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Plasma Levels of Transforming Growth Factor-Beta 1 in Women with Pelvic Organ Prolapse

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Abstract

Objective: In women with pelvic organ prolapse (POP), decreased expression of transforming growth factor-beta 1 (TGF-β1) has been shown in POP tissues. However, no studies have evaluated plasma TGF-β1 levels in patients with POP, so it is unknown whether they are also changed or not. Therefore, we compared plasma TGF-β1 levels in women with and without POP. **Methods**: Participants were 49 women with POP and 23 healthy control women. All participants were postmenopausal. We measured plasma TGF-β1 and compared data between patients with POP and controls, and between patients with uterine prolapse (UP, n = 19) and those with a cystocele (CC, n = 30). In addition, in patients, we assessed the POP quantification system (POP-Q) stage. **Results**: Plasma TGF-β1 levels were significantly lower in patients than in healthy controls. POP-Q stage was not significantly different between the UP and CC subgroups, but POP-Q stage IV was diagnosed in 63% of patients with UP and 7% of those with CC. Plasma TGF-β1 levels were significantly lower in the CC subgroup than in the UP subgroup. **Conclusion**: Plasma TGF-β1 is decreased in POP. It remains unclear whether the lower levels indicate a reduction in systemic TGF-β1 activity, but they can be assumed to reflect reduced TGF-β1 expression in POP tissues.

Keywords

Cystocele, Pelvic Organ Prolapse, Transforming Growth Factor-Beta 1 (TGF-β1), Uterine Prolapse

1. Introduction

Pelvic organ prolapse (POP) is characterized by the weakening of pelvic supportive tissue in women, which leads to prolapse of the uterus, bladder, and rectum outside the pelvis through the vagina [1]. POP, which is more common in older women, affects approximately 9% of women worldwide and greatly impacts their quality of life [2] [3]. A large community-based retrospective cohort study identified factors that increase the risk of POP, *i.e.* older age, postmenopausal status, higher parity, elevated intraabdominal pressure, and overweight [4] [5] [6]. In addition, a combination of support defects in the anterior, posterior, and apical vaginal segments and abnormalities of connective tissue structure or its repair mechanism might predispose women to develop POP [4] [5] [7]. Recent studies on POP have focused on the abnormal structure and organization of pelvic floor connective tissue and the molecular alterations in uterosacral ligaments [8] [9] [10]. Notably, a breakdown of the extracellular matrix is commonly reported [11] [12], and this process was shown to decrease the strength of supportive structures and contribute to the pathogenesis of POP [13] [14]. However, the exact molecular mechanisms underlying the breakdown of the extracellular matrix are not yet fully understood.

The cytokine transforming growth factor-beta 1 (TGF-β1) remodels the extracellular matrix by regulating multiple enzymes and extracellular matrix components [15]. In women with POP, decreased expression of TGF-β1 has been shown in fibroblasts, the pubovaginal fascia, and cardinal ligament tissues [16] [17] [18] [19] [20]. The expression level of TGF-β1 is positively correlated with collagen expression [20], so low levels of TGF-β1 expression might be associated with the occurrence of POP. To date, no studies have evaluated plasma TGF-β1 levels in patients with POP, so it is unknown whether they are also decreased. Therefore, this study compared plasma TGF-β1 levels in women with POP and healthy control women.

2. Participants and Methods

Participants (N = 72) were 49 female patients (49 - 85 years old) who were diagnosed with POP between December 1, 2011 and March 31, 2013, and 23 healthy female controls (49 - 75 years old). Patients were selected from women attending a consultation at the Department of Urology at Okinawa Kyodo Hospital for that period. POP and POP quantification system (POP-Q) stage [21] were diagnosed by cystography and pelvic examination, and patients were asked whether they had stress urinary incontinence. Inclusion criteria for the POP patient group included POP-Q stage 2 or greater prolapse, as assessed by a single physician (K.K), and a plan for surgery by the same physician to treat the symptomatic prolapse. Healthy controls were volunteers without urinary tract symptoms who were recruited from Kitakami Central Hospital staff (nurses, helpers, and clerks) and their families for the period between December 1, 2012 and March 31, 2013.

All participants were postmenopausal and had no other urological or gynecological illnesses, diabetes, or hypertension. In all participants, blood was drawn at study visits, outpatient visits, or on admission for surgery, and plasma TGF-β1 was measured by enzyme-linked immunosorbent assay (SRL, Inc., Tokyo, Japan). Height, body weight, and body mass index (BMI) were also measured. Data were compared between patients with POP and healthy controls and between patients with uterine prolapse (UP) and those with a cystocele (CC).

This was a multicenter clinical study. The study was approved by the ethics committee of Okinawa Kyodo Hospital on behalf of all participating institutions (approval No. 2010-005). Before enrollment, all participants were given a detailed explanation of the objectives and methods of the study and gave their written consent.

Results are expressed as the mean ± standard deviation (SD). The unpaired *t* test was used for statistical analysis, and the p-value of less than 0.05 was used as the threshold for significance.

3. Results

Although all participants were postmenopausal, the healthy controls were significantly younger than the patients (Table 1). They were also significantly taller, but body weight and BMI were not significantly different between the two groups. In healthy controls, plasma TGF-β1 levels did not correlate with age, height, weight, or BMI (Table 2). Plasma TGF-β1 levels were significantly (p = 0.027) lower in patients (6.3 ± 3.6 ng/mL) than in healthy controls (8.1 ± 5.7 ng/mL) (Figure 1).

Table 1. Basic characteristics of women with pelvic organ prolapse (POP) and healthy control women (Controls).

	Controls (n = 23)	POP patients (n = 49)	p-value
Age (years old)	56.4 ± 7.5	66.3 ± 8.6	<0.001
Height (cm)	154.1 ± 3.7	148.5 ± 5.4	0.010
Weight (kg)	52.4 ± 5.5	54.7 ± 8.1	0.234
BMI (kg/m^2)	22.1 ± 2.7	24.5 ± 3.4	0.061
TGF-β1 (ng/mL)	8.1 ± 5.7	6.3 ± 3.6	0.027

Table 2. Relationship between age, height, weight or BML (x) and plasma TGF-β1 levels (y) in healthy controls.

x	y = plasma TGF-β1	Correlation coefficient
Age	y = −0.162x + 17.4	r = 0.197
Height	y = 0.658x − 92.5	r = 0.411
Weight	y = −0.374x + 28.4	r = 0.291
BMI	y = −0.982x + 30.6	r = 0.395

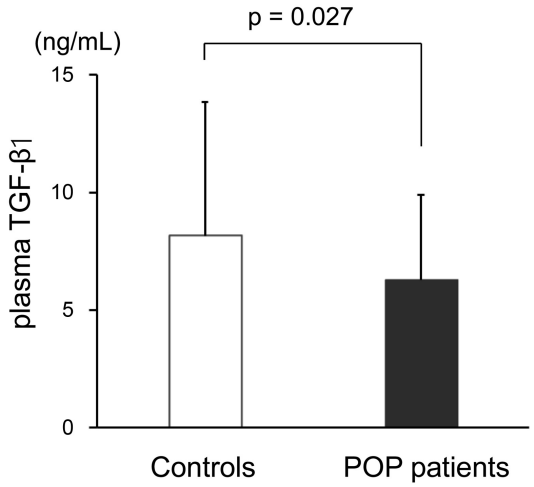

Figure 1. Comparison of plasma TGF-β1 levels between women with pelvic organ prolapse (POP, n = 49) and healthy control women (Controls, n = 23). Plasma TGF-β1 levels were significantly (p = 0.027) lower in POP patients (6.3 ± 3.6 ng/mL) than in healthy controls (8.1 ± 5.7 ng/mL) (Mean ± SD).

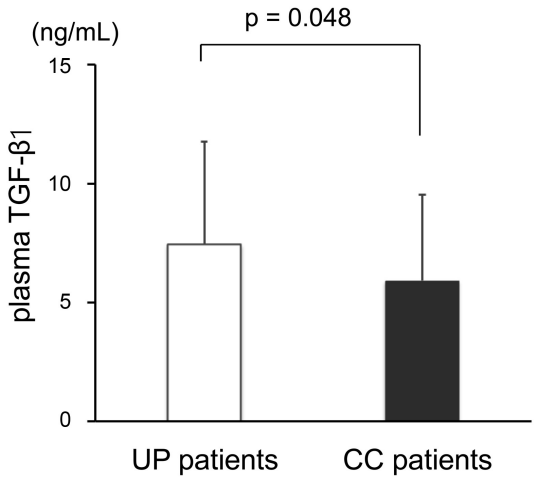

Figure 2. Comparison of plasma TGF-β1 levels between women with uterine prolapse (UP, n = 19) and those with a cystocele (CC, n = 30). Plasma TGF-β1 levels were significantly (p = 0.048) higher in the UP group (7.4 ± 4.3 ng/mL) than in the CC group (5.9 ± 3.6 ng/mL) (Mean ± SD).

Among the patients, 19 had UP and 30 CC. We found no significant differences in age, BMI, parity, and presence or absence of stress urinary incontinence between the two subgroups (**Table 3**). Although POP-Q stage was also not significantly different between the two subgroups, POP-Q stage IV was diagnosed in 63% of patients with UP but in only 7% of those with CC. Plasma TGF-β1 levels were significantly (p = 0.048) higher in the UP group (7.4 ± 4.3 ng/mL) than in the CC group (5.9 ± 3.6 ng/mL) (**Figure 2**).

Table 3. Basic characteristics of women with uterine prolapse (UP) and those with a cystocele (CC).

	UP patients (n = 19)	CC patients (n = 30)	p-value
Age (years old)	66.2 ± 7.4	66.3 ± 9.4	0.425
BMI (kg/m^2)	24.2 ± 3.4	25.3 ± 3.3	0.121
Parity (times)	3.6 ± 1.0	3.6 ± 1.0	0.389
POP-Q stage			
II	2 (11%)	4 (13%)	0.320
III	5 (26%)	24 (80%)	
IV	12 (63%)	2 (7%)	
Presence of stress urinary incontinence			
Yes	11 (58%)	13 (43%)	0.191
No	8 (42%)	17 (57%)	
TGF-β1 (ng/mL)	7.4 ± 4.3	5.9 ± 3.6	0.048

4. Discussion

The present study aimed to clarify whether plasma TGF-β1 levels are also decreased in POP patients, similar to TGF-β1 levels in POP tissues. Although the healthy controls were significantly younger than the patients, all participants were postmenopausal, and plasma TGF-β1 levels did not correlate with age, height, weight, or BMI in the healthy controls; consequently, it was determined that the healthy female volunteers were suitable as controls for patients [22]. Plasma TGF-β1 levels were significantly lower in patients than in healthy controls. This result is consistent with previous findings of reduced TGF-β1 expression in the pubovaginal fascia and cardinal ligament tissues of patients with POP [16]-[20]. Moreover, among the patients, plasma TGF-β1 levels were significantly lower in the CC group than in the UP group, indicating that plasma TGF-β1 levels might reflect TGF-β1 expression in the pelvis.

TGF-β1 is involved in the synthesis of the extracellular matrix and the inhibition of matrix metalloproteinases. Furthermore, sustained elevations of TGF-β1 have been associated with multiple other pathological conditions, such as pulmonary fibrosis, keloid formation, coronary artery restenosis, and acute respiratory distress syndrome [23]. Thus, although the molecular mechanism of TGF-β1 remains unclear, TGF-β1 expression is enhanced in conditions with increased fibrosis in tissue. Increased mechanical strain can reduce the expression of TGF-β1 [23] [24], so it is understandable that both collagen and TGF-β1 expression are reduced in POP tissues [10]. However, TGF-β1 expression was reported to be increased in the fascia of inguinal hernias [25] and POP tissues of higher stage POP (POP-Q stage IV) but not lower stage POP (POP-Q stages II and III) [22]. These

findings are interesting because both inguinal hernias and POP are associated with a loss of fascial support, so the pathophysiology of the two conditions might be similar [22]. In the present study, POP-Q stage IV was diagnosed in 63% of patients with UP and 7% of those with CC, and plasma TGF-β1 levels were significantly higher in the UP group than in the CC group; these results indicate that UP and CC may differ in the degree of TGF-β1 involvement in their disease progression.

Several diseases have been reported to be associated with elevated plasma TGF-β1, including schizophrenia [26], astrocytoma [27], open-angle glaucoma [28], advanced or metastatic cancers [29]-[33], chronic pancreatitis [34], atrial fibrillation [35] and hypertension [36] [37], and many of these diseases also show elevated TGF-β1 expression in the pathogenic tissues. However, we were unable to find any reports on diseases where plasma TGF-β1 is decreased, and the only study that found decreased plasma TGF-β1 was on physical exercise [38]. Hence, to the best of our knowledge this is the first report of a disease in which plasma TGF-β1 is decreased. The question whether decreased plasma TGF-β1 levels indicate a reduction in systemic TGF-β1 activity is unclear, but they can be assumed to reflect reduced TGF-β1 expression in POP tissues.

Angiotensin II subtypes 1 receptor antagonists and angiotensin-converting enzyme inhibitors inhibit TGF-β1 activity [36]. Tranilast, an anti-allergic agent and keloid treatment, also suppresses TGF-β1 activity [39]. Tranilast results in thinning of the bladder wall, causing interstitial cystitis-like symptoms [40]. Therefore, future studies may be able to evaluate whether these drugs affect the onset of POP by measuring plasma TGF-β1.

This study has some limitations. The number of controls was small, and age was significantly different between patients and controls, although all participants were postmenopausal. Future studies are needed to evaluate whether plasma TGF-β1 levels change with age. Moreover, because we did not compare TGF-β1 expression in POP tissues and plasma TGF-β1 levels, our findings are preliminary.

5. Conclusion

Plasma TGF-β1 levels are significantly lower in patients with POP than in healthy controls and significantly lower in patients with CC than in those with UP. It remains unclear whether the lower levels indicate a reduction in systemic TGF-β1 activity, but they can be assumed to reflect reduced TGF-β1 expression in POP tissues, especially in CC tissues. Future studies may be able to measure plasma TGF-β1 to investigate whether drugs affect connective tissue formation and the onset of POP.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

BMI: Body Mass Index;
CC: Cystocele;
POP: Pelvic organ Prolapse;
POP-Q: POP Quantification System;
SD: Standard Deviation;
TGF-β1: Transforming Growth Factor-Beta 1;
UP: Uterine Prolapsed.