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HANDLEY'S THREAD LYMPHANGIOPLASTY VS. BIOBRIDGE™ COLLAGEN MATRIX FOR LYMPHEDEMA THERAPY – OLD WINE IN NEW BOTTLES?

M. Witt, A. Ring

St. Rochus Hospital, Clinic for Plastic, Aesthetic and Reconstructive Surgery (MW,AR), Castrop-Rauxel, Germany; LMU Munich, Institute for Ethics, History and Theory of Medicine (MW), Munich, Germany

ABSTRACT

Lymphangioplasty is a technique of reconstructive lymphatic surgery where subcutaneous lymphatic neocollectors are created, using surgical threads, nanofibrillar collagen threads, plastic tubes or autologous tissue flaps. The history and success rates of these techniques are outlined and a classification for lymphangioplasty techniques is proposed. The use of absorbable surgical threads is suggested for modern attempts of thread lymphangioplasties. The results of such a thread lymphangioplasty should be compared with that of implanted nanofibrillar collagen threads or plastic tubes in order to evaluate whether the technique itself or the material used is responsible for the therapeutic success.

Keywords: Lymphatic surgery, Minimal invasive surgery, Lymphangioplasty, BioBridge™, Aligned nanofibrillar collagen

Operations in the field of lymphatic surgery can be divided into two groups based upon approach: excisional procedures (e.g., liposuction, local excisions, Charles procedure); and reconstructive approaches to achieve improved or normalized lymphatic flow in lymphedematic tissue by creating new lymphatic pathways. Such reconstructive techniques are lymphovenous anastomoses (LVAs) and vascularized lymph node transfers (VLNTs). Another technique to be presented here is the so-called lymphangioplasty. It can rightfully be described as the oldest and at the same time the youngest procedure in reconstructive lymphatic surgery – the oldest technique because it is the first reconstructive approach, described by Handley in 1908) (1), and the newest due to its recent revival using nanofibrillar collagen threads.

The principle of lymphangioplasty is as follows (*Fig. 1A and 1B*): a thread is implanted or rather tunneled through the subcutaneous tissue extending from lymphedematous to healthy tissues to create lymphatic neo-collectors. Along the implanted threads, the lymph drains into healthy lymphosomes, probably driven by capillary forces and a pressure gradient. This is why the implanted threads should definitely reach into healthy lymphosomes. With respect to the therapeutic mechanism, the German surgeon Erich Lexer (2) suggested the more descriptive name "capillary thread drainage" instead of "lymphangioplasty".

MATERIALS AND METHODS

A comprehensive review of the literature on this topic was carried out, including less accessible publications in French, Spanish,

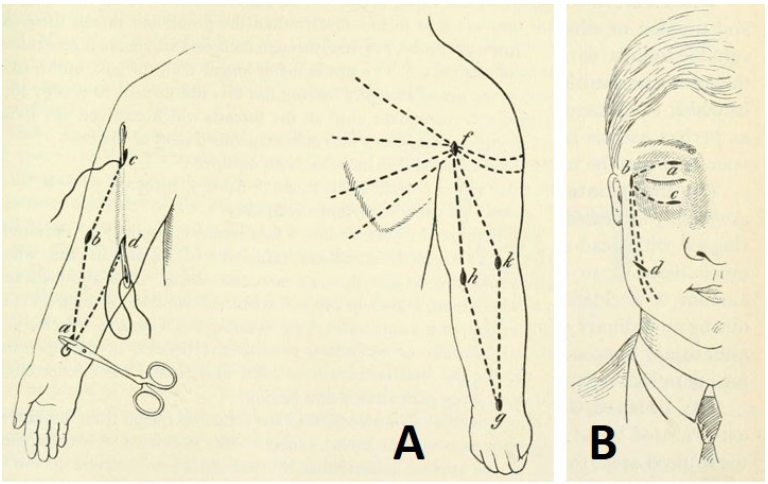

Fig. 1A and 1B: *Illustration depicting Handleys lymphangioplasty technique and location on the arms (A) and face (B). Reproduced from Binnie in 1911 (2).*

and German (partly not indexed in PubMed/ Medline), as well as older book publications. In many of these publications, the name lymphangioplasty does not appear in the title. The historical methods and their success rates are summarized. The comprehensive review given here aims to provide a theoretical and historical background which is necessary to critically evaluate methods introduced in recent years. Along with that, a classification for different techniques of lymphangioplasty is proposed.

Some 30 publications on lymphangioplasty (case reports and retrospective studies) appeared between 1908 and 1987. They outline (mainly successful) therapies of lymphedema patients using lymphangioplasties with various kinds of non-absorbable threads [silver (3), silk (3-8), nylon, thread size 1 (9,10), Teflon™ (11), Tevdec™ (dacron with PTFE cover; Deknatel, Teleflex Inc., Mansfield, MA) thread size 0 or 00 (=2-0) (9), plaited womens' hair (12), etc.]. After this technique had been forgotten, it was revived around 2016, however, not with surgical threads as subcutaneous inlays, but with an absorbable nanofibrillar collagen thread (BioBridge™). In this context, the term lymphangioplasty is currently not used (13-20), even though the implantation of BioBridge™ is nothing but a variant of Handley's classic thread lymphangioplasty.

RESULTS

Historical Development of Lymphangioplasty

Lymphangioplasty is based on fairly mechanistic ideas ("the same idea as draining a marshy field", Handley 1909) (3), similarly to the so-called Southey tubes which were first described in 1877 (21). Southey tubes are short rigid perforated silver tubes that were temporarily implanted into edematous tissue and from which the edema gradually drained into bottles via connecting pipes. This technique was used for temporary and forced tissue drainage from 1877 until the 1960s, before potent diuretics became available. Lymphangioplasty may have been inspired by these Southey tubes, on the quest for a less invasive and more permanent procedure.

But even before Handley, experiments with threads for tissue drainage had been carried out. Lauenstein in Hamburg, around the year 1900, is said to have used subcutaneously implanted silver threads to treat scrotal lymphedema (3). Lambotte (1905) (22) performed abdominal ascites drainage with silk

threads in a similar way.

In the history of lymphangioplasty, three phases can be distinguished: the era of silk threads (until around 1945), since 1945 the era of synthetic threads, and since around 2015 the era of nanofibrillar collagen threads. Handley and his successors used silk threads, which were used as surgical suture material at that time. These silk threads measured one meter or more in length and were partly implanted in double strands. Binnie in 1911 (23) recommended "a double line of silk more than twice as long as the arm" for lymphangioplasty of the upper extremity. These long threads were tunneled subcutaneously, through several skin incisions, from edematous tissue into healthy one.

Mechanism of Action: Capillary Forces or Formation of New Lymph Vessels?

Lymphangioplasty was thought to work via capillary forces and creating a lymphatic flow along the implanted thread. On the other hand, it was speculated, by Hartley in 1937 (24) and Zieman in 1951 (25), that a new formation of lymphatic vessels might be stimulated by this technique. Decades later, a theory of secondary lymph vessel formation was experimentally verified by Boardman and Swartz (26,27) and Rutkowski, Boardman, and Swartz (28). They did, however, not have Handley's thread lymphangioplasty in mind when doing their research. In animal experiments with mice, a portion of skin was removed from a mouse tail and a collagen solution was applied in this defect, solidifying there, and forming the so-called collagen dermis equivalent (CDE). It was demonstrated that lymphatic flow was maintained along the collagen patch, with secondary endothelial lymphatic cells migrating into the CDE, organizing themselves and forming a new lymphatic network under the influence of vascular endothelial growth factor-C (VEGF-C). Formation of lymphatic vessels was hereby demonstrated to be distinct from that of blood vessels: in blood vessels, tubular structures are first created and after that filled with blood (26). In the lymphatic system, however, an interstitial flow must be present or, as in lymphangioplasty, created, before lymphatic channels secondarily arise along these pathways.

Success Rates

In an early review article by Syms in 1913 (29) publications on lymphangioplasties with silk threads were evaluated (mostly individual case reports) and the success rates of this technique were determined as follows, according to the treated body part (note: Syms' analysis is partly incorrect. It has been corrected here after reading the original articles his work is based upon. Syms incorrectly considers some lymphangioplasties as failures which had been described as successes. Furthermore, he does not realize that sometimes the same case was published in different journals, counting it multiple times):

- 50% in arms (10 successes, 10 failures)
- 25% in legs [5 successes or significant improvement, 2 successes, but relapse after 2 years, 13 failures (note: The failures reported are largely from a paper by Madden et al (7), which was widely criticized for its methodology and a too short a follow-up period.)]
- 100% in the face/eyelid (3 successes)
- 100% in abdominal ascites (10 successes, but risk of infection due to connecting the abdominal cavity with the subcutaneous tissue; some patients therefore died early).

Matas in 1913 (30) reported four cases of lymphangioplasties of the lower extremities that were successfully done in Russia and not included in Syms' study. Meyer in 1913 (31) relates one additional successful case of lymphangioplasty of the upper extremity performed in Strasbourg. Lefèbvre in 1923 (32) gives an account of 26 cases of lymphangioplasty (partly the same ones as in Syms [29]), 22 of which were an immediate success. 13 of these cases were followed up. In 12 of them, there was a recurrence which took place between several months and two years after the operation. Only one patient remained

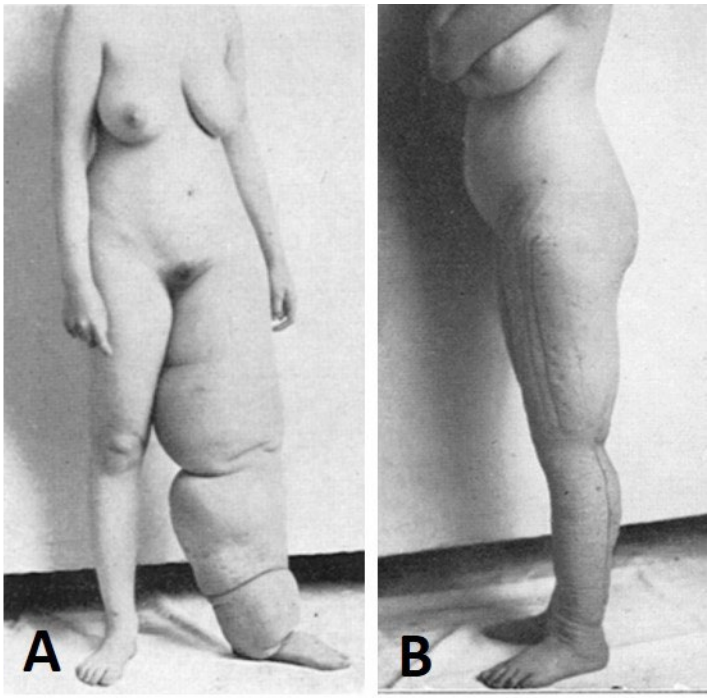

Fig. 2A and 2B: *Photographs of a patient with lymphedema who was treated with the Handley-Lexer procedure (subfascial lymphangioplasty) according to Keysser in 1927 (7). Preoperative image (A) and postoperative (B).*

permanently cured.

Gorman in 1965 (35) performed lymphangioplasties in nine patients with primary lymphedema of the lower extremities using 92 cm (36 inch) long 0 or 00 (= 2-0) Tevdec™ sutures. The thread was tunneled over the entire length of the leg to the proximal thigh or lower abdomen. With a follow-up of 2-13 months, 88% of the patients had a benefit from the treatment, with a progressive decrease of circumference of the extremity or at least an improvement (softening) of the tissue.

In 1976, Silver and Puckett (11) published a retrospective study about a 10-year follow-up of lymphangioplasties with Teflon™ threads, performed in 16 patients (6 upper and 10 lower extremities). In all patients they noted a rapid decrease in tissue edema with limbs becoming softer, less heavy, and significantly more mobile. In the first few months the average decrease in circumference was 1.2cm, with the effect lasting 6 months to 7 years (average 13 months).

Other Forms of Lymphangioplasty

A modified (subfascial) version of lymphangioplasty was introduced by Lexer in 1919 (36). After excising the thickened fascia he directed silk threads from the subcutaneous layer into the muscles. This technique was further investigated by Keysser in 1927 (6) (*Fig. 2A and 2B*). The Handley-Lexer method yielded favorable results in patients with lymphedema of the lower extremities (six cases), in two with lymphedema of the arm and in two with lymphedema of the face and scrotal lymphedema respectively. Keysser reports failures only with other operative procedures, not with Handley-Lexer's method.

Kaufmann et al (12) published a study in 1983 in which lymphangioplasty was not carried out with surgical threads, but with sterilized plaited hair from the patients, with three hairs being twisted to a thread. Lymphangioplasties according to Handley, Handley-Lexer (subfascial) or a combination of both methods

were carried out. Between six and 20 threads were implanted in each patient. The retrospective study examined a collective of 11 patients (4 primary lymphedema of the lower extremity, 6 secondary lymphedema of the lower extremity, and 1 secondary lymphedema of the hand and forearm) with a follow-up of 2-4 year years after surgery. A complete and persistent remission was observed in three cases and a partial remission in four cases (success rate 64%).

Others did not use threads as inlays for neocollectors, but subcutaneously implanted perforated metal tubes [Janssen in 1914 (37)], rubber tubes [Walter in 1918 (38,39)], polyethylene [Hogemann in 1955 (40)] or silicone tubes (41-47). This technique may be regarded as a permanent variant of Southey tubes, so to speak. It is advisable to call this procedure tube lymphangioplasty, although the authors who investigated it did not use this term. A recent systematic review shows that, in patients with advanced stage lymphedema, lymphangioplasties with silicone tubes lead to an average limb volume reduction of 700-887 ml and a limb circumference reduction of 3.1- 8 cm (48). There has always been criticism that thread and tube lymphangioplasties create static fluid columns, but do not provide any motor force for draining the lymph (7,24). A response to that criticism is the LymphoPilot™ and LymphoDrain™ devices (Lymphatica Medtech SA, Lausanne, Switzerland). Both constitute a sort of pump-enhanced tube lymphangioplasty: a perforated plastic tube is subcutaneously implanted and the lymph fluid collecting it is transported by a equally subcutaneously implanted micropump to an area with functioning lymphatics. The first clinical study with LymphoPilot™ (a device not commercially available) was made in 2021-2023 (results not yet published). The successor product LymphoDrain™ is not yet available on the market. The manufacturer claims that a decrease of lymphedema by 30% can be obtained with these devices.

In an attempt to perform lymphangioplasties without foreign bodies, biological materials were explored as well. Krogius [in 1911 (49)] used autogenous vena saphena magna transplants to treat scrotal and penile lymphedema. He furthermore suggested to try an arteria femoralis transplant instead of the great saphenous vein or to transpose parts of the omentum maius into the scrotum. After succeeding with implanted perforated metal tubes to cure elephantiasis of the penis, Janssen [in 1914 (49)] replaced them, equally successfully, with homogenous vein grafts taken from another patient. Lanz [in 1911 (50)] transposed long pedicled fascia lata flaps into the medullary cavity of the femur (through drilled holes) in order to create deep drainage routes. Others transposed fascia flaps into muscle tissue (51-53). Sokolowski [in 1925 (54)] used autogenous omentum flaps and buccal flaps for drainage of hydrocephalus. These early attempts of (mostly) autogenous lymphangioplasties were revived in the 1960s in Spain, where proximally pedicled fascia lata flaps (55), omental flaps (56) and deepithelialized skin flaps (57) were used for autogenous lymphangioplasties.

BioBridge™ Collagen Matrix

A study by Lai et al in 2012 (58) suggests that nanofibrillar collagen regulates the organization and migration of endothelial cells. Inspired by this idea, a thread-like nanofibrillar porcine collagen matrix was developed and tested since 2015 (59) (BioBridge™, Fibralign Inc., Union City, Ct., USA). BioBridge™ may be considered an acellular dermal matrix (ADM) for performing thread lymphangioplasties – "a new twist to an old idea" (59), as described by one of its inventors. BioBridge™ is available in the USA since 2018 (used in pilot studies since 2016), and in Germany since 2022.

BioBridge™ is a white, not particularly tear-resistant collagen thread with a specific nanostructure. It has tubular elements in its core and a bark-like surface, structures that are generated by condensing collagen sheets to a thread (*Fig. 3A-G*). A single BioBridge™ thread measures 0.3mm x 18cm and is commercially available in a set of five threads (current cost approx. 3000 EUR per set, in the USA $1500). According to the manufacturer,

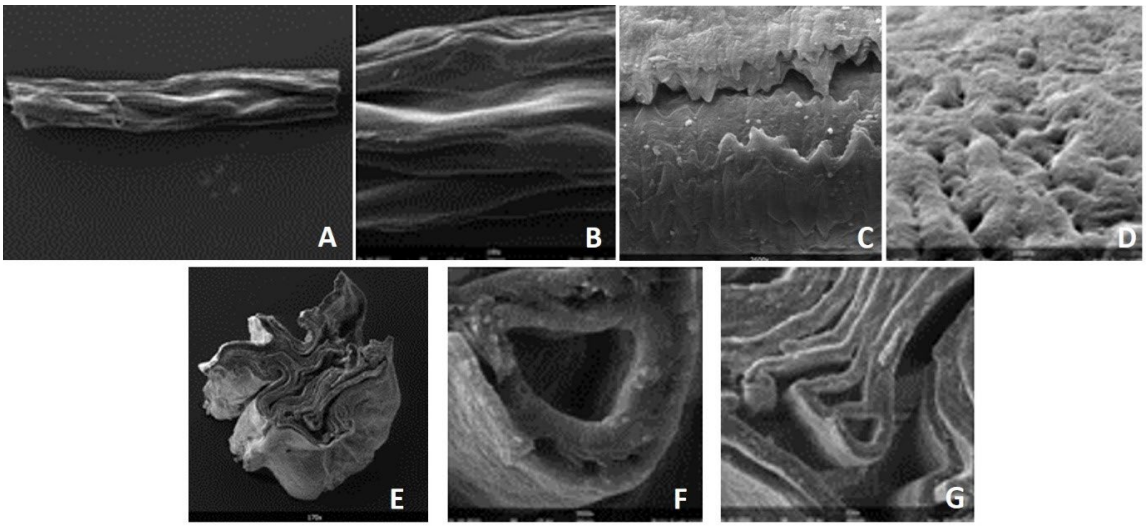

Fig. 3A-G: *Scanning electron micrographs of a BioBridgeTM thread: longitudinal and surface (top, A-D) and cross-sectional (bottom, E-G) (courtsey of Enrico Fruth, Institute of Pathology, Ruhr University Bochum, Germany; magnifications A-D: 38x, 190x, 2600x, 10000x, magnifications E-G: 170x, 930x, 3500x).*

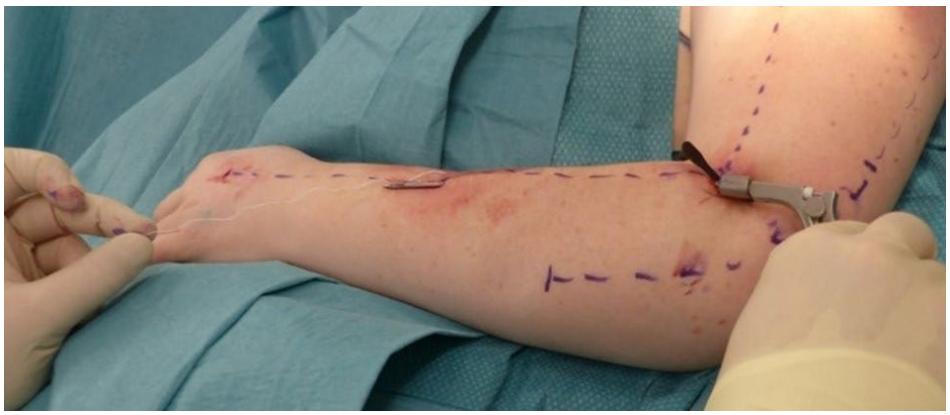

Fig. 4: *Intraoperative photograph of implantation of BioBridgeTM (white fiber in left hand) using an endoscopic needle holder (Berci needle = Gore suture passer).*

BioBridge™ is absorbed after 6 months (determined by its complete loss of tensile strength). However, the tubular core structures of BioBridge™ remain histologically detectable in the tissue for a longer time, showing no sign of degradation even after 10 months (see Witt et al in this issue).

The implantation mode is exactly the same as in Handley's thread lymphangioplasty: subcutaneous tunnels are made (using a suture passer [*Fig. 4*] or, in case of highly fibrotic tissue, a liposuction cannula along with a suture passer [*Fig. 5A-D*]) and BioBridge™ threads are inserted as an inlay. The "streets" of BioBridge™ are directed from lymphedematous tissue to healthy lymphosomes. The sole difference to a conventional thread lymphangioplasty is that BioBridge™ is only 18cm long and therefore must be implanted one by one, with overlap between the single threads (which remain either unconnected or may be connected with sutures or

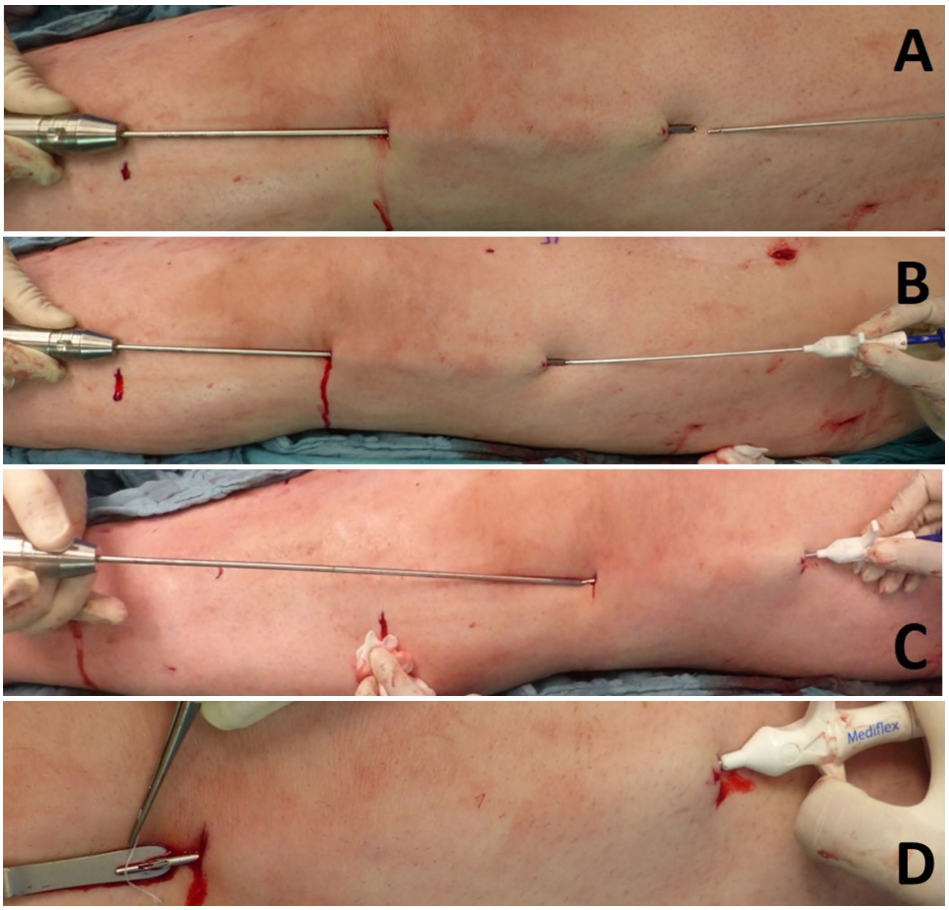

Fig. 5A-D: *Implantation of BioBridgeTM in sturdy tissue, using a liposuction cannula and a suture passer: At first, a subcutaneous channel is made with the liposuction cannula (5A). The suture passer docks into the lumen of the liposuction cannula (5B), and is pulled through the channel still docked into the cannula (5C). Finally, both instruments are disconnected and the suture passer can grasp the BioBridgeTM thread (5D).*

wound staples – note: It has not yet been investigated which technique is better and whether there is any difference at all in outcome). While in classic thread lymphangioplasties puncture needles were sometimes used for subcutaneous implantation of the threads (9,25) (at times under local anesthesia), this is not possible with BioBridge™, because the thread is not sturdy enough to slide through a hollow needle. Instead, it folds up and blocks the lumen after a short distance.

Classification of Lymphangioplasty Methods

The traditional name "lymphangioplasty" is nowhere used with reference to BioBridge™, as stated above. It is however advisable to refer to implantations of BioBridge™ or other biomaterials (e.g., subcutaneous tubes) by the term lymphangioplasty as well. For all of these procedures are based on the same principle, only the implanted biomaterial varies. The following classification of lymphangioplasty procedures is suggested:

1. *Alloplastic lymphangioplasty*

    a. Thread lymphangioplasty

- Non-absorbable threads: silk, nylon,

Teflon™, Tevdec™
- Absorbable threads: BioBridge™, polydioxanone (PDS II)

b. Tube lymphangioplasty

- Metal / rubber/polyethylene/silicone tubes
- LymphoPilot™, LymphoDrain™ (pump-enhanced, with implanted micropump)

2. *Biologic lymphangioplasty*

a. autogenous

- Fascia flaps
- Deepithelialized skin flaps
- Omentum flaps
- Arteries, veins
- plaited hair (thread lymphangioplasty)

b. allogenous

- veins

DISCUSSION

Studies with BioBridge™, Problems and Research Desiderata

With BioBridge™, experimental lymphangioplasties have been carried out in animals. It was shown that BioBridge™ improves blood perfusion and haemangiogenesis (arteriogenesis) (59,60). In other studies, lymphatics of rats were experimentally destroyed by lymphadenectomy and irradiation. It was shown in these animals that BioBridge™ promotes lymphatic drainage and lymphangiogenesis (18), that it can both prevent lymphedema – when implanted prophylactically, as a substitute for the destroyed lymphatics – and reduce existing lymphedema (17).

There is, however, a problem with all of these studies: as control groups animals were used that remained completely untreated after the lymphatics had been artificially destroyed. More convincing results could have been obtained if the control groups had received thread lymphangioplasties with other materials (e.g., surgical threads). This would have made it possible to determine whether the technique of lymphangioplasty per se yielded therapeutic success or whether the material (collagen) or the structure (aligned nanofibrillar collagen threads with central channels) were responsible for the therapeutic benefit. This has still to be proven. The historical studies presented above demonstrate that surgical threads made from a wide variety of materials have a good and very similar therapeutic effect. The abovementioned studies by Swartz, Boardman et al (26-28) prove that simple collagen (not aligned nanofibrillar one) promotes directed lymphangioneogenesis as well. It would therefore a desired research study to repeat the animal experiments using BioBridge™ threads, solid collagen threads, and simple surgical suture material (e.g., polydioxanone threads) in comparison. This is the only way to show to what degree BioBridge™ may be superior to conventional thread lymphangioplasties.

To date, BioBridge™ has only been studied, on human subjects, in combination with other procedures of lymphatic surgery like LVA or VLNT. According to a recent metanalysis, such combined BioBridge™ lymphangioplasties lead to an average excess limb volume reduction of 1-10.7% [47]. An ongoing study in Stanford and Chicago is examining the therapeutic benefits of LVAs alone versus LVAs plus lymphangioplasty with BioBridge™, in a group of approximately 80 patients. In order to filter out which effect is due to the LVA and which one to BioBridge™, studies with BioBridge™ lymphangioplasties as sole therapeutic means are being carried out. A study in Japan with BioBridge™ implantation plus compression therapy is ongoing. In our clinic, a similar study (Bio-Bridge™ plus compression therapy, including a control group with compression therapy alone) is running. To date, BioBridge™ has only been implanted subcutaneously. The effect and benefit of BioBridge™ used in the sense of a subfascial lymphangioplasty accord-ing to Handley-Lexer still needs to be investi-gated.

Whether the same effect of a lymphangioplasty with BioBridge™ or at least a similar one can be achieved using cheaper materials,

such as surgical sutures (as in historical lymphangioplasties), and whether BioBridge™ is significantly superior to simple suture materials has not yet been investigated. Such studies would however be highly desirable. Costs could be reduced, and a broader range of patients treated. Even if it turns out that lymphangioplasties with BioBridge™ are significantly superior to conventional thread lymphangioplasties, it still needs to be investigated whether both methods can be combined, e.g., BioBridge™ implanted in critical areas and, additionally, absorbable thread material as a cheap alternative, to extend the BioBridge™ pathways into other tissue sections and over longer distances. In historical lymphangioplasties, the threads were usually tunneled along the length of the entire limb, in several continuous strands. This can hardly ever be achieved with BioBridge™ alone, for mere financial reasons. In our clinic, lymphangioplasties with absorbable surgical suture material (polydioxanone threads, sizes 0, 2-0 and 4-0) were performed for the first time. The threads were tunneled along the whole extremity, as in historic thread lymphangioplasties. We used polydioxanone threads because they are absorbable, while having a smooth surface as the non-absorbable threads previously used for lymphangioplasties. Furthermore, polydioxanone threads are monofilaments (decreased risk of infection) and have a similar resorption time as claimed for BioBridge™ (approx. 6 months). In our clinic, this technique yielded similar results and volume reductions in the weeks and months after implantation as in patients who had received lymphangioplasties with BioBridge™ threads. Whether the results are lasting in a similar way has to be investigated. A final evaluation of our patient population treated this way is still pending.

All these new developments show that the supposedly historical technique of lymphangioplasty is more innovative than ever before and that it still offers plenty of research potential.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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Mathias Witt MA MD PhD
Associate Professor (Privatdozent),
Institute for Ethics, History and Theory of Medicine, LMU Munich, Germany
and
Senior Consultant and Head of the Subunit of Reconstructive Lymphatic Surgery
St. Rochus Hospital, Clinic for Plastic, Aesthetic and Reconstructive Surgery, Castrop-Rauxel, Germany
E-Mail: mathias.witt@med.uni-muenchen.de and mat.witt@lukas-gesellschaft.de