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Arthrodesis of the Proximal Interphalangeal Joint in Dupuytren Contracture: A Qualitative Systematic Review

Artrodesis de articulación interfalángica proximal en enfermedad de Dupuytren: Una revisión sistemática cualitativa

Javier Francisco García García¹ María Segovia González¹ Alicia González González¹ Alejandro Mendieta Baro¹ Pablo Benito Duque¹

¹ Department of Plastic, Esthetic, and Reparative Surgery, Hospital Universitario Ramón y Cajal, Madrid, Spain

Rev Iberam Cir Mano 2022;50(2):e133-e141.

Address for correspondence Javier Francisco García García, MD, Servicio de Cirugía Plástica, Estética y Reparadora, Hospital Universitario Ramón y Cajal, Ctra. de Colmenar Viejo Km 9.100, 28034, Madrid, España (e-mail: javierfcomplutense1992@gmail.com).

Abstract

Introduction One of the typical features of Dupuytren contracture is its tendency for recurrence. Reintervention surgery has a high rate of complications, which increases with successive surgeries. Repeated fasciectomies can be contraindicated in severe, recurrent contractures, with arterial insufficiency or poor-quality soft tissue, due to a risk of severely compromising the viability of the skin. In these cases, finger amputation can be avoided by performing arthrodesis of the proximal interphalangeal (PIP) joint. Arthrodesis is also an alternative to amputation in contracted fingers affected by arthritis or arthrofibrosis of the PIP joint. Knowledge about this procedure is scarce due to its rarity. We performed a qualitative systematic review of the results and complications of arthrodesis of the PIP joint of digits 2 to 5 in adults with Dupuytren contracture.

Materials and Methods Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, we conducted a search on the PubMed, Cochrane and Embase databases. The risk of bias was assessed with the modified Newcastle-Ottawa Scale. We recorded the intraoperative and postoperative variables, and those related to complications, improvement in pain and function, and the level of patient satisfaction.

Keywords

 Dupuytren contracture
arthrodesis

systematic review

Results For the systematic review, we selected 4 case series totalling 65 patients and 71 arthrodesis. Significant improvements in terms of pain and function were not observed, but, in all studies, patient satisfaction was high. The rate of complication was of 11.3%, and they included 1 case of skin necrosis, but no vascular or nervous lesions were observed.

received October 9, 2021 accepted October 7, 2022 DOI https://doi.org/ 10.1055/s-0042-1758547. ISSN 1698-8396. © 2022. SECMA Foundation. All rights reserved.

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Conclusion Despite the fact that no improvements in pain or function were reported, this procedure is associated with a high level of patient satisfaction, and an extremely low rate of skin ailments or vascular or nervous lesions. The level of evidence regarding the results and complications is low.

Resumen Introducción La enfermedad de Dupuytren (ED) se caracteriza por una alta tendencia a la recidiva. Las reintervenciones asocian elevado riesgo de complicaciones, incrementado tras cada cirugía. En contracturas graves y recidivantes, con insuficiencia vascular o mala calidad tisular, nuevas fasciectomías pueden estar contraindicadas por el riesgo de comprometer gravemente la viabilidad cutánea. En estos casos, artrodesar la articulación interfalángica proximal (IFP) es una alternativa a la amputación. La artrodesis también es una alternativa en aquellas contracturas que asocien artrosis o artrofibrosis de la articulación IFP. El limitado conocimiento sobre esta intervención se justifica por su escasa frecuencia. Realizamos una revisión sistemática cualitativa de resultados y complicaciones de artrodesis de la articulación IFP del segundo al quinto dedos en adultos con ED.

> **Materiales y Métodos** Según la declaración de los Ítems Preferidos de Reporte para Revisiones Sistemáticas y Metanálisis (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA, en inglés), desarrollamos una búsqueda en las bases de datos PubMed, Embase y Cochrane Library. Evaluamos el riesgo de sesgo mediante la Escala de Newcastle-Ottawa modificada. Junto a variables intra y preoperatorias y complicaciones, se registró las mejorías funcional y del dolor, y el grado de satisfacción.

> **Resultados** Para esta revisión sistemática, se seleccionaron 4 series de casos, con 65 pacientes y 71 artrodesis. No evidenciamos mejorías significativas en términos de dolor o funcionalidad, pero sí un alto grado de satisfacción en todos los estudios. El 11,3% de las complicaciones incluyó una necrosis cutánea, pero ninguna lesión vascular o nerviosa.

Palabras clave

- enfermedad de Conclusión Pese a no demostrar mejoría en dolor o funcionalidad, este procedi-Dupuytren miento asocia alto grado de satisfacción y muy baja tasa de afectación cutánea o de
 artrodesis lesiones vasculares o nerviosas. El nivel de evidencia sobre resultados y complicaciones
- revisión sistemática

Introduction

Dupuytren disease (DD) is a benign fibroproliferative disease that affects the hand and fingers. Initially, it causes hard painless nodules in the glabrous skin that adhere to the palmar and digital fascia. These nodules precede the formation of cords which contract and result in fixed flexion deformities of the digital joints.¹

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The exact cause of DD remains unknown. However, researchers have identified genes related to the disease, in addition to predisposing factors, including alcoholism, smoking, diabetes, and epilepsy.² The prevalence of DD ranges from 0.5% to 11% of the population, and it occurs more commonly among males, usually those in the sixth decade of life, and as a bilateral condition.³

This disease mostly affects the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, especially those of the fourth and fifth fingers.

The diagnosis is clinical and based on the identification of nodules, cords, and fixed, usually painless, digital flexion deformities. The table top or Hueston test (which involves placing the palm of the hand on a table) reflects the deficit in extension.⁴

Management is expectant up to a contracture $\geq 30^{\circ}$ in the MCP joint or $\geq 15^{\circ}$ in the PIP joint.⁵ The most common therapeutic options are percutaneous aponeurectomy (PA), fasciectomy, and dermofasciectomy.

The course of DD is unpredictable, and recurrence is common and complex. We define recurrence as a passive extension deficit $> 20^{\circ}$ in at least 1 of the treated joints compared with the postoperative outcome and in the presence of a palpable cord. In addition, it is necessary to rule out causes of immobility secondary to tendon or joint function deficits.⁶

Surgery is the treatment of choice in cases of severe recurrence accompanied by diffuse fibromatosis. The risk

of recurrence is high with all techniques, ranging from 12% to 39% after fasciectomy,⁷ and it is higher in PIP compared to MCP contractures.⁸

Removing new areas of palmar fibrosis carries an increased risk of nerve or arterial injury and compromised skin viability. The development of residual changes in joint or tendon structures makes diagnosis difficult and increases the technical requirement of the procedure.

Digital amputation is an option after the failure of several interventions in patients with DD and non-functional fingers or sensorial alterations. Arthrodesis of the PIP joint is an alternative to amputation in cases with significant cicatricial PIP contracture along with arthritis or arthrofibrosis, as long as finger sensitivity is spared.

In severe and recurrent contractures with vascular insufficiency or poor-quality tissue, a new fasciectomy may be discouraged due to the risk of severely compromising skin integrity.⁹ In these situations, if the finger preserves its sensitivity, a PIP joint arthrodesis can also prevent amputation.

Since these "salvage" surgeries are infrequent, evidence of their safety and results remains scarce.^{10–12} The preswnt systematic review compiles the existing evidence on the outcomes and complications of the different techniques for PIP joint arthrodesis in DD.

Materials and Methods

We performed this qualitative, systematic review of the outcomes and complications of PIP joint arthrodesis in DD following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

Inclusion criteria

The inclusion criteria were as follows: articles on the surgical treatment of DD or its sequelae, including PIP joint arthrodesis; studies with patients older than 18 years; records of previous treatments of the finger submitted to arthrodesis, if any; records of arthrodesis complications; records of at least one of the following three variables after arthrodesis – level of satisfaction, improvement in pain, and functional improvement; postoperative follow-up ≥ 6 months; and clinical trials or observational studies with n > 4.

Exclusion criteria

The exclusion criteria were as follows: arthrodesis for reasons other than DD or its sequelae; thumb arthrodesis; And systematic reviews, meta-analyses, presentations, or communications at congresses.

Search strategy

We conducted a bibliographic search on PubMed, Embase, and Cochrane Library databases from their creation until August 2021. For PubMed, the search terms were as follows: (*Dupuytren* [Title/Abstract] OR *palmar* [Title/Abstract]) AND (*arthrodesis* [Title/Abstract] OR *salvage* [Title/Abstract] OR *recidivant* [Title/Abstract] OR *recurrent* [Title/Abstract]).

Evaluation of the methodological quality

All authors collaborated in the evaluation of the selected papers. The risk of bias in observational studies was assessed through a modification of the Newcastle-Ottawa Scale (NOS).¹³ We evaluated three sections: selection of the study groups; comparability; and results. Each study could score a maximum of 9 points.

The preoperative variables recorded included the following: type of study; number of patients and fingers submitted to arthrodesis in each study; gender; mean age; affected finger; DD severity; degree of PIP joint contracture in flexion; and previous treatments of the affected finger.

The intra- and postoperative variables included the following: method of arthrodesis; additional procedures performed during surgery on the finger submitted to arthrodesis; approach; postoperative angulation; postoperative mobilization protocol; improvement in pain improvement; level of satisfaction; functional improvement, followup period; and complications.

The Tubiana system was used to quantify DD severity. The angulation of the PIP joint was expressed quantitatively in degrees, with mean and range values from each study. Age, previous treatments, and follow-up period were equally shown as mean and range values.

The number of complications in each paper was expressed as a percentage. The variables "improvement in pain" and "level of satisfaction" were expressed according to the the visual analog scale (VAS), and the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire or a subjective assessment of the patients was used to determine the "level of functional improvement."

Results

Paper selection process

The electronic search on the databases yielded a total of 973 articles. After excluding duplicates and reading titles and abstracts, we chose 29 papers for a full-text analysis. **– Figure 1** shows the selection process. The rate of agreement between the reviewers was of 99.69%, with a Cohen k index of 0.95 (near perfect agreement).

Out of the 29 papers, we selected 4 case series for the qualitative synthesis after applying our inclusion and exclusion criteria.

Assessment of methodological quality

We employed a modified version of the NOS for observational studies. The higher total score was of 6/9, while the remaining papers scored 5/9. The scores were higher for the "results" section, followed by "selection of the study groups;" the lowest score was for "comparability."

- Table 1 summarizes the methodological quality assessment of the papers included in the present review.

Characteristics of the studied subjects

The papers included 65 patients; of them, 73.8% were men, and 9.2% were women; gender was unspecified for 16.9% of the sample. In total 71 fingers underwent arthrodesis, with

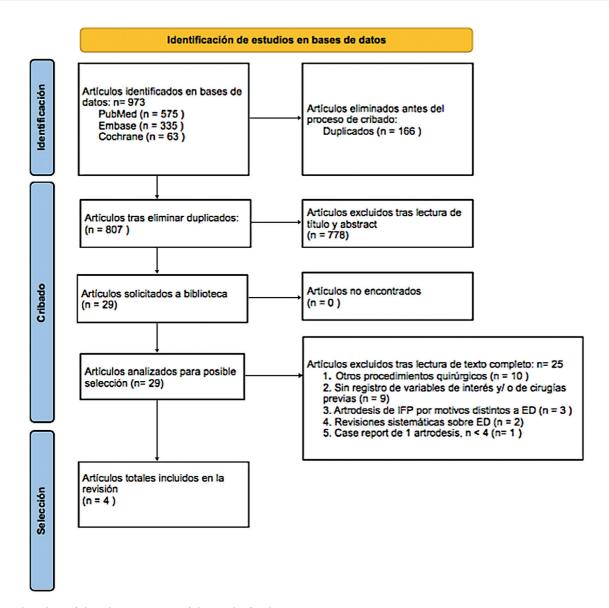


Fig. 1 Flow chart of the selection process of the articles for the systematic review.

the following 5th-4th-3rd-2nd ratio: 54-15-1-1. The mean age at the time of the surgery ranged from 55 to 64 years. The mean number of treatments before arthrodesis was of 1.96, ranging from 1 to 4 per finger. Severity was \geq III. When reported, the average PIP joint contracture in flexion for each finger was of 87.5°. **- Table 2** shows this data.

Treatment

The arthrodesis methods were the following: osteotomy of the proximal and middle phalanges followed by fixation with two Kirschner wires and a wire tension band (71.8%); condylar drilling with implantation of the APEX (Extremity Medical, LLC, Parsippany, NJ, US) interlocking screw (8.5%); and osteotomy and arthrodesis with two Kirschner wires (19.7%).

The approach was dorsal in 80.3% of the cases. Only Watson and Lovallo¹⁴ used a volar approach in their patients.

The mean arthrodesis angle, when reported, was of 38° for the 4th and 5th fingers. $^{\rm 14-16}$

- Table 3 details the type of arthrodesis, the associated procedures, and other postoperative variables.

Results and complications

For "improvement in pain," Novoa-Parra et al.¹⁵ showed a non-significant decrease of 1.6 points on the VAS. Watson and Lovallo¹⁴ reported they did not observe changes. The remaining papers did not mention this variable.

Regarding "level of satisfaction," Novoa-Parra et al.¹⁵ and Bolt et al.¹⁷ reported that all patients would repeat and recommend this surgery. Watson and Lovallo¹⁴ noted that all of their patients were satisfied. Pillukat et al.¹⁶ used the VAS to quantify this variable, obtaining a score of 8/10.

The "functional improvement" variable was quantified using the DASH by Novoa-Parra et al.,¹⁵ showing a nonsignificant decrease of 2.7. Watson and Lovallo¹⁴ reported improvements in prehensile strength in the operated hand. Bolt et al.¹⁷ pointed out that the patients presented regular performance in their basic and instrumental activities of

Authors	Representativeness of Selection of the the exposed cohort (maximum C) (maximum C)		Exposure verification (maximum 3)	Result not present Comparability at the beginning of (maximum Q Q) the study (maximum Q)		Outcome Follow-up Freevaluation (maximum 🖒 (maximum 🏷)	Follow-up period (maximum	Follow-up suitability (Maximum	Total
Novoa-Parra et al. ¹⁵	-	-	0	0	I	0	0	0	00000
Watson and Lovallo ¹⁴	0	-	1	0	I	0	0	0	00000
Bolt et al. ¹⁷	0	-	0	0	I	C)	0	Q	000000
Pillukat et al. ¹⁶	0	I	0	0	I	Q	0	0	000000

Table 1 Assessment of the methodological quality of the studies included in the systematic review

Note: The section "Selection of study groups" includes the four columns on the left; the next column belongs to the section "Comparability;" and the remaining are from "Results."

Table 2 Preoperative characteristics of the patients included in the systematic review

Paper	<u>د</u>	Fingers	Gender	Age (years)	5th _4th _3rd -2 nd Fingers	Severity	Proximal interphalangeal joint contracture in flexion (degrees)	Previous treatments
Novoa-Parra et al. ¹⁵	9	6	Male: 6	Mean: 60; range: 48–78	4-2-0-0	IV (100% of the subjects)	Mean: 88.3°; range: 80°–100°	Mean: 2.7; range: 2–3
Watson and Lovallo ¹⁴	11	14	Male: 9; female: 2	Mean: 55; range: 31–67	11-3-0-0		≥ 70°	Mean: 2.1; range: 1–4
Bolt et al. ¹⁷	11	11	Not reported	Mean: 64; range: 53–73	10-1-0-0	=	Mean: 102°; range: 80°–120°	Mean: 2; range: 2
Pillukat et al. ¹⁶	37	40	Male: 33; female: 4	Mean: 57; range: 42–70	29-9-1-1	IV (100% of the subjects)	Mean: 83.4°; range: 60°–115°	Mean: 1.8; range: 1–3

Paper	Arthrodesis method	Associated surgeries	Angulation after proximal interphalangeal joint surgery (degrees)	Postoperative mobilization	Follow-up period	Complication rate (%)
Novoa-Parra et al. ¹⁵	Condylar drilling + implantation of APEX (Extremity Medical, LLC, Parsippany, NJ, US) interlocking screw	Fasciectomy in 100% of the cases + release of checkrein deformities in 33% of the cases	30° in the 4 th finger; 45° in the 5 th finger	Immediate	Mean: 1 year and 10 months; range: 7 to 33 months	%0
Watson and Lovallo ¹⁴	Osteotomy of theproximal and middle phalanges, fixation with 2 Kirschner wires	Fasciectomy in a few cases	37° in the 4 th finger; 30° in the V finger	Splint for 6 weeks	Mean 4 years and 1 month; range 6 to 113 months	%6
Bolt et al. ¹⁷	Osteotomy of the proximal and middle phalanges, fixation with 2 Kirschner wires + wire tension band	Percutaneous aponeurectomy or fasciectomy in 100% of th cases	Not reported	Variable	Mean: 8 years and 9 months; range: 9 to 199 months	%0
Pillukat et al. ¹⁶	Osteotomy of the proximal and middle phalanges, fixation with 2 Kirschner wires + wire tension band	Fasciectomy in 100% of the cases	40° in all fingers	Splint up to consolidation	Mean: 5 years and 10 months; range: 18 to 152 months	19%

Table 3 Intra- and postoperative variables of the patients included in the systematic review

Pillukat et al.¹⁶ reported that all complications required reintervention: two, due to recurrence, two, for inadequate angulation, one, for Kirschner wire rupture, and one, for skin necrosis. Watson and Lovallo¹⁴ reported a fracture through the arthrodesis as the only complication.

There were three short-term complications (two cases of Kirschner wire rupture and one case of skin necrosis) and five long-term complications (recurrence, inadequate angulation, and fracture).^{14,16}

Discussion

A defining characteristic of DD is its tendency to recur according to its treatment. Recurrence surgery, recommended in severe contractures with diffuse fibrosis, increases the risk of vascular or nerve injury. This risk can be ten times higher compared with that of primary surgery.¹¹ Skin viability compromise occurs in up to 43% of recurrence surgeries.¹²

The risk of complications also varies depending on the contracture site. Compared with MCP fasciectomy, PIP fasciectomy has a higher postoperative extension deficit and more unpredictable outcomes.¹⁵

Recurrent DD can result in clinical situations in which a new fasciectomy carries a high probability of failure due to the possibility of recurrence and nerve or vascular injury. These interventions may compromise the viability of fingers with poor vascular supply or fragile skin coverage.

The hand surgeon must perform salvage techniques when a new fasciectomy is not an appropriate option. Amputation is often reserved for cases of severe recurrence with fingers without sensitivity or those with little functionality. Arthrodesis of the PIP joint is an alternative to amputation for fingers with preserved sensitivity subjected to multiple previous surgeries in which a new fasciectomy would critically compromise their integrity. Another candidate group for this intervention consists of fingers with preserved sensitivity and severe PIP joint flexion contracture accompanied by arthritis or arthrofibrosis.

We are unaware of any article comparing the outcomes of digital amputation and PIP joint arthrodesis in DD. Advocates of arthrodesis¹⁴ stress the importance of preserving much of the length of the finger and its prehensile strength, thus giving it a more esthetic appearance. The outcomes of digital amputation depend on several variables, including the affected finger, the etiology of the injury, and the instrumented level. Amputations at the MCP level in central fingers, such as the ring finger, can compromise the ability to perform fine movements or grasp small objects. Resections of an entire radius of the hand reduce this problem and provide a more acceptable cosmetic appearance but decrease the strength and grasp ability. The complications of amputation include the development of neuromas or phantom limb syndrome, with an incidence higher than 20% in digital amputations due to DD.¹⁸

Since PIP joint arthrodesis is an infrequent procedure, evidence regarding its short- or long-term outcomes and complications is scarce. The present systematic review intends to synthesize the evidence on this surgical procedure.

Osteosynthesis material

One of the most remarkable findings of the present review is the variety of arthrodesis techniques. Three studies used Kirschner wires: and two of them, by Bolt et al.¹⁷ and Pillukat et al.,¹⁶ reinforced the arthrodesis with a wire tension band. Watson and Lovallo¹⁴ used Kirschner wires without any other reinforcement material and reported a fracture through the arthrodesis as a complication. On the other hand, two patients receiving a tension band¹⁶ required a reintervention because of failure of the osteosynthesis material.

Novoa-Parra et al.¹⁵ used interlocking screws and were the only authors allowing immediate postoperative mobilization of the intervened finger in all patients with no complications.

Associated procedures and approach

In three of the studies,^{14,16,17} PIP joint arthrodesis required some adherence release (fasciectomy, PA, release of checkrein deformities) to reduce the flexion contracture to the desired angulation. These procedures have a more limited extent than conventional fasciectomies. They did not increase nerve or vascular involvement considerably, with a single case of skin necrosis out of 57 arthrodeses. This rate of healing alterations of 1.7% is much lower than that observed in primary fasciectomies.¹¹

Watson and Lovallo¹⁴ performed a more ambitious bone shortening of the middle phalanx compared with other authors; thus, they were able to dispense with a fasciectomy in many cases. The authors did not report any cicatricial, nervous, or vascular complications or patient complaints due to the reduced bone length.

According to the literature consulted, no study on PIP joint arthrodesis in DD establishes clear indications regarding the volar or dorsal approach, citing only the personal preference of the surgeon to use one or the other. Supporters of the dorsal approach consider it advantageous due to the proximity to the bone tissue and a hypothetical lower possibility of vascular or nerve injury.¹⁶ The volar approach, solely used by Watson and Lovallo,¹⁴ was safe in this regard, as it was not associated with any lesion of this type. The authors defend their approach as providing greater ease to release a cicatricial contracture volar to the joint if required.

Angulation

The information collected is not detailed enough to compare the pre- and postoperative degree of flexion contracture of the fingers submitted to arthrodesis in the different studies.

The literature does not agree on the ideal angle for PIP joint arthrodesis for the fifth, fourth, third, and second fingers. While some authors consider that angulations should increase by 5° per finger compared with its radial

neighbor,¹⁹ others choose to perform a 40° arthrodesis in all of them. For the little finger, angles ranging from 35° to 70° do not result in significant differences in prehensile strength. However, angles around 55° lead to better outcomes in hand functionality tests than 35°- or 70°-arthrodeses.²⁰ Novoa-Parra et al.¹⁵ performed the arthrodesis based on the angulation of the screws. The slight differences in angulation in the selected studies seem to be solely due to surgeon preference, with no functional repercussions.

Improvement in Pain

Pain is usually not an initial symptom of DD. However, the prevalence of complex regional pain syndrome (CRPS) ranges from 0% to 12.8% a year after fasciectomy.²¹ Therefore, CRPS is common in patients undergoing multiple previous surgeries, as is the case of arthrodesis candidates.

In the present systematic review, only two papers mentioned patient-reported pain before and after surgery. Novoa-Parra et al.¹⁵ used the VAS to quantify a slight, nonsignificant decrease. Watson and Lovallo¹⁴ observed no changes.

We believe PIP joint arthrodesis, with limited fasciectomies and sparing collateral nerves, carries a lower probability of CRPS than alternatives such as amputation²² or aggressive fasciectomies. However, it does not seem to have benefits over pain.

Functional improvement and patient satisfaction

Several scores are inappropriate to determine postoperative functional improvement in DD patients.²³ Only Novoa-Parra et al.¹⁵ used the DASH and observed a non-significant improvement. Two papers employed subjective, patient-reported assessment tools. Watson and Lovallo¹⁴ reported an increase in prehensile strength in the intervened hand, while Bolt et al.¹⁷ highlighted the ability to complete basic and instrumental activities of daily living. However, no paper indicated the preoperative functional degree.

We cannot prove that this surgery results in greater functional improvement. However, it enables the preservation of a large part of the length of the intervened finger, maintaining the prehensile strength and the ability to perform digital pinch maneuvers. A digital amputation or significant contracture suppresses these skills. A potential reoperation enables the correction of unsatisfactory postoperative angulations, as occurred in two subjects in the study by Pillukat et al.¹⁶

These characteristics probably account for the high level of patient satisfaction with this procedure. Pillukat et al.¹⁶ quantified this satisfaction as 8/10, and Novoa-Parra et al.¹⁵ and Bolt et al.¹⁷ reported that all their patients would repeat this surgery and recommend it to their families. Watson and Lovallo's¹⁴ patients were satisfied with the intervention.

The correction of the flexion contracture is the determining factor in the satisfaction of the operated patient. The measurement of results from the perspective of a DD patient highlights the functional and esthetic improvement of the hand.²⁴

Complications

The complication rate in our systematic review was of 11.3%, which is consistent with the rate of 17.4% attributable to primary fasciectomy.²⁵ We highlight the absence of nerve or vascular injuries, and the low rate of healing problems, with a single case of skin necrosis.

The scant literature related to amputation in DD patients and the possibility of amputations at different levels make it difficult to compare the complications of this surgery with those of arthrodesis. However, amputation seems associated with a higher percentage of neuroma-type complications, phantom nerve syndrome, or CRPS.¹⁸

Because of the osteosynthesis material, the arthrodesis has specific complications, including instrumentation fracture or inadequate angulation, as infrequent but potential causes for reintervention.

Limitations

The present systematic review has several limitations. First, it consists of retrospective case series with a moderate risk of bias. Next, the heterogeneity observed in variables with different indicators makes comparison and conclusions difficult.

There was no MCP involvement in arthrodesed fingers in the present review, assuming a significant source of bias.

The focus on PIP joint arthrodesis alone excluded other similar interventions, such as arthrodesis of the proximal and distal phalanges with complete middle phalanx resection.²⁶

Further prospective studies with greater homogeneity in the presentation of results and better-defined measurement methods will increase the quality of future research. In addition, they will enable comparisons with other therapeutic alternatives.

Conclusion

Arthrodesis of the PIP joint is an alternative to amputation in selected patients with severe and recurrent DD and preserved finger sensitivity. Patients with associated arthrosis or arthrofibrosis are candidates for this procedure, as well as those patients in whom a new fasciectomy threatens finger viability due to vascular insufficiency or poor-quality tissue.

With an acceptable rate of complications, we emphasize the low risk of nerve or vascular injury. Despite not resulting in an objective improvement in postoperative pain or functionality, patient satisfaction was high. Because of the low level of scientific evidence of the present systematic review, further prospective studies are required to compare the outcomes of this technique with those of other therapeutic alternatives.

Ethical responsibilities

The authors declare that the procedures complied with the standards of the institutional Clinical Research Ethics Committee (which approved this study) and the Declaration of Helsinki.

Data confidentiality

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Conflict of interests

The authors have no conflict of interests to declare.

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