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Peyronie's Disease: A Literature Review On Epidemiology, Genetics, Pathophysiology, Diagnosis and Work-Up

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ABSTRACT
Peyronie's disease (PD) is a disorder of tunica albuginea of the corpus cavernosum penis, characterized by pain, plaque, penile curvature, and plaque calcification. The epidemiological data on PD is inconsistent with recent reports stating a prevalence of up to 9%, affecting men of all ages, from teenagers to men older than 70 years. Evidence showing the role of genetics as a causative factor in PD is just being understood. Chromosomal abnormalities and single-nucleotide polymorphisms have been shown to be associated with the fibrotic diatheses. In addition, tunical mechanical stress and microvascular trauma are also contributory factors in the patho-physiology. Diagnosis of PD is usually apparent from the patient's history and clinical examination and other conditions should be excluded. Extensive understanding of molecular patho-physiology is necessary for identifying and developing newer and more effective drug targets for the disease.
Key words: Peyronie's disease, Tunica albuginea, infertility, men

I. BACKGROUND

Peyronie's disease (PD) can have devastating psychological and physical effect on the male patient. Often, the condition is also associated with erectile dysfunction (EF) and, therefore, can also impact the psychological well-being of the sexual partner. PD is a disorder of penis curvature which is manifested by a fibrous inelastic scar at tunica albuginea, observable with a flaccid penis. Such scar causes the penis to abnormally curve, narrow, and shorten leading to painful erection and difficulty in coitus. The condition was first described by Frannois de la Peyronie in the year 1743. From then, numerous treatment modalities have been tried and researched around the world by scholars, but unfortunately, none of the treatments available are reliable enough to provide a significant cure. Still today PD remains a therapeutic dilemma for the healthcare fraternity. [1]

The present literature review outlines the prevalence, genetics, patho-physiology, diagnostic methods, and work-up of Peyronie's disease. Recent advances in the knowledge about PD have been included, research information which provided no significant outcomes has been omitted from this review.
The main objective for this review is to provide a practical approach to the understanding of Peyronie's disease which can lead to significant positive treatment outcomes.
It is noteworthy that PD is not an infectious disease and do not get transferred from one partner to the other [2]

II. EPIDEMIOLOGY

Most of the healthcare providers feel that there is probably underestimation of PD as most men feel embarrassed about reporting this [2,3] as till date no convincing cohort data have clearly characterized the incidence and /or prevalence of PD among the general population . This is actually a risky behavior since such tendency prevents them from seeking proper medical attention and getting positive outcomes when the symptoms are mild and properly manageable. Whereas, Hellstrom mentioned that the incidence of symptomatic PD may be increasing which is explained by the increasing number of patients seeking medical help.[4]

It is estimated that the condition is present in around 0.39% to 13.1% men around the world. The prevalence may increase further in certain sub-population. For example, the prevalence of PD in men operated for radical prostatectomy is up to 16%.[5]

Till date, the biggest prevalence study for PD has been done by Schwarzer et al. (2001) which recruited 8000 men for the questionnaire-based study. Out of 8000, a total of 4432 (55.4%) men responded to the questionnaire. The results showed that 3.2% subjects had newly developed palpable plaque. The prevalence for age groups 30-39, 40-49, 50-59, and 60-69 years was 1.5%, 3%, 3%, and

4% respectively. The prevalence was maximum (6.5%) in men older than 70 years. [6]

Peyronie's disease is commonly associated with some comorbid conditions and risk factors such as diabetes, hypertension, hyperlipidemia, erectile dysfunction and excessive consumption of alcohol [7-8]

The exact etiology of Peyronie's disease is not understood properly and numerous theories are available, penile trauma is considered a major causative factor. Penile trauma might be caused by acute and severe conditions like accidents or surgical procedure, or it may be due to repetitive microtrauma occurred during coitus. Although all men are exposed to some level of penile trauma during sex, very few of them develop PD due to microtrauma. This indicates that other factors like genetics also contributes to the development of PD. Some potent risk factors for PD are a history of nongonococcal urethritis, smoking, an inflammatory genital disease in a partner, fibromatous lesions of the genital track, and history of genital tract surgery [9]

Controversies still exists in regards to hormonal factor as a cause of PD. Studies over the years suggested that hypogonadism is related to PD. Moreno et al. (2009) in their study of 121 PD patients found that low testosterone levels (<300 ng/dL) are found in almost 74.4% PD patients. The study also suggested that hypogonadal men have a more penile curvature as compared to eugonadal PD patients.[10] However, a study by Kirby et al. (2015) found that although hypogonadism is prevalent in PD patients, low levels of testosterone may not be associated with higher penile curvature in all the patients [11.]

In another case-controlled study, Bjekic et al. (2006) evaluated the risk factors associated with PD, 82 men with well-defined PD were compared with 264 men who never had erectile dysfunction and any signs of PD. The study identified risk factors associated with PD which is agenetic predisposition of Dupuytren contracture; minor vascular penile trauma either due to accident or surgery of genital track or prostatectomy; systemic vascular diseases like diabetes mellitus, hypertension, and hyperlipidemia; smoking; and alcohol abuse. Long-term use of beta blockers, especially propranolol, and a history of non-gonococcal urethritis were also found to be prevalent in patients with PD thus suggesting their link. [12]

It has been suggested that an early age (40-50 years) presentation of the disease and the presence of hypertension, diabetes mellitus and dyslipidaemia pose a greater risk for early disease progression.[7]

Different hypothesis about genetic etiology for PD has been proposed. These hypotheses included 1. Familial aggregation and genetic transmission mode via HLA-B7 cross-reacting group; 2. Chromosomal abnormalities like duplication of chromosome 7 and 8 and deletion of chromosome Y; 3. Single nucleotide polymorphism leading to elevated levels of transforming growth factor -β1 (TGF-β1); 4. Overexpression of gene pleiotrophin (PTN/OSF-1) and monocyte chemotactic precursor protein-1 (MCP-1) gene; and 5. Epigenetic regulation by Histone deacetylases (HDACs). Among all these theories, the familial aggregation and genetic transmission mode via HLA-B7 cross-reacting group theory is widely accepted and understood .[13]

The natural history of Peyronie's disease is variable among different patients. The progression of the condition may take place over several years. PD has been observed as a self-limiting condition in earlier research and it has been found that most of the cases resolves spontaneously. The earlier studies suggest that the penile angulation becomes stable once it is calcified. However, recent studies found that Peyronie's disease plaque gets completely resolved without treatment in only 13% of cases while 40% patients feel that their condition is in progressive stage. The remaining men (47%) reported no change in their condition. With the background of these studies, healthcare professionals suggest that the condition must be evaluated and treated as soon as the patient complains of significant coital failure. Observations suggest that the treatment of PD becomes more promising if the condition is detected as early as possible and treated.

III. GENETICS

Although the current understanding of the genetic factors associated with PD is limited, significant advances have in the past three decades.

Genetic predisposition had been suggested as a causal factor, because of the familial clustering of the condition and studies assessing mutation of human leukocyte antigen (HLA-B7) linkage have shown that PD is strongly associated with both Dupuytren's contractures(DD) and human leukocyte antigen B27-B7. [14-15]

Bias et al (1982) through pedigree analysis of three families affected by PD and DD showed that the conditions have an autosomal dominant mode of inheritance with incomplete penetrance.[16] Controversially other studies showed that familial seggregation patterns suggested independent

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assortmentof HLA loci, decreasing the likelihood that these loci contribute to the development of PD.[17]

Studies conducted by other authors detected karyotypic abnormalities in PD plaque-derived fibroblasts. Chromosomal abnormalities detected inluded three numerical changes, including duplication of chromosomes 7 and 8 and deletion of chromosome Y.[18-19]

The most common chromosomal abnormalities detected were anueploidy of chromosomes 7 and 8 , followed by chromosomes 17 and 18 and then the Y and X chromosomes. [20]

Single nucleotide polymorphism leading to elevated levels of transforming growth factor -β1 (TGF-β1). Although the mechanism for elevated levels of TGF-β1 has not been elucidated, it is hypothesized that this expression is due in part to the presence of heritable single-nucleotide polymorphisms (SNPs) that could affect gene expression. [13]Qian and associated (2004) performed a study comparing expression profiles of PD patients with those of DD patients. A series of 15 genes were upregulated and none were downregulated in the PD plaque versus the normal TA. Of the genes upregulated, the one most prominently increases were MMPs involved in collagen breakdown, specifically MMP-2 or MMP-9 in one half of the PD plaques, in addition to genes involved in actin-cytoskeleton interactions required for fibroblasts and myofibroblasis to generate the contractile forces.[14] According to the findings of another study, the lower expression of apoptotic genes may cause the persistence of collagen-producing cells that ate upregulated, consequently resulting in plaque formation. Similar expression levels of apoptotic genes in both tunica albuginea and Peyronic plaques my be caused by the generalized physiopatholgic alterations in the tunica albuginea that lead to plaque formation at a vulnerable region subjected to recurrent trauma. [15]

IV. PATHOPHYSIOLOGY

Multiple theories for PD have been proposed although the exact pathophysiology remains unclear. All these theories are discussed here.

Anatomy based hypothesis:

The anatomy of the vascular network around the tunica albuginea is unique. The arteries are on the exterior side and are protected by a cuff of loose aereolar tissues while the veins are in direct contact with the fibrous portion of tunica albuginea.[15] The most widely accepted theory is trauma or microtrauma to the tunica albuginea during erection in genetically susceptible individuals. Repeated microvascular injury to the tunica albuginea causes inflammation, disruption of the elastic fibers and deposition of fibrin.[21] Fibrin is a strong chemoattractant, thus promoting the influx of inflammatory cells and mediators like macrophages, neutrophils, mast cells, cytokines and fibroblasts. [21-22]The influx of leukocytes and macrophages, as an inflammatory response, continues via arterial flow resulting in production of large amount of cytokines. Due to constrained venous outflow, cytokines cannot be dispersed or degraded resulting in excessive production of collagen fiber and matrix, leading to the destruction of delicate collagen network and elastic fiber. [14-15]

During the early phase, inflammation and edema irritate the nerve endings leading to pain during and/or without an erection. The pain gradually subsides with the maturation of inflammation and death of nerve fibers. In the chronic phase of inflammation, erectile tissues are affected leading to erectile dysfunction. The changes occurring during both the phases are characterized by their clinical presentations viz. pain, plaque, and penile deformity during the initial phase and plaque, penile deformity and erectile dysfunction during chronic phase.[15]Ventral penile curvature has also been reported due to urethral manipulation and it is called as as Kelami syndrome or urethral manipulation syndrome. Ultrasound evidence suggests that the underlying mechanism for penile curvature is one of periurethral scarring, perhaps secondary to inflammation from urethral manipulation[a].This theory basically explains that PD is caused due to aberrant wound healing process in response to trauma within the layers of tunica albuginea.

Oxidative damage theory, autoimmunity theory, and gene theory:

Fibrogenesis in many chronic hepatic, pulmonary, and neuronal degeneration disease is caused due to oxidative stress. Studies found that free radicals generated due to oxidative stress can lead to the generation of superoxide, peroxynitrite, and peroxide species causing lipid peroxidation and tissue damage along with the enhanced activity of fibroblast and thus fibrogenesis. Excessive fibrous tissue generation is the main factor of Peyronie's disease. Therefore, the hypothesis of oxidative stress and related fibrogenesis can be applied to the pathophysiology of PD.[23] Nitric oxide synthase is produced when smooth muscle cells and macrophages are stimulated. Up regulation of nitric oxide synthase causes the generation of high levels of nitric oxide, a potent free radical leading to

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oxidative stress and poor vasorelaxation. It is thought that this process exists in PD.[24]

Studies have shown that PD shows feature of the autoimmune disorder. One of such feature is a cell-mediated response to inflammation. Since there is excess fibroblast activity and increased elastin production, studies showed the presence of elastin antibodies like anti-tropoelastin (reflecting elastin synthesis) and anti-α-elastin (reflecting elastin destruction). Increased antibody production is another feature of autoimmunity in PD.[25]

Researchers have noted that two general mechanisms aid the development of extracellular matrix in case of PD which is firstly, excavation of plasma protein like plasma fibronectin and fibrinogen and secondly synthesis of fibronectin variants by the wounded tissue. When hereditary trend for PD has been observed for a long time, the relation of HLA-B27 and HLA-B7 is still debatable.[26]

Various observations suggested that increased expression of TGF-β1 and higher levels of pro-and anti-fibrotic gene products can be observed in PD. Also, there is an increase in the ratio of nitric oxide to reactive oxygen species (ROA) in the tunica albuginea of penis. All these factors have been found to be related to formation and progression of plaque in PD patients. The genes like OSF-1 (osteoblast recruitment), MCP-1 (macrophage recruitment), and procollagenase IV (collagenase degradation), with other fibrotic genes, responsible for the generation of this plaque causing factors, are thus considered are regulatory genes for PD.[27]

Molecular mechanisms: Role of TGF-β

TGF-β (Transforming growth factor- β) has been found to be associated with fibrosis in many soft tissues as well as in erectile dysfunction. Inflammatory cells such as platelets, macrophages, and fibroblasts synthesize TGF- β, which is an inactive latent peptide. On activation, TGF- β binds to specific cell surface receptor inducing a signal transduction cascade. Such cascade leads to increased synthesis of connective tissue and inhibition of collagenase enzyme. It is noteworthy that TGF- β is also capable of inducing own synthesis as well as specific receptors. Such auto-upregulation, thus leads to a continuous cycle of connective tissue and abnormal fibrotic changes, thus leading to plaque formation. [28]

Myostatin is a member of TGF-β family also known as GDF-8. The protein induces new plaques and also condenses the plaque already formed by TGF-β. Overexpression of myostatin has been found in the majority of the PD plaques. It has also been found that synthesis and release of pro-fibrotic factors like plasminogen activator inhibitor-2 and ROS along with TGF-β aggravate after the plaque enters its chronic stage. This leads to a formation of dense fibrotic plaque which also gets calcified and ossified. Osteoblasts can also be found in chronic plaques. [15,29]

This entire knowledge of pathophysiology suggests that Peyronie's disease plaques and other related symptoms are developed due to various conditions and there is no exact and clear pathophysiology. Researchers continue to explore new physiological pathways causing the development of PD.

WORK-UP

The natural history of Peyronie's disease is variable among different patients. The progression of the condition may take place over several years. PD has been observed as a self-limiting condition in earlier research and it has been found that most of the cases resolves spontaneously. The earlier studies suggest that the penile angulation becomes stable once it is calcified. However, recent studies found that Peyronie's disease plaque gets completely resolved without treatment in only 13% of cases while 40% patients feel that their condition is in progressive stage. The remaining men (47%) reported no change in their condition. With the background of these studies, healthcare professionals suggest that the condition must be evaluated and treated as soon as the patient complains of significant coital failure. Observations suggest that the treatment of PD becomes more promising if the condition is detected as early as possible and treated.[30]

The patients with Peyronie's disease can present with combination of following conditions:

1. Pain in penis during erections
2. The curvature of the penis. The angulation can be noted during erection in some patients while in some cases palpable plaque can be noticed at the site of angulation even in a flaccid penis.
3. An hourglass deformity caused at the site of the plaque due to the indentation in the penile shaft.
4. Reduced erectile function due to loss of rigidity.
5. Problems with intercourse due to penile buckling caused by the angulation.

The curvature of the penis can reach a maximum angle of 90° and makes the treatment difficult.

Usually, the penile pain resolves without any therapy. Some patients also observe a reduction in pain or resolution of before the

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appearance of plaque or angulation. While such change was considered as a self-resolving feature of PD in an earlier time; present research suggests that resolution in pain is due to the chronic stage of PD where the nerve fibers innervating the organ dies due to extended fibrosis. [31]PD can be classified into two phases, acute and chronic. The acute phase of the condition is characterized by penile pain, minor curvature and a nodule in the penis.[32] These features indicate changing inflammatory pattern and the phase lasts for around 18-24 months. Chronic phase of PD is characterized by a stable and easily palpable plaque, calcification of plaque, and prominent angulation. Loss of erectile ability is a prominent feature of the chronic phase. Emotional and psychological disturbances, although not a physical feature of PD, are often observed in males with erectile dysfunction related to PD and warrants for psychiatric therapy and counseling.[33]

In addition to the information about sexual history, information about history of diabetes, hypertension, elevated cholesterol, and smoking as well as any evidence for vascular risk factors for erectile dysfunction.

The recently validated PD questionnaire (PDQ) addresses not only the concerns of the patient regarding structural changes of the penis but also how PD affects his overall psychological condition. [34-35]

Assessment of the erect penis through photographs taken at home is not useful clinically because of the inability to adequately represent and measure a three-dimensional deformity.[36-37]

DIAGNOSIS OF PD

The diagnostic procedure for PD includes physical examination, laboratory testing, and other tests.

Physical examination:

The diagnosis of PD is clinically determined by the patient's history and penile examination. The physical examination should include a general assessment of the femoral pulses, hands and feet for detecting possible Dupuytren's contracture or Ledderhose scarring of the plantar fascia[38], appearance of the flaccid penis, and whether it is circumcised and measurement of stretch penile length, rigidity, girth and curvature during erection. [39-40] Assessment of health of erectile tissue can be done by stretching the penile shaft. PD patients with significant corporal fibrosis-like the one with concurrent chronic diabetes loose the stretchability of the penile shaft. On the other hand, ability to stretch penis is usually normal in young patients with psychogenic or mild arteriogenic erectile dysfunction, but need differentiation for the diagnosis of PD.

Laboratory investigation:

No specific blood tests are available for diagnosis of PD. While the association between the condition and overexpression of HLA-B7 antigen has been found, it cannot be considered a specific marker for the disease. Also, only laboratory investigation of HLA-B7 is not practical as the condition needs thorough physical examination and history taking. [41]

Imaging studies:

Imaging of penile shaft is important in the diagnosis of PD in order to note calcification of the plaque as it signifies the end point of chronic PD after which no further angulation occurs. Imaging for the diagnosis of PD is done in multiple ways as follow:

1. A simple radiograph using X-ray can identify calcification in the plaque in the majority of the cases.
2. Ultrasonography of penis helps in defining the extent of the plaque. The characteristic echogenic shadowing found in a USG image helps to pinpoint calcification in the plaque.
3. Corpus cavernosograpy can also be used to define the plaque as well as any compression of the cavernosal space. However, this test is usually not applied because of its cost as well no extensive outcomes as compared to simple USG.
4. MRI is an effective way to identify the plaque in its early stages when there are only fibrous tissues present. However, this test is usually not applied because of its cost, but can be helpful in certain questionable cases. [42]

Other investigations:

Duplex ultrasonography with intracavernous injection of vasoactive substance like alprostadil, and/or dynamic infusion cavernosometry and cavernosography can be applied for the PD patients with erectile dysfunction in order to identify underlying arteriogenic ED or corporal venoocclusive dysfunction.[43]It visualizes penile tissues and detects areas of calcification[40]. A calcification grading system was published and introduced recently. Patients with grade 3, or the most extensive, calcification (>1.5cm in any dimension or multiple plaques ≥1.0cm) were more likely to undergo surgery when they also had satisfactory erectile function. This is in contradistinction to those who had less severe calcification of grade 1(<0.3mm) or

grade 2 (0.3 to 1.5 cm) or no calcification in whom there was no evidence of an increased likelihood of proceeding to surgery.[44]

V. CONCLUSION

Peyronie's disease has been notified in the healthcare field from centuries and countless non-surgical therapies have been used, but with minimal success. Collagenase clostridium histolyticum (CCH) is the only non-surgical treatment approved for clinical application by US FDA. CCH has been properly established for its safety and efficacy in long-termtrials also. While multiple theories have been proposed for the pathophysiology of PD, further understanding of the intricate physiology of PD and genetic predisposing is required. Such knowledge is extremely important to identify new drug targets for PD treatment. Numerous new drugs have been tested on human subjects for the treatment of PD, but only a few drugs like Botox, iloprost, and Peironimev-Plus have shown some promising outcomes. Still extensive and rigorous trial are required to prove reliability and repeatability of drug outcome results.

Recently, cell-based and small molecule therapies have been observed for their efficacy in vivo (decorin, HDAC2 shRNA, stem cells) and in vitro (HS-173). The promising results of these studies provide implications for future research and potential drug targets.

On the other hand, surgical therapies for PD are well-researched and applied more widely for treating PD as per its stage and clinical presentation. Ongoing research regarding molecular pathophysiology, novel drug targets, and new non-invasive therapies will provide a better future for PD patients.

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