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## Clinical Research in Diabetes and Urinary Incontinence: What We Know and Need to Know

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### Abstract

**Purpose**—To discuss epidemiologic and clinical trial research among women with urinary incontinence and diabetes and provide directions for future research.

**Materials and Methods**—Published epidemiologic and clinical trial literature examining diabetes and incontinence was presented.

**Results**—Multiple studies have now confirmed that the prevalence and incidence of incontinence is elevated in women with type 2 diabetes. Emerging evidence also suggests higher rates of incontinence in women with Type 1 diabetes as well as pre-diabetes. Clinical trial research suggests that weight loss can reduce incontinence in women with pre-diabetes. An ongoing multi-center trial will examine the effects of weight loss on incontinence in women with type 2 diabetes. Limited trial data in those with type 1 diabetes suggests that intensive glycemic control does not appear to decrease the long-term risk of incontinence in women with Type 1 diabetes.

**Conclusions**—Future research is needed to identify the risk factors, mechanisms, and most effective treatment and prevention strategies to reduce urinary incontinence in women with type 1 diabetes, type 2 diabetes, or pre-diabetes. Physicians should be alert for urinary incontinence because it is often **not reported** and therefore undertreated among women with diabetes and pre-diabetes.

### Keywords

Type 1 diabetes; Type 2 diabetes; pre-diabetes

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Type 2 diabetes and urinary incontinence in women are common, chronic, and costly disorders with major public health implications.<sup>1</sup> Type 2 diabetes affects an estimated 19.3 million American adults and another 54 million who have “pre-diabetes” or impaired fasting glucose.<sup>2,3</sup> Total estimated diabetes costs in the United States in 2002 were \$132 billion, including medical care and services, short-term and permanent disability, and premature death.<sup>3</sup> Urinary incontinence is a similarly prevalent disorder, affecting an estimated 12.7 million women, and has profound consequences on quality of life, including social isolation, stigmatization, depression, and the end of independent living for some elderly women.<sup>4,5</sup> Costs for incontinence may be as high as \$30 billion per year in the United States, greater than the annual direct costs for breast, ovarian, cervical and uterine cancers combined.<sup>6</sup>

Sound epidemiologic evidence from several studies has linked these two disorders and shown that urinary incontinence is 50 to 200% more common in women with type 2 diabetes than among women with normal glucose levels.<sup>7–10</sup> For example, in the Nurses' Health Study, a very large cohort of women, the prevalence of weekly incontinence was 17% in those without diabetes and 24% in those with diabetes.<sup>11</sup> For very severe incontinence, the differences in prevalence were also significant: 2% in women without diabetes versus 4% in women with diabetes. Data on the incidence of incontinence reflect similar patterns. In the Nurses' Health Study, the two-year incidence of weekly incontinence was 5% in those without diabetes and 9% in those with type 2 diabetes.<sup>12</sup> In this study, the prevalence and incidence of urinary incontinence remained significantly greater in the women with type 2 diabetes even after controlling for a wide variety of potential confounding factors, including body mass index. These data compliment other research<sup>9</sup> and establish type 2 diabetes as a strong independent risk factor for prevalent and incident urinary incontinence and urgency incontinence, in particular.

There has been less research with type 1 diabetics to estimate the prevalence of incontinence and how it may differ in comparison to women with normal glucose. Recent data among women with type 1 diabetes from the Urologic Complications of Epidemiology of Diabetes Intervention and Complications (Uro-EDIC) study has shown prevalence rates of nearly 20% for weekly incontinence. Specifically, women with type 1 diabetes in this study had a significant two-fold increased risk of urgency incontinence compared with non-diabetics (9% vs. 4.5%, respectively;  $p = 0.01$ ), after adjusting for age, BMI, parity, hysterectomy, and current smoking. Thus, type 1 diabetes may also be a risk factor for urinary incontinence in women.<sup>13</sup>

There is also evidence that women with pre-diabetes are at higher risk of urinary incontinence. In the National Health and Nutrition Examination Survey (NHANES) 2001–2002, women with impaired fasting glucose had an elevated prevalence of urinary incontinence similar to women with diabetes, affecting 33.4% and 35.4% of women, respectively,<sup>14</sup> and significantly ( $p < 0.001$ ) higher than among women with normal fasting glucose (16.8%). Moreover, two microvascular complications caused by diabetes, microalbuminuria and peripheral neuropathic pain, were significantly associated with incontinence. These data suggest that incontinence may be a more common consequence of hyperglycemia than other microvascular complications such as retinopathy, neuropathy, or nephropathy.<sup>14</sup>

## Risk factors and mechanisms

Well-recognized and common risk factors for urinary incontinence in women include increasing age, parity, hysterectomy, excess weight, and oral estrogen use. However, despite mounting evidence of a link between diabetes and incontinence, little is known about the mechanisms by which diabetes leads to incontinence. Some clues from epidemiologic studies provide a few possibilities. For example, investigations within women with type 2 diabetes suggest that microvascular complications further increase both the prevalence and incidence of urinary incontinence;<sup>11,14</sup> physiological, microvascular, and neurological complications of diabetes result in changes that may impair the function of continence mechanisms, including damage to the innervation of the bladder, altered detrusor muscle function or urothelial dysfunction.<sup>15–17</sup> At the same time, though, the increase in urinary incontinence seen in pre-diabetic women who generally lack these severe diabetic complications suggests that other unknown processes may also underlie the development of incontinence in women with impaired glucose.

Diabetes appears to be related to increased risk of incontinence both with or without obesity;<sup>10</sup> however, obesity is clearly a strong risk factor for both urinary incontinence and type 2

diabetes. Obesity and abdominal fat, in particular, may influence urinary incontinence by increasing pressure on the bladder and straining the muscles and connective tissue that support the urethra.<sup>18</sup> Also, the strong positive relationship between obesity and insulin resistance<sup>19</sup> suggests several potential mechanisms linking obesity and incontinence. Both improving blood glucose control and promoting weight loss have been identified as potential targets for interventions to prevent or treat urinary incontinence in women with diabetes.

## Clinical Trials

Only a few clinical treatment trials have examined ways to reduce or prevent urinary incontinence in women with diabetes. The Diabetes Prevention Program (DPP)<sup>20</sup> examined whether lifestyle intervention targeting diet and physical activity or metformin therapy could prevent urinary incontinence in overweight women with impaired glucose tolerance. Findings indicated that, after 3 years, the prevalence of urinary incontinence was significantly lower in women in the intensive lifestyle intervention group than those receiving metformin or placebo (38.3% vs. 48.1%, and 45.7%, respectively). The effects of lifestyle intervention on incontinence were observed across various subgroups of age, race, and initial body mass index. Examining subtypes of incontinence, this overall effect was due to reduced prevalence of stress, rather than urgency, incontinence most likely reflecting the age of the trial population. Interestingly, weight loss was the most important mediator of the beneficial effect of the lifestyle intervention on incontinence. Although patients and clinicians are concerned that exercise exacerbates incontinence, we found that increased physical activity did not appear to have an adverse effect on incontinence.

Whether a similar lifestyle intervention would have positive effects on urinary incontinence in women with type 2 diabetes is unknown. The Look AHEAD (Action for Health in Diabetes) trial is a randomized controlled study in overweight and obese individuals with type 2 diabetes and is designed to assess the long-term effects of an intensive weight loss program delivered over 4 years versus a control group given diabetes support and education. This study was started in 2001 with planned follow-up until 2012. The Urinary Incontinence Ancillary Study to Look AHEAD will examine the effects of the intensive lifestyle weight loss program on both the incidence and prevalence of urinary incontinence in women with type 2 diabetes.<sup>21</sup> Analysis of the baseline data from this cohort indicates that one third of women in this ethnically and racially diverse cohort has weekly urinary incontinence. Moreover, obesity was the strongest modifiable risk factor for overall incontinence and stress incontinence.

There are limited trial data among women with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) compared the effects of intensive treatment (insulin three or more times per day) or conventional therapy (insulin 1–2 times per day) in 1441 type 1 diabetics.<sup>22</sup> Results indicated that, after 6.5 years, intensive treatment reduced the risk of retinopathy, nephropathy, and neuropathy by 35% to 90% compared with conventional treatment. In 1994, the Epidemiology of Diabetes Interventions and Complications Study (EDIC) began (after the closeout of DCCT) and is a 20 year observational study of the DCCT cohort; 96% of surviving member of DCCT volunteered to participate in the EDIC. In 2001, the Urologic Complications of Diabetes Group was formed to examine urological complications of the DCCT/ EDIC cohort. Interestingly, findings indicated that DCCT intervention had beneficial effects on neuropathy, nephropathy, and retinopathy through 20 years of follow-up, but there was no significant decrease in risk of incontinence in women assigned to intensive treatment.<sup>23</sup> The reasons for this remain unclear; it is possible that treatment for diabetes does not reverse bladder dysfunction, or that improvements in incontinence associated with treatment were not apparent in this study in which control participants also had good diabetic management.

## Future Research

There are several avenues for future investigation in epidemiologic and clinical trial research, as reviewed below.

### Raising awareness

Recognition of urinary incontinence as an important medical problem remains an issue. For example, in the Nurses' Health Study – a population of health professionals – only a minority (38%) of women with new onset urinary incontinence mentioned their condition to a physician. Although there are only limited data on incontinence in men and in men with diabetes, the number of men with incontinence who seek health care for this condition is also low (~4%).<sup>24</sup> Programs are needed to increase awareness of urinary incontinence among patients with diabetes and facilitate communication about incontinence with their healthcare providers. Equally, strategies to improve physicians' diagnosis of urinary incontinence in the context of primary care are needed. Use of a simple diagnostic tool may aid primary care physicians in detecting and treating urinary incontinence in diabetic patients.<sup>25</sup> This and effectiveness trials of pharmacologic treatments for incontinence designed to increase physician involvement in treating urinary incontinence in the context of primary care merit further investigation.

### Targets for intervention

Clearly, an important area for future epidemiologic and basic science research will be investigation into the risk factors and causes of urinary incontinence in the population with diabetes or pre-diabetes. Prior studies have investigated mechanisms generally among small samples of men and women, often focusing on insulin-using elderly populations with age-related neurologic or urologic conditions, lacking adjustment for common risk factors such as age, parity, prior hysterectomy. The relationship between increased urine production in diabetics and incontinence has also received little empirical attention. Prospective research in larger and more diverse samples is needed to help identify the mechanisms and potential targets for intervention.

### Clinical trials

The clinical trial literature evaluating treatment and prevention of urinary incontinence in women with diabetes is limited. Clinical outcomes of common treatments for urinary incontinence in women with pre-diabetes and diabetes have not been critically examined. Thus, it remains unclear whether standard urinary incontinence treatments are equally effective in diabetic women; given the increasing prevalence of diabetes, the question is becoming more and more important. Randomized controlled trials are needed to assess the efficacy and safety of behavioral, pharmacologic, and surgical treatments for incontinence in women with diabetes. Comparative effectiveness studies are also needed to examine the effects of standard diabetic treatment, standard urinary incontinence treatment, and their combination in reducing or preventing urinary incontinence in women with diabetes or pre-diabetes.

Weight reduction has recently been shown to improve incontinence in obese women, and the Look AHEAD study will examine the effects of weight loss in women with type 2 diabetes. However, future research should expand this line of investigation and examine, for example, whether the dual diagnosis of diabetes and urinary incontinence creates a “teachable moment” for improving long-term weight loss outcomes. Moreover, it remains unclear whether weight loss can reduce or prevent urinary incontinence in women with type 1 diabetes. As urinary incontinence is common among women with gestational diabetes, future research should also examine whether lifestyle intervention to prevent excessive gestational weight gain could reduce and prevent urinary incontinence related to gestational diabetes.

## Conclusion

As the population ages, diabetes and lower urinary tract dysfunction will markedly increase in prevalence. Physicians should be alert for urinary incontinence because it is often unrecognized and therefore under-treated among women with diabetes and pre-diabetes. Future research is needed to identify the risk factors, mechanisms, and most effective treatment and prevention strategies to reduce the psychosocial, medical, and economic costs of this prevalent and chronic disorder affecting many women with diabetes.

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