Appendix 4

Online supplementary evidence for section 8 Peyronie's Disease

Aetiology

The aetiology of PD is unknown. However, repetitive microvascular injury or trauma to the tunica albuginea is still the most widely accepted hypothesis to explain the aetiopathogenesis [1]. Abnormal wound healing leads to the remodelling of connective tissue into a fibrotic plaque [1-3]. Penile plaque formation can result in a curvature, which, if severe, may impair penetrative sexual intercourse. The genetic components of fibrotic diatheses, including PD and Dupuytren's disease, are beginning to be understood; however, data are contradictory and we do not yet have the basis for predicting who will develop the disease or degree of severity [4, 5].

Risk factors

The most commonly reported associated co-morbidities and risk factors are diabetes, hypertension, dyslipidaemias, ischaemic cardiopathy, autoimmune diseases, ED, smoking, excessive alcohol consumption, low testosterone levels and pelvic surgery (e.g., radical prostatectomy) [6-12]. Dupuytren's contracture is more common in patients with PD affecting 8.3-39% of patients [13-16], whilst 4-26% of patients with Dupuytren's contracture report PD [15, 17, 18].

Pathophysiology

Two phases of the disease can be distinguished [19]. The first is the active inflammatory phase (acute phase), which may be associated with painful erections and a palpable nodule or plaque of the tunica albuginea of the penis; typically, but not invariably, a penile curvature may develop. The second is the fibrotic phase (or chronic phase) with the formation of hard, palpable plaques that can calcify, with stabilisation of the disease the penile deformity. Over time, the penile curvature may deterioate in 21-48% of patients or stabilise in 36-67% of patients, while spontaneous improvement has been reported in only 3-13% of patients [9, 20-22]. Overall, penile deformity is the commonest initial symptom of PD (52-94%). Pain is the second most common in 20-70% of patients during the early stages of the disease [23]. Pain tends to resolve with time in 90% of men, usually during the first 12 months after the onset of the disease [20, 21]. Palpable plaques have been reported as an initial symptom in 39% of the patients with most situated dorsally [23, 24].

In addition to the functional effects on sexual intercourse, men may also suffer from significant psychological distress. Validated mental health questionnaires have shown that 48% of men with PD have moderate or severe depression, sufficient to warrant medical evaluation [25].

Table S8.1 Genes with involvement in Peyronie's and Dupuytren's diseases adapted from Herati *et al.* [4]

Gene	Gene Symbol	Chromosomal Location	Gene Function
Matrix metalloproteinase 2	MMP 2	16q12.2	Breakdown of extracellular matrix
Matrix metalloproteinase 9	MMP 9	20q13.12	Breakdown of extracellular matrix
Thymosin beta-10	TMSB-10	2p11.2	Prevents spontaneous globular actin monomer polymerisation
Thymosin beta-4	TMSB-4	Xq21.3-q22	Actin sequestering protein
Cortactin; amplaxin	CTTN	11q13	Organises cytoskeleton and cell adhesion structures
Transforming protein RhoA H12	RHOA	3p21.3	Regulates cytoskeletal dynamics
RhoGDP dissociation inhibitor	ARHGDIA	17q25.3	Regulates Rho GTPase signaling
Pleiotrophin precursors; osteoblast specific factor 1	PTN/OSF-1	7q33	Stimulates mitogenic growth of fibroblasts and osteoblasts
Amyloid A4 protein precursor; nexin II	PN-II	21q21.3	Cell surface receptor
Defender against cell death 1	DAD1	14q11.2	Prevents apoptosis
Heat Shock 27-kDa protein (HSP27)	HSP27	7q11.23	Actin organisation and translocation from cytoplasm to nucleus upon

Macrophage-specific stimulating factor	MCSF/CSF1	1p13.3	Controls the production, differentiation and function of macrophages
Transcription factor AP-1	AP1	1p32-p31	Key mediator of macrophage education and point of recruitment for immunosuppressive regulatory T cells
Human Early growth response protein 1	hEGR1	5q31.1	Promotes mitosis
Monocyte chemotactic protein 1	MCP1	17q11.2-q12	Chemotactic cytokine for monocytes and basophils
Bone Proteoglycan II precusor; Decorin	DCN	12q21.33	Matrix proteoglycan
T-Cell specific rantes protein precursor	RANTES	17q12	Chemoattractant for monocytes, memory T cells and eosinophils
Integrin Beta-1	ITGB1	10p11.2	Membrane receptor involved in cell adhesion and recognition in a variety of processes including immune response, tissue repair and haemostasis
Osteonectin	SPARC	5q31.3-q32	Matrix protein that facilitates collagen ossification
Ubiquitin	RBX1	6q25.2-q27	Targets substrate proteins for proteasomal degradation
Transcription factor ATF-4	ATF4	22q13.1	Transcriptional regulation of osteoblasts and down-regulates apelin to promote apoptosis
Elastase IIB	ELA2B	1p36.21	Serine protease that hydrolyses matrix protein
c-myc	MYC	8q24.21	Transcription factor that regulates cell cycle progression, apoptosis, and cellular transformations
60 S ribosomal protein L13A	RPL13A	19q13.3	Repression of inflammatory genes
Prothymosin alpha	PTMA	2q37.1	Influences chromatin remodeling, anti-apoptotic factor
Fibroblast tropomyosin	TPM1	15q22.1	Actin-binding protein involved in contractile system of striated and smooth muscle
Myosin light chain	MYL2	12q24.11	Regulatory light chain associated with myosin Beta heavy chain
Filamin	FLN	Xq28	Actin-binding protein that crosslinks actin filaments and links actin to membrane glycoproteins. Interacts with integrins
Calcineurin A subunit alpha	PPP3CA	4q24	Promotes cell migration and invasion and inhibits apoptosis
DNA binding protein inhibitor Id-2	ID2	2p25	Transcriptional regulator that inhibits the function of basic helix-loop-helix transcription factors by preventing their heterodimerisation, negatively regulates cell differentiation
Smooth muscle gamma actin	ACTA2	10q23.3	Plays a role in cell motility, structure and integrity
Desmin	DES	2q35	Forms intra-cytoplasmic filamentous network connecting myofibrils
Cadherin FIB2	PCDHGB4	5q31	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing
Cadherin FIB1	DCHS1	11p15.4	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing

SMAD family member 7	SMAD7	18q21.1	Interacts with and promotes degradation of TGFBR1
Insulin-like growth factor binding protein 6	IGFBP6	12q13	Negative regulator of cellular senescence inhuman fibroblasts
Collagen 1 alpha	COL1A1	17q21.33	Encodes pro-alpha 1 chains of type 1 collagen
Transforming growth factor, beta 1	TGFB1	19q13.1	Cytokine that regulates proliferation, differentiation, adhesion and cell migration

Table S8.2: Clinical evidence supporting CCH treatment

Author/year [Ref]	Study type	Special considerations	No. of patients	No. of injections	Decrease in PC in CCH group
Gelbard *et al.* (2013) [26]	Phase 3 randomised double blinded controlled trial	Pilot study	551	8 (in 78.8% of patients)	34% (17.0 ± 14.8 degrees)
Levine *et al.* (2015) [27]	Phase 3 Open-label	IMPRESS based	347	≤ 8	34.4% (18.3 ± 14.02 degrees)
Ziegelmann *et al*. (2016) [28]	Prospective double-blinded trial	IMPRESS based	69	Mean = 6	38% (22.6 ± 16.2 degrees)
Yang and Bennett (2016) [29]	Prospective study	Included patients in acute phase	37 in SP 12 in AP	Median in SP = 6 Median in AP = 2.5	32.4% (15.4 degrees) AP = 20 degrees
Nguyen *et al* (2017) [30]	Retrospective study	Included patients in acute phase	126 in SP 36 in AP	Mean = 3.2	SP = 27.4% (15.2 ± 11.7 degrees) AP = 27.6% (18.5 ± 16.2 degrees) N/S differences in final change in curvature between group 1 (16.7º) and group 2 (15.6º) P = 0.654
Anaissie *et al.* (2017) [31]	Retrospective study	Included patients in acute phase	77	Mean = 6.6	29.6% (15.3 ± 12.9 degrees)
Abdel Raheem *et al.* (2017) [32]	Prospective study	Shortened protocol	53	Mean = 3	31.4% (17.6 degrees)
Capece et al. (2018) [33]	Prospective multicentric study	Shortened protocol	135	Mean = 3	42.9% (19.1 degrees)

SP = Stable phase; AP = Acute phase; N/S = non-significant.

Table S8.3: Studies on PRP in penile curvature and/or PD patients

Author	No of patients	Age (years)	Number of injections	IIEF score	Curvature	Decrease in plaque size	Pain	PDQ
Virag *et al*. (2014) [34]	13	57.5	4 (with HA) (2 injections /month)	Improvement in all patients	30%	53%	N/A	N/A
Virag *et al.* (2017) [35]	90	N/A	4 (2 injections /month)	+4.1	%39.65	-1.11 mm	N/A	improvement
Marcovici *et al.* (2018) [36]	1	54	2	N/A	20%	N/A	N/A	N/A
Matz *et al.* (2018) [37]	11	46	2.1	+4.14	Subjective improvement	N/A	N/A	N/A
Notsek *et al.* (2019) [38]	59	N/A	1	improvement	50%	50%	84%	N/A

HA = hyaluronic acid; IIEF = International Index of Erectile Function; N/A = not applicable; PDQ = Peyronie's disease questionnaire.

Table S8.4: Efficacy of ESWT in the treatment of PD

Author/year [Ref]	No. of cases/ controls	Inclusion criteria	Comparator	Follow -up	Treatment protocol	Results	Adverse effects
Palmieri *et al.* 2009 [39]	50 / 50	PD < 12 mo. No previous treatment	Sham therapy	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm^2, 4 Hz	**Change in IIEF** (+5.4points) **Pain reduction** (-5.1 points) **Change in curvature** (-1.4º) **Plaque size** (-0.6 in)	None
Chitale *et al.* 2010 [40]	16 / 20	Stable PD > 6 mo. No previous treatment	Sham therapy	6 month	1 session/week x 6 weeks. No other parameters mentioned.	**Change in IIEF** N/S **Pain reduction** N/S **Change in curvature** N/S **Plaque size** N/S	None
Palmieri *et al.* 2011 [41]	50 / 50	PD < 12 mo. Painful erections Presence of ED	ESWT + tadalafil 5 mg OD	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm^2, 4 Hz	**Change in IIEF** Significant in both groups **Pain reduction** Significant in both groups **Change in curvature** N/S **Plaque size** N/S	None
Hatzichristodoulou *et al.* 2013 [42]	51 / 51	Stable PD > 3 mo. Previous unsuccessful oral treatment	Sham therapy	1 month	1 session/week x 6 weeks 2000 sw, 0.29 mJ/mm^2	**Change in IIEF** N/A **Pain reduction** (-2.5 points **Change in curvature** N/S **Plaque size** N/S	Ecchymosis 4,9%

N/A = no assessed; N/S = no significant; IIEF = International index of erectile function; VAS = Visual Analogic Scale; ED = Erectile dysfunction

Table S8.5: Summary of clinical evidence of PTT as monotherapy

Author/year	Study type	Device	No. of patients	Hours of use	Result
Levine *et al.* (2008)	Pilot Prospective, uncontrolled	Fast Size®	10	2-8h 6 months	Mean reduction in PC 33% (51º-34º) SPL: + 0.5-2 cm EG: + 0.5-1 cm IIEF: + 5.3
Gontero *et al.* (2009)	Phase II Prospective uncontrolled	Andropenis®	15	5h 6 months	Mean reduction in PC: N/S SPL: + 0.8 cm (6 mo) + 1.0 cm (12 mo)
Martinez-Salamanca *et al.* (2014)	Prospective, controlled, open label Men in AP	Andropenis®	96 55 (PD) 41 (NIG)	6-9h (4.6 h/d) 6 months	Mean reduction in PC: 20º (33º-15º) p < 0.05. SPL: + 1.5 cm (6 mo) EG: + 0.9 cm (6 mo)
Moncada *et al.* (2018)	Controlled multicentre trial Men in CP	Penimaster® PRO	80 41(PTT) 39(NIG)	3-8h 3 months	Mean reduction in PC: 31º (50º-15º). SPL: + 1.8 cm (3 mo) EG: +0.9 cm (6 mo) IEEF: + 2.5
Ziegelmann *et al*. (2019) [43]	Randomised, prospective, controlled, single blind study Men in CP and controls 3:1	Restorex®	110	30-90 min/day 3 months	Mean reduction in PC (3 mo): 13.3º (PTT) +1.3º (control) P < 0.001 SPL: + 1.5 cm (PTT) + 0.cm (control) P < 0.001 IIEF: +4.3 (PTT) -0.7 (control) P = 0.01

NIG = non-intervention group; IIEF = International Index of Erectile Function; N/S = Not significant; PD = Peyronie´s Disease; AP = Acute phase; CP = Chronic phase; SPL = stretched penile length; EG = Erect girth.

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