

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

Object: 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.

Material and 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.

Conclusions: 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.**

Level of Evidence: III/IV.

Keywords: Dupuytren's disease; questionnaire; case-control study; predicting factors; risk factors; associated conditions.

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30 **INTRODUCTION**

31 Dupuytren's disease (DD) pathogenesis has been widely studied in recent decades. Genetic
32 predisposition was established by several studies, including genome-wide association studies (1).

33 Autosomal dominant and matrilineal heredity patterns were found for familial cases (2, 3).

34 Beyond the predisposing role of Dupuytren's genetic diathesis, several environmental factors
35 seem to contribute to DD development, especially for sporadic cases (4, 5). Male sex is

36 associated with major prevalence, earlier presentation and digital retraction (6). **A prospective**

37 **study by Godtfredsen et al.** considered cigarette smoke and heavy alcohol consumption risk

38 factors for DD (7). Contrasting results ascribed a causative role for DD even to hyperglycemia,

39 both type 1 and 2 diabetes, epilepsy, phenobarbital intake, acute and chronic occupational trauma

40 to hand and wrist (6, 8-11). Associations with Ledderhose's disease and Peyronie's disease are

41 well known (5). Nevertheless, sporadic reports also link DD to frozen shoulder, HIV, reflex

42 sympathetic dystrophy, dyslipidemia, cancer, increased mortality and lower incidence of

43 rheumatoid arthritis (12-17).

44 Similarly confusing information exists about recurrence and extension rates, as well as factors

45 that may predict them (5, 18). From this background, this study aimed to analyze DD clinical

46 features and associated conditions in a sample of Italian patients. The main outcome was the

47 identification of predicting factors for: 1) DD development, 2) involvement of multiple rays in

48 the same hand, 3) involvement of both hands, 4) development of radial DD, 5) development of

49 recurrences and extensions.

50

51 **MATERIAL AND METHODS**

52 **Enrolment of Patients and Controls**

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

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

73 Hence, the control group was finally composed of 104 consecutive Caucasian patients. A perfect
74 matching for age and sex between the two groups was impossible to achieve, also considering the
75 9,6% rate of new diagnoses of DD found in the initial control group.

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78 **Questionnaires**

79 The case group completed a questionnaire investigating the patients' age, sex, BMI, working
80 habits, life habits (cigarette smoking, alcohol and drugs intake), medical and pharmacological
81 history, presence of plantar fibromatosis or Peyronie's disease (Figure 1-2). Cut-offs for working
82 habit analysis were set complying with a previous French study, to standardize the results (11).

83 Dupuytren's disease was examined in depth, including familial history, both hands involvement,
84 age at first diagnosis, treatments performed, recurrences and extensions after surgery (Figure 3).

85 The control group completed the same questionnaire, with the exception of the questions
86 concerning DD. The questionnaire was anonymous. The progressive numbers of cases and
87 controls were written on the top, in order to fill in the database matching their answers with
88 clinical examination data. The questionnaire was edited in Italian, using simple words and
89 avoiding excessive use of medical terms, in order to be easily completed by patients from
90 different cultural contexts. Furthermore, it was set up with redundant questions, not to forget any
91 detail of the patients' histories. Redundancies were then eliminated during database filling.

92 Figures 1,2,3 show the English version of the questionnaire. The anonymous questionnaire was
93 preferred to a medical interview in order to reduce possible omissions due to embarrassment or
94 lack of confidence with the physicians, especially in the "drug addiction" and "Peyronie's
95 disease" sections.

96

97 **Statistical Analyses**

98 Descriptive statistical analyses were performed to analyze the features of each group.

99 Kolmogorov-Smirnov test was used to assess the distribution form of each variable. Independent
100 samples Mann Whitney U-test was used to evaluate statistically significant differences between

101 means of non-parametric variables of cases and controls (i.e. years of exposure to vibrating
102 tools). Fisher's exact test was used to compare categorical dependent variables (i.e. alcohol
103 consumption). Binary logistic regression with backward selection was used to study the impact of
104 the variables analyzed to the above listed outcomes. An adjustment was eventually performed on
105 the odds ratios (aOR) of each variable, to reduce the confounding effects following poor
106 matching. Confidence intervals were set at 95% and statistical significance was reached at
107 $p < 0.05$.

108

109 **RESULTS**

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

111 Forty-five male (76%) and 14 female (24 %) patients formed the case group. Sixty-one males
112 (59%) and 43 females (41%) belonged to the control group.

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

124 Even smoking habits were analyzed comparing same-sex subgroups (Table 3). Past or current
125 smoking resulted significantly associated with DD ($p=0.007$) in males. No significant differences
126 in the daily amount of cigarettes were found between cases and controls. No significant
127 differences in the incidence of any specific comorbidity resulted from this analysis.

128

129 **Questionnaire: Clinical Features of Dupuytren's Disease**

130 Analyzing the clinical features of DD in these patients, 40 (68%) reported an involvement of
131 more than one ray in the same hand. Thirty-five patients (59%) had bilateral DD, and 19 (32%)
132 had an involvement of radial rays. The most affected rays were the fourth (68% in the right hand,
133 54% in the left hand), the fifth (42% in the right hand, 37% in the left one) and the third (39% in
134 the left, 28% in the right). The involvement of radial rays was more frequent in the left hand (15-
135 17% compared with 10-13% in the right). Patients' distribution according to Tubiana-Michon
136 classification is shown in Table 4. The patients' age at the time of DD diagnosis ranged from 20
137 to 79 years of age (mean 60.4, SD 10.7). Nevertheless, 39 (66%) patients reported to have noticed
138 changes in their hands, consistent with DD, on average 4.9 years (SD 1.2) before the official
139 diagnosis. Forty-six (78%) patients denied a familial DD, 11 (19%) had at least a first-degree
140 relative affected and 4 (7%) had at least a non first-degree relative affected. Three (5%) patients
141 presented a matrilineal heredity pattern for DD. Twenty-seven (46%) patients underwent at least
142 a surgery for DD (aponeurectomy). Among them, 5 (19%) presented recurrences, 13 (48%)
143 showed extensions to other rays and 4 (15%) suffered from both recurrences and extensions.
144 Follow-up ranged from one to 5 years from the index procedure.

145 **Logistic Regressions and Outcome Analyses**

146 Table 5, 6 and 7 show the variables predicting DD development, multiple rays involvement in the
147 same hand and radial rays involvement, respectively. The male sex resulted to be a predictive

148 factor for bilateral DD (adjusted odds ratio – aOR - 40.18, p=0.001, 95% confidence interval
149 4.706 – 343.086). Ischemic heart disease resulted to be a negative predictor of extensions (aOR
150 0.121, p=0.017, 95% confidence interval 0.021- 0.688). No predicting variables were found for
151 recurrences.

152

153 **DISCUSSION**

154 **Study Findings**

155 The results of our case-control study suggest first that male sex, daily heavy manual work,
156 ischemic heart disease and diabetes may have a possible predictive role in DD development.
157 Dupuytren’s disease is known to occur mainly in male Caucasians, in fact male sex is included in
158 Dupuytren’s diathesis as a predisposing factor (5). The role of daily heavy manual work and
159 vibration exposure is controversial in the medical literature: several studies do not report an
160 association with DD (7). Nevertheless, our study reports a high aOR for daily heavy manual
161 work. Heavy manual work for more than two hours a day is associated to DD in the affected
162 males, in agreement with some recent findings (6, 11). Moreover our patients, compared to
163 controls, reported they have spent significantly more years performing heavy manual works and
164 using vibrating tools. On the other hand, the years of occupational exposure seem to have a minor
165 impact relative to past studies, and no predictive role for vibration exposure has been found.
166 Diabetes has a well-known association with DD, denied by few papers (19). Recent findings have
167 linked DD to high levels of fasting blood glucose more than to diabetes itself (6, 7). A possible
168 explanation for this trend could be the pathogenic role of hyperglycemia itself (20). During the
169 last few years, the development of new drugs and higher medical attention to prevent
170 microvascular complications has led to a finer control of blood glucose levels in diabetic patients
171 (21). Consequently, DD could develop only in those patients with a long history of diabetes and

172 poorly controlled glycaemia (22). Ischemic heart disease is a strong predictor of DD according to
173 this study. Although little historical evidence support this association, the result should not be
174 surprising (23). Ischemic heart disease, in its multiple expressions (from stable angina to
175 myocardial infarction and sudden cardiac death) is consequent to an atherosclerotic process
176 damaging coronary arteries (24, 25). Coronary artery disease symptoms are a clue of an
177 atherosclerotic process extended to arteries in the whole body, hands included. Atherosclerosis,
178 cigarette smoking, hyperglycemia in poorly controlled diabetes and work-related hand micro-
179 trauma have vascular damage as a common result. This fits with the “hypoxia” theory of DD
180 pathogenesis, stating that microangiopathy may stimulate fibroblasts proliferation through ROS
181 production following hypoxia (26). In this regard, cigarette smoking is also a recognized dose-
182 related risk factor for DD (6, 7). Even in this study, a history of past cigarette smoking is
183 associated with DD in males. Furthermore, a recent study showed an immune-mediated
184 microvascular damage in the narrowed vessels of the DD-affected fascia (27). Finally, a slightly
185 lower BMI than that of the controls was associated to DD in a past study, but this finding was not
186 confirmed by others (6, 7). In our study, no association has been found between any BMI class
187 and DD. However, our male cases show to be mostly overweight, compared to female cases and
188 controls from both sexes, usually having normal BMI. This finding fits better with the previously
189 reported pathogenic theory, but further studies are needed to confirm it.

190 Involvement of more rays in the same hand is a clinical feature of a more aggressive DD, as well
191 as bilateral disease, that is considered part of Dupuytren’s diathesis (5). Not surprisingly, male
192 sex is their common predictor in this study. The involvement of more rays in the same hand is
193 predicted also by age and, above all, by a daily alcohol intake. This study agrees with those
194 reporting that Dupuytren’s disease prevalence increases with age, with a peak in the fifth and
195 sixth decades (2). Prevalence drops at 79 years of age for men and 85 for women on average (15).

196 This seems to be due more to an increased mortality of patients with an early onset DD, than to
197 spontaneous regressions of the disease (15, 28). Addressing alcohol intake, several studies
198 showed a dose-related risk of DD development (7). Daily alcohol intake may contribute to
199 microvascular damage, leading to DD development and worsening in patients with DD diathesis.
200 This could explain why we found no associations between DD development and alcohol intake,
201 but, at the same time, a daily alcohol intake seems to increase the risk of multiple digit
202 involvement (aOR= 10.77) and radial DD (aOR=16.8) in this study.

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

211 As explained before, dyslipidemia contributes to atherosclerosis and may worsen DD causing
212 local hypoxia through microvascular damage (24, 25). The presence of another ray that is
213 severely affected may be considered, as bilateral DD, a clinical index of an aggressive form of
214 DD (5). Familial history of DD is a strong clue of genetic predisposition and it is considered part
215 of Dupuytren's diathesis (4, 5). Nevertheless, patients in this study were probably affected mostly
216 by sporadic DD. Familial cases were rare and matrilineal heredity patterns were anecdotal. In our
217 experience, patients usually exchange DD nodules with work-related callosities: they rarely
218 consult hand surgeons before cords and digital retractions appear. Taking into consideration the
219 long waiting lists of our center, three to six months pass from reservation to the visit itself.

220 Hence, a year at least (4.9 years on average) usually passes from the cord appearance to the
221 official diagnosis. Far from considering it as scientific evidence, if patients themselves recognize
222 DD signs as pathological and not work-related before the official diagnosis, they could already be
223 affected by an aggressive or advanced stage DD.

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

232

233 **Limitations and Future Perspectives**

234 Although it has led to interesting and statistically significant results, this study has involved a
235 small sample of patients. This can be inferred by the broadness of some confidence intervals
236 reported in tables. The same limitation affects the results concerning recurrences and extensions,
237 in addition to a variable follow-up period. Moreover, the poor matching between cases and
238 controls could have influenced these results, reducing the power of the study. Further
239 prospective studies on larger matched cohorts are needed to evaluate other predictors and confirm
240 these results. Furthermore, most of these patients did not report a familial history of DD. Thus,
241 the few hereditary patterns reported, not reaching enough statistical power, were not analyzed.
242 According to this study, working habits seem to have an important role in DD development.
243 Considering that a heavy manual worker could more likely smoke cigarettes and drink alcoholics,

244 the adjusted odds ratios were always calculated, to avoid the influence of these confounding
245 variables.

246 Nevertheless, this study does not consider the genetic predisposition of patients, although most
247 cases analyzed seem sporadic. Further studies will have to quantify the role of genetics,
248 compared to acquired risk factors as working habits, in each patient DD development. This could
249 become a useful tool in those countries where compensation is provided for workers developing
250 occupational diseases.

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

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

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

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

264 Finally, the relationship between ischemic heart disease and DD should be examined in depth.
265 With regard to this, even prevalence of erectile dysfunction in DD patients should be studied,
266 considering microvascular damage is a pathogenic factor in common with ischemic heart disease.

267 In order to confirm this pathogenic theory even for DD, studies on vessels of operatory samples
268 could be carried out.

269
270 Apart from the above-mentioned limitations, first of all the small sample of patients and controls,
271 this study reveals interesting findings. A role in DD development for male sex, cigarette
272 smoking, diabetes and heavy manual work was confirmed. Development of severe and aggressive
273 DD (involving more rays, both hands and the radial side of the hand) was linked to age, male sex,
274 high alcohol intake and positive familial history, as expected. Original findings needing further
275 research regard the relationship between dyslipidemias and radial rays involvement. The dual
276 role of the ischemic heart disease, both risk factor for DD development and, simultaneously,
277 negative predictor of DD extensions, will have to be examined in depth.

278
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286 **Patient consent:** All patients gave the informed consent prior being included into the study.

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289 Research Ethics Committee (or Institutional Review Board).

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371	LEGENDS
372	Figure 1 Questionnaire - General Part
373	Figure 2 Questionnaire - Medical History
374	Figure 3 Questionnaire – Dupuytren’s disease – specific part
375	Table 1 BMI in case and control groups
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