University of Groningen

Peyronie's disease - Beyond the bend

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DOI:
[10.33612/diss.150703782](https://doi.org/10.33612/diss.150703782)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Mohede, D. (2021). *Peyronie's disease - Beyond the bend: Historical, epidemiological, clinical, genetic and molecular biological aspects*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.150703782>

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Peyronie's Disease - Beyond the Bend

Historical, epidemiological, clinical, genetic
and molecular biological aspects

Daan Carel John Mohede

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ISBN: 978-94-6423-095-6

Cover art: Safira Taylor

Layout and design: Wendy Schoneveld || www.wenzid.nl

Printed by: ProefschriftMaken || www.proefschriftmaken.nl

Financial support by the University of Groningen, University Medical Center Groningen and Kollf Institute is gratefully acknowledged.

Further financial support for printing of this thesis was kindly provided by ChipSoft, IPSEN and Prof. P.W. Boer Stichting.

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Peyronie's Disease – Beyond the Bend

Historical, epidemiological, clinical, genetic and molecular biological aspects

De ziekte van Peyronie – Voorbij de kromming

Historische, epidemiologische, klinische, genetische en moleculair biologische aspecten

Proefschrift

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Groningen
op gezag van de rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 13 januari 2021 om 14:30

door

Daan Carel John Mohede

geboren 12-01-1991
te Enschede

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Table of contents

	9
General introduction	
Chapter 1 Peyronie's disease – current perspectives	17
<i>Translated from: Mohede DCJ, van Driel MF, de Jong IJ, Beck J. Tijdschr Urol 2018;8:112-120</i>	
Chapter 2 Medical treatments of Peyronie's disease: past, present, and future	31
<i>Mohede DCJ, de Jong IJ, van Driel MF. Urology 2019;125:1-5</i>	
Chapter 3 Patient reported outcomes on sexual function after surgical treatment of Peyronie's disease	43
<i>Published as abstract: Mohede DCJ, Weidenaar AC, van Driel MF, van de Wiel HBM, de Jong IJ. J Urol 2018;199:e911</i>	
Chapter 4 Homosexuality and Peyronie's disease	57
<i>Submitted: Mohede DCJ, van de Wiel HBM, Meijer B, de Jong IJ, van Driel MF</i>	
Chapter 5 Prevalence of Peyronie's and Ledderhose's diseases in a series of 730 patients with Dupuytren's disease	67
<i>Mohede DCJ, Riesmeijer S, de Jong IJ, Werker PMN, van Driel MF. PRS 2020;145:978-984</i>	
Chapter 6 A genome-wide association study for Peyronie's disease	79
<i>Not for publication: Mohede DCJ, van Driel MF, Riesmeijer S, de Jong IJ, Werker PMN, Nolte IM</i>	
Chapter 7 Verteporfin as a medical treatment in Peyronie's disease	91
<i>Mohede DCJ, de Jong IJ, Bank RA, van Driel MF. Sex Med 2018;6:302-308</i>	

Chapter 8	Summary and general discussion	103
Chapter 9	Nederlandse samenvatting	113
	Appendices	124
	Dankwoord/Acknowledgements	136
	Curriculum Vitae	139
	List of publications	140

General introduction

General introduction

Peyronie's disease (PD) is named after the French surgeon Francois Gigot de la Peyronie (1678-1747), although early descriptions of it as an 'obstacle for marital bliss' go back as far as Theodoricus Borgognoni (1205-1298) and Nicolaes Tulp (1593-1674). (1) PD presents commonly with the bending of the penis. Many times, pain in the penis at erection is also one of the first complaints. Another early symptom is feeling a nodule, usually on the dorsal and/or lateral side, which is commonly called 'plaque'. As a result, the patient is often anxious about malignancy. Furthermore, many patients worry about the real or imagined loss of their sexual capacity. Potential complications include insufficient rigidity (erectile dysfunction) and awkward vaginal intromission, in which the penis can be inserted only with great difficulty. The patient and his partner invariably ask questions about the cause of PD including possible heredity. As with all other disorders with a form of sexual impairment, PD is characterized by taboos. Because it is an uncomfortable topic, and therefore under-discussed in public, people tend to mistakenly believe PD is less prevalent than it actually is. (2)

Unfortunately, there is currently no cure for PD. Patients still have to depend on symptomatic medical and surgical treatments. In 2020, however, much more about its causes is known compared to previously. Fibrotic changes in the tunica albuginea (TA), the thick capsule surrounding the penile corpora cavernosa (CC), and genetic susceptibility both play a major role. At the beginning of the 1900s, the genetic association of PD with Dupuytren's disease (DD) was already mentioned in the Dutch scientific medical literature. (3)

The tunica albuginea

The TA is a two-layered structure of inner circular and outer longitudinal coats of connective tissue, encompassing the paired CC; it consists of elastin and collagen. An incomplete septum separates the CC and anchors dorsally to the circular inner layer of the TA.

Penile hemodynamics

The hemodynamic process that leads to an erection comprises four physiological mechanisms (Figures 1 and 2):

- activation of parasympathetic, non-adrenergic and non-cholinergic nerves, releasing nitric oxide through sexual stimulation;
- flow to the corpora by dilation of cavernous arteries and the helicine arterioles;
- expansion of the lacunar spaces and trapping of blood by compression of the draining venules through relaxation of the trabecular smooth muscle; and
- sufficient compression of the subtunical venules and reduction in blood outflow through compliance of the TA and the connective tissue matrix. (4)

Figure I. In the flaccid state, the arteries, arterioles and sinusoids that make up the CC are contracted. Blood can flow freely through these spaces and can exit via the emissary veins. Figure II. Arteries, arterioles and sinusoids relax during the erect state. This causes the constriction of veins and venules, preventing outflow via the emissary veins by pressure of the TA. An erection is established by vascular inflow exceeding outflow.

The role of androgens

In the 1990s, androgen ablation by castration in animal models produced a marked increase in the extracellular matrix within the TA, with an approximately two-fold concomitant reduction of the smooth muscle to connective tissue ratio. (5, 6) According to clinicians, this reduction in tissue fibro-elastic properties compromised the cavernous tissue compliance and decreased the penile hemodynamics, resulting in erectile dysfunction by impairing the veno-occlusive function of the TA. (7)

In 2003, Shen and coworkers showed that androgens are also indispensable for the maintenance of a normal ultrastructure of the TA. (8) In castrated rats, they found a significant reduction in thickness of the TA. The TA of the intact animals was rich in elastic fibers, and the architecture showed typical regular arrangements, but the TA from castrated animals showed reduced density of elastic fibers and replacement by collagen. In 2005, it was suggested that androgens modulate the extracellular matrix through expression of growth factors. (9) Alongside this, case studies corroborated the restoration of erectile function in men with venous leakage after androgen treatment. (10, 11)

After 2010, several investigators showed that low testosterone levels could contribute to the pathogenesis of PD because of the androgens' influence on collagen metabolism by modulating the activity of matrix metalloproteases and tissue inhibitors of these enzymes. (12, 13, 14) The aforementioned observations suggest that androgens play a major role in maintaining the architecture of the spongy tissue within the CC as well as the structure of the TA. This could explain why PD rarely occurs in young men.

Fibrosis

Fibrosis is the formation of excess connective tissue in an organ or tissue. This occurs in rare diseases such as idiopathic pulmonary fibrosis and systemic sclerosis, but also in more common disorders, such as liver cirrhosis, kidney disorders and inflammatory skin- and intestinal diseases. The deposition of collagen is an indispensable yet reversible part of the wound healing process. It can be disrupted, for example by repeated tissue damage in the same location or when the healing process, which normally is strictly regulated, destabilizes. Over the last few decades, there has been increasing evidence that stem cells play a major role in undisturbed wound healing. These cells counteract healing anomalies, accelerate wound contraction and reduce the density of extracellular matrix.

Fibrosis is characterized by an abnormal and increased proliferation of fibroblasts and an excessive accumulation of connective tissue, the so-called extracellular matrix. This concerns mainly collagen, but also glycosaminoglycans such as hyaluronic acid and glycoproteins such as fibronectin. In all forms of fibrosis, the differentiation and activation of cells leading to myofibroblasts is an important process. These blasts arise from locally-available fibroblasts, and from local epithelial or endothelial cells. The myofibroblasts are the main producers of collagen and other components of the extracellular matrix.

Overexpression of members of the TGF- β and other pro-fibrotic factors, such as myostatin and plasminogen activation inhibitor-2 have been found in PD plaques and are released during the acute inflammation subsequent to trauma. A fibrotic plaque then becomes apparent and can calcify or even ossify. (15) A suspected counteractor for pro-fibrotic factors is iNOS. As it leads to NO release, monocyte chemotactic protein 1 is attracted by the fibrin in the TA, probably inducing iNOS. This proposal is supported in animal experiments by the reverse correlation of pro-fibrotic factor levels and iNOS activity, regulated by gene transfer and L-N-(1-iminoethyl)-lysine acetate inhibition. (15)

Fibrocytes are circulating connective tissue progenitor cells and their transformation into myofibroblasts is influenced by various growth factors, cytokines and clotting factors. With the advance of the wound healing process, the myofibroblasts eventually disappear through apoptosis. There is evidence that epigenetic changes in fibroblasts or myofibroblasts could contribute to fibrosis formation. (16)

Genetics

PD, DD and Ledderhose's disease (LD) are largely similar fibro-proliferative disorders, characterized by abnormal collagen deposition in the TA of the penis, palmar fascia of the hand and plantar fascia of the foot, respectively. In DD, nodules and cords can form in the

connective tissue, the latter of which can cause debilitating flexion contractures of the digits. These diseases are thought to have a similar disease mechanism, indeed Abernathy (UK) first reported on their association in 1828. (17)

In the 1960s, one view was that PD patients had intercourse more frequently and more vigorously than age-matched cohorts, but in scientific practice it was impossible to prove this. However, there is no question that an accident during penetration when the penis bends excessively could induce PD. More recently, it was shown that the three disorders (PD, DD and LD) have a familial aggregation and several genetic risk variants are known to be associated. In 2004, Qian et al. already demonstrated that the patterns of gene expression alteration of certain genes in DD and PD were similar, indicating a common pathophysiology. (18) Gene expression, in this case messenger RNA is a derivative of family genetics. Biological cell studies identified an overlap in patterns of chromosomal aberrations in fibroblasts from PD and DD lesions. In 2012, our research group associated nine loci to DD in the first genome-wide association study (GWAS) of DD, and one of these nine loci could also be associated with PD. (19) A more recent GWAS discovered 17 additional loci for DD. (20) Our group will soon carry out a GWAS with the new data of approximately 63,000 individuals and perform a meta-analysis of DD with other cohorts to identify additional DD loci. This also provides the opportunity to further explore the genetic correlation of DD with PD.

This thesis discusses the following questions and issues:

- What is the current knowledge about PD with regard to its history, epidemiology, pathophysiology, pathogenesis and therapeutic options, and which of these areas shows the most significant gaps? (Chapter 1)
- Which nonsurgical treatments have been proposed for PD and related fibro-proliferative disorders throughout the ages? (Chapter 2)
- What are the long-term outcomes and complications of current treatment methods and how do they compare with each other? (Chapter 3)
- How does PD influence sexuality and do homosexual patients need a different approach? (Chapter 4)
- What is the prevalence of PD in patients with DD and LD? (Chapter 5)
- Which aspects of PD (and DD) can be genetically explained and which genes are responsible? (Chapter 6)
- What are the effects of verteporfin on PD and which molecular biological pathways are involved? (Chapter 7)
- How can we improve future PD research and treatment? (Summary and general discussion)

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