DOI: 10.17624/TF.2023.4

Mechanism of Non-contact ACL Injury

What Does Delayed Onset Muscle Soreness Have to Do With Non-contact Anterior Cruciate Ligament Injuries?

Thesis

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Budapest

2023

Content

Abbreviations:

ACL: anterior cruciate ligament
ACLR: anterior cruciate ligament reconstruction
ASIC3: acid-sensing ion channel 3
ASR: acute stress response
CNS: central nervous system
COX-2: cyclooxygenase-2
FPS: frame per second
GABAergic: gamma-aminobutyric acidergic
DAMP: damage associated molecular pattern
DOMS: delayed onset muscle soreness
DRG: dorsal root ganglion
LH: luteinizing hormone
MLR: medium latency response
MP: megapixel
MSFT: multistage fitness test
NC-ACL: non-contact anterior cruciate ligament
NGF: nerve growth factor
NMDA: N-methyl-D-aspartate
NMDAR: N-methyl-D-aspartate receptor
NO: nitric oxide
NOS: nitric oxide synthase
OA: osteoarthritis
PGE2: prostaglandin E2
PIC: persistent inward currents
POIS: post-orgasmic illness syndrome
PRR: pattern recognition receptor
RBE: repeated bout effect
REC: rectus femoris
sEMG: surface electromyography
SNS: sympathetic nervous system

SLR: short latency response

TAD: terminal arbor degeneration

TrkA: tropomyosin receptor kinase A

TRPV: transient receptor potential cation channel subfamily V

UPR: unfolded protein response

VMO: vastus medialis

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1. Introduction

Anterior cruciate ligament (ACL) injury comprises the stretched, partially- or completely torn ACL ligament, while delayed onset muscle soreness (DOMS) comes with delayed onset of soreness, muscle stiffness, swelling, loss of force-generating capacity, reduced joint range of motion, and decreased proprioceptive function (1).

ACL injury dominantly occurs on a non-contact basis, entailing 70-84% of ACL injuries (2-8). The exact mechanism of non-contact ACL (NC-ACL) injury is not completely understood, like in the case of DOMS. Boden et al. (9) gathered the running theories of noncontact ACL injuries: impingement on the intercondylar notch, quadriceps contraction, quadriceps-hamstring force balance, increased knee valgus or abduction moments, generalized joint laxity, knee recurvatum, ACL size and hormonal effects of estrogen on the ACL and the axial compressive forces on the lateral aspect of the joint. Sex and anatomical differences are considered to be risks of ACL injury (10-12). Noteworthy, that impaired neuromuscular control also identified as a risk factor, like decreased neurocognitive function (13), increased trunk displacement after sudden force release (14) and the weakened neuromuscular control of core and hip muscles (10, 15, 16).

The running theories of DOMS are as follows: lactic acid, muscle spasm, inflammation, connective tissue damage, muscle damage, and enzyme efflux theory (17). Nevertheless, the current scientific viewpoint is that no single theory could explain the onset of DOMS, but it is rather a combination of them in a uniquely orchestrated way (17). We hypothesized that the bi-phasic mechanism of DOMS is primarily an acute compression axonopathy at the proprioceptive sensory terminals in the muscle spindle (18). This type of neuronal microdamage could be caused by superposition of compression forces under unaccustomed or strenuous repetitive eccentric contractions and within a cognitive demand induced acute stress response (ASR) time window (18).

We proposed a comparable dichotomous injury mechanism in NC-ACL injury, like in DOMS. Correspondingly, the critical cause could be an analogous acute axonopathy of the proprioceptive sensory nerves in the proximal tibia in the form of a nerve compression or crush injury. Important to note, that the axial impulsive force theory accredited also two compression forces as the cause of the damage in noncontact ACL injury, namely the compressing valgus force due to leg buckling and the compressive

anterior force due to quadriceps contraction (9). However, we suggested that the superposition of compression is causing the initial neuronal microdamage within the proximal tibia and in its periosteum and an acute nerve compression or crush injury could evolve due to these extreme superimposed forces, like in DOMS.

We have emphasized the similarity of the innervation of periosteal bone compartments and the muscle spindles in our previous publications (18, 19). Both compartments are innervated by non-nociceptive and nociceptive sensory neurons (18, 19). Accordingly, we proposed that damaging superposition of compression forces are microdamaging the proprioceptive sensory terminals of the muscle spindle in DOMS, and the encapsulated proprioceptive afferent terminals in the periosteum of the proximal tibia in noncontact ACL injury leading to compression or crush nerve injury (18-20).

2. Objectives

The objective of my dissertation is to examine the theory whether proprioceptive terminal microinjury could lead to non-contact injuries, like it is suspected in NC-ACL injury and DOMS. Furthermore, we found it important to test the hypothesis whether the infrapatellar nerve innervated area at the medial proximal tibia could have a potential role in the injury mechanism as is presumed in our theory (19).

Proske et al. demonstrated that repetitive eccentric contractions alter or even damage proprioception (21). Accordingly, we hypothesized that these repetitive unaccustomed or strenuous eccentric contractions under a cognitive demand induced acute stress response time window could microdamage the proprioceptive axon terminals in the muscle spindles and even in the periosteum of the proximal tibia (18, 19, 22). We suggested that this terminal microinjury is a terminal arbor degeneration (TAD) like mechano-energetic lesion on the peripheral ends of these pseudounipolar proprioceptive fibers (18). Important to note, that paclitaxel-based chemotherapy shows this type of terminal sensory lesion and evolves after a dose limiting, threshold driven manner and not associated with classical axonal degeneration (23).

Furthermore, we theorized that DOMS impacts the static encoding of the mostly unaffected stretch reflex of the preprogrammed postural control (22). We also proposed that this, seemed to be negligible, alteration is due to the exchange of monosynaptic static

encoding of the stretch reflex derived from impaired Type Ia afferents to Type II polysynaptic static afferent ones (22). Noteworthy, that both Types Ia and Type II sensory fibers transduce static phase firing encoding, but dynamic encoding is transduced only by Type Ia fibers. We hypothesized that the encoding of the dynamic changes component of the sensory encoding is basically unaffected, like it is the case in paclitaxel-based chemotherapy (24). Correspondingly, we expected no delay in the latency of the short latency response (SLR) of the stretch reflex due to DOMS effect. Indeed, the only available scientific publication in reference to this topic showed that no delay of SLR could be detected after DOMS effect (25).

We further theorized the mechanism of the actual microdamage that could lead to this Type Ia impairment, namely an energy depleted mitochondria induced dysfunctional glutamate vesicular release and Piezo2 channelopathy (20, 26). Important to note, that Piezo2 ion channels are demonstrated to be the principal mechanotransduction channels for proprioception (27). We suggested that the microdamage evoked secondary compensatory pathway on the spinal dorsal horn is preprogrammed (19,22). We also recommend that this switch of static monosynaptic Type Ia afferent connection to Type II polysynaptic afferent ones is indicated in the delayed latency of the medium latency response (MLR) of the affected stretch reflex (22, 28, 29). Notable, that the conduction velocity of Type II sensory fibers is slower compare to Type Ia fibers, like the polysynaptic signaling is slower compared to monosynaptic signaling. Furthermore, this proposed switch to polysynaptic signaling within the proprioceptive system is more energy consuming neuro-energetically than monosynaptic signaling, especially if we consider that the proprioceptive system is suggested to have an overall resource limitation (19, 22). Numerous studies concluded that MLR is presumably Type II afferent mediated dominantly (30-39). In summary, our first objective was to test whether the proposed proprioceptive microdamage induced exchange of static phase firing encoding from Type Ia fibers to Type II fibers could delay the MLR of the stretch reflex. This delay of MLR could be a diagnostic evidence of proprioceptive impairment.

Our new NC-ACL injury mechanism hypothesis suspects the above TAD like lesion of the proprioceptive terminal at the periosteum of the medial proximal tibia (19) and the same transient Piezo2 channelopathy is proposed as in DOMS (26). This hypothesis is based on the suggested to be analogous innervation of the medial ankle (40),

Correspondingly, we proposed that the infrapatellar branch of the saphenus nerve innervates not just the skin, but the periosteum and joint capsule as well. Accordingly, our second objective was to develop a measurement method and to demonstrate its applicability in order to approximate the point of attack of the resultant force (hereinafter knee point) in the knee in a geometric way. We hypothesize that in the provocative position of the NC-ACL injury (that is the almost fully extended knee with minimal knee flexion) (41, 42), the evolvement of the point of attack of the resultant force will be at the medial proximal tibia due to the repetitive superimposed compression forces (19).

3. Methods

Hereby, we detailed the methods of investigation of our research objectives. Important to note that in this section, the text and figures of the proposed measurement method of the knee point at the NC-ACL injury provocative position are part of a manuscript that is published in the journal of Biomechanica Hungarica (43).

3.1. Test measurement of the knee point at the NC-ACL injury provocative position

3.1.1. Participants

The anthropometric data of the examined person is as follows: female, age 22 years old, body height 178 cm and body weight 72 kg. The tested individual has been a competitive handball player for more than 15 years. She is participating on practices 9 times a week and training 3 times a week off season. She suffered an ACL injury on her right knee three years ago on a handball match during the game. She underwent an ACL reconstruction (ACLR) three times (2018, 2018, 2019). Before the test examination she was informed about the protocol, and signed a written consent. The Ethical Committee of the University of Physical Education approved the experimental study.

3.1.2. Procedure

The measurement was taken in the laboratory of the Department of Mechanotronics, Optics and Mechanical Engineering Informatics, Budapest University of Technology and Economics. We used OPTITRACK (NaturalPoint, Corvallis, Oregon, USA), an optical

motion analysis system of the laboratory. The motion analysis was followed by 18 pieces of Flex 13 type cameras and with the assistance of Motive:Body software. The resolution of the cameras is 1.3 megapixel (MP), with 56° vision angle and the pictures were taken in infrared range with a maximum recording speed of 120 frame per second (FPS). In our test measurement, the sample recording frequency was 100 FPS. Ball shaped markers covered with a reflective material with a diameter of 5 mm were used to track the motion of anatomical points.

It is important to choose the right biomechanical model in motion analysis. The subject of our test measurements was the lower limb, specifically the motion of the knees. Accordingly, the markers were applied to the adequate anatomical points with the extension of Rizzoli Lower Body Protocol marker set. The abbreviations of the examined anatomical points are listed in Table 1. The markers were applied directly to the skin or on the clothing with medical tapes.

Table 1.: The anatomical locations of markers used during measurements (43)

Marker abbreviations	**Anatomical locations:**
LPSI	Spina iliaca posterior superior lateris sinistri (l.s.)
RPSI	Spina iliaca posterior superior lateris dextri (l.d.)
LASI	Spina iliaca anterior superior l.s.
RASI	Spina iliaca anterior superior l.d.
LLE	Femoralis epicondyle l.s.
RLE	Femoralis epicondyle l.d.
LME	Medial femoralis epicondyle l.s.
RME	Medial femoralis epicondyle l.d.
LHF	Caput fibulae l.s.
RHF	Caput fibulae l.d.
LMF	Medial condyle l.s.
RMF	Medial condyle l.d.
LTT	Tuberositas tibiae l.s.
RTT	Tuberositas tibiae l.d.
LLM	Malleolus lateralis l.s.
RLM	Malleolus lateralis l.d.
LLM	Malleolus lateralis l.s.
RMM	Malleolus lateralis l.d.
LCA	Calcaneus l.s.
RCA	Calceneous l.d.

Optitrack system was calibrated prior to analysis measurements, in order to gain adequate precision under the circumstances. After the calibration, the average measurement error was 0.47 mm during measurements.

After a brief warm-up session, three jump tasks were needed to be executed during the analysis by the participant. The first task was a vertical jump with both legs and landing on both feet. The second task was a vertical jump with both legs again and landing on the right (injured) foot. The third task was a vertical jump with both legs and landing on the left (healthy) foot. The optical motion detector system recorded all the three tasks.

3.1.3. Exercise protocol

Processing data of the motion analysis measurements is a complex task and it is exhibited on Figure 1. The motion detection system recorded the exercise task with the Motive:Body software. This program records the spatial coordinates of markers and with its help, we could calculate biomechanical parameters and partition the recordings to cycles.

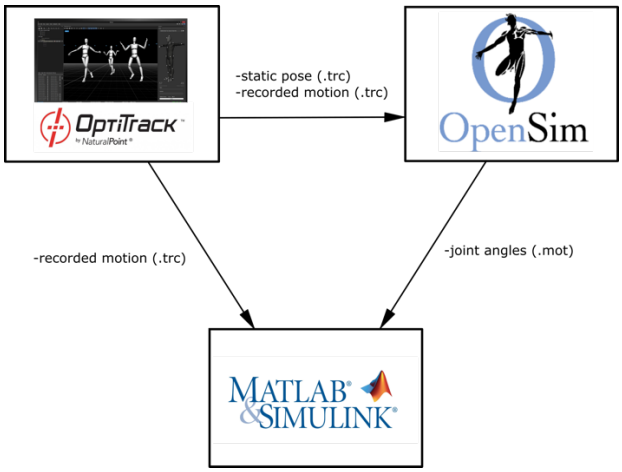

Figure 1.: The flowchart of the data processing (43)

The biomechanical parameters were calculated from the spatial coordinates of markers in multiple steps. The knee flexion/extension angle, the section of the axis of the tibia and plane of the knee (defined as knee point), and the rate of change of the relative angle offset of the tibia from frontal direction were examined. We used the OpenSim (NIH Center for Biomedical Computation, Stanford University) software with its Inverse Kinematic tool for the calculation of the joint angles. After the processing of the data by the software, we exported in .mot (motion files) format in order to analyze the data

further. This analysis was executed in MATLAB (2021a, MathWorks, Massachusetts, USA) software with self-made program code.

We examined the intersection point of the tibia axis and sagittal knee plane from frontal view, because we wanted to show whether the point of attack of the resultant force skew to medial or lateral side after vertical jump. We approximated the axis of the tibia in a way that the midpoint of the connecting axis of the applied markers on the ankle (LLM, LMM; RLM and RMM) and the midpoint of the connecting axis of the applied markers on the proximal tibia were connected with a line from a frontal direction. The approximation of the knee plane was carried out in a way that the midpoint of the connecting line of the applied markers on the distal femur (LLE and LME; RLE and RME) and the midpoint of the connecting line of the applied markers on the proximal tibia (LHF and LMF; RHF and RMF) were connected with a line from a frontal direction. We approximated the point of maximum force transfer with the point of intersection of the above lines and that is the knee point. The approximated knee point was presented on Figure 2.

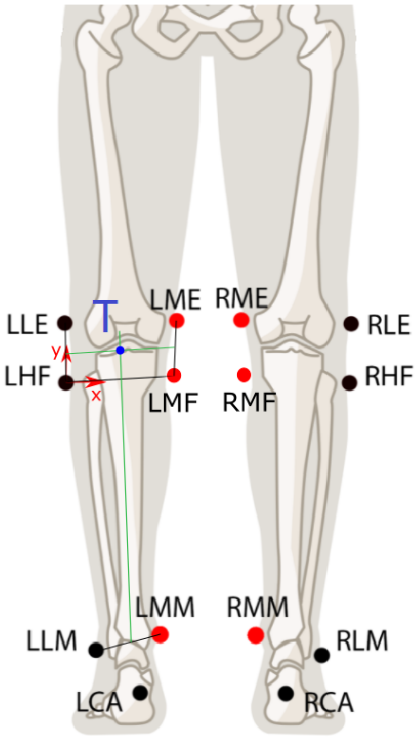

Figure 2.: Geometrical calculation of the approximate knee point (marked with blue letter T) with the assistance of markers in reference to the left knee (43)

The x and y coordinates of the approximated knee point was exported. The origin of the local grid in reference to the right knee is the RHF marker and LHF marker in reference to the left knee correspondingly. The relative angle offset of the tibia was calculated with the assistance of the tibia axes. The relative angle offset of the tibia was continuously compared to the axis of the tibia at first frame of record.

The partition to cycles was executed by examining the coordinates along the vertical axis of the markers applied to the external ankle. The highest point of the vertical jump was where the markers applied to both ankles were at local maximum measures. One analyzed cycle lasted from the peak point of vertical jump to the point just after landing. The duration of the whole cycle was determined to be 1 second. We analyzed the cycles of the three separate tasks independently. Furthermore, we investigated the biomechanical parameters of the cycles of each task, namely the knee joint flexion/extension angle, the intersection point of the tibia axis and the plane of the knee, and the relative angle offset of the tibia from frontal direction.

3.2. MLR study

3.2.1. Participants

Nine female professional handball players (mean ± SD age: 24,11±3,72) took part in our electrophysiological study. They were informed about the protocol, and signed a written consent prior to the electrophysiological measurements. The Ethical Committee of the Hungarian University of Sports Science (TE-KEB/26/2021) approved the experimental study.

3.2.2. Procedure

The goal of this electrophysiological study was to explore how an acute fatiguing, preferably DOMS inducing task changes the time characteristics of the MLR based on the SLR. After a warm-up session, the protocol involved two surface electromyography (sEMG) measurements before and after a 20 m multistage fitness test (MSFT). The two measurements recorded the EMG activity of the vastus medialis (VMO) and the rectus femoris (REC). The dominant leg of the handball players was measured.

One of the examiners controlled the sEMG software, while the other had the responsibility to induce the stretch reflex. The participants were seated with electrodes

placed on their dominant leg in 90 degree flexion, and their task was to hold this 90 degree flexion, while one of the examiners pulled their leg forward with an elastic band which was placed around the ankle of the dominant leg. The participants were told that without any sign, the examiner will suddenly release the elastic band, and their job is to get back to the 90 degree flexion as fast as they possibly can. Two measurements were recorded, one before and one after the fatiguing MSFT.

3.2.3. Exercise protocol

The MSFT is a test often used by trainers to evaluate aerobic fitness. This test consists of continuous running between two lines 20 meters apart in time to recorded beeps. The speed at the start of the test is slow. After one minute, an increase in speed happens, and the time between beeps decreases. Each minute time between beeps decreases so a level consists of 1 minute. If the line is reached before the beep sounds, the subject must wait until the beep sounds before continuing. If the line is not reached before the beep sounds, the subject is given a warning and after the second warning subject is excluded.

3.2.4. Electromyography

Noraxon MyoResearch Master Edition 1.08.27 software was used for sEMG data processing. Frequency range under 5 Hz, over 350 Hz were cut, while 50–60 Hz frequency domains were filtered and the whole signal was smoothened by the built-in smoothening module of the Noraxon software.

3.2.5. Statistics

Due to the limited sample size and for the purpose of selecting the adequate statistical procedure Shapiro Wilk's W test was calculated for checking the normal distribution of the data. Only the VMO before the MSFT is not normally distributed, so for comparing the VMO data, the Wilcoxon nonparametric test was used, while comparing the REC data, a dependent *t*-test was used. To further support the results of this study Effect size (ES-Cohen's d) value is calculated and included. Statistical Power is also calculated for the significant differences. StatSoft STATISTICA 13.2 is used for the statistical analysis, significance level is set for $p < 0.05$.

3.2.6. Muscle soreness questionnaire

Statement form was sent out on email one day after the MSFT to the professional handball players to declare whether they experienced DOMS after the fitness test. All players sent back the statement form with their declaration within 48 hours. After filling out the questionnaire, 6 of 9 participants acclaimed DOMS after the fatiguing protocol.

4. Results

4.1. Measurement method for the knee point at the NC-ACL injury provocative position

The exhibited biomechanical parameters were the knee joint flexion/extension angle, the intersection point of the tibia axis and the plane of the knee, and the relative angle offset of the tibia from frontal direction. We could approximate at what extent and what direction of the knee joint cartilage is compressed from the x directional component of the intersection point of the tibia axis and the plane of the knee (knee point). The biomechanical parameters of vertical jumps with both legs is shown on Figure 3.

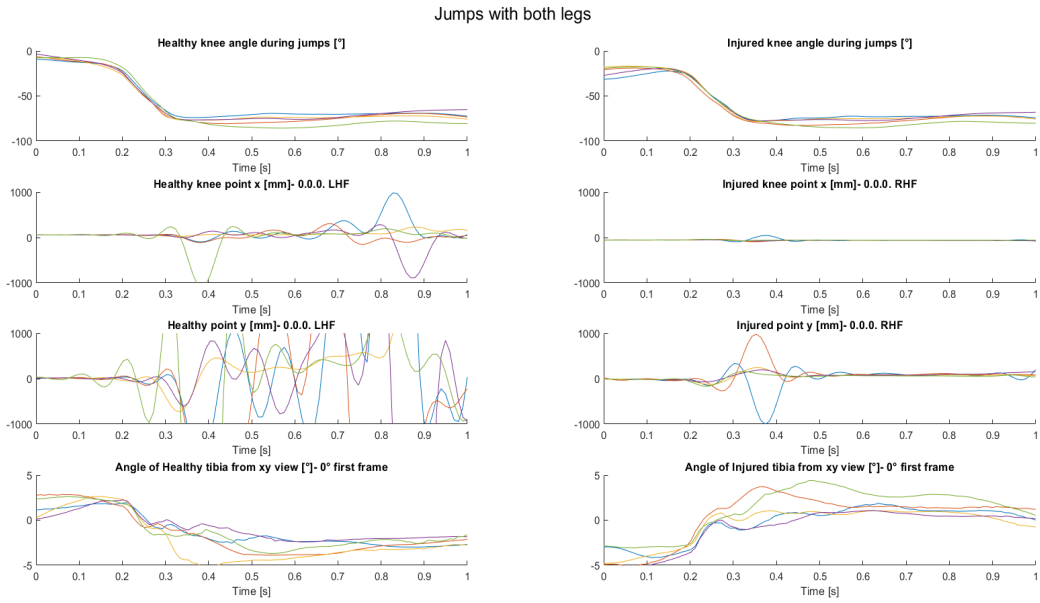

Figure 3.: Presentation of biomedical parameters during landing followed by jumping with both legs (43)

The Figure 4. and 5. present the biomechanical parameters of the landings with one leg. On both figures, the biomechanical parameters of the jumping leg are the relevant ones, because they have to bear the loading and they also have to attenuate the shock effect. They are demonstrated in two separate exhibits due to the characteristics of the lines of the graphs.

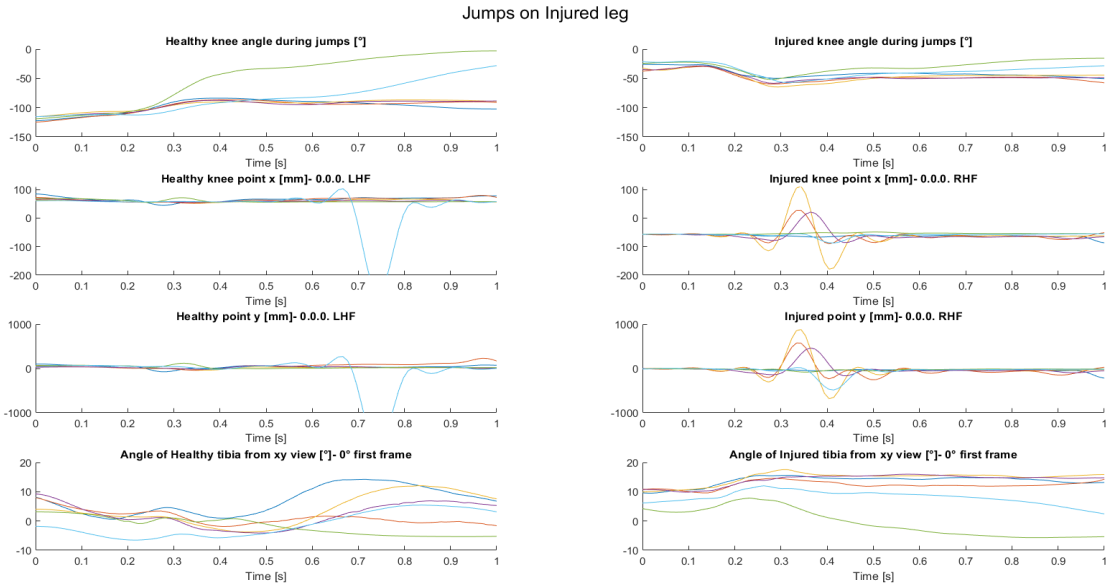

Figure 4.: Presentation of biomedical parameters during landing with injured leg that is followed after jumping – the biomechanical parameters of the jumping (injured) leg are the relevant ones (43)

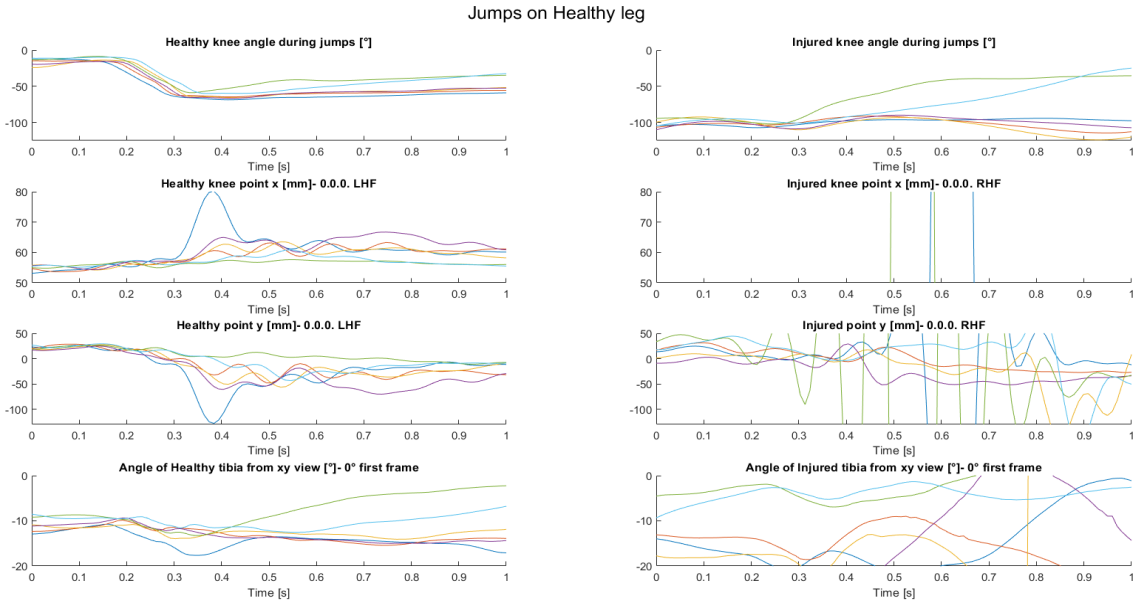

Figure 5.: Presentation of biomedical parameters during landing with healthy leg, that is followed after jumping – the biomechanical parameters of the jumping (healthy) leg are the relevant ones (43)

Finally, Figure 6. demonstrates the biomechanical parameters of the jumping legs for comparison purposes.

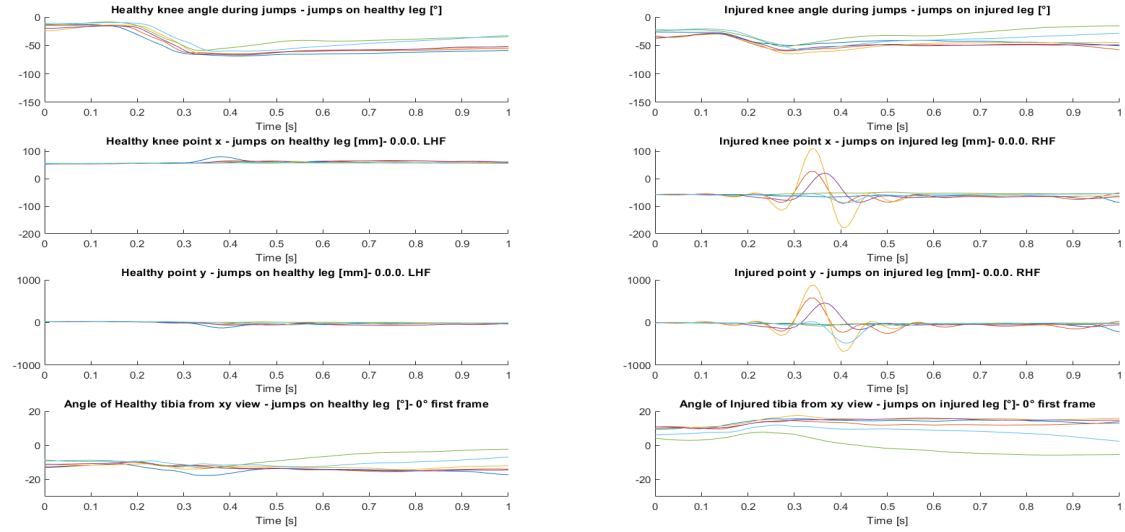

Figure 6.: Presentation of biomedical parameters during landing with one leg, that is followed after jumping. The left exhibit presents the biomedical parameters during landing with healthy leg, while the right exhibit presents the biomechanical parameters during landing with the injured leg (43)

The Figure 3. presented the biomechanical parameters of landing on both legs after jumping. It is shown on Figure 3. that the amplitude of the x directional motion of the knee point at the healthy leg is higher, meaning there is an increased deviation of the tibia axis from the base state (in this state it could be considered perpendicular to the sagittal plane of the knee), suggesting that the healthy leg had to bear a higher load, therefore the maximal stress will be invoked in it. Furthermore, it could be seen on Figure 3. that the x directional component of the knee point at the healthy leg not only had a higher amplitude, but the motion was more extended time wise, than the injured leg, suggesting that the stress or shock attenuation control is better in the healthy leg, therefore stress absorption is prolonged time wise. In contrast, the shock absorption of the injured leg is worse, because it must bear the stress loading in shorter time span, that could promote the accelerated degeneration of the knee joint.

The Figure 4. and 5. present the biomechanical parameters of landing after a one leg jump. The relevant data is in reference to the jumping leg at both exhibits, due to the fact that these jumping legs need to bear the loading and they are the ones that could attenuate the shock effect. The graphs are demonstrated in two separate exhibits, because of the characteristics of the curves. We could observe on Figure 4. that the x directional component of the knee point of the injured leg conveys an alternating motion, suggesting that the compression surface of the knee joint cartilage is continuously changing from frontal plane and as a result the knee point is changing all the time. In the case of the x directional component of the knee point of the injured leg, the negative directional diversion means the diversion towards the medial proximal tibia. It is also shown on Figure 4. that x directional component of the knee point of the injured leg has a relatively higher amplitude and pursues a more restricted motion in regards to time and returns quickly to the take-off state.

The oscillating motion of the x directional component of the knee point at the healthy leg could be detected on Figure 5. We could conclude that the knee joint cartilage compressive surface continuously changing from the frontal plane and as a result the knee point is changing all the time. The positive directional deviation of the x directional component of the knee point at the healthy leg means the diversion toward the medial proximal tibia. It is apparent that the x directional component of knee point does not return back to the take-off state, in fact it deviates from it, that could be interpreted form the

local grid as it is diverted towards the medial proximal tibia, in contrast to the point prior to jumping. It is suggested that during landing the knee point of the tibia deviates towards the medial proximal tibia. The Figure 5. displays, that the amplitude of the x directional component of the knee point at the healthy leg is relatively lower and presents a timely distribution of motion, which means that the knee joint attenuation takes more time and does not return to the take-off state, suggesting that the stress attenuation is better in contrast to the injured leg.

4.2. EMG activity of the observed muscles

After the evaluation of the obtained data from the measured sEMG signal (Figure 7-8.), the latency values between the SLR-MLR and the SLR-LLR for the measured muscles are compared.

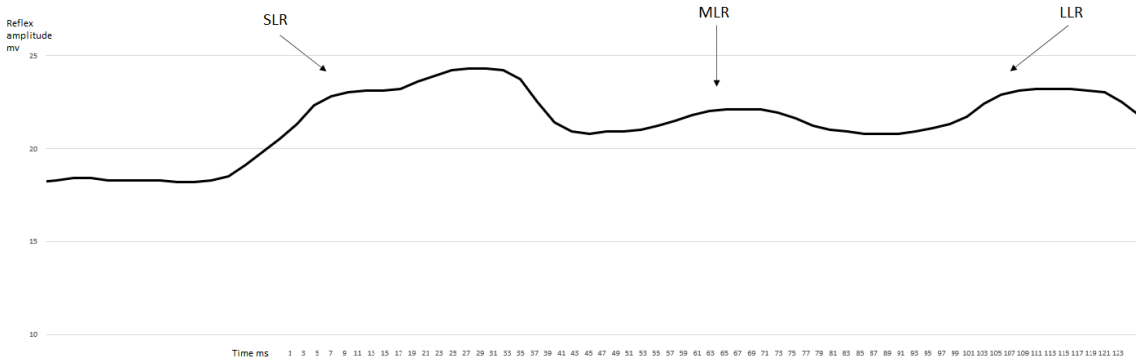

Figure 7. Representative rectified, filtered and smoothened curve of the EMG activity for the rectus femoris muscle before the fatiguing protocol (29)

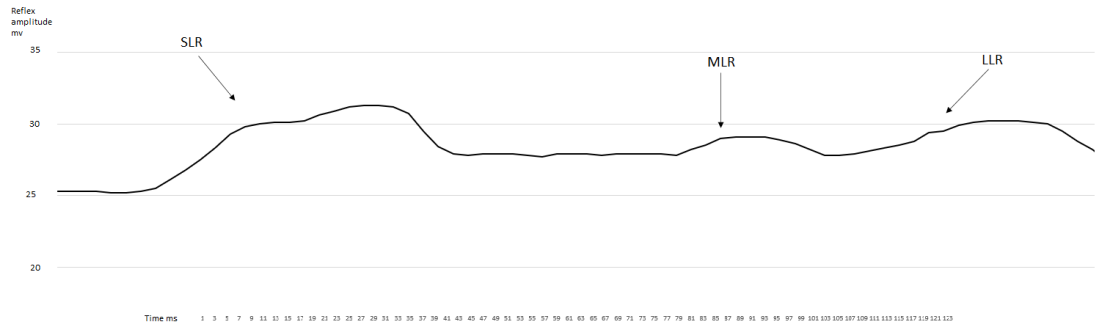

Figure 8. Representative rectified, filtered and smoothened curve of the EMG activity for the rectus femoris muscle after the fatiguing protocol (29)

Statistically significant increase is only observed in the latency of MLR (Figure 9.) compared with the SLR of rectus femoris muscle after the fatiguing protocol ($p<0.05$, ES=1.14, power=0.59).

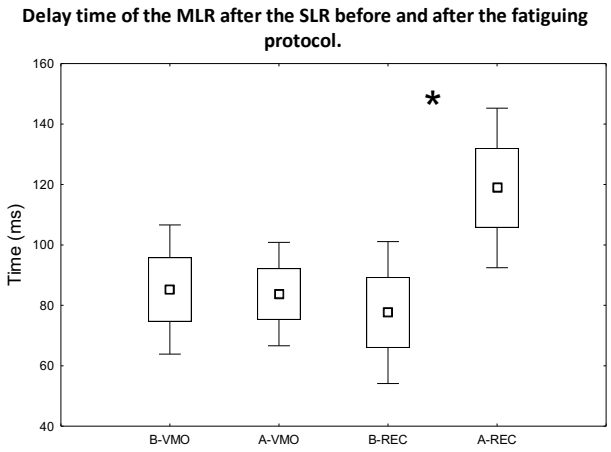

Figure 9.: Delay time of the MLR after the SLR before and after the fatiguing protocol (B-VMO, B-REC measurement data taken on the muscles before fatiguing protocol; A-VMO, A-REC measurement data after fatiguing protocol). Box: mean±SE, whiskers: mean±2SE. * indicates significant difference between B-REC and A-REC ($p<0.05$). No significant difference could be observed between B-VMO and A-VMO ($p>0.05$). (29)

Significant differences could not be observed in the comparisons between the before-after latency values (Figure 10.).

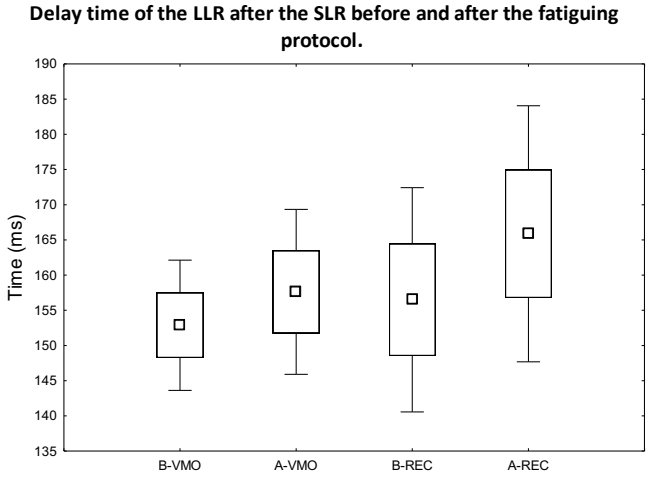

Figure 10.: Delay time of the LLR after the SLR before and after the fatiguing protocol. Box: mean±SE, whiskers: mean±2SE. No significant difference could be observed between B-VMO and A-VMO and between B-REC and A-REC respectively ($p>0.05$).

5. Discussion

Herewith, I find it important to weigh some of the underlying crucial mechanisms of non-contact injuries, specifically NC-ACL injury, and to list notable issues that bear significance in our hypotheses.

5.1. Compressive loading and hyperexcitation

Two types of large fiber sensory neurons could be found in the periosteum of the proximal tibia: the non-nociceptive encapsulated large fiber sensory neurons (44, 45) and the nociceptive stretch reactive ones with free fiber endings (44, 46). Our hypothesis of the mechanism of NC-ACL injury comprises that the large Aβ fiber range encapsulated sensory neurons in the periosteum could be responsible for proprioception, because they entail the features of high conduction velocity and highly energized sensory terminal compartments (19). Notable, that osteocytes, who provide 90-95% of bone cells, are mechano-receptive to mechanical stress, not to mention when it comes to shear stress (19, 47). Moreover, osteocytes could act as an endocrine organ for muscle cells by prostaglandin E2 (PGE2) release mechanism (48) and by doing so bones and muscles could be even considered as a functional continuum when it comes to excitation/hyperexcitation of these tissues (19). Correspondingly, I suggested that osteocytes behave as neuromodulators, namely the elevated level of PGE2 could excite the proprioceptive sensory terminals conducting in the Aβ range within the periosteum of the proximal tibia (19). Furthermore, it is known that large-sized primary sensory neurons may become hyperexcitable under pathological condition due to PGE2 pathway (49). In conclusion, hyperexcitation of large fiber sensory neurons could be an important underlying factor in NC-ACL injury mechanism, as is the case in DOMS as well (18, 19).

Important to note, that proprioceptive nerves are involved in the guidance of the spine on a continuous basis and when it comes to prevent pathology there is a prompt response to maintain postural control in case of a bone fracture (50). Furthermore, Blecher et al. (51) demonstrated the contribution of muscle spindles and Golgi tendon organs to spine realignment and fractured bone realignment. We suggested that the proprioceptors with

encapsulated terminals in the Aβ range of the proximal tibia also serve this postural control stabilizing purpose when bone micro- or stress fractures happens, in an orchestrated way with the assistance of muscle spindles. In support of this theory, recent animal research showed that spontaneous fracture repair is guided by the active involvement of monosynaptic stretch reflex circuitry in a non-autonomous way (50). Epiphyseal large fiber sensory neurons in the tibia have been suggested to play a remarkable role in the maintenance of bone structure (52), in remodeling or as in spontaneous microfracture repair like it is suggested aforementioned (19).

We suggested that vertebral compression fractures, that are secondary fractures, are analogous with the NC-ACL injury mechanism (19). The primary fracture, called burst fracture, is caused by sudden axial compression and this biomechanical impairment leads eventually to the secondary compression fracture (53). This bi-phasic injury mechanism often occurs in younger patients in speedboat vertebral fractures (54). We offered the translation of these findings that the sudden damaging axial load could microdamage the proprioceptive axon/terminals compressively and as a result the impaired proprioception leads the way to a more mediolateral sway in the joints, namely a joint subluxation (19). We also proposed that the secondary compression fracture prevails due to impaired proprioception induced inadequate postural control, inadequate shock absorption, inadequate anti-gravity protection and inertness (see Figure 11.) (19). It is noteworthy, that Grassi et al. presented recently their findings that seems to support the secondary subluxation in NC-ACL injury (55), correlating with our novel NC-ACL injury hypothesis.

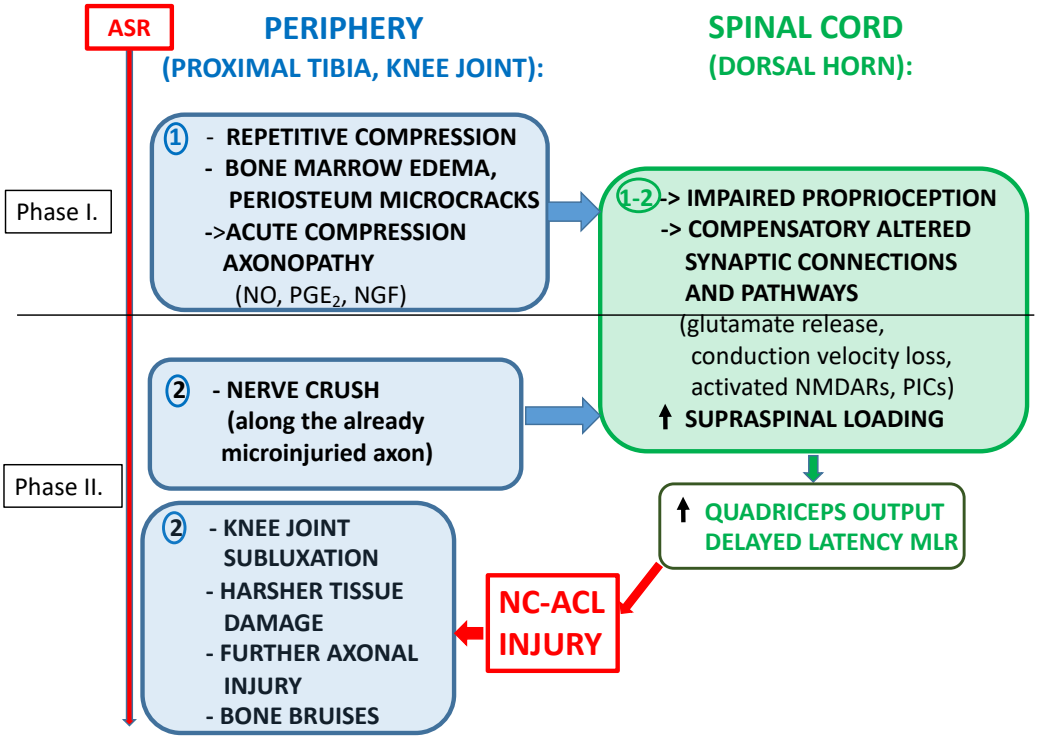

Figure 11. Schematic representation of the peripheral and central mechanisms involved in NC-ACL Injury (19) At the periphery NC-ACL injury is comprised of 2 phases: Phase I: The acute compression axonopathy of proprioceptive sensory fibers in the proximal tibia. Phase II: Nerve crush along the already microinjuried axon. A more extensive secondary damage occurs, including further tissue damage and bone bruises. This is the phase when the actual NC-ACL injury happens. In the spinal cord, the peripheral alterations cause changes in the functional properties of sensory afferent fibers: a: The hyperexcited, microdamaged large encapsulated Aβ fibers exert less presynaptic inhibition, or even presynaptic facilitation, on proprioceptive Type I fibers, by activating presynaptic NMDA receptors. This causes some of the monosynaptic static encoding of stretch reflex to be altered to polysynaptic pathways and it is the hypothetical basis of the delayed latency of the medium latency response (MLR) and impaired proprioception. Glutamate spillover from Type I fiber central terminals could in turn induce presynaptic facilitation on Type II fiber terminals, increasing the release of glutamate. This leads to the excitation of spinal cord motoneurons, evoking persistent inward currents (PICs) and enhancing the quadriceps output, that could be further increased by decreased GABAergic inhibition. b: The conduction velocity of the hyperexcited, microdamaged large encapsulated Aβ fibers decreases as the parasympathetic withdrawal of ASR evades. This reduces the presynaptic inhibition on pain fibers (Aδ and C), opening the gate for pain transmission. (19)

Peripheral nerves are prone to compression injury in locations where nerves travel through constricted anatomical pathways (56). We suggested that the periosteum, epiphysis and the subchondral region of the proximal tibia could be such an environment under mechanical stress prior to the actual NC-ACL injury (19). Notable, that crush injuries do not involve nerve transection when an acute traumatic compression prevails (56). We further proposed that constrained and rigid anatomical structures of bone canals could make the large sensory fibers, like proprioceptive ones, more susceptible to nerve compression or crush injury, particularly if we consider that these nerves could be in hyperexcited state and fatigued (19).

In summary, we suggested that in the primary damage phase of the NC-ACL injury the excessively elevated PGE2 from osteocytes could lead proprioceptive hyperexcitation and axial burst force could cause sensory impairment on the hyperexcited compressed or crushed Aβ range large fibers in the periosteum, epiphysis or/and the subchondral region of the proximal tibia in a cognitive demand induced acute stress response time window of unaccustomed and strenuous repetitive eccentric contraction based athletic moments (19). Correspondingly, this acute compression proprioceptive axonopathy results in impaired proprioception and postural control, leading to a secondary harsher damage including the NC-ACL injury (19).

Mechanical stress, including shear force, induces osteocytes to release nitric oxide (NO) as a crucial signaler (47). The released NO gradually stimulates the osteoblasts (57, 58). It is known from earlier in vivo results that shutting off the NO synthase (NOS) activity causes dysfunctional mechanical load- induced bone formation and fracture repair (59, 60). Moreover, upregulation of NOS is needed in both mechanical load-induced bone growth and fracture repair (57, 59, 61-66). NO signaling exerts its effect in a dose dependent and biphasic manner (60). NO has a role in maintaining bone homeostasis at low concentrations by controlling the stimulation of osteoblasts, osteocytes and osteoclast-mediated bone resorption (60).

Contrariwise, NO might have a role in bone loss at high concentrations (67). Noteworthy, that NO at high concentrations may also instigate demyelination of sensory axons selectively when axonal injury is present and as a result Wallerian-like degeneration prevails (68). Nevertheless, we suggested that this type of classical sensory

axonal degeneration could occur rather in the secondary harsher damage phase of the NC-ACL injury due to sizeable nerve crush (19).

We proposed that the primary injury could be an abrupt axial superposition of compression of the knee proprioceptors in the periosteum, epiphysis or/and the subchondral region of the proximal tibia under unaccustomed or strenuous athletic moments (19). Consequently, we hypothesized two possible proprioceptive axonal injury scenarios in this primary stage of the NC-ACL injury (19).

First, the axial burst induced microfracture could be so harsh that the Aβ range large fiber afferents with free nerve endings are crushed in the proximal tibia, leading to such a severe neuronal injury type that was suggested in the secondary stage of the NC-ACL injury (19). In this case the released NO could further damage proteins, lipids, and peripheral sensory axons (69), resulting an energetic failure (70) or even apoptosis (71). Ultimately this scenario could give rise to increased nociception and distal degeneration of the proprioceptive axons (23). Nevertheless, we put forward that this proprioceptive nerve injury scenario could also induce a valgus collapse acutely (19).

In the second theoretical proprioceptor injury scenario, suggested to be the more prevalent one, the axial burst loading could mechano-energetically microinjure the entrapped axon terminals of the encapsulated large fiber sensory neurons in the periosteum (19). This microdamage mechanism is suggested to be analogous to the first phase of the acute compression sensory axonopathy theory of DOMS (18, 19). Noteworthy, that sophisticated task execution of strenuous or unaccustomed eccentric exercise moments under an ASR could impair proprioception due to sudden reallocation of neuro-energetic resources (72). Consequently, the encapsulated proprioceptive large fiber endings in the periosteum of the proximal tibia could be vulnerable to free radical damage (73).

The results of our measurement method of the knee point could suggest that they are in accordance with our novel NC-ACL injury hypothesis, namely the knee point of the tibia is suspected at the medial part of the proximal tibia in the provocative position (19). The knee point of the healthy lower limb skewed toward the medial head of the tibia during landing. Furthermore, the limited stress attenuation capacity of the injured leg correlates with other studies, since proprioceptive nerve injury is likely due to the NC-ACL injury itself and to reconstructive surgical intervention (19). Indeed, from a

functional point of view these proprioceptive nerve injuries are the equivalent of the transient or permanent proprioceptive terminal microinjury after the first injury phase, but before the second phase of NC-ACL injury (19).

Correspondingly, earlier video analyses showed that prior to NC-ACL injury handball players arrived to the ground floor with a hindfoot or with the foot flat, in contrast to those who did not suffer ACL injury who arrived on foot front (7, 19). Not to mention, that the injured players landed on the ground with a lower planthar-flexion and 50% earlier (8). All these phenomena could be ascribed to the impaired proprioception and as a result to the limited stress attenuation capacity and limited protection against gravity (19).

5.2. TAD like lesion

According to our non-contact injury mechanism theory, the force due to the superposition of compression under cognitive demand could cause such a severe mechano-energetic insult on axonal mitochondria in the proprioceptive sensory terminals of the muscle spindles and periosteum that impairs the axon's energy supply, which is analogous to the hypothesis of Bennett et al. describing TAD (23). Bennett et al. stated "if the energy deficiency is severe enough then degeneration happens, and the threshold for degeneration will be lowest in the neuronal compartment that has the highest energy requirement" (23). They proposed that the compartment with the highest energy requirement is at the sensory axon's terminal arbor. Accordingly, we suggested that the proprioceptive sensory terminals could be analogous compartments with the highest energy requirement in the muscle spindle and in the periosteum in unaccustomed or strenuous eccentric exercise induced DOMS and NC-ACL injury moments (18, 19).

Holland et al. (74) have implicated the possibility of a "terminal axonopathy" in 1998, which is similar to the TAD concept. Noteworthy, that the number of mitochondria is elevated in such a location where the metabolic and neuroenergetic demand is high (75, 76). Correspondingly, the proprioceptive sensory terminals of the muscle spindles, and most likely in the periosteum of the medial proximal tibia as well, are abundant in mitochondria (77, 78). Bennet et al. (23) showed that paclitaxel induced mechano-allodynia and mechano-hyperalgesia with a delayed onset. Notable, that paclitaxel and

oxaliplatin are axonopathy-causing chemotherapeutic agents (73). Furthermore, the evolvement of the delayed onset of symptoms was threshold driven and dosage dependent based on accumulating toxicity (23). Interestingly, the neuropathic pain induced by this accumulating toxicity at lower threshold was not accompanied by classical Wallerian like degeneration to the peripheral axons, but TAD lesion alone was enough to cause mechano-hyperalgesia (23, 73).

We suspected an analogous TAD like lesion on the nerve terminals of the proprioceptive sensory terminals in the muscle spindle and in the periosteum that causes the primary mechano-energetic lesion in DOMS and NC-ACL injury (18, 19). Accordingly, the force due to the superposition of compression induced by unaccustomed or strenuous eccentric contractions under a cognitive demand derived ASR could possibly cause such a severe mechano-energetic lesion on the axon terminals (18, 19).

In summary, the energy supply of the mitochondria in the terminals of the suspected proprioceptive large fiber sensory neurons of the periosteum are harmed in a way, which is similar to the TAD hypothesis of Bennett et al. (19, 23). Supporting evidence is emerging for the participation of these large fiber sensory involvement in the periosteum since oxaliplatin has neurotoxic effects in an acute and chronic manner (73). Periosteal apposition in the long bones, referring to the chronic neurotoxic effect, was most visible on the proximal tibia presented in an eight year follow up study of oxaliplatin chemotherapy (79). Moreover, the periosteal apposition was also attended with noninflammatory arthritis of the knees (79). Overall, the clinical picture takes after a primary disease, called hypertrophic osteoarthropathy (79), in which circulating PGE2 level is remarkably elevated (79-81).

5.3. Dichotomous non-contact injury mechanism

Morgan et al. (82) and Hody et al. (83) have implicated the dichotomous injury mechanism of DOMS. However, our bi-phasic acute proprioceptive compression axonopathy or alternatively the non-contact proprioceptive neuronal injury mechanism was first presented through the new theory of DOMS (18, 20). Accordingly, the proprioceptive neuronal primary injury is hypothesized to happen when an ASR induced energy depletion at the primary afferent's peripheral terminal prevails under

unaccustomed or strenuous repetitive eccentric contractions (18, 20). As a result, the mechano-energetically harmed mitochondria could impair the glutamate vesicular release system in addition to the mechanical impairment of the proprioceptive mechanotransduction Piezo2 ion channels (20), causing the proposed mechano-energetic lesion (18, 19, 22, 26).

We suggested that these types of proprioceptive terminal impairments could act in an analogous way that are seen as a side effect of axonopathy-causing chemotherapy and could evolve after a dose limiting, threshold driven manner and not associated with a classical, Wallerian axonal degeneration (18, 20, 22, 23). As a result of the primary non-contact proprioceptive terminal microdamage, a secondary injury phase could succeed in the form of a harsher tissue damage (18, 19). The more severe tissue damage is due to the loss of protective proprioceptive capacity and this is what could be experienced in DOMS and NC-ACL injury (18, 19). Noteworthy, that secondary preprogrammed compensatory microcircuits and persistent inward currents (PIC) come into play when these non-contact primary sensory terminal microinjuries occur in order to provide exaggerated protection in the form of enhanced postural control, enhanced shock attenuation and support the body against gravity at the injured segmental level (19, 20, 22).

Proprioception was named as our sixth sense by Sir Charles Bell in 1830 (84). It is referring to the sense of the position and actions of the extremities, but far from an entirely known system. Proprioception and especially the terminal lesion of the proprioceptive sensory neurons could be considered as the no men's land in clinical medicine, because it rather concerns the peripheral nervous system despite the fact that it involves profound preprogrammed pathways in the central nervous system (CNS). Further challenge is that these suggested TAD like lesions of proprioceptive terminals are seldom appreciated by neurologists, but barely understood by other clinicians. However, we proposed that numerous symptoms should be associated with the microdamage of proprioceptive nerve terminals, as DOMS and non-contact injuries, like NC-ACL (18-20).

Important to note, that one finding of my doctoral research work, namely the delayed latency of MLR is present in DOMS (29), substantiates our theory that non-contact injuries initiate a proprioceptive impairment and the inducement of secondary preprogrammed protective microcircuits (19).

5.4. Damaging eccentric contractions

Important characteristics of eccentric contractions are absorbing energy from an external load (85), supporting the body against gravity, absorbing shock, and storing recoil energy for accelerating contractions (83, 86). No wonder why eccentric contractions have been called as negative muscular work by Abbott et al. (85). However, we should know from our studies from physics that there is no such thing as negative work, but eccentric contractions could store recoil energy from, e.g., ground reaction forces (83) (that is, the force carried out by the ground as a reaction to the forces a body applies on it) (87). A differential could arise when the storing of energy from the external load, coming from the accelerating movement, cannot "recoil" in the decelerating movement (22). We suggested that the excess "unrecoiled" energy coming from accelerating eccentric movements is partially absorbed by surrounding tissue like muscles, bones, connective tissues and even neurons in a damaging way (22).

Difficult task execution under enhanced cognitive demand and ASR could facilitate the force generation of eccentric contractions in acceleration and deceleration movements (19). Another important characteristic of eccentric contractions that it exerts higher cortical excitation and lower motor unit discharge (83, 88), providing the base for consolidating task execution according to cognitive demand (19). Overall the result will be high force generation by accelerating or decelerating eccentric contractions that could exert substantial compression load on the knee joint and on the proximal tibia (19). However, we postulated that "the storing of recoil energy from superposition of compression forces by eccentric contractions (83, 86) in the accelerating phase could backfire in the decelerating phase, because the excess energy will be even more damaging, due to acute compression axonopathy- induced- impaired proprioception" (19).

Indeed, Proske and Gandevia showed that damaging eccentric contractions are accountable for the impairment of proprioception (21). Kouzaki et al. even exhibited that eccentric contractions increase the latency of M-waves, that is the earliest EMG response to motor nerve stimulation, and implicated that it is to blame for a reversible motor nerve microdamage (89). Furthermore, it has been demonstrated that eccentric contractions

impair both joint position and force sense (21, 90, 91). However, other studies in reference to the knee joint showed that the tendon organs and the muscle spindles were not responsible for this impairment (21, 92, 93).

5.5. Microtubule stress - Mitochondrial trafficking

We suggested that we could learn from chemotherapy again that this kind of eccentric contraction induced proprioceptive impairment is most likely due to inhibition of tubulin polymerization resulting from the disruption of microtubule function along the axon length, as it is the case in chemotherapy (94). Microtubules are essential for maintaining cell structure by forming the cytoskeleton, but they also have a role in mitochondrial transport. In an intact microtubule system, the efficient distribution of mitochondrial transport along neurons is important, especially to synaptic terminals (95-98). I suggest that damaging eccentric contractions inhibit the proper assembly of microtubules and even more importantly disrupt the proper distribution within the mitochondrial transport system. Eventually, the disruption of respiratory chain along the axon could evolve (97), providing the base but not causing TAD like lesion.

In summary, we proposed that unaccustomed or strenuous eccentric exercise fatigued proprioceptive sensory fibers could not execute the recoil characteristics of eccentric contractions efficiently, therefore the excess unrecoiled energy could damage even the microtubule system and the respiratory chain of proprioceptive axons leading to improper mitochondria supply at the proprioceptive terminals, especially under an ASR. Correspondingly, there is evidence that mitochondrial proteins take part in mitochondrial stress response (99).

5.6. Evolutionary and ontogenetic relevance

Berger et al. hypothesized that the evolvement of bones has evolutionary relevance in order to enhance capability to escape from danger (100). They showed in animal and human studies that stressors facilitated an abrupt outflow of circulating osteocalcin, leading to the inducement of an ASR (100). Osteocalcin blocks post-synaptic parasympathetic neuronal activity and as a result the sympathetic tone will be unopposed (100). We proposed that DOMS could have an analogous important role in ontogenesis

as bones and the deferred initiation of pain sensation could assist escape from danger evolutionary (18). Correspondingly, the impediment of pain sensation could evolve only hours after the proposed microinjury of proprioceptive primary afferent terminals, but by this time the escape from danger could be carried out (18).

Furthermore, our neuronal non-contact injury mechanism theory of DOMS implies that it has ontogenetic growth relevance (18). We even proposed that DOMS should be regarded as an overexcitement of a physiological reflexive growth mechanism by overtriggering nerves and surrounding tissues and as a result causing muscles to grow and commanding the nervous system to guide this growth process (18). We also suggested that the roots of our theory could be found in the Law of Hilton. Correspondingly, the early explanation of Hilton's Law postulated "that the branches of same nerve trunk supply not only the group of muscles that are moving a joint, but the corresponding skin over the same muscle and the interior of the relevant joint as well" (19, 101). Nevertheless, we offer the conceivable extension of the Hilton's law. Accordingly, we published our hypothesis that large fiber somatosensory nerves of the periosteum of long bones could be also subscribed to proprioception (19), like in the case of skin. This could be an insinuation that muscles, skins, joints and even long bones could lengthen arm in arm in an analogous mechanism as suggested by the Hilton's Law (18). The proprioceptive sensory neurons are the ones encoding our inner knowledge of position sense, inner knowledge of body map and inner knowledge of body ownership formation (21), hence we have a reason to suspect that these nerves subscribe not only to the growth process of muscles, skins, joints and bones, but to regeneration and remodeling of them as well (18, 19, 22).

"The most fundamental life sustaining genetically preprogrammed hardwiring of humans could be compromised by the proposed mechano-energetic terminal microlesions of these proprioceptive sensory neurons" and as a result we theorized that "the static encoding of postural control of the affected tissues are also impaired by this encroachment" (19, 20, 22). Interestingly, it seems that evolution have provided a secondary preprogrammed compensatory pathway for these non-contact proprioceptive terminal microinjuries (19, 20, 22). Nevertheless, the impediment of full regeneration of the microinjured primary afferent and holding on to the secondary compensatory microcircuits could be dear in terms of neuroenergetics or even progressive, because it

always involves more neuronal synaptic connections, meaning transduction delays and enhanced neuroenergetic loading (19, 20, 22). This is why we proposed that "these proprioceptive terminal lesions or Piezo2 channelopathies, and the resultant low-grade neuroinflammation are impacting our CNS to the extent of how many overlapping preprogrammed reflexes and microcircuits are involved in the initial injury" (20, 22).

We further suggested that a learning and memory consolidation mechanism unfolds in the CNS in case of the encroachment of this reflexive genetic preprogram (19, 20, 22, 26). Moreover, we implied that there is an ontogenetic differentiation of how long of a memory term is accompanied with certain secondary preprograms or compensatory microcircuits (20). For example, in the case of the repeated bout effect (RBE) the suggested memory transmitters are osteocalcin, activated N-methyl-D-aspartate (NMDA) and substance P, while in the case of post-orgasmic illness syndrome (POIS) even the highly rewarding opioid system is pre-encoded and that could imply higher ontogenetic relevance due to higher importance in life sustainment (18, 20, 22).

Significant, that fundamental genetic knockout of Piezo1 is mortal in even embryonic life, as the analogue Piezo2 constitutive knockout mice dies at birth too (102-104). This additionally substantiates the Piezo channels' essential life sustaining physiological and evolutionary role in the genetically preprogrammed encoding (103).

We also emphasized the importance of the concealed location of these proprioceptive sensory nerve terminals (18, 19). We believe that these shielded anatomical structures, like the muscle spindle, periosteum, deep layer of skin and the cornea are not accidental and it could further bear relevance of ontogenetic importance (18, 19, 105, 106).

5.7. Acute stress response

There are circumstances, especially in sport activities, when muscle performance should be sustained cognitively at a higher level regardless that fatigued muscles are not capable of adequate force production, therefore over-reaching is aspired for the sake of achievement (22). Over-reaching response is purposefully integrated in training sessions by coaches (107, 108), due to the fact that successive over-reaching training sessions, in conjunction with sufficient recovery periods, could lead to an elevated level of homeostasis through acute adaptation (109). This divergence from resting homeostasis is

called super-compensation (109). Noteworthy, that these over-reaching and supercompensation responses are controlled by the autonomic nervous system (108).

It is improbable that motoneurons are autonomously competent to exert an over-reaching response by increasing their excitation beyond their normal limits (110). Therefore, induced microcircuits are needed in order to drive homeostatic response by increasing the firing rate of motoneurons (110). We proposed that ASR could be such a homeostatic driver, possibly transducted by the direct sympathetic innervation of the muscle spindles (111). Furthermore, we suggested based on the work of Berger et al. that a rapid outflow of circulating osteocalcin is needed in order to induce an ASR (18, 100). As a result, osteocalcin blocks the post-synaptic parasympathetic neurons in order to let the sympathetic tone become unopposed by the parasympathetic tone (100).

5.8. Proprioceptive sensory Piezo2 ion channelopathy

The Noble Prize in medicine and physiology 2021 awarded to Ardem Patapoutian, who identified the Piezo2 transmembrane proteins with his team, including Viktor Lukács, as the principal mechanotransduction channels for proprioception (27). We were the first to address that Piezo2 ion channels could be microdamaged at the terminals of hyperexcited proprioceptive neurons in an ASR time window of unaccustomed and strenuous eccentric exercise moments, in a similar fashion as in TAD like lesions (18, 20, 26). Hence, not only the more than 100 years of DOMS enigma could come across as settled, but the concept that these channels function differently in an ASR induced microinjured state could provide us with new translational opportunities in medicine. Our theoretical interpretation that the TAD like lesions at the primary afferent terminals of the muscle spindles in DOMS are parallel with the ASR induced neuronal mitochondria energy depletion derived mechanical terminal microinjury of the Piezo2 channels, led us to propose our novel non-contact injury model (18, 20, 22, 26).

Indeed, we suggested that overreaching the limits of proprioception or more importantly the functionality of the Piezo2 channels is analogous of the principal gateway between physiology and pathophysiology (20, 28, 106). We applied a reverse eyesight to the currently used in our mechanism modelling, namely we could gain better translation of certain medical conditions if we follow a neurocentric view. Correspondingly, muscles,

bones, skin, joints or the cornea are ‘only’ neuromodulators according to our interpretation and they could excite/hyperexcite proprioceptive nerve terminals. Furthermore, we suggested that these hyperexcited nerve endings could be even microdamaged during a cognitive demand induced ASR (18). We theorized the gateway of this microinjury are the Piezo2 channels and the ASR derived mechano-energetic lesion of these channels is the locus where low grade neuroinflammation is initiated (20, 26).

Piezo ion channels are great in size with multiple transmembrane segments (103). Nonetheless, several characteristics of this protein channel are far from known, like topology, pore formation, mechanical force detection and its gating function (103). In light of this hiatus, we also proposed that the ASR induced axon terminal mitochondrial energy deficiency of DOMS could impair glutamate vesicular release leading to glutamate spillover at the proprioceptive sensory terminals of the muscle spindles (20, 22, 29). Moreover, we hypothesized that microinjured Piezo2 ion channels could become pathologically leaky even to glutamate when they should be inactivated (20, 26, 28, 29, 106). Ultimately, we put forward in our mechanism theory that this glutamate excitotoxicity could activate N-methyl-D-aspartate receptors (NMDARs) at the presynaptic central terminals of these pseudounipolar proprioceptive sensory neurons at the spinal dorsal horn (22, 112, 113).

Nonetheless, the proposed primary phase of these non-contact injuries, namely the microdamage of the Piezo2 channels, is silent or unnoticed, because the associated pain is either delayed onset (18), suppressed by sympathetic nervous system (SNS) activity, suppressed by the immediate sharp pain of the secondary injury phase (19) or more importantly pain or mechanical hyperalgesia cannot develop entirely due to the absence of secondary harsher tissue damage or more specifically in the absence of C-fiber contribution (20). Informing signs of this primary microdamage could be the impaired proprioception and the transient autonomic disbalance (20, 22).

We have implicated in five of our publications that the peaching sign of impaired proprioceptive function is a minor alteration of the stretch reflex in the affected striated muscles (19, 20, 22). We accredited this lesion to the compromised static-phase firing sensory encoding of the stretch reflex (19, 20, 22). Correspondingly, Bewick et al. demonstrated that stretch-evoked static-phase firing of proprioceptive terminals in the

muscle spindle is more sensitive to glutamate than dynamic firing (114). I suggested that the static encoding of the primary Type Ia afferents' is delayed by activated NMDARs on the spinal dorsal horn due to the TAD like lesion and glutamate spillover (22). Accordingly, some of the monosynaptic static encoding of stretch reflex could be switched to secondary preprogrammed microcircuits and this could be the ground for the delayed latency of the MLR of the stretch reflex and the reduced range of motion (19, 20, 22). As a result of the TAD lesion, the constantly firing, non-adapting Type II static impulses could be conducted earlier to the spinal dorsal horn than the delayed adapting Type Ia static sensory impulses associated with activated NMDAR (22). Moreover, this switch of static encoding between the primary and secondary afferents could shed light for the increased inducement of persistent inward currents (PIC) on motoneuron dendrites, leading to exaggerated contractions and reduced range of motion (22).

As a conclusion, we hypothesized that the ASR invoked microinjury of the Piezo2 ion channel and the impaired vesicular glutamate release switch to a secondary preprogrammed microcircuit of postural control, associated with reduced range of motion and exaggerated contractions in order to overstabilize posture and to provide supranormal protection against gravity (19, 20, 22, 26). This is a protective secondary measure at the microinjury affected segmental level due to the encroachment of postural control (19, 22). For the moment, the overall proprioceptive system could be impaired, because the neuro-energetic demand of the secondary overprotective compensatory microcircuit of postural control could be so elevated at the affected segment that it could give on to lost control of other unaffected segments due to the resource limitation of the overall proprioceptive system (22). The functional restoration of the genetically preprogrammed postural control last about 24–120 hours and that could be the regeneration time interval of the microinjury of the proprioceptive axon terminal (22, 115).

An over-reaching response could be induced in order to attain the cognitive demand of maintaining or even elevating muscle performance, regardless of fatigue (19). Noteworthy again, that the adequate frequency of over-reaching training sessions with necessary regeneration periods could set a heightened level of homeostasis. This increment from resting homeostasis is called super-compensation and commanded by the autonomic nervous system (19, 22, 108, 109). However, we suggested that these processes involve the proprioceptive system as well, namely the Piezo2 ion channels at

the proprioceptive terminals and their dose limiting and threshold driven characteristics could contribute to these phenomena (19, 22, 26). Accordingly, we proposed that ASR is a cognitive demand derived homeostatic driver in this over-reaching response when force production is fatigued in strenuous or unaccustomed exercise moments in order to attain the sustainment or even elevation of muscle performance (19, 22).

We further proposed that Piezo2 channels at the proprioceptive sensory terminals are the critical loci in the suggested osteocalcin induced over-reaching ASR time window when DOMS and its microinjury could be initiated (18, 20, 26). It is a known physiological mechanism when Piezo channels are inactivated due to hyperexcitation and it is considered to be within homeostasis (114, 116). Moreover, it is also familiar that stress could modify the kinetics of Piezo channels under pathological conditions (116). However, we were the first who suggested the ASR derived transient microinjury of the Piezo2 ion channels in our acute proprioceptive axonopathy theory of DOMS (18, 20, 26). The findings that bradykinin could upregulate Piezo2 currents (103, 104) and is associated with mechanical hyperalgesia (103) are also in line with our hypothesis. As our theory, that bradykinin could increase the permeability of the selective barrier of muscle spindles' in DOMS through cyclooxygenase (COX)-2-bradykinin-nerve growth factor (NGF) signaling (18, 22, 117, 118). Indeed, this could be one signaling pathway how bradykinin brings the Piezo2 ion channels of the hyperexcited primary afferents into play in DOMS mechanism (18, 20, 22). Significant, that Nencini et al. found that Piezo2 also has a role in bone afferent neurons when it comes to noxious mechanical stimulation, not to mention its role in NGF induced bone afferent sensitization to mechanical stimulation (119). Hence, bradykinin could have role in the secondary injury phase as well.

Piezo1 ion channels also contribute to the maintenance of homeostasis and in the mechanotransduction of certain tissues, like in cartilages (120), dorsal root ganglion (DRG) neuron physiology (121), peripheral trigeminal and neuronal nociception (122, 123). Earlier findings provide evidence that Piezo2 channels are associated with the maintenance of homeostasis in sensory neurons (123-125) even in the cornea (106, 126). In tissues, including bones, both Piezo channels contribute to physiology involving the somatosensory neurons (123, 127). Notable, that Piezo1 channels have a role in cell alignment based on their shear stress sensor capability (123, 128) and this signaling could

have relevance in loading of bones and joints, not to mention remodeling. Overall it is safe to say that Piezo1 channels in tissues, like in bones, behave as cellular mechanoceptors and the Piezo system cross-modulation with the somatosensory Piezo2 contributes to the control of homeostasis regulation (106).

Nevertheless, the ASR induced mechano-energetic microinjury of Piezo2 channels in the proprioceptors could open the gateway to pathophysiology on a non-contact basis, as we suggested in non-contact injuries, like the mechanism of NC-ACL injury (19, 26). As a result, the impairment of the Piezo2 related static-phase firing sensory encoding of proprioceptive neurons or the sensory neurons contributing to proprioception could lead to impaired postural control with potential long-term consequences (19, 26). Important to note again, that there is a secondary preprogrammed compensatory pathway for these non-contact primary sensory terminal microinjuries (19).

5.9. Sex differences

Anatomical and sex differences as a risk of ACL injury have been observed and reported in the scientific literature (10-12). We suggested that excessively elevated PGE2 levels could be an explanation of the phenomenon that female athletes are almost 4 times more susceptible to ACL injuries, especially in the pre-ovulatory phase of the menstrual cycle (129, 130). Noteworthy, that a marked increase of estrogen is due to luteinizing hormone (LH) in the pre-ovulatory phase (129, 130). However even more importantly, LH through interleukin-1β stimulates the NGF-tropomyosin receptor kinase A (TrkA) axis in the ovarian cells as well and promotes TrkA and NGF gene expression and PGE2 release (131). This pre-ovulatory signaling could additionally elevate PGE2 in excess of the levels generated by osteocytes due to mechanical stress in strenuous athletic moments (19, 48). The pre-ovulatory transient surge of TrkA mRNA and NGF mRNA and parallel PGE2 surge induced by LH is even more prominent in puberty (131), which could be a further explanation why young female athletes are even more prone to NC-ACL injury (132, 133).

Not to mention, that it could provide a clue why young female athletes have heightened quadriceps activity and reduced hamstring activity (134), which are both considered to be a risk factor of NC-ACL injury (19). Notable again, that bone afferent neurons that expresses Piezo2 and co-expresses TrkA are the ones that have high affinity

for NGF (119). Moreover, Piezo2 has a role in bone afferent neurons when it comes to noxious mechanical stimulation, not to mention its role in NGF induced bone afferent sensitization to mechanical stimulation (119).

5.10. Quad-phasic non-contact injury model

Emerging research shows that DOMS has a tertiary or longitudinal injury phase, lasting up to a year, in the form of the RBE (19, 20, 22, 135). The initial bout of severe DOMS inducing exercise could be reintroduced for at least 6 months with the same exercise bout in an attenuated way, but is lost between 9 to 12 months (136). Correspondingly, we have postulated that non-contact injuries do have their own RBEs, with longitudinal consequences, like POIS (20). Overloading the initially microinjured proprioceptive sensory neurons in this longitudinal or third injury phase could result re-injury or earlier aging, like as it is experienced in ACL re-injury and early osteoarthritis (OA) (see Table 2.) (19, 137). Since the primary phase of these non-contact injuries are learning related, it is no surprise that the activation of pattern recognition receptors (PRRs) are critically involved in this sterile inflammatory process by responding to released endogenous stimuli (138, 139). These endogenous molecules are called damage associated molecular patterns (DAMPs) (139, 140) and they are released into the cytoplasm as a result of CNS injury (139). The chronic activation of PRRs could lead to inflammatory diseases (139). Heat shock proteins are examples for DAMPs in RBE of DOMS, but DAMPs have a role in OA as well (138, 141).

The link between ion channel expression and the activated innate immune system and inflammatory response in the pathogenesis of several diseases has been identified (142). Noteworthy in line with this theory, that acid-sensing ion channel 3 (ASIC3) ion channels play an essential role in secondary hyperalgesia of joint inflammation in rats, that we suggested to be the equivalent of the tertiary injury phase of this non-contact injury model, but not in primary hyperalgesia (143, 144). Correspondingly, research demonstrates that the gradual upregulation of ASIC3 channels in DRG primary afferent neurons of knee joints in osteoarthritic rats and the activated immune cells in the neural tissue are critical factors in the evolvement of this secondary hyperalgesia and the degeneration process of OA (143). Niibori et al. interpreted these findings as the damages

resulted in stronger mechanical impact to nociceptors in the bones of the knee (143). However, we theorized that these large fiber primary afferents in the proximal tibia not only could contribute to muscular stretch reflex and proprioception, but to growth, regeneration and remodeling as well (18-20).

Accordingly, the recurrent overloading of these large fibers after the primary mechano-energetic microdamage could lead the way to re-injury, earlier aging and OA in a dose dependent, cumulative way (19). Noteworthy, that Lin et al. showed in research with mice that ASIC3 also contribute to mechanotransduction in proprioceptors (145), as Piezo2 predominantly does (27). Moreover, ASIC3 channels could also have a longitudinal role in memory formation (146), once Piezo2 channel microdamage opens the activated NMDAR related memory pathways, including immune memory (19, 20, 22, 26). We suggested that the cross modulation of micorinjured Piezo2 and ASIC3 channels are very likely under this overloaded pathological environment, not to mention the possible involvement of other ion channels, like transient receptor potential cation channel subfamily V (TRPV)1, TRPV4. Indeed, acid-induced inward currents under these pathological circumstances, that are ASIC like, persisted in proprioceptive ASIC3 DRG neurons (145).

Repetitive eccentric contraction or resistance exercise induced overloading of these primary afferent sensory neurons could induce unfolded protein response (UPR) (147). I interpreted this phenomenon as the hyperexcitation of these proprioceptive neurons could reach a level in a dose limiting and threshold driven way that causes intracellular micro-damage and neuroinflammation (22). Moreover, I hypothesized that unfolding proteins are not random, but initially they are serving a protective purpose in order to provide physical counter balance to micro-damaging physical currents and impacts due to lost barriers protection (22). Correspondingly, I suggest that the intrusion of Piezo subthreshold imbalanced and ASIC evoked currents could be such micro-damaging physical waves in acute and chronic pathological conditions in the absence of selective barrier and Piezo2 channel protection and suggested to be propagated by eccentric contractions along the affected axons. Ultimately, this phenomenon could be the explanation why misfolded protein formation in neurodegenerative diseases could not be accidental, but they are initially part of a protective mechanism to provide physical

counter support to these non-resolving, micro-damaging currents due to selective barrier permeability increase and possible pathological Piezo2 leakage (22).

Eventually, this longitudinal low grade neuroinflammatory link could be brought back or inflated by the preprogrammed aging mechanism. Aging is considered to be an untamable, progressive low-grade neuroinflammation process (148) and we proposed as the quadric phase of the suggested non-contact injury model (see Table 2).

Table 2.: The adapted quad-phasic non-contact injury model (106)

PIEZO2 MICROINJURY INDUCED POTENTIALLY QUAD-PHASIC NON-CONTACT INJURY MODEL				
ENVIRONMENTAL FACTORS		**PRIMARY INJURY PHASE**		GENETIC PREDISPOSITION
	→	Repetitive unaccustomed or strenuous forced lengthening contractions	←	
		Fatigue induced acute stress response		
	→	Energy depletion of the mitochondria in the sensory terminal contributing to proprioception	←	
		Impairment of vesicular glutamate release and Piezo2		
	→	Acute Piezo2 chanellopathy	←	
		SECONDARY INJURY PHASE		
	→	Harsher tissue damage due to impairment of Piezo2 or proprioception and C-fiber contribution	←	
		Acute compression axonopathy		
	→	**TERTIARY INJURY PHASE**	←	
		Repeated bout effect or re-injury could evolve into chronic condition and earlier aging due to overload and ASIC3 involvement		
	→	Chronic neuroinflammation and ganglionopathy	←	
		QUADRIC INJURY PHASE		
		Aging or non-resolving neuroinflammation with CNS involvement		

Notable, that the initiation of the low grade neuroinflammation in this quad-phasic injury model is already rooted at the point of the primary damage phase. Inadequate regeneration of proprioceptive or sensory nerves contributing to proprioception and the

repetitive re-injury of them could be consolidated in memory (19, 20, 22). It could be indicative of our theory and this memory consolidation process that POIS attacks could revive heightened sensitivity and pain of former perceived to be healed scars of trauma and/or latent illness (149). Noteworthy, that this transient allodynia lasts only until the symptoms of POIS go away in 3-7 days (149). Moreover, the volume of repetitive re-injury and overloading of these channels could matter in a cumulative way as we could learn it from oncotherapy (19, 22, 23). Correspondingly, we suggested that the volume of low-grade neuroinflammation kept in memory alive from earlier lifespan does matter, because the lingering process of aging could revive and augment them (26, 106).

In summary, we suggest that the more secondary compensatory proprioceptive microcircuits are kept alive at the spinal and supraspinal level when we arrive to aging, the more neuronal synaptic connections and compensatory microcircuits are loading the CNS throughout the aging process in order to sustain the genetical preprograms of postural control (22, 106). Accordingly, we proposed that these parallel and interlinked phenomena of aging and progressive use of compensatory microcircuits is a gradual neuronal energy depleting mechanism (22, 106). Eventually these progressive loading processes could lead to dysfunctional microcircuits, dysfunctional synchronization of central pattern generators and eventually to progressively impaired CNS repair (22).

5.11. Rehabilitation

Light to moderate concentric exercise without resistance could ease the symptoms of this proposed proprioceptive terminal microinjury (18, 22, 26, 150). We suggested that these mechano-energetic TAD like lesions could be the result of an ASR derived mitochondrial energy depletion and mechanical Piezo2 ion channel microinjury, evolving in unaccustomed or strenuous eccentric, not to mention learning related, exercise moments (18, 20, 22, 26). Therefore, we put forward the strategy to keep the mitochondrial ‘breathing capacity’ of these microdamaged proprioceptive axon terminals and axons in good condition or even enhance it with concentric training for at least a year or even longer after ACL injury or after ACLR, otherwise their functional regeneration could be compromised and the longitudinal memory consolidation will be facilitated (26). Correspondingly, a more optimal rehabilitative environment could be promoted for these

impaired proprioceptive terminals/axons, in addition the injury related memory reconsolidation could be prevented or possibly memory extinction could be promoted (26). Important to emphasize the significance of keeping these proprioceptive sensory neurons in good shape, because they are suggested to contribute to guiding growth, regeneration and even remodelling (18, 26). We proposed that lost proprioceptive regeneration and remodelling capacity could promote the way to earlier aging in the form of OA, namely the 'third injury phase' (26). Notable again, that the magnitude of lost functional proprioceptive sensory capacity could be critical in terms of longevity.

Important to note, that quadriceps torque variability increases over time after ACLR (151, 152), as it could be observed in osteoarthritic patients (26, 153). Based on these findings, Tayfur et al. put forward that long-term neuromuscular alteration of the quadriceps motor control could be a factor that could promote the onset of knee OA (152). However, we suggested that the impaired proprioceptive sensory feedback could be the primary reason of this alteration of the quadriceps motor control (26, 29). Notable again, that as a result of the TAD like lesions of the proprioceptive terminals is theorized to be PICs induced exaggerated contractions and that could even potentially contribute to the non-contact injury of the ACL (19, 26). Moreover, arthrogenic muscle inhibition evolves as a repercussion of ACL injury that is hypothesized to be part of a preprogrammed protective secondary compensatory microcircuit (19, 26). Regardless, there is no change in cortical excitability or in spinal-reflex excitability in the short-term after ACL injury (152). However, in the longer term the cortical excitability is decreasing and spinal-reflex excitability is increasing (152). We suggested that this long-term modified excitability is due to the impaired proprioceptive sensory feedback too (26). Remarkable, that the precise control of movement is assumed to be essential for knee function (151, 152). The compromised control could modify joint loading and as a consequence it could lead to degenerative cartilage changes (151, 152, 154). According to Onate et al., ACLR is like "torn electrical cord is appropriately put back together, but the cord does not properly conduct electricity in its previous fashion" (155).

The cardinal part of our recommended strategy is to avoid further proprioceptive sensory injury, fatigue, overuse and overloading, especially in the period of one year after ACL injury or after ACLR (26). Otherwise re-injury and overloading could promote the inducement of compensatory secondary microcircuits with concomitant low-grade

neuroinflammation and detrimental facilitation of long-term memory reconsolidation (19, 26). Fortunately, peripheral nerves have an astonishing capability for regeneration, but the reinstatement of their breathing capacity should enjoy special focus, with maintenance or even enhancement by training and adaptation on an extended way, considering that TAD like terminal lesions and non-contact injuries are suggested to be fatigue related (26). It should not be excluded that full functional regeneration is out of the picture in some cases of proprioceptive nerve injuries due to ACL injury or ACLR surgery, therefore the question is rightly addressed in these cases whether "does it ever get back to normal" (26, 151). No matter what, even in these cases maintaining or enhancing the breathing capacity of proprioceptive sensory neurons may circumvent reinjury or delay the initiation of OA (26).

Significant, that the occurrence of a second ACL injury is about 23% (156), not to mention early OA that develops in more than 4/5 of the cases after ACL injury (157). In order to defer or prolong the third injury phase, we suggested a non-pharmacological exercise therapy which is the extended, minimum up to a year, light to moderate home-based concentric exercise in the form of stationary bicycle training with low resistance (22, 26). It should be a supplemental exercise strategy to the currently used with a potential threefold benefit (26). First, concentric exercise promotes aerobic capacity and as a result the mitochondrial breathing capacity and efficient mitochondrial trafficking of the impaired proprioceptive terminals could be restored, sustained or even improved (26). Second, exercise with unloaded proprioception is theorised to even facilitate proprioceptive terminal regeneration (22, 26). Third, supraspinal loading could be attenuated with low resistance stationary biking (22, 26).

Noteworthy, there are two consequences of proprioceptive loading after ACLR (26). First, the secondary spinal compensatory microcircuits are using more synaptic connections, as a result the neuro-energetic loading is increased (26). We theorised that this secondary compensatory mechanism is represented in the delayed latency of the MLR of the stretch reflex and affects the static encoding of the stretch reflex (19, 22, 26). Indeed, it is presented that the latency of the MLR is delayed after ACL rupture (158). The second consequence of proprioceptive loading is the heightened amplitude of MLR, in addition to enhanced short-latency responses due to postural threat which further demands excess neuro-energetic mobilization in the form of increased stretch reflex

dynamic sensitivity (26, 159). Important to note, that athletes with ACLR show not only arthrogenic muscle inhibition (19, 160, 161), but enhanced cognitive loading on neuromuscular control (161). We put forward that the increased cognitive loading is due to the heightened postural threat that could be devoted to the greater knee joint position sense error even after ACLR (26, 161).

Noteworthy from animal studies, that ASIC3 ion channels, in addition to the principal Piezo2 channels, contribute to proprioceptive mechanotransduction (27, 145). More importantly, ASIC3 expression in the dorsal root ganglion of proprioceptive sensory neurons innervating the knee joint in OA rats showed gradual increase as OA progressed, not to mention that ASIC3 play a critical role in secondary hyperalgesia, but not an essential one in primary hyperalgesia (143, 144). Moreover, the increased expression of ASIC3 induces sustained inward currents (145) and these inward currents are hypothesized to play a role in the mechanism of NC-ACL injury and in exaggerated contractions, potentially leading to reinjury (19, 26). ASIC3 channels could alter acid-evoked currents in the brain as well, that could lead to fear conditioning (146). This supraspinal fear conditioning could reinforce the enhanced postural threat from the periphery and the increased dynamic sensitivity of the stretch reflex over time (26, 159).

We further put forward that the two consequences of proprioceptive loading could be interlinked through gamma-aminobutyric acidergic (GABAergic) pathways (26). On one hand, the reduction of GABAergic inhibition in the spinal cord ventral horn could contribute to the generation of persistent inward currents and exaggerated quadriceps contractions (19, 26, 162), on the other hand the reduction of GABAergic inhibition within the motor cortex is presumed as a cause of quadriceps arthrogenic muscle inhibition (19, 26, 163). Besides, GABAergic signalling has a role in fear memory acquisition, consolidation, reconsolidation and extinction (164), not to mention that ASICs contribute to GABAergic neuronal activity in the regulation of hippocampal neuronal activity (165) and that is where fear memory is encoded (166). Knee injury associated fear is a known and serious psychological impediment preventing athletes' return to sports following ACLR (167, 168). Indeed, it could lead into conscious overthinking or cognitive overloading of already learnt, routine, mainly unconscious manoeuvres (168). Nevertheless, we argued that knee injury-related fear in reference to NC-ACL injury is rooted initially in the periphery due to the primary proprioceptive

microdamage, but evidence is pointing to the direction that peripheral mechano-energetic trauma gradually extend its effect to the CNS as proposed by Kakavas et al. (26, 170).

Both of the aforementioned loading consequences could be alleviated or circumvented by the strategy we suggested, namely low resistance moderate intensity stationary bicycle training (22, 26). Since the primary microdamage is suggested to be learning and memory related (19, 22), thus external focus motor learning techniques in ACLR rehabilitation is preferred in contrast to internal focus of attention (171), because the altered supraspinal cognitive loading factor in the long-term memory consolidation of the primer neuronal microinjury is suggested to be minimized (22, 26). Correspondingly we put forward, that the theoretical basis for unloading of proprioception by "closed gate" concentric stationary biking, which is the circumvention of central sensory-loading or supraspinal loading, is that activated NMDA receptors of motoneurons could actively produce intrinsic rhythmic activity along with the central pattern generators of locomotion on the spinal level (22, 26).

Over and above, the symmetric loading and cyclic feature of cycling have a beneficial impact on postural control and gait performance (22) since it relieves the asymmetric joint loading nature of this post-injury state (26, 171). We emphasized, that following our recommended strategy of extended stationary biking should be supplemental to the currently used best practice exercise therapy, not alternative (26). The currently used best practice solutions in ACLR rehabilitation are as follows: targeting the neuromuscular control system, sport specific rehabilitation and individually tailored motor-learning techniques (26). Not complying with extended stationary cycling could lead to ACL injury related spinal and supraspinal changes permanent or even worse, progressive (26). We argued that few weeks of rehabilitative cycling with positive outcome, that is the currently used rehabilitation technique, is not adequate time for the proprioceptive nerves to regenerate fully, maintain, not to mention enhance mitochondrial breathing capacity (26). We further specified our extended moderate intensity low resistance stationary cycling recommendation to pursue it after eccentric muscle actions (172), rehabilitation sessions and at the end of the day, but not as late to interfere with sleeping, because shortage of sleeping time is also a very important risk factor of neuronal regeneration (26).

6. Conclusion

The results of one of our study substantiate our hypothesis that DOMS inducing exercise significantly delays the latency of the MLR (Figure 8.). Moreover, the significantly delayed latency of MLR supports the theory of muscle spindle involvement in DOMS (18, 29). Furthermore, this muscle spindle involved impairment can be measured by EMG right after DOMS inducing exercise and hours before the onset of mechanical hyperalgesia. Noteworthy, that muscle soreness starts at about 8 hours after DOMS inducing exercise (173), so evidence of impairment could be detected earlier, indeed right after DOMS inducing exercise. The study also found that LLR is unaffected by DOMS (Figure 9.), which correlates with earlier findings of Hjortskov et al. (25) and with our hypothesis (22).

The above findings could be indicative of our theory in which the microinjury of the Type Ia afferent fibers is suggested to be a Piezo2 ion channelopathy (20). The inactivation of Piezo2 channels in a hyperexcited state is a physiological response and it is considered to be within homeostasis (114, 116). However, we theorized that the inactivated Piezo2 channels could be microdamaged under a cognitive demand induced ASR in unaccustomed or strenuous eccentric exercise moment and could become leaky even to glutamate (20, 26). Glutamate is a key and also fast neurotransmitter under pathological conditions of the nervous system as in the case of traumatic injuries (22, 174, 175). Part of our theory that unaccustomed or strenuous, eccentric contractions and a cognitive demand derived ASR on top of it could induce energy depletion at the hyperexcited proprioceptive terminals and as a result dysfunctional mitochondria could impair glutamate vesicular release leading to glutamate spillover and leakiness of Piezo 2 ion channels to excessive glutamate (20).

This finding is a step forward, because it further substantiates the proprioceptive sensory involvement in non-contact injuries, like in DOMS. Correspondingly, we put forward that microinjured proprioceptors in the proximal tibia could alter the stretch reflex in the form of a delayed latency of MLR prior to ACL injury (19). It has been demonstrated that the latency of MLR is longer at the thigh muscles after ACL injury and that is due to the ruptured ACL (158). The reflex excitability is altered as a result of the

proprioceptive deafferentation and it is suggested to lead to the "giving way" symptoms (158). Indeed, proprioceptors could be found in ACL (176, 177). Considering the source of knee joint instability from the angle of proprioceptive afferents after ACL injury, there are three potential sources: muscle spindle, ligament/capsule and bone derived. Dhaher et al. ruled out muscle spindle origin and suggested the knee capsule as a source (178). However, when it comes to the injury moment prior to ACL injury, we suggested that the superimposed burst axial compression forces cannot reach the magnitude on a non-contact basis to microdamage the proprioceptors in the joint capsule due to the soft and resilient tissue features (19). In contrast, the stress loading of the proximal tibia by the superimposed burst compression forces is higher, because of the more rigid tissue characteristics, leading to oedema and microcracks in the periosteum of the proximal tibia (19). Accordingly, we theorized that the fatigued proprioceptors in the proximal tibia could become oedematous and entrapped in the constrained bony canals and as a result they could be more susceptible to compression or crush injury even at the sensory terminals (19). Noteworthy, that our test measurements seem to substantiate that the point of attack of the resultant force is in the medial part of the proximal tibia in the NC-ACL injury provocative (that is the almost fully extended knee with minimal knee flexion), point which is the innervation area of the infrapatellar branch of the saphenous nerve (19).

The cornerstones of our hypotheses and my dissertation are as follows, especially those that are put forward firs by our hypotheses in the scientific literature:

- DOMS could be an acute compression axonopathy derived from the muscle spindles (18),
- The initiation of DOMS and NC-ACL injury could be the cognitive demand derived ASR during repetitive unaccustomed or strenuous eccentric contractions induced superposition of compression forces leading to a mechano-energetic lesion of proprioceptive nerve terminals (18, 19),
- The loci of initiation of DOMS and POIS could be the muscle spindles, while the periosteum of the proximal tibia is suspected in the case of NC-ACL injury (18-20),
- Mitochondrial electron transport chain generated free radical involvement and dysfunctional mitochondria trafficking due to unaccustomed or strenuous

eccentric contractions are suspected in the TAD-like lesion mechanism of DOMS, NC-ACL injury, POIS (18-20),

- NC-ACL injury is proposed to have an analogous dichotomous injury mechanism, like DOMS (19),
- The primary injury could mean the microinjury of the proprioceptive afferent terminal and concomitant microcracks in the periosteum in NC-ACL (19),
- The secondary damage in NC-ACL is a harsher tissue damage when the ACL injury evolves, leading to a subluxated knee joint, to bone bruises and to other tissue damages (19),
- Increased PGE2 and NO are suggested to have a crucial role propelling the proprioceptors of the proximal tibia to hyperexcitation and eventually to the initiation of axon terminal microdamage in a dose limiting and threshold driven manner (19),
- LH induced significant TrkA and NGF gene expression and PGE2 release and the resultant hyperexcitation of proprioceptors could explain why NC-ACL injury is at least three-times more prevalent among female athletes (19),
- The critical mechanism in the CNS is suggested to evolve on the spinal dorsal horn (19),
- Activated NMDA receptors under an ASR are proposed to have a critical role in altering the spinal sensory input due to the peripheral terminal microinjury with longitudinal consequences (19),
- Delayed latency of MLR is suggested to be a sign of proprioceptive impairment and could be translated as some of the monosynaptic static encoding of the stretch reflex are switched to a secondary polysynaptic static encoding (19, 22),
- The primary proprioceptive microdamage in non-contact injuries could lead to a transient autonomic disbalance (20, 22),
- The primary proprioceptive microinjury at the axon terminal of non-contact injuries, like DOMS, NC-ACL, POIS, is proposed to be a transient Piezo2 channelopathy and that is analogous with the mechano-energetic TAD like lesion (20, 26),

- The transient Piezo2 channelopathy could also mean the leakiness of these giant ion channels to unwanted subthreshold imbalanced currents and even to glutamate (20, 22, 26),
- Two additional longitudinal phases are suggested in addition to the bi-phasic none contact injury mechanism. Herein, suggested to be termed quad-phasic non-contact injury model, where the third injury phase is the accelerated aging or degeneration, while the fourth is the inflammaging process associated with aging,
- Extended cycling minimum up to a year is recommended after ACL injury or ACLR in order to restate, maintain or even boost mitochondrial breathing capacity of proprioceptive terminals (26),
- Finally, the knee point of the tibia in the provocative position of the NC-ACL injury is suggested to be at the medial proximal tibia and that overlaps the innervating are of the infrapatellar branch for the saphenous nerve.

Accordingly, the findings of our research support our hypothesis that DOMS alters the stretch reflex and delayed latency of MLR is present (29). Furthermore, we hypothesized that the delayed latency MLR could also play a critical role in the NC-ACL injury mechanism (26). The aforementioned seem to support those earlier observations that DOMS could lead to increased injury risk and reinjury. Afterall, it is no surprise since the primary injury of the bi-phasic non-contact injury mechanism is suggested to be a proprioceptive microdamage (18, 19) and it is known that DOMS comes with impaired proprioception (1).

7. Summary

The aim of the current dissertation was twofold. First, to outline our novel non-contact injury mechanism hypothesis, pertaining to DOMS and more importantly to NC-ACL injury (18-20). Second, to introduce research results that substantiate these hypotheses (29). The initial cause of the dichotomous non-contact injury mechanism in NC-ACL injury is proposed to be an acute microdamaging compression injury of the proprioceptive sensory axon terminals with a concomitant micro- or stress fracture in the periosteum of the medial proximal tibia (29). We also suggested that DOMS has an analogous bi-phasic non-contact injury mechanism where the primary injury is the microdamage of the proprioceptor in the muscle spindle followed by the secondary, even harsher tissue damage (18). The primary damage could evolve in a cognitive demand induced ASR moment when fatiguing unaccustomed or strenuous eccentric contractions are executed (18, 19), more specifically these are accelerating and decelerating moments prior to NC-ACL injury (19). The resultant impaired proprioception could lead to injury of the ACL in the secondary damage phase in a decelerating moment with concomitant harsher tissue injury (19).

In summary, we are the first to publish that Piezo2 ion channels in the terminals of proprioceptive sensory fibers could be microinjured in the primary phase of non-contact injuries due to cognitive demand derived ASR influenced unaccustomed or strenuous eccentric exercise moments, like DOMS, NC-ACL injury and POIS (18-20, 26). Noteworthy, that Ardem Patapoutian received the Nobel Prize this year for his work on Piezo receptors, but we theorized first, even earlier, that Piezo2 ion channel could go through a transient microdamage on somatosensory terminals (Piezo2 channelopathy) (20) and the researches presented in this dissertation, namely the significant delay of MLR, could be a partial proof of our hypotheses, not to mention that our measurement method seems to substantiate that the knee point at the provocative position of NC-ACL injury is the medial proximal tibia.

Összefoglaló

Doktori munkálataim célja kettős volt. Először, egy általános mechanizmus hipotézis felállítása a nem-kontakt sérülések kialakulására, mint az izomláz vagy még inkább a nem-kontakt elülső keresztszalag sérülés (NK-EKSZ) (18-20). Másodszor, olyan kísérletieredmények bemutatása, amelyek alátámasztják a fenti hipotéziseket (29).

A primer oka a két fázisú NK-EKSZ sérülésnek a proprioceptív idegvég heveny kompressziós mikrokárosodásában feltételezett, amely együtt jár a sípcsont fejének mediális oldali mikro- vagy stressztörésével az elmélet szerint (19). Izomlázban szintén egy analóg két-fázisú nem kontakt sérülés mechanizmust javasoltunk, ahol a primer sérülés az izomorsóban található proprioceptív idegvég mikrosérülése, míg a másodlagos sérülés egy nagyobb szöveti roncsolással járó folyamat (18). Az elsődleges sérülés olyan fárasztó nem megszokott vagy hosszantartó erőkifejtéssel járó excentrikus izomösszehúzódások során alakul ki, mikor már akut stressz reakció is indukálódik a kognitív cél elérése érdekében (18, 19), még pontosabban ezek akcelerációs vagy decelerációs pillanatok az NK-EKSZ sérülést megelőzőleg (19). Az elsődleges sérülés következménye lesz a megzavarodott propriocepció, ami az EKSZ sérüléséhez vezethet a másodlagos sérülés decelerációs pillanatában, együtt járva egy nagyobb szöveti roncsolással (19).

Összefoglalva, először vetettük fel, hogy a nem-kontakt sérülések primer sérülési folyamatában a Piezo2 ion csatorna mikrosérülésen mehet ár a proprioceptive szenzoros idegvégeken fárasztó nem megszokott vagy hosszantartó erőkifejtéssel járó excentrikus izomösszehúzódásokkal járó akut stresszhelyzetekben, mint az izomláz, NK-EKSZ sérülés vagy POIS (18-20, 26). Figyelemreméltó, hogy Ardem Patapoutian kapta a Nobel díjat 2021-ben a Piezo csatornák felfedezéséért, de még ezt megelőzően mi vetettük fel, hogy a Piezo2 ion csatorna átmeneti mikrosérülésen (Piezo2 channelopathia) mehet át a szomatoszenzoros idegvégeken (20) és a disszertációmban bemutatott kísérlettel, nevezetesen az MLR szignifikáns csúszásával (29), részlegesen bizonyítottuk a nem-kontakt sérülés mechanizmus hipotézisemet. Továbbá kialakítottunk egy olyan vizsgálati módszert is, amely szintén alátámasztja hipotézisem azáltal, hogy az eredő erő támadáspontja az NK-EKSZ sérülés provokatív pozíciójában (majdnem teljesen nyújtott térd) a sípcsont fejének mediális oldalán található.

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Impact factor: 1.93

Acknowledgements

I am very grateful to my supervisor Prof. István Berkes for his constant support of my ideas, introducing me to the University of Physical Education and guiding me through my doctoral work. I am also grateful to Prof. Zsolt Radák for his numerous advice of preparing my manuscripts for publication and for his guidance in the scientific world. I would like to thank Erika Koltai who provided invaluable technical assistance to my work.

I am also thankful to Cecília Molnár, Rita Kiss, Bence Kopper and Ádám Hegedűs for their support and contribution in our joint research work.

I would like to thank my parents for supporting me in my pursuit of higher education and especially to my father who promoted me the respect for science and love for daily exercise and sports activity.

Last but not least, I am deeply indebted to my loving wife and my kids for their continuous support in my scientific efforts and writing my PhD thesis, not to mention their patience, especially in Covid pandemic times when nicely saying information technology resources were absolutely scarce in the family. Without them I could not write my dissertation. Furthermore, I am grateful in life that I have had ample opportunities to belovingly watch my family playing sports and could analyze their kinesthetic and proprioceptive capabilities. Not to mention the great joy of spending time pursuing sport activities together, especially skiing which is a typical DOMS inducing eccentric exercise. Without them these hypotheses could not evolve and put on paper!