Aus der Klinik für kleine Haustiere
des Fachbereichs Veterinärmedizin
der Freien Universität Berlin

Biomechanical Properties of Canine Cruciate Ligament Prostheses

Inaugural-Dissertation
zur Erlangung des Grades eines
Doktors der Veterinärmedizin
an der
Freien Universität Berlin

vorgelegt von
Göknil Wohlrabe, geb. Kalayci
Tierärztin aus Bolu, Türkei

Berlin 2022
Journal-Nr.: 4309

mbvberlin | mensch und buch verlag

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Gedruckt mit Genehmigung des Fachbereichs Veterinärmedizin

der Freien Universität Berlin

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Deskriptoren (nach CAB-Thesaurus):

dogs, horses, stifle, tendons, regeneration, biomechanical phenomena (MeSH), veterinary medicine, surgical operations

Tag der Promotion: 02.05.2022

Bibliografische Information der *Deutschen Nationalbibliothek*
Die Deutsche Nationalbibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über <https://dnb.de> abrufbar.

ISBN: 978-3-96729-175-9
Zugl.: Berlin, Freie Univ., Diss., 2022
Dissertation, Freie Universität Berlin
D188

*Ebeveynlerim **Muazzez & Sinan'a,** eşim **Martin'e** ve oğlum **Valentin'e***

*Gewidmet meinen Eltern **Muazzez & Sinan**, meinem Mann **Martin***
*und meinem Sohn **Valentin***

*Dedicated to my parents **Muazzez & Sinan**, my husband **Martin** and my son **Valentin***

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Abbreviations

ACL	Anterior cruciate ligament
approx.	approximately
BPTB	Bone-patellar tendon-bone
BW	Body-weight
CaCL	Caudal cruciate ligament
$CaCl_2$	Calcium chloride
CCCT	Canine common calcaneal tendon
CFI	Capsular fascial imbrication
cm	centimetre
cm^2	square centimetres
CrCL	Cranial cruciate ligament
CRCET	Canine radial carpal extensor tendon
CT	Computed tomography
CTT	Cranial Tibial Thrust
CTWO	Cranial tibial wedge osteotomy
DPBS	Dulbecco's Phosphate Buffered Saline
DMEM-1X	Dulbecco's Modified Eagle Medium, high glucose
ECM	Extracellular matrix
ECS	Extracapsular stabilisation
ECSS	Extracapsular suture stabilisation
EDDFT	Equine deep digital flexor tendon
e.g.	exempli gratia = for example
et al.	and others
F	Femur
FBS	Fetal bovine serum
Fmax	Maximum force
Fmin	Minimum force
g	gravity
HD	Hip Dysplasia
ICS	Intracapsular stabilisation
i.e.	id est = that is
kg	kilogram
kN/s	kilonewton per second

Lig.	Ligamentum
Ligg.	Ligamenta
LCL	Lateral collateral ligament
M	Mean value
M.	Musculus
min	minute
ml	millilitre
Mm.	Musculi
mm	millimetre
mm/min	millimetre per minute
MCL	Medial collateral ligament
$MgCl_2$	Magnesium chloride
MMP	Modified Maquet Procedure
MRI	Magnetic resonance imaging
MSC	Mesenchymal stroma cells
n	Number
N	Newton
NaCl	Saline (0.9% Sodium chloride solution)
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
PBS	Phosphate Buffered Saline
PS	Penicillin/streptomycin
QM	Quadriceps muscle
SD	Standard deviation
St.	Saint
T	Tibia
TnBP	Tri-n-butyl-phosphate
Triton X-100	T-octyl-phenoxypolyethoxyethanol
TPLO	Tibial plateau levelling osteotomy
TPA	Tibia Plateau Angle
TTA	Tibial tuberosity advancement
TTO	Triple tibial osteotomy
U	Units
UK	United Kingdom
USA	United States of America
µl	microlitre

µm	micrometre
%	Percent
>	More than
<	Less than
°	Degree
°C	Degree Celcius
-	minus

1. INTRODUCTION

Cranial (anterior) cruciate ligament rupture in humans and dogs is arguably the most common ligament injury nowadays. In humans, rupture occurring in the context of high-performance, or when playing sports, is the result of a diverse injury mechanism. It is provoked by acute trauma or is a result of chronic instability solely due to hyperextension or hyperflexion, forced valgus or varus rotation, as well as a contraction of the quadriceps muscle (M. quadriceps (QM)), e.g. on landing with a flexed stifle joint following a jump (Garrick and Requa 2000; Petersen et al. 2005; Petersen and Zantop 2006). In contrast, a cranial cruciate ligament rupture in dogs is only exceedingly rarely the result of a defined acute trauma. The aetiopathogenesis remains largely unresolved in virtually all cases, despite intensive clinical and theoretical research since the original description in 1926 (Carlin 1926). Today, there is an indisputable indication for surgery in cases of rupture of the cranial cruciate ligament in dogs. There are over 100 surgical techniques applied, strongly attesting to the fact that no single technique has been developed to-date whereby the stifle joint can be fully restored without a loss in functionality on side comparison.

The aim of the study was to carry out biomechanical testing on different stifle angles of native cranial cruciate ligaments, as well as biomechanical testing on various preparations of native, de- and re-cellularised tendons from dead horses and dogs, to assess their suitability as a substitute for the cranial cruciate ligament. In addition, this study includes the measurements of the depth, length and width of the ligament in dogs of different sizes, in preparation for possible tissue grafting, while facilitating the prediction of the appropriate graft size whilst reducing the risk of damaging other intra-articular tissues. Apart from this, the relative distance of the rupture to the femur and tibia of native cranial cruciate ligaments was measured after the biomechanical tests to further understand whether different angles have any correlation with the ruptured zone. Moreover, the biomechanical results of different detergents (Tx-100 and TnBP) used in decellularisation on tendon were compared.

2. LITERATURE

2.1. EPIDEMIOLOGY

2.1.1. Rupture incidence

A rupture of the cranial cruciate ligament (CrCL) is indisputably the most common musculoskeletal lesion in dogs and an incidence of rupture up to 94% has been cited for all ligament and tendon injuries (Paatsama 1952; Hohn and Newton 1975; Mayer 1993; Brinker et al. 1997; Witsberger et al. 2008; Cook 2010). The incidence of bilateral CrCL rupture at diagnosis is 14.4-37% (Doverspike et al. 1993; Timmermann et al. 1996), whilst the risk of a unilateral CrCL rupture later (months to years) is 21-60% (Pond and Campbell 1972; Braden 1980; Doverspike et al. 1993; Brinker et al. 2006; McCarthy 2007a; Buote et al. 2009). Rupture of the caudal cruciate ligament (CaCL), on the other hand, is very rare and accounts for only 0.6-5% (Loeffler 1964; Schnell 1986) as it is more densely vascularised and exposed to less mechanical stress (Zahm 1964; Geyer 1966; Kuepper 1971; Yucel 1971; Alm and Stroemberg 1974; Schnell 1986). CrCL injuries constitute up to 100% of all ligament injuries in the stifle joint (Tab. 1). Traumatic ruptures of the CrCL are very rare and in more than 90% of ruptures the exact cause is uncertain (Brunnberg 1987). The disease is said to be multifactorial in etiology (Griffon 2010; Knebel and Meyer-Lindenberg 2014).

Table 1. Rupture of the cruciate ligaments in dogs (Brunnberg 1987)

Autors	N*	CrCL** n(%)****	CaCL*** n(%)	CrCL+CaCL n(%)
Paatsama (1952)	177	168 (95)	9 (5)	---
Loeffler (1964)	63	61 (97)	1 (1.5)	1 (1.5)
Lampadius (1964)	30	10 (33)	---	20 (66)
Geyer (1966)	154	150 (97)	1 (0.6)	3 (1.9)
Childers (1966)	7	7 (100)	---	---
Zahm (1966)	72	66 (92)	---	6 (8)
Yucel (1971)	142	131 (92)	5 (3.5)	6 (4.2)
Kuepper (1971)	328	271 (82)	11 (3.3)	46 (14)
Lewis (1974)	77	19 (25)	---	58 (75)
Schnell (1986)	194	191 (98)	---	3 (1.6)
Hulse et al. (1986)	---	---		
Johnson and Olmstead (1987)	---	---		14
Aron (1988)	---	---		often
Harari (1993)	---	---	<2%	
Sumner et al. (2010)	24		21 (88)	6 (25)

*Number, **Cranial Cruciate Ligament, ***Caudal Cruciate Ligament, ****Number of Cases

2.1.2. Incidence according to breed

Although the CrCL can rupture in any dog, comparisons have been provided for giant/large (>25 kg) breeds with an incidence of 43-67%; for medium-sized (10-25 kg) breeds; and for small breeds (<10 kg) with an incidence of 20-40% (Brunnberg 1987; Manchi 2011; Berger 2014). In particular, far in excess of 100 breeds or mixed-breeds have been mentioned in retrospective clinical studies in the literature (Tab. 2).

The Rottweiler, Boxer, Labrador and Golden Retriever, Chesapeake Bay Retriever, Newfoundland, as well as the Bernese Mountain Dog, St. Bernard, Dogue de Bordeaux, Dalmatian, German Shepherd, Hovawart, Caucasian Shepard Dog, Landseer, Leonberger, Mastiff, Neapolitan Mastiff, Ovcharka, Pyrenean Mountain Dog, Rhodesian Ridgeback, Giant Schnauzer, Cane Corso, Pointer and different mixes thereof are most commonly mentioned amongst the giant/large breeds (Barnes 1977; Vasseur 1984; Bennett et al. 1988; Duval et al. 1999; Wingfield et al. 2000).

The American Pit Bull, American Staffordshire Terrier, Basset Hound, Beagle, Cocker Spaniel, English Bulldog, Standard Schnauzer, Bedlington Terrier, Chow Chow, Small Münsterlaender and several mixed-breeds are listed amongst the medium-sized dog breeds (10-25 kg). The West Highland White Terrier, Yorkshire Terrier, Mixed breeds, Cairn Terrier, Dwarf Spitz, Jack Russel Terrier, Shi Tzu, Dwarf Poodle, amongst the small breeds (<10 kg) (Vasseur 1984; Whitehair et al. 1993; Duval et al. 1999; Manchi 2011) .

*Table 2: Predisposed breeds (from retrospective clinical studies)**

Authors	Breeds
Paatsama (1952)	Boxer, Rottweiler, Newfoundland
Lampadius (1964)	Boxer, Chow Chow
Loeffler(1964)	Boxer, Chow Chow, German Shepherd, Pointing dogs
Geyer (1966)	Boxer
Yucel (1971)	Boxer, Chow Chow
Punzet and Walde (1974)	Poodle, Boxer, Chow Chow, Pointing dogs
Shires et al. (1984)	Poodles
Schnell (1986)	Poodle, Boxer, Rottweiler, German Shepherd, Bernese Mountain Dog
Brunnberg (1990)	Poodle, Boxer, Rottweiler, German Shepherd, Bernese Mountain Dog, Chow Chow
Schaefer (1991)	Boxer, Rottweiler
Slocum and Slocum (1993)	Labrador Retriever, German Shepherd, Golden Retriever, Rottweiler
Whitehair et al. (1993)	Rottweiler, Newfoundland, Staffordshire Terrier
Metelman et al. (1995)	Labrador Retriever, Golden retriever, Crossbreeds
Timmermann (1995)	Bernese Mountain Dog
Duval et al. (1999)	Mastiff, Akita Inu, Bernese Mountain Dog, Rottweiler, Newfoundland, Labrador Retriever, American Staffordshire Terrier
Mager (2000)	German Shepherd Dog, Bernese Mountain Dog, Poodle, Rottweiler
Lampman et al. (2003)	Boxer, Golden Retriever, Labrador Retriever, Rottweiler, Crossbreed
Pacchiana et al. (2003)	Labrador Retriever, Rottweiler, Golden Retriever, Newfoundland dog, German Shepherd
Priddy et al. (2003)	Labrador Retriever, Rottweiler, German Shepherd, Boxer

Brahm (2004)	Boxer, Golden Retriever, Rottweiler
Moeller et al. (2010)	Labrador Retriever, Golden Retriever, Rottweiler, Boxer
Stauffer et al. (2006)	Labrador Retriever, Golden Retriever, Rottweiler, Newfoundland, Mastiff
Boyd et al. (2007)	Labrador Retriever, Boxer, Rottweiler, English Springer Spaniels
Corr and Brown (2007)	Rottweiler, Mastiff, Labrador Retriever, Newfoundland
Hurley et al. (2007)	Labrador Retriever, Rottweiler, mixed breed, German Shepherd
Guastella et al. (2008)	Labrador Retriever, Rottweiler, Boxer
Manchi (2011)	Crossbreeds, Rottweiler, Boxer Retriever, German Shepherd, Golden Retriever, Labrador retriever, Bernese Mountain Dog, Doberman, Great Dane, Mastiff

*(Hoepfl 2011)

2.1.3. Incidence according to age

Although the CrCL can rupture at any age, Witsberger et al. (2008) postulated in their study on the basis of an analysis of more than one million dogs with a CrCL rupture that ruptures more frequently occur between the 2nd and 10th year of age. A rupture is significantly less frequent in dogs up to 4 years of age than in older dogs. Numerous retrospective studies – some with up to 800 patients – have documented in detail that the CrCL ruptures significantly more frequently in giant/large breeds up to 6 years of age, and in medium-sized and small breeds only after the 8th year of age (Kuepper 1971; Brunnberg 1990; Elkins et al. 1991; Whitehair et al. 1993; Metelman et al. 1995; Innes and Barr 1998; Mager 2000; Alt 2000; Hayashi et al. 2004; Kloene 2005; Dismukes et al. 2007; Hurley et al. 2007; Manchi 2011).

2.1.4. Incidence according to sex

Clinical retrospective studies on incidence according to sex do not allow for a disposition on the basis of sex to be inferred, even though the percentage of affected female animals is slightly higher (51-60%) than for male animals (Paatsama 1952; Loeffler 1964; Geyer 1966; Pond and Campbell 1972; Gambardella et al. 1981; Schnell 1986; Brunnberg 1990; Hofer 1990; Robins 1990; Weiss 1990; Schaefer 1991; Whitehair et al. 1993; Timmermann 1995; Alt 2000; Lampman et al. 2003; Robinson et al. 2006; Fitzpatrick and Solano 2010; Moeller et al. 2010; Manchi 2011). The incidence of CrCL rupture is, however, significantly higher in

castrated animals of both sexes as compared to non-castrated dogs (Whitehair et al. 1993; Duval et al. 1999; Slauterbeck et al. 2004; Witsberger et al. 2008). Necas et al. (2002), de Rooster (2001), Manchi (2011), as well as Pecin et al. (2017) could not confirm these correlations.

2.1.5. Body-weight

It remains uncertain whether the frequently-emphasised increased body-weight (Paatsama 1952; Vasseur 1984; Rahlfs and Fehr 1986; Schnell 1986; Whitehair et al. 1993; Duval et al. 1999; Lampman et al. 2003; Witsberger et al. 2008) and obesity (Dueland 1966) can be assigned a key role in cruciate ligament rupture. Hayashi et al. (2004) could not demonstrate a correlation between body-weight and cruciate ligament rupture.

2.2. DIAGNOSIS

2.2.1. Clinical symptoms

Partial as well as complete ruptures of the CrCL are clinically characterised by sudden onset (Paatsama 1952; Arnoczky and Marshall 1977; Fetto and Marshall 1980; Robins 1990; Corr 2009) or insidious-progressive lameness of different grades (Johnson and Johnson 1993). Most of the lameness begins insidiously (Johnson and Johnson 1993), and improves, particularly in Toy-breed dogs but also in larger breeds, although this occurs only to a lesser extent in the first 6 weeks following the tear (Brinker et al. 2006; Fossum 2009), only to worsen again significantly as a result of arthrosis (Johnson and Johnson 1993). When standing at rest, the injured limb is only supported by the tiptoes (Henderson and Milton 1978); during motion, the range of motion of the stifle joint is not used to its full extent. A sitting dog will stretch out the ruptured side with a lateral external rotation (Slocum and Slocum 1998). After the CrCL rupture, muscle atrophy is visible, especially in the quadriceps femoris muscle (Brass 1955; Marshall and Olsson 1971; Lewis et al 1987; Robins 1990; Corr 2009).

2.2.2. Palpation

Stifles of giant, large and medium-sized breeds of dogs with CrCL rupture are characterized by a palpable joint effusion in the paraligamentary region to the patellar ligament (Lig. patellae). After a few weeks a bony protuberance (fibrosis, a so-called ‘medial buttress’) can

be felt medial to the proximal tibia as a sign of chronicity (Harasen 2002), but this is not the case in small breeds.

2.2.3. Clinical instability tests

Anterior drawer test

If the CrCL is ruptured, the tibia can be pushed 2-9.5 mm forwards in the sagittal direction along the femur, like a drawer, when the stifle joint is flexed 120-150° ("cranial drawer phenomenon") (Carlin 1926; Arnoczky and Marshall 1977; Henderson and Milton 1978; Korvick et al. 1994; Tashman and Anderst 2003). Generally, an internal tibial rotation from 6° to 15° is possible in a sound stifle during sitting and trot (Vasseur and Arnoczky 1981). Furthermore, the tibia can be internally rotated by 14° as the CrCL is also neither unable to limit the internal rotation (in its function as secondary stabiliser), nor the abduction of the tibia in full extension (Warzee et al. 2001; Kim et al. 2009 a, Kim et al 2009b).

Tibial- compression- test (Henderson and Milton 1978)

With the stifle joint in full extension and repeated flexion/extension of the tarsal joint, the tibial tuberosity (Tuberositas tibiae) is dislocated cranially following CrCL rupture (Henderson and Milton 1978; Johnson and Johnson 1993; Watt 2000; Harasen 2002).
The sensitivity of both tests on conscious dogs is 60-64%, and on sedated dogs is >90%, whilst the specificity is cited at 82-100% (Schaefer 1991; Carobbi and Ness 2009).

2.2.4. Partial CrCL rupture

Both clinical instability tests are less diagnostic in cases of a partial rupture of the CrCL, as the increase in instability is not more than 3 mm (Heffron and Campbell 1978; Scavelli et al. 1990). In case of a CrCL partial rupture, the caudolateral component is taut only in extension however, the craniomedial component is taut in extension and flexion and there is no instability palpable (Arnoczky and Marshall 1977). If signalment, lameness and joint filling are indicative of a CrCL rupture, but instability is questionable or cannot be detected, then a painful response to a stress-hyperextension will serve as sufficient proof of a partial rupture (Brunnberg et al. 2014). Due to the tension in the craniomedial and caudolateral parts of an intact CrCL during extension of the stifle joint, healthy dogs do not show any pain symptoms during stress-hyperextension (Arnoczky and Marshall 1977). Arthroscopy plays a decisive role in the diagnosis of a partial CrCL rupture and the decision on early treatment (Beale et al. 2018).

2.2.5. Radiography

Radiographs of the pelvis with stifle joints in the ventro-dorsal beam path (Hip Dysplasia (HD) position I) and of both stifle joints laterally in the medio-lateral beam path are essential for differential diagnosis, as well as for diagnostic/prognostic considerations (Zahm 1966; Schnell 1986; Brunnberg 1987; Brunnberg et al. 1992), in order to exclude coincident HD, osteoarthrosis, coxarthrosis, aseptic femoral head necrosis, transitional vertebrae, and bone tumour at distant sites from the stifle joints (Brunnberg et al. 2014). In the stifle joint, patella dislocation (Kaiser et al. 2001), osteochondrosis dissecans (Horst 2000), avulsion of the extensor digitorum longus muscle (Fitchl and Beale 1998), and neoplasia such as osteosarcoma, synovial cell sarcoma or rheumatoid polyarthritis (Bennett 1987; Bennett et al. 1988; Clements et al. 2004) must be excluded.

In the stifle joint region, evidence of CrCL rupture in the soft tissues includes increased joint filling, displacement of the infrapatellar corpus adiposum, expansion of the joint capsule (Zahm 1964; Schnell 1986; Brunnberg 1987) and, degenerative joint changes in the skeletal region because of soft tissue versus bony changes (Paatsama and Sittnikow 1972; Gambardella et al. 1981; Lewis et al. 1987; Schrader 1989; Elkins et al. 1991; Brunnberg et al. 1992).

A rupture of the CrCL can sometimes be documented as an incident finding in standard lateral projections in small breed dogs as the tibia appears as cranially dislocated (Singleton 1957; Pond and Campbell 1972; Kirby 1993; Corr 2009; Kim et al. 2011). CrCL rupture is only directly detectable in stress images (Brook 1932; Schreyer 1937; Brass 1955; Hulse and Shires 1985; Brunnberg 1987; Brunnberg 1989a; Brunnberg 1989b; Brunnberg et al. 2014). In contrast, a partial CrCL rupture can be detected using tibial-compression stress radiography with a high sensitivity and 100% specificity in dogs of all breeds (de Rooster et al. 1998; de Rooster and van Bree 1999a; de Rooster and van Bree 1999b; Zatloukal et al. 2000; Bhandal et al. 2008; Plesman et al. 2012). If the popliteal sesamoid bone (fabella, Os sesamoideum musculi poplitei) is distally dislocated in the lateral projection, the sensitivity (99%) and specificity (100%) serve as proof of CrCL rupture (de Rooster and van Bree 1999b).

2.2.6. Ultrasound scans

CrCL rupture can only be detected on ultrasound in 19.6% of cases (Reed et al. 1995; Engelke 1996; Engelke et al. 1997; Gnudi and Bertoni 2001). This rate can be increased by means of different manipulations (Seong et al. 2005), such that the sensitivity can be increased to 82%

(Schnappauf et al. 2007; Soler et al. 2007; Arnault et al. 2009; Nayseh et al. 2015) for both complete and partial ruptures.

2.2.7. Computed tomography (CT)

Computed tomography is a valuable tool for diagnosing CrCL ruptures (Samii and Dyce 2004; Marino and Loughin 2010). Reports from Samii et al. and Marino and Loughin on using CT arthrography to assess intra-articular structures with naturally occurring ligamentous disorders of the stifle joint, show that the sensitivity and specificity for detecting CrCL rupture were 96-100% and 75-100%, respectively (Samii et al. 2009; Marino and Loughin 2010).

2.2.8. Magnetic resonance imaging (MRI)

The accuracy of MRI in cases of CrCL lesions in dogs is very low at 72.7% (Richter et al. 1997; Baird et al. 1998a; Baird et al. 1998b; Banfield and Morrison 2000; Foltin et al. 2004; Konar et al. 2005a; Konar et al. 2005b; Soler et al. 2007; Marino and Loughin 2010; Galindo-Zamora et al. 2013). To-date, there is no data on the sensitivity and specificity of MRI in the diagnosis of CrCL rupture.
In contrast, the sensitivity of MRI for the diagnosis of rupture of the CrCL in humans is, depending on the author, given as 90-100% with an accuracy of 80-100% (Gross et al. 1992; Robertson et al. 1994; Umans et al. 1995; Stoller 2007), whilst for the outdated one it is only about 57%.

2.2.9. Synopsis

In summary, the sensitivity of the cranial drawer and tibial-compression tests in the awake dog is low, whilst it is significantly high in the sedated dog. Findings on palpation, together with X-rays findings, have shown excellent sensitivity, specificity, positive-predictive value and negative-predictive value (Carobbi and Ness 2009).

Compared to this, other imaging techniques have proven to be more effective in detecting a rupture of the cruciate ligament in dogs. However, musculoskeletal ultrasound is time-consuming as both stifle joints have to be visualised side-by-side (Cook 2016). Computed tomography (CT) is not suitable for proving the integrity of the cruciate ligaments or menisci (Gielen and van Bree 2018). The usefulness of magnetic resonance imaging (MRI) for cruciate ligament diagnostics in dogs has not yet found a significant place, except for scientific questions (Scrivani 2018).

2.2.10. Arthrotomy – Arthroscopy

The possibilities for magnification available to us today due to zoom lenses allow almost every detail of the stifle joint interior to be seen and treated, whereby knee arthroscopy is considered the gold standard of diagnostic imaging of this organ (Ertelt 2003; Pozzi et al. 2008; Ertelt and Fehr 2009). Arthroscopy and integrated palpation, e.g. of the meniscus, increase the visual assessment alone from 37% to 83% and the specificity from 84% to 96% (Pozzi et al. 2008). By using a stifle joint distractor, results can be further optimised (Boettcher et al. 2009; Gemmill and Farrell 2009).
In terms of treatment, arthroscopy is still limited to possible indications of (partial) meniscus resection and/or resection of the ligament stumps of the ruptured CrCL (Whitney 2002; Ertelt and Fehr 2009).

Of all the imaging procedures available, lateral/medial arthrotomy and arthroscopy are the most effective. Not only for examining the internal structures of the stifle joint (corpus adiposum, cruciate ligaments, menisci, original tendon of the extensor digitalis longus muscle), but also to investigate the knee subsequent to pathology (rheumatoid arthritis, chondromalacia patellae, osteochondrosis dissecans, adipositis, tearing of the extensor digitalis longus muscle). Furthermore, for removing of the biopsy samples and proving any required treatments during the same session (Bennett and May 1991; Ayral 1996; Ralphs and Whitney 2002; Hoelzler et al. 2004; Ertelt and Fehr 2009).
A purely diagnostic arthrotomy or arthroscopy of the stifle joint is indicated as the sole procedure only in the case of significant complaints that cannot be explained despite clinical or imaging examination, or in the case of contradictory findings from imaging procedures. However, arthrotomy and arthroscopy are always performed with a mind to continue to carry out a surgical repair. In other words, the arthroscopy procedure must allow for an open or arthroscopic treatment for the findings to be carried out in the same session.

According to the first description by Nilsson (1943), *arthrotomy* of the stifle joint has become more and more standardised over the years (Johnson KA 2013 Piermattei's Atlas of Surgical Approaches), to ensure clear access to the joint. In order to optimise exploration of the menisci in particular, a Hohmann retractor (Hulse and Shires 1981) or stifle joint distractor (Boettcher et al. 2009) can be used. Arthrotomy requires only a few complex instruments and is inexpensive (Braden 1980; Bennett and May 1991; Dupius and Harari 1993; Brinker et al. 1997; Abercomby 1997). With arthrotomy, morbidity increases proportionally to the experience

of the surgeon. In stable stifle joint of dogs with partial CrCL rupture, especially for the meniscal diagnosis, arthrotomy was found to be more sensitive (Pozzi et al. 2008).

Arthroscopy in animals (horse, cattle) was first systematically performed in Vienna by the Austrian veterinarians Knezevic and Wruhs (1975) and for the stifle joint in dogs and Siemering (1978) on this animal species. Kivumbi and Bennett (1981) provide detailed information on the diagnostic potential of this technique in the stifle joint. The methodology was standardised (Person 1985) and backed by numerous studies (Miller and Presnell 1985; van Gestel 1985; Heer 1986; Siemering and Eilert 1986; Lewis et al. 1987; Bardet 1995; Necas et al. 2002). Arthroscopy reduces short-term postoperative morbidity compared to arthrotomy in dogs with cruciate ligament rupture (Hoelzler et al. 2004). Furthermore, it is more advantageous than arthrotomy in terms of illumination of tissue growth and provides more detailed access to the anatomical joint regions as well as assessment of the joint structures in a fluid medium (Beale et al. 2018).

Combining arthroscopy with arthrotomy is easier to perform and more beneficial because of identical intraarticular images, reduced fluid leakage into the periarticular soft tissues and reduces post-operative morbidity (Beale et al. 2018).

2.3. ANATOMY

The macroscopic anatomy of the CrCL, its insertion zones on the femur and tibia, its location and form, as well as its anatomical course through the stifle joint are consistently described in the literature (Singelton 1957; Zahm 1964; Alm et al. 1974; Arnoczky and Marshall 1977; de Rooster and Comerford 2018). The anatomical textbooks state that the CrCL is an intra-articular, but extra-synovial joint ligament (Vollmerhaus et al. 1994b; Budras et al. 2000; Miller and Evans 2019). As is the case with the caudal cruciate ligament (CaCL) (Lig. cruciatum caudale), the CrCL is delimited by a meso-like fold of the synovial stratum (Stratum synoviale) of the articular cavity (Fig. 1) (Alm et al. 1974; Heffron and Campbell 1978; Arnoczky et al. 1979). The membranous fold contains numerous holes interspersed within it through which the synovial fluid can flow to reach the cruciate ligaments (Ligg. cruciata) (Kobayashi et al. 2006).

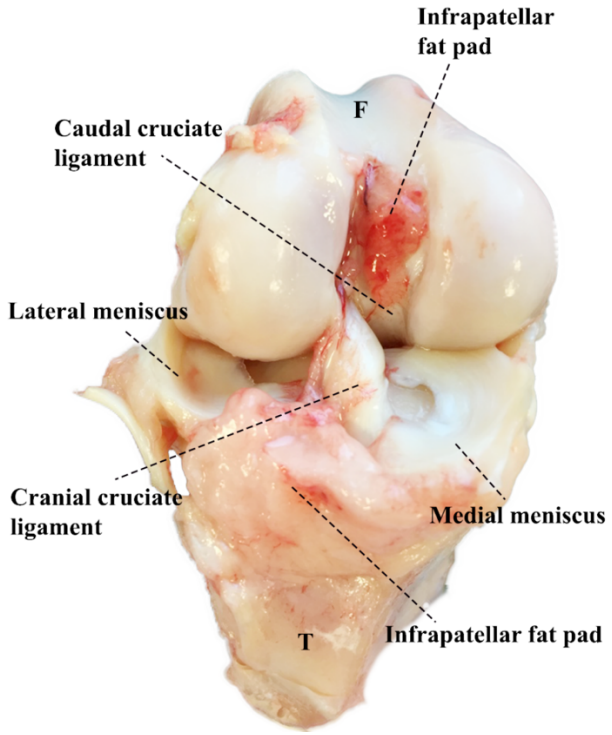


Figure 1. Right side of stifle joint from a 2-year-old German Shepherd. F: Femur; T:Tibia.

The CrCL's origin is located axially within a semilunar ligament groove at the caudal end of the medial surface of the lateral femoral condyle (Dyce et al. 1952; Loeffler 1964; Muller 1969; Arnoczky and Marshall 1977). Only Weiss (1990) describes the ligament groove as triangular, whereby the sagittal area of origin on the lateral femoral condyle is covered by a small roof-like horizontal segment up to the intercondylar fossa (Fossa intercondylaris). The proximal corner of this area of origin protrudes into the intercondylar fossa by 1-2mm, thus giving a small portion of the CrCL's fibre bundles a horizontal origin site (Reese 1995). The ligament groove has the form of a centrally split pileolus with three sides of equal length. The size of the pileolus formed depends on the size of the dog - whether this be giant, large, middle-sized or small breeds – and, on the other hand, also exhibits interindividual variation (Arnoczky and Marshall 1977; Vasseur et al. 1985; Arnoczky 1988; Weiss 1990; Arnoczky 1993).

The comma-shaped site of origin in the central intercondylar area (Area intercondylaris centralis) is shaped in a somewhat citriform-convex manner, oriented cranio-caudally and inclined somewhat cranio-distally (Dyce et al. 1952; Loeffler 1964; Muller 1969; Arnoczky and Marshall 1981; Weiss 1990). The insertion area is delimited cranially and medially by a low osseous ridge in the form of a horizontal “L”. The cranial meniscotibial ligament (Lig. meniscotibiale craniale) and the caudal meniscotibial ligament (Lig. meniscotibiale caudale) of

the lateral meniscus delimit the insertion area cranially and caudally, respectively (Reese 1995; de Rooster et al. 2006).
Over its anatomical course, the CrCL widens distally and tapers out in a fan-like fashion into its insertion area (Sonnenschein 1951; Zahm 1964; Weiss 1990). The cross section thereby changes from round to transverse-oval (Zahm 1964; Weiss 1990; Reese 1995). The ligament twists around its own longitudinal axis, such that the fibres originating cranially insert laterally and the fibres originating caudally insert medially (Sonnenschein 1951; Loeffler 1964; Arnoczky 1988; Reese 1995). Torque is increased during flexion (Muller 1969; Brunnberg 1989a; Arnoczky 1993). This phenomenon is more pronounced in dogs of larger breeds in comparison to small breeds (Paatsama 1952). Torsion is greatest in the middle third of the CrCL during flexion at approx. 120° and in extension at approx. 30° (Reese 1995).

The CrCL twists due to the fact that the fibre bundles originating caudo-proximally insert craniolaterally, and the fibre bundles originating cranio-distally insert caudally into the central tibial intercondylar area (Area intercondylaris centralis tibiae) (Brunnberg 1989a; Weiss 1990). The fibres with the craniodistal origin wind themselves in a spiralling course from lateral to caudal to medial, around the out-stretched and longer fibres originating caudo-proximally (Zahm 1964; Weiss 1990). Torque is increased in flexion, as the femoral area of origin rotates clockwise from a medial point of view. As such, the origin of the fibre bundles originating caudo-proximally migrates caudally and distally. At the same time, the fibre bundles originating cranio-distally move cranially. The distance of the fibre bundles originating caudo-proximally to their cranially located tibial insertion is thereby increased. In contrast, the distance of the fibre bundles originating cranio-distally to their caudally-located tibial insertion is decreased, such that this fibre bundle is relaxed during flexion (Arnoczky and Marshall 1977; Heffron and Campbell 1978; Weiss 1990; de Rooster et al. 2006).

The CrCL contracts over its course through the stifle joint: in flexion at 135°, its caudal fibres are located in the insertion area caudally in the central intercondylar area (Area intercondylaris centralis) whilst being under tension over the medial tubercle of the tibial intercondylar eminence (Tuberculum mediale- Eminentia intercondylaris tibiae). If the angle is <95°, the CrCL with its segment closest to its origin is pressed against the larger lateral tubercle of the tibial intercondylar eminence (Tuberculum laterale; Eminentia intercondylaris tibiae) (Arnoczky and Marshall 1977; Welsh 1980; Monahan et al. 1984; Jaegger et al. 2002). With increasing extension, the CrCL with its segment most distal to its insertion is pressed against the transverse genicular ligament (Lig. transversum genus). The CrCL increasingly winds itself around the CaCL during internal rotation of the lower limb and in a flexed stifle joint, whilst at the same time the external rotation around its own longitudinal axis is reduced. At the same

time, the tension of the fibre bundles over the medial tubercle of the tibial intercondylar eminence decreases, whilst the other fibre bundles in this section remain under considerable tension. The CrCL only contacts with the lateral femoral condyle (Condylus lateralis ossis femoris) on extreme internal rotation. The middle of the CrCL is pressed against the lateral femoral condyle in flexion and external rotation of the lower limb, whilst the pressure against the lateral tubercle of the tibial intercondylar eminence is reduced (Arnoczky and Marshall 1977; Welsh 1980; Jaegger et al. 2002; de Rooster et al. 2006).

The CrCL consists of multiple fibre bundles (Zahm 1964; Arnoczky 1983; Weiss 1990). Paatsama (1952) was the first to describe two distinguishable functional portions: a craniomedial and a caudolateral portion in the CrCL of dogs. Soon after, all clinical-casuistic (Loeffler 1964; Geyer 1966; Muller 1969; Heffron and Campbell 1978; Fox and Baine 1986; Brunnberg 1989a; Brunnberg 1989b; Robins 1990) and clinical-experimental studies (Arnoczky and Marshall 1977), as well as surgery/orthopaedics textbooks (Kowalski et al. 2017) started to describe this morphologic-functional division (portion, part, ligament, fibre bundle) of the CrCL, and this description is maintained to this day.

A morphologic differentiation of the CrCL into two portions could not be verified anatomically in either dog foetuses, puppies or adult dogs of any breed, despite elaborate methods being used (Zimmermann 1933; Weiss 1990; Reese 1995) macroscopic and light/electron microscope examination were similarly unsuccessful in doing so (Reese 1995). Only Dyce et al. (1952) found this type of morphological division (craniomedial, caudolateral portion) in dogs as an extremely rare variant.

The CrCL consists of multiple fibre bundles of up to 0.5 mm thickness and of different lengths. The lengths vary depending on the breed or individual. The length is influenced by the sagittal attitude angle of the area of origin, as well as the horizontal insertion area, and their respective heights (Reese 1995). The fibre bundles of the CrCL are positioned in such a way that individual fibres are under tension in every position of the stifle joint. To deduce a functional division (Paatsama 1952) from this would be an unjustified simplification (Weiss 1990), as every fibre bundle of the CrCL has its own function. To put this in simple terms, the craniomedial fibre bundles are under tension at every joint position, whilst the caudolateral fibre bundles are relatively relaxed in flexion (Arnoczky and Marshall 1977; Heffron and Campbell 1978; Chaudieu and Fonck 1984).

Structurally, the CrCL is comparable with a tendon (Butler et al. 1978; Milz et al. 2009) whereby the course can be differentiated on microscopic-anatomical examination into three portions

with fluid transition zones. Origin and insertion segments resemble a traction-type tendon. The middle third resembles a gliding-type tendon (Reese 1995). Traction tendons consist of dense, tendinous tissue organised in parallel. The subtle wavy and densely-packed collagen fibres are arranged in the direction of tension (Lullmann-Rauch 2003) with 60-80% of the fibre mass of tendons of this type consisting of collagen type-I as their main component (Goodship et al. 1994; Vogel and Meyers 1999; Kjaer 2004), with smaller amounts of collagen type-III, V and VI (Benjamin and Ralphs 1998). Collagen type-I forms fibres of particularly large diameter (Tillmann 2003).

Collagen type-III forms thin and less organised fibrils (Lapiere et al. 1977). It can be found in the surrounding connective tissue layers of tendons and ligaments (Benjamin and Ralphs 1998; Duance et al. 1977), as well as in the insertion areas of tendons that are exposed to heavier loads (Fan et al. 1997). Collagen type-III combined with type-I not only gives the tissue stability, but also flexibility and the ability to change its form (Tillmann 2003). The bimodal distribution of a few thin (15 mm) and predominately thick (330 mm) fibres is characteristic of tension tendons (Merrilees and Flint 1980) and is optimal for high tensile loads (Parry an Craig 1978; Parry et al. 1978a; Parry et al. 1978b).

A gliding segment develops when a tendon is diverted by a counterfort (hypomochlion, bony protuberance, retinaculum) and this tendon region has to withstand the resultant pressure and tension loads. The zonal structure of fibrocartilage with large, rounded chondroid cells that are typical of gliding tendons develops in the tendon region facing the hypomochlion. Horizontal to the longitudinal axis, loosely-packed collagen fibrils permeate the chondroid cell groups (which are disorganised, or arranged like a string of beads) in a reticular fashion. The collagen network consists mainly of type-I and type-II collagen (Koch and Tillmann 1995).

Type-II collagen forms substantially thinner fibrils with a higher water content as compared to type-I. They do not consolidate to form fibres. The high water content means that collagen type-II fibrils can withstand higher compression loads (Grynpas et al. 1980).

Collagen fibres, and especially the covalent cross-links within single fibrils, are predominantly responsible for the stability of tendons (Parry 1988; Dowling et al. 2000; Koob and Summers 2002). It is possible to differentiate between reducible and non-reducible cross-links with the common amino acid components lysine and hydroxylysine (Ross and Dyson 2003).
Proteoglycans consist of a small protein component (5-10%) and a large glycan component (Tillmann 2003). The protein component is the backbone for the covalent bonds of the glycosaminoglycans (heparan, keratan, chondroitin, dermatan sulphates) (Lullmann-Rauch

2003). In a gliding tendon region the proteoglycan concentration is 15-20-times higher as compared to the tension tendon segments (Gillard et al. 1977). According to Vogel and Koob (1989), aggrecan is the most abundant protein cell filament of all the proteoglycans in these sections exposed to high pressures. In combination with chondroitin sulphate, it particularly increases water binding capacity and hence resilience to compression forces (Benjamin and Ralphs 1998). The interactions between proteoglycans and collagen fibres are substantially responsible for their viscoelastic properties and elastic deformation mechanisms (Robinson et al. 2004; Screen 2007). They can reversibly change shape when exposed to external forces as they have a characteristic molecular structure and are integrated into the extracellular matrix (ECM) (Tillmann 2003).

Elastic fibres consist of an amorphous core composed of elastin, and are encapsulated by organised microfibrils (Liebich 2004). This portion barely makes up 1% of the dry matter (Kirkendall and Garret 1997). Elastic fibres are branched, creating an interwoven network that interacts with collagen to act as a single complex (Tillmann 2003). One can differentiate between different precursors during the formation of elastic fibres: oxytalan fibres comprised of bundles of elastic microfibrils; and elaunin fibres, which are characterised by pre-complexed elastin (Tillmann 2003). Oxytalan fibres develop under high mechanical loads (Cotta-Pereira et al. 1976). Elastic fibres can stretch up to 150% and subsequently contract back to their former shape. They play a crucial role as they store and release enormous amounts of energy.

Insertion:
The most common insertion of tendons and ligaments is a chondroapophyseal (fibrocartilaginous) enthesis (Benjamin and Ralphs 1998). The CrCL also inserts chondroapophyseally onto the femur and tibia via four zones (Reese 1995):
- dense connective tissue;
- non-calcified fibrocartilage;
- calcified fibrocartilage;
- osseous tissue.

This complex interlocking guarantees high levels of mechanical stability of the entheses (Benjamin and Ralphs 1998).

2.3.1. Cranial cruciate ligament - middle third

The middle third of the CrCL has the structural characteristics of a gliding tendon:
- decreased cell count;
- chondroid cells;
- high proteoglycan concentration.

(Zahm 1964; Vasseur et al. 1985; Brunnberg 1987; Robins 1990; Reese 1995). The fibrocartilaginous tissue remodelling of the CrCL's gliding region progresses in dogs with increasing body-weight, as well as increasing age (Vasseur et al. 1985; Brunnberg 1987; Reese 1995). In comparison to the typical zonal structure of a gliding tendon, which is normally caused by the high unilateral pressure due to a hypomochlion, Reese (1995) demonstrated in the CrCL of dogs that the fibrocartilage is distributed over the entire cross-sectional area of the CrCL's middle third. This is the case since the CrCL is exposed to high mechanical pressure loads through its own torque, especially when in flexion. Cotta-Pereira et al. (1976) describe oxytalan fibres as a sign of high mechanical load bearing. Reese (1995) detected them in the CrCL.

The fibrocartilaginous changes in the CrCL were historically (Paatsama 1952; Zahm 1964; Geyer 1966; Singleton 1969; Tirgari 1978; Brunnberg 1987; Brunnberg 1990; Robins 1990) and still today (Hayashi et al. 2004; Harasen 2008; Perry and Fitzpatrick 2010; Hayashi et al. 2011; Comerford et al. 2011) considered as signs of ageing and degeneration, alongside other histological findings such as metachromasia, loss of fibre structure, liquefactive necrosis, karyolysis, demasking of fibrils, homogenisation and reduced cell density (Paatsama 1952; Zahm 1964; Brunnberg 1987).

Gliding zones in tendons/ligaments, as seen for example in the middle segment of the CrCL in dogs, exhibit lower levels of vascularisation as a further characteristic (Fackelman 1973; Tillmann and Kolts 1993). Zahm (1964), Geyer (1966), Alm et al. (1974), Arnoczky et al. (1979) and Brunnberg (1987) provide evidence of this regarding the CrCL. Reese (1995) demonstrated that the vessel density in the middle segment of the CrCL in dogs decreases as early as the 6th month of age in parallel with fibrocartilage development/differentiation, whilst the hyaluronic acid concentration increases. Intra-ligamentous vessels are obliterated as a result of vessel-wall hyalinoses (Gilbertson et al. 1979; Reese 1995).

*The fibrocartilage typical of gliding tendons develops and differentiates in 1-month-old dogs (Reese 1995), and not only after the 8th (Zahm 1964) or 5th (Robins 1990) month, as seen in dogs heavier than 15 kg body-weight (Vasseur et al. 1985). Only the torque of the CrCL around its longitudinal axis, especially in flexion of a dog's stifle joint, creates uniform compression

over the entire cross-sectional area of the middle segment of the ligament. The ligament adapts to this formative stimulus and forms fibrocartilage (Reese 1995).

2.4. A SHORT HISTORY OF CRANIAL (ANTERIOR) CRUCIATE LIGAMENT RUPTURE IN HUMANS AND DOGS

It seems fitting to recall the history of cranial (anterior) cruciate ligament rupture in both humans and dogs in order to understand the diversity of this significant orthopaedic problem in both species. Questions remain in relation to this issue in all fields, as can be gleaned from the literature. Reviewing history according to a faithful chronology proves to be frustrating as the first to describe or innovate in this area came to be forgotten. The literature search was not exhaustive, nor was it limited to literature in English, as can be seen particularly in the case of cruciate ligament rupture in humans.

Humans: When searching for the first descriptions of cranial (anterior) cruciate ligament rupture in humans, one inevitably comes across the Lachman test. The test is named after the American orthopaedist John Lachman (1919 – 2007), who worked at Temple University in Philadelphia (Kim and Kim 1995). His successors, Torg et al. (1976), described this test. The Greek doctor Noulis, who described the test in detail for the first time in his doctorate, written 101 years earlier (1875), remains mostly forgotten (Ritchey 1960). Even today, this functional test has a 85% sensitivity and 95% specificity rate for diagnosis of cranial cruciate ligament rupture in humans (Zantop et al. 2016).

Hey (1782) from Leeds, England, was the first to reduce a dislocated medial meniscus in an internal derangement of the knee. Despite no mention of this from Hey, it is conceivable that a cruciate ligament was also ruptured in the patient (Hey 1805).

The Weber (1836) brothers from Göttingen, Germany, first detected an abnormal anterior-posterior movement of the tibia after transection of the anterior cruciate ligament (anterior drawer sign) and described the rolling-sliding mechanism of the knee joint as well as the tension patterns of the different cruciate ligament bundles (Weber and Weber 1836).

Bonnet (1845) from Lyon, France, must be regarded as the pioneer of knee ligament surgery, as he was first to acquire knowledge in this respect that is still valid today on the basis of experimental cadaveric studies:

- the anterior cruciate ligament usually tears at the femoral origin and rarely at the tibial insertion;
- in valgus stress, the medial collateral ligament (MCL) usually tears at the femoral origin;
- after cruciate and/or collateral ligament rupture(s), hemarthrosis develops.

He described for the first time:

- the subluxation phenomenon as a consequence of such ruptures as “des deplacements qui font crosier a une luxation incomplete”;
- the knee joint pain experienced following these types of injuries is a consequence of the sudden overstretching of the joint’s innervation.

With regard to therapy, he states:

- immobilisation leads to cartilage degradation;
- in stifle distortion, the primary option for treatment is cooling with ice packs.

Stark (1850) in Edinburgh, Scotland, was the first to report on an acute cruciate ligament rupture in patients, whereby moderate therapy success was achieved through bracing.

Dittel (1876) from Vienna, Austria, followed the experimental studies by Bonnet (1845) on the ligaments of the stifle joint, confirming and expanding on Bonnet's findings.

Segond (1879) in France was the first to describe the clinical findings in detail: pain; a clinically-audible “pop”; and joint effusion.

Annandale (1885) from Edinburg, Scotland, successfully performed suturing of a torn meniscus the first time.

Robson (1895) from Glasgow, Scotland, was the first to sew cruciate ligaments with catgut (Robson 1903).

Lange (1903) from Munich, Germany, successfully stabilised 4 genu laxum (“flail knee”) patients using silk ligaments, but this failed in studies by Herz (1906) (Herz 1906; Lange 1907).

Giertz (1913) from Umeå, Sweden, was the first to replace the torn anterior cruciate ligament with a strip of fascia lata (Giertz 1913).

Nicoletti (1913) from Italy was the first to successfully replace the torn cranial cruciate ligaments with fascia lata, periosteum and tendons in dogs in an experimental study. Within

two weeks, the joints were stable and the dogs were weight-bearing. The best results were observed with periosteum, and the poorest with fascia.

Hesse (1914) from Germany published the femoral and tibial bone tunnel grafting technique, which Gracov (1911) from Saint Petersburg, Russia, first used to anchor a free fascia graft and implanted intra-articularly in the direction of the anterior cruciate ligament in the tibia and femur three years earlier than Hey-Groves (Hesse 1914). Hey-Groves (1919) in Bristol, England, published the same technique years later.

Zur Verth (1917) in Hamburg, Germany, replaced the ruptured cruciate ligaments with parts of the likewise torn meniscus, as described by Hoelzel (from Germany) in 1917.

Mattj (1918) from Bern, Switzerland, first restabilised a knee joint after cruciate ligament rupture in an extra-articular technique with a free fascia lata strip, 18 years before Bosworth and Bosworth (1936) would describe this technique again.

Edwards (1926) from England used hamstring tendons for the first time, for cruciate ligament replacement.

Ludloff (1927) from Frankfurt, Germany, replaced the ruptured cranial cruciate ligament with an augmented fascia strip. He covered a thick silk thread with a sheath made from a strip of fascia and anchored the combined suture in tunnels in the tibia and femur.

Bircher (1933) replaced torn cruciate ligaments with kangaroo tendons without post-operative immobilisation of the stifle using a cast (Bircher 1929; Micheli 1933).

Zur Verth (1933) replaced a ruptured cranial cruciate ligament with a distally attached strip in front of the patellar ligament 4 years before Campbell (1936) published the same method once again.

Wittek (1936) from Graz, Austria, fixed the patellar ligament strip caudo-proximally to the caudal cruciate ligament using sutures.

Campbell (1939) used parts of the patellar ligament to replace the torn ligament.

Brueckner (1966) is considered the father of modern cruciate ligament surgery. He replaced the torn cruciate ligament for the first time using a free central third of the patellar ligament.

The concept was later optimised by Alm (1973) and Clancy et al. (1981) by transplantation with pendant bone blocks from the patella and tibial tuberosity as so-called bone patellar tendon bone (BPTB). Over much of 80 years of the past century, the replacement of the torn cruciate ligament using a variety of synthetic materials has gained a lot of momentum. Implanted materials were made from carbon fibre (Carbon®: Jenkins 1978; Wolter 1983; Jenkins 1983; Jenkins 1985; Claes and Neugbauer 1985), polyester (Dacron®: Contzen 1985; Mockwitz 1985; Siebert et al. 1985), and polytetrafluoroethylene (Gore-Tex®: Bolton and Bruchman 1985). They have not fulfilled the high expectations and, due to the often successful revision interventions, are today of no significance in up to 80% of cases in humans (Arnoczky et al. 1986; Frank and Jackson 1997).
Almost 30 years after Brueckner (1966), autologous tendons of the semitendinosus or gracilis muscles and/or of the distal tractus ileotibialis were used by numerous authors for replacements using drilled channels into the tibia and femur, with suture fixation proximally in the extra-articular region.
Others requireed a replacement with a tendon that was still attached to muscles proximally to achieve a dynamic stabilisation effect. The tendons were doubled (Larson 1996) or even quadrupled (Fowler 1993; Rosenberg 1993; Maeda et al. 1996).
The main findings are that free grafts heal with stalked, not diminished grafts. Pendant bone blocks facilitate fixation onto the tibia and femur using the press-fit technique, interference screws or extra-articular suture reinforcement (Kurosaka et al. 1987; Hertel et al. 1996; Boszotta 1997; Nagano and Tilney. 1997). The two bone blocks heal more reliably and faster than pure tendon tissue.

Free autologous grafts, such as the central third of the patellar ligament with pendant bone blocks, such as the hamstring tendons (Mm. semitendineus and gracilis) and the quadriceps tendon, are considered the gold standard of cruciate ligament surgery in humans today (Adam et al. 2001; Drogset et al. 2010).

Dog: If one disregards Nicoletti's (1913) animal studies concerning the substitution of CrCL with fascia, periosteum and tendons in dogs, Carlin (1926) from Sweden was the first to report on CrCL rupture in 2 dogs from a clinical point of view in the “Archiv der wissenschaftlich-praktischen Tierheilkunde” (Archive of Scientific Practical Veterinary Medicine). He described the instability of the stifle joint with respect to the cranial drawer phenomenon, as well as the excessive internal rotation of the lower limb, referring to these as being pathognomonic. Both dogs (10 year-old male, mixed-breed; 1.5 year-old male, Gordon Setter) were euthanised. The stifle joints were filled with blood and the CrCL was torn at the femoral insertion area in each case. Carlin (1926) interpreted this as a justified sing of a (sudden-onset, haemarthrosis, CrCL

rupture in femoral origin) traumatic CrCL rupture. 6 years later, Brook (1932) from England published a further case report on a traumatic CrCL rupture in a 9 year-old Scottish Terrier. The ligament was torn at its tibial insertion. Brook (1932) expanded on the instability findings by Carlin (1926) in reference to “drawer instability”. He was the first to describe that a “cranial displacement of the tibial crest” can indirectly indicate a CrCL rupture on mediolateral-projection X-ray. In his thesis (dissertation), Jarosch (1940) in Vienna was the first to clinically test the loss of stability after transecting different ligaments in side comparison in dogs. He determined that after transecting the CrCL, a “characteristic dorsoplantar sliding movement” was possible in the stifle joint. Schroeder and Schnelle (1941) in the USA defined the clinical diagnostics of the CrCL rupture more precisely through palpation as “the free forward motion of the tibia”. Nilsson (1943 and 1949) in Stockholm was the first to perform meniscectomies in 60 dogs, some of whom had suffered from CrCL ruptures.

2.5. THERAPY

2.5.1. Conservative therapy

Numerous conservative measures such as hyperaemic treatment with rubefacients (Carlin 1926), periarticular punctual thermal cauterisation (Lambert 1979), ‘hyperaemising’ and immobilising bandages (Jarosch 1940; Schroeder and Schnelle 1941; Geyer 1966; Weick 1967), cage rest, weight loss, autologous blood injection, analgesics/anti-inflammatories (Pond and Campbell 1972; Barnes 1977; Heffron and Campbell 1979; Vasseur 1984) and chondro-protective drugs (Vasseur 1984; Comerford et al. 2013) have been utilised to restore function to the instable stifle joint. No success could be achieved in large dogs, whilst a functional improvement was frequently observed in small dogs (Vasseur 1984; Brinker et al. 1997).

2.5.2. Surgical treatment

2.5.2.1. Intra-articular substitution of the CrCL

Nilsson (1943) in Sweden was the first to open dogs' stifle joints following CrCL rupture. In the so-called “cleaning up” technique, he resected the remaining areas of ligament and the cranial horn of the medial and, if necessary, the lateral meniscus. By resecting the remnants of the cruciate ligament and the damaged parts of the medial meniscus, inflammatory reactions are interrupted (autoimmune: Niebauer and Lubec 1980), such that following a CrCL rupture, the progressive stifle joint degeneration reactions (inflammation of the knee/gonarthrosis) are

slowed down to cupped (De Angelis and Lau 1970; Flo 1975; Gambardella et al. 1981; Monnet et al. 1995; Puymann 1996; Puymann and Knechtl 1997; Allgoewer and Richter 1997; Allgower et al. 2000; Sandman and Harari 2001; Frese et al. 2002; Selmi et al. 2002). On the basis of a high number of patients, Paatsama (1952) as well as Geyer (1966) and Weiss (1990) determined that using this method, a functional recovery could only be achieved in up to 50% of cases in large dogs, but in up to 80% of cases in small dogs.

Saki Paatsama (1952) from Helsinki (Finland) must be regarded as the pioneer of CrCL rupture surgery in dogs. As an employee in the Nilsson group in Stockholm (Sweden), he operated on 242 dogs with internal disorders of the stifle joint. Paatsama operated on 43 of these with CrCL rupture. As part of "cleaning up" (ligament stump & partial meniscal resection), he was only able to achieve moderately-acceptable functional end results as the joint remained unstable. Therefore, he was the first to substitute the CrCL with a strip of fascia lata, like Grekow (1911) (Hesse, 1914) from St Petersburg (Russia) and Giertz (1913) (Lobenhoffer and Tscherne 1993) from Umeå (Sweden), in a procedure that Hey-Groves (1919) from Bristol (England) had utilised in humans. He guided the fascia strip (imitating the anatomical course of the ligament) dorsolateral-distally through a tunnel in the lateral femoral condyle → in/through the joint, through a tunnel in the medial tibial condyle, fixing it with a suture onto the patellar ligament (Lig. patellae).
Disregarding the *fascia lata et genu* as in humans (Zur Verth 1933; Jones 1963), different autologous tissues with a close anatomical connection to the stifle joint were utilised to reconstruct the CrCL in dogs, such as the middle distal pediculated third of the patellar ligament with an attached bony wedge from the patella (Strande 1964; Dueland 1966; Denny and Barr 1984) free transplant from the middle third of the patellar ligament with an attached bony wedge from the tibial tuberosity (Tubersositas tibiae) and the patella (Lakatos and Spoerry 1974); the medial third of the patellar ligament with a wedge from the medial side of the patella (Arnoczky et al. 1979). The transplants were pulled through the joint, through a tunnel in the femoral condyle, or through a tunnel in the tibia and femur or "over the top" (Arnoczky) and fixated with sutures. Good/very good functional results were achieved with these techniques in up to 95% considering the sum of all patients and dogs from animal studies (Strande 1966; Dueland1966; Lakatos and Spoerry 1974; Alm and Stromberg 1974; Chiroff 1975; Arnoczky et al. 1979; Arnoczky et al. 1982; Denny and Barr 1984).

The "over-the-top" technique with a lateral strip of fascia obtained from the parapatellar region with inclusion of the lateral third of the patellar ligament (Brunnberg et al. 1985; Schnell 1986; Brunnberg et al. 1992; Timmermann et al. 1996) or with inclusion of tendinous strips from the insertion of the semitendinous (M. semitendinosus), gracilis (M. gracilis) as well as the medial

fascia of the tibialis cranialis muscle (M. tibialis cranialis), twisting of the strip and guiding it through a tunnel medial in the tibial condyle and through the joint (Lopez et al. 2003) are modifications, whereby good functional results can be expected, (79- 86% of cases) but only very delayed (approx. 13 months post-operative) (Comerford et al. 2011).

The clinically and experimentally-validated method (Leonard 1961; Rex 1963; Paatsama 1963; Vaughan 1963; Loeffler 1964; O'Donoghue et al. 1966; Dietz and Schmidt 1968; Salomon et al. 1970; Mc Curnin et al. 1971; Punzet and Walde 1974; Dietz et al. 1980) included numerous modifications (Brass 1955). In the fixation of the strip (Singelton 1957), through translocation of the tunnel in the femoral condyle (Yucel 1971), dispensing with the tunnels in the femur and tibia (Dickinson and Nunamaker 1977; Pichler et al. 1982), twisting of the strip into a cord (Hickman and Walker 1964; Whittick 1974), guiding the twisted strip only through a tunnel in the medial tibial condyle (Schawalder and Sterchi 1981a; Schawalder and Sterchi 1981b), guiding the strip from distomedial to dorsolateral to the fabella (Os sesamoideum musculi gastrocnemii) (Piermattei and Moore 1981; Eld and Long 1983; Chaudieu 1985) and reinforcing the strip with a lateral third of the patellar ligament (Hulse et al. 1980; Brinker et al. 1983; Shires et al. 1984; Denny and Barr 1984; Butler et al. 1985; Brunnberg et al. 1985; Hulse and Shires 1985; Schnell 1986) yielded improved to good/very good functional results in 70-90% across all of the studies. The results were poor in 10% of cases. Interestingly, the modifications to the original technique by Paatsama (1963) did not statistically influence the end result.

Paatsama (1952) was the first to substitute a ruptured CrCL in a dog with the end tendon of the semitendinous or gracilis muscle. Others used either the available pediculated tendon of the fibularis longus muscle (M. fibularis longus) (Rathor 1960) or flexor digitalis longus muscle (M. flexor digitalis longus) (Strande 1964) or transposed the tendon of origin of the extensor digitalis longus muscle (M. extensor digitalis longus) (Hohn and Miller 1967; Roush et al. 1970; Frost 1973; Lewis 1974). Across all of the studies, good/very good functional results were achieved in up to 68% of cases, with less favourable results in up to 32% of cases, if the respective tendon was used as the implant. Transposing the tendon produced good/very good results in only 30% of cases. Chauvet et al. (1996), however, demonstrated significantly inferior clinical, radiographic and gait-analysis results from the conservative approaches compared to those approaches which involved stabilisation with sutures. This was also shown in small breed dogs.

2.5.2.2. Extra-articular stabilisation methods

Especially in the USA, numerous surgeons were fervently opposed to Paatsama's method and preferred extra-articular stabilisation methods following CrCL rupture.
Childers (1966) was the first to plicate the *fascia genu et lata* laterally and in the parapatellar region on a closed joint using catgut Chrome® sutures. Thus, the joint was stabilised and the tibia externally-rotated. Numerous modifications for this method have been described. As a first, lateral mono-layered and medial multi-layered fascial plication with non-absorbable material (Pearson 1969; Pearson 1971; Mc Curnin et al. 1971; Mc Curnin and Sceli 1975; Beckmann et al. 1992; Olmstead 1993; Vasseur 1993; Korvick et al. 1994; Olmstead 2000). Second, lateral capsulorrhaphy and fascial plication (retinaculum) with a ligature of non-absorbable material (De Angelis and Lau 1970. Third, is fixing the caudal to the lateral fabella and into the patellar ligament (Lig. Patellae) with wire. Another possibility is the lateral multi-layered plication suture; (Dietrich 1974) or the lateral and medial single non-absorbable suture fixated in drilled tunnels into the tibial tuberosity (Tuberositas tibiae) (Flo 1975; Kasa and Kasa 1980; Henschel et al. 1981; Dulisch 1981a; Dulisch 1981b; Richter et al. 1997; Allgoewer et al. 2000) lateral capsulorrhaphy and retinacular plication (Mc Curnin and Sceli 1975); lateral retinacular plication including the patellar ligament and lateral collateral ligament (Lig. Collaterale laterale) (LCL) (Gambardella et al. 1981); and caudomedial and lateral retinacular plication with transposition of the caudal part of the sartorius muscle (Pars caudalis – M. sartorius) (Hohn and Newton 1975). Knecht et al. (1977) amplified the lateral suture's effect of plication with a distally-pediculated fascia strip, which was guided under the LCL and tendon of the lateral head of the gastrocnemius muscle (Caput laterale – M. gastrocnemius), or through a subperiosteal tunnel (Pichler et al. 1982) and then sutured back onto itself. The purpose of the resulting capsular/fascial fibrosis was to provide secondary reinforcement to the primary stabilisation (Singleton 1969; Mc Curnin et al. 1971; Fox and Baine 1986; Aiken et al. 1992; Olmstead 1993; Brinker et al. 1997; Olmstead 2000; Stoerk et al. 2001). According to Leighton (1999), the lateral suture stabilisation from Flo (1975) modified retinacular imbrication technique is still today the most common extra-articular technique. Across all the dogs from all studies treated with this technique, a very good/good functional result was achieved in 60% of cases. The capsulorrhaphy/fascial plication (Meutstege 1980) was especially found to be superior, with 93% of cases recovering to become no longer lame (Allgoewer et al. 2000), ahead of the De Angelis and Lau (1970) technique, with an 83.8% lame-free rate. Permanent joint stability by means of capsular fibrosis could only be achieved in approx. 20% of patients. The method correlates with different rates of development of progressive osteoarthrosis (OA) (Alt 2000).

Smith and Torg (1985) transposed the fibular head, in order to translocate the LCL craniolaterally to neutralise both the cranial drawer phenomenon and internal rotation of the tibia. They reported a good/very good functional recovery rate of 90%. According to Weiss (1990), Dupius et al. (1991 and 1994) as well as Chauvet et al. (1996), the biomechanics of the stifle joint were heavily impaired, resulting in an insufficient LCL and a rapid progression of osteoarthritis (OA). The functional results are comparable to those treated with conservative therapy: as early as 4 weeks post-operatively the rate of ipsilateral meniscal lesions increases by 25%. After 10 months, there is an increase of 50%.

For retinaculoraphy, capsulo-fascial implantation, curbing of the cranial dislocation and excessive internal rotation of the tibia following CrCL rupture, not only were various surgical techniques used, but also various different (suture) materials were employed. The physical and biomechanical properties of these materials should be as similar as possible to those of the CrCL, or at most two-fold the property parameters, (Bruchmann et al. 1987) and should not be susceptible to infection (Capron and Roe 1996).

With the exception of Childers (1996), who used absorbable chromium catgut, materials used today are, almost without exception: non-absorbable mono- or polyfilament (coated/uncoated) materials, such as nylon, polypropylene, polyester, caprolactam and orthopaedic wire, or titanium wire (De Angelis and Lau 1970; Dulisch 1981a; Dulisch 1981b; Olmstead 1993; Korvick et al. 1994; Capron and Roe 1996; Frese et al. 2002). Capsulo-fascial impregnation is only performed with absorbable sutures (Ertelt 2003). A disadvantage is a relatively high infection rate, which Korvick et al. (1994) reporting only 1%, and others rates from 18%-21% (Dulisch 1981a; Dulisch 1981b); or 58.8% (De Angelis and Lau 1970). Poly-filamentous materials proved to be more susceptible to infection (Lovell 1945; Everett 1970) than monofilaments (Budsberg et al. 1988; Capron and Roe 1996). However, monofilament materials are more likely to break. This is especially true for wire. This was already found to be broken after 6 weeks in 78.8% of dogs (Stoerk et al. 2001).

The functional success of extra-articular suture stabilisation depends significantly on isometric positioning, as Roe et al. (2008) and Fischer et al. (2010) first determined. They experimentally determined the isometric points lateral to the stifle joint in two dimensions. On the femur, the point is positioned immediately distal to the lateral fabella, directly cranial to the caudal margin of the femur. On the tibia, the point is located caudal to the margin of the extensor groove (Sulcus extensorius) directly distal to the osseous delimitation of the joint. If the ligatures are anchored at these points with a stifle joint angle of 100°, good/very good functional results can be achieved, similarly to the *in vogue* dynamic osteotomy techniques (Lazar et al. 2005; Casale and McCarthy 2009; Snow et al. 2010; Au et al. 2010; Cook et al. 2010; Boeddeker et al. 2012;

Christopher et al. 2013). If the isometric points are missed, the risk of arthrosis is increased 5.78-fold (Lazar et al. 2005).

2.5.2.3. Alloplastic CrCL replacements

In veterinary medicine, the CrCL was replaced early on with alloplastic materials due to the long duration for remodelling and good incorporation of the autografts/allografts. The physical properties were favourable for achieving immediate mobilisation (load bearing) of the primary stabilised joint without further immobilising measures. Westhues (1956) from Munich, Germany was the first to substitute the ruptured CrCL in clinical cases (dogs) with a polyamide fibre bundle (Supramid®). The rationale was to comparably reconstruct the normal elasticity of the CrCL with a substitute ligament and suitable fixation (Westhues1961; Geyer 1966; Westhues 1969). Numerous alloplastic materials like polyamides (Perlon®, Nylon®), polyethylene terephthalate (Terylen®, Dacron®, Dacrofil®), polytetrafluoroethylene (Teflon®), sucrose and glycerine (Lafil®), carbon fibres (Flexfil®, Ti-Cron®, Tevdek®, Polydek®) were utilised for this purpose by numerous surgeons. If the quantity of material is disregarded, the methods particularly differ in their fixation in drilled tunnels into the femur and tibia (Johnson 1960; Omrod 1963; Denny and Goodship 1980; Bejui et al. 1982). Clinical case summaries including nearly 1000 patients document a high biocompatibility, independentle of the material (Vaughan 1963; Rex 1963; Singleton 1963; Lampadius 1964; Loeffler 1964; Butler 1964; Zahm 1966; Cameron et al. 1968; Gupta and Brinker 1969; Singleton 1969; Salomon et al. 1970; Kuepper 1971; Pond and Campbell 1972; Saidi et al. 1976; Vaughan and Edwards 1978; Vaughan 1979; Hinko 1981). Depending on the author, good/very good functional success rates of 62-91% have been reported without a correlation being found with the material used. Treatment failures, in order of frequency, were due to implant breakage, before cranial loosening and in very rare cases, infection (<2%). If the CrCL replacement material was passed through drill channels in the femur, tibia and/or tibial tuberosity, an osteolytic widening of the drill channels could be detected at an early stage in about 70% of patients (Stoerk et al. 2001).

2.5.2.4. Allogenic CrCL transplants in dogs

Allogeneic transplants as a CrCL substitute in dogs have barely seen any increase in their significance. Initially, Lampadius (1964) used tendons of the tail musculature from recently euthanised dogs in animal studies. Matis (1973) used lyophilised human dura mater. Jaeger and Wirth (1978) used dura mater to augment a synthetic ligament. Brunnberg (1987) from Munich, Germany, was the first to utilise fresh end tendons of the flexor digitalis profundus

muscle (M. flexor digitalis profundus) from slaughtered beef cattle. The materials were processed in a specific way before implantation. The results were soberingly poor as the materials ruptured or the joint was destroyed due to the formation of radicals (Brunnberg 1987).

2.5.2.5. Dynamic osteotomy techniques: CTWO, TPLO TTA, TTO, MMP

Based on Henderson's and Milton's (1978 and 1980) drilling findings “that the angle formed between the tibial plateau and the tibial longitudinal axis produces the Cranial Tibial Thrust (CTT)”, Barclay Slocum and Theresa Divine (1983) from the USA were the first to introduce a radical innovative therapy concept for CrCL ruptures in dogs. “Cranial tibial wedge osteotomy (CTWO): A technique for eliminating cranial tibial thrust in cranial cruciate ligament repair without replacing the cruciate ligament. In this technique, the tibial plateau angle is reduced to 5-6.5° through a tibia wedge osteotomy in the proximal third of the tibia, enabling a muscular compensation of the cranial drawer movement during load bearing. At the 6-week post-operative follow-up, approx. 53% of the operated joints had very good functional results: 79% had no drawer instability, and 100% had no (progression) of osteoarthrosis (OA). At the 12-week post-operative follow-up, 78% had very good functional results without a drawer instability and the same OA findings. Oxley et al. (2013) modified the CTWO technique, but ultimately came to the same clinical and radiological results. The healing process was accompanied by severe complications in up to 9.5% of cases, whilst 90-97% of cases achieved a good functional end result.

Just 10 years later, Slocum and Slocum (1993) optimised the 1983 osteotomy in the form of a proximal radial tibial osteotomy so that the proximal tibial segment can be rotated on the wedge-shaped osteotomy surface until it is perpendicular to the limb’s functional axis with respect to the tibial plateau levelling osteotomy (TPLO). In order to plan and perform TPLO correctly, the tibial plateau angle (TPA) must first be precisely measured (Headrick et al. 2007; Boudrieau 2009). Interindividual and intraindividual variability in measurements (Caylor et al. 2001; Fettig et al. 2003; Reif et al. 2004; Headrick et al. 2007; Hurley et al. 2007; Ritter et al. 2007; Schmerbach et al. 2007) can be observed, as well as tibial deformities (Lambert and Wendelburg 2010), which can complicate measurements. At the 90th day of life, the Tibia Plateau Angle (TPA) can be determined precisely. Determining TPA on the basis of analogue X-ray is somewhat complicated, but is certainly possible and accurate (Grierson et al. 2005). However, it is easier to measure the TPA using digital radiographs and computer software (Serwa et al. 2009; Unis et al. 2010a; Unis et al. 2010b). The results are compatible with those as seen in conventionally measured of the TPA according to Serwa et al. (2009), whilst Baroni et al. (2003) and Lister et al. (2008) found significant discrepancies (Lazar et al. 2005 ; Boyd et al. 2007 ; Au et al. 2010). Nowadays it is considered the most common surgical technique

for treatment of CrCL rupture in dogs. Healing results can be achieved in approx. 90% of cases (Leighton 1999; Rayward et al. 2004; Imholt et al. 2011; Nelson et al. 2013; Berger 2014).
The Tibial Tuberosity Advancement (TTA) of Montavon et al. (2002) is ultimately based on studies by Maquet (1976) in human medicine to decrease progrssing, painful, cartilage damaging and OA inducing retropatellar pressure. Maquet (1976) displaced the tibial tuberosity cranially as an “Advancement of the tibial tuberosity” (ATT). The tibial crest is then elevated and kept free by using a 2-3 cm thick piece of pelvic bone placed as proximal as possible, directly under the anterior tuberosity” (Maquet, 1976). Maquet’s ATT neutralises “knee joint flexion/extension shear forces, axial loading, translational knee joint instability, retropatellar pressure, femoratibial contact forces, patellar tendon forces, and cruciate ligament forces (loading of the anterior and posterior cruciate ligaments)” (Nisell 1985; Nisell et al. 1986, Nisell et al. 1989; Li et al. 1998; Griffin et al. 2006; Shirazi- Adl and Mesfar 2007). For the dog, these biomechanical backgrounds of TTA have been investigated in numerous in vivo/ ex vivo (Tepic et al. 2002; Kim et al. 2008; Hoffmann et al. 2011) as well as in vivo/ clinical studies (Montavon et al. 2002; Hoffmann et al. 2006; Dennler et al. 2006; Schwandt et al. 2006; Lafaver et al. 2007; Stein and Schmoekel 2008; Kim et al. 2009a; Kim et al. 2009b; Moeller et al. 2010; Hoepfl 2011; Guerrero et al. 2011; Boudrieau 2011; Boettcher et al. 2013; Skinner et al. 2013; Millet et al. 2013; Beer et al. 2018; Schwede 2019). In the Triple Tibial Osteotomy (TTO), Bruce et al. (2007) CTWO was combined with TTA. In the form of the Modified Maquet Preocedure (MMP), Maquet’s ATT (1976) was adopted to the canine knee by Etchepareborde et al. 2010a; Etchepareborde et al. 2010b) and the results substantiated in kinetic studies (Ness 2016; Ramirez et al. 2015; Eberle et al. 2017).
As one can glean from the history of CrCL rupture and its therapy in the dog, approx. 140 surgical techniques or modifications thereof could be found in the literature. A literature search in PubMed concerning CrCL disorders in dogs yielded 602 original articles, accounting only for the years 1963-2021.

All of these works reveal that:
- In up to 60% of cases, conservative therapy with cage rest, walking on a leash, physiotherapy, and NSAIDs can lead to satisfactory/good functional results in dogs <15kg. Secondary meniscal damage can be expected as a complication (Carlin 1926; Geyer 1966; Weick 1967; Vasseur 1984; and many more).
- In up to 81% of cases, intracapsular stabilisation (ICS) with autologous or synthetic material leads to good/satisfactory functional results (Paatsama 1952; Piermattei and Moore 1981; Brunnberg et al. 1985; Conzemius et al. 2005; Uv.a.m).
- In 92% of cases, extracapsular stabilisation with (1) joint capsule imbrication and (2) extracapsular suture techniques leads to good functional results with a complication rate of

16%. Of these, 8% are severe complications (Childers 1966; Flo 1975; Allgoewer et al. 2000; Conzemius et al. 2005; and many more).

- One can expect good/satisfactory functional results in 87% of cases treated with intra-articular stabilisation with autologous or exogenous material (Westhues 1969; Schawalder and Sterchi 1981a; Schawalder and Sterchi 1981b; Arnoczky et al.1982; Schawalder and Gitterle 1989).

Osteotomy:

- In 90% of cases, tibia-plateau-levelling osteotomy (TPLO) leads to good/very good functional results with a complication rate of 18-28%. Of these, 5-9% are severe complications (McCarthy 2007a; McCarthy 2007b; Boudrieau 2009).
- In 80% of cases, tibial tuberosity advancement (TTA) leads to good functional results with a complication rate of 18-59%. Of these, 10% are severe complications (Lafaver et al. 2007; Boudrieau 2009).

2.5.2.6. Synopsis

According to Conzemius et al. (2005), TPLO vs. TTA exhibit comparable success and complication rates.

In a force-plate comparative analysis comparing intracapsular stabilisation (ICS) vs. extracapsular stabilisation (ECS) vs. tibial-plateau-levelling osteotomy (TPLO), TPLO and ECS were superior to ICS, whilst ECS and TPLO were equivalent (Conzemius et al. 2005).

Cook et al. (2010) reported that the TPLO and TightRope® CrCL techniques are equivalent in the functional end result, and both are superior to tibial tuberosity advancement (TTA).

According to Krotscheck et al. (2016), the function in dogs when trotting following TPLO is better than following TTA and ECSS (extracapsular suture stabilisation). Only with TPLO could good functional results be achieved in 100% of cases. The results from TTA are equivalent to those obtained using ECSS.

TPLO is markedly superior to TTA (Beer et al. 2018). In comparison between TPLO vs. capsular fascial imbrication (CFI), no significant differences were observed with regards to the end result (Boeddeker et al. 2012).

To summarise, the sensitivity of the cranial-drawer and tibial-compression tests in the awake dog is low, whilst it is significantly high in the sleeping dog. These palpation findings, together with X-ray findings, have excellent sensitivity, specificity, positive-predictive value and negative-predictive value (Carobbi and Ness 2009).

Independently of the surgical techniques, good functional results can be achieved in up to 90% of cases with a surgical intervention for CrCL rupture in dogs (Moore and Read 1995). The functional convalescence is shorter following osteotomy as compared to following ICS or ECSS. Progression of osteoarthrosis is markedly slower and less pronounced following use of osteotomy techniques. The osteotomy methods exhibit a markedly higher complication rate for severe complications, and are associated with significantly higher costs (Pacchiana et al. 2003; Stauffer et al. 2006). According to Evans (2006), this is 6-times more benefit to be derived by means of ECSS than potential harm, whilst this benefit-harm ratio amounts to only 3-times for the TPLO.

2.6. BIOMECHANICS OF THE CAPSULO-LIGAMENTOUS APPARATUS IN THE STIFLE JOINT OF DOGS

2.6.1. Osseous stabilisation

Osseous stabilisation of the stifle joint is incomplete. Considered from a technical standpoint, both the cylindrical femoral condyles with their cranial, groove-shaped patellar surface (Facies patellaris) and the ventrally-adjoining intercondylar fossa (Fossa intercondylaris) correspond to a segment of a pulley. The intercondylar eminence (Eminentia intercondylaris) of the tibia protrudes into the groove of this pulley and into its conceived extension in the form of the crest-like boarders of the patellar articular surface. By this mechanism, a lateral deviation of the convex femoral condyles on the relatively shallow-grooved tibial articular surfaces is largely prevented when we consider the osseous components (Evans 1993).

If the tibial intercondylar eminence (Eminentia intercondylaris tibiae) formed a longitudinal ridge between the tibial articular surfaces, only flexion/extension movements of the stifle joint would be possible. Since the eminence only protrudes conically into the centre of the proximal articular surface of the tibia (Facies articularis proximalis tibiae), the ability to rotate the joint is preserved (Evans 1993).

In profile, the cartilaginous surfaces of the medial and lateral femoral condyle resemble spirals of different sizes, which twist in the caudal direction. As such, there is no uniform axis of curvature. The centres of curvature fall on the evolute, which is tangential to the radius of curvature (Lanz and Wachsmuth 1972; Vollmerhaus et al. 1994a; Vollmerhaus et al. 1994b). The medial and lateral articular surfaces of the tibia also exhibit different curvatures. Whilst the medial articular surface is bi-concave, the lateral articular surface is concave in the frontal view

and convex in the sagittal plane. Complying with the curvature proportions of the medial and lateral joint members, the joint movements are different for both joint components (Vasseur and Arnoczky 1981).

The flexion/extension movement of the stifle joint is a rolling-gliding movement. In the first phases of stifle flexion, the rolling movement predominates; with progressing flexion, the gliding movement becomes more predominant. The joint position, in which the predominant rolling movement is replaced by a gliding movement, is different on the medial and lateral side, i.e. the initially increased lateral rolling movement is markedly extended compared to the medial side (Vasseur and Arnoczky 1981).

2.6.2. Ligamentous stabilisation

2.6.2.1. The crossing four-bar linkage joint system

The connection of both joint members via the cruciate and collateral ligaments determines a guided joint movement. This does not involve a centred hinge movement. Knese (1949) compared this movement with a gear mechanism that has a wandering pivot axis. The variable pivot axis can be recorded as a herpolhode or polhode, depending on which joint part is in motion. The construction of these centrodes is only possible as a model if the stifle joint is classified as a mechanical system: a so-called crossing, closed, even, kinematic four-bar linkage. This classification is permitted if one assumes that the cruciate ligaments (which form the four-bar linkage together with the femur and tibia) are at full length in every phase of motion of the joint. The collateral ligaments then make the spatially restricted movement of the stifle joint possible in one plane. The location of the pivot point of the stifle joint in different joint positions then corresponds to the respective crossing points of the cruciate ligaments, and the recording of the different crossing points corresponds to the centrodes. Menschik (1974a and 1974b), an Austrian veterinarian, was the first to decipher this extremely complex movement sequence in the stifle joint of the horse. Although the understanding of the stifle joint movements in human/veterinary medicine is still based on his work to this day, he is rarely cited by his veterinarian colleagues.

2.6.2.2. The main ligaments of the stifle joint

The main ligaments of the stifle joint consists of two collateral ligaments and two cruciate ligaments. These ligaments control the joint movement in the three spatial planes. Due to the different spatial arrangements of the ligaments and the incongruence of the joint members,

different tension relationships result for each of the four main ligaments in the motion sequence. According to the literature, the tension behaviours of the individual ligaments in dogs is an area which still requires clarification (Jaegger et al. 2002; Allen et al. 2009).

The cranial margin of the medial collateral ligament (Lig. collaterale mediale) is under tension with increasing flexion, whilst the caudal margin is placed under tension with increasing extension. The middle segment is under tension in full extension and in medium flexion. Valgus stress and external rotation both increase the tension across the ligament's middle section in a moderately flexed stifle joint (Korvick et al. 1994).
Varus stress and internal rotation do not alter the tension pattern.
The lateral collateral ligament (Lig. collaterale laterale) is under tension in hyperextension and is under progressively reduced tension with proportionally increased flexion. Varus stress and internal rotation first result in a loss of tension in the LCL with increasing flexion. With valgus stress and external rotation, tension is reduced first during early flexion, but with progressing flexion the tension increases once again (Korvick et al. 1994; Pozzi and Kim 2018) .

2.6.3. Cranial cruciate ligament

The CrCL consists functionally of craniomedial and caudolateral fibre bundles. The craniomedial bundle is under tension in all phases of movement, whilst the caudolateral bundle is only under tension in extension, and relaxed in flexion. Varus stress and internal rotation increase the tension during progressive flexion. Valgus stress and external rotation decrease the tension on the ligament (Arnoczky and Marshall 1977).

The weaker caudal functional fibre bundle of the caudal cruciate ligament (CaCL) is under tension at 180° extension and relaxed at 90°. By comparison, the sturdier cranial fibre bundle is relaxed at 180° extension, and under tension at 90° flexion (Arnoczky and Marshall 1977).

2.6.4. Muscular guidance of the stifle joint

The quadriceps (rectus femoris, vastus lateralis, vastus medialis, vastus intermedius) is the main extensor of the stifle joint. It is somewhat supported by the tensor fascial latae muscle, which flexes the hip joint to a small extent (Solomonow et al. 1987; Pozzi and Kim 2018).
The two-headed caudolateral biceps femoris muscle acts as an extensor with the pars cranialis, which inserts on the fascia lata on the patella and patellar tendon. Its pars caudalis,

which extends to the tibial tuberosity and further with the tractus calcaneus lateralis to the heel bone, flexes the knee and stretches the ankle joint (Miyatsu et al. 1993).
The semitendinosus muscle at the margo cranialis tibiae inserts medially. It bends the knee and stretches the hip joint.
The semimembranosus muscle inserts medially at the condyles of femur and tibia. In the leg-supporting phase, the hip joint and stifle joint are stretched; and in the leg-slope phase, the limb is rotated (guided) inwards and backwards (Evans 1993).
The sartorius muscle draws medially with its pars cranialis and caudalis, merges with the fascia genus and that of the lower leg and insert at the cranial margin of the tibia. It fixs the hip, extends the stifle joint and leads the limb forward as well as inwards (Evans 1993).

The gracilis muscle originates from the pelvic symphysis and, like the sartorius muscle, connects with the fascia cruris. It extends the stifle joint, adducts the limb and pronates the lower leg (Evans 1993).
The popliteus muscle lies caudally on the stifle joint capsule. It originates from the popliteal fossa of the lateral condyle of femur and moves caudomedially to the tibia. It bends the stifle joint and pronates the lower leg (Evans 1993).
The gastrocnemius muscle with its lateral or medial head originates caudodistally from the femur and inserts with its end tendon of the Achilles tendon on the calcanean tubercle. It flexes the stifle joint and extends the ankle joint (Evans 1993).
The extensor digitorum longus muscle origines from the Fossa extensoria of the lateral condyle of femur and inserts at the processus extensorius of the phalanx distalis. It is primarily a toe extensor, but also extends the stifle joint (Evans 1993).
The flexor digitorum superficialis muscle originates from the lateral supracondylar tuberosity of femur between the two gastrocnemius heads and is inserted on the plantar surface at the middle phalanx. At the calcaneal tubercle, the widened tendon forms the calcaneal cap. It is an auxiliary flexor of the stifle joint and superficial toe flexor (Evans 1993).

3. MATERIALS AND METHODS

3.1. CRUCIATE LIGAMENT HARVEST AND STORAGE

A total of 56 stifle joint samples were gathered from 28 canine patients that died or were euthanised for reasons unrelated to this study at the “Klinik fuer kleine Haustiere, Fachbereich Veterinaermedizin der Freie Universitaet Berlin” (Berlin, Germany) and whose patient owners consented to participation in this study. (Fig. 2, see appendix). The patients’ medical records had to meet the following inclusion criteria:

1. Age of two years or older
2. No history of diseases that could affect the musculoskeletal apparatus
3. No tumours or infectious diseases affecting the hind limbs
4. No inflammation or arthritis affecting the hind limbs
5. No vascular pathology affecting the hind limbs

If patients met all the above criteria, bilateral stifle joint samples were obtained by amputating the distal half of both the femur and the tibia within 24 hours of time of death. Breed, age, weight and date of harvest were recorded (see Tab. 3). In addition to checking clinical records, all samples were tested for cruciate ligament rupture by means of a cranial drawer test and further examined through radiological and computer tomographic imaging according to the standards set by Waibl et al. (2005). Samples that showed pathological changes of skeletal or soft tissue structures were excluded from the study.

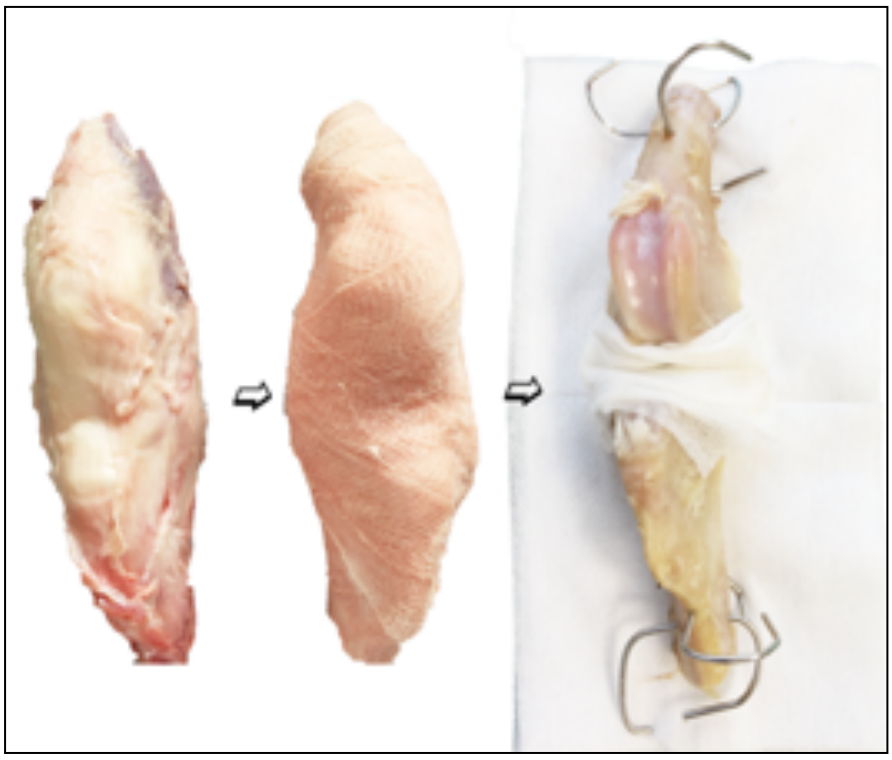
The soft tissue surrounding the femur and tibia was stripped from samples included in this study, whilst the joint capsule and muscle insertions in close proximity to the cranial cruciate ligament were preserved in situ. The samples were wrapped in an elastic cotton bandage (NOBAMED Paul Danz AG, Wetter/Ruhr, Germany), soaked in normal saline (0.9% sodium chloride solution, B. Braun, Melsungen, Germany) and frozen at -20°C. Samples were defrosted at 4°C for 24 hours prior to biomechanical testing. Soft tissues surrounding the stifle joint were removed one hour prior to testing, after which the normal saline-soaked bandage was reapplied and only removed for the test. Samples were tested at room temperature (18°C).

Table 3. 28 canine cranial cruciate ligament samples were obtained from euthanised, dogs in good musculoskeletal health.

	Breeds	**Age (years)**	**Weight (kg)**	**Date of harvest**
1	Crossbreed	8	34	25.02.2015
2	Crossbreed	14	25	27.02.2015
3	Crossbreed	8	13	27.02.2015
4	Boxer	11	39	01.03.2015
5	German shepherd	10	36	03.03.2015
6	German shepherd	2	23	07.03.2015
7	Airedale Terrier	10	23	07.03.2015
8	Crossbreed	14	12	08.03.2015
9	Bernese Mountain Dog	7	34	11.03.2015
10	Flanders Cattle Dog	6	36	11.03.2015
11	Crossbreed	11	15	21.03.2015
12	French Bulldog	5	10	19.04.2015
13	Bernese Mountain Dog	8	40	21.04.2015
14	Labrador	13	27	21.04.2015
15	Rottweiler	10	30	17.11.2015
16	Rhodesian Ridgeback	10	49	18.11.2015
17	Golden Retriever	12	32	20.11.2015
18	Crossbreed	8	27	21.11.2015
19	German shepherd	12	25	11.12.2015
20	German shepherd	14	38	20.12.2015
21	Crossbreed	10	26	20.12.2015
22	Great Dane	10	35	31.01.2016
23	Old English Bulldog	2.5	19	31.01.2016
24	Doberman	12	35	09.03.2016
25	Crossbreed	15	35	16.03.2016
26	Longhair Dachshund	12	19	23.03.2016
27	English Bulldog	7	30	29.05.2016
28	Labrador	12	40	31.01.2016

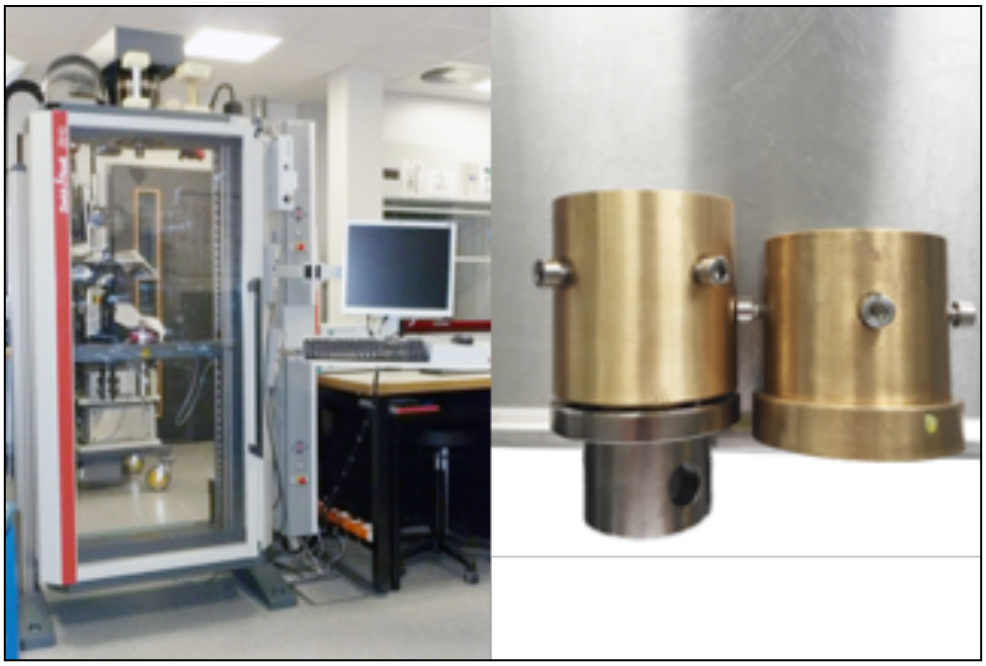
3.2. PREPARATION OF THE CANINE CrCL

The cranial cruciate ligament breakage test was performed with a Zwick/Roell 1455 machine (Zwick/Roell GmbH & Co KG, Ulm, Germany). Samples were fixed into custom containers using a two-component methyl-methacrylate-based adhesive (Technovit, Kulzer Technik GmbH, Wehrheim, Germany) and 0.8mm diameter Kirschner wires (Königsee Implantate, Allendorf, Germany). The wires were inserted through transverse pinholes, distanced 6 cm from the stifle joint and drilled at 90° angles (Fig. 3). After placing the femur into the centre of a container ensuring correct positioning by means of laser beams, the adhesive was applied and allowed to set for 30 minutes. The same method was used to place the tibia into the opposing container (Fig. 4). Once the samples were potted, the containers were placed into the test machine (Fig. 5).



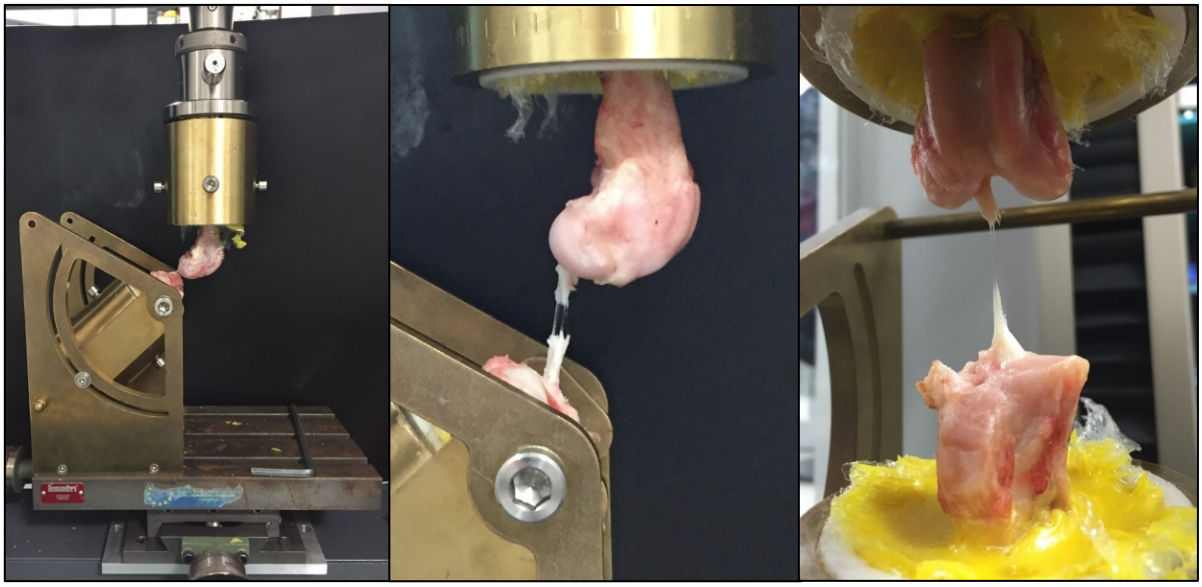
A B C

Figure 3. (A) Stifle joint harvested from a 10-year-old German Shepherd, after stripping of the soft tissue from femur and tibia. (B) Bandaged and saline-soaked sample prepared for -20°C storage. (C) Defrosted sample after removal of the stifle joint soft tissue and insertion of the pins.



A B

Figure 3. (A) Zwick/Roell 1455 test machine and (B) custom fixation containers.



A B C

Figure 5. Lateral view of a stifle sample before (A) and after (B) the biomechanical test at 140° median flexion and extension. Frontal view of the same sample after the test (C).

The samples included in this study were divided into five test groups, which were tested at different flexion and extension angles. The first group consisted of bilateral stifle joint samples obtained from four large dogs (>25 kg), four medium dogs (16-25 kg) and four small dogs (10-15 kg), which were tested at 120° median flexion and extension angles, or 60° flexion. The second group included bilateral stifle joint samples obtained from four large breed dogs, which were tested at 60° median flexion and extension angles, or 120° of flexion. The third group consisted of bilateral stifle joint samples obtained from four large dogs and was tested at 90° median flexion and extension angles, or 90° flexion. The fourth group included bilateral samples obtained from four large dogs and tested at 140° median flexion and extension angles, or 40° flexion. The fifth group consisted of bilateral samples from four large breed dogs and was tested at 160° median flexion and extension angles, or 20° flexion (Tab. 4).

Table 4. Number of samples, as well as mean age (years) and mean weight (kg) of the specimens from which the samples were obtained from small, medium and large dog breeds. Samples were divided into five groups tested at different angles.

	Size	**Number**	**Mean age**	**Mean weight**
Group 1 (120°)	Large (>25 kg)	8	11	34
	Medium (16-25 kg)	8	6.62	21
	Small (10-15 kg)	8	9.5	12.5
Group 2 (60°)	Large (>25 kg)	8	11.2	32.5
Group 3 (90°)	Large (>25 kg)	8	10	32.5
Group 4 (140°)	Large (>25 kg)	8	9.7	36.75
Group 5 (160°)	Large (>25 kg)	8	9.75	34.5

Before setting up the CrCL samples in the test containers, length, as well as width (medio-lateral) and depth (cranio-caudal) were measured. Width and depth were measured at midway length as well as the tibial and the femoral end of the ligament.

3.3. BIOMECHANICAL TESTING OF CANINE CrCL

The biomechanical tests were performed at the Julius Wolff Institute for Biomechanics and Musculoskeletal Regeneration of the Charité Medical University (Berlin, Germany). Biomechanical testing of the CrCL included breaking strength and elongation testing, through elongation of the ligament when naturally attached to femur and tibia. Breaking strength was measured as standard force (N) absorbed before breaking, whilst elongation was measured as maximum length (mm) before breaking (Fig. 6). The native CrCL samples were tested at a loading rate of 0.1 kN/s at 3000-4000 N with 10 mm/min test velocity.

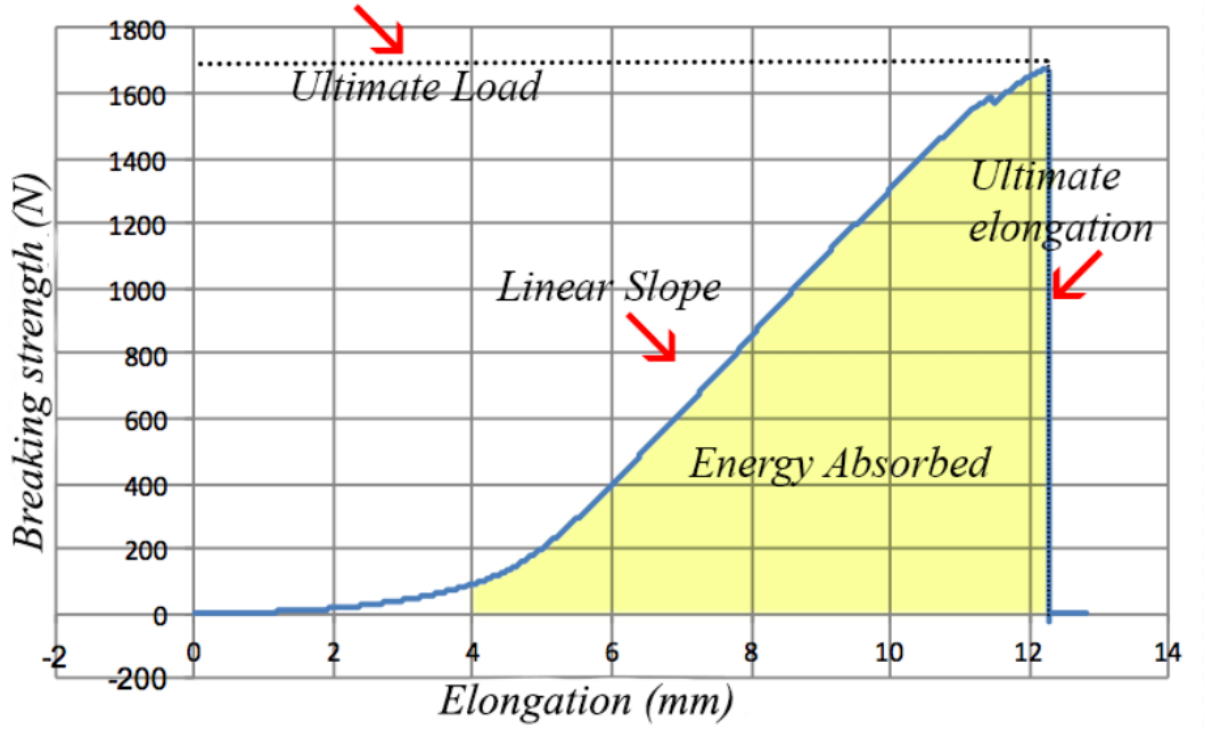


Figure 6. Example of breaking strength-elongation curve

A normal breaking strength curve for the bone-ligament-bone samples tested is shown in Fig. 7. Three phases were observed: an initial phase, during which elongation slowly proceeds with continuous increase of force; an elongation phase, during which elongation proceeds more rapidly; and a rupture phase, during which elongation stops abruptly after multiple partial ruptures have occurred.

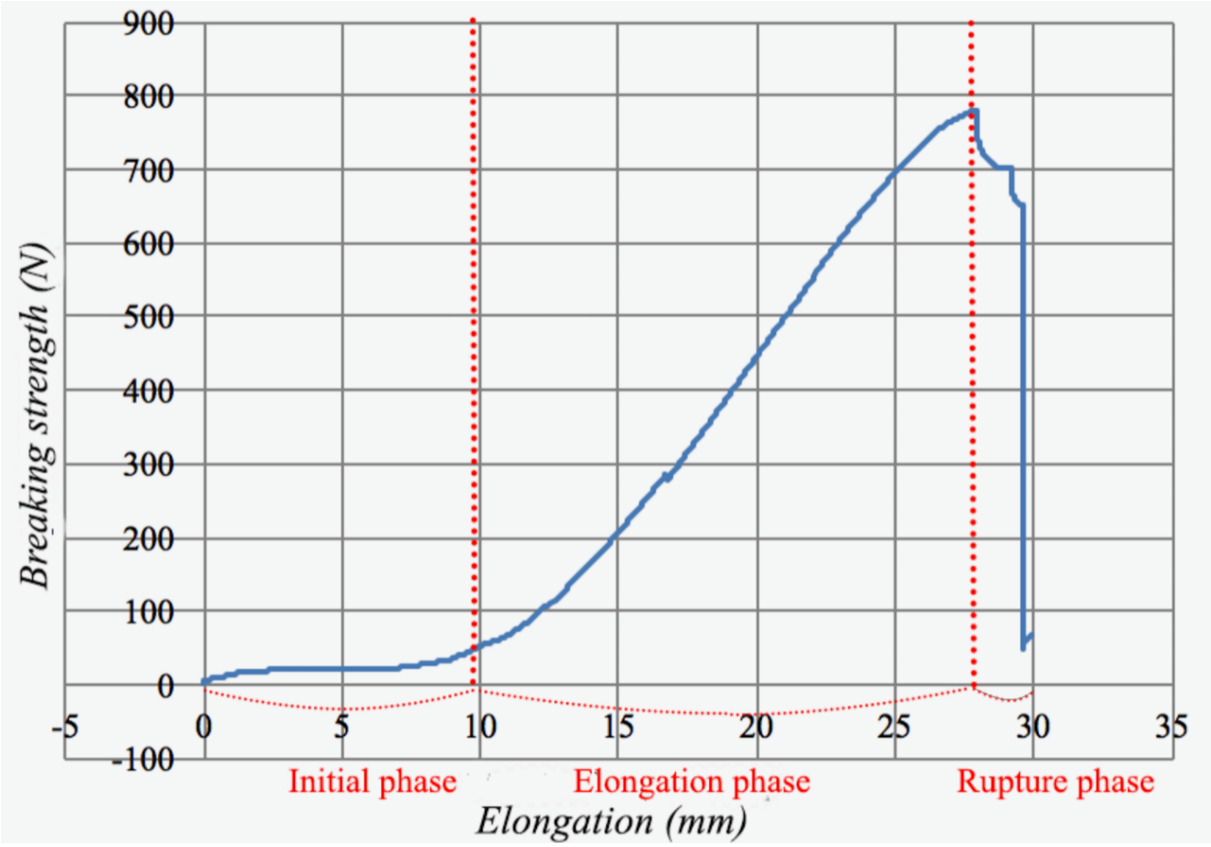


Figure 7. Three phases were observed during the biomechanical tests of bone-ligament-bone samples: initial phase, elongation phase and rupture phase.

3.4. HARVEST AND STORAGE OF CANINE AND EQUINE TENDONS

A total of 121 canine common calcaneal tendons (CCCT) *(1. M. flexor digitalis superficialis, 2. M. biceps femoris and 3. M. gastrocnemius)* (n= 49) and canine radial carpal extensor tendons (CRCET) *(M. extensor carpi radialis)* (n= 27) and equine deep digital flexor tendons (EDDFT) *(Tendo m. flexor digitalis profundus)* (n= 45) were obtained from 30 euthanised dogs and two horses (Tab. 5a-b). CCCT and CRCET samples were gathered from canine patients and EDDFT samples were gathered from horse patients who had died or were euthanised for reasons unrelated to this study at the “Klinik fuer kleine Haustiere of the Freie Universitaet Berlin” (Berlin, Germany) and whose patient owners consented to participation in this study (Fig. 8, see appendix). Patient’s medical records had to meet the following inclusion criteria:

1. No history of diseases that could affect the musculoskeletal apparatus
2. No tumours or infectious diseases affecting the limbs
3. No inflammation or arthritis affecting the limbs
4. No vascular pathology affecting the limbs

EDDFT samples were obtained from slaughtered or dissected horses at the “Institut fuer Tierpathologie Fachbereich Veterinaermedizin der Freien Universitaet Berlin” (Berlin, Germany). All tendon samples were obtained within 24 hours of time of death. After sterile extraction, tendons were washed in normal saline and stored at -20°C before processing further.

Table 5. List of sample origins (a = canine, b = equine), including breed, weight (kg) and age (years) of the specimens as well as date of sample harvest.

a.	Breed	Weight (kg)	Age	Date of harvest
1.	Boxer	30	10	25.01.16
2.	Labrador	35	12	30.01.16
3.	Labrador	35	14	30.01.16
4.	Boxer	24	12	30.01.16
5.	Labrador	35	14	20.02.16
6.	Labrador	35	12	20.02.16
7.	Labrador	29	13	27.02.16
8.	Golden Retriever	25	12	16.02.17
9.	Labrador	30	11	17.03.17
10.	Boxer	30	10	20.03.17
11.	Labrador	25	12	22.03.17
12.	Golden Retriever	35	15	22.03.17
13.	Labrador	30	10	22.03.17
14.	Bernese Mountain Dog	30	12	20.04.17
15.	Labrador	30	11	17.05.17
16.	German shepherd	23	11	07.06.17
17.	German shepherd	23	11	10.06.17
18.	Bordeaux Dogue	25	12	23.10.17
19.	Border Collie	20	14	23.10.17
20.	Crossbreed	35	15	25.10.17
21.	Golden Retriever	25	9	01.11.17
22.	Kuvarsz	39	9	01.11.17
23.	Kuvarsz	25	9	01.11.17
24.	Golden Retriever	32	12	07.11.17
25.	Golden Retriever	25	12	07.11.17
26.	German Shepherd	23	10	07.11.17
27.	Golden Retriever	28	15	07.11.17
28.	Labrador	37	9	22.11.17
29.	Crossbreed	35	9	25.11.17
30.	Swiss Mountain Dog	58	10	03.12.17

b.	Breed	Age	Date of preparation
1.	Heavy Warmblood	13	30.01.15
2.	German Riding Pony	7	30.01.15

3.5. PREPARATION OF NATIVE, DECELLULARISED AND RECELLULARISED TENDONS

In preparation of biomechanical testing, 27 native tendon samples were thawed for 24 hours at 4°C, trimmed to 7-10 cm length, and stripped of soft tissue. The equine tendons were sliced into strips of 4-5 mm depth and width. Samples were heated up to 37°C in a water bath before testing. The remaining 94 samples were thawed, trimmed, sliced and stripped of soft tissue following the same method. Then, samples were washed and incubated in distilled water and 1% penicillin/streptomycin (PS, 10,000 units/ml, Biochrom, Berlin, Germany) at 4°C for 24 hours, with medium changes every four hours. Following this, samples were frozen in liquid nitrogen (-196°C) for 2 minutes and thawed in Dulbecco's Phosphate Buffered Saline (DPBS, Gibco, Life Technologies, Paisley, UK) at 37°C for 10 minutes. This was followed by five consecutive freeze-thaw-cycles, conducted according to Omae et al.'s decellularisation protocol (2012). The samples were then divided into two groups. Groups A's decellularisation was continued with a 24-hour incubation at room temperature in DPBS with 1%T-octyl-phenoxy-polyethoxyethanol (Triton-X 100); whilst groups B was incubated in DPBS and 1% tri-n-butyl-phosphate (TnBP) (Tab. 6). After incubation, samples from both groups were washed three times for 15 minutes each in DPBS. All samples were then incubated in DNase-I solution (350 U/ml, Roche, Mannheim, Germany) at 37°C for 12 hours, followed by three 15 minutes DPBS wash cycles. Decellularised samples were stored in DPBS for up to three days before proceeding to either recellularisation or biomechanical testing.

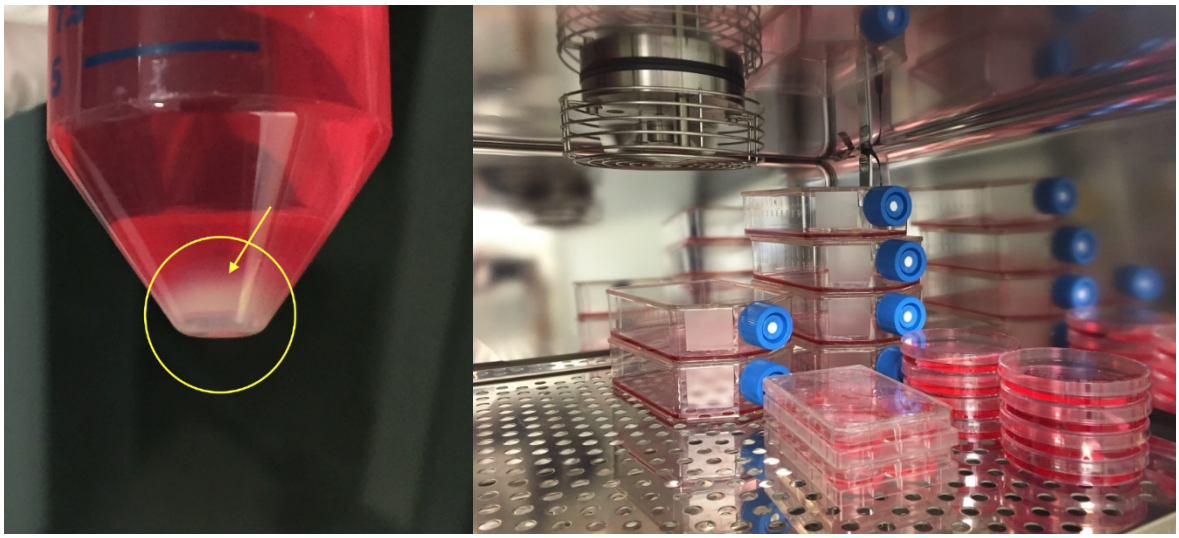
From the 94 decellularised samples, 58 were recellularised using canine mesenchymal stroma cells (MSC). MSC were isolated from aspirated fat tissue, extracted from euthanised or intra-operatively deceased dogs immediately after death had occurred. The cell isolation and differentiation phase was investigated as part of another dissertation (van Staa, 2019) in connection with this study. To mention it briefly, the fat tissue was washed with DPBS (Dulbecco's phosphate-buffered saline), calcium chloride ($CaCl_2$) and magnesium chloride ($MgCl_2$) in a centrifuge (350 x g, 5 minutes) before the isolation. Collagenase (0,2 U ml^{-1}) was added and the fat tissue was digested at 37°C for 45 minutes with regular swirling. The suspension was centrifuged with PBS only (350x g, 10 minutes) and the fat supernatant was discarded. The residual cell pellet was resuspended with PBS and cells isolated from tissue remnants through a 70 µm cell strainer. MSC were cultured in a custom growth medium, composed of DMEM-1X (Gibco, Life Technologies, Paisley, UK), DMEM GlutaMAX-I (Gibco, Life Technologies, Paisley, UK), 10% Fetal Bovine Serum (FBS) (Biochrom, Berlin, Germany) and 100 U/ml penicillin/streptomycin (PS) (Gibco, Paisley, UK). MSC were seeded into 175 cm^2 cell culture flasks (Falcon, Fisher Scientific GmbH, Schwerte, Germany) with daily medium

changes (Fig. 9). Appropriate, cells were passaged using trypsin (1:250, Biochrom, Berlin, Germany) and EDTA (0.05%/0.02%, Biochrom, Berlin, Germany) and seeded into larger flasks until a sufficient number of cells had grown. To count cells, MSC were washed from flasks using trypsin/EDTA as described above, centrifuged for 5 minutes at 300 g and resuspended in growth medium. 20 µl of cell suspension were extracted and dyed with trypan blue (Merck kgaA, Darmstadt, Germany). Cells were counted using a Neubauer chamber (Paul Marienfeld GmbH & Co.kg, Lauda Königshofen, Germany) and diluted into 1 ml seeding batches of at least 850,000 cells. Before seeding MSC, decellularised tendons were washed with ethanol (hygi.de GmbH & Co.kg, Telgte, Germany) once for 10 minutes, followed by three DPBS wash cycles. The tendons were placed into petri dishes (Falcon, Fisher Scientific GmbH, Schwerte, Germany). Cells were seeded exteriorly and interiorly in two steps. First, 0.3 ml of the seeding batch cell suspension was applied interiorly, whilst 0.2 ml were applied exteriorly and incubated at 37°C for two hours. Then, the tendons were turned over and another 0.3 ml of cell suspension were seeded interiorly, whilst 0.2 ml were seeded exteriorly and incubated for two hours at 37°C. After the seeding process, custom growth medium was added and cells were incubated for 7 days at 37°C, with daily medium changes.

Table 6. Number of samples, as well as mean age (years) and mean weight (kg) of the specimens the samples were obtained from. Tendons were grouped according to their preparation type. Group A was decellularised using Triton-X 100, whilst group B was decellularised using TnBP.

	Tendon type	**Number**	**Mean age**	**Mean weight**
Group 2 (Native)	CCCT	9	10	28.3
	CRCET	9	12	31.2
	EDDFT	9	9	0
Group 3A (Decellularised)	CCCT	9	12	31.3
	CRCET	0	0	0
	EDDFT	9	9	0
Group 3B (Decellularised)	CCCT	9	11	26.6
	CRCET	0	0	0
	EDDFT	9	10	0
Group 4A (Recellularised)	CCCT	11	12	28.8
	CRCET	9	12	32.8
	EDDFT	9	9	0
Group 4B (Recellularised)	CCCT	11	12	29
	CRCET	9	10	33.4
	EDDFT	9	10	0

Abbreviations: CCCT = Canine common calcaneal tendon; CRCET = Canine radial carpal extensor tendon; Equine deep digital flexor tendon).

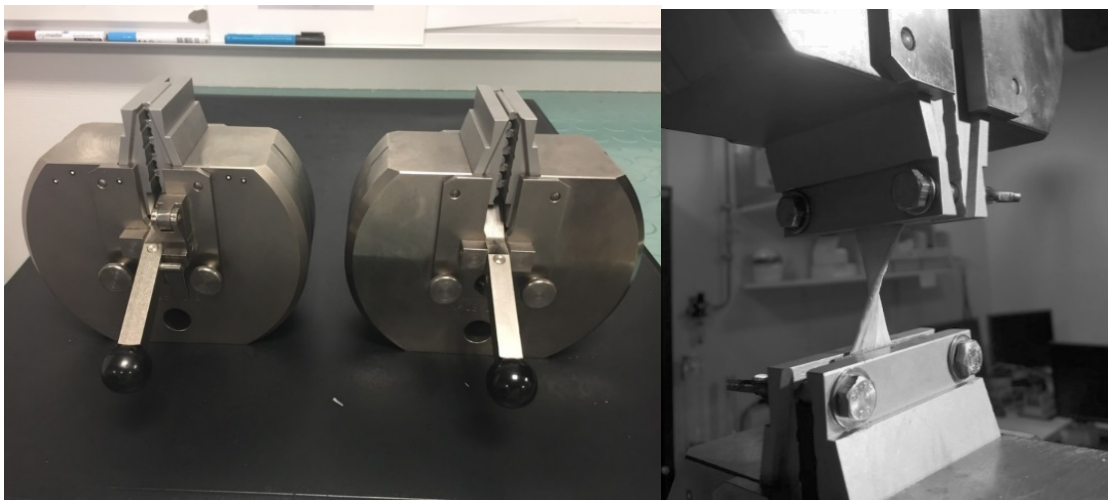


A B

Figure 9. (A) Circle and arrow point to centrifuged canine mesenchymal stroma cells (B) Recellularised tendon samples in the incubator.

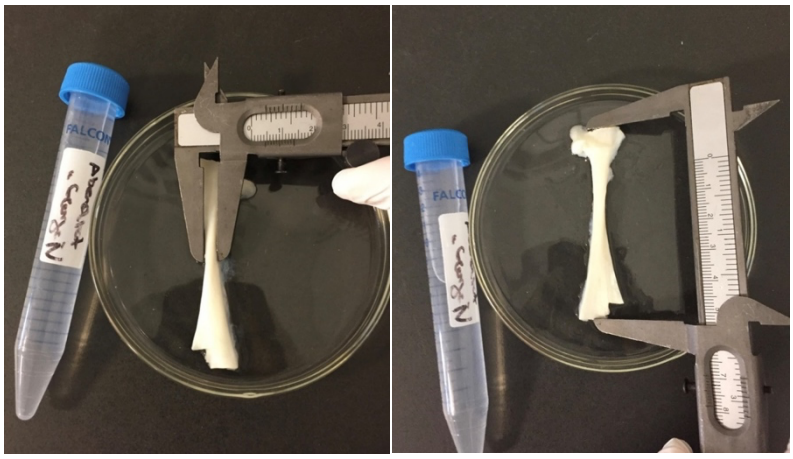
3.6. BIOMECHANICAL TEST OF CANINE AND EQUINE TENDONS

The biomechanical test was performed with a Zwick/Roell 1455 machine (Zwick/Roell, Ulm, Germany). Tendon samples were firmly fixed between two custom metal vices (Fig. 10, 12) and rotated by 90° to simulate the physiological positioning of cruciate ligaments. The width and length of the samples were measured prior to the test (Fig. 11). The distance between the metal vices was measured before (M = 20 mm) and after the biomechanical test. Samples were elongated at a loading rate of 0.1 kN/s with a test velocity of 10mm/min.



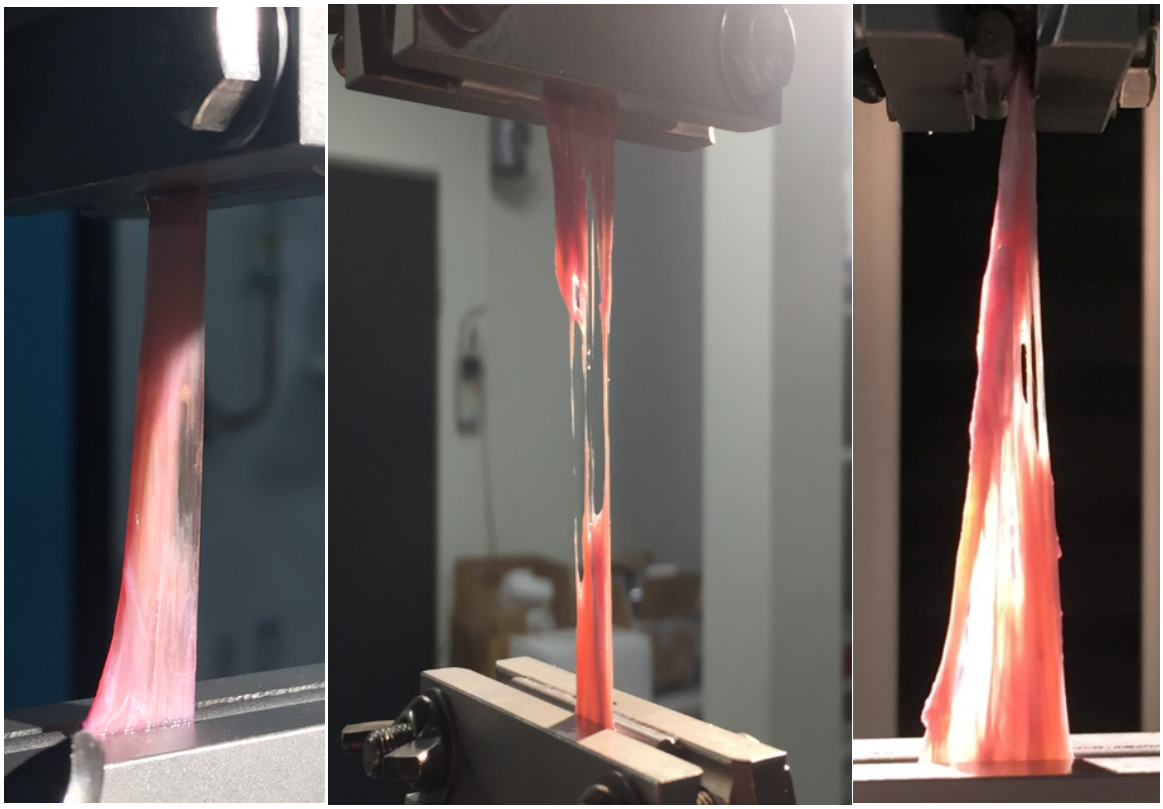
A *B*

Figure 10. (A) Two metal graft fixation clips (vices) used for the biomechanical testing of the tendons. (B) A tendon sample fixated in the metal vices and rotated by 90°.



A B

Figure 11. Measuring of width (A) and length (B) of a sample prior to biomechanical testing.



A B C

Figure 12. Biomechanical test of recellularised samples at 90° rotation: (A) CCCT, (B) CRCET and (C) EDDFT.

Biomechanical properties that were assessed included breaking strength (N), elongation (mm) (Fig. 13), tensile strength (N/kg) as well as the relative distance of the rupture point to the femur and the tibia. Breaking strength was defined as the maximum force before the rupture occurred. Elongation was measured as distance of elongation before the rupture occurred.

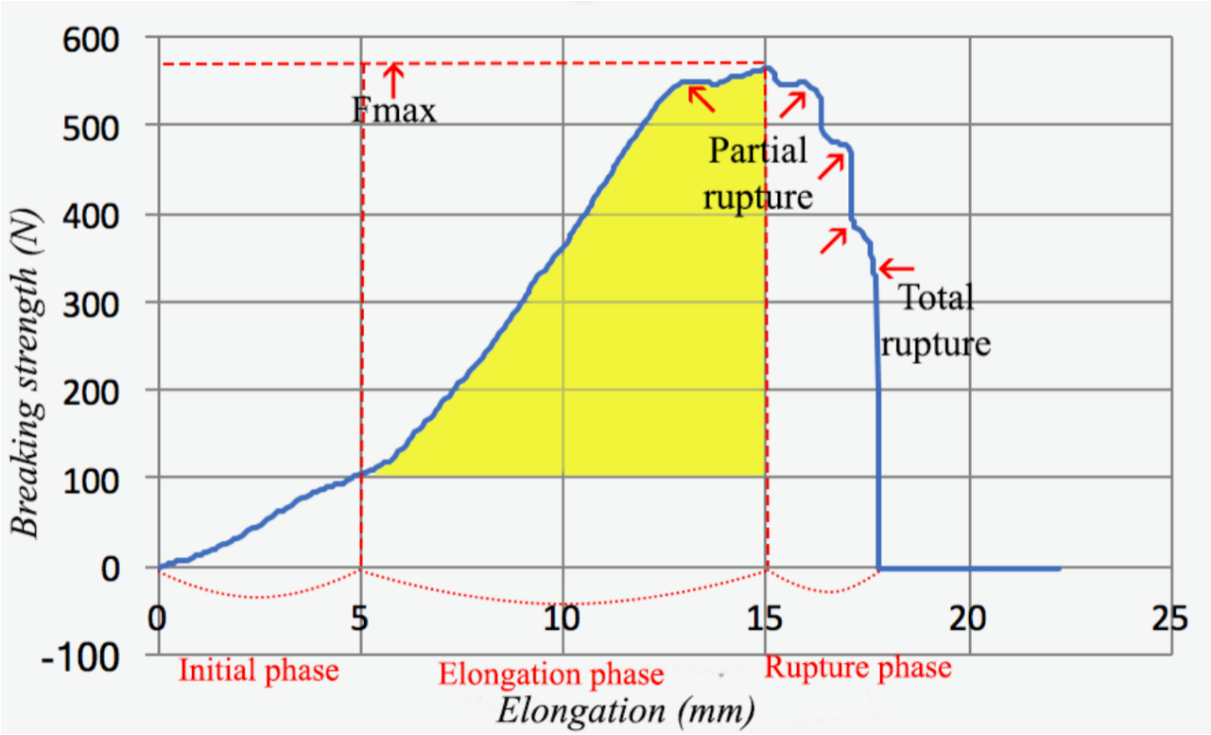


Figure 13. Three phases observed during the biomechanical tests of metal-tendon-metal samples: initial phase, elongation phase and rupture phase.
Abbreviation: Fmax= maximum force.

3.7. STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS Version 22 (IBM, Armonk, USA). Due to the small sample size in the different groups, non-parametric tests that do not assume a normal distribution were chosen. The Mann-Whitney-U test was used to compare two independent samples. For comparing three or more independent samples, the Kruskal-Wallis Test was used. In case of a statistically significant result, post-hoc tests were performed. To compare results between pairs, a Mann-Whitney-U test with the Bonferroni-Holm method was used. The relationship between breaking strength (N), elongation (mm) and number of seeded MSC were analysed using Spearman's rank correlation. A p-value < 0.05 was considered to be statistically significant (Field 2013).

4. RESULTS

4.1. ANATOMICAL VARIATIONS OF THE CANINE CrCL

Across the dogs included in this study, the average weight of small dogs was M = 11 kg (SD = 2), whilst average body-weight of medium dogs was M = 19kg (SD = 2 kg) and an average of M = 35 kg (SD = 3 kg) was found among large dogs (Tab. 7).

Amongst large dogs, the average length of the CrCL was M = 19mm (SD = 0.2 mm); whilst the average length amongst small and medium dogs was M = 15mm (SD = 0.2 mm).

In small dogs, an average width of M = 2.25mm (SD = 0.25) and depth of M = 2.75mm (SD = 0.25) were found at midway length in small dogs. At the tibial end, an average width of M = 4.25 mm (SD = 0.25) and depth of M = 2mm (SD = 0) were found, whilst an average width of M = 2mm (SD = 0.5) and depth of M = 3mm (SD = 0) were found at the femoral end in small dogs.

In medium dogs, at midway length the average width was M = 3.5 mm (SD = 0.5) and the average depth was M = 4.5mm (SD = 0.5). At the tibial end, an average width of M = 7.75 mm (SD = 0.25) and depth of M = 4 mm (SD = 1) were found; whilst an average width of M = 5 mm (SD = 1) and depth of M = 7.5 mm (SD =1) were found at the femoral end in medium dogs.

In large dogs, at midway length the average width was M = 4 mm (SD = 1) and the average depth was M = 4.5 mm (SD = 0.5). At the tibial end, an average width of M = 9 mm (SD = 0) and depth of M = 7.25 mm (SD = 0.75) were found; whilst an average width of M = 5.5 mm (SD=0.5) and depth of M = 7.75 mm (SD = 1.25) were found at the femoral end in large dogs.

Table 7. Measurements of length, width (medial-lateral) and depth (cranial-caudal) of canine cranial cruciate ligaments in mm.

Small dogs (Weight: M = 11 kg)	**Right CrCL (n= 4)**		**Left CrCL (n= 4)**	
	M	**SD**	**M**	**SD**
width (midway)	2.25	0.25	2.25	0.25
depth (tibial end)	2.75	0.25	2.25	0.25
width (tibial end)	4.25	0.25	4.25	0.25
depth (tibial end)	2	0	2	0
width (femoral end)	2	0.5	2.5	0.5
depth (femoral end)	3	0	3	0

Medium dogs (Weight: M = 19 kg)	**Right CrCL (n= 4)**		**Left CrCL (n= 4)**	
	M	**SD**	**M**	**SD**
width (midway)	3.5	0.5	3.5	0.5
depth (tibial end)	4.5	0.5	4.5	0.5
width (tibial end)	7.75	0.25	7.75	0.5
depth (tibial end)	4	1	4	1
width (femoral end)	5	1	5	1
depth (femoral end)	7.5	1	7.25	1.25

Large dogs (Weight: M = 35 kg)	**Right CrCL (n= 20)**		**Left CrCL (n= 20)**	
	M	**SD**	**M**	**SD**
width (midway)	4	1	4	1
depth (tibial end)	4.5	0.5	5	0
width (tibial end)	9	0	9	0
depth (tibial end)	7.25	0.75	7.25	0.75
width (femoral end)	5.5	0.5	6	0
depth (femoral end)	7.75	1.25	7.75	1.25

4.2. BIOMECHANICAL PROPERTIES OF CANINE CrCL

The individual results for all canine CrCL samples included in this study are listed in the appendix (Tab. 8).

No significant difference was found between the five groups of CrCL tested at different angles of extension and flexion (p=0.68). The mean breaking strengths of the test groups were found at M = 1138.6 N (SD = 479.7), M = 1315.9 N (SD = 702.4), M = 1208.4 N (SD = 263.1), M = 982.3 N (SD = 309.5) and M = 1171.3 N (SD = 445.2) for groups 1 (60°), 2 (90°), 3 (120°), 4 (140°) and 5 (160°), respectively (Fig. 14).

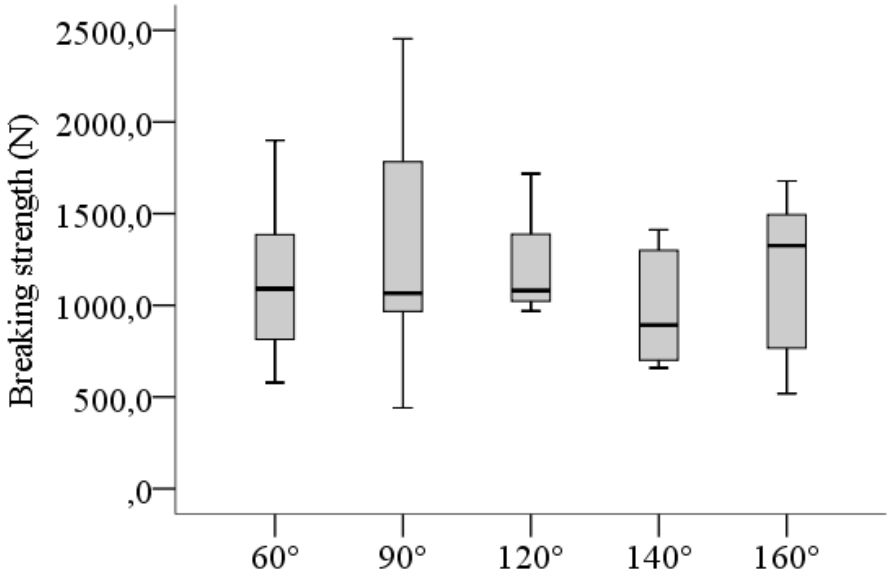


Figure 14. Breaking strength (N) of the five CrCL test groups, tested at different flexion and extension angles.

A significant difference between elongation and the different test angles was found (p = 0.001). The post-hoc test revealed that samples tested at a small angle (60° and 90°) showed a higher elongation compared to samples tested at larger angles (Fig. 15). The average elongation values were M = 22.6 (SD = 4.1 mm), M = 20.7 (SD = 16.3 mm), M = 11.7 (SD = 2.8 mm), M = 14.9 (SD = 3.7 mm), M = 10.2 (SD = 3.7mm) for groups 1 (60°), 2 (90°), 3 (120°), 4 (140°) and 5 (160°), respectively.

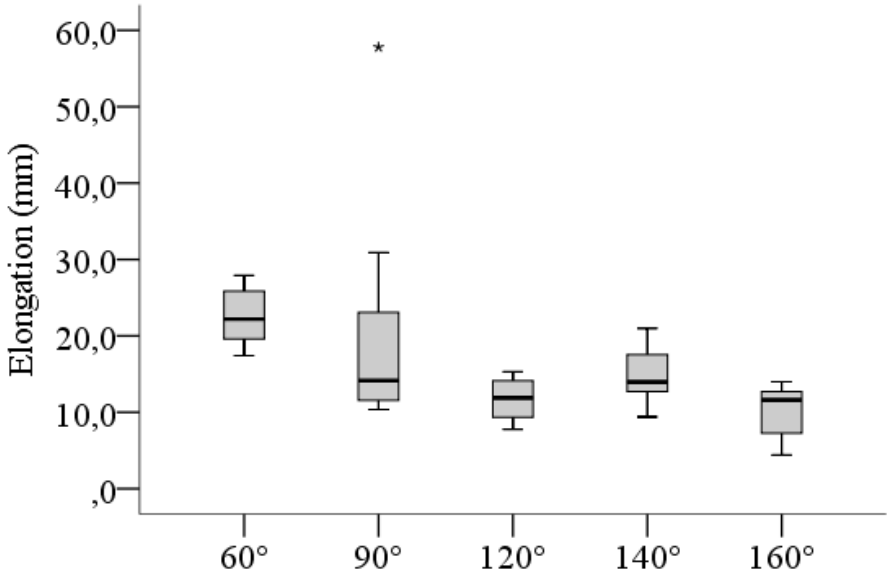


Figure 15. Elongation (mm) of CrCL samples tested at different flexion and extension angles.

The distance between the rupture point and the femur and tibia, respectively, were measured and compared relative to the fixed ligament's length prior to the test. The average relative distance to the femur was found at M = 65.5% (SD = 17.8 %), M = 44.3% (SD = 20.9%), M = 37.6% (SD = 23.9%), M = 78.0 (SD = 23.8%), M = 54.5% (SD = 20.4%) for groups 1 (60°), 2 (90°), 3 (120°), 4 (140°) and 5 (160°), respectively (Fig. 16). The average relative distance to the tibia was found at M = 34.4% (SD = 17.8%), M = 55.7% (SD = 20.9%), M = 62.4% (SD = 23.9%), M = 22.0% (SD = 23.8%), M = 45.5% (SD = 20.4%) for groups 1 (60°), 2 (90°), 3 (120°), 4 (140°) and 5 (160°), respectively. (Fig. 17).

Three different types of test failures were observed during the biomechanical tests. Lateral condyle fractures occurred in one sample of a large dog in group 1 (60°) and one sample of a medium dog in group 3 (120°). The femoral insertion of the CrCL fractured in one sample of a large dog in group 2 (90°) and one sample of a large dog in group 3 (120°). In group 4 (140°), the tibial insertion of the CrCL fractured in three cases. These samples were included in the study. In all other cases, the CrCL samples ruptured somewhere between the femoral and tibial insertion points. Most samples (61%, N = 33) ruptured close to the midway point of the CrCL (Fig. 17). Furthermore, it was observed that the rupture occurred closer to the femur with increasing angle. Contrary to this, the average breaking point in group 4 (140°) was closer to the tibia than the femur. However, rupture point and angle were significantly correlated ($p = 0.009$). The individual results for all canine CrCL samples included in this study are listed in the appendix (Fig. 18, Tab. 8).

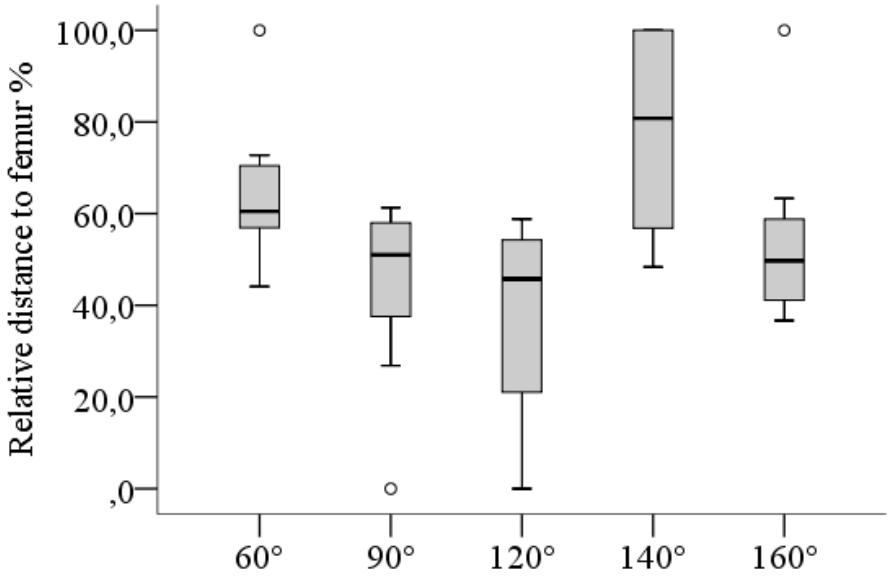


Figure 16. Relative distance to femur of the rupture point to the femoral insertion (%) in the five CrCL test groups, tested at different flexion and extension angles.

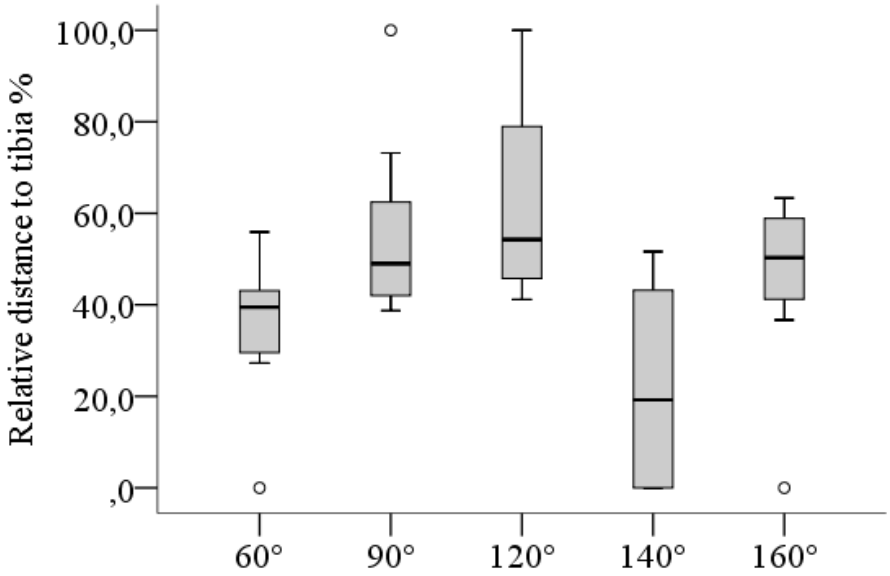


Figure 17. Relative distance to tibia of the rupture point to the femoral insertion (%) in the five CrCL test groups, tested at different flexion and extension angles.

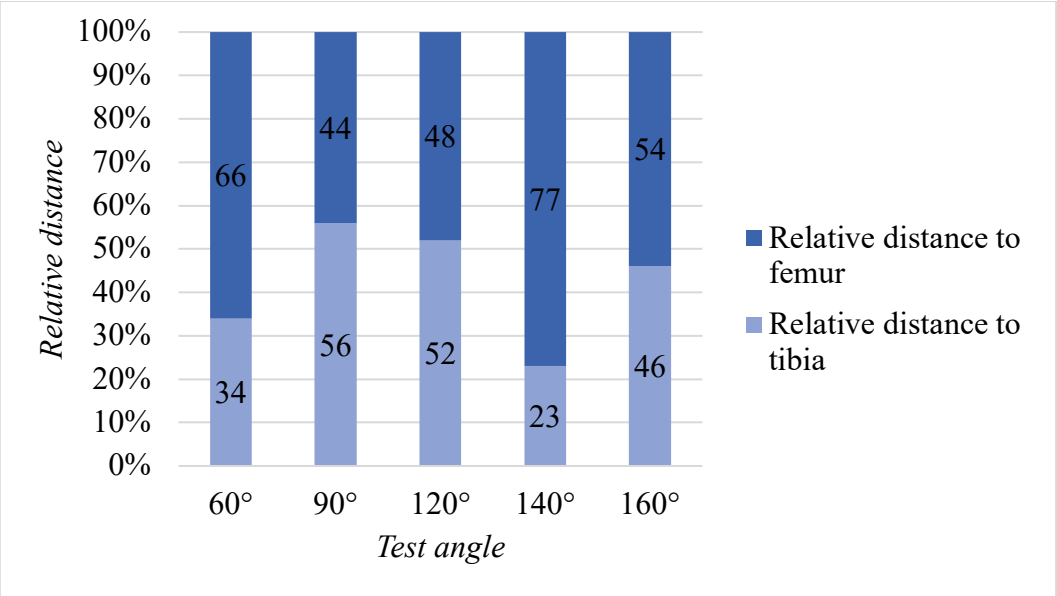


Figure 18. Relative distance of the rupture to the femur and tibia, respectively.

The ultimate load (Fmax) in medium dogs (M = 1302 N, SD = 222.3) was significantly higher (p = 0.001) than in large dogs (M = 1208.4; SD = 263.1) and small dogs (M = 577.5; SD = 22.3) (Fig. 19). The tensile strength in medium dogs (M = 62.9 N/kg; SD = 14.4) was significantly higher (p = 0.018) than in large dogs (M = 39.2N/kg; SD = 12.5) and small dogs (M = 44.4N/kg; SD = 20.7) (Fig. 20). The elongation of samples from medium dogs (M = 14.9; SD = 2.9) was significantly higher (p = 0.042) than in samples obtained from large dogs (M = 11.7 mm; SD = 2.8) and higher than samples from small dogs (M = 10.3 mm; SD = 3.7) (Fig. 21).

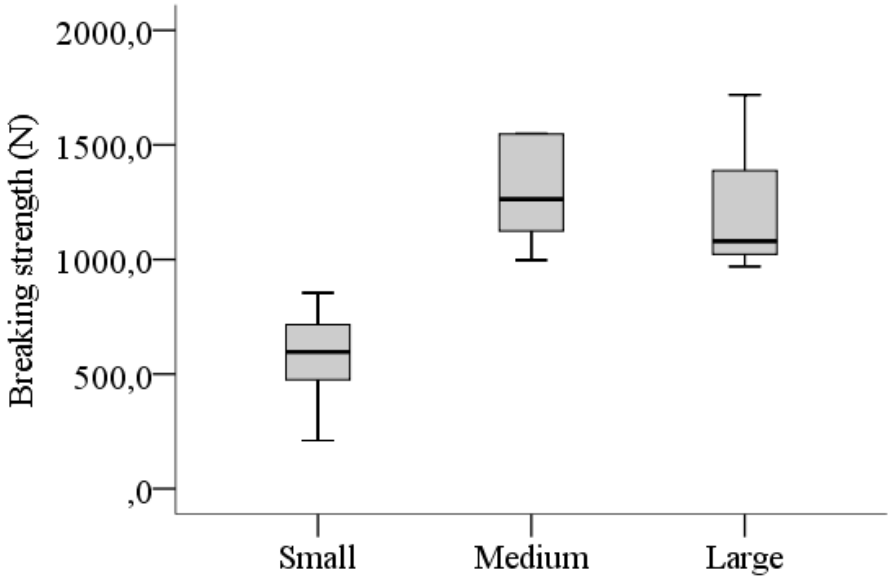


Figure 19. Breaking strength of small, medium and large dogs tested at 120° median flexion angles.

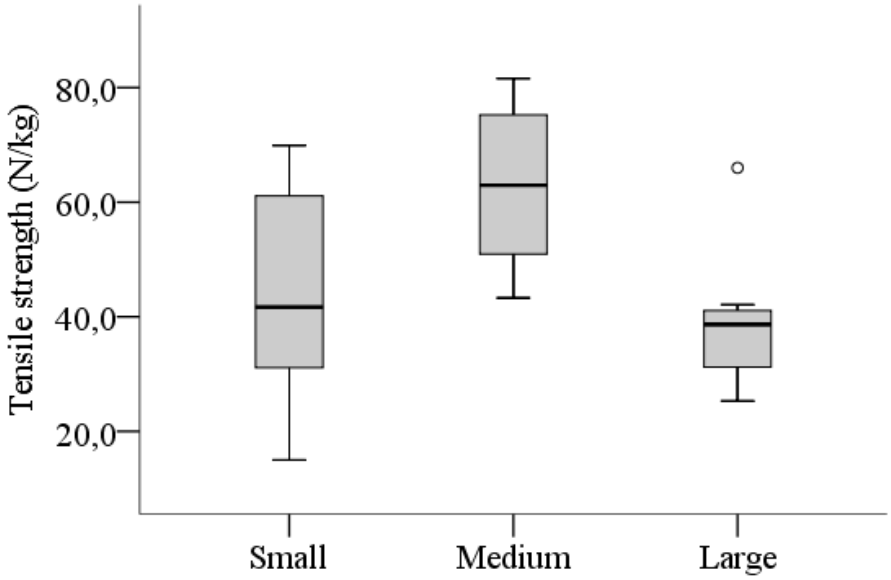


Figure 20. Tensile strength (N/kg) of small, medium and large dogs tested at 120° median flexion angles.

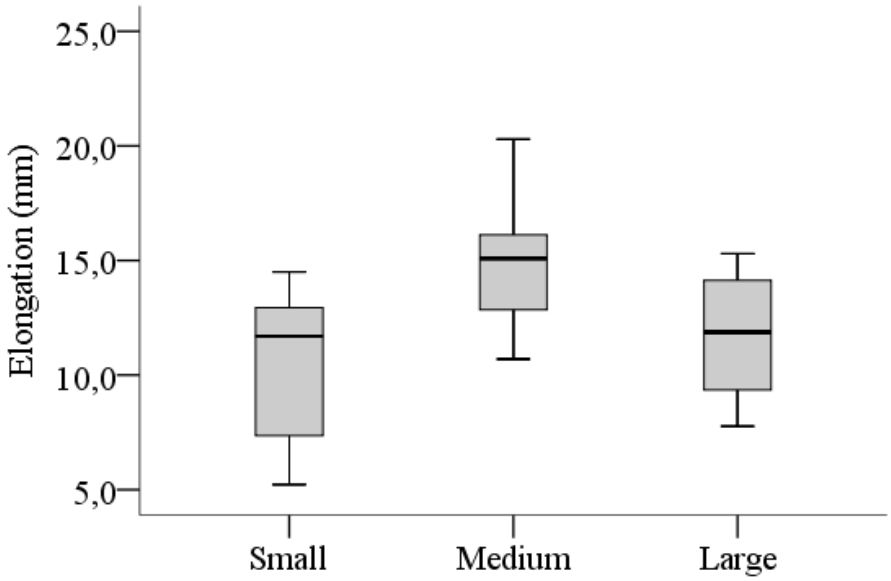


Figure 21. Elongation of small, medium and large dogs tested at 120° median flexion angles.

4.3. ANATOMICAL VARIATIONS OF THE CANINE AND EQUINE TENDONS

All CCCT and CRCET samples were obtained from large dogs. The average length of the CCCT samples was M = 74 mm (SD = 14, N = 49); whilst the average length of CRCET samples was M = 91 mm (SD = 26; N = 27). The average length of the EDDFT samples was M = 76 mm (SD = 10; N = 45) (Tab. 9). Combining all three types, the CCCT samples had an average depth of M = 3 mm (SD = 1) at midway length. The average depth of the CRCET samples was M = 3 mm (SD = 1) at midway length, whilst the average depth of the sliced EDDFT samples was M = 4 mm (SD = 2 mm) (Tab. 9).

Table 9. Average length and depth (mm) of the CCCT, CRCET and EDDFT samples before the biomechanical test.

Tendon type	**Number**	**Mean length**	**SD**	**Mean depth**	**SD**	**Mean width**	**SD**
CCCT	49	74	14	3	1	3	1
CRCET	27	91	26	2	1	4	2
EDDFT	45	76	10	3	2	4	2

Abbreviations: CCCT = Canine common calcaneal tendon, CRCET = Canine radial carpal extensor tendon, EDDFT= Equine deep digital flexor tendon.

4.4. BIOMECHANICAL PROPERTIES OF NATIVE TENDONS

The individual results for all tendon samples included in this study are listed in the appendix (Tab. 10). Amongst the native tendon samples (N = 27), the equine EDDFT samples showed significantly higher breaking strength (M = 604.9 N; SD = 138.3 N; p = 0.049) and greater elongation (M = 15.6 mm; SD = 4,5 mm; p = 0.04) compared to the CCCT (M = 441.6; SD = 130.5 and M = 10.6 mm; SD = 3.2) and CRCET (M = 559 N; SD = 133.2 and M = 10.9, SD = 3.5) samples (Fig. 22 and 23).

The breaking strengths of decellularised CCCT (M = 427.7; SD = 140.5) and EDDFT (M = 374.8 N; SD = 96.1) samples were not significantly different (p = 0.184). Moreover, the elongation of CCCT (M = 11.6 mm; SD = 4) and EDDFT (M = 15.6 mm; SD = 6.6) was not statistically significant (p = 0.054) (Fig. 22 and 23).

Across the recellularised samples, there was no statistically significant correlation (p = 0.1) between the breaking strength and CCCT (M = 495.2 N; SD = 103.2), CRCET (M = 458.1 N;

SD = 137.7) and EDDFT (M = 547.2 N; SD = 169.1) (p = 0.1) (Fig. 22). However, a significant difference in elongation was found (p = 0.004) between EDDFT (M = 16.8 mm; SD = 3.5) and CCCT (M = 13 mm; SD = 4.1) (Fig. 23).

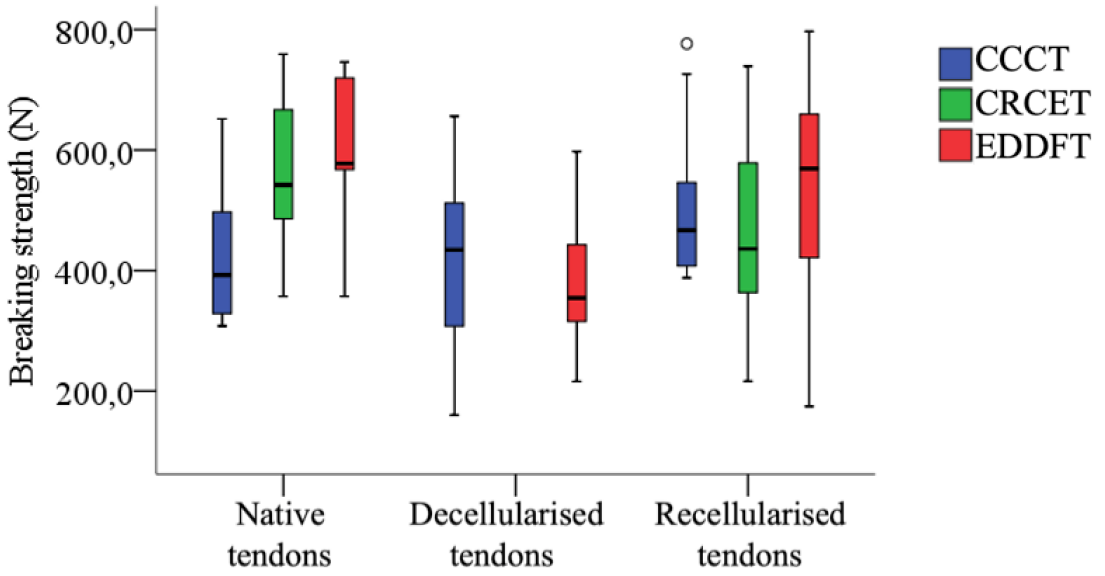


Figure 22. Breaking strength (N) of native, decellularised and recellularised CCCT, CRCET and EDDFT samples.

Abbreviations: CCCT = Canine common calcaneal tendon, CRCET = Canine radial carpal extensor tendon, EDDFT= Equine deep digital flexor tendon.

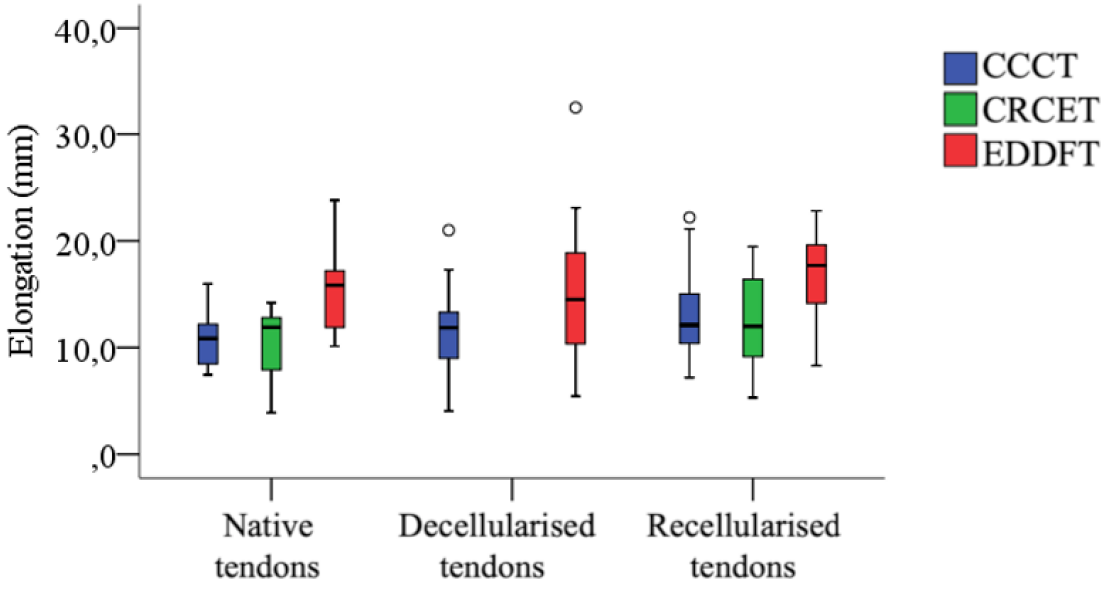


Figure 23. Elongation (mm) of native, decellularised and recellularised CCCT, CRCET and EDDFT samples.

Abbreviations: CCCT = Canine common calcaneal tendon, CRCET = Canine radial carpal extensor tendon, EDDFT= Equine deep digital flexor tendon.

4.5. BIOMECHANICAL PROPERTIES OF CCCT, CRCET AND EDDFT SAMPLES

In CCCT samples, no statistically significant differences in breaking strength were found ($p = 0.224$) between native, decellularised and recellularised samples (Fig. 24). It was observed that the elongation of CCCT samples was greatest amongst the recellularised samples; however, this was not statistically significant ($p = 0.471$) (Fig. 25).

Amongst the CRCET samples, it was observed that recellularised samples had a lower breaking strength and smaller elongation compared to native samples; however, these differences were not statistically significant ($p = 0.095$; $p = 0.382$) (Fig. 24 and 25).

Native EDDFT samples had the highest breaking strength (M = 604.9 N; SD = 138.3) compared to other tendon and preparation types. It was observed that the breaking strength was significantly lower in decellularised EDDFT samples (M = 374.8; SD = 96.1) compared to native EDDFT samples ($p = 0.001$). In addition, high breaking strength was found in recellularised samples (M = 547.2; SD = 169.1). Recellularised EDDFT samples showed a lower elongation compared to native samples; however, this difference was not statistically significant ($p = 0.475$) (Fig. 24).

Amongst the decellularised samples, there was no significant difference in breaking strength between groups A and B. Group A (Tx-100) showed a higher breaking strength (M = 464.8 N; SD = 138.5) in CCCT samples compared to group B (TnBP) (M = 390.6 N; SD = 140.2) in CCCT samples ($p = 0.222$). EDDFT samples in group A also had a higher breaking strength (M = 411.6 N; SD = 106) compared to group B (M = 338N; SD = 72.9) ($p = 0.258$) (Fig. 24).

A significant difference in elongation in decellularised samples was found between groups A and B. CCCT samples from group A had a less elongation (M = 9.74 mm; SD = 2.8) compared to CCCT samples from group B (M = 13.5; SD = 4.2) ($p = 0.04$). Moreover, EDDFT samples in group A showed less elongation (M = 11.1 mm; SD = 3.5) compared to group B (M = 20.0 mm; SD = 5.7) ($p = 0.001$) (Fig. 25).

Across the recellularised samples, there was no significant difference in breaking strength

between groups A and B. The recellularised CCCT samples from group A showed a higher breaking strength (M = 507.6 N; SD = 129.6) than CCCT samples from group B (M = 482.8 N; SD = 72.0) (p = 1.0). However, the recellularised CRCET samples from group A showed a lower breaking strength (M = 434.7 N; SD = 127.4) compared to CRCET samples from group B (M = 481.4 N; SD = 151) (p = 0.387). In addition, the breaking strength of recellularised EDDFT samples in group A was lower (M = 531.2 N; SD = 140) than in EDDFT samples from group B (M = 563.0 N; SD = 201.4) (p = 0.546) (Fig. 24).

No significant difference in elongation was found between recellularised samples from groups A and B. Recellularised CCCT samples from group A showed lower elongation (M = 12 mm; SD = 4.1) than samples from group B (M = 13.9 mm; SD = 4) (p = 0.243). In CRCET samples, elongation was lower in group A (M = 11.9 mm; SD = 4) than group B (M = 12.9 mm; SD = 4.8) (p = 0.6). Recellularised EDDFT samples from group A showed greater elongation (M = 18 mm; SD = 2.9) compared to samples from group B (M = 15.5 mm; SD = 3.6) (p = 0.161) (Fig. 25).

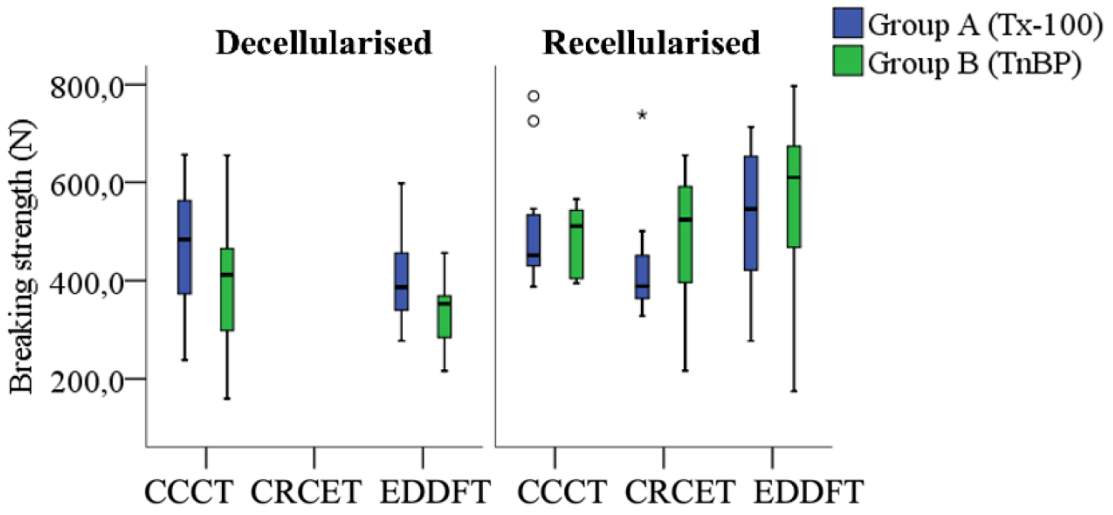


Figure 24. Breaking strength of decellularised and recellularised CCCT, CRCET and EDDFT samples from groups A and B. Group A was decellularised with Tx-100, whilst group B was decellularised with TnBP.
Abbreviations: CCCT = Canine common calcaneal tendon, CRCET = Canine radial carpal extensor tendon, EDDFT= Equine deep digital flexor tendon.

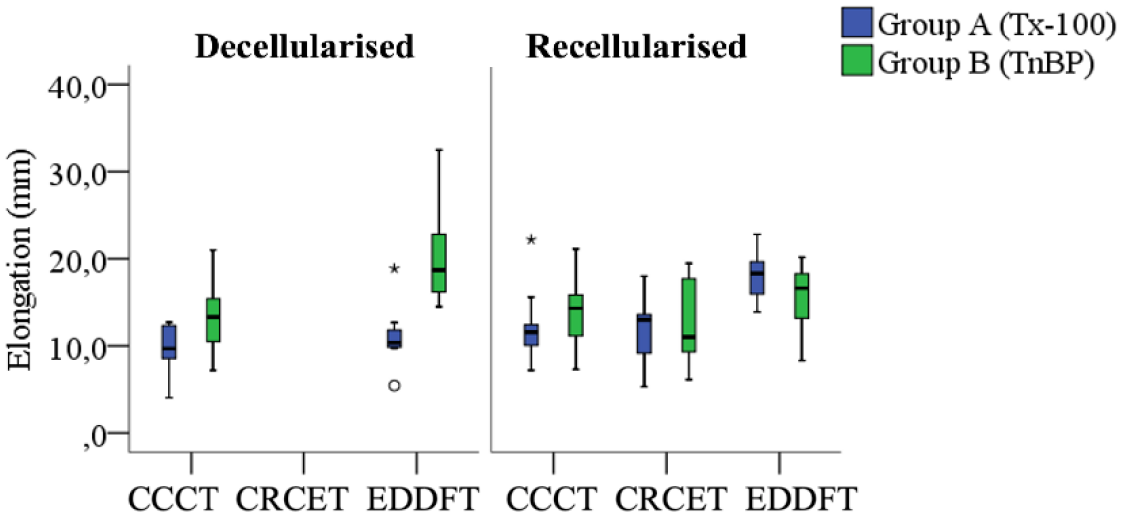


Figure 25. Elongation of decellularised CCCT, CRCET and EDDFT samples from groups A and B. Group A was decellularised with Tx-100, whilst group B was decellularised with TnBP. Abbreviations: CCCT = Canine common calcaneal tendon, CRCET = Canine radial carpal extensor tendon, EDDFT= Equine deep digital flexor tendon.

4.6. NUMBERS OF SEEDED MSC CELLS OF RECELLULARISED TENDONS

There was no statistically significant difference in breaking strength between samples recellularised with different numbers of MSC (r = -0.029; = 0.829) (Fig. 26). Otherwise, significant difference in elongation was found (r = -0.307; p = 0.019) between samples recellularised with different numbers of MSC (Fig. 27). The number of cells seeding is negatively correlated with elongation. Increase in cell capacity on and within the tendon increased elasticity only in the seven days incubation time.

The highest breaking strength amongst recellularised equine tendon samples was found in a EDDFT sample recellularised with approx. 930,000 MSC (797.1 N). The highest breaking strength among recellularised canine tendon samples was found in a CCCT sample (776.55 N) recellularised with approx. 1,450,000 MSC. The lowest breaking strength amongst recellularised equine tendon samples was found in a EDDFT sample recellularised with 1,200,000 MSC (174 N). The lowest breaking strength among recellularised canine tendon samples was found in a CRCET sample (216 N) recellularised with approx. 865,000 MSC.

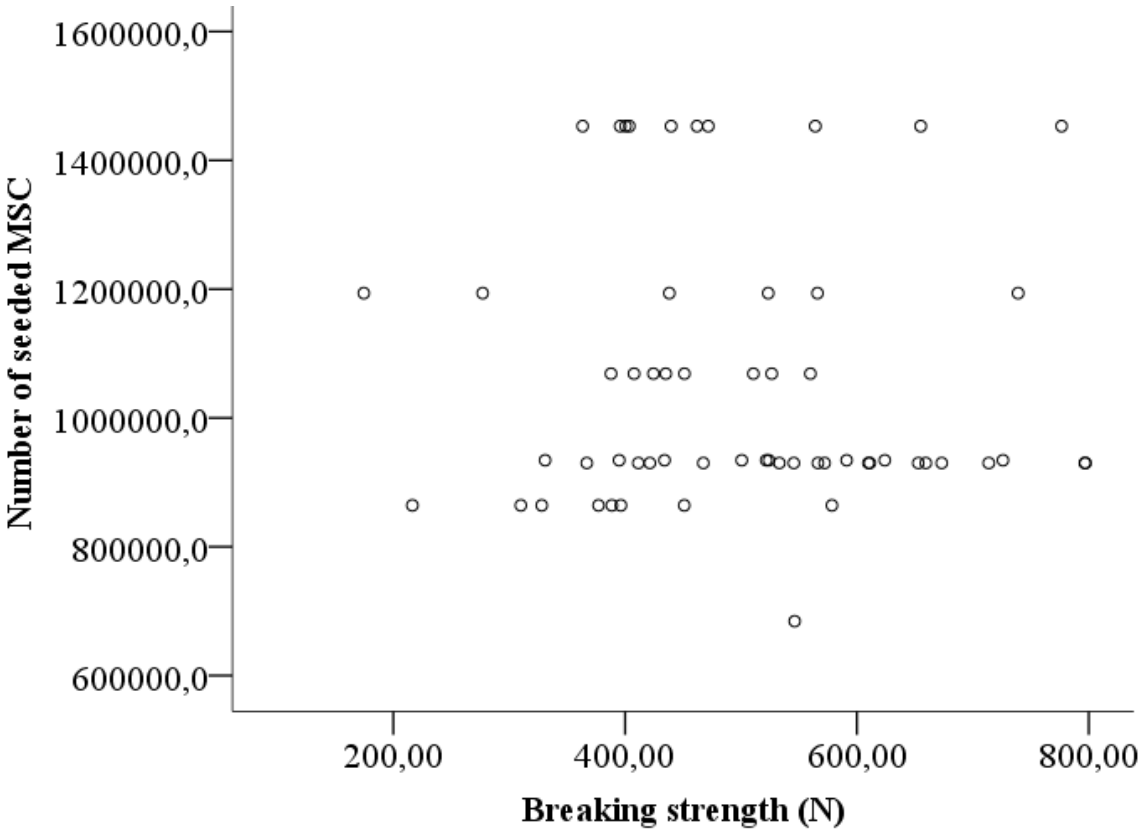


Figure 26. Breaking strength of recellularised tendons seeded with different numbers of MSC.

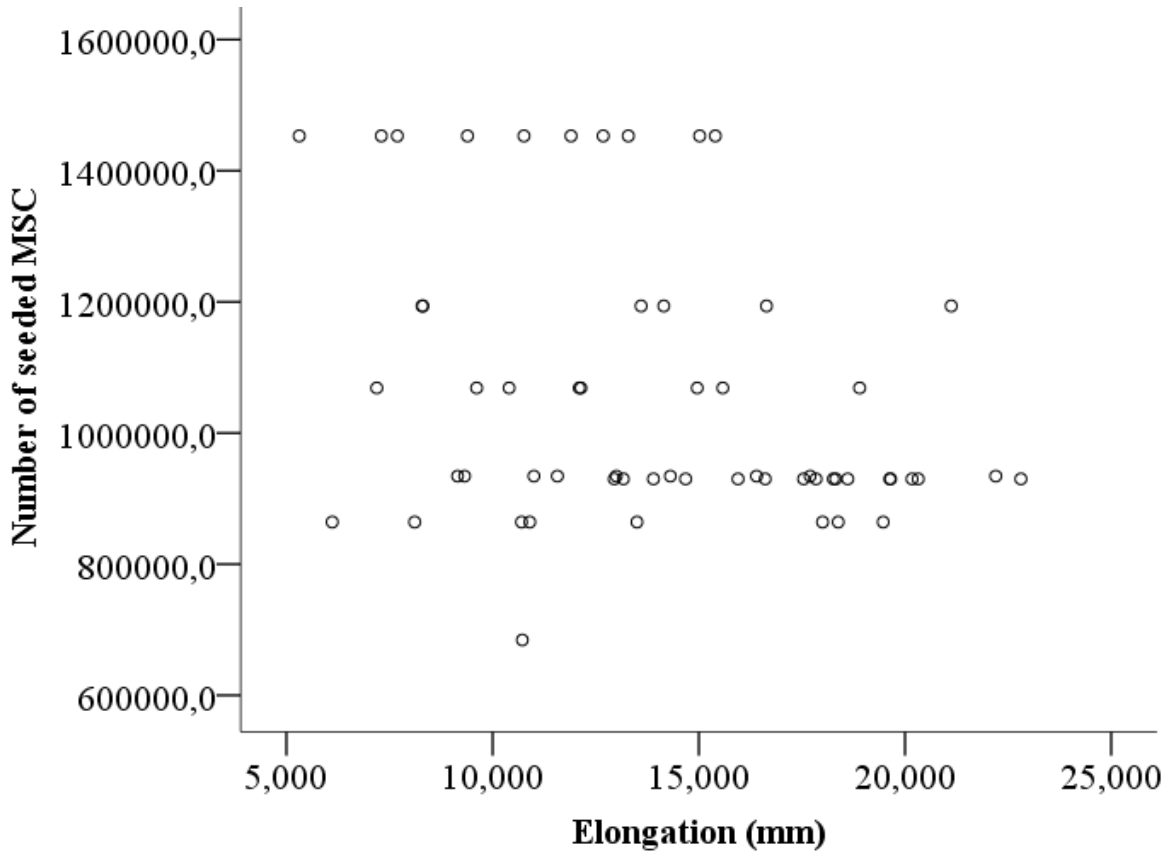


Figure 27. Elongation of recellularised tendons seeded with different numbers of MSC.

4.7. COMPARISON OF CANINE CRANIAL CRUCIATE LIGAMENT TO CANINE AND EQUINE TENDON SAMPLES

The breaking strength of canine CrCL samples (M = 1187.4 N; SD = 425.3) was significantly (p = 0001) higher than the breaking strength of decellularised canine and equine tendons (M = 401.3 N; SD = 121.6), as well as recellularised canine and equine tendons (M = 499.8 N; SD = 139.6) (Fig. 28)

The elongation of native CrCL samples (M = 15.7 mm; SD = 8.3) was higher than in decellularised canine and equine tendons (M = 13.6 mm; SD = 5.7) as well as recellularised canine and equine tendons (M = 14.0 mm; SD = 4.4). However, the observed differences were not statistically significant (p > 0.5) (Fig. 29).

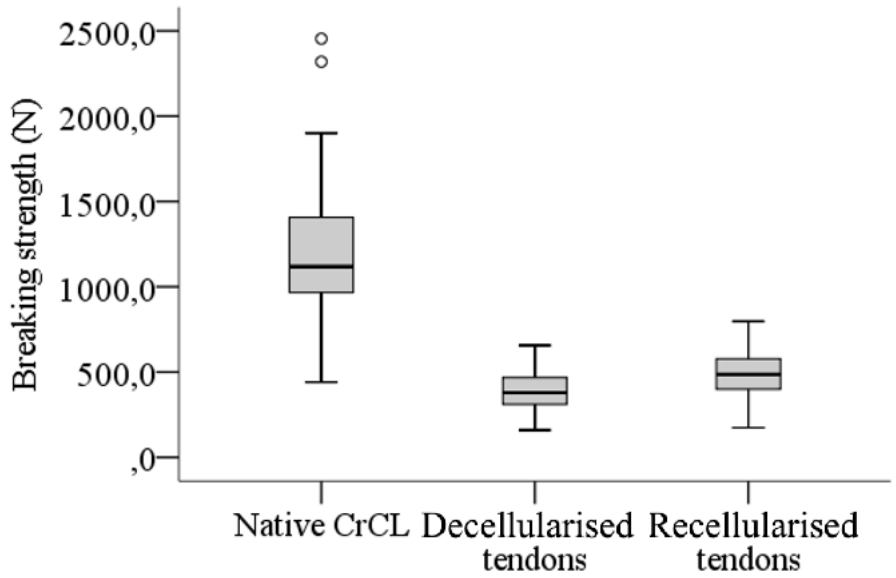


Figure 28. Breaking strength of native CrCL as well as decellularised and recellularised tendon samples.

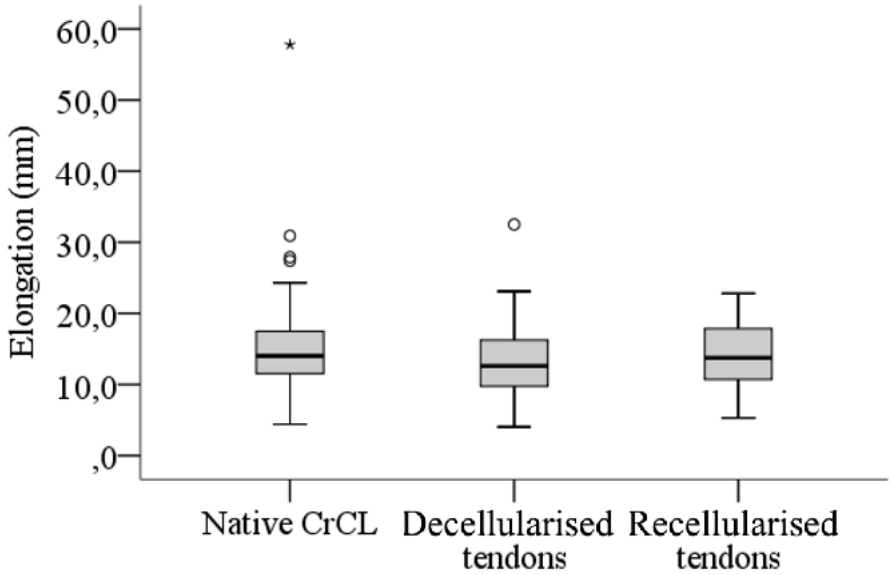


Figure 29. Elongation of native CrCL, as well as decellularised and recellularised tendons.

5. DISCUSSION

Since cranial cruciate ligament rupture is the most common orthopaedic pathology found in dogs of all ages, breeds and genders (Brunnberg 1987; Whitehair et al. 1993; Duval et al. 1999), it has been researched intensely over the past decades. Since the natural healing ability of injured ligaments is very limited, surgical intervention is often necessary to restore adequate function (Hayashi et al. 2003a; Hayashi et al. 2003b; Chamberlain et al 2009; Kiapour and Murray 2014). According to Gupta and Brinker (1969), the main objective of surgical repair techniques is to stabilise the stifle joint by eliminating cranial drawer movement.

Osteotomy stabilization techniques, especially TPLO, have achieved good success rates over the last 15 years. However, considering more objective measurements such as pressure platform analysis, radiographic scoring, thigh circumference and outcomes of tibial osteotomies in a series of studies have shown that operated stifles do not function like native stifles (Evans et al. 2005; Voss et al. 2008). It shows that, although there are various and successful treatment methods in veterinary medicine, the optimal treatment method has not yet been determined (Wucherer et al. 2013).

In contrast to the osteotomy method, intra-articular repair techniques are relatively less complicated methods. However, in recent years, the osteotomy techniques have become more popular and are preferred over intra-articular repair techniques. Studies have found that an autologous patellar tendon transplant can be an ideal course of treatment to restore full functional ability in dogs suffering from CrCL rupture (Strande 1966; Dueland 1966; Lakatos and Spoerry 1974; Alm and Stromberg 1974; Chiroff 1975; Arnoczky et al. 1979; Arnoczky et al. 1982; Denny and Barr 1984). Also in humans, intra-articular graft placement is considered the gold standard for anterior cruciate ligament rupture, however, there is disagreement about the ideal graft (Murray 2009). This approach carries a risk of donor site complications, such as persistent pain around the patella, lack of muscle strength in the stifle joint and consequently, a loss in joint stability and progressive cartilage degeneration (Asselmeier et al. 1993; Centers for Disease Control and Prevention 2001; Barber 2003). Similar disadvantages have been reported in dogs (Butler et al. 1983; Elkins et al. 1991; Innes et al. 2000; Johnson et al. 2001; Innes et al. 2004; Conzemius et al. 2005; Snow et al. 2010; Moelsae et al. 2014).

If autologous transplants are not an option, allografts may be a good alternative for both, humans and dogs. However, allografts may cause severe immunologic responses and carry a risk of transmitting infectious diseases (Asselmeier et al. 1993; Centers for Disease Control and Prevention 2001). Long-term outcomes of patients treated with allogenic transplants have shown poor results (Scheffler et al. 2008). Complications include ligament laxity and extension as well as decreased mechanical stability (Poehling et al. 2005). More recent studies have proposed that acellular tissue-engineered ligaments may provide a promising alternative to

native allografts regarding complications (Gilbert et al. 2006; Butler et al. 2008; Liden et al. 2008; Carey et al. 2009).

This study's objective was to obtain detailed information on the biomechanical properties of native CrCL as well as native, decellularised and recellularised allografts and xenografts as potential transplant materials for ruptured CrCL.

Different materials have been studied and used as replacements for CrCL. The most important stress factors to consider are fixation security, strength, mechanical creep, biological compatibility of synthetics, gliding properties and dimensional stability.

- Monofilament materials allow for crimp fastening and are associated with less susceptibility to infection, tissue reactions and sinus formation, subsequent meniscal tears, peroneal nerve damage, pain and instability (Cook 2010; Muir 2010).
- In 1954, Platt said that theoretical and experimental studies on the tensile strength of twist yarn demonstrated that the optimal helix angle of fibres was 20°-30°. Approximately 15 years later, Gupta et al. (in 1969 and 1971) reported the mean tensile strength/kg body-weight (BW) of the CrCL in dogs was 46.1 N/kg BW and the meaning elongation was 4.20 mm. The result of the study by Alm et al. in 1974 on 41 Beagle dogs showed a mean tensile strength of 59.4 N/kg body-weight and mean elongation of 5.4 mm. In this test, at maximum load a series of partial ruptures started, indicated by a stepwise decrease in load uptake. The whole sequence of deformation i.e. from start of load uptake to total rupture, was completed within 1 sec and the greatest tensile strength/kg body-weight was found at an angular position of 0°, corresponding to the normal anatomical position of the stifle joint. 93.7% of the ruptures occurred in the mid-part of the CrCL. In the remaining 6.3%, the ruptures occurred in either of the 2 attachments and included a small bone fragment. Then the tensile strength and elongation of the CrCL were maximal when the stifle joint was in the normal anatomical position (Gupta et al. 1969; Gupta et al. 1971; Alm et al. 1974).

  Gupta et al. (1971) devised a procedure to measure the cross-sectional area of cranial cruciate ligaments in dogs. The cross head holding the tibia was moving at a speed of 0.2 cm/minute up until the time of ligament rupture. Gupta et al. found the average length of the CrCL was 0.81 cm, ligaments seemed to be moderately elastic, and the percentage of elongation varied between 40.0% and 77.6% before reaching the plastic range (heights point of breaking load) and the fracture load of the CrCL varied between 21.5 kg and 56.7 kg.; whereas the actual tensile strength was between 176.0 and 446.0 kg/cm^2. In most specimens, detachment started caudally and rupture occurred cranially, leaving a few ligamentous stands attached to the tibia (Gupta et al. 1971).

  In 1985, Vasseur et al. measured the mean length of the CrCL was 18.6 ± 3.8 mm and

the CrCL length varied significantly ($p < 0.0001$) with body-weight according to the relationship ($\log_L = 0.4431 \log_{BW} + 1.5548$). At < 5 years of age, there was a significant relationship ($p < 0.0001$) between the bodyweight and maximum load. The mean of the maximum load was 51.0 N/kg (Vasseur et al. 1985). In 1995, a study by Reese (1995) found a maximum strength force between 197.4 N (3.2 kg body-weight) and 1771 N (73 kg body-weight); and tensile loads/kg of 34.6 ±11.5 N/kg body-weight of the CrCL in different breeds of dog. Wingfield et al. (2000) researched the biomechanical properties of the CrCL in Rottweilers (n=13, BW= 32- 46 kg) and racing Greyhounds (n=11, BW= 26.9- 37.3 kg) and it was noted that the Rottweiler CrCL exhibited more variable behaviour at 130° knee flexion (SD= 925N). Additionally, ligament stiffness was also significantly greater in the racing greyhound at 150°. Recently, de Rooster et al. in 2001 tested in 44 dogs load-controlled tensile of CrCL and test elongated at a loading rate of 0.1 kN/s. The result breaking load of the CrCL varied from 150 N to 1230 N (Moss and Ferguson 1980; Butler et al. 1983; Korvick et al. 1994; Wingfield et al. 2000; de Rooster et al. 2001).

- Compared to earlier studies, from: Gupta et al. (1971), Alm et al. (1974), Vasseur et al. (1985), Reese (1995), Wingfield et al. (2000) and de Rooster et al. (2001), my study is the larger experimental study with experiments for native CrCL biomechanical tests in 28 dogs (n=54 stifle joint) and for biomechanical tests of native, decellularized and recellularised tendons in 30 dogs (n=76 tendons) & 2 horses (n=45 tendons).

Anatomical variations

My findings regarding average CrCL **length** of 19mm in large dogs and 15 mm in medium and small dogs are in line with reports from previous studies. Whilst Vasseur et al. (1985) found a CrCL length of 18.6 mm, study from Gupta et al. (1971) including 12 purebred Beagle dogs found a value of 8.1 mm. The average **width** of native CrCL in small, medium and large dogs ranged from 2.25 mm to 4 mm at mid-length; whilst the width at the femoral and tibial insertion sites ranged from 2 mm to 6 mm, and 4 mm to 9 mm respectively. In addition, the average **depth** of native CrCL in small, medium and large dogs ranged from 2.25 mm to 5 mm at mid-length; whilst it was found to range from 3 mm to 7.75 mm and 2 mm to 7.25 mm at the femoral and tibial insertion, respectively. It was observed that the width at the tibial insertion was larger than at the femoral insertion, whilst the depth was greater at the femoral insertion than the tibial insertion site. To the best of knowledge, no previous study has provided data on width and depth of native canine CrCL. In proportion to varying body sizes, canine CrCL naturally grow to different sizes. To avoid friction and irritation to surrounding tissues, implants

can be smaller in depth and width, but should not be larger than the natural CrCL of the individual patient. Hence, in addition to length, it is advisable to measure the precise depth and width of the patient's natural CrCL, e.g. in a healthy contralateral limb, to select a perfectly matched implant. Computed tomography with intraarticular contrast and magnetic resonance imaging can provide reliable in vivo measurements of the cranial cruciate ligament. The data provided by this study could contribute to the refinement of CrCL replacement grafts and offer guidance for cases in which a healthy contralateral CrCL is not available for size comparison.

Biomechanical properties of canine CrCL

To set a baseline for comparison of different CrCL prostheses, the breaking strength, elongation and rupture point of native CrCL were tested at different angles of flexion and extension to mimic physiological ranges of motion. To test breaking strength, a continuously increasing force was applied along the y-axis of bone-ligament-bone samples. The average **breaking strength** of CrCL samples ranged from 982.3 N to 1315.9 N at different test angles. Although differences in breaking strength were observed, the test angle was not significantly correlated to the breaking strength.

Previous studies found CrCL breaking strength at 197.4 N and 1771 N in small and large dogs at the 180° test angle respectively (Reese 1995). In addition, de Rooster et al. (2001) found a breaking strength of between 150 N to 1230 N in 44 dogs of different sizes and at the 140° test angle.

The average **elongation** ranged from 10.2 mm to 22.6 mm and was significantly correlated to the test angle in this study. The greatest elongation was found at the smallest test angle (60°), whilst the smallest elongation was found at the greatest test angle (160°).

A biomechanical study of CrCL in dogs by Gupta et al. (1971) reported elongation at 4.20 mm, whilst a study by Alm et al. (1974) reported mean elongation at 5.4 mm at a 90° test angle.

In this study, 61% (n = 33) of **ruptures** were observed at mid-length or close to mid-length of the ligament; whilst 24% (n = 13) ruptures were found close to the femoral insertion and 14.8% (n = 8) of ruptures occurred close to the tibial insertion. Moreover, it was observed that with increasing test angle, most ruptures occurred closer to the femur. Contrary to this, the samples tested at 140° had an average rupture point that was closer to the tibia than the femur. However, this could be due to the high number of sample failures (50%; n = 4) observed in this test group, which may have influenced the rupture point. Test angle and rupture point were significantly correlated, indicating a non-linear correlation between rupture point and test angle. This could be due to the complex three-dimensional anatomy of the CrCL and the stifle joint. Further studies are warranted to confirm observations and test this theory.

By comparing samples from dogs of different sizes, found that average tensile strength (N/kg) in small dogs (M = 44.4N/kg, SD = 20.7 N/kg) was significantly lower than in medium (M = 62.9 N/kg, SD = 14.4 N/kg) and large dogs (M = 39.2 N/kg, SD = 12.5 N/kg). Moreover, the tensile strength in large dogs was inferior to that of medium dogs. The highest tensile strength was found in medium and large sized dogs at 120° test angle.

Previous studies by Gupta et al. (1971) and Alm et al. (1974) of beagles and small dogs (7.8 kg and 15.7 kg) found mean tensile strengths of 46.1 N/kg and 59.4 N/kg respectively at a 90° test angle. Moreover, they found significant differences between breaking strength and body-weight of the dogs from whom the samples were obtained. In addition, Reese (1995) found tensile strengths of 61.68 N/kg in small dogs and 24.26 N/kg in large dogs (n= 36 stifle joints), the maximum tractive force achieved was between 197.4 N for the smallest dog (3.2 kg) and 1771.5 N for the largest dog (73 kg); and for the maximum tensile load/kg, an average value of 34.6 ± 11.5 N/kg was achieved at 180°.

Whilst the aetiology of CrCL rupture remains controversial, age-related degeneration, increased body-weight, breed, conformation abnormalities and immune-mediated arthropathies have been identified as risk factors. Breed-associated predispositions for CrCL deficiencies are more common in larger (> 22 kg) than small (<22 kg) breeds of dog (Vasseur et al. 1985; Johnson and Johnson 1993; Whitehair et al. 1993; Galloway and Lester 1995; Lawrence et al. 1998; Duval et al. 1999; Selmi and Padilha Filho 2001), which could be connected to the differences in tensile strength found in this study. Other factors, such as gender, age, breed and lifestyle should be considered in future investigations. Moreover, although the chosen test method simulates a variety of forces and angles, it cannot account for muscle redundancy, co-contraction and different postures. Consequently, natural joint forces during physiological activity remain elusive.

5. 1. CANINE CrCL PROSTHESES

5.1.1. Anatomical variation of the canine and equine tendon prostheses

Before trimming, the average lengths of tendons ranged from 91 mm in CRCET to 71 mm in EDDFT, whilst the overall average of CCCT samples was 71 mm. The different types of CCCT ranged from 85 mm to 60 mm in length.

In 1984, Noyes et al. (1984) compared the structural characteristics of biological tissues commonly used as cruciate ligament replacement grafts, including the patellar tendon, semitendinosus tendon, tensor fascia lata, gracilis tendon, distal iliotibial tract, and the medial, central, or lateral portion of the quadriceps tendon-patellar retinaculum-patellar tendon

complex. The only graft stronger than the ACL was the 14 mm patellar tendon; the next strongest were the semitendinosus, and gracilis tendons in humans. (Noyes et al. 1984).

5.1.2. Comparison of biomechanical properties of native and prepared tendons

As expected, native equine tendons, trimmed to match the canine tendons in size, showed a higher breaking strength (M = 604.9N) and greater elongation (M = 15.6mm) than canine samples tested in this study. Breaking strength of untrimmed native equine EDDFT is approximately 10 fold higher. Since the method chose in this study to trim EDDFT samples to comparable sizes damaged the longitudinal tendon structure, it is possible that this negatively influenced breaking strength results of our EDDFT samples. CRCET samples showed a higher mean breaking strength (M = 559 N) than CCCT samples (M = 441.6 N), which is contrary to findings of a recent study by Heintel (2013). Mean elongation in canine samples ranged from 10.6 mm to 10.9 mm.

Contrary to expectations, decellularised tendons did not show significant differences in breaking strength and elongation compared to native samples. Although decellularised EDDFT samples showed a significant decrease in breaking strength compared to native EDDFT, did not find a significant difference in breaking strength between decellularised and native CCCT. Moreover, decellularised CCCT samples showed a slight increase in mean breaking strength. Unfortunately, due to the limited sample material available, decellularised CRCET could not be tested for their biomechanical properties.

As expected, recellularised tendons did not show significant differences in breaking strength and elongation compared to native samples. Moreover, did not find significant differences in breaking strength and elongation between samples decellularised with Tx-100 and TnBP.

Within the equine samples there was a significant difference in breaking strength between native and decellularised, as well as decellularised and recellularised samples. However, no difference in elongation was found. In addition, there were no significant differences in breaking strength and elongation between native and prepared canine tendon samples.

The reason for this may be that the tendon and ligament lengths and widths of horses are much greater than in dogs, and all ligament and tendon structures physically show thinning and form changes in relation to their attachment to bone or muscle. The horse tendons used in the tests belonged to the same shape at the beginning and at the end. However, the thinning and change in shape of the tendon from the centre to the edges in dogs was reflected in the test results in this manner.

5.1.3. Decellularisation and recellularisation procedures

There was no significant difference in breaking strength between samples decellularised with Tx-100 and TnBP. However, elongation was significantly higher in samples decellularised with TnBP. Nevertheless, mean elongation results of both decellularisation groups were in line with data found in native CrCL samples. Amongst the recellularised tendon samples, there were no significant differences in breaking strength and elongation between groups decellularised with Tx-100 or TnBP.

Decellularisation aims to evade inflammation reactions and immune rejection by reducing the number of foreign antigens of biological scaffolds (Crupi et al. 2015). In view of the fact that immunogenic antigens are distributed on the surface of cell membranes and in the form of glycol- and/or lipo-proteins, it is important that donor tissues be sufficiently decellularised to avoid inflammation reactions and immune rejection (Arnoczky et al. 1982; Gilbert et al. 2006; Xu et al. 2017). An ideal decellularisation technique would successfully dissolve cell membranes and nuclear remnants as well as leave the tendon scaffolds intact and free of chemical residue (Arnoczky et al. 1982; Gilbert et al. 2006), thereby preserving their biomechanical properties. The chosen decellularisation techniques include a combination of chemicals (enzymes and detergents), which can damage the tendon's scaffold and cause a loss in breaking strength and elongation (Leys et al. 2012). Courtman et al. (2001) showed that Triton-X 100 successfully removed cells from tissues, including bovine pericardium, without damaging the collagen structure or reducing the collagen strength. In addition, Xing et al. (2014) tested a variety of decellularisation agents and found that single reagents generally showed a higher retention of collagen structures, and TnBP produced the least damage with respect to collagen structures. Moreover, they found that the decellularisation effect was related to the type and concentration of detergents as well as the order and the exposure time. Consecutive studies found that it was advantageous to use a combination of agents for multiple short periods of time, separated by several wash cycles, to increase efficiency of decellularisation as well as to reduce the exposure time to the individual agent, compared to single agent techniques, thereby reducing collagen destruction (Gilbert 2012; Xu et al. 2017). Results indicate that the chosen decellularisation protocols did not cause significant decreases in breaking strength or elongation. In addition, despite losses in breaking strength and elongation, the decellularised canine tendons could serve as suitable CrCL replacements. Moreover, results demonstrate that breaking strength and elongation capacity are largely regained through recellularisation. The number of MSC seeded for recellularisation did not significantly affect breaking strength. The ability to connect cells to each other reduces elongation while at the same time strengthening the tendon. This can be seen due to the fact

that the cellular density of the tendon improves its denseness and durability against sudden forces imposed on the implanted recellularized tendon during daily activities.
However, the elongation of recellularised tendons was found to decrease with an increase in seeded MSC. This could be due to the medium imbedded in the tendons after recellularisation.

5.1.4. Comparison of CrCL to allografts and xenografts

Although the breaking strength of native CrCL samples was significantly higher than in all decellularised and recellularised tendon samples, the tested tendon types and preparation methods could still serve as suitable replacement grafts.
Firstly, differences in the test setup between the CrCL and the tendon samples need to be accounted for. Whilst the CrCL samples were tested in their natural attachment to femur and tibia, the tendon samples were held between vices, which do not resemble surgical anchorage of the replacement grafts and may have influenced biomechanical results. In previous studies, vice-tendon-vice complexes were cooled to -80°C before biomechanical testing to prevent slipping and shear forces (Riemersa and Schamhardt 1982; Shadwick 1990; Heintel 2013; Reutter 2014). In this study, vice-tendon-vice complexes were kept at room temperature to avoid cell damage and simulate natural conditions.
Secondly, the biomechanical results found for tendons tested in this study could be lower than expected due to the selection of a small part of the tendon. Komi et al. (1992) found that the CCCT tendon was the body's strongest tendon (in humans) and was able to carry up to 12 times the total body-weight during flight responses.
Thirdly, earlier studies (Woo et al. 1991a; Woo et al. 1991b; Kim et al. 2015) found that the force acting on the stifle joint during normal activity is much smaller than the force at breaking strength. Moreover, the force is spread across the surrounding supportive tissues and ligaments, such as the menisci, collateral ligaments etc.
In veterinary medicine, a study by Gupta et al. (1969) proved that the breaking load of the CrCL appeared to be almost 4 times the body-weight, and they defended that the breaking strength of prosthetic material for anterior cruciate ligament substitution should approximate 4 times the body weighting of the dogs (Gupta et al. 1969).

In human knee joints, performing tensile testing of the bone-ligament-bone complex, Woo et al. (1999a and 1999b) reported the ultimate failure load of the native femur-ACL-tibia complex in younger cadaveric specimens to average 2160 ± 157 N, whilst mean ACL stiffness was 242 ± 28 N/mm. They were also able to demonstrate that the ultimate failure load both significantly decreased with age and with the axis of loading. Ultimate failure loads in older specimens being loaded in an anterior drawer mechanism averaged 496 ± 85 N. Given this data, Noyes

et al. (1984) concluded that the initial fixation strength of an ACL graft required for sufficient knee stability during daily activities should exceed 450 N, although earlier studies performed by Shelbourne and Gray (1997) reported excellent clinical results using graft fixation techniques with a significantly lower initial failure strength of only 248 N (Noyes et al. 1984; Shelbourne and Gray 1997; Woo et al. 1999a; Woo et al. 1999b; Dargel et al. 2007).

Choice of tendons for this study, earlier studies and the shape of tendons were considered. Physiological joint forces are much lower than breaking forces. As a result, breaking strength should not be the primary factor for the graft choice. Even though extensor tendons have lower breaking strength compared to flexor tendons (Heintel 2013; Reutter 2014), their 3D size, form and accessibility make them promising transplant candidates. Due to the structural feature of bifurcation in the distal part, the CRCET was preferred for graft material fixation with a two-bone tunnel system on the tibial part, and this would ensure for better biomechanical stability in the stifle joint.

Fourthly, several authors have emphasised the importance of increasing strength of autogenic and allogenic grafts with time and have documented its occurrence mechanically (Jackson et al. 1993; Stoerk et al. 2001; Leys et al. 2012; Mahalingam et al. 2015).

Factors contributing to the success of a CrCL repair include size and activity of the patient, ease and time of the procedure, post-operative complication rate, biocompatibility of implants, and concurrent meniscal damage (Brunnberg et al. 2014; Conzemius and Evans 2018). Immunologic factors may contribute to the pathogenesis of CrCL injury. The high activity and early post-operative weight-bearing of most dogs, however, accentuate the need for adequate repair strength and stiffness in the immediate post-operative period (Johnson and Johnson 1993; Brunnberg et al. 2014).

Due to the different assemblies, decellularised and recellularised tendons also need to be (re)tested in the bone-material-tendon assemblies following this study . With this complex, the breaking force of graft materials will show more breaking strength than with the metal complex.

5.1.5. Limitations

Native CrCL breakage tests and tendons tests were affected by the specimen angulation, sizes of breeds, different procedures and type of tendons. Six different failure modes of the tests were observed. For Native CrCL: 1. Technovit failure, 2. Lateral condyles fracture, 3. Tibial eminence fracture; for Canine and Equine tendons test : 1. Tendon gliding owing to clips fixation inefficiency, 2. Rupture in to the chips owing to over- tighten, 3. Deterioration of sterilisation during recellularisation. The failure modes were found to be a different result between test specimens, whereby test failure results were removed from the test.

6. SUMMARY

The aim of this study was to biomechanically test ligaments in different preparations from dead horses and dogs with respect to their suitability as a substitute for the cranial cruciate ligament. ***Native CrCL breakage tests:*** The biomechanical properties of the bilateral native cranial cruciate ligament (CrCL) from 28 dog were tested in different 5 geometrical stifle joint angles. The resulting biomechanical findings were related to the respective weights of the examined dogs, and were compared to the biomechanical properties of the CrCL.

Tendon breakage tests: The native suitability of canine common calcaneal tendons (CCCT) and canine radial carpal extensor tendons (CRCET) from 30 euthanised dogs, and native equine deep digital flexor tendons (EDDFT) were obtained from two horses (euthanised or recently deceased). These were treated with a variety of decellulariation, and subsequently recellularisation methods and the biomechanical changes were evaluated. By comparing the effects of various methods on the collagen structure and biomechanics, the aim of the study was to identify the most effective decellularisation method and to determine which decellularisation method has more impact biomechanically on recellularised ligaments. Moreover, a variety of combinations were investigated, including t-octyl-phenoxypolyethoxyethanol (Triton-X 100) and tri-n-butyl phosphate (TnBP), in order to determine which combination exhibited the greatest biomechanical decellularisation effect in dogs' and horses' tendons. The biomechanical properties of all CrCL and canine and equine tendons were investigated in breaking-strength and elongation tests. The breaking strength of the specimens was elongated at a loading rate of 0.1 kN/s, force interspace: 3000 – 4000 N, test velocity: 10 mm/min. By way of a general overview for native CrCL and tendon breakage tests, the average breaking strength was found for canine CrCL samples (M = 1187.4 N; SD = 425.3), Fmax 2454 and Fmin 441N. For decellularised canine and equine tendons (M = 401.3 N; SD = 121.6), Fmax 656.2 N and Fmin 160 N; as well as recellularised canine and equine tendons (M = 499.8 N; SD = 139.6), Fmax 797.1 N and Fmin 174 N were measured. The breaking strength of canine CrCL samples was significantly higher than the breaking strength of decellularised canine and equine tendons, as well as recellularised canine and equine tendons. The test showed a significant effect of native CrCL and implant materials on the breaking strength. Additionally, the results for the elongation of native CrCL samples (M = 15.7 mm; SD = 8.3) was higher than in decellularised canine and equine tendons (M = 13.6 mm; SD = 5.7) as well as recellularised canine and equine tendons (M = 14.0 mm; SD = 4.4). Information obtained during this study could be applied to prostheses used in dogs with CrCL rupture, and it was suggested that a constant factor related to body-weight could be used to evaluate the approximate strength and elasticity of the CrCL.

7. ZUSAMMENFASSUNG

Goeknil Wohlrabe geb. Kalayci: Biomechanische Eigenschaften von Hunde-Kreuzbandprothesen

Ziel der vorliegende Studie war es, bestimmte Sehnen von toten Pferden und Hunden, die unterschiedlich präpariert wurden, biomechanisch auf ihre Eignung als Ersatz des gerissenen kranialen Kreuzbandes (CrCL) beim Hund zu testen.

Native CrCL-Reissfestigkeitstest: Die biomechanischen Eigenschaften des nativen beidseitig intakten (CrCL) von 28 Hunden wurden im Seitenvergleich unter 5 verschiedenen Kniegelenkswinkeln getestet. Die Messergebnisse wurden mit dem jeweiligen Körpergewicht der Kadaver korreliert.

Sehnenreissfestigkeitstest: Für die Untersuchungen der intakten gemeinsamen Kalkaneus-Sehne (CCCT) und die der radiokarpalen Strecksehne (CRCET) von 30 euthanasierten Hunden sowie die der tiefen Beugesehne (EDDFT) von 2 euthanasierten bzw. kürzlich verstorben Pferden wurden entnommen und dahingehend getestet. Diese wurden in verschiedener Weise dezellularisiert und anschließend mit verschiedenen Methoden rezellularisiert und nochmals biomechanisch getestet, um etwaige morphologische (Kollagenstruktur) und/oder biomechanische Alterationen festzustellen. So sollte die optimalste Methode sowohl der De- als auch Rezellularisation gefunden werden, um das gerissene CrCL beim Hund gegebenenfalls mit einer der so präparierten Sehnen von Hund oder Pferd ersetzen zu können. Die Dezellularisation erfolgte mit verschiedene Substanzen und deren Kombination, darunter t-Octyl-Phenoxypolyethoxyethanol (Triton-X 100) und Tri-n-Butylphosphat (TnBP), um festzustellen, welche Kombination den größten biomechanischen Dezellularisierungseffekt bei Sehnen von Hunden und Pferden aufweist. Die damit dezellularisierten Sehnen wurden sodann biomechanisch im Hinblick auf Bruchfestigkeit und Dehnung getestet. Die Reissfestigkeit der Proben wurde bei einer Zugkraft von 0,1 kN/s, Kraftzwischenraum: 3000 - 4000 N, Prüfgeschwindigkeit: 10 mm/min gedehnt. Ein Gesamtübersicht für native CrCL- und Sehnenreisstests wurde die durchschnittliche Reissfestigkeit für canine CrCL-Proben ermittelt (M = 1187,4 N; SD = 425,3), Fmax 2454 und Fmin 441N. Für dezellularisierte Hunde- und Pferdesehnen (M = 401,3 N; SD = 121,6) wurden Fmax 656,2 N und Fmin 160 N; sowie für rezellularisierte Hunde- und Pferdesehnen (M = 499,8 N; SD = 139,6) Fmax 797,1 N und Fmin 174 N gemessen. Die Reissfestigkeit der caninen CrCL-Proben war signifikant höher als die Reissfestigkeit der dezellularisierten caninen und equinen Sehnen sowie der rezellularisierten caninen und equinen Sehnen. Der Test zeigte einen signifikanten Einfluss des nativen CrCL und der Implantatmaterialien auf die Reissfestigkeit. Zusätzlich waren die Ergebnisse für die Dehnung von nativen CrCL-Proben

(M = 15,7 mm; SD = 8,3) höher als bei dezellularisierten Hunde- und Pferdesehnen (M = 13,6 mm; SD = 5,7) sowie bei rezellularisierten Hunde- und Pferdesehnen (M = 14,0 mm; SD = 4,4). Die in dieser Studie gewonnenen Informationen könnten auf Prothesen angewandt werden, die bei Hunden mit einer CrCL-Ruptur eingesetzt werden. Es wird vorgeschlagen, dass ein konstanter Faktor in Bezug auf das Körpergewicht verwendet wird, um die ungefähre Festigkeit und Elastizität des CrCL zu bewerten.

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9. APPENDIX

Figure 2. Consent form for donation of the hind limbs of the deceased animal to medical research.

Überlassungserklärung

Ich, _____ (Tierbesitzer/in) erkläre mich hiermit einverstanden, dass die Hintergliedmaßen meines in der Klinik für kleine Haustiere der Freien Universität Berlin am ___. ___. _____ gestorbenen bzw. euthanasierten Hundes postmortal amputiert werden dürfen um sie als Probenmaterial für biomechanische Forschungsversuche zu nutzen.

Berlin,den ___.___._____ _____
Unterschrift (Tierbesitzer/in)

_____
Unterschrift (Tierarzt/Tierärztin)

Figure 8. Consent form for donation of the tendons of the deceased dogs (A) and horses (B) to medical research.

A

Überlassungserklärung

Ich, _____ (Tierbesitzer/in) erkläre mich hiermit einverstanden, dass die Sehnen meines in der Klinik für kleine Haustiere der Freien Universität Berlin am ___. ___. _____ gestorbenen bzw. euthanasierten Hundes postmortal entnommen werden dürfen um sie als Probenmaterial für biomechanische Forschungsversuche zu nutzen.

Berlin,den ___.___._____ _____
Unterschrift (Tierbesitzer/in)

_____
Unterschrift (Tierarzt/Tierärztin)

B

Überlassungserklärung

Ich, _____ (Tierbesitzer/in) erkläre mich hiermit einverstanden, dass die Sehnen meines in der Pferdeklinik der Freien Universität Berlin am ___. ___. _____ gestorbenen bzw. euthanasierten Pferdes postmortal entnommen werden dürfen, um sie als Probenmaterial für biomechanische Forschungsversuche zu nutzen.

Berlin,den ___.___._____ _____
Unterschrift (Tierbesitzer/in)

_____
Unterschrift (Tierarzt/Tierärztin)

Table 8. List of individual biomechanical test results from all canine CrCL samples (n=54), including test angle, breed, weight (kg), age (years), breaking strength (N), elongation (mm), tensile strength (N/kg) as well as relative distance of the rupture to the femur (%) and tibia (%).

N	Angle	Breed	Weight	Age	Breaking strength	Elongation	Tensile strength (N/kg)	Relative distance to femur %	Relative distance to tibia %
1	60°	RW	30	10	1900	27,4	63,33	44,11	55,89
2	60°	RW	30	10	1661	24,29	55,36	53,84	46,16
3	60°	DB	35	12	1110	19,2	31,71	60,5	39,5
4	60°	DB	35	12	1090	20	31,14	60	40
5	60°	EB	30	7	780	27,9	26	100	0
6	60°	L	40	12	850	22,2	21,25	68,18	31,82
7	60°	L	40	12	579	17,4	14,47	72,72	27,28
8	90°	C	27	8	1247	14,5	46,18	56	44
9	90°	C	27	8	1147	11,68	42,48	52	48
10	90°	GR	32	12	986	15,26	30,8	26,83	73,17
11	90°	GR	32	12	441	10,36	13,78	0	100
12	90°	GS	36	10	964	11,43	26,7	48,28	51,72
13	90°	GS	36	10	969	13,8	26,9	50	50
14	90°	GD	35	10	2454	57,79	70,11	61,29	38,71
15	90°	GD	35	10	2319	30,91	66,25	60	40
16	120°	RW	35	15	1404	14,04	40,1	55,88	44,11
17	120°	RW	35	15	1371	10,08	39,1	58,82	41,18
18	120°	L	27	13	1032	8,62	38,2	42,1	57,9
19	120°	L	27	13	969	7,77	35,8	43,47	56,53
20	120°	BMD	40	8	1013	15,3	25,32	52,63	47,37
21	120°	BMD	40	8	1065	12,9	26,62	48	52
22	120°	C	26	10	1095	10,84	42,1	0	100
23	120°	C	26	10	1718	14,23	66	0	100
24	120°	GS	23	2	1216	10,7	52,8	56	44
25	120°	GS	23	2	1545	16,24	67,1	47	53
26	120°	AT	23	10	1130	14,48	49,1	100	0
27	120°	AT	23	10	997	12,5	43,3	38,7	61,3

N	Angle	Breed	Weight	Age	Breaking strength	Elongation	Tensile strength (N/kg)	Relative distance to femur %	Relative distance to tibia %
28	120°	LD	19	12	1310	13,2	68,9	46,15	53,85
29	120°	LD	19	12	1118	20,29	58,8	57,14	42,86
30	120°	BD	19	2,5	1550	16	81,57	80,95	19,05
31	120°	BD	19	2,5	1550	15,7	81,57	90,47	9,53
32	120°	C	13	8	735	5,22	56,5	30,76	69,24
33	120°	C	13	8	855	5,52	65,7	40	60
34	120°	C	12	14	585	12,3	41,7	42,85	57,15
35	120°	C	12	14	210	13,58	15	56	44
36	120°	FB	10	5	696	9,2	69,9	39,13	60,87
37	120°	BC	15	11	596	14,5	37,9	66,66	33,34
38	120°	BC	15	11	365	11,69	24,3	0	100
39	140°	CO	25	14	1412	21	56,48	100	0
40	140°	CO	25	14	702	13,55	28,8	48,38	51,62
41	140°	B	39	11	841	12,1	21,56	100	0
42	140°	B	39	11	659	13,3	16,89	57,14	42,86
43	140°	C	34	8	1310	9,4	38,52	56,52	43,48
44	140°	C	34	8	1290	14,4	37,94	61,58	38,42
45	140°	GS	38	14	943	17,57	24,81	100	0
46	140°	GS	38	14	701	17,54	18,44	100	0
47	160°	GS	25	12	536	4,8	21,44	54,28	45,72
48	160°	GS	25	12	519	4,4	20,76	63,33	36,67
49	160°	RR	49	10	1410	11	28,77	52,2	47,8
50	160°	RR	49	10	1580	12,9	32,24	44	56
51	160°	RDF	36	6	1678	12,22	46,61	100	0
52	160°	RDF	36	6	1330	9,7	36,94	47,22	52,78
53	160°	BMD	34	7	1320	14	38,82	38,23	61,77
54	160°	BMD	34	7	997	12,5	29,32	36,66	63,34

Abbreviations: AT=Airedale Terrier, B=Boxer, BC=Border Collie, BD=Bulldog BMD=Bernese Mountain dog, C=Crossbreed, CO=Collie, DB=Doberman, EB=English Bulldog, GD=Great Dane, GR=Golden Retriever, GS= German shepherd, L=Labrador, LD= Longhair Dachshund, FB= French Bulldog, RW= Rottweiler, RDF=Router des Flandes, RR=Rhodesian Ridgeback.

Table 10. List of biomechanical results of all tendon samples including preparation type, weight of sample specimen (kg), breaking strength (N), elongation (mm) and estimated number of seeded canine mesenchymal stroma cells (MSC) for recellularized samples.

Types	Preparation	Weight	Breaking strength	Elongation	MSC
CCCT – 1	Native	25	497.17	10.86	
CCCT – 2	Native	30	471.97	15.98	
CCCT – 3	Native	30	392.53	8.19	
CCCT – 4	Native	30	328.74	15.86	
CCCT – 5	Native	30	378.17	8.49	
CCCT – 6	Native	30	651.88	8.49	
CCCT – 7	Native	25	308.1	12.19	
CCCT – 8	Native	30	316.1	7.45	
CCCT – 9	Native	25	629.36	10.9	
CCCT – 10	Decellularized B	32	424	14.8	
CCCT – 11	Decellularized B	25	335	13.3	
CCCT – 12	Decellularized B	32	412	17.3	
CCCT – 13	Decellularized B	25	160	7.2	
CCCT – 14	Decellularized B	32	296	9.4	
CCCT – 15	Decellularized B	25	298	21	
CCCT – 16	Decellularized B	23	465	10.5	
CCCT – 17	Decellularized B	23	471	13	
CCCT – 18	Decellularized B	23	655	15.4	
CCCT – 19	Decellularized A	35	307.6	4.04	
CCCT – 20	Decellularized A	35	656.21	11.39	
CCCT – 21	Decellularized A	29	562.52	12.32	
CCCT – 22	Decellularized A	29	511.91	12.7	
CCCT – 23	Decellularized A	30	483.81	9.7	
CCCT – 24	Decellularized A	30	605.69	12.51	
CCCT – 25	Decellularized A	35	444.64	7.53	
CCCT – 26	Decellularized A	35	372.68	8.99	
CCCT – 27	Decellularized A	24	238.32	8.55	
CCCT – 28	Recellularized B	35	407.71	9.612	1068750
CCCT – 29	Recellularized B	35	559.83	18.9	1068750
CCCT – 30	Recellularized B	25	526.49	10.4	1068750
CCCT – 31	Recellularized B	25	510.63	14.96	1068750

Types	Preparation	Weight	Breaking strength	Elongation	MSC
CCCT – 32	Recellularized B	39	564.08	15.02	1453125
CCCT – 33	Recellularized B	24	395.75	13.29	1453125
CCCT – 34	Recellularized B	25	400.38	7.3	1453125
CCCT – 35	Recellularized B	35	394.85	14.31	934375
CCCT – 36	Recellularized B	28	523.44	16.64	1193750
CCCT – 37	Recellularized B	24	565.93	21.12	1193750
CCCT – 38	Recellularized B	25	462	11.9	1453125
CCCT – 39	Recellularized A	25	546.21	10.72	684375
CCCT – 40	Recellularized A	25	435.06	12.14	1068750
CCCT – 41	Recellularized A	25	451.15	15.58	1068750
CCCT – 42	Recellularized A	35	424.4	7.19	1068750
CCCT – 43	Recellularized A	35	387.83	12.1	1068750
CCCT – 44	Recellularized A	25	471.66	10.76	1453125
CCCT – 45	Recellularized A	24	403.68	7.69	1453125
CCCT – 46	Recellularized A	39	439.7	12.68	1453125
CCCT – 47	Recellularized A	35	521.74	11.57	934375
CCCT – 48	Recellularized A	25	726	22.2	934375
CCCT – 49	Recellularized A	24	776.55	9.39	1453125
CRCET-1	Native	30	532	3.9	
CRCET-2	Native	30	357	6.8	
CRCET-3	Native	35	409	7.9	
CRCET-4	Native	35	667	13.7	
CRCET-5	Native	30	486	11.9	
CRCET-6	Native	30	701	12.8	
CRCET-7	Native	23	542	11	
CRCET-8	Native	23	578	14.2	
CRCET-9	Native	45	759	12.8	
CRCET-10	Recellularized B	35	591.1	9.32	934375
CRCET-11	Recellularized B	25	216.44	6.11	864285714
CRCET-12	Recellularized B	39	396.28	18.38	864285714
CRCET-13	Recellularized B	39	578.39	19.47	864285714
CRCET-14	Recellularized B	58	438.14	8.29	1193750
CRCET-15	Recellularized B	20	624	11	934375
CRCET-16	Recellularized B	25	524	17.7	934375

Types	Preparation	Weight	Breaking strength	Elongation	MSC
CRCET-17	Recellularized B	35	310	10.9	864285714
CRCET-18	Recellularized B	25	655	15.4	1453125
CRCET-19	Recellularized A	20	433.99	16.4	934375
CRCET-20	Recellularized A	35	500.64	9.15	934375
CRCET-21	Recellularized A	24	388.53	8.11	864285714
CRCET-22	Recellularized A	58	739.06	13.6	1193750
CRCET-23	Recellularized A	25	331	13	934375
CRCET-24	Recellularized A	25	363.37	5.31	1453125
CRCET-25	Recellularized A	37	377	13.5	864285714
CRCET-26	Recellularized A	37	451	18	864285714
CRCET-27	Recellularized A	35	328	10.7	864285714
EDDFT 1	Native		567.51	14.33	
EDDFT 2	Native		746.19	15.83	
EDDFT 3	Native		743.39	16.16	
EDDFT 4	Native		719.65	11.88	
EDDFT 5	Native		446.49	10.12	
EDDFT 6	Native		575.57	23.8	
EDDFT 7	Native		357.06	10.9	
EDDFT 8	Native		710.43	17.19	
EDDFT 9	Native		577.6	20.52	
EDDFT 10	Decellularized B		353	16.2	
EDDFT 11	Decellularized B		284	14.5	
EDDFT 12	Decellularized B		369	23.1	
EDDFT 13	Decellularized B		356	18.7	
EDDFT 14	Decellularized B		412	22.2	
EDDFT 15	Decellularized B		280	22.8	
EDDFT 16	Decellularized B		456	16.3	
EDDFT 17	Decellularized B		216	32.5	
EDDFT 18	Decellularized B		316	14.5	
EDDFT 19	Decellularized A		386.59	11.82	
EDDFT 20	Decellularized A		351.37	9.94	
EDDFT 21	Decellularized A		442.69	9.84	
EDDFT 22	Decellularized A		315.75	5.44	
EDDFT 23	Decellularized A		597.71	10.35	

Types	Preparation	Weight	Breaking strength	Elongation	MSC
EDDFT 24	Decellularized A		277.53	11.28	
EDDFT 25	Decellularized A		537.51	18.88	
EDDFT 26	Decellularized A		456.09	12.69	
EDDFT 27	Decellularized A		340	9.72	
EDDFT 28	Recellularized B		797.1	12.95	930000
EDDFT 29	Recellularized B		609.93	17.54	930000
EDDFT 30	Recellularized B		796.63	20.17	930000
EDDFT 31	Recellularized B		366.92	14.68	930000
EDDFT 32	Recellularized B		611.08	18.61	930000
EDDFT 33	Recellularized B		673.11	18.26	930000
EDDFT 34	Recellularized B		467.46	16.61	930000
EDDFT 35	Recellularized B		572.15	13.17	930000
EDDFT 36	Recellularized B		174.53	8.31	1193750
EDDFT 37	Recellularized A		411.45	13.9	930000
EDDFT 38	Recellularized A		545.53	15.95	930000
EDDFT 39	Recellularized A		533.01	19.65	930000
EDDFT 40	Recellularized A		652.95	22.81	930000
EDDFT 41	Recellularized A		713.75	18.32	930000
EDDFT 42	Recellularized A		566.33	19.63	930000
EDDFT 43	Recellularized A		421.3	20.32	930000
EDDFT 44	Recellularized A		659.42	17.84	930000
EDDFT 45	Recellularized A		277.11	14.15	1193750

Abbreviations: CCCT = Canine common calcaneal tendon, CRCET = Canine radial carpal extensor tendon, EDDFT= Equine deep digital flexor tendon.

10. ACKNOWLEDGEMENTS

I would especially like to thank Professor Dr. Dr. h. c. Leo Brunnberg, who offered me an opportunity to study in Germany. He provided me with this interesting theme and worked intensively for me in the supervision of the doctoral thesis, other publications and my Master Thesis. Furthermore, I would like to thank Professor Brunnberg for his general support and the establishment of many contacts that made this project possible. I owe my professional training to his vast and extensive surgical, orthopedical and radiological experience and high level of motivation as well as his willingness to pass both on to me.

Special thanks go to the Technical Head of the Biomechanics Lab of Dipl. Ing. Dag Wulsten and Prof. Dr.- Ing. Georg Duda from the Julius Wolff Institute of Biomechanics and Musculoskeletal Regeneration. Not only did they allow me to work with their biomechanical machines, but they also introduced me to the specifics of working with them and helped me a lot in the process.

I would like to thank Prof. Dr. Andreas Kurtz and his team from the Berlin-Brandenburg Centre for Regenerative Therapies (BCRT) for the opportunity to work in the laboratory. I would also like to thank Meike van Staa for her good cooperation in the lab and in this project.

I would like to thank the respective colleagues of the Small Animal Clinic of the Free University of Berlin for their help in collecting and obtaining the samples of material from dogs.

Finally, I would like to thank my beloved family, especially my parents, my husband, my brothers, and my parents-in-law without whose help and support this doctoral thesis would not have been possible.

11. DECLARATION OF AUTHORSHIP

I hereby declare that the thesis submitted is my own unaided work. All direct or indirect sources used are acknowledged as references.

SELBSTÄNDIGKEITSERKLÄRUNG

Hiermit bestätige ich, dass ich die vorliegende Arbeit selbständig angefertigt habe. Ich versichere, dass ich ausschließlich die angegebenen Quellen und Hilfen in Anspruch genommen habe.

Berlin, den 02.05.2022

Göknil Wohlrabe geb. Kalayci

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49,90 Euro | ISBN: 978-3-96729-175-9