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Preoperative Urodynamic Parameters (Valsalva Leak Point Pressure and Maximum Urethral Closure Pressure), Urinary Collagen and Plasma Vitamin D Levels as Predictors of Mid Urethral Sling Surgery Outcome

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Purpose: To determine the best predictor of the mid urethral sling outcome we calculated the AUC of ROC curves of preoperative parameters, including Valsalva leak point pressure, maximum urethral closure pressure, urinary NTx (N-telopeptide of crosslinked type I collagen) and plasma vitamin D values (D2, D3 and D2 plus D3).

Materials and Methods: This was an ancillary study of TOMUS (Trial of Mid-urethral Slings) and the ValUE (Value of Urodynamics Evaluation) trial in which subjects underwent mid urethral sling surgery for stress urinary incontinence. Valsalva leak point pressure and maximum urethral closure pressure were measured in 427 subjects, whereas NTx, vitamin D2, vitamin D3 and vitamin D2 plus D3 levels were obtained from 150, 116, 115 and 116 subjects respectively. Outcome success was defined using identical outcome (subjective and objective) variables for all subjects. ROC curves with corresponding AUC values were compared.

Results: TOMUS and ValUE subjects were significantly different in age, body mass index, UDI (Urogenital Distress Inventory) scores. TOMUS subjects had a lower surgical success rate compared to ValUE subjects (66.3% vs 76.0%, $p = 0.03$). The AUC values of Valsalva leak point pressure, maximum urethral closure pressure, NTx, and vitamins D2, D3 and D2 plus D3 were 0.542, 0.561, 0.702, 0.627, 0.645 and 0.640, respectively. The AUC of NTx was significantly higher than the AUCs of Valsalva leak point pressure and maximum urethral closure pressure ($p = 0.02$ and 0.03 , respectively).

Conclusions: Urinary NTx was the best predictor of the mid urethral sling outcome. This test is not only noninvasive, it is also modifiable. Finding ideal modifiable risk factors prior to mid urethral sling surgery should be subject to future investigations.

Key Words: urethra, suburethral sling, urodynamics, biomarkers, outcome assessment (health care)

Abbreviations and Acronyms

MUCP = maximum urethral closure pressure

SUI = stress urinary incontinence

VLPP = Valsalva leak point pressure

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STRESS urinary incontinence is a symptom which, if bothersome, can be treated with a pessary, behavioral modification with pelvic floor rehabilitation or surgery, including mid urethral sling surgery, which is common. Before performing mid urethral sling surgery urodynamics may be performed. Recent studies have provided varying conclusions regarding the predictive role of urodynamics in patients treated for SUI.^{1–3} A secondary analysis of TOMUS concluded that women with VLPP or MUCP in the lowest quartile were twofold more likely to experience mid urethral sling failure.² However, in the large, randomized ValUE study of office evaluation for SUI with or without urodynamics in women undergoing surgery for SUI those who underwent urodynamics did not have a better mid urethral sling surgical outcome than patients with only the basic office examination only.³ UITN (Urinary Incontinence Treatment Network) findings showed that urodynamic results rarely altered the surgeon decision to cancel, change or modify surgical plans.⁴

A previous study indicated that mid urethral sling surgery was significantly less likely to fail in women with lower baseline urinary NTx.⁵ NTx is a biomarker for bone type I collagen turnover and higher levels of urinary NTx correlate with higher bone resorption. As vitamin D is critical for promoting overall bone and muscle health, NTx levels are potentially modifiable based on vitamin D metabolism. Prior studies have demonstrated that vitamin D deficiency was associated with a worse or a higher prevalence of urinary incontinence in women and men.^{6,7} Vitamin D deficiency would be associated with increased bone resorption and, thus, with higher levels of urinary NTx.

Performing a mid urethral sling procedure for uncomplicated SUI does not require objective testing. The ability to incorporate a laboratory based objective test that predicts mid urethral sling outcomes would allow for more personalized SUI care. The primary aim of this study was to measure the prognostic ability of urodynamic measures of incontinence (VLPP and MUCP) and markers of bone turnover (urinary NTx and plasma vitamin D levels, including D2, D3 and D2 plus D3) for predicting the mid urethral sling outcome using ROC curves. AUC values were calculated from the ROC of each of these preoperative tests. The AUC values were then used to assess the strength of each test for predicting the mid urethral sling surgical outcome.

MATERIALS AND METHODS

TOMUS was an equivalence trial that randomized subjects to a retropubic or a transobturator mid urethral

sling.⁸ The ValUE trial evaluated the usefulness of performing urodynamics in patients before surgical treatment of SUI.³ In that trial approximately 95% of patients received a mid urethral sling.³ Therefore, subjects in TOMUS and ValUE underwent similar treatments for SUI.

Standardized postoperative measures were collected on subjects in both trials, enabling the use of the same outcome definition of treatment success. Outcome success after mid urethral sling surgery was defined 12 months postoperatively as all of certain results in a subject, including a 70% decrease in the UDI score, a score of 1 or 2 on PGI-I (Patient Global Impression of Improvement) and a negative provocative stress test.

Because TOMUS and ValUE collected the same outcome measures, we used common definitions of success and failure in this analysis. However, we could only use preoperative VLPP and MUCP data on TOMUS subjects because by design half of the ValUE subjects did not undergo urodynamics and the other half who underwent urodynamics were not required to have VLPP or MUCP data recorded in the study. Conversely, preoperative urinary NTx and plasma vitamin D data could only be obtained from ValUE subjects because our biospecimen repository protocol by which urine and blood specimens were collected was not established until after all TOMUS subjects had already undergone mid urethral sling surgery.

The protocol to collect, store and perform urine and blood tests was approved by the institutional review board at each participating institution as part of the UITN consortium. Using this protocol preoperative urine and blood specimens could be obtained only in ValUE subjects since this protocol was activated after all TOMUS subjects had already undergone mid urethral sling surgery.

The ROC curves of VLPP and MUCP were constructed from data on 427 TOMUS subjects. The ROC curves of urinary NTx, and vitamins D2 and D3, and total D were constructed from specimens from a subset of ValUE subjects. Specifically, preoperative urinary NTx was collected from 150 subjects, and preoperative levels vitamins D2, D3 and D2 plus D3 were measured in 116, 115 and 116, respectively. Urinary NTx was measured with an Osteomark® enzyme-linked immunosorbent assay kit. Values normalized to urinary creatinine in mg/ml were also measured by enzyme-linked immunosorbent assay. Plasma vitamin D2 and D3 levels were measured by a liquid chromatography tandem mass spectrometry method that enabled separate measurements of vitamins D2 and vitamin D3, of which the sum provided total vitamin D.

Logistic regression was done to assess the association between the different vitamin D levels and the outcome, which was the 12-month failure rate, controlling for treatment group, age and concomitant surgery. ROC analyses were performed to determine whether there were obvious threshold values or cutoff points for each biomarker and the association with surgical outcome. Analysis was performed to compare the lowest quartiles of vitamin D2/vitamin D3/vitamin D2 plus D3 with the higher 3 quartiles. Each measure was log transformed to decrease skewness.

ROC analysis was calculated based on the 12-month failure rate. AUCs were calculated and then compared using large sample test methods. A predictive test is considered perfect at AUC = 1.0, an excellent (grade A) test is generally considered at 0.90 to 1.0, a good (grade B) test is 0.80 to 0.90, a fair (grade C) test is 0.70 to 0.80, a poor (grade D) test is 0.60 to 0.70 and a failed (grade F) test is 0.50 to 0.60.

RESULTS

The table shows a comparison of characteristics in the women who participated in TOMUS and the ValUE trial, and provided specimens for this study. TOMUS subjects were 2.5 years older ($p = 0.01$), 1.4 kg/m² heavier ($p = 0.01$) and scored 6.7 points higher on UDI ($p = 0.001$) compared to ValUE subjects. The surgical success rate was lower in TOMUS than in ValUE subjects (66.3% vs 76.0%, $p = 0.03$).

Figure 1 shows ROC curves of VLPP, MUCP and NTx normalized to urinary creatinine (AUC 0.542, 0.561 and 0.702, respectively). The AUC of NTx was significantly higher than that of VLPP ($p = 0.02$) and MUCP ($p = 0.03$). Mean \pm SD total vitamins D, D3 and D2 were 33.5 \pm 14.4, 30.3 \pm 13.8 and 5.2 \pm 13.0 ng/ml, respectively. Logistic regression analysis showed no significant association between any measured vitamin D levels (D2, D3 or D2 plus D3) and the mid urethral sling outcome (data not shown). Figure 2 shows the ROC curves of

preoperative vitamins D2, D3 and total D2 plus D3 (AUC 0.627, 0.645 and 0.640, respectively).

DISCUSSION

The impetus for this study was the prior finding that lower urinary NTx levels significantly decreased the odds of mid urethral sling surgery failure.⁵ Because NTx is a well-known marker of bone resorption, we also hypothesized that plasma vitamin D levels may also predict the mid urethral sling outcome since vitamin D has an important role in bone metabolism.

We also wished to characterize how urinary NTx as a predictor of the mid urethral sling outcome would compare to the more studied urodynamic parameters VLPP and MUCP. A recent systematic review concluded that "preoperative MUCP and VLPP values may add insight into postoperative outcomes after surgical treatment for SUI."⁹ However, patients with uncomplicated SUI randomized to a preoperative basic office evaluation had non-inferior SUI surgery outcomes compared to those randomized to preoperative urodynamics,³ suggesting a limited value of urodynamics.

The impact of the current study is that urinary NTx and plasma vitamin D levels are modifiable as well as relatively noninvasive tests whereas VLPP and MUCP are not. Our study shows that the noninvasive urinary NTx test was best for predicting postoperative mid urethral sling outcomes.

We used AUC values derived from ROC curves to compare the prognostic abilities of several biomarkers (NTx and vitamin D levels) and urodynamic parameters (VLPP and MUCP) to predict the surgical outcome. We found that urinary NTx with an AUC value of 0.702 was the best predictor based on the highest AUC. Therefore, urinary NTx is between fair to poor for predicting the mid urethral sling outcome. However, VLPP and MUCP with even lower AUC values (0.542 and 0.561, respectively) would be considered failed tests to predict the mid urethral sling outcome.

We expected plasma vitamin D levels to also predict mid urethral sling outcomes since NTx and vitamin D are related to bone metabolism/resorption. However, AUC values of the different forms of vitamin D were between the VLPP/MUCP and urinary NTx AUC values. We performed regression analyses of the levels of the different forms of vitamin D against the outcome, identical to that previously published for urinary NTx.⁵ However, logistic regression analysis revealed no significant associations between any vitamin D level (D2, D3 or D2 plus D3) and the mid urethral sling outcome.

The 2 subcohorts from TOMUS and ValUE used in this analysis were statistically different in age,

Baseline clinical and demographics factors in women in 2 trials

	ValUE	TOMUS	p Value
No. pts	150	427	
Mean \pm SD age	51.40 \pm 10.09	53.86 \pm 10.68	0.01
Mean \pm SD body mass index (kg/m ²)	28.79 \pm 5.17	30.19 \pm 6.69	0.01
% NonHispanic white	80.0	89.1	0.005
% Parous (1+ pregnancies)	96.7	95.6	0.56
Mean \pm SD mos incontinence	109.44 \pm 02.52	104.94 \pm 111.39	0.66
% Postmenopausal	47.3	54.3	0.15
% Current:			
Estrogen replacement therapy	31.9	44.2	0.04
Smoking	7.3	13.4	0.05
% Any nonsurgical urinary incontinence treatment history	58.7	53.2	0.25
Mean \pm SD post-void residual urine vol (ml)	19.15 \pm 23.50	23.51 \pm 4.18	0.10
Mean \pm SD UDI irritative symptoms	34.96 \pm 22.78	41.69 \pm 25.16	0.004
Mean \pm SD MESA (Medical, Epidemiological and Social Aspects of Aging) index:			
Stress	74.04 \pm 17.71	72.34 \pm 17.29	0.30
Urge	31.87 \pm 22.71	35.95 \pm 22.15	0.054
Mean \pm SD PGI-S	3.09 \pm 0.78	2.99 \pm 0.91	0.22
% UDI 70% decrease, PGI-I score 1 or 2 + neg stress test	76.0	66.3	0.03
% Pos 12-mo provocative stress test	7.3	14.7	0.02

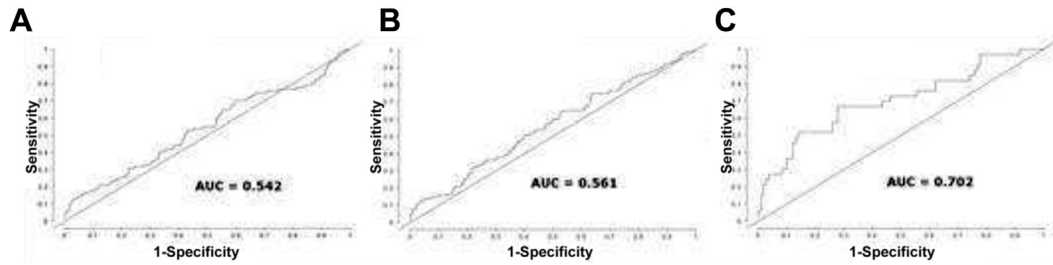


Figure 1. ROC curves and AUCs of VLPP (A), MUCP (B) and NTx (C)

body mass index, race, current estrogen replacement therapy, current smoking status, UDI irritative symptoms and surgical outcomes (see table). Some of these differences had minor clinical significance, such as the age difference (51 vs 53 years) and the body mass index difference (28 vs 30 kg/m²). However, the increase of 7 points in the UDI irritative score in the TOMUS over the VALUE subcohort might explain the lower success rate in the TOMUS subcohort. We previously determined that for every 10-point increase in the UDI irritative subscore the odds of objective surgical failure increased by 10%.¹⁰ It is difficult to speculate whether these population differences impacted the prognostic ability of the preoperative tests. To the extent that both of these subcohorts are generalizable to any SUI population undergoing surgery, the prognostic value of the diagnostic tests can be directly compared.

The plausibility of urinary NTx as a biomarker for urinary incontinence is supported by prior studies showing that vitamin D deficiency, a condition that would be associated with increased urinary

NTx, was associated with urinary incontinence in women and men.^{6,7} However, the precise mechanisms linking bone metabolism to urinary incontinence are unknown. It might be speculated that decreasing urinary NTx preoperatively could improve the mid urethral sling surgical outcome. Clinical trials have shown that pharmacological agents such as potassium citrate alendronate and estrogen significantly decrease urinary NTx in postmenopausal women, reflecting decreased bone resorption.^{11–13} Future improvements to surgical treatments of SUI should involve modulation of the relevant biological mechanisms.

CONCLUSIONS

Preoperative urinary NTx outperformed VLPP, MUCP and vitamin D levels for predicting the mid urethral sling surgical outcome based on AUC values. Further studies are needed to determine whether initiating strategies to decrease urinary NTx preoperatively would improve the mid urethral sling surgical outcome.

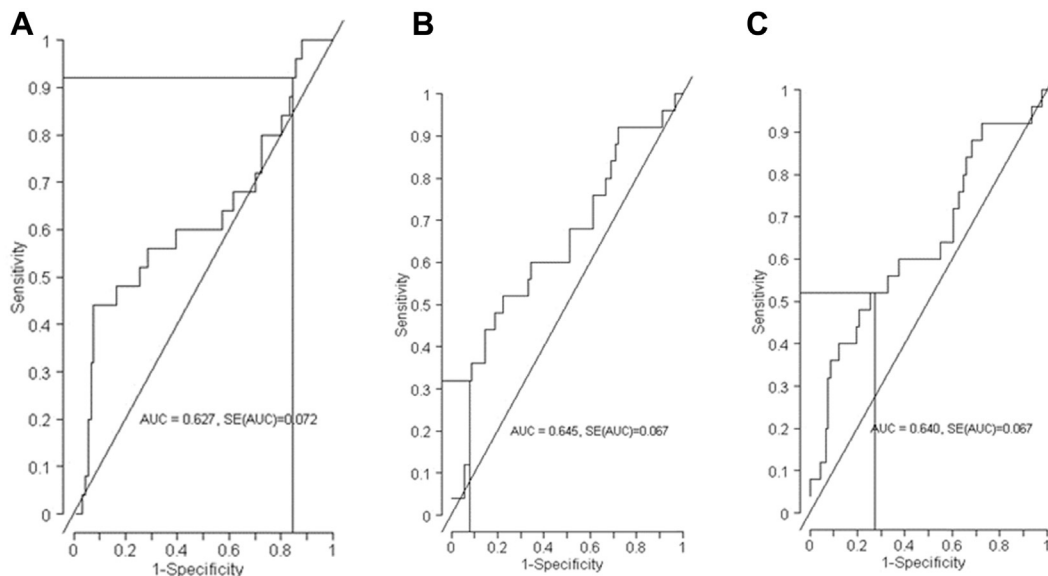


Figure 2. ROC curves and AUCs of vitamin D2 (A), D3 (B) and D2 plus D3 (C)

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