Direct mechanical characterisation of prostate tissue – a systematic review

Title

Authors

Niall P Kelly, Hugh D Flood, David A Hoey, Patrick A Kiely, Subhasis K Giri, J Calvin Coffey, Michael T Walsh.

Affiliations

Niall P Kelly¹,²,³, Hugh D Flood¹, Patrick A Kiely²,³, David A Hoey⁴,⁵, Subhasis K Giri¹, J Calvin Coffey², Michael T Walsh³.

1. Department of Urology, University Hospital Limerick, Limerick, Ireland
2. Graduate Entry Medical School, University of Limerick, Limerick, Ireland
3. BioScience BioEngineering Research (BioSciBER), Health Research Institute (HRI), Bernal Institute, School of Engineering, University of Limerick
4. Trinity Centre for Bioengineering, Trinity Biomedical Sciences Institute, Dept. of Mechanical and Manufacturing Engineering, School of Engineering, Trinity College Dublin, Ireland
5. Advanced Materials and Bioengineering Research Centre, Trinity College Dublin & RCSI

Corresponding Author

Niall Kelly Niall.kelly@ul.ie, niall.p.k@gmail.com +353-87-6646005

MS1-013-033, Materials and Surface Science Institute, University of Limerick, Limerick, Ireland

Department of Urology, University Hospital Limerick, Limerick, Ireland

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NP Kelly Study conception and design: Acquisition of data: Analysis and interpretation of data: Drafting of manuscript
HD Flood Study conception and design:
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MT Walsh  Study conception and design: Drafting of manuscript: Critical revision:

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Direct mechanical characterisation of prostate tissue – a systematic review

Abstract

Background

Direct mechanical characterisation of tissue is the application of engineering techniques to biological tissue to ascertain stiffness or elasticity, which can change in response to disease states. A number of papers have been published on the application of these techniques to prostate tissue with a range of results reported. There is a marked variability in the results depending on testing techniques and disease state of the prostate tissue. We aimed to clarify the utility of direct mechanical characterisation of prostate tissue in identifying disease states.

Methods

A systematic review of the published literature regarding direct mechanical characterisation of prostate tissue was undertaking according to PRISMA guidelines.

Results

A variety of testing methods have been used, including compression, indentation and tensile testing, as well as some indirect testing techniques, such as shear-wave elastography. There is strong evidence of significant stiffness differences between cancerous and non-cancerous prostate tissue, as well as correlations with prostate cancer stage. There is a correlation with increasing prostate stiffness and increasing lower urinary tract symptoms in patients with benign prostate hyperplasia. There is a wide variation in the testing methods and protocols used in the literature making direct comparison between papers difficult. Most studies utilise ex-vivo or cadaveric tissue, while none incorporate in vivo testing.

Conclusion

Direct mechanical assessment of prostate tissue permits a better understanding of the pathological and physiological changes that are occurring within the tissue. Further work is needed to include prospective and in vivo data to aid medical device design and investigate non-surgical methods of managing prostate disease.
Direct mechanical characterisation of prostate tissue – a systematic review

1. Introduction

Direct mechanical characterisation of a biological tissue allows for an objective assessment of the stiffness of that tissue, and this can be linked to histological changes within the tissue. This utilises engineering techniques to establish the stiffness or elasticity of a tissue, which can alter in response to changes at a cellular level. This is a confirmation of the findings of clinical palpation, a subjective assessment of changes that occur within a tissue or organ in response to physiological and pathological processes, which affect not just cells, but also the surrounding extracellular matrix niche. The results of direct mechanical characterisation can be used to improve methods of diagnosing, staging, treating and understanding disease.

Prostate cancer is the most common cause of cancer in men and the 3rd most common cause of cancer death\(^1\). However, the prevalence of benign prostatic hyperplasia (BPH) and its effects on the lower urinary tract system are significantly more common and will affect all men to some degree as they age\(^2\). The digital rectal examination (DRE) of the prostate remains an integral part of the clinical evaluation of a urology patient and can be used to identify a possible malignant change in a prostate gland. The use of DRE is currently advocated in the main guidelines for the diagnosis of prostate cancer. There are however well-published inter- and intra-observer variability with DRE results, with specificity of the examination for prostate cancer as low as 40%\(^3\). Neither a positive nor negative DRE test result is sufficient to enable a conclusive diagnosis without further evaluation\(^4\). Thus, improving upon the inaccuracies associated with DRE are of important interest to the assessment, monitoring and understanding of prostate-related diseases. This can be achieved with direct mechanical characterisation of the tissue.

The aim of this review is to evaluate the methods of direct mechanical characterisation of prostate tissue, and to a lesser extent, the indirect methods, with respect to the different prostate processes. We explore the literature associated with the various techniques of tissue mechanical characterisation and compare the results obtained for the varying histological prostate diagnoses. We also review the mechanical characterisation literature with respect to patient-reported prostate-related symptoms. Finally, we review some of the methods of management that incorporate tissue mechanical properties in their methodology.

2. Methods

2.1. Study Design
A systematic review was performed following PRISMA guidelines using the search engines PUBMED and SCOPUS and the search terms "(((prostat* AND (mechanic* OR tensile OR compress* OR indent* OR elastic* OR modulus OR stiff*) AND (symptoms))))". The latest search was performed on 6th December 2017. Searches were limited to the English language.

Institutional review board approval was not sought as this study was a systematic review.

2.2. Eligibility Criteria

The titles and abstracts of all 1530 potentially suitable studies were inspected, articles meeting the inclusion criteria were retrieved and reviewed by one reviewer (NK). The reference lists of retrieved papers were further screened for additional eligible publications. The results of the process are illustrated in the PRISMA flowchart [Fig 1].

Inclusion criteria for this review were:

- Studies which characterised human prostate tissue using direct mechanical or indirect imaging-based characterisation techniques
- Studies assessing benign or cancerous prostate tissue.

Excluded from the review were:

- Studies which characterised prostate cells or cell lines
- Studies relating to non-human prostates
- Studies which did not report values used for mechanical assessment.

2.3. Data Extraction

The following information regarding each eligible trial was recorded: author’s names, journal, year of publication, tissue source (cadaveric, transurethral prostatectomy, radical prostatectomy), additional steps used, site of testing, reported elastic moduli (EM) and standard deviations. Data regarding lower urinary tract symptoms (LUTS) was also collected if available. Reviewed manuscripts that met inclusion criteria were categorised into two groups, with further internal divisions:

Studies investigating mechanical properties using direct assessment methods, including

- Compression testing
- Indentation testing
- Tensile testing
Studies investigating mechanical properties using indirect imaging-based characterisation techniques, including

- Elastography
- Resonance testing

2.4. Statistical Analysis

Due to the heterogeneous nature of the available literature and lack of randomised controlled trials a formal meta-analysis was not conducted, and statistical analysis was limited.

3. Methods of Mechanical Characterisation

Several different modalities have been reported in the assessment of the mechanical characteristics of the prostate. These can be broadly divided into 2 groups, direct mechanical testing and indirect assessment. Direct testing involves applying a force directly on the tissue and recording the resulting deformation. The load-deformation curve can then be converted to a stress-strain curve from which an elastic modulus (EM), a measure of tissue stiffness, can be calculated (Figure 2). By contrast, indirect characterisation utilises mathematical models to infer tissue stiffness because of the application of a variety of stimuli to the tissue. Indirect assessment methods have recently been reviewed by Good et al.\(^5\)

3.1. Direct characterisation

There are 3 main methods of direct characterisation of prostate tissue reported in the literature, compression testing, indentation testing and tensile testing. Figure 3 provides a brief schematic detailing the process by which these methods work.

3.1.1. Compression testing

Compression testing involves the application of a force over a whole sample, that is, where the sample is smaller than the compression plate. These are usually tested in an unconfined manner\(^6\) so that there is no restriction on the deformation the tissue may undergo. However, there are a number of other factors that have to be taken into account, such as friction between the compression plate and tissues, which require complicated biomechanical calculations. Thus, there are fewer publications on the use of compression testing on biological tissues, especially on non-weight-bearing tissues such as the prostate. Krouskop et al. is the only publication which performed compression testing on prostate tissue, and indeed was one of the first papers to perform direct mechanical testing of any method on prostate tissue\(^7\). Testing was performed on small samples of tissue cut from a prostate gland within 30 minutes of resection and findings were confirmed with histology. They compared EM of tissue from cancerous and non-cancerous prostates, and the EM of tissues from different areas
of the prostate. There was no difference in the EM between the anterior and posterior portions of the normal prostate gland. There was however a significant difference in the EM of the cancerous and non-cancerous prostate, with cancer being stiffer, confirming the long-held understanding about the changes that occur within tissues at the development of malignancy as detected on clinical palpation. These findings were replicated in breast tissue within the same article.

3.1.2. Indentation testing

Indentation testing is the process by which the mechanical properties of a tissue are evaluated by the application of a force through the tip of the indenter, which have a much smaller geometry than the tissue to which it’s being applied (Figure 3). There is maximum deformation of the tested tissue at the point of indentation, which decreases radially from the tip, giving the most accurate values to the area of tissue closest to the tip.

There are similarities in the method of indentation testing and the clinical digital rectal examination (DRE) of the prostate. Kowalik et al. used indentation assessment to identify the parameters required for an abnormality to be detected on DRE. They identified the elastic properties of cancerous lesions in surgically-removed prostate glands and then developed a prostate simulator to mimic these findings. They found that while the EM of prostate tissue, as detected by the indenter, correlated with tumour stage, there needed to be a difference of at least 50kPa between normal and cancerous prostate tissue before it could be detected on a DRE. Furthermore, the abnormality needed to be at least 7.5mm in diameter before it could be palpated. This provided some objective data as to the utility of the DRE in cancer detection.

The DRE however remains an important aspect of the evaluation of a patient with prostate-related conditions, both benign and malignant, despite having poor sensitivity and being subject from significant inter- and intra-observer variability. Some groups have attempted to eliminate this variability via the development of robotically controlled probes for assessing the prostate. These would produce objective data and laboratory-based experiments have demonstrated good success, though it has not been introduced to clinical practice. Ahn et al. have published a series of papers regarding their efforts to map the mechanical properties of the prostate to improve prostate cancer detection. In one paper, mechanical properties from 735 sites across the posterior surface of 35 ex-vivo prostates were compared with the histological findings. As with Krouskop previously, there was a significant difference between the cancerous and normal prostate tissue. Ahn also showed that there was no significant difference in the mechanical properties of different areas of the posterior surface of the prostate,
as long as the histopathology was the same\textsuperscript{12}. Carson et al.\textsuperscript{13}, Phipps et al.\textsuperscript{14} and Yang et al.\textsuperscript{15} reported similar findings, though they used different testing rigs as compared to the robot indenter of Ahns studies.

An aim of this work is to try to improve upon the sensitivity of trans-rectal prostate biopsies which, due to the random nature of the biopsy protocol, can miss smaller cancers. Ahn et al. took indentation testing results further and applied them to a robotic-based prostate biopsy device which can obtain mechanical information about the target tissues, that can then be used to localise suspicious areas for biopsy\textsuperscript{16}. While some success in phantom models was achieved, tests on ex-vivo prostates yielded poorer results, with sensitivity of the robotic-indenter reaching only 42\% and thus further work on this is required, in particular to account for the potential effect that the presence of rectal wall tissue and Denon Villiers fascial tissue may have on the probe. These tissue layers are found between the prostate and probe in vivo but would not have been present during the indenter bench tests.

Hoyt et al. compared indentation testing of radical prostatectomy specimens with sonoelastographic results, a form on indirect testing, and the histological findings\textsuperscript{17}. There were again significant differences between cancerous and non-cancerous tissue, as well as a level of agreement between the testing modalities (indentation and elastography) to suggest that elastography could have a place in the characterisation of the prostate. This was one of the first papers to link direct mechanical testing with indirect tissue assessment. The group repeated the experiment to compare indentation and crawling wave estimation with highly congruous results between the two modalities\textsuperscript{18}. Murayama et al.\textsuperscript{19} performed a similar study using indenter tests to validate a micro-tactile resonance-based sensor for establishing elastic properties.

Indentation testing has some limitations however. While it most directly mimics the DRE, a number of the previous papers use simplified assumption that prostate tissue is homogenous and linear, and this has consequences for the interpretation of the results obtained. Kim et al.\textsuperscript{20} attempted to address this by applying a number of models to the indenter results obtained. While there was again a significant difference between benign and cancerous prostate tissue, there was a wide range in the absolute values reported, depending on the model used, highlighting the difficulties associated with indentation testing. Furthermore, the heterogeneity of biological tissues can make it difficult to generalise the results of indentation testing to a whole tissue sample, which is of particular concern in the development of a diagnostic device or method, as has been the aim of a number of the previous papers. The size of the indenter tip is of importance here. Results using a small tip may miss possible cancerous regions and could be associated with a significant time commitment to complete the
testing, while using larger size tips may fail to discern abnormal regions from normal due to a lack of sensitivity. Thus, significant work is required to improve indentation as a method of tissue diagnoses for prostate cancer, 3.1.3.  

**Tensile Testing**

Tensile testing involves stretching a sample held securely between two grips and has an advantage over compression and indentation testing in that it can better accommodate sample irregularities and allows for the bulk of the sample being assessed to be included in the analysis.

Ma et al. performed tensile testing on samples of peri-urethral prostate tissue from prostates removed as part of a prostatectomy for prostate cancer. They identified a correlation between the stiffness of prostate tissue and the subjective symptoms scores recorded by the patients. The stiffness was further correlated with the collagen content and fibrosis of the peri-urethral tissues, and it was proposed that this may be a cause for the development of obstructive urinary symptoms. Kelly et al. subsequently performed tensile testing on prostate tissue retrieved from symptomatic patients at the time of transurethral resection of the prostate (TURP) and identified a similar correlation between symptoms and the tensile properties of the prostate tissue. They also found, as in the Ma study, that there was no statistically significant relationship between the prostate tissue stiffness and glandular content in the tissue specimens, but they did identify a negative relationship between the patient age and prostate stiffness, with older patients having softer prostates. This is similar to results found in other studies of ageing-process-related changes that occur within collagens with time and may be an explanation as to the findings reported.

Tensile testing results tend to be higher than compression or indentation results, and this is seen in the reported results for prostate tissue as depicted in Figure 4. The higher values are thought due to the presence of other tissue products, such as extracellular matrix proteins or the effect of constrained water, which are included in tensile testing due to measurements across the tissue bulk but excluded from indentation testing. While indentation testing likely has a role in differentiation of histological types of prostate tissue and can probably help in the detection of prostate cancer if the aforementioned limitations are addressed, the data from tensile testing gives an overall picture of the mechanical properties of this heterogeneous tissue. This can be used to better reflect the contribution that mechanical properties may have on the gland as a whole and thus the effect that the gland may have on patient symptoms and the obstructive nature of lower urinary tract symptoms.

3.2.  **Indirect characterisation**
Alternative methods of tissue characterisation have been developed that do not involve direct tissue testing. The most discussed techniques involve imaging-based technologies, which include ultrasound and magnetic resonance elastography. These have been extensively reviewed by Good et al. In brief, the technology is based on the monitoring for changes to the images, taken either by US or MR, in response to the application of a force or compression wave. The application of a compression wave changes the morphology of the tissue, with stiffer tissue experiencing less change than flexible tissue. Crawling-wave elastography is a variation on ultrasound-based sonoelastography, where the interference of two waves of different frequencies from separate sources on the tissue are detected by a third probe. Crawling wave elastography has slightly higher sensitivity than sonoelastography. Figure 2 is a schematic showing how the technologies work.

Tactile resonance methods and other related resonance techniques are another form of indirect characterisation. Changes in resonance frequencies are detected by a probe placed in contact with a tissue, and these can be related to the elasticity of the tissue. These have had some success in detecting areas of abnormality, some of which correspond to cancerous regions, but a widespread roll-out of the technology has not occurred, primarily due to a lack of clinical-trial based data.

3.3. In-vivo characterisation

The bulk of the literature on prostate mechanical properties has been developed using ex vivo or in vitro specimens. This is due to the need to verify the results of the experiments, which are predominantly trials of new techniques, with accurate histological findings. Some groups however, have endeavoured to apply a degree of in vivo testing to their work. Some elastography-based studies have been successful in incorporating preoperative in vivo results with post-operative histological findings due to the ability to add the technology to already available ultrasound machines. Several prototypes for robotic indentation for direct measurement have been developed but no reported in vivo tests have been reported. Tensile testing usually results in a degree of destruction of the tissue and thus no in vivo studies for this have been developed.

4. Prostate pathologies and mechanical characteristics

4.1. Prostate histopathology and mechanical characterisation

Almost all of the studies that have sought to assess the prostate mechanical properties have done so with the aim of comparing cancerous and non-cancerous prostate tissue. Indeed, only the paper from Ma et al. utilised exclusively benign tissue in their study, albeit from prostates removed that were known to have prostate cancer in other areas. All have reported that the EM of prostate cancer is higher than that of normal
prostate tissue, which reflects clinical experience. Unfortunately, due to the wide variation in testing methodologies used, direct comparison of the results between the papers is difficult. BPH prostate tissue was noted to be slightly softer than normal prostate tissue in the studies that tested it\(^7,\,13\). Table 1 displays the results of the published papers, with a brief explanation of the variances on the testing methods, and the data is displayed graphically in Figure 3.

Aside from differences in histological subtypes, few hypotheses have been put forward to explain the differences noted between benign and cancerous tissue. Phipps et al. and Ma et al. identified trends in collagen content and tissue stiffness\(^{14,\,23}\) and associations between increasing cancer stage and increasing stiffness have also been reported\(^{12,\,13}\). The amount of glandular tissue present seems to have less influence on the tissue stiffness\(^{23,\,24}\) thus leading to suggestions that it is the extracellular matrix and stromal component of the prostate that contributes most to prostate tissue stiffness. Indeed, there is evidence that at a cellular level prostate cancer cells have significantly lower elastic moduli than BPH cells, which is believed to help them in the development of metastases\(^33\).

4.2. Tissue Storage and Handling

The processes that a tissue undergoes prior to testing can have an influence of the results. Much of the published literature on mechanical characteristics of the prostate has utilised prostate tissue taken from radical prostatectomy specimens; usually removed in the management of prostate cancer. There are some studies that have utilised cadaveric samples also\(^{13,\,23}\). Yang et al. used the prostate resected as part of a radical cystoprostatectomy\(^{15}\) while further studies by Phipps et al. utilised samples removed during TURP\(^{14,\,31}\).

All studies to date utilised fresh prostate tissue. Those samples removed at time of surgery were tested within 2 hours of resection time, while those from post mortem samples were tested within 2 days of removal. No studies have tested the mechanical properties of the prostate after a period of cryopreservation, or after fixation. While frozen tissues do have significantly different mechanical properties to fresh tissue\(^34\), soft tissues that have been thawed after short periods of freezing (<7 days) do not seem to have significantly altered mechanical properties. This has been shown in the case of porcine liver\(^{35}\), porcine thoracic aortae\(^{36}\) and human placenta\(^{37}\). Indeed, only heating the tissues above body temperature was shown to influence the mechanical properties\(^{35}\). However, longer periods of cryopreservation may cause some alteration to the mechanical properties, with higher failure strains and lower failure stresses reported for bovine liver specimens frozen for 30 and 60 days, as compared with samples tested fresh\(^{38}\). Interestingly, there was no difference noted in
parameters between the 30-day-frozen or 60-day-frozen samples. Furthermore, refrigerating samples does not seem to be associated with significant decreases in ultimate stress and elastic modulus in arterial tissue.

### 4.3. Effect of site of testing on characterisation

No significant difference in EM of prostate tissue was reported when different areas of the same prostate were compared. Krouskop et al. performed indentation testing on samples of normal prostate tissue from the anterior and posterior portion of the gland without any difference. Similarly, Ahn et al. performed indentation tests across regions of the posterior surface of the prostate, for both cancer and benign tissues, without any significant difference within the histological types.

### 4.4. Peri-urethral tissues, lower urinary tract symptoms and mechanical characterisation

Despite the significantly higher prevalence of BPH and associated LUTS as compared to prostate cancer, there is little in the literature regarding the effect of prostate mechanical properties may have on the development and severity of the symptoms. Indeed, the contribution of the prostate in obstructive urinary flow is evident by the rate of male incontinence post-radical prostatectomy. Urethral profile pressures (UPP) have been used previously to record the intraluminal pressures throughout the urethra, not specifically the prostate, but require significant technical expertise and thus are not in routine practice. Furthermore, as mentioned above, few studies have utilised peri-urethral tissue in their characterisation.

Cantiello et al. investigated peri-urethral prostate tissue, removed from radical prostatectomy specimens, and correlated their findings with LUTS. While not specifically addressing mechanical testing, they did identify a positive association between the degree of inflammation and the collagen content with the IPSS symptom score of the patient. Ma et al. then performed tensile tests on similar tissue, taken from the peri-urethral portion of a radical prostatectomy prostate, and identified a correlation between IPSS scores, collagen content and tissue stiffness.

Kim et al. reported results of indentation tests on a prostate and the relationship with LUTS. While they did show an association between increasing prostate stiffness and increased severity of LUTS, there are some significant limitations with respect to their methods. Their indentations were performed at the posterior surface of the prostate and only to a depth of 3mm, while the median prostate volume in the series was 43.4mL. While indentation tests at the posterior surface of the prostate have some relevance with regards prostate cancer detection, as most prostate cancer occurs in the posterior zone, given the distance from the posterior surface
of the prostate to the peri-urethral prostate, a more likely contributor to LUTS, it is unlikely that their mechanical characteristics could reasonably be attributed to the LUTS reported.

Phipps et al.\textsuperscript{31} however did perform indentation testing on prostate samples retrieved at time of TURP and identified a correlation between stiffness of the prostate and the amount of smooth muscle in the sample. They unfortunately did not have symptom data, but this is one of the few papers to utilise TURP tissue in the investigation of mechanical properties of the prostate. Kelly et al.\textsuperscript{24} performed tensile testing on TURP specimens and identified a correlation with patient symptoms.

4.5. Mechanical properties and prostate management.

A benefit of a better understanding of the mechanical properties of the prostate and their effects on bladder outlet obstruction (BOO) and urine flow, is that it may allow us to improve our assessment and management of same. Chronic bladder outlet obstruction can have significant changes on the native bladder and there is strong evidence that the bladder undergoes hypertrophy in response to long-term outlet obstruction\textsuperscript{42} and that damage can be detected from a very early stage\textsuperscript{43}. This can lead to long term problems with the bladder function including bladder instability and bladder failure, even after correction of the obstruction\textsuperscript{44}, and thus early intervention is mandated. Most importantly, the correct intervention is required. 30\% of all patients will stop their medication, usually within 2 years\textsuperscript{45} and many of these will require surgical management of their BOO.

The gold standard of the management of BOO is the TURP, but there has been a growing interest in other methods of relieving obstruction, that do not have the associated morbidity of a TURP. These include prostatic stents and adjustable prostatic inserts, such as the UroLIFT\textsuperscript{46}. These devices physically retract the impinging prostate lobes to widen the urethral lumen and thus rely on a better understanding of the mechanics of the prostate tissue. Indeed, it is probable that the paucity of data available on the peri-urethral prostate tissue has contributed to the slow uptake of these devices and the ongoing issues with complications.

Briefly, the UroLIFT system is a series of cystoscopically-placed implants that are placed from the other prostate capsule to the inner luminal aspect of the prostate, and work to manually retract the prostate lobe under tension. This has good effects in improving a patients symptoms scores\textsuperscript{47} but is associated with haematuria and dysuria. It has been approved for use in the most recent European Association of Urology guidelines, though long-term efficacy data is still unavailable\textsuperscript{48}. Insertion usually requires a light anaesthetic. Approximately 10\% of patients require re-intervention, either by way of replacement of the UroLIFT or TURP within 3 years\textsuperscript{49,50}, rising to 13.6\% by 5 years\textsuperscript{49}. The use of prostatic stents, seen initially as a long-term alternative to indwelling urethral
catheters, have had a less successful uptake. While there is often a reported improvement in the voiding symptoms, the placement of stents is associated with a number of significant side-effects, including stent migration, stent misplacement, exacerbation of LUTS and perineal pain\textsuperscript{48}.

There is little data available on the forces exerted by the UroLIFT and prostatic stents on the luminal aspect of the prostate. Made from a variety of different materials, as detailed by Aoun et al.\textsuperscript{51}, including steel, nitinol and polyurethane plastics, it would appear that these devices have been manufactured to create and maintain a fixed luminal diameter, resisting inward compression from the prostate lobes, rather than ensure continued prostate compression. The prostate undergoes a degree of deformation during the micturition cycle\textsuperscript{52} and thus, if the stents are of a fixed diameter, a failure to account for the deformation may be the main contributing factor to their migration and lack of generalised uptake.

Indeed, there is an overall paucity of data that assesses the effect of the prostate, from a mechanical perspective, on the voiding cycle. The morphological changes of the bladder outlet have been visualised using trans-rectal ultrasound\textsuperscript{52} and MRI\textsuperscript{53}, and the effects of the prostate can be inferred from urodynamic pressure-flow studies\textsuperscript{54}.

There have been attempts to computationally address the effect of the prostate on voiding patterns\textsuperscript{55} using idealised models, but there has been no direct measurement of the in-vivo mechanical properties of the prostate nor of their effect on the voiding.

\textbf{5. Conclusion}

The mechanical properties of the prostate have a lot of potential to advance our understanding of the diseases that affect it. Our review has shown that there are significant mechanical differences between benign and cancerous prostate tissues, confirming the previously-known clinical findings, which have been reproduced on a number of occasions, although the variety of testing methods used, including tensile and indentation testing, makes the use of absolute numbers for comparison and diagnosis difficult.

The changes that occur to the mechanics of the prostate gland as a result of ageing and BPH, which can be correlated with a progression of lower urinary tract symptoms, is of significant interest as it could be used to help improve the non-surgical device management of this condition and avoid the morbidity of surgery. However, the lack of in vivo and prospective data needs to be addressed to allow for further advancements in this field.
References


Figures

Figure Legend

Figure 1.
PRISMA flow diagram detailing the exclusion process for this systematic review.

Figure 2. Idealised Stress-Strain Curve
This graph demonstrates an idealised stress-strain curve, as would be generated from displacement and force data during direct mechanical testing. The elastic modulus (EM) is calculated from the slope of the curve and is a measure of the tensile properties of a tissue.

Figure 3
Schematic comparing methods of direct and indirect mechanical characterisation of tissues.

Figure 4.
Figure detailing the mean and standard deviation of the elastic moduli reported in the literature for direct mechanical testing of prostate tissue, via the three predominant methods. Sections in red correspond to cancer tissue, blue to benign tissue, and green to BPH tissue. The red and blue dotted lines relate to the mean value of prostate cancer and benign tissue respectively, as tested by indentation testing. Mean values for compression and tensile testing were not displayed, as there were only single studies in each case. Where multiple values for a given histological type were reported i.e. where values differ depending on testing methods and protocol, values were averaged for the purposes of this diagram.

SD= Standard Deviation. EM= Elastic Modulus
Figure 1.

PRISMA flow diagram detailing the exclusion process for this systematic review.
This graph demonstrates an idealised stress-strain curve, as would be generated from displacement and force data during direct mechanical testing. The elastic modulus (EM) is calculated from the slope of the curve and is a measure of the tensile properties of a tissue.
Schematic comparing methods of direct and indirect mechanical characterisation of tissues.
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SD= Standard Deviation. EM= Elastic Modulus
### Table 1

Comparison of the reported elastic moduli from the published literature. All results reported in mean and standard deviation (SD), except Kim et al, where median and interquartile range was reported.

<table>
<thead>
<tr>
<th>Author</th>
<th>Source</th>
<th>Variables</th>
<th>Tissue Variables (kPa). All mean values with SD, unless otherwise mentioned</th>
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<td>Krouskop, 1998&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Precompression strain applied (Pre). Sinusoidally varying strains at different frequencies applied to tissue. Tissue elastic modulus calculated from force required.</td>
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<td>RP</td>
<td>Hoyt, 2008&lt;sup&gt;17&lt;/sup&gt;</td>
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<td>RP</td>
<td>Ahn, 2010&lt;sup&gt;13&lt;/sup&gt;</td>
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<td>RP + PM</td>
<td>Carson, 2011&lt;sup&gt;15&lt;/sup&gt;</td>
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<td>Kim, 2014&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>Ma, 2012&lt;sup&gt;23&lt;/sup&gt;</td>
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**Note:** Comp = Compression testing. Indent = Indentation testing. TURP = transurethral resection of the prostate. RP = radical prostatectomy. PM = post-mortem, relates to cadaveric samples. BPH = Benign prostatic hyperplasia. TT= Tensile testing.