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Review

The role of patient characteristics and the effects of angiogenic therapies on the microvasculature of the meniscus: A systematic review

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ABSTRACT

Background: Considerable interindividual variation in meniscal microvascularization has been reported. The purpose of this review was to identify which patient characteristics affect meniscal microvascularization and provide a structured overview of angiogenic therapies that influence meniscal neovascularization.
Methods: A systematic literature search was undertaken using PubMed, Embase, Web of Science, Cochrane library and Emcare from inception to November 2021. Studies reporting on (1) Patient characteristics that affect meniscal microvascularization, or (2) Therapies that induce neovascularization in meniscal tissue were included. Studies were graded in quality using the Anatomical Quality Assessment (AQUA) tool. The study was registered with PROSPERO(ID:CRD42021242479).
Results: Thirteen studies reported on patient characteristics and eleven on angiogenic therapies. The influence of Age, Degenerative knee, Gender, and Race was reported. Age is the most studied factor. The entire meniscus is vascularized around birth. With increasing age, vascularization decreases from the inner to the peripheral margin. Around 11 years, blood vessels are primarily located in the peripheral third of the menisci. There seems to be a further decrease in vascularization with increasing age in adults, yet conflicting literature exists. Degenerative changes of the knee also seem to influence meniscal vascularization, but evidence is limited. Angiogenic therapies to improve meniscal vascularization have only been studied in preclinical setting. The use of synovial flap transplantation, stem cell therapy, vascular endothelial growth factor, and angiogenin has shown promising results.
Conclusion: To decrease failure rates of meniscal repair, a better understanding of patient-specific vascular anatomy is essential. Translational clinical research is needed to investigate the clinical value of angiogenic therapies.

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Contents

1. Introduction

Menisci contribute to load transmission, decrease contact stresses, and increase the contact area and congruity of the knee [1,2]. Furthermore, they have a critical function in the knee joint's stability, lubrication, and proprioception [3–5]. In the past decades, it has been demonstrated that damage of the meniscus hampers its biomechanical functions and contributes to osteoarthritis in the long term [6]. Therefore, it is essential to preserve the meniscus and strive for surgical repair of a meniscus tear [7]. Nevertheless, despite careful patient selection, improved surgical techniques, and postoperative rehabilitation, meniscal repair failure rates as high as 24% have been reported [8]. Failed meniscal repairs often require a second surgery and cause increased morbidity and additional operative risks.

The meniscal healing process is based on two fundamental principles: a solid primary fixation obtained during surgery, and a well-functioning biological process of cicatrization, in which vascularization plays a significant role [9]. The extent of vascularization in the surrounding tissue of a meniscal tear affects the likelihood of successful repair [10]. It has been shown that vascularization is present throughout the developing meniscus [11]. However, with increasing age, the inner portion of the meniscus loses its vascularization, and only the peripheral border of the crescent-shaped meniscus remains well supplied with blood through the perimeniscal capillary plexus [12]. Interestingly, significant differences in the extent of vascularization are reported, as measured from the capsule to the most centrally located blood vessel, ranging from 0 to 48% (Figure 1) [13].

To this day, little is known about the causes of the differences in the extent of vascularization. If patient characteristics could be identified that affect meniscal vascularity, a more accurate estimate of the individual patient's vascularization could be established. Consequently, this may facilitate a more accurate preoperative prediction of successful meniscal repair and contribute to the decision whether a tear is suitable for surgical repair.

Meniscal vascularization may be affected by patient characteristics known for their effect on the microvasculature throughout the human body, such as diabetes mellitus, hypercholesterolemia, hypertension, smoking, and BMI [14,15]. These factors might affect both the extent and density of vascularization of the meniscus (Figure 1) as well as the quality of the meniscal blood vessels, which will influence the healing process of meniscal tears. For example, patients with diabetes mellitus are at significant risk for developing peripheral artery disease and thereby have higher failure rates of wound healing of diabetic foot ulcers [16]. Notably, these characteristics may partly account for the differences in vascularization of the meniscus in the elderly population; they do not explain the differences found in the younger population.

Although the meniscal vascularization is variable to some extent, the inner part of the meniscus becomes avascular in young adulthood [12,13]. Angiogenesis (i.e., blood vessel formation) is a critical step in the wound-healing process as it facilitates the supply of growth factors, inflammatory processes, and fibrous tissue ingrowth [17–19]. In recent years the

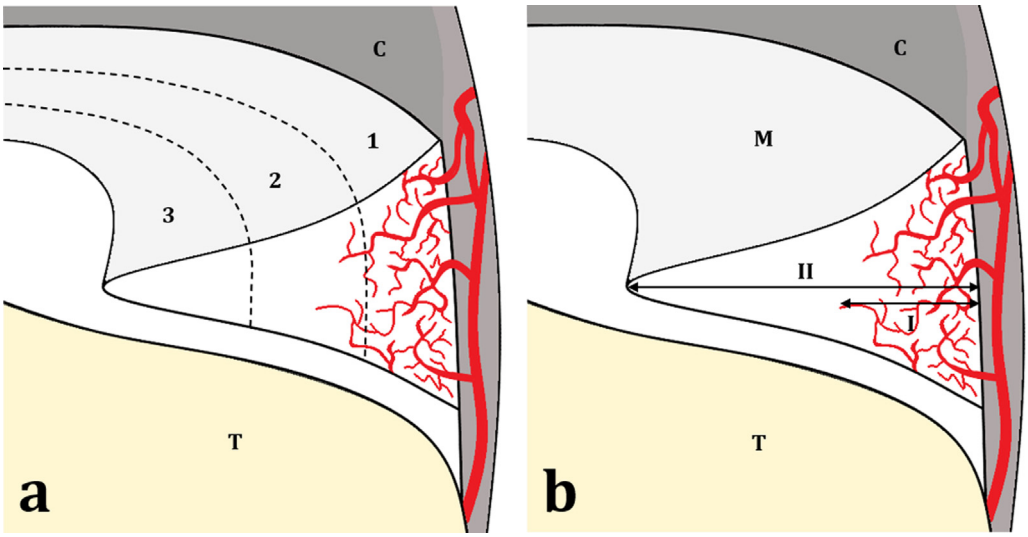

Figure 1. A schematic cross-section of the meniscus. **a** The meniscus is divided into 3 zones based on the Cooper classification. The vascular density of the meniscus is measured as the percentage of the area of the cross-section that is occupied by blood vessels. Vascular density can be calculated for the whole cross-section of the meniscus or independently for each specific zone. **b** The extent of vascularization is calculated by dividing the distance between the meniscocapsular junction and the most centrally located blood vessel (I) by the total width of the meniscus (II) multiplied by 100%. 1 = Zone 1 or "Red-red" zone, 2 = Zone 2 or "Red-white" zone, 3 = Zone 3 or "White-white" zone, C = Capsule, T = Tibia, M = Meniscus.

induction of neovascularization has been widely explored to increase the success rate of meniscal tear repair [19]. Stimulating the formation of new blood vessels might enhance the healing of the repaired meniscal tear. However, therapeutic methods that stimulate blood vessel formation remain limited in clinical practice. Numerous surgical interventions, such as meniscal rasping, marrow stimulation, adding fibrin clots, and meniscal trephination, attempt to increase the success of surgical repairs [20–23]. These interventions all address the difficulty of meniscal repair in the absence of blood vessels in the inner meniscus. However, it is not known whether these techniques contribute to the actual inducement of angiogenesis.

This systematic review provides an up-to-date overview of the evidence on (1) Patient characteristics affecting meniscal microvascularization, and (2) Therapeutic interventions inducing neovascularization in the meniscus. Knowledge of patient-specific vascular anatomy and angiogenic therapies will guide clinical decision-making and provide a more personalized approach for meniscal repair surgery.

2. Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered with PROSPERO (ID:CRD42021242479) prior to the screening of studies [24].

2.1. Literature search & study selection

A search strategy was constructed by an experienced librarian (JS). PubMed, Embase, Web of Science, Cochrane library, and Emcare were first searched for publications on January 28, 2021. The search was updated on November 12, 2021. The search was constructed using the main components "vascularization" OR "blood supply" AND "meniscus" (Appendix A). Articles were included if they reported on (1) Patient characteristics related to the extent of vascularization in the human meniscus, or (2) Methods used to induce neovascularization in meniscal tissue. To be included, studies had to assess and quantify the microvasculature of the meniscus, and there were no restrictions for the methods used to visualize the blood vessels. Articles that fail to report the vascularity but only describe the influence of a factor on the "healing" of a meniscal tear defect were excluded. Studies investigating vessel ingrowth in tissue-engineered scaffolds or meniscal autografts instead of original meniscal tissue were also excluded. Articles had to be available in full-text and present original data to be included (i.e., systematic review were excluded). No language restrictions were applied and publications were translated if required.

Two reviewers (TvL and MG) screened titles/abstracts, and full-texts independently. Any disparity was resolved through discussion. A senior researcher (PvD and PvS) was available if consensus could not be reached.

2.2. Data extraction and synthesis

Data from included studies were extracted, collected, and evaluated. Data on patient characteristics or treatments for stimulating meniscal vascularity were extracted, as well as the first author's name, year of publication, specific study population, sample size, and vascular imaging techniques. For the analyses of results, studies were grouped based on the specific patient characteristics or angiogenic therapies that were reported. No statistical analysis was performed due to the methodological heterogeneity and variability in outcome definitions. There is no standardized metric for the quantification of meniscal vascularization. Therefore, it is recommended to refrain from pooling as the resulting estimate will be unreliable [25]. No meta-analysis of effect estimates was performed. The key characteristics and quantitative results of the included studies were reported in both the text and tables.

2.3. Quality assessment

The Anatomical Quality Assessment (AQUA) tool, specifically designed to assess the quality and risk of bias in anatomical studies, was applied to all studies in the final inclusion (Appendix B) [26]. This tool assesses the risk of bias (RoB) following five domains: (1) Objectives and subject characteristics, (2) Study design, (3) Methodology characterization, (4) Descriptive anatomy, and (5) Reporting of results. Each domain was categorized as either "low", "high", or "unclear" RoB. Each study was graded as *high* quality (HQ) (all 5 domains had low RoB), *intermediate* quality (IQ) (3–4 domains with low RoB), or *low* quality (LQ) (0–2 domains with low RoB). This review included all studies independent of the AQUA score and reported the RoB for every study, with the rationale that RoB could be considered when weighting study results, whereas excluding studies with medium or low RoB could result in the loss of potentially valuable information. The quality of each study was assessed independently by two reviewers (TvL and MG).

3. Results

3.1. Literature search

The search identified 411 articles, of which 352 were excluded based on title and abstract screening, and another twenty-five after full-text reading (Figure 2) [24]. Thirteen studies were included, which reported on patient characteristics affecting the microvasculature of the human meniscus (Table 1) [11–13,27–36], and another eleven studies reported on therapies enhancing the microvascularization of meniscal tissue (Table 2) [37–47]. Quality of the included studies, as assessed by the AQUA tool, is provided in Table 3.

4. Patient characteristics

4.1. Age

Ageing results in gradual reduction of vascularization in various organ systems, including the skin, kidney, and heart, due to a decrease in the number and size of blood vessels [48–50]. These structural changes may also be present in the microvasculature of the meniscus.

Ten studies (3 HQ, 3 IQ, and 4 LQ) reported the effect of age on the microvascularization of the human meniscus (Table 1) [11–13,27–32,35]. Cadaveric studies have shown that the entire meniscus is vascularized around birth, but with increasing age, the vascularity gradually decreases from the inner to the peripheral margin [11,28]. Inline, fetal and young children have a higher overall meniscal vascular density than adults [11,28–30,32]. An overall decrease in meniscal vascularization between the ages of one month and eleven years has been reported and by the age of ten to eleven years, blood vessels were already only located primarily in the peripheral one-third of the menisci, like in the adult population [28,31].

In the adult population, there is less consensus on the effect of age on meniscal vascularization. In twenty adult cadaver specimens aged 53–95 years, the extent of peripheral vascular penetration was found that ranged from 10 to 30% (Figure 1). In this study (IQ), no identifiable pattern (i.e., correlation) of vascular decline related to age was observed [12]. In a recent study by Crawford et al. (HQ) a wider range of vascular penetration into the meniscus was found in specimens from adults <35 years of age (0–48%), but median values remained consistent compared with specimens from older individuals [13]. Cadaveric studies by Petersen et al. (LQ) and Cohen et al. (IQ), however, reported a continuous decrease of meniscal vascularization in the adult population >50 years of age [11,29]. Petersen et al. did not provide any quantification of meniscal vascularity. However, they described that in patients aged 50–72, blood vessels were present in the outer quarter of the meniscus, whereas in patients aged 75–80 vessels could only be found in the outer margin [11]. Cohen et al. reported a continuous decrease of the percentage of vascular penetration measured from the peripheral capsule to the most central blood vessel in patients between 50 and 80 years [29]. Also, histological examination of menisci after subtotal meniscectomy in patients with a meniscal tear demonstrated that the average age of patients with perilesional blood vessels was lower than that of patients without blood vessels near

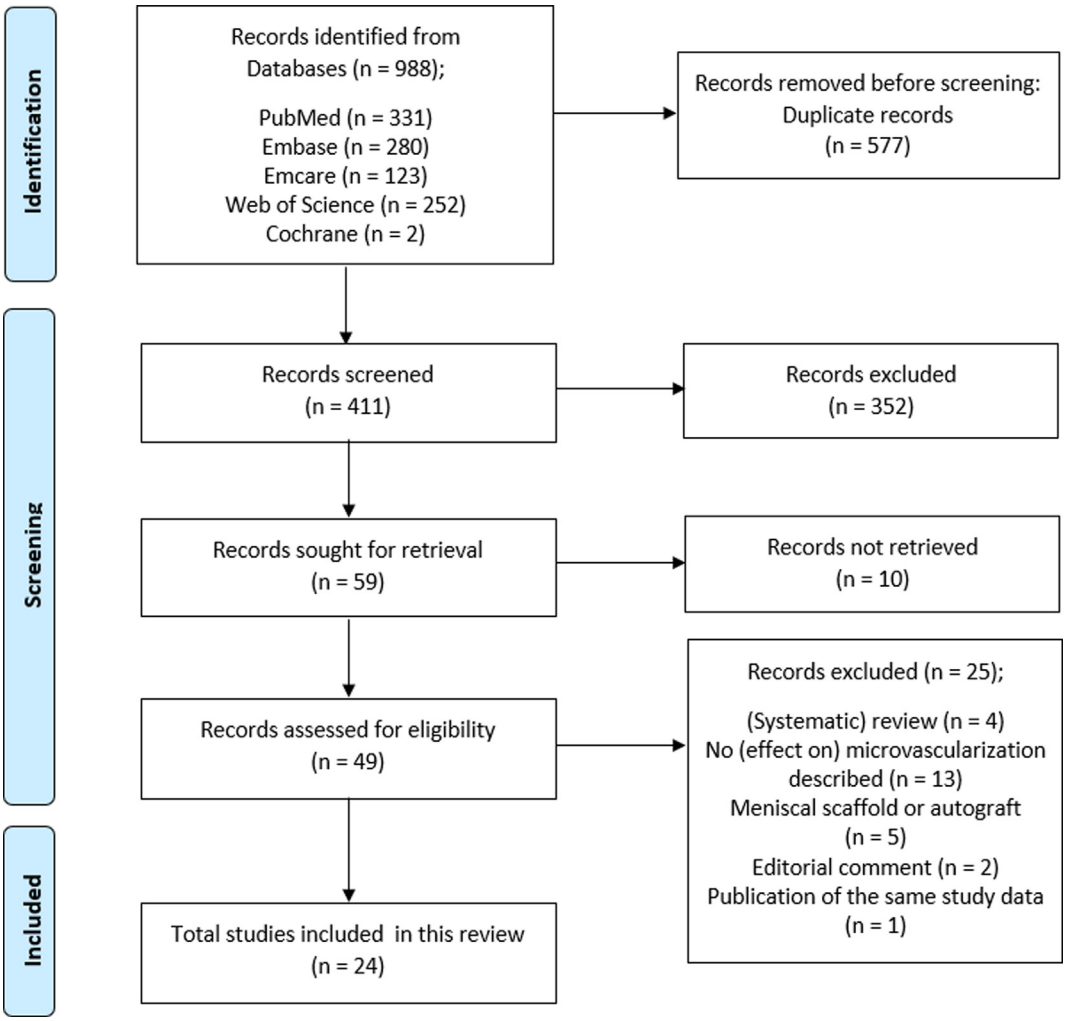

Figure 2. PRISMA (2020) flow diagram of the literature search on patient characteristics and angiogenic therapies affecting the microvasculature of the meniscus.

the lesion (22 years versus 27 years) [27]. This finding suggests a decrease in vascularization even within early adulthood; however, the study by Cipolla et al. was of low quality and did not provide any statistical analysis [27]. Recently, a study (HQ) of 51 menisci, collected from patients who underwent tumor resection or received TKR (total knee replacement), reported a lower overall vascular density in the menisci in the 61–80 year age group compared to the groups of 0–10, 11–20 and 21–30 years and a negative linear trend was detected with increasing age (slope, −0.007; p = 0.016) [35]. No vessels were detected in the red-white or white-white zone after adolescence within this study group (Figure 1).

If there is a correlation for age and vascularization, the failure rate after meniscal repair might differ between age groups. Multiple clinical studies have investigated the influence of age on failure rate after meniscal repair [51–53]. However, no difference was found when evaluating failure rate as a function of age above or below thresholds of age 25, 30, 35, and 50 [54]. It is essential to clarify that it is not possible to conclude from these clinical studies that there is no relation between age and meniscal vascularization. The primary limitation of all these nonrandomized studies is that age may introduce selection bias regarding selecting appropriate patients for meniscal repair. Moreover, multiple other factors, such as concomitant anterior cruciate ligament reconstruction and tear complexity, influence meniscal repair outcomes [55]. Surgeons may only seek ideal candidates in the older population, whereas younger patients may have less stringent adherence to indications for meniscal repair.

In conclusion, children's menisci are more vascularized than menisci of adults. There seems to be a continues decrease in meniscal vascularization with increasing age in the adult population, yet conflicting literature exists. Considerable variation in meniscal vascularization between patients is reported; therefore, high-quality studies including a substantial number of patients, are needed to precisely determine the influence of age on the vascularization of the meniscus.

Table 1
Association between patient characteristics and meniscal microvascularization.

Patient Characteristic	Author and year	Study population	Study size	Vascular imaging technique	Summary of findings
Age, gender and race	Arnoczky et al. 1982 [12]	Cadaveric specimens (aged 53–93 years)	20 knees	Histological examination with arterial contrast injection technique	No correlation for vascular penetration could be established with regard to age, sex, or race.
Age, gender and race	Crawford et al. 2020 [13]	Cadaveric specimens (aged 22–34 years)	13 knees	Histological examination with arterial contrast injection technique	The vascular supply of menisci in specimens from young adults (<35 years of age) extended farther than what was reported in specimens from older individuals; however, median values remained consistent. There was no correlation between the depth of vascular penetration and sex or race.
Age	Cipolla et al. 1992 [27]	Patients who received a reconstructive ACL operation with partial medial meniscectomy (aged 16–36 years)	40 knees	H&E staining	Presence of significant blood vessels in the menisci in patients with an average age of 22 years; absence of significant blood vessels in patients with an average age of 27 years.
Age	Clark et al. 1983 [28]	Cadaveric specimens (prenatal and postnatal ages ranging from 3 months to 14 years and 3 young adults)	277 knees	H&E staining	The postnatal meniscal vascularity progressively decreases from the inner to the outer regions of the meniscus.
Age	Cohen et al. 1998 [29]	Cadaveric specimens (aged 4 months to 88 years)	14 knees	H&E staining	The "Index of Meniscal Vasculature" (=percentage of vascular penetration measured from the peripheral capsule to the most central blood vessel) decreases with age.
Age	Day et al. 1985 [30]	Cadaveric specimens (one 34-week-old fetus and ages ranging from the sixth to the tenth decade)	23 knees	Histological examination with arterial contrast injection technique	The vascular pattern of the meniscus in the fetus is more extensive than that in the adult.
Age	Fedje-Johnston et al. 2021 [31]	Cadaveric specimens (aged 1 month to 11 years)	26 knees	H&E staining and immunohistochemistry using factor VIII-related antibodies	Age was associated with a decrease in meniscal vessel count.
Age	Lin et al. 2020 [32]	Cadaveric specimens (5 neonatal, age 0–6 months; 5 adult, 34–67 years)	10 knees	MRI with arterial contrast injection	Younger menisci appear to receive proportionally greater overall arterial contribution even though the distribution of arterial contribution to peripheral and central zones remains similar.
Age	Michel et al. 2021 [35]	Patients who (1) underwent wide resection of a malignant bone tumor at the distal femur or proximal tibia or (2) received TKR surgery because of OA.	28 knees	Immunohistochemistry using alpha-smooth muscle actin (a-SMA) staining	The overall vascular density decreased with increasing age. No vessel formations were detected in the RW and WW zones after adolescence.
Age	Petersen et al. 1995 [11]	Cadaveric specimens (aged 22 weeks of gestation to 80 years)	20 knees	Immunohistochemistry using anti-laminine antibodies	Decreasing meniscal vascular penetration with increasing age.
Chondropathy	Ashraf et al. 2010 [33]	Cadaveric specimens (median age "high" group 69 years, "low" group 41 years)	40 knees	Immunohistochemistry using anti-α-actin antibodies	Vascular densities were increased in menisci from the high compared with the low chondropathy group, both in the synovium and at the fibrocartilage junction.
Degenerative meniscus	Danzig et al. 1983 [34]	Cadaveric specimens (aged from 40 to 80 years)	25 knees	Histological examination with arterial contrast injection technique	The blood supply to the pathologic meniscus did not significantly differ from that to a normal meniscus; no increase of vascularity in response to chronic tears or meniscal degeneration could be identified.
Degenerative meniscus	Wang et al. 2020 [36]	Patients receiving TKR surgery (aged from 46 to 87 years)	10 knees	H&E staining	In menisci with a higher grade of degeneration, diminished blood supply was noted within the vascular region.

Abbreviations H&E = Haematoxylin and Eosin, ACL = Anterior Cruciate Ligament, TKR = Total Knee Replacement, OA = Osteoaarhtritis, RW = Red-White, WW = White-White.

Table 2
Therapeutic interventions to induce angiogenesis and their effect on meniscal neovascularization.

Treatment method	Author and year	Study model	Sample size	Vascular imaging technique	Summary of findings
Synovial flap transfer	Cisa et al. 1995 [37]	Rabbit (in vivo)	44 animals	H&E staining and Masson's trichrome staining	The transfer of a synovial flap induced varying degrees of neovascularization in the avascular meniscal body at 8, 12, 24, and 48 weeks
Synovial flap transfer	Kobuna et al. 1995 [38]	Canine (in vivo)	21 animals	Histological examination with arterial contrast injection technique	In the group of menisci with a synovial flap, capillary was found in the tear sites at 1 week, and neovascularization from the parameniscal area to the suture sites occurred at 6 weeks. At 12 weeks, the vasculature had decreased.
Synovial flap transfer	Shirakura et al. 1997 [39]	Canine (in vivo)	35 animals	Histological examination with arterial contrast injection technique	Capillaries grew from the periphery, but they did not reach the tear after 2, 6, 8, and 12 weeks.
Autologous bone marrow cells	Abdel-Hamid et al. 2005 [40]	Canine (in vivo)	8 animals	Immunohistochemistry using CD-31 and alpha smooth-muscle actin antibodies	Marked angiogenesis and increased microvessel density as compared with noninjected menisci after 12 weeks.
Autologous bone marrow material	Duygulu et al. 2012[41]	Sheep (in vivo)	12 animals	Masson's trichrome staining	There was significantly more neovascularization in the experimental group than the control group ($p = 0.003$) at the 16th postoperative week.
SVF	Diaz Heredia et al. 2014 [46]	Pig (in vivo)	4 animals	H&E staining	The postoperative intra-articular injection of SVF might increase the neovascularization 15 days after repair.
VEGF	Kopf et al. 2010 [42]	Sheep (in vivo)	18 animals	Immunohistochemistry using factor VIII antibodies	The local application of VEGF as eluted from suture did not increase meniscal angiogenesis at 59 days.
VEGF	Xu et al. 2020 [43]	Rat (in vivo and in vitro)	12 animals	H&E staining	PAR1-activated platelets release a high VEGF level and enhanced meniscal healing via promoting blood vessel formation after 8 weeks.
Fibrin sealant	Hashimoto et al. 1992 [44]	Canine (in vivo)	15 animals	H&E staining and Masson's trichrome staining	The use of fibrin sealant in combination with ECGF enhanced neovascularization. However, The number of vessels observed in the defect decreased and almost completely disappeared at 24 weeks.
Angiogenin	King et al. 1991 [45]	Rabbit (in vivo)	75 animals	H&E staining	Localized neovascularization occurred in 52% of the angiogenin-treated animals and in 9% of the controls at 3, 6, 8, 9, 12, and 26 weeks.
Joint immobilization	Bray et al. 2001 [47]	Rabbit (in vivo)	26 animals	Vascular volume of the menisci was determined using carmine red dye perfusion	Immobilization of the joint did not affect the angiogenic response to injury in the medial meniscus 4 weeks postoperatively.

Abbreviations H&E = Haematoxylin and Eosin, SVF = Stromal Vascular Fraction, VEGF = Vascular Endothelial Growth Factor.

Table 3
Summary table for the risk of bias across the included studies.

Study	Risk of Bias					
	Objective(s) and study characteristics	Study design	Methodology characterization	Descriptive anatomy	Reporting of results	Quality of Study
Arnoczky [12]*	Low	Low	Low	High	High	**Intermediate**
Cipolla [27]*	High	High	High	High	High	**Low**
Clark [28]*	Low	Low	Low	High	High	**Intermediate**
Cohen [29]*	Low	Low	Low	Low	High	**Intermediate**
Crawford [13]*	Low	Low	Low	Low	Low	**High**
Day [30]*	High	Low	High	High	High	**Low**
Fedje-Johnston[31]*	Low	Low	Low	Low	Low	**High**
Lin [32]*	Low	High	High	High	Low	**Low**
Michel [35]*	Low	Low	Low	Low	Low	**High**
Petersen [11]*	High	Low	Low	High	High	**Low**
Ashraf [33]*	Low	Low	Low	Low	Low	**High**
Danzig [34]*	Low	High	Low	High	High	**Low**
Wang [36]*	Low	High	Low	High	High	**Low**
Cisa [37]**	Low	Low	Low	High	High	**Intermediate**
Kobuna [38]**	Low	Low	High	High	High	**Low**
Shirakura [39]**	Low	Low	Low	High	High	**Intermediate**
Abdel-Hamid [40]**	Low	Low	Low	Low	High	**Intermediate**
Duygulu [41]**	Low	Low	Low	High	Low	**Intermediate**
Diaz Heredia [46]**	Low	Low	High	High	High	**Low**
Kopf [42]**	Low	Low	Low	Low	Low	**High**
Xu [43]**	Low	Low	Low	Low	Low	**High**
Hashimoto [44]**	Low	Low	High	High	High	**Low**
King [45]**	High	Low	Low	High	High	**Low**
Bray [47]**	Low	Low	Low	Low	Low	**High**

The Quality of Study is assessed with the Anatomical Quality Assessment (AQUA) tool (Appendix 2). Each domain was categorized as either "low", "high" or "unclear" risk of bias (RoB). Each study was graded as high quality (HQ) (all 5 domains had low RoB), intermediate quality (IQ) (3–4 domains with low RoB), or low quality (LQ) (0–2 domains with low RoB).

* Studies addressing patient characteristics affecting meniscal microvascularization.

** Studies addressing therapeutic interventions inducing neovascularization in the meniscus.

4.2. Degenerative knee

Osteoarthritis (OA) is one of the most common joint disorders globally and increased synovial, and osteochondral angiogenesis is often found in OA knees [56–58]. Because menisci are partially covered with a layer of synovial tissue, which supplies blood vessels to the underlining meniscal tissue, the vascularization of menisci itself might also be increased in a degenerative knee joint [30].

Three studies (1 HQ and 2 LQ) reported on the influence of degenerative changes in the knee joint on meniscal vascularization (Table 1) [33,34,36]. In the first study (HQ) menisci were obtained postmortem from patients with high and low grade tibiofemoral chondropathy [33]. Vascular densities were increased in menisci from the high compared with the low chondropathy group both in the synovium (3.8% (IQR 2.6–5.2), 2.0% (IQR 1.4–2.9), p = 0.002) and at the fibrocartilage junction (2.3% (IQR 1.7–3.1), 1.1% (IQR 0.8–1.9), p = 0.003). An increase in meniscal vascularization is suggested in this study to be a homeostatic response to minimize meniscal damage in osteoarthritic patients. On the other hand, in another study (LQ), no change in the vascularization of degenerative human menisci compared with that of normal menisci was described [34]. In this study however, Danzig et al. did not specify how they quantified the vascular pattern of the degenerative and normal menisci. A third study (LQ) even noted fewer blood vessels in the vascular region of more degenerative menisci [36]. Notably, the latter two studies only included a small number of menisci (n = 6 and n = 10, respectively) [34,36].

In clinical practice, acute (traumatic) meniscal tears suitable for repair mainly occur in active young patients [59]. The decision of whether to repair an acute meniscal tear in young patients without any degenerative changes in the knee joint will not be affected by the influence of OA on the meniscal vascularization. Due to repeated loads and due to years of microtraumas and ageing of the menisci, degenerative tears typically involve middle-aged or older patients, and conservative treatment with physical therapy and painkillers are usually the first choice of treatment for these types of tears [60,61]. However, a traumatic meniscal tear can also occur in patients with OA. If the meniscus of these patients happens to be very well-vascularized, such tears might also be considered suitable for repair. Importantly, these considerations should always be weighed against other factors that influence the chances of successful healing of a tear after repair, such as tissue quality of the menisci, type of tear, and degree of OA.

4.3. Gender and race

Two studies (1 HQ and 1 IQ), both using menisci of adult cadaveric specimens, reported the absence of a relation between the extent of vascularization and either gender or race (Table 1) [12,13]. These studies did not provide any specific correlation or statistical analysis to substantiate this finding. Based on current literature, there is no evidence to conclude that there is a difference in microvascular anatomy of human menisci between gender or race.

5. Angiogenic therapies

5.1. Synovial flap

A peripheral synovial fringe only extends a short distance over both the femoral and tibial surface of the meniscus [12]. Transplantation of synovial tissue into an avascular tear might induce neovascularization because the synovial membrane is well vascularized and contains cells with various biological potential [38].

Angiogenesis after transplantation of a synovial flap into an avascular area of the meniscus was investigated in three preclinical studies (2 IQ and 1 LQ) [37–39]. Successful inducement of neovascularization in the avascular zone of a rabbits' menisci was reported after transfer of a pedunculated synovial flap (IQ) [37]. In the study conducted by Kobuna et al. (LQ), a synovial flap was sutured into a longitudinal incision in the avascular portion of the meniscus in 21 dog knees [38]. They showed that vessels over the femoral surface of the menisci and vessels of the inner portion of the menisci, arising from the perimeniscal capillary plexus in the capsular tissue, had reached the suture site after 6 weeks. However, this vascular response was subsided at 12 weeks. In contrast, Shirakura et al. (IQ) sutured free synovium into an avascular meniscal tear in a dog model, but they found no vessels of the capillary plexus from the parameniscal area to reach the sutured tear after 12 weeks [39].

Although some favorable results are demonstrated in a preclinical setting, literature is scarce on the effect of synovial flap transplantation, either using a free or pedunculated synovial flap, on meniscal angiogenesis. In clinical setting, there is some data suggesting that additional transplantation of a vascularized synovial pedicle flap during meniscal repair promotes tear healing [62]. However, these results of this surgically challenging technique have not led to implementation in clinical practice.

5.2. Stem cells

If tears are located in a vascularized part of the meniscus; the capillary network supplies undifferentiated mesenchymal cells (MSCs) with nutrients to induce healing [9]. MSCs have been examined widely in various animal models to evaluate their use as an adjunct treatment strategy for repairing avascular meniscal tears [63]. Further, stem cells can differentiate into various cell types and can promote endogenous angiogenesis by microenvironmental modulation [64].

5.2.1. Bone marrow cells

Endothelial precursors have been identified in adult bone marrow (BM), and these precursors, as well as other bone marrow-derived cells, contribute to the growth of endothelium-lined vessels (angiogenesis) [18]. By stimulating angiogenesis and thereby the supply of growth factors and inflammatory processes, BM cells might encourage the repair of avascular meniscal tears [63].

Two studies (2 IQ) reported the effect of autologous BM cells on meniscal neovascularization. In one study (IQ), a longitudinal incision was made in the red-white zone of the lateral meniscus in both knees of 8 dogs [40]. Autologous BM cells aspirated from the iliac bone were injected into the right knee using the left as a control. The microvascular density was measured by choosing immunolabelled vessels on a x400 field. Every immunolabelled endothelial cell separated from adjacent microvessel or other connective tissue element was counted as a single microvessel. After 12 weeks, a significantly greater microvessel density was found in the BM group. Another study (IQ), using 12 sheep, created a tear in the red-white zone of the medial meniscus, injected autologous BM in one knee, and used the other knee as a control [41]. A modified scoring system consisting of four grades (none, low, moderate, high) was used to assess neovascularization. They also found more neovascularization in the BM injection group ($p = 0.003$).

5.2.2. Stromal vascular fraction cells

Adipose stromal vascular fraction (SVF) cells are a heterogeneous group of cells comprised of endothelial cells, macrophages, pericytes, and stem cells. SVF cells have been shown to spontaneously form vessel-like networks in vitro and robust, patent, and functional vasculature in vivo [65].

One study (LQ) assessed the use of purified SVF, derived from abdominal adipose tissue, injected into pig's knees [46]. After simulating a longitudinal tear of 10 mm in the avascular area of the medial meniscus in both knees, SVF was postoperatively injected into one of the knees, while the other knee was used as control. Although meniscal neovascularization in the SVF group was somewhat higher than in the control group after 15 days, the difference was non-significant. Therefore, there is no evidence indicating that SVF induces angiogenesis in meniscal tissue.

5.3. Vascular endothelial growth factor (VEGF)

VEGF is a key regulator of physiological and pathological angiogenesis [66]. The endothelial cell-specific mitogen promotes angiogenesis and stimulates vascular permeability [67,68]. During the proliferative phase of wound healing, VEGF mediates the angiogenic activity [69]. It has been shown that local application of VEGF to avascular tissue, like the cornea induces angiogenesis [70]. This led to the hypothesis that local application of VEGF could induce angiogenesis in avascular meniscal tissue [42].

Two studies (2 HQ) evaluated the effect of VEGF on meniscal vascularization. Kopf et al. (HQ) divided a total of 18 sheep into three groups according to the suture material used for repair of a meniscal tear (I) Uncoated sutures, (II) Sutures coated with VEGF, and its carrier Poly(D,L-Lactide) (PDLLA), and (III) Sutures coated with PDLLA alone [42]. A fourth group consisted of the eighteen healthy medial menisci of the contralateral knee and served as the control group. The local application of VEGF, as eluted from coated sutures, was found not to increase meniscal angiogenesis or improve meniscal healing. Factor VIII, used as a marker of endothelial cells, did not significantly differ after eight weeks between all groups. On the other hand, a more recent study (HQ) showed that platelets releasing high levels of VEGF after being activated by protease-activated receptor 1 (PAR1) enhanced the vascularization of rat menisci in vivo [43]. Healing of wounded rat menisci was explored in 12 rats treated with either (1) Unactivated platelets, (2) Thrombin activated platelets, (3) PAR1 activated platelets, or (4) PAR4 activated platelets. PAR4 activated platelets release high levels of endostatin, which is an endogenous inhibitor of angiogenesis. High levels of both VEGF and endostatin are released from human platelets when thrombin activates them. It was shown that 4 times more blood vessels were found in the healed wound areas treated with either thrombin or PAR1 compared to the wound areas treated with unactivated platelets or with PAR4 ($P < 0.05$), demonstrating a positive effect of VEGF on blood vessel formation in meniscal tissue.

Naturally elevated concentrations of VEGF in meniscal tissues, in response to meniscal injury, are not sufficient to induce angiogenesis in the avascular zone of the meniscus [71]. In addition, multiple isoforms of VEGF have been described, which differ in their expression patterns as well as their biochemical and biological properties.[66] Future research on VEGF to stimulate angiogenesis in avascular meniscal tissue should therefore focus on both the specific dose of locally applied VEGF, as well as the types of VEGF isoforms.

5.4. Fibrin sealant

Fibrin sealant has been reported to have adhesive and wound healing capability by activating fibroblasts. Enhancement of the meniscal healing process in the avascular portion of the meniscus with the use of a fibrin clot has been described [22,72]. Only one study was found by our literature search that specifically described neovascularization of the meniscus after using fibrin sealant [44].

Hashimoto et al. (LQ) reported the angiogenic effect of fibrin sealant alone and fibrin sealant in combination with endothelial cell growth factor (ECGF) on dog menisci [44]. Defects in the avascular area of 30 menisci from adult dogs were treated by either: (1) Leaving the defect empty, (2) Filling the defect with fibrin sealant, or (3) Filling the defect with fibrin sealant and ECGF. They found that the combination of fibrin sealant and ECGF enhanced the neovascularization and formation of granulation tissue, which accounted for increased healing levels in the avascular portion of the meniscus (no statistical analysis reported). Although a similar healing process was noted in the group in which fibrin sealant was used alone, a greater level of healing was observed in the group in which ECGF was added. Based on this LQ study, it is not possible to conclude that fibrin sealant alone induces meniscal neovascularization.

5.5. Angiogenin

Angiogenin is another potent inducer of blood vessel formation [73]. It is reported to induce new blood vessel formation in rabbit corneas [74]. Further, angiogenin is involved in pathophysiological processes, including tumorigenesis, neurodegeneration, and inflammation [75].

King et al. (LQ) found that angiogenin promotes neovascularization in meniscal tissue [45]. In 75 rabbits, a vertical incision was made in the avascular body of the lateral meniscus, subsequently treated with angiogenin. Localized neovascularization was found in 52% of the animals treated with angiogenin compared with only 9% in the control group ($p = <0.0001$). These interesting findings have not been studied in clinical trials yet.

5.6. Postoperative joint immobilization

Mechanical forces are important regulators of cell and tissue phenotype [76]. Angiogenesis is influenced by various environmental forces, including mechanical factors [77,78]. Postoperative weight-bearing after meniscal repair remains a point of debate among physicians. The rationale for immobilization after surgical repair is that weight-bearing after repair might compromise healing of the tear [63]. However, it was demonstrated that immediate weight bearing after meniscal repair does not result in a higher failure rate than non-weight-bearing [79,80].

One study (HQ) reported the effect of joint immobilization on meniscal vascularization. Bray et al. quantified blood flow and angiogenesis in the meniscus following injury in rabbits' immobilized and non-immobilized limbs [47]. Angiogenesis was explored after 4 weeks by assessing the vascular volume of the meniscus by carmine red dye perfusion. Immobilization did not significantly affect angiogenesis in the injured menisci. However, immobilizing the knee reduced the healing process in injured menisci and diminished the blood flow into the repaired area compared with mobilized knees. Complete immobilization following meniscal repair may, therefore, even negatively impact meniscal healing.

6. Discussion

Meniscal vascularization is characterized by wide interindividual variation. The influence of four factors (*Age, Degenerative knee, Gender, and Race*) on meniscal vascularization was reported in the current literature. With increasing age, vascularization gradually decreases from the inner to the peripheral margin and around 11 years blood vessels are primarily located in the peripheral third of the menisci. There seems to be a further decrease in meniscal vascularization within the adult population with increasing age, yet conflicting literature exists. Degenerative changes of the knee likely influence meniscal vascularization, but there is no consensus in the current literature to what extent. Gender or race do not seem to influence the microvasculature of the meniscus. A better understanding of the effect of additional patient characteristics on meniscal vascularization will facilitate surgeons in selecting the optimal treatment (i.e., surgical repair or partial meniscectomy). Besides the patient characteristics reported above, there are more patient characteristics known for their effect on the microvasculature of the human body. For example, the body mass index (BMI) is directly linked to microvascular dysfunction; hypertension is associated with capillary density reduction; and diabetes-induced microvascular rarefaction has been described [15,81,82]. However, the relation between these factors and meniscal vascularization is not reported in current literature. Nevertheless, it is shown that patients with a BMI of >25 do not have a higher risk of failure after meniscal repair relative to those with a BMI <25 ($p = 0.14$) [83]. No study reported the effect of BMI on meniscal vascularization. Whereas smoking is associated with an increased risk of meniscal repair failure ($p = 0.0076$), its actual effect on the meniscal microvasculature has not been studied so far [84].

Numerous studies reported the effect of angiogenetic therapeutics on inducing neovascularization in animal menisci. Synovial flap transplantation, stem cell therapy, VEGF, and angiogenin have shown promising results in a preclinical setting to improve meniscal vascularization. However, there is no reliable evidence that the use of fibrin sealant during meniscal repair or postoperative joint immobilization affects neoangiogenesis of the meniscus.

A limitation of the current literature is the heterogeneity in methods used to assess and quantify meniscal microvascularization. The included studies in this review lack data amenable to statistical synthesis. The success rate of meniscal repair could be improved by more research into the patient-specific microvascular anatomy, using a standardized outcome measure. Future studies in this area should include identifying patient characteristics that affect the degree of meniscal vascularization. Specifically, patient characteristics affecting the vascularization in the population of patients in which acute meniscal tears mainly occur (i.e., young adults) are of great interest. To substantiate the clinical implementation of angiogenic therapies, unraveling their mechanism of action and effect on angiogenesis in the meniscus is important. Clinical translational studies are needed to investigate their possible application in meniscal surgery. In addition, diseases such as peripheral arterial disease and myocardial ischemia, where patients can benefit from therapeutic angiogenesis, might provide more insight into angiogenic approaches that can be used for meniscal repair. For example, in cardiovascular diseases, increased blood vessel formation is described by using fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and endothelial progenitor cells (EPC) [85,86]. Other major topics in the biological repair of avascular tears, besides vascularization, are cell recruitment, matrix deposition, and inflammation control [87]. Although outside the scope of this review, research into these areas and other augmentations will most likely contribute to new therapeutic interventions for avascular meniscal tears in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Search strategy

PubMed

((“Meniscus”[Mesh] OR “meniscus”[tw] OR “menisci”[tw] OR “meniscal”[tw] OR menisc*[tw] OR “Tibial Meniscus Injuries”[Mesh]) AND (“vascularization”[ti] OR “vascularisation”[ti] OR “vascular iz*”[ti] OR “vascularis*”[ti] OR “Meniscus/blood supply”[majr] OR “blood supply”[ti] OR “Neovascularization, Pathologic”[majr] OR “neovasculari*” [ti] OR “vascularity”[ti] OR “vascularities”[ti] OR “macrovascula*”[ti] OR “Microvasculature”[ti] OR “microvascula*”[ti] OR “micro vascula*”[ti] OR “Microvessels”[majr] OR “Micro vessel”[ti] OR “Micro vessels”[ti] OR “Arterioles”[ti] OR “Arteriovenous Anastomosis”[ti] OR “Capillaries”[ti] OR “Venules”[ti] OR “Arteriole”[ti] OR “Venule”[ti])) **OR** ((“Meniscus”[majr] OR “meniscus”[ti] OR “menisci”[ti] OR “meniscal”[ti] OR menisc*[ti] OR “Tibial Meniscus Injuries” [majr]) AND (“vascularization”[tw] OR “vascularisation”[tw] OR “vascular iz*”[tw] OR “vascularis*”[tw] OR “Meniscus/ blood supply”[majr] OR “blood supply”[tw] OR “Neovascularization, Pathologic”[Mesh] OR “neovasculari*”[tw] OR “vascularity”[tw] OR “vascularities”[tw] OR “macrovascula*”[tw] OR “Microvasculature”[tw] OR “microvascula*”[tw] OR “micro vascula*”[tw] OR “Microvessels”[Mesh] OR “Micro vessel”[tw] OR “Micro vessels”[tw] OR “Arterioles”[tw] OR “Arteriovenous Anastomosis”[tw] OR “Capillaries”[tw] OR “Venules”[tw] OR “Arteriole”[tw] OR “Venule”[tw]))

Embase

((*“Knee Meniscus”/ OR “meniscus”.ti,ab OR “menisci”.ti,ab OR “meniscal”.ti,ab OR menisc*.ti,ab OR *“Knee Meniscus Rupture”/) AND (“vascularization”.ti OR “vascularisation”.ti OR “vascular iz*”.ti OR “vascularis*”.ti OR “blood supply”. ti OR *“neovascularization (pathology)”/ OR “neovasculari*”.ti OR “vascularity”.ti OR “vascularities”.ti OR “macrovascula*”.ti OR exp *“Microvasculature”/ OR “microvascula*”.ti OR “micro vascula*”.ti OR “Micro vessel”.ti OR “Micro vessels”.ti OR “Arterioles”.ti OR “Arteriovenous Anastomosis”.ti OR “Capillaries”.ti OR “Venules”.ti OR “Arteriole”.ti OR “Venule”.ti)) OR ((*“Knee Meniscus”/ OR “meniscus”.ti OR “menisci”.ti OR “meniscal”.ti OR menisc*. ti OR *“Knee Meniscus Rupture”/) AND (“vascularization”.ti,ab OR “vascularisation”.ti,ab OR “vascular iz*”.ti,ab OR “vascularis*”.ti,ab OR “blood supply”.ti,ab OR *“neovascularization (pathology)”/ OR “neovasculari*”.ti,ab OR “vascularity”.ti,ab OR “vascularities”.ti,ab OR “macrovascula*”.ti,ab OR exp *“Microvasculature”/ OR “microvascula*”. ti,ab OR “micro vascula*”.ti,ab OR “Micro vessel”.ti,ab OR “Micro vessels”.ti,ab OR “Arterioles”.ti,ab OR “Arteriovenous Anastomosis”.ti,ab OR “Capillaries”.ti,ab OR “Venules”.ti,ab OR “Arteriole”.ti,ab OR “Venule”.ti,ab))

Web of Science

(ab=(“Knee Meniscus” OR “meniscus” OR “menisci” OR “meniscal” OR menisc* OR “Knee Meniscus Rupture”) AND ti= (“vascularization” OR “vascularisation” OR “vascular iz*” OR “vascularis*” OR “blood supply” OR “neovasculari*” OR “vascularity” OR “vascularities” OR “macrovascula*” OR “Microvasculature” OR “microvascula*” OR “micro vascula*” OR “Micro vessel” OR “Micro vessels” OR “Arterioles” OR “Arteriovenous Anastomosis” OR “Capillaries” OR “Venules” OR “Arteriole” OR “Venule”)) **OR** (ti=(“Knee Meniscus” OR “meniscus” OR “menisci” OR “meniscal” OR menisc* OR “Knee Meniscus Rupture”) AND ab=(“vascularization” OR “vascularisation” OR “vascular iz*” OR “vascularis*” OR “blood supply” OR “neovasculari*” OR “vascularity” OR “vascularities” OR “macrovascula*” OR “Microvasculature” OR “microvascula*” OR “micro vascula*” OR “Micro vessel” OR “Micro vessels” OR “Arterioles” OR “Arteriovenous Anastomosis” OR “Capillaries” OR “Venules” OR “Arteriole” OR “Venule”))

Cochrane

((“Knee Meniscus” OR “meniscus” OR “menisci” OR “meniscal” OR menisc* OR “Knee Meniscus Rupture”) AND (“vascularization” OR “vascularisation” OR “vascular iz*” OR “vascularis*” OR “blood supply” OR “neovasculari*” OR “vascularity” OR “vascularities” OR “macrovascula*” OR “Microvasculature” OR “microvascula*” OR “micro vascula*” OR “Micro vessel” OR “Micro vessels” OR “Arterioles” OR “Arteriovenous Anastomosis” OR “Capillaries” OR “Venules” OR “Arteriole” OR “Venule”)):ti,ab,kw

Emcare

((*“Knee Meniscus”/ OR “meniscus”.ti,ab OR “menisci”.ti,ab OR “meniscal”.ti,ab OR menisc*.ti,ab OR *“Knee Meniscus Rupture”/) AND (“vascularization”.ti OR “vascularisation”.ti OR “vascular iz*”.ti OR “vascularis*”.ti OR “blood supply”. ti OR *“neovascularization (pathology)”/ OR “neovasculari*”.ti OR “vascularity”.ti OR “vascularities”.ti OR “macrovascula*”.ti OR exp *“Microvasculature”/ OR “microvascula*”.ti OR “micro vascula*”.ti OR “Micro vessel”.ti OR “Micro vessels”.ti OR “Arterioles”.ti OR “Arteriovenous Anastomosis”.ti OR “Capillaries”.ti OR “Venules”.ti OR “Arteriole”.ti OR “Venule”.ti)) **OR** ((*“Knee Meniscus”/ OR “meniscus”.ti OR “menisci”.ti OR “meniscal”.ti OR menisc*. ti OR *“Knee Meniscus Rupture”/) AND (“vascularization”.ti,ab OR “vascularisation”.ti,ab OR “vascular iz*”.ti,ab OR “vascularis*”.ti,ab OR “blood supply”.ti,ab OR *“neovascularization (pathology)”/ OR “neovasculari*”.ti,ab OR “vascularity”.ti,ab OR “vascularities”.ti,ab OR “macrovascula*”.ti,ab OR exp *“Microvasculature”/ OR “microvascula*”. ti,ab OR “micro vascula*”.ti,ab OR “Micro vessel”.ti,ab OR “Micro vessels”.ti,ab OR “Arterioles”.ti,ab OR “Arteriovenous Anastomosis”.ti,ab OR “Capillaries”.ti,ab OR “Venules”.ti,ab OR “Arteriole”.ti,ab OR “Venule”.ti,ab))

Appendix B. Anatomical Quality Assessment (AQUA) tool

Note: Assessment of each domain ends with a risk of bias question which is marked in bold in the grey box. (Each domain has a set of signaling questions to assist in evaluations and judgements about risk of bias pertaining to the domain). The signaling questions are answered as "Yes", "No", or "Unclear". For these signaling questions, "Yes", "No", and "Unclear" indicate low, high, and unclear risk of bias, respectively. On the other hand, the risk-of-bias question is judged as "Low", "High", or "Unclear". If all signaling questions for a domain are answered "Yes", then risk of bias can be judged "Low". If any signaling question is answered "No", this indicates the potential for bias. Review authors should then reach a consensus regarding this. The "Unclear" option should be used only when the reported data are insufficient to allow for a clear judgment.

Domains & Questions	Option (Please Select)		
	Yes	No	Unclear
Domain 1: OBJECTIVE(S) AND SUBJECT CHARACTERISTICS			
• Was (Were) the objective(s) of the study clearly defined?	☐	☐	☐
• Was (Were) the chosen subject sample(s) and sample size appropriate for the objective(s) of the study?	☐	☐	☐
• Are the baseline and demographic characteristics of the subjects (age, sex, ethnicity, healthy or diseased, etc.) appropriate and clearly defined?	☐	☐	☐
Could the method of subject selection have in any way introduced bias into the study?	RISK: **Choose an item.**		
Domain 2: STUDY DESIGN			
• Does the study design appropriately address the research question(s)?	☐	☐	☐
• Were the materials used in the study appropriate for the given objective(s) of the study?	☐	☐	☐
• Were the methods used in the study appropriate for the given objective(s) of the study?	☐	☐	☐
• Was the study design, including methods/techniques applied in the study, widely accepted or standard in the literature? If "no", are the novel features of the study design clearly described?	☐	☐	☐
Could the study design have in any way introduced bias into the study?	RISK: **Choose an item.**		
Domain 3: METHODOLOGY CHARACTERIZATION			
• Are the methods/techniques applied in the study described in enough detail for them to be reproduced?	☐	☐	☐

(*continued on next page*)

• Was the specialty and the experience of the individual(s) performing each part of the study (such as cadaveric dissection or image assessment) clearly stated?	☐	☐	☐
• Are all the materials and methods used in the study clearly described, including details of manufacturers, suppliers etc.?	☐	☐	☐
• Were appropriate measures taken to reduce inter- and intra-observer variability?	☐	☐	☐
• Do the images presented in the study indicate an accurate reflection of the methods/techniques (imaging, cadaveric, intraoperative, etc.) applied in the study?	☐	☐	☐
Could the characterization of methods have in any way introduced bias into the study?	RISK: **Choose an item.**		
Domain 4: DESCRIPTIVE ANATOMY			
• Were the anatomical definition(s) (normal anatomy, variations, classifications, etc.) clearly and accurately described?	☐	☐	☐
• Were the outcomes and parameters assessed in the study (variation, length, diameter, etc.) appropriate and clearly defined?	☐	☐	☐
• Were the figures (images, illustrations, diagrams, etc.) presented in the study clear and understandable?	☐	☐	☐
• Were any ambiguous anatomical observations (i.e. those likely to be classified as "others") clearly described/depicted?	☐	☐	☐
Could the description of anatomy have in any way introduced bias into the study?	RISK: **Choose an item.**		
Domain 5: REPORTING OF RESULTS			
• Was the statistical analysis appropriate?	☐	☐	☐
• Are the reported results as presented in the study clear and comprehensible, and are the reported values consistent throughout the manuscript?	☐	☐	☐
• Do the reported numbers or results always correspond to the number of subjects in the study? If not, do the authors clearly explain the reason(s) for subject exclusion?	☐	☐	☐
• Are all potential confounders reported in the study, and subsequently measured and evaluated, if appropriate?	☐	☐	☐
Could the reporting of results have in any way introduced bias into the study?	RISK: **Choose an item.**		

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