. 2002). Polyuria, or the production of abnormally large volumes of dilute urine, is common in children who are prediabetic (American Diabetes Association 2000). We speculate that obese children and adolescents may be prediabetic which further leads to polyuria; however, this warrants further investigation.

In this study, obese was defined using gender specific weight-for-age percentile charts, with those in the greater or equal to 95th percentile were considered obese, although it is common to define obesity using BMI or height-to-weight percentiles. However, this may not be the most accurate way to define obesity in children and adolescence, as it does not differentiate between fat and fat-free mass (Khoury et al 2012). To assess children for cardiometabolic risk, Khoury et al. concluded that the waist-to-height ratio should be included in screening and assessment of overweight and obese children as this measurement further specifies the risk for this population (Khoury et al 2013). The waist-to-height ratio is a better measure when assessing overweight and obese children, taking into account visceral fat; therefore, future studies should use this measure as a surrogate for obesity. This may have an effect on the results this study and future studies should use the waist-to-height ratio to explore the effects of obesity on bladder capacity.

5.2 Study Limitations

The primary limitation of this study is the lack of information on presence of constipation in both the controls and LUTS patients. Additionally, this study lacked a means to objectively measure the accuracy or compliance of home measurements using the hat-style urine collector. Another limitation is the retrospective collection of the voiding diaries of the LUTS patients. Although these patients were seen for LUTS, we cannot be sure of the duration of time the patient experienced LUTS. Another criticism of this study is not having height or waist circumference information in order to calculate BMI or waist-to-height ratio. Instead, we used weight-to-age percentiles, which could have made a difference in the categorization of obese versus healthy weight. Lastly, increasing the number of patients may improve the results of this study.

5.3 Future Directions

Because this study was a pilot study, I plan on increasing the number of patients in both groups and making it a priority that height and waist circumference are recorded at the time of the patient's visit to allow for the calculation of BMI and waist-to-height ratio. This is measured at the top of the posterior iliac crest as the subject is standing (Khoury et al 2012). By increasing the number of patients, we are able to use the functional bladder capacities from two-day voiding diaries and correlate them with waist-to-height ratio and whether or not patient is experiencing LUTS to create more accurate estimations of bladder capacities for healthy weight and obese children. This will further improve the guidelines used by clinicians worldwide to allow for a more specific formula that takes into account an important body parameter. A surrogate for paper voiding diaries is the iUflow device, which connects to a smartphone through an auxiliary cord and functions using an application on Apple or Android phones. Using this device will improve the accuracy of the voiding diaries and may even improve compliance.

5.4 Conclusion

Although this study has low statistical power due to a small sample size, trends show a lower functional bladder capacity in obese children compared to non-obese children with LUTS. Therefore weight counseling should be included in the management of these children. In this study population, the prevalence of LUTS is not higher in obese children compared to non-obese children. Lastly, the Koff formula appears to underestimate functional bladder capacity in non-LUTS obese children.

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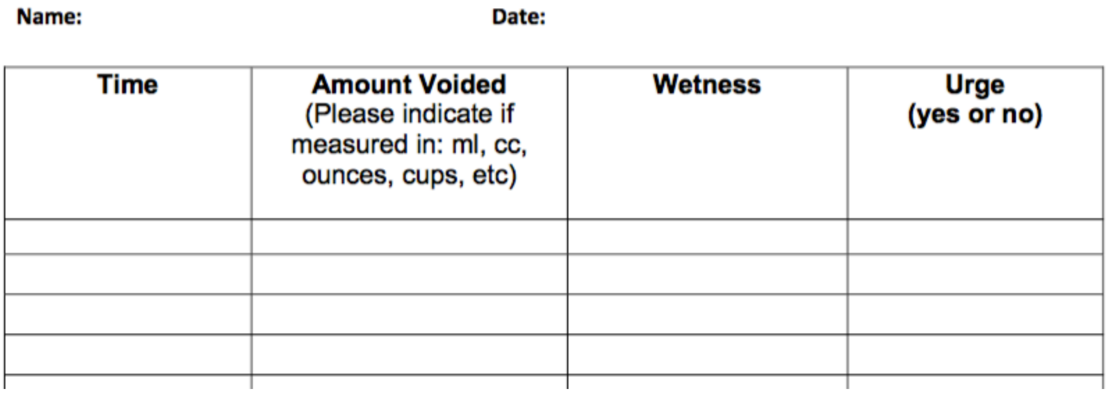
APPENDIX 2.1

Sample Voiding Diary



Name: **Date:**

Time	**Amount Voided** (Please indicate if measured in: ml, cc, ounces, cups, etc)	**Wetness**	**Urge** **(yes or no)**

(CHOC Children's Pediatric Urology Patient & Family Resources).

APPENDIX 2.2

Hat-Style Urine Collector

(Urol Collection Devices - Amazon).