Original Article

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Evaluation of Similar Genetic Pathophysiology Underlying Diabetes Mellitus and Peyronie's Disease: *WNT-2* and *TGF Beta-1* Genes

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Abstract

Aim: Some recent studies on PD have focused on the *WNT-2* and *TGF-β1* gene loci, but its genetic basis is still not clearly known. In this context, we aimed to evaluate the presence of *WNT-2* and *TGF-β1* gene expression and genetic similarity between patients with Peyronie's disease (PD) and comorbidities, especially diabetes mellitus (DM).

Methods: Between May 2020 and April 2021, 57 patients diagnosed with PD were included in this cross-sectional study. The presence of comorbidities [Dupuytren's contracture (DC), DM, hypertension (HT), dyslipidemia, and erectile dysfunction (ED)] was recorded. For genetic analysis, the *WNT-2* and *TGF-β1* genes were analyzed in the patients' serum.

Results: The mean age was found to be 50.2. 45.6% of the patients had DM, 19.1% had HT, 14% had dyslipidemia, 5.3% had DC, and 40.4% had ED. *TGF-β1* gene expression was found to be increased in all patients; *WNT-2* gene expression was found to be increased in 80.7%. When subtypes of the *TGF-β1* and *WNT-2* gene expression were analyzed, 52.6% of patients with *WNT-2* gene expression and 95.5% of patients with *TGF-β1* gene expression were found to be homozygous, and the others were found to be heterozygous. Patients with DM and PD had significantly higher homozygous *WNT-2* gene expression (p=0.03). No significant relationship was found between other comorbidities and these genes.

Conclusion: Homozygous *WNT-2* gene expression was found to be increased in PD with DM. These data could be used to explain the genetic pathophysiology of PD in diabetic patients.

Keywords: Diabetes mellitus, Peyronie's disease, *TGF-β1*, *WNT-2*

Introduction

Peyronie's disease (PD) is an acquired penile deformity characterized by hard fibrotic plaques, particularly on the dorsal surface of the penis. Its prevalence ranges from 0.3% to 13.1%. The most accepted hypothesis for the pathophysiology of PD is that recurrent trauma causes microvascular damage to the tunica albuginea. Myofibroblasts do not undergo apoptosis because of microtrauma, and collagen accumulation persists, which is the most accepted hypothesis for PD pathophysiology (1-3). Diabetes mellitus (DM), hypertension (HT), lipid metabolic disorders, ischemic cardiopathy, erectile dysfunction (ED), smoking, and excessive alcohol intake are considered to be the most prevalent risk factors for PD (4).

The genetic background of PD has been investigated using newly developed technologies to explain its etiology and pathophysiology. Patients underwent various genetic tests, including human leukocyte antigens (HLA), single nucleotide polymorphisms, karyotypic abnormalities, and gene expression variations. In particular, some recent studies on PD have focused on the

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WNT-2 and *TGF-β1* gene loci, but its genetic basis is still not clearly known (5,6).

In this study, we aimed to determine the association between the gene loci *WNT-2* and *TGF-β1*, which may be related to PD, and DM and other comorbidities associated with PD and these gene loci.

Methods

Compliance with Ethical Standards

Ethical approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Prof. Dr. Cemil Tascioglu City Hospital (approval no.: 446, and date: 29.12.2020).

Study Design

Fifty-seven informed and voluntary patients who were examined at the andrology outpatient clinic between May 2020 and April 2021 were included in this cross-sectional study. Patients with a congenital penile curvature, previous penile surgery, or penile curvature secondary to a known trauma were excluded (Figure 1). All patients in our study were evaluated for the presence of DM, Dupuytren's contracture (DC), hypertension, lipid profiles, smoking and alcohol consumption, and ED. All patients' *WNT-2* and *TGF-β1* gene expressions were examined and recorded for genetic evaluation. The international index of erectile function-5 score was used to evaluate erectile functions (7).

The expression of the *WNT-2* and *TGF-β1* genes was determined by analyzing blood samples from each patient. Gene expression analyses of *WNT-2* and *TGF-1* were performed with a real-time device (the Thermo Fisher Quants Studio 6 Pro real-time device). Individual genetic analyses were performed on each patient using both TaqMan SNP Genotyping Assays (rs1800471 and rs4730775).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) mac version 21 (SPSS Inc., Chicago, IL, USA) software was used to evaluate the research data. Descriptive statistics are presented as numbers and percentages for categorical variables and as mean, minimum, and maximum for numerical variables. Nominal variables were analyzed using the chi-square or Fisher's exact test. The statistical significance level for all parameters was 95% confidence interval, and p-value less than 0.05 was considered significant.

Results

The average age of the 57 participants was 50.23±10.17 years. 45.6% of the participants had DM (all of them had type 2 DM; no patient had type 1 DM, 19.1% had hypertension, 14% had lipid metabolism disorders, 5.3% had DC, and 40.4% had ED (Table 1).

At the genetic evaluation of the patients, it was found that the increased expression of the *TGF-β1* gene was present in all patients. An increase in *WNT-2* gene expression was found in only 46 (80.7%) patients. *WNT-2* homozygous gene expression was found to be significantly higher in patients with PD, especially those with DM (p=0.03) (Figure 2).

Contrary to *WNT-2* homozygous gene expression, no statistical significance was observed between *TGF-β1* gene expression and the presence of DM (p>0.05). There was no statistically significant difference between *WNT-2* and *TGF-1* gene expression, as well as other comorbidities associated with PD (Table 2).

Discussion

The pathophysiology of PD is still unknown, as the presence of a genetic basis has been the study's focus for many years. There are only a few studies on the relationship between PD and genetic pathologies. For many years, researchers have conducted various genetic

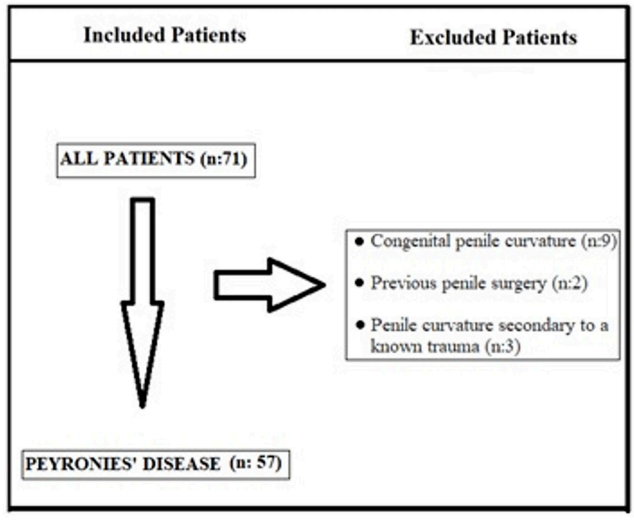

Figure 1. Flowchart of study

Table 1. Demographic data of patients	
	Mean ± SD (Min.-Max.)
Age	50.2±10.1 (30-69)
	n (%)
Diabetes mellitus	26 (45.6%)
Hypertension	11 (19.1%)
Lipid metabolism disorder	8 (14%)
Smoking	13 (22.8%)
Dupuytren's contracture	3 (5.3%)
Erectile dysfunction	23 (40.4%)
n: Number, SD: Standard deviation, Min.: Minimum, Max.: Maximum	

analyses, including autoimmunity, to explain the etiology and pathogenesis of PD.

A family history was found in 1.9% of patients with PD, and 17% of patients found that they have some genetic factors in their etiopathogenesis, according to current studies (6). A study analyzing the mutation of HLA found a genetic predisposition to PD. According to the same study, HLA was a potential predictive factor for PD. A strong association between PD and the *HLA-B27* gene was shown in autoimmunity-related studies, but no significant association was found between PD and other HLA types. In addition, other studies analyzing the relationship between idiopathic PD and HLA have shown that patients with idiopathic PD have higher HLA-B7 cross-reactions (8).

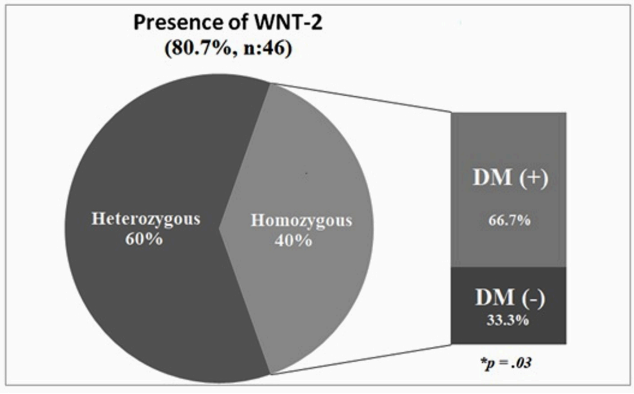

Figure 2. Relationship between *WNT-2* gene and DM
DM: Diabetes mellitus

A significant relationship was found between chromosomal abnormalities and PD in other studies. Chromosomal numerical anomalies such as Y chromosome deletion and duplication of the 7th and 8th chromosomes were found to be related to PD. Invertion [such as 46XY, inv(7)(p22q36)] and reciprocal translocation [such as 46XY, t(11;12)(q11,p11)] of chromosomes are known as other chromosomal abnormalities that were also found to be significantly associated with PD (9,10).

Several studies have focused on inherited single-nucleotide polymorphisms as the genetic cause of PD. Various hereditary single nucleotide polymorphisms such as rs1982073 (T + 29C), rs1800469 (C-509T), and rs1800471 (G915C) have been found in the *TGF-β1* gene of patients diagnosed with PD. Of all these single nucleotide polymorphisms, only the G915C polymorphism has been found to be related to PD (11).

The TGF- pathway, which is an oxidative stress and cytokine release factor, may play a role in the pathogenesis of PD. Abnormal gene expression in the TGF- pathway may lead to the formation of these abnormal fibrotic plaques (6,12,13). In another study, the expression of polymorphisms in *TGF-β1* was evaluated, and no statistically significant difference was found between *TGF-β1* and PD. According to the same study, it was found

Table 2. The presence of *TGF-β1* and *WNT-2* gene expression according to comorbidity status of patients with PD

		Presence of *WNT-2* expression (n=46, 80.7%)		Presence of *TGF-β1* expression (n=57, 100%)	
		Type of the expression			
		Homozygous	Heterozygous	Heterozygous	Homozygous
Diabetes mellitus n (%)	-	6 (33.3%)	18 (64.3%)	1 (50%)	30 (54.5%)
	+	12 (66.7%)	10 (35.7%)	1 (50%)	25 (45.5%)
	p-value	0.030*	0.086*	0.899**	0.899*
Hypertension n (%)	-	14 (87.5%)	24 (80%)	1 (50%)	45 (81.8%)
	+	2 (12.5%)	6 (20%)	1 (50%)	10 (18.2%)
	p-value	0.417*	0.887*	0.263**	0.263*
Dyslipidemia n (%)	-	13 (81.3%)	27 (90%)	1 (50%)	48 (87.3%)
	+	3 (18.8%)	3 (10%)	1 (50%)	7 (12.7%)
	p-value	0.522*	0.355*	0.136**	0.136*
Dupuytren contracture n (%)	-	14 (87.5%)	30 (100%)	1 (50%)	53 (96.4%)
	+	2 (12.5%)	0 (0%)	1 (50%)	2 (3.6%)
	p-value	0.126*	N/A	0.087**	0.087*
Erectile dysfunction n (%)	-	10 (62.5%)	18 (60%)	1 (50%)	33 (60%)
	+	6 (37.5%)	12 (40%)	1 (50%)	22 (40%)
	p-value	0.784*	0.061*	0.777**	0.777*

*Chi-square test, **Fisher's exact test
n: Number, N/A: Not applicable, PD: Peyronie's disease

that *TGF-β1* expression might help in pathogenesis, but it was not a major genetic risk factor for PD. Additionally, the expression and activity of Smad transcription factors in the *TGF-β* pathway were found to be increased in PD. Patel et al. (14) found that *TGF-β1* was more common in patients with PD (14,15). Similar to previous studies, our findings show an increase in *TGF-β1* expression in patients with PD. An increase in *TGF-β1* gene expression was observed in all patients. Upregulation of the *WNT-2* signaling pathway and high catenin levels in plaques indicate that the *WNT-2* pathway may also be related to the pathogenesis of PD (16). In immunohistochemical studies of genetic markers in Peyronie's plaques, high levels of *WNT-2* gene expression were found in the tunica albuginea of patients with PD (14,17,18). In our study, we examined the level of *WNT-2* expression in the blood samples of patients and found an increase in *WNT-2* expression of 80.7%.

Several studies on other non-genetic risk factors have analyzed the etiopathogenesis of PD. According to these studies, DM was found to be strongly associated with PD (16,19-21). In a study by Gelbard and Rosenbloom (22) evaluating the association between patients with DC and PD and the presence of DM, it was found that both DC and PD were diagnosed at a higher rate in DM patients, and that both diseases progressed more aggressively in DM patients. This relationship was found to be similar for all DM types (20). Crocetto et al. (4) showed that PD was diagnosed more frequently in patients with high insulin resistance and non-alcoholic fatty liver disease, especially in diabetic patients. It has been shown that this detected PD would progress more aggressively (4). Similarly, the higher diagnosis rate of PD in diabetic patients with a serum HbA1c level above 7 could support the hypothesis that DM and PD are associated with each other (19). None of the studies evaluating the relationship between DM and PD performed genetic analysis, and they only analyzed this relationship using retrospective data. Our study revealed a significantly higher increase in *WNT-2* homozygous gene expression in diabetic patients. Based on our findings, we hypothesize that elevated *WNT-2* homozygous gene expression may be the pathophysiological basis for the increased incidence of PD in diabetic patients. In addition, we did not find any statistically significant difference between patients diagnosed with HT, dyslipidemia, ED, and DC, which are risk factors other than DM.

Study Limitations

Our study has some limitations. First, we have a limited number of patients to analyze separately for each gene. Our findings should be supported by studies that include large patient populations. Second, in our study, the duration of comorbidities (such as DM, HT) was not analyzed. There is no published information on this subject, but there may be a correlation between comorbidity duration and gene expression. The presence of such a relationship may be investigated in the future. Third, all of the diabetes patients in our study were diagnosed with type 2 diabetes, and none of our patients had type 1 diabetes. The relationships between type 1 and type 2 DM disease subtypes and genetic expressions should be analyzed in studies with large patient populations. Another limitation is that only serum was analyzed for the presence of gene expression, and the tissue of Peyronie's plaque was not analyzed for the presence of gene expression. The results obtained from this study could be the basis for future studies that investigate the presence of gene expression at the tissue level. Despite these limitations, our study is, to the best of our knowledge, the first to evaluate the similarity of the genetic basis of PD and DM.

Conclusion

WNT-2 and *TGF-β1* gene expressions were found to be increased in PD. Although *WNT-2* heterozygous gene expression was found to be higher than that in non-diabetic patients, *WNT-2* homozygous gene expression was only found to be statistically significantly higher in patients with DM than in non-diabetic patients. According to these findings, the increase in *WNT-2* homozygous gene expression, especially in patients with DM, may play a role in the development of PD. A relationship between increased *WNT-2* gene expression and other non-diabetic risk factors (hypertension, lipid metabolic problems, and ED) could not be shown in PD. Multicenter clinical studies with a large population must support these significant relationships between increased *WNT-2* gene expression in patients with DM and PD.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Prof. Dr. Cemil Tascioglu City Hospital (approval no.: 446, date: 29.12.2020).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.T., A.G., Concept: E.T., A.O., H.L.C., Design: E.T., A.O., H.L.C., Data Collection or Processing: E.T., A.G., Analysis or Interpretation: E.T., E.T.K., H.L.C., Literature Search: E.T., H.L.C., Writing: E.T., E.T.K.

Conflict of Interest: No conflicts of interest were declared by the authors.

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