RESEARCH ARTICLE

Dupuytren's Disease: Predicting Factors and Associated Conditions. A Single Center Questionnaire-Based Case-Control Study

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Abstract

Background: Conflicting studies link several conditions and risk factors to Dupuytren's disease (DD). A questionnaire-based case-control study was set to investigate associated conditions and clinical features of DD in a sample of Italian patients. The main purpose was the identification of predicting factors for: DD development; involvement of multiple rays; involvement of both hands; development of radial DD; development of recurrences and extensions.

Methods: A self-administered questionnaire was used to investigate medical and drug histories, working and life habits, DD clinical features, familial history, recurrences and extensions. Binary logistic regression, Mann Whitney U-test and Fisher's exact test were used for the statistical analysis.

Results: A role in DD development was found for male sex, cigarette smoking, diabetes and heavy manual work. The development of aggressive DD has been linked to age, male sex, high alcohol intake, dyslipidemias and positive familial history.

Conclusion: Further studies might explain the dual relationship between ischemic heart disease and DD. According to our results, the questionnaire used for this study revealed to be an easy-handling instrument to analyze the conditions associated to DD. Nevertheless, its use in further and larger studies is needed to confirm our results as well as the role of the questionnaire itself as investigation tool for clinical studies.

Keywords: Associated conditions, Case-control study, Dupuytren's disease, Predicting factors, Questionnaire, Risk factors

Introduction

Dupuytren's disease (DD) pathogenesis has been widely studied in recent decades. Genetic predisposition was established by several studies, including genome-wide association studies (1). Autosomal dominant and matrilineal heredity patterns were found for familial cases (2, 3). Beyond the predisposing role of Dupuytren's genetic diathesis, several environmental factors seem to contribute to DD development, especially for sporadic cases (4, 5). Male sex is associated with major prevalence, earlier presentation and digital retraction (6). A prospective study by Godtfredsen et al. considered cigarette smoke and heavy alcohol consumption risk factors for DD (7). Contrasting results ascribed a causative role for DD even to hyperglycemia, both type 1 and 2 diabetes, epilepsy, phenobarbital intake, acute and chronic occupational trauma to hand and wrist (6, 8-11). Associations with Ledderhose's disease and Peyronie's disease are well known (5). Nevertheless, sporadic reports also link DD to frozen shoulder, HIV, reflex sympathetic dystrophy, dyslipidemia, cancer, increased mortality and lower incidence of rheumatoid arthritis (12-17).

Similarly confusing information exists about recurrence and extension rates, as well as factors that may predict them (5, 18). From this background, this study aimed to analyze DD clinical features and associated conditions in a sample of Italian patients. The main outcome was the identification of predicting factors for: 1) DD development, 2) involvement of multiple rays in the same hand, 3) involvement of both hands, 4) development of

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radial DD, 5) development of recurrences and extensions.

Materials and Methods

Enrolment of Patients and Controls

From October 2013 to June 2014, 59 consecutive patients affected by DD were enrolled. The patients were admitted to San Raffaele Hospital in the Orthopedics and Trauma Surgery Department, or visited as outpatients in the Hand Pathology Unit. Fourteen patients asked for medical consultation from the Hand Pathology outpatient Unit. Nineteen were admitted to the Orthopedics and Trauma Department for other medical reasons. Eight out of them underwent selective aponeurectomy for DD. Twenty-six patients were recruited during follow-up visits after selective aponeurectomy (performed in the period 2009-2013 at the same hospital). Each patient underwent a clinical examination to assess the presence of DD. A progressive number was assigned to everyone, guaranteeing anonymity in data collection. Data concerning the affected rays, Tubiana-Michon stage, as well as clinical appearance (nodule or cord), were registered in a database. For the follow-up patients, recurrences or extensions after aponeurectomy were noted and pre-surgical clinical features of DD were obtained from photographs and medical records. This was done after taking the patients' informed consent.

An initially age- and gender-matched control group was designed, including Caucasian patients reaching the Orthopedics and Trauma Surgery Department for traumatic reasons (hence, apparently unrelated to DD). Before the enrolment of controls, possible unrecognized DDs were ruled out by the clinical examination of hands. A progressive number was assigned to each control. Among the 19 inpatients enrolled in the case group, 11 were originally meant to belong to the control group: DD was incidentally diagnosed during routine physical examination, thus they were eventually considered as cases.

Hence, the control group was finally composed of 104 consecutive Caucasian patients. A perfect matching for age and sex between the two groups was impossible to achieve, also considering the 9, 6% rate of new diagnoses of DD found in the initial control group.

Questionnaires

The case group completed a questionnaire investigating the patients' age, sex, BMI, working habits, life habits (cigarette smoking, alcohol and drugs intake), medical and pharmacological history, presence of plantar fibromatosis or Peyronie's disease [Figures 1; 2]. Cut-offs for working habit analysis were set complying with a previous French study, to standardize the results (11). Dupuytren's disease was examined in depth, including familial history, both hands involvement, age at first diagnosis, treatments performed, recurrences and extensions after surgery [Figure 3]. The control group completed the same questionnaire, with the exception of the questions concerning DD. The questionnaire was anonymous. The progressive numbers of cases and controls were written on the top, in order to fill in the database matching their answers with clinical examination data. The questionnaire was edited in Italian, using simple words and avoiding excessive use of medical terms, in order to be easily completed by patients from different cultural contexts. Furthermore, it was set up with redundant questions, not to forget any detail of the patients' histories. Redundancies were then eliminated during database filling. Figures 1, 2, 3 published in the Appendix, show the English version of the questionnaire. The anonymous questionnaire was preferred to a medical interview in order to reduce possible omissions due to embarrassment or lack of confidence with the physicians, especially in the "drug addiction" and "Peyronie's disease" sections.

Statistical Analyses

Descriptive statistical analyses were performed to analyze the features of each group. Kolmogorov-Smirnov test was used to assess the distribution form of each variable. Independent samples Mann Whitney U-test was used to evaluate statistically significant differences between means of non-parametric variables of cases and controls (i.e. years of exposure to vibrating tools). Fisher's exact test was used to compare categorical dependent variables (i.e. alcohol consumption). Binary logistic regression with backward selection was used to study the impact of the variables analyzed to the above listed outcomes. An adjustment was eventually performed on the odds ratios (aOR) of each variable, to reduce the confounding effects following poor matching. Confidence intervals were set at 95% and statistical significance was reached at $P<0.05$.

Results

Questionnaire, General and Medical Part: Comparison Between Case and Control Groups

Forty-five male (76%) and 14 female (24 %) patients formed the case group. Sixty-one males (59%) and 43 females (41%) belonged to the control group.

The age ranged from 44 to 80 (mean 65.4, SD 8.8) among patients and from 40 to 79 (mean 59.4, SD 10.2) among controls. BMI distribution is shown in Table 1. Regarding working habits, most patients from both groups reported doing heavy manual works for more than two hours a day and denied a daily use of vibrating tools. Heavy manual work for more than two hours a day only showed a significant association with Dupuytren's Disease presence in males ($P= 0.026$). No associations were found between vibrating tools exposure and DD. Nevertheless, case and control groups showed differences in the number of heavy-working years. The mean years spent performing heavy manual work were 40.3 (SD 13) for the case group against 33.5 (SD 13.5) for the control group ($P=0.03$). Similarly, cases showed a mean of 38.7 (SD 14.9) years of vibrating tools use against the 30.8 (SD 14.5) years of controls ($P=0.03$). No significant differences in alcohol consumption were found after a sex-stratified analysis [Table 2].

Even smoking habits were analyzed comparing same-sex subgroups [Table 3]. Past or current smoking resulted significantly associated with DD ($P=0.007$) in males. No

Table 1. BMI in case and control groups

BMI	Under-weight <18.5 N (%)	Normal 18.5-24.9 N (%)	Overweight 25-29.9 N (%)	Obese Class I 30-34.9 N (%)	Obese Class II 35-39.9 N (%)	Obese Class III ≥40 N (%)
Male cases	0	16 (35)	26 (58)	3 (7)	0	0
Female cases	0	9 (64)	2 (14)	3 (22)	0	0
Male controls	0	27 (44)	22 (36)	9 (15)	2 (3)	1 (2)
Female controls	0	20 (47)	16 (37)	5 (12)	1 (2)	1 (2)

Table 2. Alcohol consumption

Sex		Alcohol consumption*				Total patients N (%)
		<1/month N (%)	≥1/month N (%)	≥1/week N (%)	≥1/day N (%)	
Male	Cases	9 (20)	10 (22)	6 (13)	20 (45)	45 (100)
Male	Controls	20 (33)	13 (21)	11 (18)	17 (28)	61 (100)
Female	Cases	6 (43)	3 (21.5)	3 (21.5)	2 (14)	14 (100)
Female	Controls	27 (63)	7 (16)	4 (9)	5 (12)	43 (100)

* Alcohol consumption reported as frequency of consumption of at least an alcohol unit.

Table 3. Smoking habits

	Never smoker N (%)	Former smoker N (%)	Current smoker N (%)	Total N (%)
Male cases	10 (22)	25 (56)	10 (22)	45 (100)
Male controls	19 (31)	24 (39)	18 (30)	61 (100)
Female cases	10 (71.5)	1 (7)	3 (21.5)	14 (100)
Female controls	23 (53)	14 (33)	6 (14)	43 (100)

significant differences in the daily amount of cigarettes were found between cases and controls. No significant differences in the incidence of any specific comorbidity resulted from this analysis.

Questionnaire: Clinical Features of Dupuytren's Disease

Analyzing the clinical features of DD in these patients, 40 (68%) reported an involvement of more than one ray in the same hand. Thirty-five patients (59%) had bilateral DD, and 19 (32%) had an involvement of radial rays. The most affected rays were the fourth (68% in the right hand, 54% in the left hand), the fifth (42% in the right hand, 37% in the left one) and the third (39% in the left, 28% in the right). The involvement of radial rays was more frequent in the left hand (15-17% compared with 10-13% in the right). Patients' distribution according to Tubiana-Michon classification is shown in Table 4. The patients' age at the time of DD diagnosis ranged from 20 to 79 years of age (mean 60.4, SD 10.7). Nevertheless, 39 (66%) patients reported to have noticed changes in their hands, consistent with DD, on average 4.9 years (SD 1.2) before the official diagnosis. Forty-six (78%) patients denied a familial DD, 11 (19%) had at least a first-degree relative affected and 4 (7%) had at least a non first-degree relative affected. Three (5%) patients presented a matrilineal heredity pattern for DD. Twenty-seven (46%) patients underwent at least a surgery for DD (aponeurectomy). Among them, 5 (19%) presented recurrences, 13 (48%) showed extensions to other rays and 4 (15%) suffered from both recurrences and extensions. Follow-up ranged from one to 5 years from the index procedure.

Table 4. Frequency of Tubiana-Michon stages

Tubiana-Michon stage	Frequency	Percent
0	22	37
I	15	25
II	14	24
III	6	10
IV	2	3

Logistic Regressions and Outcome Analyses

Table 5, 6 and 7 show the variables predicting DD

Table 5. Variables predicting DD development

Variables	Odds Ratio	*P value*	95% Confidence intervals
Male sex	2.27	0.025	1.108 - 4-634
Daily heavy manual work	7.36	0.015	1.482 - 36.550
Heavy manual work (years)*	1.05	0.007	1.014 - 1.090
Ischemic heart disease	4.06	<0.001	2.004 - 8.224
Diabetes (Type 1 and 2)	2.94	0.018	1.206 - 7.172

* Heavy manual work (years)= Past or present daily heavy manual workers for at least 2 years.

Table 6. Variables predicting the involvement of more than one ray in the same hand

Variables	Odds Ratio	*P value*	95% Confidence Intervals
Age	1.24	0.008	1.061 - 1.465
Male sex	9.23	0.002	2.189 - 38.916
Daily alcohol assumption	10.77	0.019	1.486 – 78.149

Table 7. Radial rays involvement

Variables	Odds Ratio	*P value*	95% Confidence intervals
Dyslipidemias	5.238	0.008	1.554 – 17.653
Daily alcohol intake	16.8	0.012	1.870 – 150.936
At least a ray at III stage (Tubiana-Michon)	31.667	0.006	2.683 – 373.735
Presence of DD signs preceding the official diagnosis	6.955	0.017	1.415 – 34.174
First-degree relative affected	4.197	0.025	1.194 – 14.756
Relative affected (first-degree and not)	2.7	0.034	1.076 – 6.778

development, multiple rays involvement in the same hand and radial rays involvement, respectively. The male sex resulted to be a predictive factor for bilateral DD (adjusted odds ratio – aOR - 40.18, *P=0.001*, 95% confidence interval 4.706 – 343.086). Ischemic heart disease resulted to be a negative predictor of extensions (aOR 0.121, *P=0.017*, 95% confidence interval 0.021- 0.688). No predicting variables were found for recurrences.

Discussion

Study Findings

The results of our case-control study suggest first that male sex, daily heavy manual work, ischemic heart disease and diabetes may have a possible predictive role in DD development. Dupuytren's disease is known to occur mainly in male Caucasians, in fact male sex is included in Dupuytren's diathesis as a predisposing factor (5). The role of daily heavy manual work and vibration exposure is controversial in the medical literature: several studies do not report an association with DD (7). Nevertheless, our study reports a high aOR for daily heavy manual work. Heavy manual work for more than two hours a day is associated to DD in the affected males, in agreement with some recent findings (6, 11). Moreover our patients, compared to controls, reported they have spent significantly more years performing heavy manual works and using vibrating tools. On the other hand, the years of occupational exposure seem to have a minor impact relative to past studies, and no predictive role for vibration exposure has been found. Diabetes has a well-known association with DD, denied by few papers (19). Recent findings have linked DD to high levels of fasting blood glucose more than to diabetes itself (6, 7). A possible explanation for this trend could be the pathogenic role of hyperglycemia itself (20). During the last few years, the development of new drugs and higher medical attention to prevent microvascular complications has led to a finer control of blood glucose levels in diabetic patients (21). Consequently, DD could develop only in those patients with a long history of diabetes and poorly controlled glycaemia (22). Ischemic heart disease is a strong predictor of DD according to this study. Although little historical evidence support this association, the result should not be surprising (23). Ischemic heart disease, in its multiple expressions (from stable angina to myocardial infarction and sudden cardiac death) is consequent to an atherosclerotic process damaging

coronary arteries (24, 25). Coronary artery disease symptoms are a clue of an atherosclerotic process extended to arteries in the whole body, hands included. Atherosclerosis, cigarette smoking, hyperglycemia in poorly controlled diabetes and work-related hand micro-trauma have vascular damage as a common result. This fits with the "hypoxia" theory of DD pathogenesis, stating that microangiopathy may stimulate fibroblasts proliferation through ROS production following hypoxia (26). In this regard, cigarette smoking is also a recognized dose-related risk factor for DD (6, 7). Even in this study, a history of past cigarette smoking is associated with DD in males. Furthermore, a recent study showed an immune-mediated microvascular damage in the narrowed vessels of the DD-affected fascia (27). Finally, a slightly lower BMI than that of the controls was associated to DD in a past study, but this finding was not confirmed by others (6, 7). In our study, no association has been found between any BMI class and DD. However, our male cases show to be mostly overweight, compared to female cases and controls from both sexes, usually having normal BMI. This finding fits better with the previously reported pathogenic theory, but further studies are needed to confirm it.

Involvement of more rays in the same hand is a clinical feature of a more aggressive DD, as well as bilateral disease, that is considered part of Dupuytren's diathesis (5). Not surprisingly, male sex is their common predictor in this study. The involvement of more rays in the same hand is predicted also by age and, above all, by a daily alcohol intake. This study agrees with those reporting that Dupuytren's disease prevalence increases with age, with a peak in the fifth and sixth decades (2). Prevalence drops at 79 years of age for men and 85 for women on average (15). This seems to be due more to an increased mortality of patients with an early onset DD, than to spontaneous regressions of the disease (15, 28). Addressing alcohol intake, several studies showed a dose-related risk of DD development (7). Daily alcohol intake may contribute to microvascular damage, leading to DD development and worsening in patients with DD diathesis. This could explain why we found no associations between DD development and alcohol intake, but, at the same time, a daily alcohol intake seems to increase the risk of multiple digit involvement (aOR=10.77) and radial DD (aOR=16.8) in this study.

Radial DD involves the thumb and the first web space: a previous study associated it to bilateral DD, ectopic lesions and recurrences, suggesting to consider it as a part of Dupuytren's diathesis (29). In agreement with it, in this study no patients have presented an exclusive involvement of radial rays, that, when present, added to the classical distribution on the ulnar side of the hand. Indeed, radial DD seems to be associated with a more aggressive DD, involving multiple rays. This outcome is to be predicted by: the presence of dyslipidemias, daily alcohol intake, severe involvement of at least a ray (Tubiana-Michon stage III), familial DD and patients' awareness of DD signs before the official diagnosis.

As explained before, dyslipidemia contributes to atherosclerosis and may worsen DD causing local hypoxia through microvascular damage (24, 25). The presence of another ray that is severely affected may be considered, as bilateral DD, a clinical index of an aggressive form of DD (5). Familial history of DD is a strong clue of genetic predisposition and it is considered part of Dupuytren's diathesis (4, 5). Nevertheless, patients in this study were probably affected mostly by sporadic DD. Familial cases were rare and matrilineal heredity patterns were anecdotal. In our experience, patients usually exchange DD nodules with work-related callosities: they rarely consult hand surgeons before cords and digital retractions appear. Taking into consideration the long waiting lists of our center, three to six months pass from reservation to the visit itself. Hence, a year at least (4.9 years on average) usually passes from the cord appearance to the official diagnosis. Far from considering it as scientific evidence, if patients themselves recognize DD signs as pathological and not work-related before the official diagnosis, they could already be affected by an aggressive or advanced stage DD.

Curiously, the presence of ischemic heart disease seems to be a negative predictor of extensions. How to interpret this result is challenging, especially considering the small sample of patients analyzed. Patients' premature death could justify this result, but no deceased patients were found in the cohort of our surgical cases in follow-up. A possible explanation could be that ischemic heart disease is associated with DD development, but drugs taken later for coronary artery disease may also hinder DD from worsening, healing the microangiopathy at both levels (coronary arteries and hand micro-vessels) (30). A possible protective role might be examined for drugs usually taken by those patients (such as beta-blockers, calcium channel blockers, nitrates, statins).

Limitations and Future Perspectives

Although it has led to interesting and statistically significant results, this study has involved a small sample of patients. This can be inferred by the broadness of some confidence intervals reported in tables. The same limitation affects the results concerning recurrences and extensions, in addition to a variable follow-up period. Moreover, the poor matching between cases and controls could have influenced these results, reducing the power of the study. Further prospective studies on larger matched cohorts are needed to evaluate other predictors and confirm these results. Furthermore, most of these patients did not report a familial history of DD. Thus, the few hereditary patterns reported, not reaching enough statistical power, were not analyzed.

According to this study, working habits seem to have an important role in DD development. Considering that a heavy manual worker could more likely smoke cigarettes and drink alcoholics, the adjusted odds ratios were always calculated, to avoid the influence of these confounding variables.

Nevertheless, this study does not consider the genetic predisposition of patients, although most cases analyzed seem sporadic. Further studies will have to quantify the

role of genetics, compared to acquired risk factors as working habits, in each patient DD development. This could become a useful tool in those countries where compensation is provided for workers developing occupational diseases.

Through the questionnaire, this study tried to investigate glycemic control in diabetic patients. Unfortunately, few patients answered those questions. Further studies could overcome this limitation requesting patients' clinical documentation and blood tests.

For purposes of simplifying the questionnaire, the use of alcoholic units to exactly quantify alcohol consumption had been avoided. This led to poor standardized results concerning the alcohol intake, but allowed all patients to answer these questions easily. In our opinion, in order to reach higher standardized results, the use of alcoholic units could be introduced in further studies in a separate part of the questionnaire, administered (and explained) by the physician.

However, we recommend entrusting any possible "embarrassing" questions to the self-administered part of the questionnaire, to let reticent patients answer sincerely.

The use of a questionnaire, like the one used in this study, should be encouraged. This, submitted to larger cohorts of patients from different countries, could be a useful tool to standardize results and better orient further researches concerning DD.

Finally, the relationship between ischemic heart disease and DD should be examined in depth. With regard to this, even prevalence of erectile dysfunction in DD patients should be studied, considering microvascular damage is a pathogenic factor in common with ischemic heart disease. In order to confirm this pathogenic theory even for DD, studies on vessels of operatory samples could be carried out.

Apart from the above-mentioned limitations, first of all the small sample of patients and controls, this study reveals interesting findings. A role in DD development for male sex, cigarette smoking, diabetes and heavy manual work was confirmed. Development of severe and aggressive DD (involving more rays, both hands and the radial side of the hand) was linked to age, male sex, high alcohol intake and positive familial history, as expected. Original findings needing further research regard the relationship between dyslipidemias and radial rays involvement. The dual role of the ischemic heart disease, both risk factor for DD development and, simultaneously, negative predictor of DD extensions, will have to be examined in depth.

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All patients gave the informed consent prior being included into the study.

All procedures involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments. The study was approved by the Research Ethics Committee (or Institutional Review Board).

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References

1. Dolmans GH, Werker PM, Hennies HC, Furniss D, Festen EA, Franke L, et al. Wnt signaling and Dupuytren's disease. N Engl J Med. 2011; 365(4):307-17.
2. Hu FZ, Nystrom A, Ahmed A, Palmquist M, Dopico R, Mossberg I, et al. Mapping of an autosomal dominant gene for Dupuytren's contracture to chromosome 16q in a Swedish family. Clin Genet. 2005; 68(5):424-9.
3. Carvalhana G, Auquit-Auckbur I, Milliez PY. Dupuytren's disease: state of knowledge and research in physiopathology. Chir Main. 2011; 30(4):239-45.
4. Dolmans GH, de Bock GH, Werker PM. Dupuytren diathesis and genetic risk. J Hand Surg Am. 2012; 37(10):2106-11.
5. Hindocha S, Stanley JK, Watson S, Bayat A. Dupuytren's diathesis revisited: evaluation of prognostic indicators for risk of disease recurrence. J Hand Surg Am. 2006; 31(10):1626-34.
6. Gudmundsson KG, Arngrìmsson R, Sigfùsson N, Björnsson A, Jònsson T. Epidemiology of Dupuytren's disease: clinical, serological and social assessment. The Reykjavik Study. J Clin Epidemiol. 2000; 53(3):291-6.
7. Godtfredsen NS, Lucht H, Prescott E, Sørensen TI, Grønbaek M. A prospective study linked both alcohol and tobacco to Dupuytren's disease. J Clin Epidemiol. 2004; 57(8):858-63.

8. Noble J, Heathcote JG, Cohen H. Diabetes mellitus in the aetiology of Dupuytren's disease. J Bone Joint Surg Br. 1984; 66(3):322-5.
9. Arafa M, Noble J, Royle SG, Trail IA, Allen J. Dupuytren's and epilepsy revisited. J Hand Surg Br. 1991; 17(2):221-4.
10. Elliot D, Ragoowansi R. Dupuytren's disease secondary to acute injury, infection or operation distal to the elbow in the ipsilateral upper limb--a historical review. J Hand Surg Br. 2005; 30(2):148-56.
11. Descatha A, Bodin J, Ha C, Goubault P, Lebreton M, Chastang JF, et al. Heavy manual work, exposure to vibration and Dupuytren's disease? Results of a surveillance program for musculoskeletal disorders. Occup Environ Med. 2012; 69(4):296-9.
12. Bower M, Nelson M, Gazzard BG. Dupuytren's contractures in patients infected with HIV. BMJ. 1990; 300(6718):164-5.
13. Livingstone JA, Field J. Algodistrophy and its association with Dupuytren's disease. J Hand Surg Br. 1999; 24(2):199-202.
14. Arafa M, Steingold RF, Noble J. The incidence of Dupuytren's disease in patients with rheumatoid arthritis. J Hand Surg Br. 1984; 9(2):165-6.
15. Mikkelsen OA, Høyeraal HM, Sandvik L. Increased mortality in Dupuytren's disease. J Hand Surg Br. 1999; 24(5):515-8.
16. Wilbrand S, Ekbom A, Gerdin B. Cancer incidence in patients treated surgically for Dupuytren's contracture. J Hand Surg Br. 2000; 25(3):283-7.
17. Smith SP, Devaraj VS, Bunker TD. The association between frozen shoulder and Dupuytren's disease. J Shoulder Elbow Surg. 2001; 10(2):149-51.
18. Armstrong JR, Hurren JS, Logan AM. Dermofasciectomy in the management of Dupuytren's disease. J Bone Joint Surg. 2000; 82(1):90-4.
19. Eadington DW, Patrick AW, Frier BM. Association between connective tissue changes and smoking habit in type 2 diabetes and in non-diabetic humans. Diabetes Res Clin Pract. 1991; 11(2):121-5.
20. Roy S, Trudeau K, Roy S, Behl Y, Dhar S, Chronopoulos A. New insights into hyperglycemia-induced molecular changes in microvascular cells. J Dent Res. 2010; 89(2):116-27.
21. Wiernsperger N, Rapin JR. Microvascular diseases: is a new era coming? Cardiovasc Hematol Agents Med Chem. 2012; 10(2):167-83.
22. Larkin ME, Barnie A, Braffett BH, Cleary PA, Diminick L, Harth J, et al. Musculoskeletal complications in Type 1 Diabetes. Diabetes Care. 2014; 37(7):1863-9.
23. Yeh CC, Huang KF, Ho CH, Chen KT, Liu C, Wang JJ, et al. Epidemiological profile of Dupuytren's disease in Taiwan (Ethnic Chinese): a nationwide population-based study. BMC Musculoskelet Disord. 2015; 16(1):20.
24. Lusis AJ. Atherosclerosis. Nature. 2000; 407(6801): 233-41.
25. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med. 2011; 17(11):1410-22.
26. Goldblum JR, Folpe AL, Weiss SW. Benign fibroblastic/myofibroblastic proliferations, including superficial fibromatoses. Enzinger and Weiss's Soft Tissue Tumors. 6th ed. Philadelphia: Elsevier Saunders; 2014. P. 188-255.
27. Mayerl C, Del Frari B, Parson W, Boeck G, Piza-Katzer H, Wick G, et al. Characterisation of the inflammatory response in Dupuytren's disease. J Plastic Surg Hand Surg. 2016; 50(3):171-9.
28. Gudmundsson KG, Arngrìmsson A, Sigfùsson N, Jònsson T. Increased total mortality and cancer mortality in men with Dupuytren's disease: a 15-year follow-up study. J Clin Epidemiol. 2002; 55(1):5-10.
29. Abe Y, Rokkaku T, Ofuchi S, Tokunaga S, Takahashi K, Moriya H. Dupuytren's disease on the radial aspect of the hand: report on 135 hands in Japanese patients. J Hand Surg Br. 2004; 29(4):359-62.
30. Bellosta S, Bernini F, Ferri N, Quarato P, Canavesi M, Arnaboldi L, et al. Direct vascular effects of HMG-CoA reductase inhibitors. Atherosclerosis. 1998; 137(Suppl):S101-9.

Patient's data: Age…. Sex…. Height…. Weight…. BMI….

Working habits:

- Do you perform any heavy manual work during the day? How often? (Please tick one of the following options and specify since when you have been using your hands so frequently):
  - Never…
  - Not daily…
  - Daily (less than 2 hours)…
  - Daily (more than 2 hours)…
- Circle your job if included in the following list: hair stylist – housewife – painter – bricklayer – musician – farmer – butcher – factory worker (assembly lines) – unloader - hand polisher – jobs including hand sorting, packing, spinning, needlework? How long have you been doing this job? …
- How often do you use vibrating tools? (Please specify how long you have been using them at the selected frequency)
  - Never…
  - Not daily…
  - Daily (less than 2 hours)…
  - Daily (more than 2 hours)…

Life habits:

- Do you smoke cigarettes? YES NO How many a day? ….
- Are you a former smoker? YES NO How many cigarettes a day did you use to smoke?.... How long have you been smoking? ….
- How often do you drink alcoholic beverages? Please write which kind on the side of the frequency:
  - Never….
  - Few times a month….
  - At least once a week….
  - At least once a day….
- Have you ever taken soft or heavy drugs? If yes, please specify how often and the drug type. …..

Figure 1. Questionnaire - General Part.

Have you ever suffered from any of the following conditions? (Please specify disease name next to the option selected):

- Hypertension (high blood pressure)
- Metabolic syndrome
- Dyslipidemias (abnormal level of blood fats)…
- Autoimmune diseases….
- Blood diseases…
- Chronic infections (HIV, HBV, etc.)
- Mouth, esophagus, stomach, bowel, anus, pancreas, gallbladder or bile ducts diseases (gastrointestinal tract diseases)…
- Thyroid/parathyroid glands problems
- Endocrine glands diseases (i.e. pituitary, adrenal glands)…
- Lungs and/or airways diseases…
- Heart and blood vessels (arteries, veins) diseases …
- Musculoskeletal diseases…
- Neurologic or psychiatric disorders...
- Skin diseases…
- Urological diseases (concerning prostate, kidneys, bladder, urinary tract, penis)...
- Gynecological or obstetric disorders...
- Sexual dysfunctions/ infertility…
- Tumors…

Do you suffer from diabetes? YES NO Please specify: Type.....…Age of onset….
Therapy……
Is blood glucose level/glycosylated hemoglobin currently normal with drugs? YES NO
Do you suffer from epilepsy? YES NO Please specify: Type.....…Age of onset….
Therapy……
Please list here any drug you usually take (specifying the reason you use it for)…….
Please list here any past surgical operation, specifying the reason…….
Do you suffer from Ledderhose's disease? YES NO Have you ever noticed nodules or cords possibly causing pain when walking in your feet soles? YES NO
Do you suffer from Peyronie's disease (also called induratio penis plastica)? YES NO
If you suffer from any of the following conditions, please underline it/them:
Premature ejaculation - Loss of/reduced sensitivity on part of the penis - Pain or bothersome sensations during erections - Inability to develop or maintain the penile erections - Development of an acquired abnormal curvature of the penis - Pain or rupture sensation or sudden penile collapse during sexual activity.

Figure 2. Questionnaire - Medical History.

Please fill in the following questions concerning your Dupuytren's disease.

Age of onset (at official diagnosis)…

Before medical diagnosis, did you notice any change in your hands that later revealed to be due to Dupuytren's disease? YES NO

If yes, please write how old you were when those changes occurred…

Have you ever noticed similar nodules/cords (or have you ever heard about a confirmed diagnosis of Dupuytren's disease) in any of your relatives' hands? YES NO

If yes, please tick them and write the number of afflicted relatives beside each kinship degree. Relatives-in-law are excluded from this survey.

- Father
- Mother
- Brothers…
- Sisters…
- Paternal grandfather
- Paternal grandfather's siblings (please specify number and sex) …
- Maternal grandfather
- Maternal grandfather's siblings (please specify number and sex) …
- Paternal grandmother
- Paternal grandmother's siblings (please specify number and sex) …
- Maternal grandmother
- Maternal grandmother's siblings (please specify number and sex) …
- Paternal aunts…
- Paternal uncles…
- Maternal aunts…
- Maternal uncles…
- Sons…
- Daughters…

Does Dupuytren's disease affect both your hands? YES NO

Did you ever undergo any treatment for Dupuytren's disease in the past? YES NO

If yes, please tick the treatment and specify the treated rays:

- Aponeurectomy (open surgery)…
- Collagenase injection…
- Percutaneous needle-aponeurotomy …

Have you had a Dupuytren's disease recurrence after treatment? If yes, please specify the afflicted sites:

- The same rays afflicted before the treatment (recurrence)
- Previously uninvolved rays (extension)
- Both (extension and recurrence)

Figure 3. Questionnaire – Dupuytren's disease – specific part.