The Effects of Diabetes Mellitus and Obesity to Pelvic Organ Prolapse in Postmenopausal Women

Diabetes Mellitus ve Obezitenin Postmenopozal Dönemdeki Kadınlardaki Pelvik Organ Prolapsusu Üzerine Etkileri

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ÖZET

Amaç: Diabetes mellitus ve obezitenin postmenopozal dönemdeki kadınlarda pelvik organ prolapsusuna(POP) olan etkilerini değerlendirmeyi amaçladık.

Yöntemler: 49-79 yaşları arasındaki POP bulunan 104 kadın grup I(non-diabetik ve non-obez) grup II(non-obez ve diabetik) grup III(obez ve non-diabetik) ve grup IV(obez ve diabetik) olmak üzere 4 gruba ayrılmıştır. Her bir grupta POP-Q (POP-Q) sistemi kullanılarak uterin prolapsus, sistosel ve rektosel varlığı değerlendirildi.

Bulgular: Sağlıklı kadınlarla karşılaştırıldığında obezitenin ve diabetes mellitusun(DM) sistosel, rektosel ve uterin prolapsus progresyonuyla ilişkili olduğu saptanmıştır($p<0.001$). Obezite olan gruplardaki uterin prolapsus evresi diyabetik gruplardan belirgin olarak daha ileri bulunmuştur($p<0.001$).

Sonuç: Obezite ve DM; POP için risk faktörü olarak görülmektedir. Obezite, uterin prolapsusu DM'den daha fazla etkilemektedir ve modifiye edilebilir bir risk faktörüdür. Dolayısıyla yeni tedavi stratejilerinin geliştirilmesi önem arz etmektedir.

Anahtar Kelimeler: sistosel, diabetes mellitus, obezite, pelvic organ prolapsus, rektosel ve uterine prolapsus

ABSTRACT

Objective: We aim to evaluate the effect of diabetes and obesity on pelvic organ prolapse (POP) in postmenopausal women.

Methods: 104 women with POP, ages 49 to 79 were divided as group I (non diabetic-non obese), group II (non obese-diabetic), group III (obese-non diabetic) and group IV (obese-diabetic). For each group, presence of uterine prolapse, cystocele and rectocele using POP Quantification (POP-Q) system were assessed.

Results: Obesity and diabetes mellitus (DM) were associated with progression in cystocoele, rectocele and uterine prolapse compared with healthy women ($p<0.001$). Uterine prolapse stages of the obesity groups were also significantly higher than in the diabetic group ($p<0.001$).

Conclusions: Obesity and DM seem to be risk factors for POP. However, obesity as a modifiable risk factor has more effect on developing uterine prolapse than diabetes and it is important for developing new therapy strategies.

Key Words: cystocele, diabetes mellitus, obesity, pelvic organ prolapse, rectocele and uterine prolapse

Abbreviations

POP: pelvic organ prolapse,
POP-Q: POP Quantification
DM: diabetes mellitus
BMI: body-mass index
LUT: lower urinary tract
UI: urinary incontinence
C: cervix
D: posterior fornix
TVL: total vaginal length
ER-b: 17b-estradiol
WHI: US Women's Health Initiative
OR: odds ratio
CI: confidence interval

INTRODUCTION

Pelvic organ prolapse (POP) is descent of pelvic organs (bladder, uterus, and rectum) through the vagina. It affects anterior and posterior vaginal wall, uterus, and/or vaginal apex. POP are often associated with disorders such as urinary and fecal incontinence. The prevalence of POP in the general population is estimated 37%, however, it reaches to 64.8% in older women (1). The pathogenesis of POP is not fully understood, but genital prolapse may have multifactorial etiology. Epidemiologic studies showed that parity, mode of delivery, menopausal estrogen deficiency, higher body mass index, previous pelvic surgery, genetic factors, family history and co morbidity such as diabetes mellitus and hypertension were contributing factors for the occurrence of symptoms of pelvic floor dysfunction in women (2). Genes have been identified that may result in alteration of the normal metabolism of various structural proteins which may ultimately predispose some women to both urogenital prolapse and stress incontinence.(5%) Mechanical stability of the genito-urinary tract depends on intact functional collagen fibers, which support the bladder neck, urethra, and pelvic organs. Interstitial collagen type I is the most abundant connective tissue protein. Increased collagen breakdown may play an important role in the onset and development of POP (2,3). Within the pelvic organ prolapse risk factors, decompensate factors, such as tissue atrophy and weakness related to aging, disease, medication, and/or debility, are thought to account for the increasing prevalence of POP seen with aging (3). Recent research shows that family history is an important risk factor. Pelvic floor dysfunction impairs the quality of life of a large proportion of women of all ages throughout the world. A higher life expectancy, owing to modern medical achievement, adds about 10 years or even more to a woman's previous life expectancy of 65 years. The occurrence of pelvic floor dysfunction increases progressively during aging process in women (4). Findings of a cross-sectional study of menopausal women indicated an augmented risk of pelvic organ prolapse in individuals aged 52–55 years or older compared to younger ones (5).

Although menopause has often been cited as a risk factor for pelvic organ prolapse, most researchers studying hormonal status and prolapse have failed to find an association between oestrogen status and POP (4;6). However, selective oestrogen-receptor modulators might be linked to prolapse and other pelvic-floor disorders (7).

Increased body-mass index (BMI) also seems to have a role in development of pelvic organ prolapse. Overweight (BMI 25–30 kg/m^2) and obese (BMI>30 kg/m^2) women are at high risk of developing pelvic organ prolapse (8).

Vaginal childbirth being the one most frequently risk factor associated with prolapse in women younger than 60 years (9). Other obstetric factors that have been associated with an increased risk of pelvic organ prolapse are delivery of a macrosomic infant, prolonged second stage of labour, and age younger than 25 years at first delivery (10).

Women have a higher prevalence of lower urinary tract (LUT) complications, contributing to the high prevalence of urinary incontinence (30–60%) in diabetic women (11). A significantly higher prevalence of urinary incontinence (UI) was reported in diabetic women, compared to non diabetic subjects (12). Because of pre-existing alterations in lower urinary tract and vaginal tissues of diabetic women, such as autonomic neuropathy or myopathy, diabetic women may sustain greater injury and do not recover as well as non diabetic women from the birth trauma. Anterior vaginal wall prolapse has a strong association with urinary urgency and frequency, urinary incontinence, incomplete emptying, and voiding dysfunction (13).

The aim of current study was to investigate the effect of diabetes mellitus and obesity on the pelvic floor in postmenopausal women in order to understand and emphasize the importance of modifiable lifestyle factors in POP and potential risk factors.

MATERIALS AND METHODS

We performed a descriptive analysis of the clinical records of 104 postmenopausal Turkish women with POP at the Hospital. Our study was approved by the institutional review board of hospital. Written informed consent was obtained from all patients.

The patients were divided into 4 groups: Group 1: Non diabetic-non obese (n:31; 29.8%); Group 2: Non obese-diabetic (n:24; 23.07%); Group 3: Obese-non diabetic (n:26; 25%); Group 4: Obese-diabetic (n:23; 22.11%). Non diabetic-non obese group consisted of 31 patients were used as control. Patients with Type 2 diabetes mellitus were enrolled in the study as diabetic subjects. Patients with neurological or mental disorder, lung disease, asthma, history of depression, history of surgery for pelvic organ prolapse repair or surgery for incontinence, family history of pelvic organ prolapse and patients with collagen vascular disease, constipation, chronic bowel disease,

using hormone replacement therapy and smokers were excluded from the study. All patients were examined by the same gynecologist and urogynecology nurse in the dorsal lithotomic position. Degree of pelvic organ prolapse was quantitatively assessed using pelvic organ prolapse quantification (POPQ) staging system (14). BMI calculated as weight (kg)/ [height (m^2)]. Parity, delivery type (normal, caesarean or instrumental) was documented for each patient. Blood samples were drawn for fasting glucose determination at the research clinic visit to identify previously undiagnosed diabetes. If the result was >125 mg/dl, the woman was diagnosed as diabetic.

POP was graded according to Pelvic Organ Prolapse Quantification (POP-Q) system for a quantitative description (14). Stage 0: No prolapse; Aa, Ba (anterior vaginal wall points), Ap and Bp (posterior vaginal wall points) are all at –3 and C (cervix) or D (posterior fornix) is between –TVL (total vaginal length) and – (TVL – 2) cm. Stage I: the most distal prolapse is > 1 cm above the level of the hymen (< –1). Stage II: the most distal prolapse is between 1 cm above and 1 cm below the hymen (at least one point is –1, 0, or +1). Stage III: the most distal prolapse is > 1 cm below the hymenal ring (> +1) but no further than 2 cm less than TVL. Stage IV: Complete vaginal eversion; the most distal prolapse protrudes to at least (TVL -2) cm.

The study was framed as a descriptive series, and statistical comparison was performed between four groups of patients for the stages of anterior vaginal defect, apical vaginal defect and posterior vaginal defect. The data are expressed as the mean ± SD for the parametric variables. Statistical analyses included ANOVA, Kruskal Wallis and chi-square and SPSS for windows 10.0 statistical programme were used.

RESULTS

The mean parity, age and POP stages of 104 patients are shown in Table 1. When the groups were compared in terms of parity and age, there were no significant differences between all groups (p>0.05). However, as seen in table 1, anterior vaginal defect stages of non obese-diabetic, obese-diabetic and obese-non diabetic patients were significantly higher comparing to non diabetic-non obese patients (p<0.001). Apical vaginal defect stages of non obese-diabetic, obese-diabetic and obese-non diabetic groups were significantly higher than non diabetic-non obese group. Apical vaginal defect stages of obese-diabetic and obese-non diabetic groups were also significantly higher than non obese-diabetic group (p<0.001). Posterior vaginal defect stages of non obese-diabetic, obese-diabetic and obese-non diabetic groups were significantly higher than non diabetic-non obese group (p<0.001).

As shown in Table 1, anterior vaginal defect stages of non obese-diabetic (1.54±0.83), obese-diabetic (2.00±0.52) and obese-non diabetic (1.77±0.76) patients were significantly higher compared to non diabetic-non obese patients (0.84±0.73) (p<0.001). Apical vaginal defect stages of non obese-diabetic (1.46±0.83), obese-diabetic (2.04± 0.77) and obese-non diabetic (1.77±0.86) groups were significantly higher than those of non diabetic-non obese group (0.77±0.72) (p<0.001). Posterior vaginal defect stages were significantly higher in non obese-diabetic (1.17±0.70), obese-diabetic (1.61±0.66) and obese-non diabetic (1.38± 0.64) groups compared to non diabetic-non obese group (0.65±0.61) (p<0.001). Mean stages of anterior vaginal defect or apical vaginal defect were slightly higher than posterior vaginal stages in all groups.

Table 1. The patient characteristics and comparison of four groups.

	Non diabetic-Non obese		Non obese-Diabetic		Obese-Non diabetic		Obese-Diabetic		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p**
Parity	3,55	1,98	3,46	1,95	3,38	1,79	3,96	2,12	,753
Age	62,13	6,81	63,17	6,15	62,73	6,73	64,35	7,81	,851
Anterior defect stage	,84	,73	1,54	,83	1,77	,76	2,00	,52	,000***
Apical defect stage	,77	,72	1,46	,83	1,77	,86	2,04	,77	,000***
Posterior defect stage	,65	,61	1,17	,70	1,38	,64	1,61	,66	,000***

The ratio of anterior vaginal defect stage 2 or stage 3 was found significantly higher in non obese-diabetic (58.3%), obese-diabetic (87.0%) and obese-non diabetic (73.1%) groups compared to non diabetic-non obese group (19.4%) ($p < 0.001$). There were no significant differences between other groups (Table 2).

The ratio of vaginal apical defect stage 2 and stage 3 in non obese-diabetic (58.3%), obese-diabetic (87.0%) and obese-non diabetic (73.1%) groups were statistically significant than those in non diabetic-non obese group (16.1%) ($p < 0.001$). But there were no differences between other groups. Moreover apical vaginal defect stage 3 was remarkable higher percent in obese-diabetic (13.0%) and obese-non diabetic groups (15.4%) compared to non obese-diabetic group (4.2%) (Table 2).

There were notably higher posterior vaginal defect stage 2 and stage 3 in non obese-diabetic (33.3%), obese-diabetic (60.9%) and obese-non diabetic (46.2%) groups compared to non diabetic-non obese group (6.5%) ($p < 0.001$). There were no remarkably differences between other groups (Table 2).

Table 3 shows delivery status of the patients. We observed that normal vaginal delivery was significantly higher than caesarean or instrumental delivery in all groups. 80.6% of non diabetic-non obese, 83.3% of non obese-diabetic, 76.9% of obese-non diabetic and 82.6% of obese-diabetic patients had normal vaginal childbirth (Table 3).

Table 2. The evaluation of anterior, apical and posterior defect stage of four groups.

	Nondiabetic-Non obese		**Non obese-Diabetic**		**Obese-Non diabetic**		**Obese-Diabetic**			
	n	**%**	**N**	**%**	**n**	**%**	**n**	**%**	**Chi-square**	**p**
Anterior defect Stage										
0	11	35,5	3	12,5	2	7,7	0	0		
1	14	45,2	7	29,2	5	19,2	3	13,0		
2-3	6	19,4	14	58,3	19	73,1	20	87,0	31,22	0,000***
Apical defect stage										
0	12	38,7	4	16,7	3	11,5	1	4,3		
1	14	45,2	6	25,0	4	15,4	2	8,7		
2-3	5	16,1	14	58,3	19	73,1	20	87,0	32,26	0,000***
Posterior defect stage										
0	13	41,9	4	16,7	2	7,7	1	4,3		
1	16	51,6	12	50,0	12	46,2	8	34,8		
2-3	2	6,5	8	33,3	12	46,2	14	60,9	26,45	0,000***

Table 3. The patient comparison of four groups according to delivery types.

	Non diabetic-non obese		**Non obese-Diabetic**		**Obese-Non diabetic**		**Obese-Diabetic**			
	n	**%**	**N**	**%**	**n**	**%**	**n**	**%**	**Chi-square**	**p**
Delivery										
Caesarean	3	9,7	2	8,3	3	11,5	2	8,7		
Normal	25	80,6	20	83,3	20	76,9	19	82,6		
Instrumental	3	9,7	2	8,3	3	11,5	2	8,7	0,40	0,999

DISCUSSION

Estrogen receptors are present in all of the muscles and ligaments with the exception of the levator ani and dome of the bladder (15). Estrogen receptors are present in the squamous epithelium and uterosacral ligaments throughout the lower urinary tract. Squamous endothelial tissue is most directly influenced by estrogen. Circulating endogenous estrogen affects the maturation of vaginal tissues (16). These receptors have effects on the proximal and distal urethra, vagina, and trigone of the bladder in the form of 17b-estradiol (ER-b) that is a recently identified glycoprotein (15). Estrogen increases urethral resistance, sensory (proprioceptive) threshold of the bladder, and adrenoreceptor sensitivity in the urethral smooth muscle, and promotes beta 3-adrenoceptor-mediated relaxation of the detrussor muscle (17,18).

As estrogen deficiency is a known risk factor for POP, estrogen replacement therapy (ERT) traditionally has been used to improve structural integrity of the pelvic tissue with favourable effects on urinary incontinence. Estrogen receptors (ER) were identified in the nuclei of connective tissue and of the smooth muscle cells of the bladder trigone, urethra, vaginal mucosa, levator ani and uterosacral ligament. These receptors participate in maintaining the pelvic supportive system by increasing synthesis or by decreasing breakdown of collagen. Several studies report an increase in the expression for collagens I and III in ERT. These findings suggest that estrogen increases the turnover of connective tissues of the pelvic floor (1-3).

Furthermore progesterone and androgen receptors are present in the lower urinary tract, but not as consistently widespread as estrogen receptors. Progesterone receptors are mostly found in sub epithelial tissues (15).

Diabetic state produces dramatic changes in vaginal tissue structure and function, which is characterized by decreased blood flow, atrophy of the muscular layer and attenuation of epithelial proliferation. These changes were also accompanied by alterations in sex steroid hormone receptors and key enzymes that regulate blood flow. Previous studies in the rat demonstrated that preservation of normal vaginal tissue structure and blood flow was dependent upon estrogen signalling (19). On a gross level, the histological and physiological changes in the study of Kim et al. resemble those observed in vaginal tissue from ovariectomized animals in previous studies (19, 20). Vaginal tissue from diabetic animals exhibited decreased ER· protein in the nucleus; it is likely that additional mechanisms that interfere with estrogen receptor signalling are triggered. This perspective is further supported by the observation that in vaginal tissue of ovariectomized animals, ER· increases in the nuclear compartment but decreases in the cytosolic compartment (19). DM also cause dysfunction of neuropathic and myopathic components of the pelvic floor (21, 22).

In this sample of postmenopausal women, the frequency of anterior vaginal defect stages 2 and 3 were reported in 87% of the group with obesity and diabetes, 73.1% of the group with obesity but not with diabetes, 58.3% of the group with diabetes but without obesity while only 19% of the postmenopausal women without obesity and diabetes developed anterior vaginal defect. A study by Boreham et al (23) showed that the fraction of smooth muscle in the anterior vaginal wall decreased significantly in women aged 60 years or older compared with that in women under 50 years old. Lin et al (24) investigated the changes in the connective tissues located in the upper portion of the anterior vaginal wall of women with or without prolapse and also found that quantitative immune reactivity of collagen I and III had significant positive correlations with aging. Collagen and elastin have been shown to be decreased or disordered in many women with POP (25). In terms of postmenopausal stage, any weakness of pelvic muscles results in increased load on pelvic ligaments and connective tissue (26).

Damage to the pudendal nerve by chronic or acute stretch injury, neurologic disease or diabetes weakens muscle strength in the pelvic diaphragm and increases the risk of prolapse (22, 27).

In accordance with our findings, chronic elevated intraabdominal pressure increase prolapse risk (28). Potential sources of increased intraabdominal pressure that have been associated with pelvic organ prolapse include obesity, chronic respiratory disease and/or related cough, chronic constipation, repetitive occupational activities, and pregnancy (3). For example, an analysis of the data from the US Women's Health Initiative (WHI; N: 27,342) reported that women with a waist circumference greater than 88 cm had an increased risk of cystocoele and rectocele (odds ratio (OR), 1.17; 95% confidence interval (CI), 1.06–1.29), but not of uterine prolapse (8). In a large population study in Italy (N: 21,449), uterine prolapse was associated with a body mass index (BMI) over 27.2 (OR, 1.6; 95% CI, 1.3–1.9) (5). Increased BMI was also implicated in a case-controlled study of women presenting for surgery (n: 160; OR for uterine prolapse in women with a BMI: 26 was 3.7; 95% CI, 2.1– 6.5) (29).

In our study we found that apical vaginal defect stages of non obese-diabetic, obese-diabetic and obese-non diabetic groups were significantly higher than non diabetic-non obese group and obese-diabetic and obese-non diabetic groups were also significantly higher than non obese-diabetic group. These outcomes show obesity and diabetes increases the risk factor for apical vaginal defect (uterine prolapse) Lawrence et al. (30) showed that the prevalence of stress urinary incontinence, anal incontinence, and any pelvic floor disorders increased in the following manner: non obese /non diabetic (lowest),

non obese /diabetic, obese / non diabetic, and obese / diabetic (highest), while women who were obese, regardless of whether they had diabetes, were most likely to have overactive bladder. Those results support our findings that women, who are obese, regardless of whether they have diabetes, are more likely to have anterior or apical vaginal defect slightly more than posterior vaginal defect. Other published studies have suggested that weight loss may reduce the prevalence of incontinence among this group of high-risk women (30). Given the aging of the population, the increased prevalence of obesity, and the concurrent increase in the prevalence of diabetes, women and health care professionals should be made aware of the associations between pelvic floor disorders and obesity and diabetes. Women who are obese, regardless of whether they have diabetes, should be advised that they may be more likely to develop a pelvic floor disorder associated with their weight and should be encouraged to adopt patterns of physical activity and dietary intake to promote healthy weight loss and maintenance of a healthy weight. Obesity and diabetes are independent modifiable risk factors for pelvic organ prolapse and this knowledge is important for the development of new treatment and prevention strategies of the patients with prolapse. However, obesity seems to become higher risk factor than diabetes itself for apical vaginal defect development. In our subjects, we found that obesity, regardless of having diabetes, increased the likelihood of having an anterior, apical and posterior vaginal defects compared with non-obese women.

The strength of this study is using a carefully validated instrument to assess a spectrum of vaginal defects in a large, postmenopausal population distributed across a wide age range including obese and non-obese women with or without diabetes. Obesity and diabetes are separetely risk factors in POP. POP has increased prevalans in diabetic postmenopausal women and obese postmenopausal women. However POP has more increased prevalans in diabetic obese postmenopausal women than obese postmenopausal women and diabetic postmenopausal women.

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