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Biomechanical aspects of Peyronie's disease in development stages and following reconstructive surgeries

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Peyronie's disease is a disorder of the penile connective tissues that leads to development of dense fibrous or ossified plaques in the tunica albuginea, causing penile deformity and painful erection. A biomechanical model of the penis was utilized for analyzing the mechanical stresses that develop within its soft tissues during erection in the presence of Peyronie's plaques. The model's simulations demonstrated stress concentrations around nerve roots and blood vessels due to the plaques. These stresses may irritate nerve endings or compress the vascular bed, and thus cause penile deformity and/or painful erection. The model was further used to elaborate the effects of different biological or artificial materials for reconstruction of the penis following plaque removal. Clinical applications of the present model can range from analysis of the etiology of the disease to assisting in the determination of optimal timing for therapeutic interventions and in the selection of patch material for penile reconstructions.
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Introduction

Peyronie's disease is characterized by local alteration in the collagen fibers of the tunica albuginea. Through the course of the disease, painless dense and fibrous plaques develop in single or multiple sites in the tunica albuginea. As the disease progresses, parts of the dorsal/middle aspect of the tunica albuginea may ossify.[1,2] Painful erections during the acute stage (prominent in 30–40% of the patients) and angulation of the erect penis toward the plaque during the chronic stage are common symptoms of the disease, which is also accompanied by erectile dysfunction in at least 20% of the cases.[3] During normal erection, mechanical stresses within the penis are adequately distributed to obviate intensive local pressure on nerve endings or within the vascular bed.[4,5] The above-described local pathological stiffening of parts of the tunica albuginea in Peyronie's disease may break down the delicate mechanical interaction occurring during erection and, thereby, induce elevated mechanical stresses and/or structural deformities. The blood vessels and nerves located at the dorsal aspect of the penis are especially sensitive to intensified mechanical stresses. The dorsal artery supplies blood to the fascia and skin of the penis, and is also responsible for engorgement of the glans penis during erection.[6] The dorsal nerves of the penis innervate the glans and thus support its function as a sensory structure.[7] Our earlier computational simulations predicted that structural and functional damage to the dorsal tissues of the penis decreases the capability to achieve a normal erection due to interference of neural activity or obstruction of blood vessels.[4] In support of this contention, blood flow abnormalities have been associated with impotence in Peyronie's disease patients.[8,9]

Medication treatments of Peyronie's disease are unpredictable and effective in less than 50% of patients.[3] Controversies also exist regarding the optimal surgical approach. Surgery is usually recommended in long-term cases in which the disease is stabilized and the deformity prevents intercourse.[10] The two most common surgical methods are: (i) removal or expansion of the plaque followed by placement of a patch of skin, saphenous vein or artificial material; and (ii) the Nesbit procedure, which involves removal of the tissue from the side of the penis opposite the plaque in order to decrease or eliminate penile angulation during erection.[10,11] The former method may result in partial loss of

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erectile function, especially rigidity, while the latter method may cause a shortening of the erect penis. These problems have been attributed to damage of the erectile nerves during penile surgery. Thus, it is sometimes more efficacious to treat severe cases of Peyronie's disease with the placement of an artificial penile prosthesis after incising and releasing the plaque.[3] Several biological (eg dermis, saphenous vein, tunica vaginalis) and artificial (polymeric) materials have been used to replace the damaged tunica albuginea, but, thus far, no graft material has entirely succeeded in replacing the diseased tunica.[3] Skin grafting, for instance, tends to contract after several months, while the use of polymeric biomaterials bears the risks of foreign body reaction and infection.[12] Recently, successful use of vein graft has been reported.[3]

The mechanisms by which Peyronie's disease develops are still not well understood, and this naturally affects patient management.[13] In order to refine our understanding of the mechanical aspects involved in the etiology and progression of this disease, we employed a computational model of the penis that allows for quantitative analysis of the stress distribution within its tissues during erection.[4] In the present study, we utilized this model to determine: (i) the mechanical factors responsible for pain and penile deformities during erection in Peyronie's disease; and (ii) the biomechanical performance of various reconstruction grafts that are currently used during surgical interventions.

Methods

The biomechanical model of the penis

The methodology used to develop a two-dimensional (2D) biomechanical model for analysis of mechanical stresses in the penile tissues is described in detail in Gefen *et al*.[4] Its essential components that are relevant to the present paper are given here.

The penile structures incorporated within the model include the tunica albuginea, the skin, the dorsal blood vessels and the urethral channel (Figure 1a). The model was simplified by excluding the corpus spongiosum whose cross-sectional area is significantly smaller compared to that of the corpus cavernosa. The geometry of the model was extracted from a schematic cross-section through the middle of the penis, and was scaled to conform to dimensions of 4 cm (lateral) by 3 cm (dorsal–ventral). The penile soft tissues were assumed to be made of homogeneous, isotropic, and linear elastic materials. The mechanical characteristics for each component, that is the elastic modulus and Poisson's ratio, are given in an earlier work.[4]

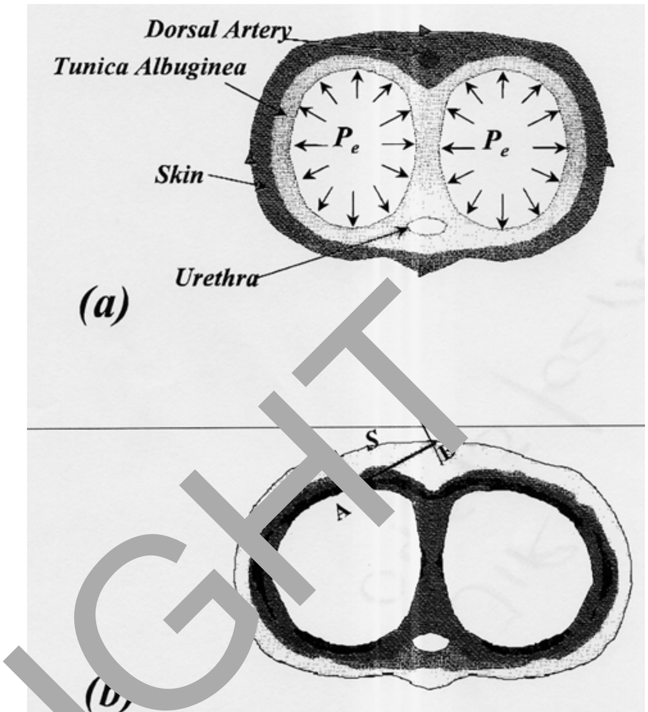

Figure 1 Biomechanical model of a cross-section through the healthy human penis: (a) geometry and components of the model; and (b) distribution of equivalent stresses during normal erection. The constraints at the model boundaries are marked by triangles on the top figure.

The erectile pressure which is applied to the inner boundary of the tunica albuginea was assumed to be $P_e = P_a - \sigma_{cc}$ where $P_a = 100$ mmHg ($\sim$13.3 KPa) is the inflation pressure induced by arterial blood flow into the penile cavities,[14] and σ_{cc} is the resistance stress of the spongy corpus cavernosa tissue. At maximal erection and rigidity, the corpus cavernosal volume is assumed to be $V_E = 100\%$ of the total corporal capacity (TCC). When blood drains and the penis becomes flaccid, the corporal volume is reduced to $V_F = 35\%$ TCC.[15] Assuming that the corpus cavernosal tissue is unstressed at V_F, the characteristic stretch ratio λ from flaccid to any larger penile volume V during erection can be obtained using the generally accepted relationship

$$\lambda = \frac{l}{l_0} = \left(\frac{V}{V_F}\right)^{1/3} \tag{1}$$

which defines the stretch ratio λ as being the ratio of stretched (l) to neutral (l_0) characteristic lengths, or as the cubic root of the ratio of expanded (V) to flaccid (V_F) characteristic volumes. Accordingly, $\lambda_{max} = (V_E V_F)^{1/3} = 1.42$ after substituting the values for full erection and flaccid volumes. In the absence of any data in the literature describing the stress-deformation relationship of the corpus cavernosal tissue, the resistant stress was estimated from the mechanical behavior of the lung parenchyma, which is of a similar microstructure,[4] to be $\sigma_{cc} = 7$ KPa at λ_{max}. The stress distribution within the penile tissues and the corresponding geometry during erection were determined by employing a commercial finite element analysis software package (ANSYS). The computer simulations provided the mechanical stress distribution in terms of an equivalent stress distribution, which weighs the effects of both tension and compression stresses (Figure 1b).

Simulation of Peyronie's plaques

A recent statistical analysis of biopsy specimens showed that the tunica albuginea tissues in Peyronie's disease contain significantly decreased amounts of elastin fibers.[16] In the absence of any available experimental data on the mechanical properties of fibrotic or ossified tunica albuginea (that is, elastic modulus and Poisson ratio), we assumed that the trend of changes is similar to that of calcified bovine cartilages.[17] Accordingly, we assumed that the maximal elastic modulus (E_{max}^{plaque}) of a stabile Peyronie's plaque is 320 MPa and the Poisson ratio is 0.3, as compared to 12 MPa and 0.4 in the healthy tunica albuginea.[4] Intermediate values of plaque elasticity (ie 25, 50 and 75% of E_{max}^{plaque}) were also used throughout the analysis in order to study the process of plaque development.

The formation of symmetrical ossification at the dorsal aspect of the tunica and along the tunical septum for progressing stages of the disease, ie when the plaque occupied approximately 5, 10, 20 and 40% of the total tunical cross-sectional area, had been simulated in a previous work[8] (Figure 2, left panel). Development of non-symmetric ossification was analyzed for plaques that occupied about 10% of the tunical area and were located at the dorsal, lateral and ventral aspects as well as for a completely enveloped right cavernosum (Figure 3, left panel)

In order to obtain a parametric representation of the biomechanical effects of progressive local fibrosis of the tunica albuginea, we examined two types of parameters. The first, $\bar{\sigma}$, quantifies the averaged value of the mechanical stresses that are transferred to the dorsal nerve roots and blood vessels for different plaque sizes. Since deformation of the penis during erection varies among the different cases, we defined the average stress at this region as:

$$\bar{\sigma} = \frac{1}{S}\int_0^s \sigma d\xi \qquad (2)$$

where σ are the stress values (in MPa) along the length S. The course of S crosses the dorsal nerve

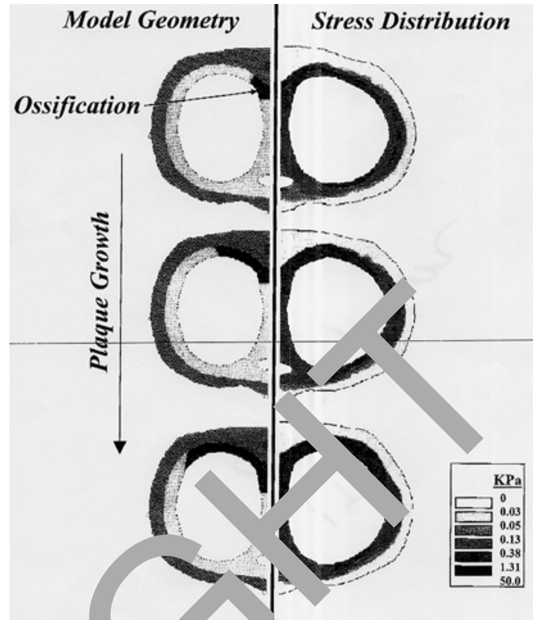

Figure 2 Simulation of progressive stages of symmetric ossification of the dorsal and middle parts of the tunica albuginea, occupying 5, 20 and 40% of the tunical area from top to bottom, respectively. Two diagrams are shown for each of the earlier stages; the left one is the axisymmetric geometry of the model and the right one is the axisymmetric equivalent stress distribution developing during erection.

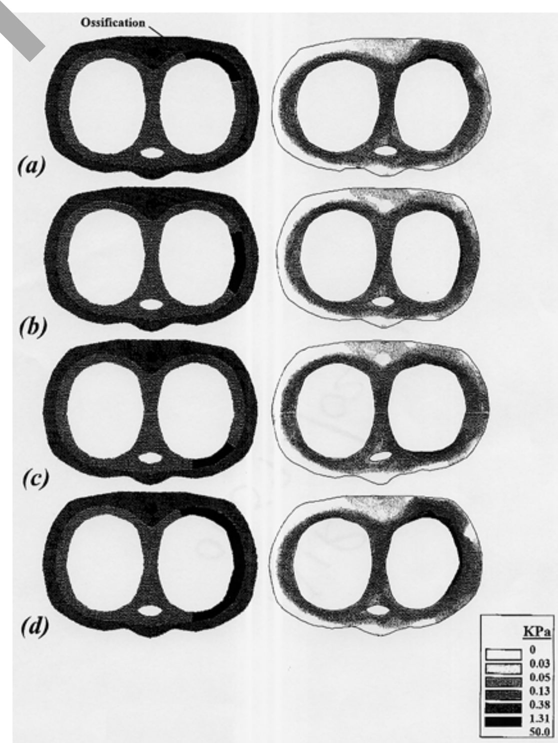

Figure 3 Simulation of different conditions of asymmetric ossification: (a) dorsal plaque; (b) lateral plaque; (c) ventral plaque; and (d) a plaque enveloping the right cavernosum. Two diagrams are shown for each of the earlier stages: the left one is the geometry of the model and the right is the equivalent stress distribution developing during erection.

roots and the nerves branching to the tunica albuginea by originating at the center of the dorsal face of the penis cross-section (above the dorsal vein and artery) and terminating at the apex of the corpus cavernosum (Figure 1 b).

The second parameter defines the level of asymmetry of the cross-section of the penis during erection, and is given by:

$$\rho = \frac{A_r}{A_l} \tag{3}$$

where A_r is the right and A_l is the left cavernosal cross-sectional areas of the penis model. It is expected that an asymmetric cross-section in the vicinity of the plaque — while the rest of the erect penis is usually symmetric — is responsible for the curved and angulated penis in Peyronie's disease.

Simulation of surgical interventions

In order to evaluate the post-surgical state of mechanical stresses we simulated surgical interventions during which the removed Peyronie's plaque was replaced by the following alternatives: (i) vein grafting; (ii) cadaveric pericardium grafting treated with glutaraldehyde for increased durability as recently proposed in small-scale clinical studies;[19,20] (iii) skin grafting; and, (iv) polytetrafluoroethylene grafting (Gortex™). The skin and Gortex grafting were assumed to be elastic materials with linear stress-deformation relation of:

$$\sigma = E\lambda \tag{4}$$

where λ is the stretch ratio (Equation 1) and E is the elastic modulus (Table 1). The vein and pericardium patches were assumed to behave as non-linear elastic materials with a stress–strain relation of:

$$\sigma = a\lambda^5 + b\lambda^4 + c\lambda^3 + d\lambda^2 + e\lambda + f \tag{5}$$

The coefficients *a, b, c, d, e, f* were determined (in MPa) by curve fitting to experimental data;[19–21] for the vein, $a=2.40[illegible]8$, $b=-12.813$, $c=26.536$, $d=-26.[illegible]6$, $e=[illegible]2.616$, $f=-2.3448$ and, for the pericardium, $a=1.2821$, $b=-3.5839$, $c=-2.9254$, $d=19.087$, $e=-21.256$, and $f=7.4067$. As detailed in Table 1, the biological patch materials are characterized by a lower elastic modulus, and are thereby more compliant than the polymeric tissue replacements, eg Gortex.

Table 1 Evaluation of biomechanical compatibility of different patch materials for reconstruction of the penis following removal of Peyronie's plaque

Patch material	*Elastic modulus [MPa] (for small deformations)*	$\bar{\sigma}$ *[KPa]*	ρ
Vein grafting	0.30	0.13	1.08
Pericardium	0.40	0.15	1.06
Skin grafting	0.50	0.20	1.05
Gortex	2.80	0.25	1.03
Normal tunica	12.00	0.30	1.00

The patch is located within the dorsal aspect of the tunica albuginea above the right cavernosum, as shown in Figure 5.

Results

The predicted mechanical stresses for a simulated penis with Peyronie's plaque at progressing stages of symmetric ossification at full erection are shown in Figure 2. The stresses were seen to be transferred mainly through the stiffer tunica albuginea that envelops the corpus cavernosa, while the penile skin appeared to bear a negligible load. In the healthy penis, the stresses were shown to concentrate on the dorsal and lateral aspects of the tunica (Figure 1b). In the model simulating a penis with Peyronie's plaque, the stresses were significantly larger at the dorsal aspect of the tunica and also tended to expand to its middle part (or septum) as the area of ossification increased. Contrarily, in the lateral aspects, stresses were shown to decrease with the increase in plaque size (Figure 2).

In cases of an asymmetric Peyronie's plaque located dorsally, laterally or ventrally to the right corpus cavernosum, a significantly asymmetric shape of the penis is obtained during erection, with little relation to the plaque size (Figure 3). Inflation of the neutral, elliptical cross-sectional shape of the cavernosum during normal erection in the healthy penis yielded a more circular corporal profile (Figure 1b). Formation of a symmetric dorsal plaque constrained the expansion of both corpora, imposing an erect corporal profile that became closer to elliptic as the plaque size increased (Figure 2). The overall cross-sectional shape of the penis, however, remained symmetric because the symmetric nature of the plaque equally affected the deformation of both corpora. When an asymmetric plaque was generated, expansion of only one cavernosum (ie the one adjacent to the plaque), was constrained, while the other cavernosum was free to expand to a nearly-normal circular profile, resulting in an asymmetric deformation of the overall cross-section of the penis (Figure 3).

A comparison of the average stresses generated in the region of the dorsal nerves and blood vessels ($\bar{\sigma}$) as a result of progressive asymmetric ossification of the dorsal, lateral and ventral aspects of the tunica albuginea is displayed in Figure 4a. Elevated stresses in the vicinity of the dorsal tunica albuginea in the model of Peyronie's disease are seen to significantly increase with the increased stiffness of the plaque. The dorsally located plaques were shown to induce the highest stresses on the dorsal nerves and blood vessels. A completely ossified plaque occupying about 10% of the tunical area

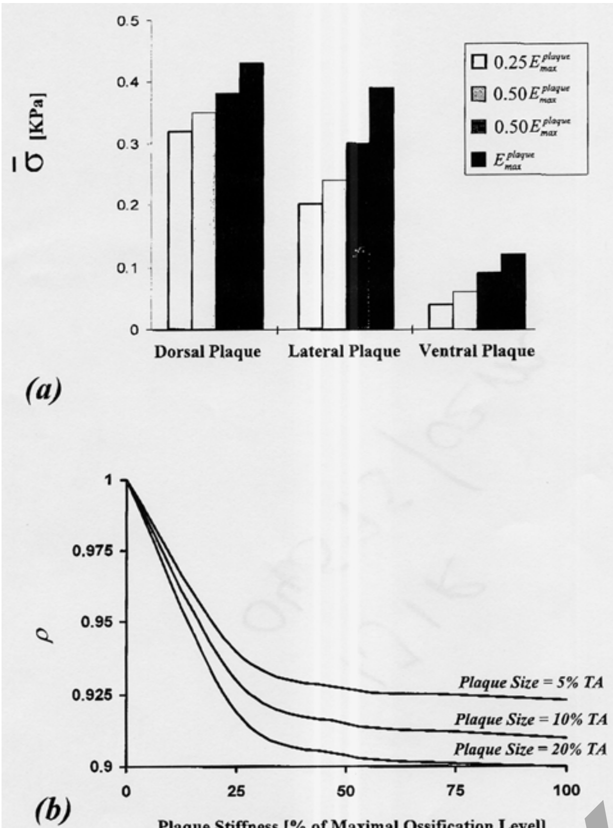

Figure 4 Parametric analysis of the biomechanical effects of Peyronie's disease: (a) the average stress generated in the region of the dorsal nerves and blood vessels ($\bar{\sigma}$) for dorsally, laterally and ventrally located plaques (shown in Figure 3a–c) with different stiffness characteristics; and (b) the ratio of right-to-left cavernosal cross-sectional areas, ρ, indicating the severity of deformity of the penis during erection under the effect of dorsally located plaques with different degrees of stiffness and different sizes. Severity of the deformity increased as the ratio of cavernosal areas was shifted from the normal unity value. TA: tunical area.

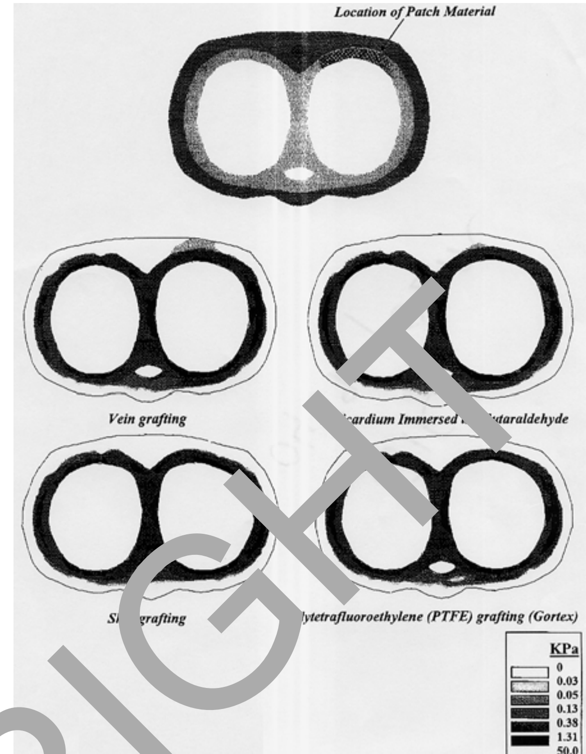

Figure 5 Simulation of the stress state and geometry of the cross-section of the penis following surgical replacement of the ossified Peyronie's plaque with different biological/artificial grafting materials: vein, pericardial tissue treated with glutaraldehyde, skin, and polymeric polytetrafluoroethylene (Gortex) grafting.

caused the average stresses acting upon the dorsal nerve roots and vascular bed to rise by 45%, compared to the stress value which resulted from the simulation of normal erection. A fully ossified lateral plaque was also shown to induce a substantial (33%) rise of the dorsal stress level compared to the normal case. Figure 4b details the extent to which different sizes of plaques that were located dorsally and asymmetrically in respect to the penile septum (as in Figure 3a) caused a distortion in the overall cross-sectional geometry of the erect penis, depending upon their degree of ossification. These results demonstrated that distortion of the overall geometry of the erect penis was almost independent of the size of the plaque. The ratio of right-to-left cavernosal cross-sectional area, ρ, varied by no more than 3% when the plaque size was increased from 5 to 20% the tunical area. In contrast to the limited influence of the plaque size, stiffness of the plaque was shown to be a more critical factor in causing distortion of the penile erect shape. Local increase in stiffness of parts of the dorsal aspect of the tunica, by as little as 25% from the normal value, was shown to cause a drop of as much as 7–9% in the value of ρ, indicating a significant distortion in the erect penile geometry which may cause angulation of the erect penis, as demonstrated in Figure 3a.

The model was further used to evaluate the biomechanical performance of several grafting materials as alternatives for the damaged tunica albuginea after Peyronie's plaque removal. The comparison between the stress states and deformed penile shapes following the insertion of vein, pericardium, skin and Gortex grafting materials as substitutes for a segment of the dorsal tunica albuginea above the right cavernosum are shown in Figure 5. The values of the averaged stress transferred to dorsal nerves and blood vessels ($\bar{\sigma}$) and the ratio of right-to-left cavernosal cross-sectional areas (ρ) which were calculated for each patch material, are detailed in Table 1. All patches were shown to provide adequate biomechanical compatibility with the penile tissues in terms of the parameters $\bar{\sigma}$ and ρ. Averaged stress values $\bar{\sigma}$ did not exceed the values predicted for normal erection (ie 0.3 KPa) and the cavernosal expandability ratio, ρ, was close to unity for all the cases tested. It is evident, however, that as the elastic modulus of the patch becomes similar to that of the normal tunica, ie approximately 12 MPa,[4] both the stress state and the deformed penile shape during erection approach the normal condition (Table 1). In light of this finding, the Gortex patch, which is stiffer than the biological patch materials and provides a more similar elastic modulus to that of the tunica (Table 1), would be expected to provide biomechanical compatibility superior to the vein, pericardial and skin grafting materials. Yet, the greater biological compatibility of the latter materials should also be considered.

Discussion

The model which was utilized in this study is capable of predicting the distribution of stresses within the different tissue structures of the penis, thereby offering a new perspective on the role of biomechanics in the pain and erectile deformities observed in patients with Peyronie's disease. The model was also used to evaluate the stress transfer between the grafting material and penile tissues during erection for different patch materials that are used for surgical correction. In the healthy penis, model simulations have indicated that the dorsal aspect of the tunica albuginea carries a significant part of the load during erection.[4] Since this site contains the tunical nerves and is adjacent to the dorsal nerve roots as well as to the dorsal blood vessels, it is especially vulnerable to intensified mechanical stresses. This sensitivity is characteristically augmented in Peyronie's disease, because the dorsal part of the tunica is often the site of ossification.[1,2]

Biomechanical consequences of Peyronie's disease

Peyronie's disease has been characterized by ultrastructural changes in the tunica albuginea, and one resultant functional abnormality is the loss of elasticity.[6] This pathological tissue stiffening leads to significantly magnified and unevenly distributed stresses in the tunica albuginea of affected individuals. The present model provides a tool for predicting the pathological stress distribution within and around the affected tissue whose simulated local stiffness is gradually increased to represent the development of ossification. The numerical predictions show that the healthy tunica albuginea sustains an average dorsal stress of 0.3 KPa, while the tunica in Peyronie's disease may bear local stresses of more than twice this value, depending upon the plaque stiffness as well as on its size and location (Figures 2, 4, 5a). Although they may be too small to cause mechanical failure of the tunica albuginea itself,[22] these elevated stresses within the penile tissues of patients with Peyronie's disease are transferred to the tunical nerves as well as to the adjacent dorsal nerves and blood vessels. The intensified mechanical load may irritate the nerves, especially near their roots, and impose an abnormally large pressure on the vascular bed, leading to pain from the resultant ischemia. These events are likely to cause discomfort or painful erections in the early stages of the disease, and may lead to penile deformation, erectile insufficiency and/or inability to maintain functional erection in the more advanced stages.

Peyronie's plaques which cover only one of the corporal bodies (ie asymmetric plaques) may not only produce local stress concentrations (Figure 3), but may also cause penile deformities during erection. We demonstrated that different sizes of plaques located asymmetrically with respect to the penile axis constrained the expansion of one cavernosum but enabled expansion of the other (Figure 3). The uneven cavernosal expansion resulted in asymmetric deformation of the overall cross-section of the penis during erection due to the non-homogeneous resistance to expansion on the part of the surrounding tissue. The severity of the deformity was shown to be more dependent on the local stiffness characteristics of the forming plaque, ie on the level of its fibrosis or ossification, than on its size. Fibrosis causing an increase of stiffness that exceed the normal value by only 25% was shown to induce significant distortion of the penile cross-sectional shape during erection, and appeared very likely to cause substantial angulation of the erect penis (Figure 4b).

As for the three-dimensional (3D) structural effects, it is most likely that the above-described mechanism is responsible for the penile deformities occurring during erection in patients with Peyronie's disease. The local distortion caused by an irregularly shaped plaque results in curvature or torsion deformities of the erect penis, structural abnormalities which are very likely to further increase the local mechanical stresses acting around nerves and blood vessels at the vicinity of the plaque. This phenomenon may subsequently inhibit the development of a normal, functional erection.

Knowledge of the mechanism by which the plaque develops is a key for accurate characterization of its material properties, which constitute its mechanical interaction with the normal penile tissues *in vivo*. For instance, the local alteration in collagen within the tunica albuginea through the course of the disease can be histologically studied using *in vitro* models, animal models and biopsy specimens taken from patients in order to determine the non-uniformity in mechanical properties of fibrous and ossified tissues, eg the variation in their local stiffness. Incorporation of non-homogenous plaques with more realistic material properties into the present model can be used to numerically simulate the stress state in specific clinical cases, for the evaluation of treatment approaches in individual patients.

Application to surgical treatment planning

The surgical approaches for rehabilitation of erectile dysfunction in patients with Peyronie's disease often involve replacement of the ossified tissue with a natural or artificial patch in order to reconstruct the penis. Evaluation of the mechanical stress interaction between the graft material and the surrounding tissues showed that Gortex provides the best results from a biomechanical perspective, by yielding a level of stiffness that most closely approach that of the natural tunica, and, thereby, inducing a stress-deformation behavior of the penis which most successfully mimicked the normal condition (Table 1). The clinical overall success rate for this patch type is reported to be approximately 70%, with infection being the most significant postoperative complication.[23,24] Biological materials, such as venous grafts, are reported to produce somewhat higher success rates, ranging from 80 to 90%, most likely due to the milder inflammatory response that they induce.[3] The optimal surgical approach and selection of patch material should be patient-specific and consider the effects on penile rigidity, degree of curvature, shaft narrowing and erectile response.

The asymmetry parameter ρ (Equation [illegible]) provides a practical measure of the severity of the penile deformity pre- and post-treatment. Ideally, in the normal, healthy penis, the ratio of cavernosal areas during erection ρ should equal 'one', but if, for example, the right cavernosal body is constrained by the presence of a plaque which limits its expansion during erection, the value of ρ drops. If a patch with reduced stiffness is surgically inserted to replace the plaque, the value of ρ may rise again and even exceed 'one' when the patch material is more complaint than the natural tunical tissue. The magnitude ρ thereby emerges as a useful dimensionless indicator of the severity of deformity, and may also be clinically measured through ultrasound imaging.

In conclusion, our model demonstrated that ossification of the dorsal, middle and lateral parts of the tunica albuginea induces intensified stresses that may irritate nerves and/or cause vasopathology, leading to loss of capability to achieve or maintain a functional erection. The computational simulations further predict that severe penile deformity during erection can also be expected to develop in cases of asymmetric plaques. Analysis of several grafting materials for surgical correction of the penile deformity caused by Peyronie's plaque demonstrated that Gortex provides the best biomechanical compatibility. Finally, the present study demonstrated the potential of computational modeling in analysis of the realistic structural behavior of the human penis. The modeling approach may provide the means to greatly enhance clinical decision-making, by simulating the biomechanical consequences of complex surgical reconstructions and other procedures for treating Peyronie's disease.

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