Recent Australian contributions to the management of Dupuytren’s disease

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Abstract

Introduction: While the history and epidemiology of Dupuytren's disease (DD) is well documented, its aetiology and risk factors, pathogenesis and treatment to this day are still being studied. This paper explores and summarises the significant contributions Australian researchers have made to the understanding of DD and its treatment methodologies.

Methods: We performed a systematic search on EMBASE from 1947 until March 2019 to identify all English literature using keywords: 'Dupuytren/Dupuytrens/Dupuytren's disease' and 'Australia/Australian/Australasian'. Relevant articles were also identified through bibliographic links. A separate search was conducted using Google Scholar, Research Gate and PubMed using the same keywords. In total, 40 articles were identified. A library search was also conducted, with one book identified with an Australian author. The Royal Australasian College of Surgeons Journal of Surgery was also analysed for published abstracts pertaining to DD from conference presentations between 2014 to 2019.

Results and discussion: We present a narrative discussion of Australian research that has contributed to the understanding of DD from its aetiology to treatment methodologies.

Conclusion: Numerous Australians have made significant contributions to the understanding of DD, its pathogenesis, development and multiple treatment modalities, both non-surgical and surgical. Dupuytren's disease is a progressive disease that reoccurs despite our best efforts and will continue to be a topic of focus for some time to come.

Keywords: Australia, Dupuytren contracture, microbial collagenase, treatment outcome, fasciectomy
Introduction
First described by Baron Guillaume Dupuytren in 1833 as a disease of the palmar fascia, Dupuytren's disease (DD) is a progressive fibroproliferative disorder of the palmar fascia. Although its pathogenesis was described initially by Baron Dupuytren, it was later corrected by French surgeon Jean-Gaspard Blaise ‘Dr G.’ Goyrand as a disease formed by ‘newly formed fibrous cords, some of which passed from the palmar aponeurosis to insert distally to the flexor sheath or the edges of the phalanges’. Dupuytren's disease is most prevalent in Northern European caucasians, with a prevalence of up to 30 per cent in the Norwegian population aged over 60, and with an overall incidence in the United Kingdom of around four per cent. While the disease history and epidemiology is well documented, its aetiology and risk factors, pathogenesis and treatment to this day are still being studied. Australian researchers have made significant contributions to the understanding of DD’s pathogenesis and its treatment methodologies which this paper aims to explore and summarise.

Methods
We performed a systematic search on EMBASE from 1947 until March 2019 to identify all English language literature using keywords: ‘Dupuytren/Dupuytrens/Dupuytren's disease’ and ‘Australia/Australian/Australasian’. Relevant articles were also identified through bibliographic links. A separate search was conducted using Google Scholar, Research Gate and PubMed using the same keywords. Letters and non-published abstracts were excluded from analysis. Articles with at least one Australian author were included in the analysis. In total, 40 articles were identified. A library search was also conducted, with one book identified with an Australian author. Local conferences with published abstracts were also included in the analysis, with The Royal Australasian College of Surgeons Journal of Surgery queried for published abstracts from conferences over 2014 to 2019 for presentations pertaining to DD. Although the Australian Hand Surgery Society annual scientific meeting has a preponderance of DD data presented from both national and international presenters, abstracts from this conference are not published. Hence this national conference and its presentations were excluded from analysis.

Results and discussion
One of the earliest contributions to the understanding of DD by an Australian is attributable to Mr John T Hueston, a plastic surgeon working at the Royal Melbourne Hospital. Based on his personal experience with over 6000 subjects and drawing on the available literature at the time, Hueston’s 1963 book titled *Dupuytren’s contracture* describes in detail the history, rates of incidence, macro and microscopic pathology, principles of management and recurrence of the disease. Throughout his career he continued to publish articles and present lectures on DD, its aetiologies, prevalence, associations, pathogenesis (including the review of theories arising from biochemical investigations), treatment methodologies and associated complications, and theories as to why they occurred. His large contributions to the understanding of DD can be best summarised by his own opinion that ‘such an unsolved problem as Dupuytren's contracture should be reviewed regularly’ and developing the concept of ‘firebreak’ grafting, a skin graft inset to areas of flexion crease to act as a ‘firebreak’ between areas where DD may potentially reoccur, which to this day is still used.

Aetiology and pathology from Dupuytren’s disease
A significant histopathological study by MacCallum and Hueston in 1962 elucidated and consolidated the understanding of DD’s pathogenesis by demonstrating the change in DD as one primarily of progressing perivascular fibrous replacement of the fatty palmar tissue overlying and involving the palmar aponeurosis. The contracture occurs in this newly-formed tissue, and while hyperplasia would classically not have been associated with contracture, it was noted that concomitant fibrosis accounted for the tension developed, and the eventual deformity.

Dorsal Dupuytren's disease had been first described between the level of the proximal interphalangeal
joints (PIP) joint and distal interphalangeal joints (DIP) joint by Hueston in 1982, with the extensor expansion involved in a Dupuytren's nodule, excision of which resolved the contracture. In 1986 Cleland and Morrison went on to further describe a pattern of DD in the thumb, a central cord rather than the more usual pattern of radial disease, not described previously. In 1994, Boyce and Tonkin expanded on this by presenting a case of dorsal DD causing ‘swan-neck’ deformity, in contrast to the well-known association of boutonniere (‘button-hole’) deformity with the disease.

While theories have been developed as to the causes of DD, it was known that trauma to the hand can precipitate or aggravate it. However, in 1996, Morrison and Lanzetta were the first to report on the onset of DD after surgical trauma on the hand for unrelated pathology in a case series of three patients.

Neurovascular bundle (NVB) displacement from DD is known to occur when disease superficial to the NVB is connected to disease deep to it, causing spiraling of the NVB, typically proximal in origin. Hettiaratchy, Tonkin and Edmunds presented six cases of distal spiral cord formation, warning that to prevent injury, the NVB should be identified proximally and dissected distally throughout its course to avoid damage.

Tonkin and Bellity further presented a rare case of DIP joint contracture arising from a retrovascular cord taking origin from mid-proximal phalanx level and inserting into the terminal phalanx, flexor tendon sheath and skin distal to the DIP joint, and its treatment in 2016, with a summary of the limited literature on this phenomenon.

While epidemiological studies have demonstrated a significant preponderance of DD in the European population, DD exists in the Asian population, which has largely been overlooked. A review by Slattery in 2010 identified 595 cases of DD in China, Thailand, Vietnam, India and Japan, with a positive family history reported in nine per cent, demonstrating a low but significant incidence of DD across Asia. Sixty-five per cent of the patients had risk factors such as diabetes, trauma, alcoholism and manual labour occupations, lending support to the hypothesis of a widespread genetic susceptibility to the disease, and present risk factors that may lead to the expression of DD in this population.

**Treatment methodology**

**Radiotherapy**

In 2014, Grenfell and Borg explored the role of radiotherapy in the management of DD by analysing six consecutive cases of early DD treated with radiotherapy between 2008 and 2011 at their institution. All six cases demonstrated reduced symptoms with minor toxicities including lethargy, local skin reaction, oedema and pain. When compared to a systematic review of the literature, seven studies were identified by the authors between 1946 and 2013 using radiotherapy as the primary treatment for the disease, with the authors’ study adding credibility to the notion of using radiotherapy as an effective management option for patients with early disease to prevent its progression.

**Percutaneous needle fasciectomy**

In a review of a single institutional experience in 2009, Lee and Hunter-Smith looked at 37 patients and found that by using the disabilities of the arm, shoulder and hand score (DASH) patient recorded outcome measure (PROM), 65 per cent reported significant improvement, with 85 per cent of patients willing to recommend the procedure to their friends. Although recurrent disease was present in some at the six to 12 month mark, none required surgical intervention, with the authors concluding that, in the correct population group, percutaneous needle fasciectomy (PNF) was a suitable treatment methodology.

A further study at the same institution by Toppi and colleagues in 2013 analysed 73 PNF and 52 open fasciectomies (OF), identifying no significant differences in terms of immediate or medium-term deformity correction, tendon/nerve injury or circulatory complications and satisfaction scores. Postoperative infection rates were 7.57 times higher with OF when compared to PNF.
Collagenase clostridium histolyticum

An enzyme produced by clostridium histolyticum, collagenase clostridium histolyticum (CCH) was investigated for the efficacy and safety in patients with Dupuytren’s contracture in 2010. It was a prospective, randomised, placebo-controlled trial, with 66 patients enrolled, 45 cords receiving CCH, and 21 cords receiving placebo. Statistically, more cords with CCH injection met the primary endpoint of reduction in contracture to 0–5 degrees of normal 30 days after last injection, (44.4% versus 4.8%, p<0.001). The authors concluded that CCH was the first US Food and Drug Administration-approved, nonsurgical treatment option for adult DD with a palpable cord that was effective and well tolerated. A randomised control study by Costas and colleagues analysed CCH use for Dupuytren’s disease nodules and was able to demonstrate significantly improved palmar nodule size and hardness when compared to placebo, with a similar safety profile as CCH use in Dupuytren’s contracture.

Another study with two concurrent nine-month, open-label studies, JOINT I (United States) and JOINT II (Australia and Europe) was conducted to evaluate the efficacy and safety of CCH in DD with Australian and international investigators involved in the trial. Collagenase clostridium histolyticum was administered in 587 patients (879 joints) at 14 US and 20 Australian/European sites. The concurrent studies demonstrated similar outcomes, with 57 per cent of joints achieving clinical success, defined as a reduction in contracture to within 0 to five degrees of normal within 30 days of injection. More metacarpophalangeal (MCP) joints achieved clinical success than PIP joints (70% versus 37% respectively).

A follow-up study evaluating CCH at up to five years post treatment involving Australian and international investigators found the overall recurrence rate of 47 per cent was comparable to surgical treatment.

A systematic review by Paynter and colleagues in 2018, drawing on data from 18 studies of CCH use in DD to evaluate its effectiveness, safety and recurrence rates, found that clinical success—defined as primary joint contracture reduction to 0–5 degrees of full extension by 30 days after last CCH injection—was between 41 per cent and 72.5 per cent, with the most success present for those treated for MCP joint contracture (up to 91% success). However, treatment-related adverse effects were reported between 57.5 to 100 per cent of participants in studies analysed, including oedema, contusion, injection site hemorrhage, swelling, pain, skin tears and lymphadenopathy. Collagenase clostridium histolyticum was previously indicated for injection of only one cord at a time during a 30-day treatment cycle. In 2012 Coleman and colleagues concluded that treatment of two cords could be performed concurrently, after conducting an exploratory study using CCH to analyse if concurrent administration of two injections of CCH into two palpable cords on the same hand would result in comparable safety and efficacy when compared to a single injection into one cord. A similar study analysing the efficacy and safety of concurrent CCH injections for two joints in the same hand at the same time by Gaston and colleagues demonstrated no greater risk of adverse events than treatment of a single joint with the exception of skin lacerations. Similar findings were previously demonstrated in a study by Coleman and colleagues.

To clarify if CCH was an effective and safe outpatient treatment in the Australian public health setting, Fletcher and colleagues, in a prospective cohort study, enrolled 54 patients to treatment of 81 joints using CCH. Forty-eight per cent of patients achieved reduction in contracture of 0–5 degrees of full extension four weeks after injection, with 68 per cent of patients either satisfied or very satisfied at 12-month follow-up. Reported side effects were minor, with 87 per cent developing oedema and 85 per cent developing bruising. All complications had resolved by the four-week review. The authors concluded that CCH was a safe and efficacious treatment in the Australian public health setting. Another study analysing DD use with IV sedation for manipulation 48 hours post injection, demonstrated treatment of up to
five cords was achievable in the one session in a hospital setting.\textsuperscript{32}

When comparing CCH to fasciectomy, Muppavarapu and colleagues analysed 142 patients undergoing either procedure, noting that fasciectomy achieved a greater rate of clinical success that persisted for longer (46% of MP joints treated with CCH versus 68% treated with fasciectomy, at 14.2 months follow up for collagenase and 16.3 months for fasciectomy).\textsuperscript{33}

When comparing the cost of CCH and fasciectomy in 2018 in a population of 25 digits being treated by fasciectomy in 18 patients, and 23 digits being treated by collagenase in 21 patients, Sefton and colleagues determined that, on average, the treatment cost of the fasciectomy group was US$5738.12 when compared to US$2076.83, representing a significant cost saving (64%) when using CCH.\textsuperscript{34}

A similar study in 2019 by Elliot and colleagues, analysing the cost of single-digit surgical fasciectomy compared to CCH treatment delivered in the outpatient setting, with 37 patients in the CCH group and 38 patients in the fasciectomy group, determined that, on average, treatment cost of the fasciectomy group was AU$6155 when compared to AU$2589.\textsuperscript{35}

Another study in 2019 by Livingston and colleagues again demonstrated cost superiority of CCH over surgical treatment, with the cost of surgical treatment on average AU$5852 per patient when compared to AU$1176 for patients undergoing CCH.\textsuperscript{36}

Fasciectomy

In 1978, Rank and Chang published an article analysing surgical interventions over a longer term something which, at that time, had been lacking.\textsuperscript{37} Follow-up was up to 50 years, with 536 operations (mostly limited fasciectomies) analysed and 50 cases, with an average follow-up period of 14.8 years. Early and persistent complications were described, with 20 per cent not developing recurrence, 45 per cent developing DD outside of the operative field (30% of which needed further surgery) and 35 per cent developing local recurrence (60% of which needed further surgery). The authors' conclusion were that the disease had a high recurrence rate, and close follow up is warranted, something still regularly integrated in todays practice.

In a descriptive study with a case series of 32 patients between 2004 and 2011, Behan explores the palmar deficits arising from surgical correction of DD, describing the application of keystone principles as an alternative to Hueston’s firebreak graft. By using keystone perforator island flaps in conjunction with Bruner’s flaps to produce hypervascularity, hypothetically via a sympathectomy effect, the author was able to repair palmar defects created by surgical excision of DD with minimal complications, and no recurrence to date.\textsuperscript{38}

Dissection of the neurovascular structures is also a significant task, with up to a 7.8 per cent complication rate reported.\textsuperscript{39} Nikkhah and colleagues describes the use of a microscope to assist in dissection, with increasing benefits for those with digital cords encasing the neurovascular bundles in primary disease, or in recurrent disease where no planes can be identified, with dense scar tissue surrounding structures.\textsuperscript{39}

Complications

A systematic review by Leung and colleagues further elucidates management complications of DD by analysing morbidity of interventions in untreated disease. The authors found infection rates, nerve injury and complex regional pain syndrome were higher in open procedures such as fasciectomy, when compared to closed procedures, primarily PNA and CCH treatment. Rates of arterial and tendon injury were comparable between open and closed procedures, while skin tears were more prevalent with closed procedures. However, the authors found that most studies pooled data from primary and recurrent disease, and hence lack of isolated data from each treatment group meant that complication profiles for primary and recurrent disease could often not be accurately determined.\textsuperscript{40}
Presentations

In conjunction with publishing articles, Australians have made contributions to the understanding of DD and its treatment through presentations at conferences such as the Royal Australasian College of Surgeons annual scientific congress (RACS ASC). An internationally recognised conference drawing on presenters both locally and internationally, with attendees from around the world, the RACS ASC is another platform which provides an avenue for Australian authors to present their findings.

At the 2014 RACS ASC, Hunter-Smith presented an algorithm to help surgeons deal with more complex cases for DD that involves incorporating PNF, and subsequently CCH, into his clinical practice for the treatment of the disease. Coleman discussed the clinical use of CCH in DD, its advantages and disadvantages in use at a single institution.

At the 2016 RACS ASC, Livingston and Wagels presented a cost-benefit analysis of CCH, finding that a mean minimum saving of AUD$4717 when comparing CCH versus surgical treatment, making surgical treatment four times more expensive than CCH treatment. Chan and colleagues also analysed CCH versus open fasciectomy, finding that on average the CCH treatment cost AUD$1929 per case compared to AUD$3440 for open fasciectomy.

At the 2018 RACS ASC, as has been the trend with increasing amount of research into DD, multiple Australian surgeons presented their study findings. Phan and Cavallo analysed CCH and PNA treatment at a single institution, determining that the difference between the two treatment outcomes was not statistically significant in improvement in MCP and PIP joint extension or complication rates. Burgess and colleagues introduced a multidisciplinary approach to managing DD consisting of both group education sessions followed by individual patient reviews by surgeons and radiation oncologists to tailor the best treatment plan for individual patients, an approach that had never been implemented previously. Bilbao and colleagues introduced the concept of using a ‘parachute neurovascular island flap’ for tissue coverage post amputation for recurrent DD to create a sensate stump that in the process avoids transecting the neurovascular bundle, leading to reduced incidences of neuroma and tip sensitivity. Chae and colleagues presented a delayed seven-day manipulation protocol after CCH injection in a single institution demonstrating it was safe and well tolerated. Leung and colleagues investigated the eponyms ‘Dupuytren’s’, ‘Dupuytren’ or ‘Dupuytrens’ disease usage in the literature, finding that all three are used interchangeably but that Dupuytren's is the more common term, although with changes in medical convention and terminology, the non-possessive form, ‘Dupuytren disease’ should be used.

Conclusion

Australians have enhanced the understanding of DD's pathogenesis and aetiology through anatomical, histological and population studies, treatment methodologies such as non-surgical and surgical management and analysis of durability and complications arising from treatment that allows surgeons to better counsel patients. Through published books, papers and presentations that span over 50 years, these contributions continue to influence clinicians both locally and on the international stage. Dupuytren's disease is a progressive disease that reoccurs despite our best efforts and will continue to be a topic of focus for some time to come.

Disclosure

The authors have no financial or commercial interests to disclose.

References


