Introduction
The pathophysiology of stress urinary incontinence (SUI) is both complex and multifactorial. However two prevailing mechanisms frequently used as reference points in discussing SUI are 1: loss of urethral support as evidenced by rotational decent of the proximal urethra and/or 2: loss of internal urethral integrity as evidenced by funneling within the proximal urethra. One or both mechanisms are present during episodes of increased abdominal pressure (stress) resulting in leaks.

Past and current treatment modalities for SUI have predominantly focused on addressing the first mechanism by restoring the anatomic positioning of the urethra, by either suspending the bladder neck from above and attaching it to ligamentous structures in the pelvis or by elevating the urethra from below using various synthetic and non-synthetic sling devices. Both of these support mechanisms restore the descended urethra to a point similar to its nascent anatomic position and/or reduce rotation during stress, but do not directly address the second important aspect of incontinence: the lost of internal urethral integrity and the resultant funneling of the proximal urethra.

In 2000, the use of trans-urethral non-ablative low-energy radiofrequency (RF) heating was identified as a possible solution for treating SUI primarily related to funneling of the proximal urethra. The method applies low-energy RF to cause heating (65ºC) at multiple small sites within the submucosal periurethral collagen of the proximal urethra. The focused application of RF energy to these sites denatures isolated foci of collagen within the treated periurethral tissue and reduces the functional compliance of this tissue without any changes to the gross anatomy. Continent function thereby improves as the compliance of the proximal urethra is changed. Subsequent studies in animal models and clinical trials in humans confirmed this hypothesis to be true and validated the concepts behind the Renessa® System.

The Renessa System described below uses this method of low-energy RF application to denature collagen in the submucosal tissue of the bladder neck and proximal urethra. The System consists of a compact RF generator and a single-use balloon-tipped transurethral probe with four needle electrodes which deliver energy into the periurethral tissue during a total treatment time of nine minutes.

This manuscript will review the evolution of RF application in soft tissue with specific focus on periurethral collagen as it relates to changes in the mechanical properties of the funneled proximal urethral tissue and the overall improvement of continent function in women.

Pathophysiology of SUI
In genuine stress incontinence, the intrinsic structure of the urethral sphincter is intact. However, with the loss of structural support from various surrounding ligaments, dense fascia, and muscles, its ability to close is greatly diminished. The descent of the vesicourethral junction from its normal resting position in the pelvis disrupts the uniform distribution of abdominopelvic pressures, causing the bladder to receive more pressure than the urethra; this increased intravesical pressure exceeds the ability of the urethra to remain closed. These rotational-descent related pressure changes have been clearly and causally associated with SUI. However, while this mechanism appears to be well defined, several authors believe that this factor alone does not provide a complete and comprehensive explanation of incontinence. 
A second mechanism of SUI, bladder neck funneling, also appears to be a significant contributory factor to SUI. In 2008 Schorge et al demonstrated using translabial ultrasound or voiding cystourethrogram that when persistent downward pressures were placed on the bladder, compromised urethral integrity was demonstrated by the presence of proximal urethral dilatation (funneling of the bladder neck). Furthermore, Hajebrahiemi concluded that bladder neck funneling was present significantly more frequently in women with SUI compared to women without incontinence (52.5% and 15%, p<0.01) [3].

In addition, a recent study evaluating funneling before and after the tension free vaginal tape (TVT) procedure for the management of SUI revealed that the continence rate was 57.5% in subjects with persistent postoperative funneling vs. 96.2% in those without postoperative funneling (P<0.0001). This same study found that the procedure’s success rate in those with preoperative funneling was 77.5% as compared to 96.6% in those without (P<0.0001) [2]. These results suggest a strong association between proximal urethral funneling and SUI. And although it cannot be definitively discerned whether funneling is itself causative of SUI, these studies do suggest that it plays an important role in SUI pathophysiology and treatment.

The Evolution of RF Application

First used in medicine almost 75 years ago, radiofrequency (RF) energy is an effective method of heating tissue and is well-known for its many applications and modern surgical tools such as the Bovie® and Ligasure™. Radiofrequency devices generate heat as a result of tissue resistance to the movement of electrons within the RF field as described by Ohm’s law (Fig. 1). Heat is produced in places where the current sees maximal resistance, such as at the electrode tip of a physician’s handpiece or applicator.

Figure 1:

\[ \text{Energy} = I^2 \times Z \times t \quad (\text{Ohm’s Law}) \]

Energy (heat) is generated by the tissue’s impedance (Z) of the movement of electrons relative to the amount of current (I) and time (t).

An important safety advantage of RF current (over previously used low frequency AC or pulses of DC) is that it does not directly stimulate nerves or heart muscle because the frequency is above the response times of these structures; typically between 100 kHz and 4 MHz.

Depending on the energy settings applied and the arrangement of the electrodes, RF can be used to generate high temperatures to cut, coagulate or ablate/necrose tissues, or lower temperatures to denature proteins. RF tissue ablation, as distinct from RF collagen denaturation, has been proven to be a safe and successful non-surgical modality for the treatment of benign prostatic hyperplasia [7], sleep apnea [8], menorrhagia [9] and hepatic metastatic disease [10].

However, there are situations where tissue ablation and necrosis is not desired. Notably, in the management of luminal barrier functional disorders such as stress urinary incontinence, fecal incontinence, and gastroesophageal reflux disease. For treating luminal structures, the application of lower temperature RF has been shown to successfully treat functional disorders through localized collagen denaturation while avoiding tissue necrosis [6; 7; 8]. Similar techniques of collagen denaturation are also being widely employed in dermatology for tissue tightening [20].

Urethral Collagen

The adult female urethra is approximately 4 cm long and 8 mm in diameter at rest [6]. It consists of an epithelial lining, a submucosal layer comprised of connective tissue and spongy venous sinuses enveloped by various layers of smooth and striated muscle.
A major component of the periurethral connective tissue is fibrillar type I collagen which is the most abundant protein in the human body and the main structural component of the extracellular matrix in connective tissue [9]. Biopsies of human female periurethral tissue have revealed the collagen content to be as high as 40% [10].
The “collagen molecule,” also known as tropocollagen, is produced by fibroblasts in the extracellular matrix. It is comprised of three polypeptide chains (known as alpha chains), which are stabilized into a triple-helix arrangement by extensive hydrogen and hydroxyproline bonds. These polypeptide chains are then assembled into a parallel pattern to form collagen fibers that are further stabilized into a quaternary structure by intermolecular covalent cross-links (Fig. 3) [11]. The end result is the organization of multiple collagen microfibrils that are interdigitated with neighboring microfibrils to create the crystalline structure of Type I collagen.

**Tissue Response to RF: Collagen Denaturation**

The effects of heating collagen are well described and can be partially reversible or irreversible as the protein goes through phase shifts from solid to liquid during heating and back to solid when cooling [12]. Moderate heating at temperatures in the range of 45-55 degrees C results in local unfolding within the protein due to the
breakdown of a limited number of heat-labile hydrogen bonds. Upon restoration of normal temperatures, the protein is able to return to its native structure. However, when collagen is heated to higher temperatures in the range of 65°C, larger domains of consecutive, intramolecular hydrogen bonds are broken, and the protein undergoes a transition from a highly-organized, crystalline structure to a random, gel-like state (denaturation). Concurrent with this denaturation is local shrinkage of the collagen which is thought to occur through the combined effects of the triple helix unraveling and the residual tension forces of the heat-stable intermolecular cross-links (Fig. 4) [13].

Multiple detection modalities have verified that the temperature required to irreversibly denature collagen begins at approximately 63°C [14]. Higher temperatures do not affect the maximal shrinkage, but they do decrease the time needed to reach optimal denaturation [15]. Other than temperature history, some other major factors that affect the kinetics of the denaturation process include mechanical load, specimen hydration, chemical environment, and molecular cross-linking. Although the precise mechanism of collagen denaturation is unknown, there is clear empirical evidence that irreversible shrinkage does occur and that it can be reliably calculated (see Fig. 5) [6; 18].

**Changes in Tissue Mechanical Properties and Continence Function**

In addition to size modification, the mechanical properties of collagenous tissues are also affected with denaturation. The overall extensibility, or maximum stretching distance, of the tissue is decreased as delineated by the change in axial stretch noted in Fig. 6 [16; 19].

On the macroscopic scale of the urethra, a decrease in the extensibility of the treated tissue translates to a decrease in urethral tissue compliance. In order for the urethra to dilate to the same diameter as before, the treated tissue would reach its maximum stretching limit first. Then, the remaining untreated tissue would need to stretch over a longer distance to compensate for the
treated tissue’s decreased length. Thus, 1) more pressure will be required to dilate the urethra to the same diameter than before, and 2) the maximum diameter of the expanded urethra will also be decreased. Another way of conceptualizing this is that the treated tissue acts as a lattice work around the urethra that limits the lateral excursion of the tissue once it has expanded beyond a certain diameter (Fig. 7). Additionally, with the smaller maximum diameter, the surrounding urethral muscles will not be stretched to the same extent as before, allowing them to function more effectively [17]. This, in turn, leads to a decrease in funneling and an increase in the functional length of the urethra. Thus, a decrease in the periurethral tissue compliance not only plays a passive role in urinary continence; it also contributes to the active functioning.

**Histologic and Anatomic Changes Associated with Collagen Denaturation**

The anatomic and histologic changes associated with low energy RF applications to the proximal urethra were well described in early studies using porcine animal models [4]. As shown below the placement of low energy RF heat into the proximal urethra causes the heated areas of collagen to denture. The gross anatomic manifestations of these changes as seen in the porcine model are identified acutely by the creation of 1–2 mm diameter regions of inflammation at the sites where the RF electrode tips were located.

In the submucosal periurethral tissue the histologic changes at 90 days demonstrate 36 small islands of denatured collagen approximately 200 microns in size.

Recent tissue culture studies by the author suggest that areas treated by 65°C heat might be associated with an up-regulation in collagen biosynthesis similar to the up-regulation seen in facial treatments with RF. This combination of collagen denaturation and the resultant isolated shrinkage of collagen coupled with the up-regulation of collagen biosynthesis suggest a very robust and elegant mechanism for the treatment of SUI.

**Suggested Clinical Application of Mechanism of Action**

Although continent function has been both reestablished and improved in patients following treatments with Renessa as demonstrated by Leak Point Pressure, pad weight tests, pad count records and validated QOL questionnaires, the precise mechanism of action as it pertains to changes in the funneling characteristics of the proximal urethra remain poorly defined. Recent 4D sonographic imaging studies by Lukban (Private correspondence and studies in progress) suggest that the application of low energy RF heat to the proximal urethra in 36 well defined sites as shown in the following diagram has resulted in changes to the proximal urethra during valsalva maneuvers which are visible by sonographic imaging.
This resultant change in the compliance characteristics of the urethra as evidenced by a diminished lateral excursion of the proximal urethra with valsala is also associated with improvement in continent function. The above diagrams illustrate the urethra in a pre and post treatment state.

The above sonographic images demonstrate the changes in bladder neck funneling seen post-Renessa. The pre-treatment image shows pronounced funneling at the bladder neck during Valsalva, while the post-treatment image shows a decrease in funneling during Valsalva.

**Summary**

Stress urinary incontinence is currently considered to be a problem of inadequate urethral support and/or reduced urethral integrity. Radiofrequency energy heating, which has a long-proven track record in medicine, can be used as a safe and effective treatment modality for SUI by addressing urethral integrity (bladder neck funneling). When collagenous urethral tissue is heated with RF to low temperatures, the collagen is denatured, resulting in changes in mechanical properties at the macroscopic level. The resulting decrease in periurethral tissue compliance leads to less lateral excursion of the luminal diameters in treated tissues when compared to untreated tissues exposed to the same intraluminal pressures. With these changes in compliance the functional continent mechanism is improved in women suffering from SUI.

**About the Authors**

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Dr. Takacs is Professor of Obstetrics and Gynecology at the University of Miami, Miller School of Medicine and the Director of Gynecological Translational Research. He completed a fellowship in Female Pelvic Medicine and Reconstructive Surgery (Urogynecology) at the University of Miami. He is an avid researcher with a PhD in clinical immunology and over 10 years of clinical experience. He has authored numerous publications and presented at national and international scientific meetings. He currently conducts research in the pathophysiology of pelvic organ prolapse and urinary incontinence. Dr. Takacs specializes in treating women with pelvic organ prolapse, urinary incontinence, voiding disorders, painful bladder conditions, and recurrent urinary tract infection.

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References


