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.