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# Intensive Lifestyle Intervention Reduces Urinary Incontinence in Overweight/Obese Men with Type 2 Diabetes: Results from the Look AHEAD Trial

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### Abbreviations and Acronyms

BMI = body mass index  
DSE = diabetes support and education  
ILI = intensive lifestyle intervention  
Look AHEAD = Action for Health in Diabetes  
LUTD = lower urinary tract dysfunction  
UI = urinary incontinence

**Purpose:** We determined the effect of an intensive lifestyle intervention on the prevalence, incidence and resolution of bothersome nocturia, increased daytime urinary voiding and urinary incontinence in overweight/obese men with type 2 diabetes after 1 year in the Look AHEAD trial.

**Materials and Methods:** A subset of male Look AHEAD participants was selected for this secondary data analysis. Overall 1,910 men with an average (mean  $\pm$  SD) age of  $59.9 \pm 6.7$  years and body mass index of  $35.2 \pm 5.5$  kg/m<sup>2</sup> were randomized to an intensive lifestyle intervention or diabetes support and education group. All participants self-reported information regarding incontinence, nocturia and daytime urinary voiding at entry and 1 year.

**Results:** After 1 year the intensive lifestyle intervention group lost significantly more weight than the diabetes support and education group ( $9.4\% \pm 7.0\%$  vs  $0.7\% \pm 4.5\%$ , respectively;  $p < 0.001$ ). The odds of prevalent urinary incontinence at 1 year were reduced by 38% in the intensive lifestyle intervention group compared to the diabetes support and education group. The prevalence of urinary incontinence decreased from 11.3% to 9.0% in the intensive lifestyle intervention group and increased from 9.7% to 11.6% in the diabetes support and education group. The intensive lifestyle intervention group also had increased odds of urinary incontinence resolving (OR 1.93, 95% CI 1.04–3.59,  $p = 0.04$  and 56.0% vs 40.7%,  $p = 0.03$ ) and trend toward reduced odds of new onset, incident urinary incontinence (OR 0.66, 95% CI 0.42–1.02,  $p = 0.06$ ) compared with the diabetes support and education arm. In contrast, no differences between intensive lifestyle intervention and diabetes support and education were seen at 1 year for frequency of nocturia or frequency of daytime voiding.

**Conclusions:** Intensive lifestyle intervention should be considered for the treatment of urinary incontinence in overweight/obese men with type 2 diabetes.

**Key Words:** diabetes mellitus, weight loss, urinary incontinence, nocturia

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OBESITY and type 2 diabetes have long been linked to sexual dysfunction in men,<sup>1</sup> and are increasingly recognized as independent risk factors for lower urinary tract dysfunction<sup>2</sup> such as nocturia<sup>3,4</sup> and urinary incontinence.<sup>1</sup> Given that obesity is a modifiable risk factor, weight loss interventions targeting physical activity and diet hold promise for LUTD prevention and treatment. While studies have shown the benefits of lifestyle intervention in reducing UI in overweight/obese females with type 2 diabetes,<sup>5,6</sup> few studies have examined the impact of weight loss in the treatment of male LUTD. In 2 population based cohorts of males, weight changes (5% of baseline or greater) did not influence the onset or progression of LUTD.<sup>7</sup> With respect to type 1 diabetes, in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study randomization to conventional vs intensive treatment did not reduce the risk of moderate to severe LUTD in men.<sup>8</sup> However, only preliminary research has been conducted in obese men with type 2 diabetes,<sup>9</sup> and whether lifestyle modification would have positive effects on LUTD in overweight/obese men with type 2 diabetes remains unclear.

In the current study we determined the effect of intensive lifestyle intervention focused on weight loss on the prevalence, incidence and resolution of UI, nocturia and daytime voiding in overweight/obese men with type 2 diabetes. We hypothesized that lifestyle intervention vs control intervention would decrease the prevalence and incidence and increase the resolution rates of UI, bothersome nocturia and increased daytime voiding after 1 year of treatment.

## MATERIALS AND METHODS

### Participants

Look AHEAD is a multicenter, randomized controlled study in overweight and obese individuals with type 2 diabetes which was designed to assess the long-term effects of an intensive lifestyle intervention weight loss program vs a diabetes support and educational control program on the primary outcome of cardiovascular morbidity and mortality.<sup>10</sup> Participants were eligible if they were age 45 to 76 years and had a BMI of 25 kg/m<sup>2</sup> or greater (greater than 27 kg/m<sup>2</sup> if currently taking insulin). Exclusion criteria were high blood pressure (160/100 mm Hg or greater), elevated triglycerides (600 mg/dl or greater), uncontrolled hyperglycemia (hemoglobin A1c 11% or greater), a cardiovascular event within the last 3 months, significant renal or pulmonary disease, or conditions likely to limit adherence to the study intervention. Informed consent was obtained from all participants before screening, consistent with the Declaration of Helsinki and the guidelines of each center's institutional review board. Participants were

randomly assigned within clinic to ILI or DSE with equal probability.

The Look AHEAD recruitment began in 2001 with planned followup until 2014 from 16 clinical centers. Recently the trial was stopped after the data and safety monitoring board found no significant differences between ILI and DSE in cardiovascular events, which was the primary end point of the trial.<sup>11</sup>

The ILI was designed to produce an average of 7% or greater weight loss at 1 year.<sup>12</sup> During the first 6 months of the program the participants attended weekly meetings and were then seen 3 times per month for the following 6 months. The ILI included individual and group sessions.<sup>12</sup> Calorie restriction was the primary action used to achieve weight loss. Participants were given calorie goals of 1,200 to 1,500 if they weighed less than 250 lb and 1,500 to 1,800 if they weighed more than 250 lb, with a maximum of 30% of calories from fat. ILI participants were instructed to consume a portion controlled low fat and low calorie diet that was supplemented with liquid and frozen meal replacements. Participants were encouraged to gradually increase exercise to 175 minutes per week using moderate intensity activities such as brisk walking. The DSE group was invited to 3 group sessions during year 1 to provide basic education about diet and physical activity as well as social support opportunities. Participants in both groups continued to be seen by their own personal physicians during the study period for ongoing health care.

### Measures

Measures were completed at baseline and 1 year by trained assessors blinded to participant treatment group. Height and weight were measured in duplicate using a digital scale and standard stadiometer. Demographic and medical history information was obtained by standardized interviewer administered questionnaires. Urinary incontinence, nocturia and daytime voiding were assessed by self-report questions. To classify urinary incontinence the participants were asked if they had leaked even a small amount of urine or wet themselves in the last 7 days (yes/no). To further designate leakage type (stress or urge), participants who responded in the affirmative were asked how often they leaked with "an activity like coughing, sneezing, lifting or exercise" or had "an urge to urinate and couldn't get to the bathroom fast enough." UI was classified based on the predominant type reported. Nocturia and daytime voiding were determined using a single item question on a continuous scale. Participants were asked, "in the past 7 days, on average, how many times each day have you had to go to the bathroom to urinate a) during the day? b) during the night?" We defined bothersome nocturia and increased daytime voiding to be present (yes/no) when participants urinated 2 or more times at night (nocturia) and 8 or more times during the day (daytime frequency), respectively.<sup>13,14</sup>

### Statistical Analysis

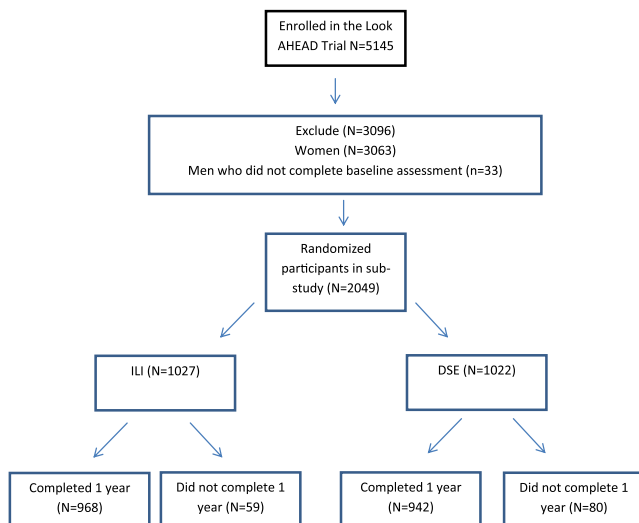
As a sensitivity analysis, men who completed baseline and 1-year assessments were compared with those who did not complete 1-year assessments of relevant baseline variables and demographic characteristics using chi-square

tests for categorical variables and ANOVA for continuous variables. A similar analysis was made comparing ILI and DSE participant baseline variables. Subsequent analyses included only participants who completed baseline and 1-year assessments.

For UI, nocturia and daytime urinary voiding we compared the proportion of men in the ILI and DSE groups with prevalent cases at baseline and 1 year, incident cases at 1 year and resolution at 1 year. Chi-square tests were used for unadjusted group comparisons. Multivariable logistic regression models were used to examine the effects of the intervention on 1-year prevalence, incidence and resolution of UI, nocturia and increased daytime voiding. Three models were reported. Model 1 was adjusted for center site only, except not for urgency predominant type incident cases of UI and resolved cases of increased daytime voiding due to scant cases at some sites. Model 2 was adjusted for center site plus baseline incontinence/nocturia/increased daytime voiding (for prevalence only), age, race/ethnicity, BMI, diabetes duration, Beck Depression Inventory and smoking status. The third model pertaining to nocturia included model 2 variables plus sleep apnea and alcohol use (ounces per week). All analyses were performed using SAS® version 9.3 for Windows®.

## RESULTS

UI, nocturia and increased daytime voiding were assessed in 2,049 men at baseline (ILI 1,027 and DSE 1,022). At baseline no significant differences were observed between the ILI and DSE groups with respect to demographic characteristics. Of these men 1,910 (93%) completed the same measure at 1 year (see figure). The ILI and DSE groups had similar completion rates (94% vs 92%,  $p = 0.06$ ). Compared to those who did not complete the questionnaires at 1 year, those who did had significantly



Flowchart of participants in male urinary symptom Look AHEAD substudy

better blood pressure and Beck Depression Inventory score, and were less likely to smoke at baseline (data not shown).

The demographic characteristics of the participants who completed the 1-year followup instrument are shown in the supplementary table (<http://jurology.com/>). The overall cohort had an average age of  $59.9 \pm 6.7$  years and BMI of  $35.2 \pm 5.5$  kg/m<sup>2</sup>. After 1 year of intervention the ILI group lost significantly more weight than the DSE group ( $9.4\% \pm 7.0\%$  vs  $0.7\% \pm 4.5\%$ ,  $p < 0.001$ ). At baseline the ILI and DSE groups had similar proportions of UI ( $11.3\%$  vs  $9.7\%$ ,  $p = 0.25$ ), bothersome nocturia ( $37.7\%$  vs  $38.2\%$ ,  $p = 0.82$ ) and increased daytime urinary voiding ( $17.3\%$  vs  $19.6\%$ ,  $p = 0.18$ ).

### Prevalent UI at 1 Year

The prevalence of UI at 12 months compared to baseline decreased from 11.3% to 9.0% in the ILI group and increased from 9.7% to 11.6% in the DSE group (table 1). Thus, relative to the DSE group the ILI group had 38% reduced odds of prevalent UI at 1 year (OR 0.62, 95% CI 0.43–0.88,  $p < 0.01$ ) after adjusting for relevant demographic and medical comorbidities (table 2).

The differences in prevalence at 1 year appeared largely due to differences in resolution and, to a lesser extent, new onset incidence rates. Specifically, among those with UI at entry, men in the ILI group had a greater likelihood of UI resolving (OR 1.93, 95% CI 1.04–3.59,  $p = 0.04$ , table 2) compared to the DSE arm (56.0% vs 40.7%,  $p = 0.03$ , table 1). Also, among those without UI at study entry the ILI group had a marginally significant reduction in odds of new onset UI developing (OR 0.66, 95% CI 0.42–1.02,  $p = 0.06$ , table 2) compared with the DSE arm (4.5% vs 6.5%,  $p = 0.10$ , table 1).

Examining UI prevalence by type, the odds of prevalent cases of urge incontinence at 1 year were

**Table 1.** Number and proportion of men with UI, nocturia and increased daytime voiding

	No./Total No. ILI (%)	No./Total No. DSE (%)	p Value (chi-square test)
Weekly or greater UI:			
Prevalence at 1 yr	87/968 (9.0)	108/942 (11.6)	0.07
Incidence at 1 yr*	39/859 (4.5)	54/851 (6.5)	0.10
Resolution at 1 yr†	61/109 (56.0)	37/91 (40.7)	0.03
Nocturia (2 or more times/night):			
Prevalence at 1 yr	404/968 (41.7)	371/942 (39.4)	0.30
Incidence at 1 yr*	118/603 (19.6)	91/582 (15.6)	0.08
Resolution at 1 yr†	79/365 (21.6)	80/360 (22.2)	0.85
Increased daytime voiding (8 or more times/day):			
Prevalence at 1 yr	174/968 (18.0)	176/942 (18.7)	0.69
Incidence at 1 yr*	80/801 (10.0)	82/757 (10.8)	0.59
Resolution at 1 yr†	73/167 (43.7)	91/185 (50.8)	0.30

\* Among men without the condition at baseline.

† Among men with the condition at baseline.

**Table 2.** Odds ratios of prevalent and incident weekly or more frequent urinary incontinence, urgency predominant incontinence, nocturia and increased daytime voiding at 1 year for ILI vs DSE

	No. Events	Model 1		Model 2		Model 3	
		OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Prevalent cases:							
Urinary incontinence	195	0.77 (0.57, 1.04)	0.08	0.62 (0.43, 0.88)	<0.01		
Urgency predominant type	103	0.53 (0.35, 0.80)	<0.01	0.36 (0.22, 0.60)	<0.0001		
Nocturia	775	1.09 (0.91, 1.31)	0.34			1.21 (0.96, 1.53)	0.12
Daytime voiding 8 or more times daily	350	0.96 (0.76, 1.22)	0.76	1.02 (0.79, 1.33)	0.88		
Incident cases:							
Urinary incontinence	93	0.71 (0.46, 1.09)	0.12	0.66 (0.42, 1.02)	0.06		
Urgency predominant type	45	0.40 (0.21, 0.76)	<0.01	0.37 (0.19, 0.72)	<0.01		
Nocturia	209	1.31 (0.96, 1.77)	0.08			1.26 (0.92, 1.73)	0.15
Daytime voiding 8 or more times daily	162	0.93 (0.67, 1.29)	0.68	0.93 (0.67, 1.30)	0.66		
Resolved cases:							
Urinary incontinence	98	1.90 (1.05, 3.44)	0.04	1.93 (1.04, 3.59)	0.04		
Urgency predominant type	54	3.10 (1.29, 7.42)	0.01	2.93 (1.19, 7.24)	0.02		
Nocturia	159	1.14 (0.43, 3.05)	0.95			0.96 (0.66, 1.40)	0.84
Daytime voiding 8 or more times daily	164	0.80 (0.53, 1.22)	0.30	0.79 (0.51, 1.21)	0.27		

lower in the ILI vs the DSE group (OR 0.36, 95% CI 0.22–0.60,  $p < 0.0001$ ). The prevalence of urge UI decreased from 6.9% to 4.0% in the ILI group and increased from 5.0% to 7.3% in the DSE group. Similarly ILI was associated with reduced incidence (OR 0.37, 95% CI 0.19–0.72,  $p < 0.01$ ) and increased resolution (OR 2.93, 95% CI 1.19–7.24,  $p = 0.02$ ) of urge UI over 1 year. There were too few cases to model the odds of the prevalence, incidence and resolution of stress incontinence in these male subjects. We examined the relationship of weight loss and UI with multivariable logistic regression. We found that each 1 kg of weight loss reduced the odds of weekly incontinence by 3% (OR 0.97, 95% CI 0.95–0.99,  $p = 0.04$ ).

### Prevalent Nocturia and Increased Daytime Voiding at 1 Year

The frequency of increased nocturia (2 or more times per night) and increased daytime voiding (8 or more times per day) was similar in each of the groups at baseline and at the conclusion of the study period. In the multiple logistic regression model being in the ILI vs DSE group did not significantly reduce the odds of prevalent (OR 1.21, 95% CI 0.96–1.53,  $p = 0.12$ , table 2) or incident (19.6% vs 15.6%,  $p = 0.08$ , table 1) nocturia at 1 year. Similarly no significant treatment effect was observed for prevalence (OR 1.02, 95% CI 0.79–1.33,  $p = 0.88$ ), incidence (OR 0.93, 95% CI 0.67–1.30,  $p = 0.66$ ) or resolution (OR 0.79, 95% CI 0.51–1.21,  $p = 0.27$ ) of increased daytime urinary voiding (table 2).

## DISCUSSION

In this study of overweight/obese men with type 2 diabetes, randomization to ILI was associated with a 38% reduced odds of having UI at 1 year relative to DSE. The fact that 10% of our cohort of obese

men with type 2 diabetes reported at least weekly incontinence is noteworthy, as is the reduction in rates of incontinence at 1 year in the intervention group. The reduced prevalence of incontinence in those in our cohort randomized to ILI seemed to be associated primarily with increased rates of remission. However, there was also a trend toward lower rates of incident UI among ILI participants.

It is informative to compare these results with the UI female cohort in Look AHEAD.<sup>5</sup> Among men and women the 1-year prevalent cases of UI were fewer in the ILI groups. Interestingly while ILI primarily improved resolution rates in men, it improved incident rates in women. Thus, weight loss interventions may be more effective for the treatment of UI in men and the prevention of UI in women with type 2 diabetes.

Also of note, urgency UI was more prevalent than stress UI in men. Moreover, ILI significantly improved remission rates and incident rates of urgency incontinence in these men. In contrast, randomization to ILI did not affect the prevalence of nocturia at 1 year or the incidence of new onset or resolution of bothersome nocturia and increased daytime voiding.

Mechanisms are unknown for why weight loss may reduce urgency UI in men. Diabetes and obesity are known risk factors for LUTD.<sup>2,3,15–18</sup> The pathophysiology of LUTD in overweight/obese men with type 2 diabetes is likely complex and potentially has interrelated, overlapping or disparate mechanisms. Diabetes is known to affect the bladder and prostate. Diabetes results in elevated insulin levels which can stimulate or accelerate benign prostatic hyperplasia development.<sup>19</sup> Higher serum concentrations of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 have been associated with an increased risk of benign prostatic hyperplasia diagnosis and surgery.<sup>20</sup> Obesity and

diabetes generated systemic inflammation may result in LUTD.<sup>21</sup> Vascular insufficiency secondary to pelvic atherosclerotic disease caused by the metabolic syndrome may lead to ischemia and bladder dysfunction. Ischemia results in increased levels of transforming growth factor beta, leading to fibrosis, collagen deposition, smooth muscle atrophy, and subsequent reduced compliance and bladder size.<sup>22</sup> Similar changes have been suggested in the prostate.<sup>23</sup> In addition to inflammatory and hormonal factors, increased central obesity and the abdominal mass effect may contribute to LUTD. Urodynamic studies have verified higher filling and voiding pressures in obese individuals.<sup>1</sup> Finally, obesity is a risk factor for sleep apnea, which can lead to increased nighttime voiding, and potentially to urinary urgency and frequency.<sup>24</sup>

To our knowledge this study was the first to examine the impact of intensive lifestyle intervention on LUTD in overweight/obese men with type 2 diabetes. Our findings suggest that in overweight/obese men with type 2 diabetes a lifestyle modification program promoting weight loss should be considered a first line intervention to promote the resolution of UI. Given that the weight loss intervention did not improve nocturia and increased daytime urinary voiding, it is less clear how effective weight loss would be in preventing and treating LUTD other than urinary incontinence.

Our study should be considered within its limitations. These results may not be generalizable to the general population of overweight/obese people with type 2 diabetes or to overweight/obese people without diabetes. Our study participants were clinical trial volunteers and the exclusion criteria were relatively strict. We did not investigate how weight loss impacts other LUTDs such as post-void dribbling, weak stream or urinary urgency without UI. Our outcomes were based on self-report and were vulnerable to recall bias.<sup>25</sup>

In addition, our single item questions assessing daytime frequency of urination and nocturia differed slightly from previous self-report instruments, which may have impacted the validity of the responses.<sup>13,14</sup> For example, our nocturia question addressed urinating at night but did not specify that the urination event caused a sleep interruption. Future investigations should include more extensive urinary outcome phenotyping at multiple points and objective measures such as voiding diaries. In addition, while the study completion rate was high (92% to 94%), completers had better blood pressure and depression scores, and were less likely to smoke compared to noncompleters. These differences may have biased our results. Lastly, we performed a subgroup analysis (male participants of Look AHEAD) which also could have introduced bias.<sup>26</sup> However, given

our large sample size and single subgroup, the subgroup analysis bias was likely minimal.

## CONCLUSIONS

ILI was associated with reduced 1-year prevalent UI and improved resolution rates. Bothersome nocturia and increased daytime urinary voiding were not improved in the treatment group. Lifestyle interventions focused on weight loss should be considered for the treatment of UI in overweight/obese men with type 2 diabetes.

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