Plasticity of morphological and mechanical properties of muscles and tendons: Effects of maturation and athletic training

Dissertation

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von
Dipl.-Sportwiss. Georgios Charcharis

Prof. Dr. Julia von Blumenthal
Präsidentin der
Humboldt-Universität zu Berlin

Prof. Dr. Christian Kassung
Dekan der Kultur-, Sozial-und
Bildungswissenschaftlichen
Fakultät

Gutachter:

1. Prof. Dr. Adamantios Arampatzis
2. Pof. Dr. Kiros Karamanidis

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Zusammenfassung

In den letzten Jahrzehnten ist die Zahl der Erwachsenen, besonders der Jugendlichen, die an nicht organisierten oder wettbewerbsorientieren Sportarten teilnehmen, gestiegen. Während der Pubertät wird die Entwicklung der Muskeln und Sehnen sowohl von der Reifung aufgrund hormoneller Veränderung, als auch durch mechanische Belastung beeinflusst. Zurzeit gibt es keine Informationen über die Interaktion dieses doppelten Stimulus, obwohl Grund zu der Annahme besteht, dass während der Pubertät bei Athleten und Nicht-Athleten Ungleichgewichte zwischen Muskelkraftkapazität und Sehnensteifigkeit auftreten können. Das Ergebnis dieses Ungleichgewichts könnte sein, dass die Sehnen einer höheren mechanischen Belastung durch die zugehörigen arbeitenden Muskeln ausgesetzt sind, was weiter zu einer Sehnenverletzung führen könnte. In Anbetracht der nicht zufrieden stellenden Beweise für die Entwicklung des muskulotendinösen Gewebes während der Pubertät und des Mangels an Wissen darüber, wie die Reifung die Muskel-Sehnen-Einheit, vor allem die Interaktion mit überlagerter mechanischer Belastung beeinflusst; untersucht diese Arbeit die morphologische und mechanische Entwicklung der Knieextensoren und der Patellasehne, indem Nicht-Athleten und Athleten aus drei verschiedenen Altersgruppen verglichen werden (d.h. frühe Pubertät: 12–14 Jahre (engl.:EA, n = 29), späte Pubertät (engl.: LA, n = 27): 16–18 Jahre und Erwachsene : 20–35 Jahre (engl.: YA, n = 25).

Die maximale Kraft der Knieextensoren, die Architektur des M. vastus lateralis (VL) und die Patellasehnensteifigkeit wurden unter Verwendung von Dynamometrie, Bewegungserfassung, Elektromyographie und Ultrasonographie untersucht. Muskelkraft und Sehnensteifigkeit nahmen von EA zu LA ohne weitere Veränderung ($p > 0.05$) von LA zu YA signifikant zu ($p < 0.001$). Athleten zeigten im Vergleich zu Nicht-Athleten eine signifikant höhere ($p < 0.001$) absolute Muskelkraft (EA: 3.52 ± 0.75 vs. 3.20 ± 0.42 Nm/kg; LA: 4.47 ± 0.61 vs. 3.83 ± 0.56 Nm/kg; und YA: 4.61 ± 0.55 vs. 3.60 ± 0.53), Sehnensteifigkeit (EA: 990 ± 317 vs. 814 ± 299 N/mm; LA: 1266 ± 275 vs. 1110 ± 255 N/mm; und YA: 1487 ± 354 vs. 1257 ± 328), und VL-Dicke (EA: 19.7 ± 3.2 vs. 16.2 ± 3.4 mm; LA: 23.0 ± 4.2 vs. 20.1 ± 3.3 mm; und YA: 25.5 ± 4.2 vs. 23.9 ± 3.9 mm). Athleten erreichten mit höherer Wahrscheinlichkeit Dehnungsgrößen von mehr als 9% Dehnung verglichen mit der Kontrolle durch Nicht-Athleten (EA: 28 vs. 15%; LA: 46 vs. 16%; und YA: 66 vs. 33%), welche auf einen erhöhten mechanischen Bedarf an der Sehne hindeuten. Obwohl die Eigenschaften der M. quadriceps femoris-Sehnen-Einheit durch sportliches Training verbessert werden, bleibt ihre Entwicklung von der frühen Pubertät bis zum Erwachsenenalter bei Athleten und Nicht-Athleten mit der Hauptveränderung zwischen früher Pubertät und LA ähnlich. Jedoch waren sowohl das Alter als auch das sportliche Training mit einer höheren Prävalenz von Ungleichgewichten innerhalb der Muskel-Sehnen-Einheit und einer daraus resultierenden erhöhten mechanischen Beanspruchung oder Belastung für die Patellasehne verbunden.

Abstract

In recent decades, the number of adults and especially adolescents who participate in some kind of non-organized or competitive sports has been increasing. During adolescence, the development of muscle and tendons is affected both by maturation, due to hormonal changes, and by mechanical loading. However, there is no information currently on the interaction of this double fold stimulus although there is reason to believe that during adolescence in athletes and non-athletes there may be imbalances developing between muscle strength capacity and tendon stiffness. The result of this imbalance could be the tendon exposure to high mechanical demand by the associated working muscles, which might further lead to tendon injury**.** Considering the not satisfactory evidence of the musculotendinous tissue development during adolescence, and the lack of knowledge about how maturation affects the muscle-tendon unity, especially in interaction with superimposed mechanical loading, this thesis investigates the morphological and mechanical development of the knee extensors and patellar tendon, by comparing non-athletes and athletes in three different age groups (i.e., early adolescents: EA 12–14 years, n = 29; late adolescents: LA 16–18 years , n = 27 and young adults: YA 20–35 years, n = 25) .

Maximum strength of the knee extensor muscles, architecture of the vastus lateralis (VL) muscle and patellar tendon stiffness were examined using dynamometry, motion capture, electromyography, and ultrasonography. Muscle strength and tendon stiffness significantly increased ($p < 0.001$) from EA to LA without any further alterations ($p > 0.05$) from LA to YA. Athletes compared to non-athletes showed significantly greater ($p < 0.001$) absolute muscle strength (EA: 3.52 ± 0.75 vs. 3.20 ± 0.42 Nm/kg; LA: 4.47 ± 0.61 vs. 3.83 ± 0.56 Nm/kg; and YA: 4.61 ± 0.55 vs. 3.60 ± 0.53), tendon stiffness (EA: 990 ± 317 vs. 814 ± 299 N/mm; LA: 1266 ± 275 vs. 1110 ± 255 N/mm; and YA: 1487 ± 354 vs. 1257 ± 328), and VL thickness (EA: 19.7 ± 3.2 vs. 16.2 ± 3.4 mm; LA: 23.0 ± 4.2 vs. 20.1 ± 3.3 mm; and YA: 25.5 ± 4.2 vs. 23.9 ± 3.9 mm). Athletes were more likely to reach strain magnitudes higher than 9% strain compared to non-athlete controls (EA: 28 vs. 15%; LA: 46 vs. 16%; and YA: 66 vs. 33%) indicating an increased mechanical demand for the tendon. Although athletic training enhances the properties of the quadriceps femoris muscle-tendon unit, their development from early-adolescence to adulthood remains similar in athletes and non-athletes with the major alterations between early and LA. However, both age and athletic training were associated with a higher prevalence of imbalances within the muscle-tendon unit and a resultant increased mechanical demand for the patellar tendon.

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List of Abbreviations

EA Early Adolescence (12–14 years)

LA Late Adolescence (16 –18 years)

YA Young Adults (20–35 years)

MVC Maximum Voluntary isometric Contraction

EMG Electromyography

PHV Peak Height Velocity

PWV Peak Weight Velocity

FFM Free Fat Mass

FM Fat Mass

CSA Cross-Sectional Area

GH Growth Hormone

IGF–I Insulin-like Growth Factor

PCSA Physiological Cross-Sectional Area

ACSA Anatomical Cross-Sectional Area

GM Gastrocnemius Muscle

VL Vastus Laterais

VI Vastus Intermendius

RF Rectus Femoris

MHC Myosin Heavy Chain

RFD Rate of Force Development

GH-IGF-I axis Growth Hormone –Insulin-like Growth Factor

1 Introduction and literature review

Even though there is some knowledge about how maturation affects muscle and tendon development in adolescence, less is known about the effects of training on muscle-tendon properties during maturation and there is no information regarding the interaction between training and maturation. The development of the quadriceps femoris muscle-tendon unit from early adolescence (EA: 12–14 years), late adolescence (LA: 16–18 years) to young adulthood (YA: 20–35 years) is studied in this thesis, as well as how athletic training influences this development. In light of maturation and increased mechanical loading, the following introduction provides a summary of the current understanding of the morphological and mechanical properties of muscles and tendons. The interplay among maturation and superimposed mechanical loading, in addition to the cutting-edge know-how of muscles and tendons non-uniform adaptation in reaction to increased mechanical loading during maturation, as well as the consequent potentiality of the tendon to be exposed to overuse are explored. The morphological, mechanical, and functional properties of musculotendinous tissue, as well as how maturation and athletic training alter these parameters, are the subject of this thesis and the literature review. Moreover, other aspects that could be affected by the aforementioned influential factors, such as neuromuscular development (e.g., neural), or other adaptations (structural, and molecular factors) are briefly explored where necessary.

2 Maturation and muscle properties

In the following chapter, a brief introductory overview about the somatic and muscle development during maturation is mentioned. After this chapter, a more detailed review of the morphological and functional properties and their development during maturation will follow.

Mirwald et al., 2002, stated, "Human maturation is the tempo and timing of the progress toward the mature state during growth processes over time". One of the life periods, when major changes occur on the human body is puberty (Beunen and Malina, 1988; Tanner, 2009; Murray and Clayton, 2013); and includes a person's transmission period from the onset of the growth spurt (Tanner et al., 1976), which is 10–11 years for the girls and 11–12 years for the boys (Zacharin et al., 2013), to early adolescence (12–14 years)(Laitinen-Krispijn et al., 1999; Schneiders, 2003; Sund et al., 2003), and late adolescence (16–18 years)(Farnham, 1968; Tanner et al., 1976).

The Tanner scale describes the somatic characteristics of both sexes puberty spurt status as the beginnings of breast development for girls and a testicular volume of 10-12 ml for boys (Tanner, 2009; Murray and Clayton, 2013). However, in the literature, there are other techniques to assess puberty growth, such as peak height velocity (PHV), a biological maturation and an adolescence index (Beunen and Malina, 1988). Taking a closer look, someone might notice, that there are differences in maturation tempo between sexes (Beunen and Malina, 1988; Murray and Clayton, 2013). For instance, according to the PHV, girls express their adolescent spurt 2 years earlier compared to boys, and reach a height development of 8cm/year coinciding with the onset of their puberty; while males reach a PHV of 10cm/year, and this occurs later, on average 14 years into puberty (Beunen and Malina, 1988; Murray and Clayton, 2013). The cessation of puberty, and therefore the stop of the longitudinal growth, is signaled when the aromatization of the testosterone (the alteration of testosterone to estrogen via enzymic attribution (Norman and Henry, 2015a, b) produces the estrogens required to fuse the metaphyseal growth plates (Murray and Clayton, 2013).

Irrespective of sex, the body dimensions development during maturation pass from puberty to adolescence is expressed differently compared to height and weight (Beunen and Malina, 1988). It seems that all of them precede peak height velocity (PHV) but some of them coincide or are expressed prior to peak weight velocity (PWV) (Beunen and Malina, 1988). The differences in maturational development between sexes are apparent regarding the increase in free fat mass (FFM), and the decrease of fat mass (FM) (Beunen and Malina, 1988). Changes in body composition at the period of growth spurt can be approximated at 11 to 13 years in girls and 13 to 15 years in boys (Beunen and Malina, 1988). FFM gains are estimated to be 3.5

Kg/year for girls and 7.2 Kg/year for boys (Beunen and Malina, 1988). Corresponding changes in absolute FM at this maturational period are estimated to be 0.7 Kg/year in boys and 1.4 Kg/year for girls; but the estimations of relative FM (fat mass as a percentage of body weight) is +0.9% for girls and –0.5% in boys (Beunen and Malina, 1988).

During early life, muscle mass (**Figure 1**) is known to progressively increase until it reaches its peak around early adulthood (~24 years) (Evans and Lexell, 1995; Deschenes, 2004; Sayer et al., 2008). Thereafter, it is fairly well maintained during the fifth decade, with a modest reduction of roughly 10% (Evans and Lexell, 1995; Deschenes, 2004). Over the age of fifty, however, this loss in muscle mass accelerates, resulting in an annual loss of up to 1.4% (Deschenes, 2004; von Haehling et al., 2010, Lang et al., 2010, Mitchell et al., 2012). In total, a reduction of approximately 40% in muscle mass and a decline in cross-sectional area (CSA) in the order of 20% can be seen by the age of eighty (Deschenes, 2004; Evans, 2010). Regarding muscle strength (**Figure 2**), a loss becomes apparent after the age of fifty years (Landi et al., 2017). Between the ages of 50 and 60 years, there is a documented annual reduction of roughly 1.5% per year (Charlier et al., 2015). After the sixth decade, the decrease can be as high as 3% every year (Baumgartner et al., 1998).

Fig.1

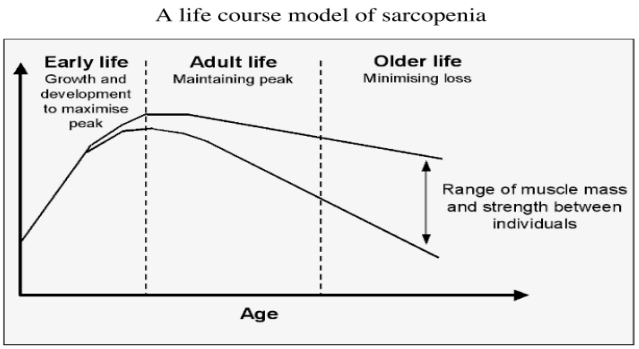

Fig.2

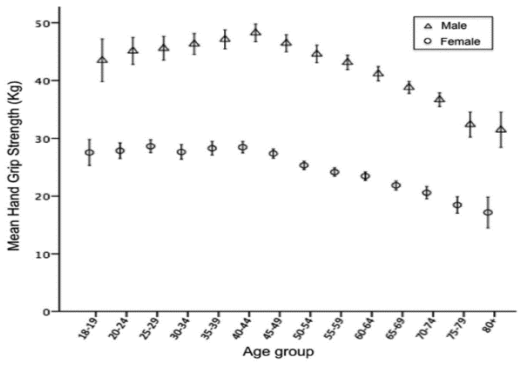

Figure 1 Sayer et al., 2008, *The Journal of Nutrition, Health & Aging,* 12(7), 1–26. p.427. Adapted with permision from Springer Nature. ***Figure 2*** Hand–grip strength (mean and SD) according to age group and gender (triangle for men, circle for women). (Landi et al., 2017, *Journal of the American Medical Directors Association,* 18(1), p. 1.e4. Adapted with permision from Elsevier). Note there is strong correltion between grip strength and total muscle strength (Tonson, 2010)

Hormonal changes during growth are the main cause for the muscle morphological and functional characteristics development (Giustina, 1998; Hulthen, 2001; Storer et al., 2003;Velloso, 2008; Murray and Clayton, 2013; Chikani and Ho, 2014). The pattern of human growth changes markedly with the initiation of, 1) the activity within the hypothalamo-

pituitary–gonadal axis leading to a large increase in the production of androgens (for males) and estrogen (in females), and 2) the activation of the growth hormone (GH)–insulin-like growth factor-I (IGF-I) axis (Murray and Clayton, 2013). GH increases during maturation (Murray and Clayton, 2013) and under the anabolic mediation of the IGF-I will lead to a greater muscle mass, cross-sectional area (CSA), and strength (Giustina, 1998; Hulthen, 2001; Velloso, 2008; Murray and Clayton, 2013). However, it is the locally produced IGF-I, acting in an autocrine/paracrine fashion which is the most important for the overall somatic growth (Velloso, 2008; Murray and Clayton, 2013).

2.1 Morphological properties

Morphological alterations of the muscle owing to radial and longitudinal changes. The number of sarcomeres in parallel is the modulation factor of the radial changes, which are best represented by changes in the muscle physiological cross-sectional area (PCSA, Haxton, 1944), which is the area of the muscle cross-section perpendicular to the fiber orientation (Brown and Sewry, 2017). According to recent findings, muscle function is influenced by the muscle architectural features, i.e., pennation angle and fascicle length (Kawakami et al., 1993, 1995; Kumagai et al., 2000). The muscles' angle of pennation rise is, however, the major factor that modulates PCSA (Aagaard et al., 2001) and facilitates fiber hypertrophy and, therefore, muscle radial growth to surpass the changes in the anatomical cross-sectional area (ACSA) regarding the whole muscle (Aagaard et al., 2001). Furthermore, the increase in the cross-sectional area of individual muscle fibers mainly contributes to the increased force-producing muscle potentiality (Johnson and Klueber, 1991; Aagaard et al., 2001; Farup et al., 2012), governed by radial muscle adaptation and related to improved myofibrillar development (MacDougall et al., 1980) and proliferation (Goldspink, 1970). The sarcomeres in series number adaptation is referred to as longitudinal muscle adaptation and is positively associated to muscle fibers' mechanical power and maximum shortening velocity (Goldspink, 1985).

In the literature, few studies are investigating the development of the morphological properties of the muscle, as well as the architectural properties, such as pennation angle, and fascicle length, that underlie this development (Kanehisa, et al., 1995a, b; Morse et al., 2008; O'Brien et al., 2010a, b; Franchi etal., 2017); moreover, all studies use different methodological approaches. New studies employing ultrasound-based and Magnetic Resonance Imaging (MRI) techniques for the assessment of the muscle dimensional and architectural properties, reported that increases in muscle volume during maturation signified by alterations in muscle morphological and architectural characteristics, such as changes in PCSA, pennation angle, and

fascicle length (O'Brien et al., 2010a), indicating a development of muscle morphological and architecture characteristics towards adulthood. However, differences between the sexes and in the tempo development between morphological and architectural properties do exist (O'Brien et al., 2010a, b). Bénard and colleagues, (2011) reported that the contribution of the increase of fascicle length during maturation of the gastrocnemius muscle (GM) was 4 times smaller in comparison to PCSA. Morse et al. (2008) and O'Brien et al. (2010b) reported that children had smaller PCSA compared to adults. However, boys had 104% smaller PCSA compared to men and girls 57% smaller than women, while the fascicle length differences were 37% and 10% accordingly (O'Brien et al., 2010a). Therefore, it is conclusive that during maturation the increase of muscle volume will be a result of the increase of PCSA and fascicle length. Since the increase of PCSA exceeds this of fascicle length (O'Brien et al., 2010a), it appears that as the muscles develop during maturation, they adopt a morphological configuration that is more suitable for producing maximum force (O'Brien et al., 2010a). Adults, on the other hand, have longer fascicles, which allows them to achieve a higher absolute maximum shortening velocity than children (O'Brien et al., 2010a). However, O'Brien and colleagues (2010a, b) investigated children and adults in order to describe the maturational development of the morphological and architectural characteristics without investigating the in-between maturation stage of adolescence. In the current literature, there are only a few studies investigating these developments during the passage from childhood to adulthood (Kanehisa, et al., 1995a, b; Kubo et al., 2001, 2014a).

Anatomical cross-sectional area (ASCA) and muscle thickness are other morphological characteristics related to muscle strength (Folland and Williams, 2007; Mersmann et al., 2016), and can be measured with no-invasive techniques (Park et al., 2014; Legerlotz et al., 2016), such as ultrasound devices, which are broadly available and affordable to assess muscle morphological parameters (Legerlotz et al., 2016). Kanehisa and colleagues (Kanehisa, et al., 1995a, b) were the first to study the morphological properties of the muscle in *vivo* during adolescence by ultrasound-based technique. They investigated the development of the muscle ACSA from pre-puberty (7–9 years) to late-adolescence (16–18 years). It was shown that muscle ACSA increased in parallel with age and longitudinal growth with the most pronounced increase between age 13–15 years (Kanehisa, et al., 1995a; **Figure3**). The sex differences became apparent at the same period of age (Kanehisa, et al., 1995b; **Figure 4**). Moreover, Kubo and colleagues, (2001, 2014a) reported that adults (~ 22 years) had higher muscle thickness when they were compared to junior high school (~ 14 years) and elementary school (~ 11 years)

students. Thus, it seems that muscle morphological development continues towards adulthood, however, there may be periods during maturation where the gains could be greater.

Fig.3

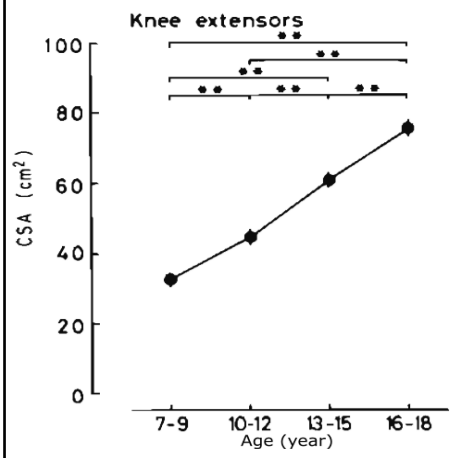

Fig.4

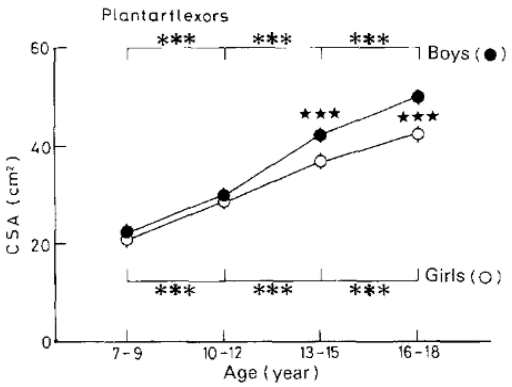

Figure 3 Chronological age changes in muscle CSAs. Values are means ± SE. Significant differences between group means are indicated: ** P < 0.01. (Kanehisa et al., 1995, *International Journal of Sports Medicine,* 16, 3–8. p. 56. Adapted with permission from Georg Thieme Verlag KG). ***Figure 4*** Changes in muscle cross-sectional area (CSA) with age. Each data point indicates the mean and standard error of the mean. *** Significant difference between adjacent are groups at P < 0.001. ★★★ Significant difference between boys and girls within the same generation at P < 0.001. (Kanehisa et al., 1995, *European Journal of Applied Physiology and Occupational Physiology,* 72(1), 150 –156. Adapted with permission from Springer Nature)

As has been reported in many studies, the angle of pennation is directly related to the PCSA, and is one of the morphological characteristics associated with muscle strength (Kawakami et al., 1995; Aagaard et al., 2001). Research has demonstrated that its development during maturation differs between muscles (Morse et al., 2008; O'Brien et al., 2010a, b), and this recommends that there may be muscle specificity. Studies conducted on the muscles of quadriceps and gastrocnemius lateralis suggest that there is no substantial increase in pennation angle during maturation, since comparing adults with children found no differences (Morse et al., 2008; O'Brien et al., 2010a, b). However, investigations on more pennate muscles (gastrocnemius medialis) have observed that the angle of pennation increases from the time of birth (0 years), and reaches a plateau after the adolescent growth spurt, but without significant increases during puberty (5 to 12 years old, **figure 5**) (Legerlotz et al., 2010; Bénard et al., 2011; Weide et al; 2015). If this was the case in accordance with the previous findings, it would mean that during adolescence not only morphological characteristics related to muscle force production would be developed, but also the differentiation of specific function between muscle would be promoted, since the different architecture properties between the muscles during development can affect their force-producing capabilities (Huijing, 1985; Kawakami et al., 1998).

Fig.5

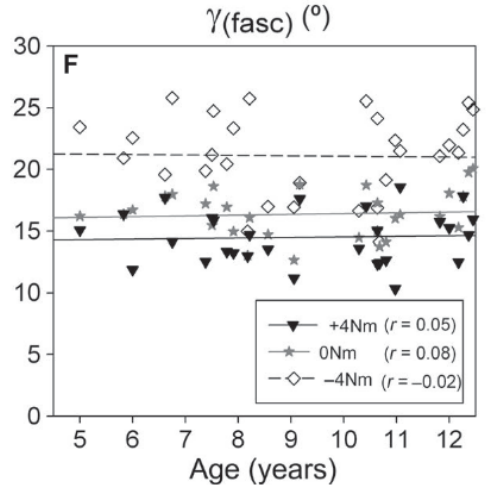

Figure 5 Effects of growth on variables of muscle geometry measured at different footplate moments (F), Fascicle –aponeurosis angle (γ_{fasc}) plotted as a function of age. The variable were measured in GM for three conditions (i.e. -4 Nm, 0 Nm +4 Nm applied to the footplate). For the regression analysis, the data of both genders were pooled, as there was no significant difference between boys and girls. Statistical analysis with GEE (factors age and footplate moment-angle) showed no significnat main effect of age on (γ_{fasc}). Coefficinet of correlation r with age is shown for the three moment conditions. (Bénard et al, 2011. *Journal of Anatomy,* 219(3), 388–402. p.395 Adapted with permission from John Wiley and Sons)

The increase in muscle PCSA during maturation is determined by the increase in the cross-sectional area that occurs in the muscle fibers and not by the creation of new ones, e.g., hyperplasia (Aherne et al., 1971; Oertel, 1988). This fiber augmentation increases and reaches its peak development during adulthood (35 years) and then decreases during the elderly (Mohamed et al., 2007). Studies have often highlighted the importance of the growth hormone (GH) and insulin-like growth factor-I (IGF-I) axis in somatic growth, whose activation increases dramatically during maturation, especially during adolescence, and results in the stimulation of the hypertrophy and the protein content of the fibers; however, it seems that myotube formation is not attributed to these hormones (Grohmann et al., 2005**).** Researchers that have investigated these hormones separately have found that both GH and IGF-I are important hormonal factors for the radial and longitudinal growth of the muscle fibers, through their contribution to myoblasts proliferation and fusion with the myotubes (Cheek et al., 1971; Allen et al., 1999; Grohmann et al., 2005). Thus one could argue that an individual's body height and single-fibers CSA are associated (Aherne et al., 1971). The sex differences regarding muscle morphological development during maturation could be explained by the levels of the sex hormone of androgen. For instance, testosterone is an androgen hormone that promotes muscle fiber radial growth (Sinha-Hikim et al., 2002). Under this hormonal concept, females would exhibit less gains in muscle growth during maturation due to the10 to 20 times lower testosterone concentration levels (Zatsiorsky and Kraemer, 2006).

2.2 Structural properties

Muscle fibers can be categorized into three major types: I, IIA and IIB (Staron, 1997; Fry, 2004). These fiber types constitute a continuum, from type I which is the slowest, to IIB which is the fastest (Fry, 2004), and are governed by the corresponding contractile protein isoforms of myosin heavy chain (MHC) such as MHC I, IIA, and IIB (Fry et al., 1994). Any differences in fiber type profile can be manifested via differentiation of the MHC (Campos et al., 2002, Fry, 2004).

The muscle volume development during maturation is marked by alteration and differences in fiber type population and dimension. Lexell and colleagues (1992) and Oertel, (1988) reported that muscle fiber size (**Figure 6 & 7**) in males and cross-sectional area (CSA) in both sexes increase from childhood to adulthood. In literature, there is conflicting evidence regarding the muscle fiber topography during maturation. While formerstudies have yielded no results regarding changes in muscle fiber distribution during muscle development (Bell et al., 1980), later ones reported a significant increase in fiber type II in males, from the age of 5 (approx. 35%) to the age of 20 (approx. 50%), indicating a transition from the fiber type I to fiber type II during maturation (Lexell et al., 1992, **Figure 6 &7**); however, these differences are not big (Lexell et al., 1992; Metaxas et al., 2014). For instance, Lexell et al. (1992) found differences between 5 to 20 years approximately 15%, while Metaxas and colleagues (2014), by comparing adolescent males 15 years to 13 and 11 years, reported differences in the order of 18.4 and 18.1% respectively. It is well-known that muscle fiber type differentiation is attributed to motor innervation (Dubowitz, 1967; Romanul, 1967; Chal and Pourquié, 2017), as a result of the maturation of the nervous system, as well as due to persons' motor abilities improvement which should trigger this physiological mechanism (Dubowitz, 1967;Thompson et al., 1990; Viru et al., 1999).

In females there is no information regarding the differentiation of the muscle fibers during maturation, however, some reports maintain that females have less fiber type II compared with males, and that these fiber type sex differences are brought about due to the influence of testosterone (Praagh and Dore, 2002). Indeed, animal studies suggest that the effect of the sex hormones such as testosterone and estrogen (Gutmann et al., 1970; Holmang et al., 1990; Holmes et al., 2007; Haizlip et al., 2015) along with that of thyroid hormone, might be fiber type-specific (Haizlip et al., 2015). Interestingly, while it could be observed muscle fiber radial growth (i.e., CSA) in both sexes throughout maturation (Oertel, 1988), in light of findings of muscle fibers biopsy studies in adults, no sex differences revealed in fiber distribution. However, males exhibited higher muscle fiber CSA in all fiber types compared to females, and

this difference is more pronounced in type IIA fibers (Staron et al., 2000). This may be indicative of the fact that muscle structural differences between sexes are most likely because of the augmentation of the muscle fibers.

Fig.6 **Fig.7**

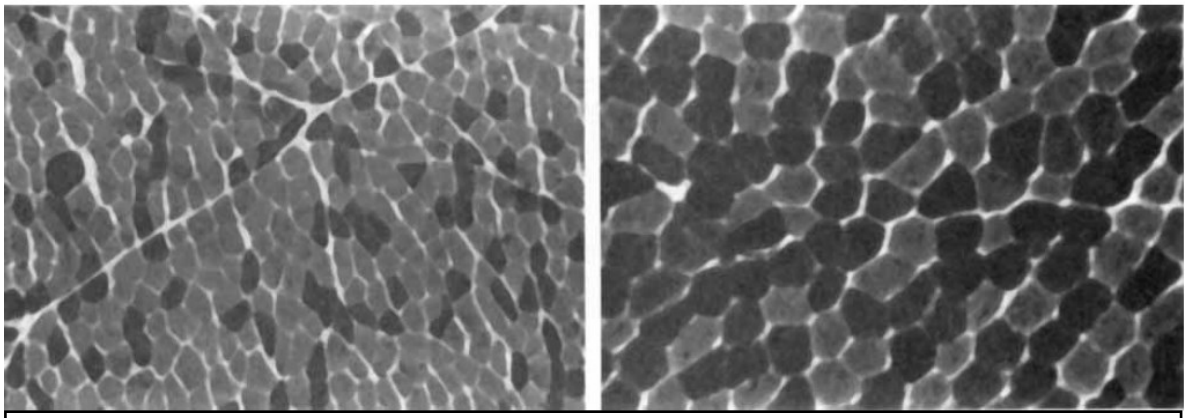

Figure 6 & 7 Stained myofibrillar adenosine triphosphatase (mATPase) at pH 10.4 to visualize type I (lightly stained) and type II (heavily stained) fibers***.Figure 6*** Sequence illustrating the general morphology in a child (age 8 years), an adult (age 18 years) ***Figure 7;*** (mATPase at pH 10.4; X80). (Lexell et al., 1992, *Muscle & Nerve*, 15(3), 404–409. p. 406. Adapted with permission from John Wiley and Sons)

Sexual dimorphism refers to the differences that characterize the two sexes and can be observed in the expression of myosin isoform genes, in insulin-like growth factor (IGF)-I-regulating proteins, as well as in myostatin signaling pathways (Welle et al., 2008), all of which could play a role in the emergence of these developmental sex discrepancies in humans (Welle et al., 2008). Moreover, these sex-differences appear to be activated throughout the endocrine development during adolescence, mainly through the interaction of various growth factors, such as growth hormone (GH) with IGF-I (Hulthen, 2001; Grohmann et al., 2005), and androgens with myostatin (Mendler et al., 2007).

2.3 Muscle activation

Adaptations in muscle strength are dependent not only on their morphological properties alterations, but also on changes in the neural drive which can reflect changes in the motor unit recruitment and firing rate (Aagaard et al., 2002; Legerlotz et al., 2016). These changes are most commonly mentioned as adaptation in muscle activation level (Knudson, 2007). The differences in the muscular strength between children and adults seem to remain, even when it is normalized with body size, and are due to the ability of the children to activate their muscles at lower levels compared to adults (Kanehisa et al., 1995a; Dotan et al., 2012). In fact, scientific evidence demonstrated that children during muscle voluntary contraction recruit a smaller percentage of their total motor-unit pool than adults (Stackhouse et al., 2005; Grosset et al., 2008). Using the interpolated-twitch technique, the results show, even though these differences are small, that children have a smaller ability of voluntary muscle activation compared with adults (children: 70–90% versus adults: 86–98%, Pääsuke et al., 2000; Praagh and Dore, 2002; Streckis et al., 2007; Grosset et al., 2008; O'Brien et al., 2010b; Dotan et al., 2012); however, other studies reported an adult-like muscle activation even in pre-puberty (Hatzikotoulas et al., 2014). Nonetheless, motor–unit activation deficits of activation appear to be decreasing with age (Belanger and McComas, 1989; Grosset et al., 2008). It is well-known that high threshold type II motor units, compared to type I, can provide faster development of force, higher shortening speeds, and they have a higher velocity at which the motor unit action potential propagates along these muscle fibers during contraction (rapid conduction velocities Sale, 1987; Soares et al., 2015). Under these previous notions, researchers have hypothesized that children's smaller capability for rapid force production is justified by their inability to employ or utilize type II motor units (Halin et al., 2003). Furthermore, the ability to employ type II motor units seems to increase towards adulthood (Dotan et al., 2012; Waugh et al., 2013).

Co-activation is the simultaneous activation of agonist and antagonist muscles around a joint (Hirokawa et al., 1991) and provides joint stability. Children manifest greater co-activation than adults, which decreases with age (Grosset et al., 2008), however, Bassa et al., (2005) reported no differences. As a result of the literature, it is convincing that the recruitment of the motor units, and the utilization capacity of the high thresholds type II motor units increase with maturation (Dotan et al., 2012; Radnor et al., 2018), all of which are influenced by the development of the central nervous systems (Viru et al.,1999; Pääsuke et al., 2000; Radnor et al., 2018). These alterations during maturation will eventually result in changes in the reported muscle activation level.

2.4 Functional properties

During maturation, muscle functional properties like muscle strength, rapid force production, muscle power, and maximum shortening velocity are developing during human life (Beunen and Malina, 1988; Viru et al., 1998, 1999; Legerlotz et al., 2016). These muscle functional properties appear to rely partly on improvements in the nervous system, and partly on muscle morphology adaptations, such as muscle fiber growth and muscle composition (Viru et al., 1999; Legerlotz et al., 2016). However, each of these functional properties follows different sensitive periods of development, in which the improvements are more pronounced during growth (Viru et al., 1998, 1999). More precisely, the review of Viru et al., (1999) reported that the improvement in muscle strength is high at the age of 6 to 9 years. During the next years, the improvement rate decreases and afterward begins to increase again. A new acceleration of strength gains occurs in boys aged 13 to 16 years and in girls of 12 to 15 years (Viru et al., 1999).

The development of the intrinsic muscle strength (specific force) during maturation might affect the muscle strength due to differentiation of the fiber type population (Kanda and Hashizume, 1992; Stienen et al., 1996). However, in the literature, it is not clear if any changes in fiber type distribution could alter the development of muscle strength during maturation. For instance, even though some studies reported that fibers type II are intrinsically stronger than type I (Powell et al., 1984; Bodine et al., 1987; Larsson and Moss, 1993), other experiments failed to support these findings (Wickiewicz et al., 1984; Fitts et al., 1989).

The performance tasks of the vertical and long jump are indirect measures of muscle power due to their simplicity (Isaacs, 1998; Lloyd and Oliver, 2012). The evidence has shown, a pronounced muscle power development from 5 to 10 years (Branta et al., 1984). It is believed that from 9 to 12 years of age in girls, and 13 years in boys, performance in the standing long jump and vertical jump increases linearly with age (Beunen and Thomis, 2000). The results of several studies have shown an intensive rise of leg power over the age range of 12 to 16 years, while others allocate these improvements at the age of 14 to 15 years (Espenschade, 1940; Beunen and Malina, 1988;Viru et al., 1999).

The ability to express muscle force development fast has an impact on human motor tasks, and it is widely known that the ability to produce muscle force rapidly increases during maturation (Weyand etal., 2000; Stone et al., 2003; Wisloff, 2004). The investigation of the muscle functional properties is of importance because any changes on them can affect the performance of different motor tasks (e.g., jumping and throwing performance, as well as the

velocity of the movement; Legerlotz et al., 2016). A review of the maturational development of the most important muscle functional properties is presented in the following chapter.

2.4.1 Muscle strength

In *vivo* cross-sectional studies in children have demonstrated smaller strength compared to adults (Tonson et al., 2008; O'Brien et al., 2010a, c), indicating a muscle strength development towards adulthood. In a more detailed examination, researchers observed that muscle strength increases with age alongside with gains in height and mass (Kanehisa, et al., 1995a; Beunen and Malina, 1988), and while this increase appears to be most pronounced for males and females between the ages of 13 and 15 years (Kanehisa, et al., 1995a, b; **Figure 8**), sex differences occur later at the age of 16–18 years (Kanehisa, et al., 1995b, **Figure 9**). Moreover, muscle strength, most probably, may reach a plateau during late adolescence (Kubo et al., 2014a; Landi et al., 2017). Since changes in the radial development of the muscle have a direct impact on its force production (Johnson and Klueber, 1991; Aagaard et al., 2001; Farup etal., 2012), the differences in muscle strength between different ages will be on account of the muscle morphological development during maturation. As a proof of this, Kanehisa, et al. (1995a) have reported that the increase in muscle strength follows that of cross-sectional area (CSA) during maturational development.

Fig.8

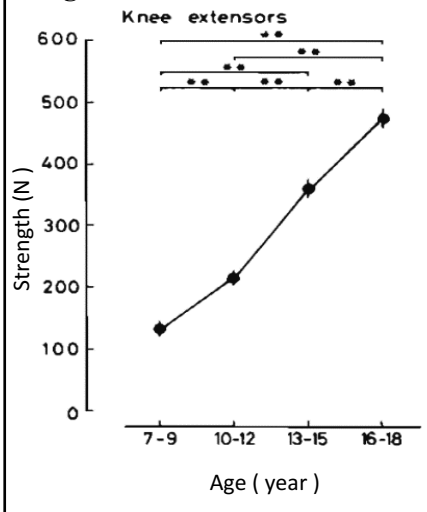

Fig.9

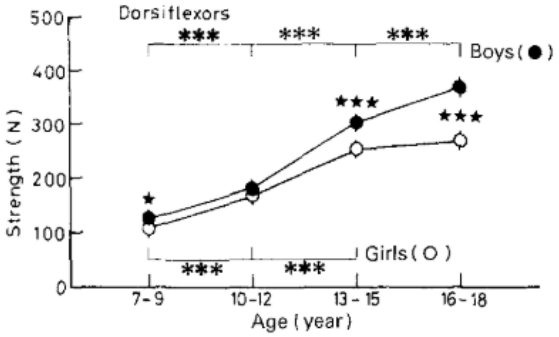

Figure 8 Chronological age changes in muscle strength. Values are means ± SE. Significant differences between group means are indicated: ** P < 0.01. (Kanehisa et al., 1995*, International Journal of Sports Medicine,* 16, 3–8.p. 57.Adapted with permission from Georg Thieme Verlag KG). ***Figure 9*** Each data point indicates the mean standard error of the mean. *** Significant difference between adjacent age groups and P < 0.001. ★★★ Significant difference between boys and girls within the same generation at P < 0.001 and P < 0.05, respectively. (Kanehisa et al., 1995),*European Journal of Applied Physiology and Occupational Physiology,* 72(1), 150–156. p.156. Adapted with permission from Springer Nature)

Hormonal effects will be instrumental in the development of muscle strength. Growth hormone (GH) as well as insulin-like growth factor (IGF-I) and androgen increase during maturation (Vermeulen et al., 1970; Murray and Clayton, 2013), and result in the augmentation of the muscle size (McCall et al., 1996; Sinha-Hikim et al., 2002; Grohmann etal., 2005), and therefore in the development of the muscle strength. Testosterone is an androgen hormone that promotes muscle fiber radial growth (Sinha-Hikim et al., 2002). Therefore, the 10–20 times lower testosterone levels of females compared to males could explain the sex differences in muscle strength during late adolescence (16–18 years) (Kanehisa, et al., 1995b; Zatsiorsky and Kraemer, 2006; Handelsman et al., 2018).

However, the increase in muscle strength during childhood and adolescence exceeds that of body and muscle size (Asmussen and Heebøll-Nielsen, 1955, 1956; Beunen and Malina, 1988; Kanehisa, et al., 1995a,b), and this is attributed to the development of the neuromuscular system (Asmussen and Heebøll-Nielsen, 1955). Thus, during maturation muscle strength will increase at a higher rate and this could be explained through quantitative changes (greater increase in muscle CSA than expected from the increase in height; Beunen and Thomis, 2000) and qualitative changes (improvements in motor-unit recruitment of type II; Williams and Amstrong, 2011; Dotan et al., 2012; Radnor et al., 2018).

2.4.2 Specific tension

It is well-known that muscle strength is related to changes in neurological factors and muscle morphology (Legerlotz et al., 2016). However, changes in muscle fiber distribution during maturation might also affect the force generated by the muscles. This hypothesis is made due to the fact that some studies have found a greater proportion of type II fibers in adults compared to young individuals (Lexell et al., 1992; Metaxas et al., 2014), and by the fact that fibers type II might be intrinsically stronger than type I (Powell et al., 1984; Bodine et al., 1987; Larsson and Moss, 1993). Nonetheless, the previous assertions have been challenged by studies supporting the absence of changes in muscle fiber type in favor of type II during maturation (Bell et al., 1980), as well as the intrinsic strength discrimination between fibers (Wickiewicz et al., 1984; Fitts et al., 1989). Myosin Heavy Chain (MHC) concentration appears to play an important role in fiber intrinsic strength (Canepari et al., 2010); so any changes in MHC during maturation would be expected to affect the muscle strength (D'Antona et al., 2003; Canepari et al., 2010). The best way to describe the intrinsic muscle strength is the specific tension which derived from the normalization of the maximum muscle force to muscle cross-sectional (the SI unit is kN/m^2) (Powell et al., 1984; Buchanan, 1995; Fukunaga et al., 1996; Maganaris et al.,

2001). To date, only two studies investigate the muscle specific tension in *vivo*. Morse and colleagues (2008) reported that adults had higher specific tension compared to children. However, taking into account that some methodological considerations like the impact of moment arms on muscle contraction, the presumption that both children and adults operate at the same area of the length–tension relations, along with the probable overestimation of the relative gastrocnemius lateralis PCSA within the total plantar flexor PCSA, could have resulted in unanticipated results that children and adults could generate the same values of specific tension.

From a methodological point of view, one of the survey which is considered reliable and measures the specific tension in *vivo* is that of O'Brien et al. (2010b), which has been supported by other research groups (Bouchant et al., 2011; Herzog et al., 2011). O'Brien et al., 2010b, reported that specific tension was similar between groups: men, 55 ± 11 N cm^{-2}; women, 57.3 ± 13 N cm^{-2}; boys,54 ± 14 N cm^{-2}; and girls, 59.8 ± 15 N cm^{-2}. Therefore, the development of muscle strength during maturation is due to the alterations in muscle activation and muscle growth and not due to changes in muscles' intrinsic force-generating capacity (O'Brien et al., 2010b).

2.4.3 Rate of force development

The ability to express force rapidly is really important for a human daily life, especially for activities where speed and power is needed (Taber et al., 2016). Rapid force production depends, on muscle morphology, fiber distribution, the recruitment of the fast-twitch motor-units, and the stiffness of the tendon (Maffiuletti et al., 2016). It is a well-known fact that muscle physiological cross-sectional area (PCSA) is associated with the rate of force development (RFD); thus, any development in muscle radial growth might have an impact on the rate of force rise (Maffiuletti et al., 2016). However, during maturation muscle PCSA increases and might be accompanied by changes in fiber type population in favor of type II (Lexell et al., 1992; O'Brien et al., 2010a). If this is so (i.e., the increase of fiber type II), the rate of force development (RFD) during maturation would be affected not only by the faster contraction speed of fiber type II (Maffiuletti et al., 2016), but also by the muscle specific tension, since fiber type II might be intrinsically stronger than type I (Powell et al., 1984; Bodine et al., 1987; Larsson and Moss, 1993). However, in literature, some studies failed to support this notion; namely, the increase of fiber type II during maturation (Bell et al., 1980), and the higher intrinsic strength of fiber type II compared to type I (Wickiewicz et al., 1984; Fitts et al., 1989). Moreover, specific tension seems to be similar between children and adults, indicating that the

development of RFD might be independent from the alterations in the intrinsic force-generating potential of the muscle, or changes in fiber topography (O'Brien et al., 2010b). In literature, there is not satisfactory evidence regarding the development of RFD. Waugh et al.(2013) reported that the rate of force development increases during growth attributed partly on neurological changes, such as the recruitment of fast-twitch motor-units (type II, Williams and Amstrong, 2011), and partly on changes in tendon stiffness (Waugh et al., 2013; Maffiuletti et al., 2016).

Summarizing, it seems that during maturation the muscle radial growth, the increasing ability to recruit the fast-twitch motor units (type II), as well as the increase of the tendon stiffness might be the main reasons that a person experiences an increase in rate force development during maturation (Williams and Amstrong, 2011; Dotan et al., 2012; Waugh et al., 2013; Maffiuletti et al., 2016).

From a hypothetical point of view, growth factors and androgens which have a direct impact on muscle growth and tendon mechanical properties could influence the RFD development, since the alterations in concentration levels of these hormones, which characterize the maturation process (Murray and Clayton, 2013), could result in different rates of muscle morphology and tendon stiffness (Inhofe et al., 1995; Velloso, 2008; Vingren et al., 2010; Boesen et al., 2014). However, literature lacks information regarding the development of RFD and its underlying mechanisms during adolescence, indicating the need for further study.

2.5 Maturation and tendon properties

The section that follows provides an overview of the current knowledge regarding the effects of maturation on tendinous tissue from early adolescence (12–14 years) to adulthood (20–35 years). Since in literature there are only few studies that can provide a satisfactory insight into tendons' morphological, mechanical, and material properties of the human in *vivo*, especially in early adolescence (12–14 years), a review of the potential effects of the endocrine mechanisms on tendinous tissue properties during human development will be given by supplementary information gathered from studies using animal models.

Tendons are considered to be a notable characteristic feature of the human anatomy, having suggested that the former has facilitated the shaping of the human evolution. The emergence of man is critically linked to his ability to run (Maffulli and Almekinders, 2007). This connective tissue links muscle to the bone, and it transmits muscle forces to the bone or recoils strain energy to the skeleton in order to facilitate human movement (McNeill Alexander, 2002). Furthermore, the non-rigidity of the tendons facilitates the operating force-length-velocity potential of the

activated muscle (Ettema et al., 1990a,b; Kawakami et al., 2002; Nikolaidou et al., 2017; Bohm etal., 2018, 2019b); hence, tendon properties would have a significant effect on human daily locomotion like walking and running (Lichtwark et al., 2007a, b; Bohm etal., 2018, 2019b). Tendons are well-vascularized tissues whose mechanical response is primarily related to the protein fiber collagen (nearly 85 to 86% of the dry weight of tendon, Mass and Phillips, 2005; Kirkendall and Garrett, 2007; Knudson, 2007). From this collagen concentration, type I, II, and III are fiber-forming collagens and make up most of the tendon collagen secreted into extracellular spaces, which eventually forms fibrils (Kirkendall and Garrett, 2007). Of these, type I makes up about 95% of the collagen in the body and is the primary collagen of tendons (Kirkendall and Garrett, 2007). The collagen fibers collateral arrangement in the tendon and cross links between fibers formulate the tendon three times stronger in tension rather than muscle (Knudson, 2007).

In *vitro* studies, three distinct regions on the force–deformation (strain) curve could be found, before the tendon rapture. In the primary region I, also referred to as the tendon "toe" region, the forces applied to the tendon do not cause any kind of damage, but rather reduce the angle of crimp of the collagen fibers at rest without causing any further stretching of them. In the following "linear" region II, loading will cause the already aligned fibers to elongate further and they will start to break and at the endpoint of this region. If the tendon is elongated beyond region II, this will bring it into region III, where additional failure will occur to the fibers in an unpredictable manner, while a complete failure can be occurred if the tendon is stretched further into region IV (Maganaris et al., 2008, see **Figure 10**).

Fig.10

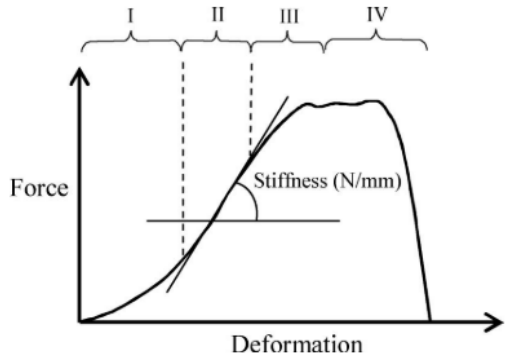

Figure 10 Representation of the force deformation relationship. (Maganaris et al., 2008, *Disability and Rehabilitation.* 30, 20–22, p. 1543. Adapted with permission from Taylor and Francis)

Stiffness refers to the tendon's resistance to length change and is measured as the slope of the elastic (linear) region of the force–deformation curve (Butler et al., 1978; Knudson, 2007; Maganaris et al., 2008). It is widely known that maturation (O'Brien et al., 2010c), as well as mechanical loading, can induce increases in tendon stiffness (Bohm et al., 2014), and the increase of body weight and muscle strength is a constantly increasing mechanical environment

influencing the development of tendon mechanical properties during maturation (Waugh et al., 2012). Two mechanisms could account for tendon's stiffness increase during development: a) changes of the tendon material (i.e., Young's modulus increase) and b) changes occur on tendon's morphological properties (i.e., increase of cross-sectional area, as well as tendon resting length, O'Brien et al., 2010c; Waugh et al., 2012). As the ultimate tendon strain is to a greater or a lesser extent constant, regardless of species (LaCroix et al., 2013), the tendon stiffness development will perform the action of maintaining physiological strain throughout locomotion. Activities such as jumping, walking, and running are thought to be vital in peoples' everyday life. Countless studies carried out within the last 10 to 15 years have provided us with invaluable information concerning both the Achilles tendon deformation and the aponeurosis during the aforementioned activities (Kurokawa et al., 2003; Lichtwark et al., 2005, 2007; Ishikawa and Komi, 2008; Albracht and Arampatzis, 2013; Lai et al., 2015, 2018). There have been published values by the researchers having calculated the maximum strain of the Achilles tendon based on the muscle fascicle behavior measurements, ranging from 4.3% in walking to 9.0% strain in fast running (Lichtwark et al., 2007; Lai et al., 2018 respectively). In the current literature, there is no satisfactory evidence about the tempo of development of tendon mechanical properties as well as the underlying mechanisms that govern these adaptations under the effects of the double stimulus of maturation and superimposed mechanical loading. In the following chapter, an effort is made to describe the course of development of tendon mechanical, material, and morphological properties during maturation.

2.5.1 Tendon mechanical, morphological, and material properties

In the literature, there are only few studies investigating the developmental changes of the tendon mechanical properties of human tendinous tissue in *vivo.* A first scientific effort has been made by Kubo et al. (2001), which has investigated the development of vastus lateralis (VL) of tendon and aponeurosis compliance by comparing children, adolescents, and adults. Tendon-aponeurotic compliance was significantly higher in young boys than in adolescent boys, while adults demonstrated the lowest. Thus, from these findings, it could be suggested that in addition to longitudinal growth of the muscle-tendon unit, tendon stiffness (i.e., the inverse of compliance) increases during the maturational interval from childhood to adulthood (Kubo et al., 2001). The developmental increase of tendon stiffness was supported also by later studies which reported greater patellar tendon stiffness in adults compared to children (Kubo et al., 2014b) and prepubescent (O'Brien et al., 2010c; Waugh et al., 2012). However, it seems that during a certain period of age, tendon stiffness increases with minor changes (Waugh et

al., 2013). In combination with the finding of (Kubo et al., 2014b) who reported no significant differences in tendon stiffness between early adolescence and adults, from the existing literature it could be speculated that tendon stiffness increases in pre-puberty, afterward follows a period with minor increments (7–10 years, Waugh et al., 2013), and then continues towards early adolescence where the major development occurs, indicating that during early adolescence a person acquires adult-like tendon mechanical properties.

Interestingly, (Kubo et al., 2001) had found that resting length increased from childhood to adulthood, given the supposition that tendon morphological (cross-sectional area: CSA) and material properties (Young's modulus) were unaltered during maturation, this increase would reduce the tendon stiffness (Butler et al.,1978; Enoka, 2008). An insight into the mechanisms underlying the development of the tendon stiffness during maturation has been given by O'Brien et al. (2010c) by measuring the patellar tendon CSA and length, calculating Young's modulus, and allocating the differences between sexes. It was shown that both Young's modulus as well CSA were higher in adults compared to children; however, there were differences in the tempo development of the morphological (CSA) and material properties (Young's modulus) between sexes. In males, the relative increase in length and cross-sectional area were approximately equal (58% and 53%, respectively). Hence, the almost in parallel growth of the two dimensions would negate one another and consequently, the alterations in tendon stiffness would not be the result of tendon hypertrophy, suggesting that in men the growth of tendon stiffness is entirely explained by an increase in Young's modulus. In females, the tendon length increased by 17%, and the CSA increased by 29%. Since the increase in CSA was greater than the increase in length, both tendon hypertrophy and Young's modulus contributed to the increase of tendon stiffness in women compared to girls.

The changes in the whole tendon Young's modulus and CSA likely reflect changes in the underlying tendon microstructure within the extracellular matrix (KJÆR, 2004). In *vitro* studies on animals provide some insight into the structural changes that underline the mechanical properties during maturation. The creation of new tendon collagen molecules through fibrillogenesis are brought together lengthwise and afterwards linked sideways to contiguous intermediate so as that via these processes, the fibrils may become mechanically functional (Bailey et al., 1998; Zhang et al., 2005; Connizzo et al., 2013). With the aid of proteoglycans and minor collagen types like III, V, XI, XII, and XIV collagen type, the regulation of this procedure is achieved (Bailey et al., 1998; Zhang et al., 2005; Connizzo et al., 2013). Nevertheless, it is prevalent that the key tendon stiffness promoting mechanisms throughout its growth are the formation of the intervening collagen molecules intrafibrillar cross-link, the

conversion of the latter cross-links from divalent to trivalent bonds owing to maturation, the further interfibrillar cross-link interactions growth in addition to the closer placement of collagen fibers with the direction of force transmission so as to smooth the progress of an increased fibril density development (Elliott, 1965; Bailey et al., 1998; Hansen et al., 2009). Furthermore, during maturation, an increase in collagen fibril diameters takes place, which may act to increase either tendon cross-section and/or the collagen fibril packing (Diamant et al., 1972; Parry, 1978a, b). This augmentation of the collagen fibrils may be inhibited by collagen type V (Dressler et al., 2002) which has been found in collagen fibrils that were immature rather than mature ones (Peters et al., 1996).

Formation of the collagen matrix is further influenced by the cartilage oligomeric matrix protein, which increases with loading and maturation, and has been strongly associated with improvement in tendon mechanical properties (Smith et al., 2010). Decorin and fibromodulin, which are thought to be specific types of proteoglycans, are considered to be unparalleled mechanisms in tendon development because there is evidence of their contribution to the fibril radial growth and cross-linking regulation (Reed and Iozzo, 2002; Iwasaki et al., 2008; Kalamajski and Oldberg, 2010).

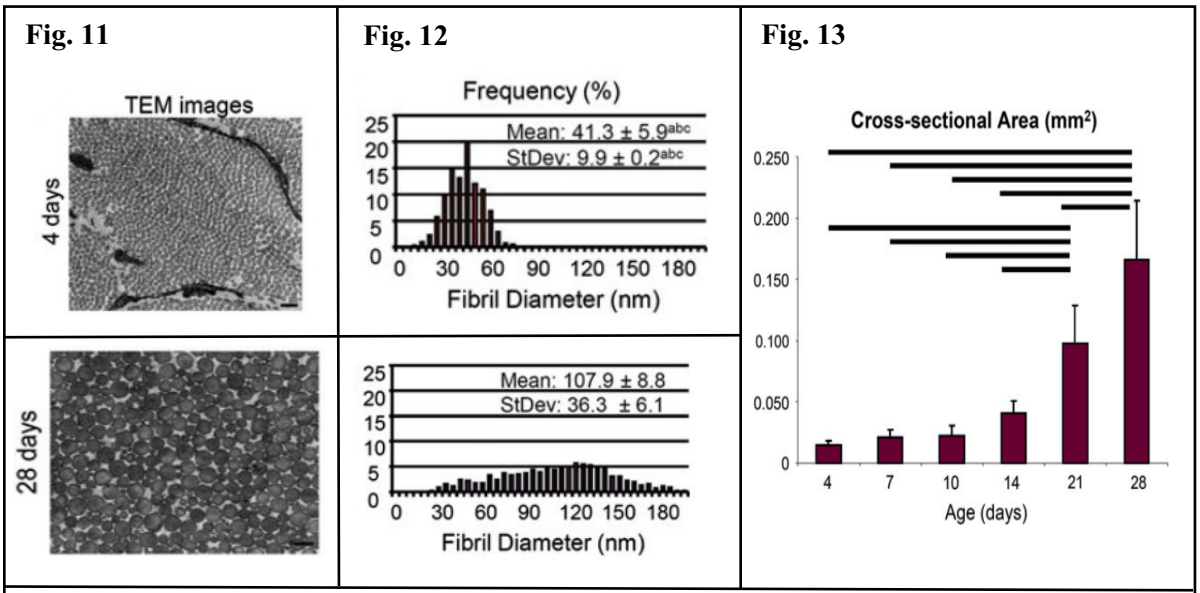

Figure 11 Representative samples of collagen fibrils throughout post-natal development, depicted by transmission electron microscopy (TEM). Scale bar = 200 μm. ***Figure 12*** Iincreased fibril diameter mean and spread throughout post-natal Achilles tendon development is demonstrated by fibril distribution histogram. ***Figure 11***: Significantly different from 28 days; there is no representation of other age-groups data here. ***Figure 13*** The cross-sectional area of the Achilles tendon increased throughout development. Mean of the parameter are represented by vertical bars, while standard deviation is represented by error bars. Significant differences between groups are represented by horizontal bars $P < 0.05$. (Ansorge et al., 2011, *Annals of Biomedical Engineering* 39, 1904-13, p. 1908 & 1911. Adapted with permission from Springer Nature). Note that mice reach a maturity at about 25–40 days (Clark, 1938)

This observation took place when diverse and different peaks of proteoglycans along the period of development expression were coeval with the fibrils' structural properties facilitation (Ezura et al., 2000; Zhang et al., 2006).

There has been an observation of an analogous pattern in a survey with rodents. More specifically, old juvenile mice that were aged 28 days manifested pattern of collagen and tendon fibrils CSAs along with tendon Young's modulus greater that those of younger juvenile mice aged four days. Consequently, there was a modification in the ultra-structure through loading responsiveness that has eventually brought about a tendon stiffness increase (Ansorge et al., 2011; Miller et al., 2012). Moreover, a further interpretation of the aforementioned findings, indicated the differences in tempo development between morphological and material properties of the tendon, where the modulation of the tendon Young's modulus will take place for the most part during the early phase of development, while tendon CSA will increase throughout the maturation (Ansorge et al., 2011; Miller et al., 2012).

The limited in *vivo* studies that investigate the time-course development of the human tendons point to a similar trend. By investigating the development of the patellar tendon material properties in elementary/high school boys, and adults, Kubo et al. (2014b) suggested that the major development increase of patellar tendon material properties from childhood to adulthood, takes place until early adolescence with an only minor increment of Young's modulus occurring thereafter. In an investigation in younger ages, Waugh et al. (2012) has shown that even though adults had higher Young's modulus compared to children, the differences with 8–10 years children were smaller compared to the younger age group (5–7 years). Thus, it seems that tendon material properties might develop to a greater extent even earlier than adolescence (i.e., before the growth spurt at the onset of adolescence).

In contrast to the development of the tendon mechanical properties (stiffness) and material properties (Young's modulus), patellar tendon hypertrophy (CSA) shows indications of a further progressive increase throughout adolescence (Kubo et al., 2014b). However, it seems that Achilles tendon CSA major development takes place during early adolescence since there were no differences in tendon CSA between early adolescence and adults (Kubo et al., 2014a). To date, there is only one longitudinal study which in *vivo* investigated the human tendon development, and it was conducted by Neugebauer and Hawkins, (2012). The authors reported that in early adolescent boys and girls, Achilles tendon CSA had decreased by 5.7% in a period of six months, which has resulted in increased tendon stress (+ 6.7%). Moreover, the decreased tendon CSA was not associated with the overall body growth rate. It is stated that both the tendon and the lower leg growth could not be expected by the overall growth only (Kubo et al.,

2014a; Martorell et al., 1988; Roche and Malina, 1983). Nevertheless, it has been suggested by Neugebauer and Hawkins, (2012) that the CSA tendon dwindling before the rise in CSA can signal a transient development stage of the tendons. So far, from the literature, it could be concluded that there are differences between the Achilles tendon and the patellar tendon regarding their radial development; since it appears that the Achilles tendon acquires adult-like CSA values early in adolescence (Neugebauer and Hawkins, 2012; Kubo et al., 2014a), while patellar tendon continues to develop into adulthood (Kubo et al., 2014b). However, by comparing the Achilles tendon CSA values reports in early adolescence from Neugebauer and Hawkins, (2012) with studies that use similar methodological approaches, the similarity with the CSA values (39mm^2) reports in younger subjects (~9 years) reported by (Waugh et al., 2012) could be observed. Furthermore, there are markedly lower values when compared to those which were obtained from adults (47 – 67 mm^2; Magnusson and Kjaer, 2003; Kongsgaard et al., 2011; Stenroth et al., 2012). In contrast to previous studies that measured the morphology of the tendon at rest, Neugebauer and Hawkins, (2012) estimated the morphology of the Achilles tendon by averaging the cross-sections of the values recorded during muscle isometric contraction corresponding to 0, 20, and 40% of the MVC. Conversely, this temperate use of force (i.e., Poisson's ratio: the ratio of transverse to axial; Poisson's ratio 0.5) which could bring on the radial deformation cannot account for the enormity of differences in CSA between cohorts of the aforesaid studies (Abrahams, 1967; Vergari et al., 2011). From the current information regarding the Achilles tendon radial growth, it could be considered that Achilles tendon CSA does not reach adult-like values in early adolescence, but also develops further towards adulthood. The alterations in CSA during maturation could be a result of the exposure of tendon in mechanical loading. Increasing mechanical loading in the human tendon in vivo has been certified that could bring about tendon adaptation in both the children and adults (Bohm et al., 2014; Waugh et al., 2014), whereas the increased customary loading in due course is believed to be the deciding factor of the tendon hypertrophy occurrence (Rosager et al., 2002; Couppé et al., 2008).

It is a given that not only does body mass increase until the period adolescence (Asmussen and Heebøll-Nielsen, 1955) but it also carries on into adulthood (Tanner et al., 1966a, b), leading to not just a rise in joint moments in the lower limbs, but tendon loading through everyday activities too (Spanjaard et al., 2008; Moyer et al., 2010; Sheehan and Gormley, 2013), which consecutively could mutually induce the radial tendon growth. The aforementioned age-related development may be strongly owed to increased mechanical loading due to changes in anthropometry and strength development. Waugh et al. (2012)

investigated the properties of the Achilles tendon from childhood (5–10 years) to adulthood and attempted to determine factors influencing tendons' stiffness and Young's modulus using a stepwise multiple regression model. The results (**figure 14 & 15**) demonstrated that age-related increases in tendon stiffness can be explained by the association of increased body mass and tendon force (78% of the stiffness variation) and by the association of the increased body mass and tendon stress for Young's modulus (61% of Young's modulus variability).

Earlier research has suggested an association between tendon force and tendon stiffness in adults irrespective of sex who were strength-trained or participated in endurance sports (Karamanidis and Arampatzis, 2006; Arampatzis et al., 2007a, b), as well within the sedentary population (Muraoka et al., 2005). Performing a review of the available data in the literature regarding the tendon mechanical properties from different age populations, it will be noticed that during maturation, a strong association amid muscle strength and tendon stiffness could be observed in children (Waugh et al., 2012; Pentidis et al., 2019), adolescent (Mersmann et al., 2019), young (Arampatzis et al., 2007a; Epro et al., 2019) and old adults (Stenroth et al., 2012; Epro et al., 2017). Looking at the previous studies, there is a pattern that tendon stiffness increases with age suggesting an association between the two. However, it is surprising that in a more thoroughly controlled study by Waugh et al. (2012), in their regression model age was not a contributional factor for the tendon stiffness prediction, while it was an additional predictor for the Young's modulus (irrespective of body mass and tendon stress).

Fig. 14

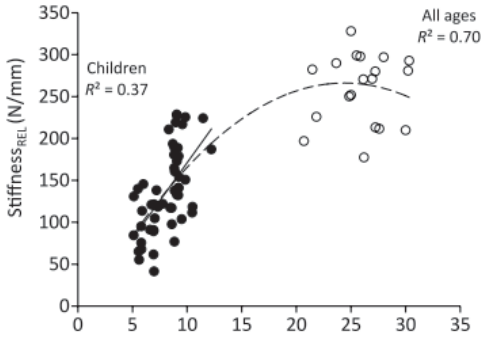

Fig. 15

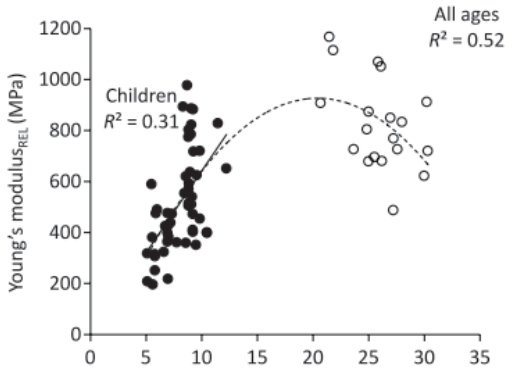

Figure 14 & 15 Relationship between age and tendon stiffness (left) and age, and Young's modulus (right) in children (filled circles) and adults (open circles). Best fited lines are shown for children (solid line) and all ages combined (dashed line). (Waugh et al., 2012, *Journal of Anatomy* 220, 144-155, p. 150. Adapted with permission from John Wiley and Sons Inc.)

Despite the fact that a large array of effects to which the tendon properties changes have been ascribed to, cannot be elucidated by the statistical models being used in numerous studies, it seems that except for the impact of the increased mechanical loading, maturation along with its related hormonal alterations could serve as **a key element**. For instance, growth hormone (GH) and insulin-like growth factor (IGF-I) increase during maturation (Murray and Clayton, 2013); Boesen et al. (2014) reported that administration in elderly men increased tendon stiffness. The mechanism of this increase is due to the fact that GH interactively increases the level of IGF-I (Marcus et al., 1990), which has been reported to positively affect tendon stiffness of flexor digitorum superficialis tendon in horses (Dahlgren et al., 2002). Furthermore, it was shown that increased levels of GH and IGF-I resulted in greater collagen content (collagen I & III) production (Doessing et al., 2010), attributed to the stimulation of the gene expression and collagen synthesis, as well as stimulate the collagen fibers cross-linking (Choy et al., 2005; Doessing et al., 2010; Boesen et al., 2014; Nielsen et al., 2014). However, some studies suggest that the increased levels of IGF-I will differentiate the level of collagen synthesis resulting in a significantly higher increase in collagen I (the primary collagen of the tendon, Maffulli and Almekinders, 2007) compared to collagen III (Dahlgren et al., 2002). Moreover, low serum levels of the above-mentioned hormones can lead the tendon ultrastructure to be disrupted (Nielsen et al., 2014). In the context of the effects of the hormones on tendon development, thyroid hormones have been shown to act as an additional contributor factor to the regulation of tenocytes growth and proliferation, as well as to the synthesis of the collagen (Oliva et al., 2013; Berardi, 2014). Therefore, tendon material, as well as CSA development, would be subjected to the effect of different concentration hormone levels during maturation.

Even though according to the current literature it is reported that during maturation, the development of tendon mechanical properties (tendon stiffness) is similar between sexes (O'Brien et al., 2010c), some studies reported that during adulthood males have stiffer tendon than females (Onambélé et al., 2007), which is attributed to the hormonal inhibitory effects of the estrogen on the collagen synthesis (Miller et al., 2007). Relaxin, is a hormone that belongs to the insulin-like superfamily (Dehghan et al., 2014a) and has been reported in numerous studies to negatively affect tendon stiffness by decreasing it, while increasing tendon laxity through activation of the collagenase (Pearson et al., 2011; Dehghan et al., 2014a,b), which in turn will stimulate collagen degradation and inhibit collagen synthesis by fibroblasts (Lee et al., 2012). On the other hand, testosterone administration in rats has been proved to increase Achilles tendon stiffness by 30% (Inhofe et al., 1995), and decrease the passive knee range of motion of the female rats by down-regulating the expression of the relaxin (Dehghan et al.,

2014b). Thus, it seems that contrary to the findings that the development of tendon stiffness from childhood to adulthood is similar between males and females (O'Brien et al., 2010c), sex differences during maturation may be apparent due to the differences in testosterone concentration. For instance, even though in both sexes testosterone elevates towards late adolescence (August et al., 1972; Ankarberg, 1999), it is well-known that males have 10 to 20 times higher concentrations compared to females (Zatsiorsky and Kraemer, 2006). To date, all information of the effects of hormones and growth factors on tendon properties has derived from studies involving human adults or animal models (Oliva et al., 2016). From the aforementioned information, it could be speculated that, besides the adaptations of the tendon properties due to mechanical environment during maturation, hormone effects may be an additional stimulus that can target the adaptations of the tendinous tissue. However, it is difficult to discriminate the effects of the growth-related factors of the endocrine system and superimposed mechanical loading.

From the studies on the patellar and Achilles tendon, we can conclude that tendon stiffness increases with maturation due to modulation of tendon material properties (Young's modulus) and tendon hypertrophy (radial development). Both maturation and increased mechanical loading through the gains in body mass and muscle strength appear to be unique factors that contribute to tendon development. However, from current literature, it is difficult to dissociate these factors making the research picture of the tendon's time-course development challenging. Hypothetically, if we had the same Young's modulus in a tendon, the higher increase of tendon resting length compared to tendon CSA during maturation would result in tendon stiffness decrease (Waugh et al., 2012), indicating that tendon stiffness development during maturation is a result of Young's modulus increase, at least in the early phase of childhood (Waugh et al., 2012). Nevertheless, it should not be overlooked that tendon stiffness progressively increases towards adulthood, and regardless of tendon CSA fluctuations during maturation, tendon radial growth may be the contribution mechanism of this increase but in the latter stages of development (Neugebauer and Hawkins, 2012; Kubo et al., 2014b). However, the assumptions that have been drawn from the above-mentioned literature should be reviewed with caution because most of the studies have used a cross-section design for the assessment of tendon properties (Kubo et al., 2001, 2014b; O'Brien et al., 2010c; Waugh et al., 2012, 2013).

3 Effects of training on muscle properties in adolescence

Nowadays, resistance and athletic training, either in an organized or no-organized way, are getting more popular and it is highly acceptable among adults as a new lifestyle in order to improve certain aspects of their physical fitness and health. However, gradually, there is a significant increase in adolescents among adults that participate in strength conditioning programs or some sports disciplines. In the past, there was skepticism regarding the participation of children and adolescents in organized resistance training programs under the notion that resistance training was not only ineffective for children but it was dangerous also for injuries, in both children and adolescents, especially in the epiphyseal plate (Shaffer et al., 1983; Naughton et al., 2000; Myer and Wall, 2006; Matos and Winsley, 2007; Barbieri and Zaccagni, 2013). This notion has been abandoned in the last years; recent studies suggest that 77.2% of all injuries are accidental and that most of them are potentially avoidable with proper supervision, the sensible progression of training based on technical competence, and a safe training environment (Myer et al., 2009; Faigenbaum and Myer, 2010; Lloyd et al., 2014). Nowadays, there is a consensus among researchers and practitioners regarding the early exposure in strength training regimes during maturation, and it is also recommended in both elite adolescent athletes, as well as in the pediatrics field (McCambridge and Stricker, 2001; Lloyd et al., 2014, 2015a). More specifically, it is proven that muscular strength development from resistance training can improve markers of health and well-being (such as insulin-sensitivity and levels of adiposity) in active and non-active youth, reduce the risk of sports-related injury, and may promote significantly the functional motor skill performance (e.g., jumping, running and throwing tasks) leading to better physical performance (Hoff and Helgerud, 2004; Wisloff, 2004; Chelly et al., 2009; Lloyd et al., 2014, 2015a). Therefore, training is a prescribed effective way to enhance the muscle functional properties such as muscle strength, velocity of movement, and muscle power (Hoff and Helgerud, 2004; Wisloff, 2004; Chelly et al., 2009; Lloyd et al., 2014, 2015a; Legerlotz et al., 2016). The cause of these improvements appears to be multifactorial since they partly rely on enhanced neuromuscular control, and partly due to adaptations on the morphology of the muscle, and particularly to changes in muscle fiber cross-sectional area, and in muscle fiber topography, i.e., changes in the distribution of the muscle fibers (Legerlotz et al., 2016). While the effects of resistance training on muscle functional properties are well investigated in adolescent athletes (Christou et al., 2006; Channell and Barfield, 2008), the information on neuromuscular adaptations and morphological as well as compositional changes of the muscle tissue are relatively sparse (Legerlotz et al., 2016), especially for the younger ages (12–14years) where the highest

hormonal and somatic changes occur (Beunen and Malina, 1988; Martha et al., 1989; Blum et al., 1993). Lastly, there is an unknown interaction between maturation and training during adolescence.

3.1.1 Training and morphological properties

Muscle strength is related to functional motor performance such as jumping, running, and throwing tasks (Hoff and Helgerud, 2004; Wisloff, 2004; Chelly et al., 2009; Schoenfeld, 2010; Lloyd et al., 2014, 2015a, b). Given the strong correlation between muscle strength and muscle hypertrophy (Maughan et al., 1983; Tesch, 1988; Schoenfeld, 2010), many athletes pursued through their training muscle hypertrophic results in order to improve their athletic performance (Schoenfeld, 2010). Contractile hypertrophy can occur either through radial or longitudinal growth (Schoenfeld, 2010). The radial growth is characterized by the addition of sarcomeres in parallel and it is best reflected by changes in the physiological cross-sectional area (PCSA) of a muscle (Haxton, 1944; Schoenfeld, 2010; Franchi et al., 2017; Mersmann et al., 2017a). In humans, strength training increased the muscle PCSA of the elbow extensors (Kawakami et al., 1995). However, architectural changes within the muscle seem to relate to gains in muscle strength also. For instance, Aagaard and coworkers, 2001, found an increase in the muscle pennation angle after heavy resistance training that promoted muscle strength. As has been mentioned in the maturation chapter of this thesis, the increase in the angle of pennation of the muscle fibers is the modulation factor of PCSA, as well as facilitates the hypertrophy of the fibers, and as a result of this, the muscle's radial growth to exceed that of its whole anatomical cross-sectional area (ACSA, Aagaard et al., 2001; Mersmann et al., 2017a). The single muscle fiber cross-sectional area (CSA) that governs the radial growth is the main mechanism contributing to the increased force potential of the muscle and is attributed to the growth and proliferation of the myofibrils (Goldspink, 1970; Zatsiorsky and Kraemer, 2006; Schoenfeld, 2010; Mersmannmet al., 2017a). During training, the overload stimulus to which muscles are subjected causes them to undergo perturbations in their myofibers and the related extracellular matrix (Vierck, 2000). Therefore, an efficient mechanism that will be used in order to maintain the skeletal muscle mass is required. The dynamic balance between muscle protein synthesis and degradation appears to be the fundamental principle of this maintenance mechanism (Toigo and Boutellier, 2006). For instance, the damaging in the myofibers, as well as in the related extracellular matrix will trigger myogenic events leading to: a) the number of the myofibrillar contractile proteins of actin and myosin to be increased, which subsequently will link up to form new filaments resulting to an increased filament density (Zatsiorsky and Kraemer, 2006),

and b) to an increase in the total number of sarcomeres and myofibrils added in parallel (Franchi et al., 2017). These actions, in turn, augment the diameter of the individual fibers and thereby result in an increase in muscle CSA (Toigo and Boutellier, 2006; Schoenfeld, 2010). Muscles longitudinal growth is due to the modulation of the sarcomeres in series (Franchi et al., 2014, 2017), and many studies have proven the positive association of this longitudinal adaptation with the muscle's maximum shortening velocity and mechanical power (Goldspink, 1985; O'Brien et al., 2010a). Studies in vivo on humans supported that; if an eccentric loading is applied on the muscle such longitudinal plasticity can be achieved (Sharifnezhad et al., 2014; Franchi et al., 2014, 2017). The accurate investigation of the muscle PCSA requires a Magnetic Resonance Technique (MRI), which is costly, time-consuming, and sometimes difficult for a young to stay motionless in order to bring the long procedure to completion. However, other morphological properties, like muscle thickness which is an indicator of muscle hypertrophy and is related to muscle strength (Mersmann et al., 2016), as well as with physiological parameters, for example, those describing muscle architecture such as the pennation angle and fascicle length, can be determined by means of noninvasive and no-time consuming techniques such as ultrasonography (Legerlotz et al., 2016; Mersmann et al., 2016). For instance, Mersmann and colleagues, 2016, found that vastus lateralis (VL) thickness was higher in volleyball athletes compared to non-athletes, and differences in muscle strength between them were related with muscle thickness. Moreover, the increase of muscle thickness is accompanied by the increase in pennation angle, but there were no changes in normalized fascicle length (fascicle length/femur length, Mersmann et al., 2016, 2017b) indicating that pennation angle was a modulation factor for the muscle thickness. While in the literature there is little knowledge about the muscle morphology plasticity due to training in adolescence, the information regarding the effects of superimposed mechanical loading on muscle architecture is sparse. The adolescence is characterized by remarkable bodily growth changes due to the up-regulation of growth factors (growth hormone, insulin-like growth factor) and sex steroids (Murray and Clayton, 2013). On the other hand, training can also induce changes in those growth factors and promote muscle hypertrophy (Kraemer et al., 1992; Tsolakis et al.,2004; Zakas et al., 2007; Schoenfeld, 2010). Thus, it seems that there is an interaction between maturation and training; however, such knowledge is missing from the existing literature.

3.1.2 Training and muscle hypertrophy

The gains in muscle volume after a training period is governed either by increases in physiological cross-sectional area (PCSA) or by development in fascicle length. Since muscle volume is calculated by the formula: muscle volume = PCSA × fascicle length (Brand et al., 1986; Maganaris et al., 2001), a training that would increase the muscle volume without any changes in its PCSA would mean that the muscle hypertrophy after a training period results in the increased fascicle length and vice versa (Mersmann et al., 2014; Legerlotz et al., 2016). The majority of traditional training protocols result from an increase in radial growth (Schoenfeld, 2010; Franchi et al., 2017), while for a longitudinal plasticity an eccentric muscle loading seems to be appropriate (Franchi et al., 2014, 2017).

In literature there is an extensive description regarding the adaptation of the muscle morphology due to superimposed mechanical loading in adults (Kawakami et al., 1995; Starkey et al., 1996; Aagaard et al., 2001), the studies investigating the training effect on the muscle morphological adaptations during adolescence are sparse. However, interestingly, by going chronologically backward, there is no satisfactory information about early adolescence (12–14 years) and there are only a few available sources about childhood regarding the effects of training on muscle morphology. During the passage from childhood to adulthood (adolescence) an increase in growth hormone (GH), insulin-like growth factor (IGF-I), and sex steroids (testosterone for the boys and estrogen for the girls) takes place, and the youth under the influence of these growth factors experiences an overall somatic growth (Murray and Clayton, 2013). Nevertheless, the spurt of the adolescence starts around 12–14 years when the secretion of growth factors (GH, IGF-I) have the maximum concentration, and sex steroids (testosterone and estrogen) upregulation initiates (Round et al., 1999; Murray and Clayton, 2013). Thus, the investigation of the training influence on the muscle morphology during a period when there is an extra hormonal muscle hypertrophy stimulus is of importance because: 1) different stages of adolescence may have different levels of morphological adaptation due to the differences in the secretion of growth factors and sex steroids (Vermeulen et al., 1970; August et al., 1972; Martha et al., 1989), and 2) there could be an interaction between training and maturation on muscle morphology since training can induce also changes in a hormonal level (Kraemer et al., 1992; Zakas et al., 2007; Tsolakis et al., 2004; Schoenfeld, 2010).

In contrast with children, muscle morphological plasticity is detectable in adolescents following a training regime (Ramsay et al., 1990; Fukunaga et al., 1992; Ozmun et al., 1994; Granacher et al., 2011; Armstrong and Mechelen, 2013; Vrijens, 1978). The first who investigated the morphological adaptation due to training in late adolescence (16 years), was

Vrijens, 1978. After a period of 8 weeks of isotonic training, 3 times per week at 75% 1RM, there was an increase in the order of ~ 4.6% for the thigh and ~14.3% for the arm muscle cross-sectional area (CSA). More recently, Mersmann and colleagues (2014), investigated the muscle hypertrophy of volleyball athletes in different age groups and sport-activity levels. Late adolescent (16 years) elite volleyball athletes demonstrated higher vastus lateralis (VL) muscle volume (~11%) compared to active former elite volleyball athletes (46.9 years). However, the maximal PCSA did not differ between groups (Mersmann et al., 2014). Since PCSA is calculated by the formula: PCSA = (muscle volume)/(fiber length) (Brand et al., 1986; Maganaris et al., 2001), it could be concluded that the differences in the muscle volume between age groups might be the result of the differences in fascicle length. When comparing late adolescent athletes with the untrained population, results regarding the morphological characteristics can deviate strongly. Kanehisa et al. (2003) observed the changes in CSA of different quadriceps muscles in 15.5–17.1 years Olympic weightlifters during an 18-month follow-up survey. While an effort was made to identify the morphological changes lengthwise the femur, by measuring CSAs at 30%, 50%, and 70% of the femur length, the changes were detectable and significant only at 30% and were of the order of ~31%. The increase at this level was allocated only at vastus lateralis (VL, 60%), vastus medialis (VM ~12%) and vastus intermedius (VI, 55%) with no changes in rectus femoris (RF). Unfortunately, the lack of a control group in this study makes it impossible to clarify the effect of maturation and athletic training. Given the fact that the authors did not find any correlation between the relative changes of quadriceps femoris CSA at 30% and height and skeletal maturation, it was argued that the observed changes might have been due to training and not maturation (Kanehisa et al., 2003). Additionally, if the quadriceps femoris CSA at the mid-thigh (50%) of the aforementioned athletic individuals is compared with that of the non-athletic boys of nearly the same chronological age (16.4 years) who were investigated in an earlier study, it is observed that the Olympic weightlifters had already achieved a 28% greater CSA (Kanehisa et al., 1995a). In a similar age group of late adolescents (16 years) elite volleyball athletes demonstrated higher VL muscle volume (~11%) compared to active former elite volleyball athletes (46.9 years) (Mersmann et al., 2014). While evidence about the effects of training on muscle morphology in adolescent males are sparse, such relative knowledge in adolescent females is even less. Mersmann and colleagues, 2014 and 2017b, measured the VL muscle, volume and PCSA in adolescent female and male volleyball players. Female volleyball athletes demonstrated higher muscle volume and PCSA compared to competitive active former elite volleyball athletes (620 cm^3 vs 476 cm^3 and 45.5 cm^2 vs 36 cm^2, respectively). However, when the aforementioned

morphological characteristics are compared, female elite athletes demonstrated lower VL muscle hypertrophy compared to peers male elite volleyball players.

Hormonal expression during maturation has a significant impact on the overall human growth and could explain the muscle hypertrophy during adolescence(Murray and Clayton, 2013). Adolescence biological maturation can be reduced in 2 chronicle points: a) the period during which the peak height velocity (PHV) occurs signaled by the onset of the adolescence growth spurt (Beunen and Malina, 1988), and b) the period after the PHV until the moment where development ceases (Tanner et al., 1966a, b, 1976; Beunen and Malina, 1988). This maturational passage has a substantial impact on physical performance (Beunen and Malina, 1988; Moran et al., 2017); for instance, a meta-analysis in adolescent boys reported that adaptations to resistance training were greater in adolescent boys when they were during (13–15 years) and after (16–18 years) PHV compared to before (puberty: 10–12 years) (Moran et al., 2017). Since muscle hypertrophy can enhance muscle strength (Zatsiorsky and Kraemer, 2006), the differences in muscle strength gains between the abovementioned biological maturation groups were attributed to muscle hypertrophy (Moran et al., 2017). During maturation, the adolescence spurt occurs at the age of ~13 years for the boys and at the age of ~11 years for the girls (Beunen and Malina, 1988), while the cessation of bone growth (epiphyseal closure; girls: 16years; boys: 17,5 years) signifies the end of the adolescence or puberty and the transition to adulthood (Roenneberg et al., 2004). The adolescence period is marked by the increasing effects of anabolic and sex steroid hormones which are responsible for muscle hypertrophy (Velloso,2008; Vingren et al., 2010; Murray and Clayton, 2013). After the performance of various training modalities, the GH increases and stimulates the production of IGF-I (Kraemer and Ratamess, 2005), which in turn will activate the protein synthesis as well as the myoblast proliferation and fusion with the myotubes so as to support radial growth (Vierck, 2000; Velloso, 2008; Schoenfeld, 2010). However, it has been reported that the local autocrine/paracrine IGF-I production is more important for muscle hypertrophy and growth compared to circulating IGF-I (Velloso, 2008; Murray and Clayton, 2013). Testosterone is one of the most potent hormones promoting muscle hypertrophy (Vingren et al., 2010). Females, even after the training (when the testosterone levels elevated), had 10 to 20 times lower concentrations compared to males(Zatsiorsky and Kraemer, 2006). Thus, the lower testosterone concentration can explain the sex differences in muscle hypertrophy following different training regimes (Zatsiorsky and Kraemer, 2006).

In conclusion, training can induce muscle morphological adaptation during maturation irrespective of maturation and sex. The hormonal effects during maturation, responsible for the

overall growth, could explain training-induced muscle hypertrophy in adolescence. However, late adolescent females will exhibit lower training-muscle hypertrophic results compared to males due to the lower testosterone concentration levels. From the existing literature, it is difficult to compare the results of different studies because of the wide variation regarding the training design and testing methodologies, analytical protocols, and subject characteristics (Malina, 2006).

3.1.3 Training and muscle architecture

As it has mentioned in a previous chapter (see **chapter 2.1**), muscle architecture characteristics have a significant impact on the muscle contractile properties. An increase in fascicle pennation angle is a modulation factor of physiological cross-sectional area (PCSA) that facilitates fiber hypertrophy attributing to the addition of sarcomeres and myofibrils added in parallel which eventually leads to an enhanced force potential of the muscle (Goldspink, 1970; Zatsiorsky and Kraemer, 2006; Schoenfeld, 2010; Mersmann, et al., 2017a). At the opposite end of the spectrum, there are muscle longitudinal adaptations, a result of the sarcomeres in series addition (Franchi et al., 2014, 2017) and is scientifically proven to be positively associated with the maximum shortening velocity and mechanical power of the muscles (Goldspink, 1985; O'Brien et al., 2010a). Although it is proven that training can induce changes in muscle architecture, different training modalities can cause different muscle architecture adaptations (Schoenfeld, 2010; Franchi et al., 2014, 2017). In fact, in literature, the majority of traditional training protocols result in an increase in sarcomeres and myofibrils added in parallel (Schoenfeld, 2010; Franchi et al., 2017). Even though there is little knowledge regarding the effects of training on muscle morphological plasticity during adolescence, the muscle architecture characteristics, which govern muscle hypertrophy, have not been well investigated.

Muscle thickness, which is a morphological property more conveniently investigated by ultrasound techniques (Legerlotz et al., 2016), is associated with muscle strength gains (Mersmann et al., 2016, 2017b), and it is related to changes in muscle architecture (Franchi et al., 2014, 2017). More recently, Mersmann et al. (2016, 2017b) investigated the vastus lateralis (VL) thickness in elite volleyball athletes. In a 12-month survey measured in 3-month intervals, late adolescent (16 years) athletes demonstrated higher VL muscle thickness (~43%) compared to habitually active controls (Mersmann et al., 2016), while in a cross-sectional design study at the same age, volleyball athletes demonstrated higher deviation in VL thickness (+ 38%) compared to their recreation-active peers. In literature, there is not sufficient satisfactory

evidence regarding the effects of training on muscle morphology in early adolescence. Takai and coworkers, 2013, investigated the effects of Body Mass-Based Squat Training on thigh muscle thickness in early adolescence (~ 14 years). By the end of the intervention period (8 weeks), anterior thigh muscle thickness increased significantly by 3.2%. In accordance with the previous (see **chapter 3.1.2**) there are disparities between males and females regarding the hypertrophic gains due to training, Mersmann and colleagues, 2014 and 2017b reported that female adolescent volleyball athletes had smaller VL thickness compared to males.

In an approach to better elucidate the architecture characteristics underlying the muscle hypertrophy due to training, pennation angle, normalized fascicle length (fascicle length/femur length) of late adolescents (16 years) elite volleyball players were investigated. In a yearly survey measured in three-month intervals, athletes showed higher VL muscle thickness (~43%) succeeded by an increase in fascicle pennation angle (~19%) compared with habitually active controls (Mershmann et al., 2016). Subsequently, in a cross-sectional examination of the same age (16 years) in females and males, volleyball athletes had higher VL muscle thickness (38%) and fascicle pennation angle (27%) compared to recreationally active adolescents, but the normalized fascicle length between them presented no disagreement. However, female athletes demonstrated lower pennation angle compared to males (Mersmann et al., 2017b). From the above-mentioned, it could be suggested that the muscle hypertrophy induced by resistance training may be associated with an increase in muscle fiber pennation angles. Indeed, Kawakami et al. (1995), after 16 weeks of high-intensity unilateral training in brachii triceps muscle, found an increase in physiological cross-sectional area (PCSA), muscle volume, and thickness with concomitant increments in fascicle angle. However, there was none such analogous development in fascicle length, suggesting that pennation angle was the modulation factor of muscle hypertrophy following resistance training. In the muscle hypertrophy training model, an additional attachment area at the aponeurosis or tendon is acquired by increasing the pennation angle (O'Brien et al., 2010a), allowing a greater packing of sarcomeres in parallel (Franchi et al., 2014). Consequently, the steepening of the fascicle angle will allow a greater PCSA for a given muscle volume (Aagaard et al., 2001).

In current literature, there is not a study that investigates the effects of training on longitudinal adaptations during adolescence. One of the main reasons for the muscle hypertrophic results in adolescence following training is the muscle damage which will eventually activate the hormonal response of the growth hormone (GH), and insulin-like growth factor-I (IGF-I, Schoenfeld, 2010), hormonal factors which are well-known that promote the radial and longitudinal growth of the fibers (Cheek et al., 1971; Allen et al., 1999; Grohmann

et al., 2005). Since the main body-research has a volleyball sport-origin, a sport which is characterized by repetitive plyometric loadings (Mersmann et al., 2016), someone would expect that such muscle-fascicle longitudinal adaptation would be possible in late adolescence due to the hormonal response (Franchi et al., 2014, 2017). In order for a longitudinal adaptation to be accomplished through training, a specific design eccentric training protocol consisting of high load and lengthening velocity on the descanting part of the force-length relationship should be applied. Sharifnezhad and coworkers (2014), investigated the effects of different eccentric training protocols on VL muscle. After 10 weeks of intervention, fascicle length increased by~ 14% only with the training eccentric protocol which provided high eccentric load and angular velocity 240 deg s^{-1} (high muscle lengthening velocity) in a 25 to 100 deg range of motion (descanting part of the force-length relationship). Interestingly, the average angular velocity for running, sprinting during the stance phase, and drop jump is 190–230 deg s^{-1}, ~ 320 deg s^{-1}, and 70–225 deg s^{-1} respectively (Arampatzis et al., 1999, 2000, 2001; Stafilidis and Arampatzis, 2007b). However, these values of these motor skills do not take place in a whole range of motion (Sharifnezhad et al., 2014). Thus, even though as a magnitude of the repetitive eccentric loadings, and in some cases the angular velocity (i.e., sprinting) of the volleyball sport-discipline could be sufficient to induce a longitudinal adaptation, the no-application of the high load and angular velocities in the whole range of motion during running and jumping, motor skills which are integrated in volleyball sport-discipline, would be the reason for the lack of muscle longitudinal adaptation. Therefore, longitudinal adaptation could be feasible in adolescents if they would participate in a specific eccentric-training protocol. This training protocol must consist of high eccentric loading and angular velocities applied throughout the whole range of motion and in particular to the descanting part of the force–length relationship. However, such knowledge on adolescence is missing from existing literature and more investigation is required.

Since a typical muscle hypertrophy induced by the training regimes is accompanied by increases in pennation angle (Kawakami et al., 1995), any increase in fascicle angles will be influenced by growth factors, such as growth hormone (GH) and insulin-like growth factor-I (IGF-I), which are responsible for the overall growth during maturation, as well as for the muscle hypertrophy which is attributed to the addition sarcomeres and myofibrils in parallel (Kraemer and Ratamess, 2005; Velloso, 2008; Schoenfeld, 2010; Franchi et al., 2017). In turn, these actions will augment the diameter of the individual fiber and thereby lead to an increase in muscle hypertrophy (Toigo and Boutellier, 2006; Schoenfeld, 2010). The subsequent increase in the pennation angle will allow a greater packing for the increased number of

sarcomeres in parallel during muscle hypertrophy after a training period (Franchi et al., 2014). Consequently, the steepening of the fascicle angle will result in a greater PCSA for a given muscle volume (Aagaard et al., 2001), and therefore in an enhanced force potential of the muscle (Goldspink, 1970; Zatsiorsky and Kraemer, 2006; Schoenfeld, 2010; Mersmann, et al., 2017a). Testosterone, an anabolic hormone that is responsible for the muscle hypertrophy(Vingren et al., 2010), is found in lower concentrations in females compared to males even after a training stimulus, in which normally every hormone is elevated (Zatsiorsky and Kraemer, 2006). Thus, the lower testosterone concentration can explain the sex differences in muscle hypertrophy and consequently in pennation angle following different training regimes (Zatsiorsky and Kraemer, 2006).

In conclusion, training can promote further changes in pennation angle beyond the maturation and irrespective of sex. Since training-induced muscle hypertrophy is accompanied by increases in pennation angle (Kawakami et al., 1995; Aagaard et al., 2001), the steepening of the fascicle angles will allow a greater packing of the increased sarcomeres in parallel resulting in a greater PCSA for a given muscle volume (Aagaard et al., 2001). The dependent relationship between muscle hypertrophy and pennation angle indicate that the elevated levels of the growth factors, GH and IGF-I, will be the reason why training-induces increase in the pennation angle in adolescence (Velloso, 2008; Murray and Clayton, 2013). Compared to males, females due to 10–20 times lower testosterone concentration levels will express lower pennation angle adaptations following training regime (Zatsiorsky and Kraemer, 2006).

3.2 Training and muscle fiber distribution

Human skeletal muscles are not characterized by their homogeneity on the cellular level, but by the muscle fibers that composed them are heterogeneous and expressed by different types (Scott et al., 2001). Research techniques that investigate the staining properties of the adenosine triphosphate enzyme (ATPase) of the globular region of the myosin head, also known as s-1, identified three major types of muscle fibers; the type of I, IIA, and IIB (Staron, 1997; Fry, 2004). Their functional characteristics are based in large part on the speed of the enzyme activity (Fry, 2004). These fiber types form a continuum from the slowest type I to the fastest IIB (Fry, 2004). The increase of muscle hypertrophy with training is most likely due to the augmentation of fibers cross-sectional area (CSA) (Toigo and Boutellier, 2006; Schoenfeld, 2010). However, until recently, the training-induced fiber type hypertrophy was not well understood. For instance, some studies in adults, males and females, supported the notion that muscle fiber hypertrophy is fiber specific since after heavy resistance training fiber type II

exhibited preferential higher gains in CSA compared to type I (Staron et al., 1990; Roman et al., 1993; Aagaard et al., 2001; Fry, 2004). However, other investigations suggested that irrespective of training loads both muscle fiber types showed similar hypertrophic results (Mero et al., 2013; Bogdanis et al., 2018). Even though the muscle fiber hypertrophy of different muscle fibers during training has been well investigated in adults, such knowledge is widely unknown on the adolescence. Metaxas and colleagues, 2014, were the first that investigated the muscle fiber type hypertrophy (I, II, IIX) of the VL, noting that fiber IIB is also referred to as IIX (Scott et al., 2001), in male elite young soccer players. After a training season of 41 weeks, early adolescence (13.1 ± 0.5 years) and late adolescence (15.2 ± 0.8 years) demonstrated greater CSA on all fiber types (I, II, IIX) compared to pubertal (11.2 ± 0.4 years); interestingly, there was no preferential growth between fast-twitch fiber type II. It has been proven, that light and heavy loads lifted to failure result in similar hypertrophy in both fiber types, which suggests that both fiber types were recruited during training and to a roughly equivalent extent (Mitchell et al., 2012). Thus, the lack of preferential growth of muscle fibers type II may be due to the sport-specific training design. Testosterone is an androgen hormone promoting muscle fiber growth (Sinha-Hikim et al., 2002). Therefore, the higher testosterone levels in early and late adolescence could explain the greater muscle fiber hypertrophy compared to pubertal children (Vermeulen et al., 1970; August et al., 1972). From the existing literature, it can be concluded that training can induce muscle fiber hypertrophy in adolescence beyond maturation without preferential growth of fibers type II. However, this might be the result of the specific training design. Due to the lower testosterone concentration level, children will exhibit less muscle fiber hypertrophy compared to early and late adolescence during training.

As it was mentioned above in this chapter, muscle fibers are categorized into three major types, I, IIA, and IIB and governed by the analogous contractile protein isoforms of Myosin Heavy Chain (MHC) such as MHC I, IIA and IIB (Fry et al., 1994). It is well evidenced that alteration in human fiber type profile can be manifested via resistance training through differentiation of the MHC (Campos et al., 2002; Fry, 2004), consequently changing the fiber type distribution irrespective of sex (Staron et al., 1990). In the literature, there is little information regarding the effects of training on fiber type distribution during adolescence. Metaxas and colleagues 2014, investigated the fiber type distribution of male young soccer players. After a 41-week training season, pubertal (11.1 ± 0.4 years), early adolescents (13.1 ± 0.5 years), and late adolescents (15.2 ± 0.6 years) demonstrated a higher percentage of fiber type IIA compared to IIX, indicating that the conversion of fiber type II due to training is independent of the maturation status. However, the adolescent groups also showed different

muscle composition, in particular, late adolescents demonstrated a greater percentage of type IIA fibers when they compared with the early adolescent and pubertal (+18.1% and 18.4% respectively), and a lower percentage of type I compared to the young (–21.3%). The aforementioned information indicates the ability of late adolescents during training to alter the fiber distribution in favor of type II to a greater extent compared to young and early adolescents, while they can convert fibers type IIB to IIA to a higher rate compared to both age groups. Interestingly, the authors attributed this outcome to differences in training intensity between groups. Even though the cross-sectional comparison between lifters and endurance runners has noted significant differences in the ratio of type I and II fibers (Prince et al., 1976), it suggests that high-intensity training may lead to a transition of type I fibers to II (Jansson et al., 1990); studies that investigated directly the effects of heavy resistance training on muscle fiber type, could not replicate these results and they have observed only conversion of type IIB fibers to IIA (Aagaard et al., 2001; Campos et al., 2002; Fry, 2004). Additionally, in a review of Fry, 2004, it has been reported that training intensity is less critical for fiber transformation, and resistance training results in a constant decrease of fiber type IIB, and a concomitant increase in the percentage of fibers IIA **(Figure 16)**. Therefore, training intensity might not be the reason for training-induced alteration in fiber type I to II in adolescence.

Fig. 16

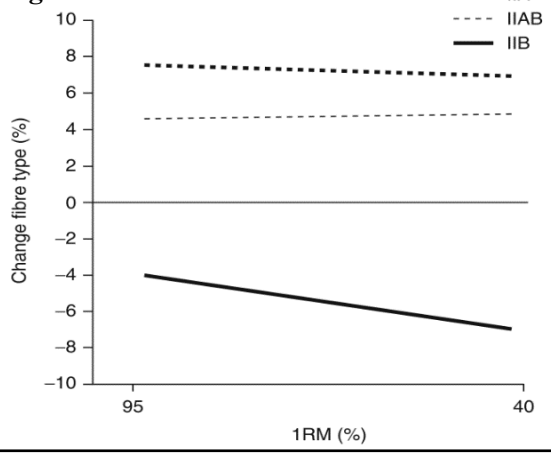

Figure 16 Regression lines representing the relationships between relative (%) change of myosin heavy chain (MHC) isoforms I, IIA and IIB, and relative intensity (% 1 repetition maximum [%1RM]). The horizontal nature of the regression lines suggests that relative intensity is not a major contributor to MHC isoform transitions. (Fry, 2004, *Sports Medicine* 34(10), p. 673. Adopted with permision from Springer Nature)

Testosterone is an androgenic hormone that is related to muscular hypertrophy (Viru et al., 1999), and to alterations in muscle fiber distribution in favor of fiber type II, particularly to the overexpression of fiber type IIA (Krotkiewski et al., 1980). It has been proven, that the concentration testosterone levels reach a peak value around the age of 20 (Vermeulen et al., 1970). Therefore, the higher testosterone anabolic effects of the late adolescents, due to maturation, may explain the greater percentage of fiber type II and the lower percentage of fiber type I compared to early adolescents and not the training intensity per se. This indicates that an

alteration in muscle composition could be another mechanism influencing skeletal muscle characteristics even in young athletes. However, androgenic control may lead to different fiber distribution results in different stages during adolescence.

3.3 Training and muscle activation

Alterations in the nervous system can be induced by training, in parallel with morphological adjustment (muscle hypertrophy). It can be well documented by the overabundance of literature information in healthy adults that the augmented muscle strength is reliant on morphological and neural factors. Nonetheless, it appears that at the early phases of training onset improvements regarding muscle contraction seem to be the chief reason for training-induced strength gains (Sale, 1987; Aagaard et al., 2002; Duchateau et al., 2006; Schoenfeld; 2010; Carroll et al., 2011). Any training-induced neural adjustment can echo as changes in regarding muscle activation, like alterations in firing rate and motor unit recruitment, being noticeable by the changes in density, size as well as the complexity of the electromyographic (EMG, estimator for muscle activation) signal (Knudson, 2007). Nevertheless, even though there has been an extensive use of the EMG technique in the literature so as to describe muscle activation (Guo et al., 2009; Akhlaghi et al., 2016; Sun et al., 2018), it is not limitless and hence can be taken into consideration only as an index of the muscle motor-unit recruitment. To exemplify, some intrinsic restrictions of the EMG technique, like the low signal-to-noise ratio, together with the incompetence to tell the difference between the deep adjoining muscle components (crosstalk) and inter-electrode distance (Alemu et al., 2003; Guo et al., 2009; Akhlaghi et al., 2016; Sun et al., 2018) could influence the EMG signals and thus the evaluation of the modifications in muscle activation because of the training. Changes that can be brought on beyond maturation by training are shown in studies enabling interpolate-twitch technique (estimation of the degree of activation level throughout a maximal voluntary contraction with regard to total muscle activation through electrostimulation). For example, there has been a report by Ramsay et al., 1990, of an increased voluntary motor-unit activation, subsequent to a long-term intervention circuit training protocol of 20 weeks in juvenile boys from 9 to 11 years. Not only that but there was an improvement in the region of ~30% in the electrically evoked twitch torque being construed as neural adaptations of the inherent muscle excitation-contraction. Yet, other possible causes were not eliminated by the researchers who could be responsible for electrical evoked twitch torque improvements, for instance alterations in motor-unit coordination, firing frequency and recruitment. It is interesting, though, that because of training, voluntary activation rises along with strength gains seem substantially

bigger in children when they are compared to adults (1.3–4.5% for adults vs 10–17% for children, Ramsay et al., 1990; Shima et al., 2002; Cannon et al., 2007; Streckis et al., 2007; Colson et al., 2009). Children's capability to activate their muscles voluntarily seems quite smaller if it is matched up to adults (Pääsuke et al., 2000; Praagh and Dore, 2002; Streckis et al., 2007; Grosset et al., 2008; O'Brien et al., 2010b; Dotan et al., 2012) and could signify children's potential to manifest adaptive changes in a possibly wider variety, reflecting in turn the findings in the present literature of larger training-induced increases, despite existing only in theory, adding to the fairly restricted alterations in muscle morphology, the high probability of augmented voluntary activation could make adult-seeming strength gains happen (Williams and Amstrong, 2011). Taking into account the present literature, there are few experimental facts to clarify the training impacts, up to a satisfactory level, on the activation of the muscle throughout the period of childhood to adulthood, at which time extraordinary growth alterations take place (Viru et al., 1999). The neural adjustments by integrated electromyographic activity (iEMG, estimator of muscle activation) were investigated by Komi and colleagues in 1978, regarding six twin pairs during adolescence (14.0 ± 0.9 years) following a period of twelve weeks of maximal isometric knee extension contraction training program. Moreover, force of the knee extension rose considerably, that is 20% post intervention period which was followed by substantial increase in maximum integrated electromyographic activity (iEMG, 38%). However, there were no similar changes regarding the untrained leg and twin control. The decrease in inhibitory input was hypothetically ascribed by the authors to the alpha-motor neuron the observed rise of iEMG, in order for a larger activation inflow to reach the muscle site (Komi et al., 1978). None of these, however, have been in fact investigated and apart from the increased agonistic muscle activation, declined muscle antagonistic co-activation acting on the same joint may bring about improved force output. The results of the comparison between adults and children indicate that the first mentioned manifest lesser antagonistic muscles coactivation, whereas longitudinal studies which have put into effect adult partakers, have exhibited the likelihood of reducing antagonistic coactivation with the training (Carolan and Cafarelli, 1992; Pensini et al., 2002; Tillin et al., 2011), facilitating, therefore, muscle output. Nevertheless, there is not sufficient evidence, up until now, to justify the training-induced reductions regarding antagonistic coactivation through adolescence period. Given the present literature, it can be deduced that exercising may stimulate muscle activation alterations regardless of age (Legerlotz et al., 2016). The evaluation of differences between adults and children could depict training impact on muscle activation throughout the period of maturation, stating clearly that higher gains will be undergone by younger people regarding muscle

activation when they are compared to adults owing to untapped motor-unit recruitment (Ramsay et al., 1990; Shima et al., 2002; Cannon et al., 2007; Streckis et al., 2007; Colson et al., 2009; Williams and Amstrong, 2011). Nonetheless, it is prevalent that activation shortage lessens with age (Belanger and McComas, 1989; Grosset et al., 2008), demonstrating that diverse maturation levels throughout the period of childhood to adulthood (adolescence) can display various adaptation gains. However, there is not sufficient evidence to validate the training caused neural adaptation during adolescence, nor concerning the neural adaptation variations between both early and late adolescence periods following training or training-induced reductions regarding antagonistic coactivation in adolescence, signaling the need for further research to explicate the aforesaid hypotheses. The inadequate present literature, though, indicates that resistance training could, in all likelihood, provoke neural adaptations in adolescence. Nonetheless, the underlying central as well as the peripheral neural modifying mechanisms have not been fully comprehended yet.

3.4 Training and muscle functional properties

In recent years, more and more adolescents are involved in a high level of some sort of sports discipline. This daily formalized and specialized training is a cause of sports-related injuries, such as patellofemoral pain (Luhmann et al., 2008; Myer et al., 2010), Osgood-Schlatter disease (Gholve et al., 2007), calcaneal apophysitis (Ogden et al., 2004), little league elbow (Kocher et al., 2000) and little league shoulder (Stein and Micheli, 2010), spondylolysis (Kruse and Lemmen, 2009), and osteochondritis dissecans (Pascual-Garrido et al., 2013) which are all common overuse injuries seen in children and adolescents. It has been proven that the development of muscle strength and power, as well as improvements in movement velocity and motor skills, are all related to the reduction of sport-related injuries incidents in athletes and non-athletes who attempt to participate in a sport or general physical activity (Lloyd et al., 2015b). Training is the medium for these improvements (Lloyd and Oliver, 2012; Lloyd et al., 2014, 2015b); nowadays-reviews suggest the training plans promoting the muscle functional motor performance and skills to be an integral part of a sport discipline (Lloyd et al., 2015b). Additionally, resistance training can lead to established improvement in motor performance through an increase in muscle functional properties, such as muscle strength and power (Chelly et al., 2009; Behringer et al., 2010), and rate of force development (Maffiuletti et al., 2016), resulting in a better athletic performance. Moreover, it has been reported that training can also induce changes in muscle functional contractile ability (specific tension) (Erskine et al., 2010). Muscle functional improvements are dependent partly on enhancements in neuromuscular

control, and partly on adaptations that occur in muscle morphology which are characterized by changes in muscle fiber cross-sectional area and length, as well as by alterations in muscle fiber distribution (Legerlotz et al., 2016). In the literature, even though there is little research about the training effects on muscle functional properties in adolescence, the underlying mechanism behind these adaptations is not well investigated. The use of the term "biological maturation" also characterizes its substantial impact on the physical performance of an individual over an extended period of time (Beunen and Malina, 1988; Yagüe and De La Fuente, 1998). Thus, different levels of growth factors that are related to overall growth during the adolescence period might induce differences in adaptation of muscle functional properties following training (Martha et al., 1989; Blum et al., 1993; Murray and Clayton, 2013). Additionally, there is an unknown interaction between maturation and training during adolescence. The aforementioned necessitate the need for further investigation in order to understand the link between muscle functional properties and the underlying mechanism in adolescence during training.

3.4.1 Training and muscle strength

Muscular strength is one of the most important muscle functional properties; this notion is based on research that has revealed a close association between muscular strength and different motor skills (Lloyd and Oliver, 2012). Studies in adolescents demonstrated that strength gains in muscle strength due to training intervention protocols resulted in better athletic performance through improvements in different motor skills, such as jumping, running, and throwing tasks (Wisloff, 2004; Hoff and Helgerud, 2004; Chelly et al., 2009; Lloyd et al., 2014). In the past, there was skepticism regarding the participation of children and adolescents in organized resistance training programs under the notion that resistance training was not only ineffective for children, but it was dangerous also in terms of injuries, in both children and adolescents, especially in the epiphyseal plate (Shaffer et al., 1983; Naughton et al.,2000; Myer and Wall, 2006; Matos and Winsley, 2007; Barbieri and Zaccagni, 2013). This notion has been abandoned in the last years; a recent review supported (Lloyd et al., 2015a), that muscle strength improvements due to resistance training can enhance physical performance, improve markers of health and well-being (such as insulin sensitivity and levels of adiposity) in active and inactive youth, and reduce the risks of sports injuries (Lloyd et al., 2015b). The term 'trainability' describes the sensitivity of developing athletes to a given training stimulus (Lloyd et al., 2014). During adolescence muscle strength increases due to maturation and growth making it difficult to fully understand the trainability at this period (Lloyd et al., 2015a), as quite often, both maturation and growth, can mask the potential training effects (Baxter-Jones

et al., 1995; Naughton et al., 2000; Lloyd et al., 2014). In order to achieve adaptations in muscle strength beyond those of growth and maturation alone, the volume and the intensity of training stimulus must be sufficient (Naughton et al., 2000; Lloyd et al., 2014). A basic exercise protocol for sufficient results is composed from 2–4 sets, a range of repetition 6–12 (Schoenfeld, 2010), intensities from low to moderate (40–80% 1repetition maximum-RM; Fry, 2004), and a minimum duration of 8 weeks (McCambridge and Stricker, 2001). However, as the training year of experience and resistance training competency increase, an adolescent can be introduced to more demanded training protocols consisting of lower repetitions (≤ 6) and higher external loads (≥ 85% 1 RM) (Lloyd et al., 2014, 2015a). The notion of non-effective results on strength trainability at the early stages of adolescence has been abandoned in the last years, and recent meta-analyses, reviews, and position statements support the effectiveness of strength training even in early adolescence (Falk and Tenenbaum, 1996; Payne et al., 1997; Malina, 2006; Matos and Winsley, 2007; Behm et al., 2008; Behringer et al., 2010; Lloyd et al., 2014, 2015a; Legerlotz et al., 2016; Moran et al., 2017). Despite the knowledge that prepubertal and adolescence athletes can show significant increments in muscle strength (13–30%), the amount of information we have about the training effects during adolescence, especially for the younger ages (12–14 years) where the highest hormonally and somatic changes occur (Beunen and Malina, 1988; Martha et al., 1989; Blum et al., 1993), is rather little due to the scarce literature.

From the existing literature, it is difficult to compare the results of different studies because of the wide variation regarding the training design and testing methodologies, analytical protocols, and subject characteristics (Malina, 2006). The relative knowledge regarding the training effects on muscle strength during early and late adolescence derives from studies that include short and long-term strength training protocols and longitudinal sport disciplines investigations. All studies reported that early (12–14 years) and late adolescent (15–18 years), who participated either in different sport disciplines or in a variety of resistance training regimes improved their muscle strength or were stronger compared to non-active peers (Komi et al., 1978; Pfeiffer and Francis, 1986; Tsolakis et al., 2004; Channell and Barfield, 2008; Takai et al., 2013; Meylan et al., 2014; Mersmann et al., 2017b; Behm et al., 2017; Peitz et al., 2018; Lesinski et al., 2020a). Additionally, strength training in athletes promoted further gains beyond their muscle strength status (Gorostiaga et al., 1999; Szymanski et al., 2004; Christou et al., 2006; Gabbett et al., 2008; Santos and Janeira, 2008; Granacher et al., 2011; Sander et al., 2013; Sarabia et al., 2015; Hammami et al., 2016; Prieske et al., 2016a, b; Makhlouf et al., 2018; Chaabene et al., 2019; Thiele et al., 2020; Lesinski et al., 2020b). The increased muscle strength resulted in a better athletic performance through the improvement of various submaximal and

maximal tasks in both active and non-active adolescence, such as running speed, throwing velocity, the distance and the height of the jump, as well as the aerobic capacity (Gorostiaga et al., 1999; Christou et al., 2006; Channell and Barfield, 2008; Santos and Janeira, 2008; Gabbett et al., 2008; Takai et al., 2013; Behringer et al., 2013).

Biological maturation has a significant impact on muscle functional properties (Granacher et al., 2016); for instance, in a recent meta-analysis reported that resistance training can promote similar greater gains in adolescents around and post-peak height velocity (PHV; Moran et al., 2017, Peitz et al., 2018). Thus, it turns out; that trainability is feasible in every stage of adolescence, and superimposed mechanical loading, expressed either as athletic or resistance training, can promote strength gains. However, females exhibit less strength gains compared to males. For instance, Mersmann and colleagues (2014, 2017b), reported that late adolescent female elite volleyball players had lower muscle strength of the knee extension muscle compared with male counterparts when they were investigated in longitudinal and cross-section design studies.

Since muscle strength is related to muscle hypertrophy (Kawakami et al., 1995), the muscle strength trainability in early and late adolescence is due to the high concentration levels of anabolic hormones such as growth hormone (GH), insulin-like growth factor (IGF-I), and androgens which are responsible for the muscle hypertrophy and growth (August et al., 1972; Martha et al., 1989; Falk and Eliakim, 2003; Sinha-Hikim et al., 2006; Velloso, 2008; Dahab and McCambridge, 2009; Vingren et al., 2010; Murray and Clayton, 2013). Testosterone is an androgen hormone that promotes the muscle fiber growth (Sinha-Hikim et al., 2002), and stimulates the development of fast-twitch muscle fiber in puberty as has been demonstrated in animal experiments (Krotkiewski et al., 1980; Dux et al., 1982). Moreover, there is a close association between muscle strength gains and fiber type distribution and cross-sectional area (CSA) (Herman et al., 2010). It is widely known that during adolescence, fiber type distribution differences and radial growth begin to manifest (Granacher et al., 2016). A longitudinal study during adolescence demonstrated that with age the area of fiber types I, IIA and IIB tended to diminish in females, but remained constant in males (Glenmark et al., 1994). Following the previous study, males reported having a greater percentage of fiber type II compared to females (Glenmark et al., 1992). Therefore, females will exhibit less strength gains due to training compared to males due to the lower testosterone anabolic effects (Zatsiorsky and Kraemer, 2006).

3.4.2 Training and muscle power

Because it incorporates time, mechanical power is an essential kinetic variable for analyzing many human movements (Knudson, 2007). Mechanical power is the time derivative of mechanical work (P = W/t or P = force × distance/time) and can also be expressed as the product of force and speed (P = force × speed, Stone et al., 2002; Knudson, 2007). Since power is the rate of doing work, the movements with the greatest mechanical power must have high forces and high movement speeds (Knudson, 2007); hence, muscle power has been considered as essential to obtain high sports performance levels (Morrissey et al., 1995; Baker, 2001; Stone et al., 2002). Muscular power determinant is the muscle volume (O'Brien et al., 2009, PCSA × fiber length), indicating that any improvement in radial and longitudinal development of the muscle due to training can induce maximum muscle power improvements (Mersmann et al., 2017a). However, besides the muscle morphology and architecture, muscle power can be further influenced by muscle functional properties, such as specific tension, as well as other important biomarkers, like fiber type topography (i.e. percentage of area or distribution; Winkler et al., 2019). Adolescence is a period of naturally occurring adaptations for various physical performances, representing a window of opportunity where training responsiveness of motor skills will be increased (Viru et al., 1999). However, even though the effects of training on muscle power have been explored little in adolescence, the underlying mechanism behind muscle power improvements is widely unknown. Major information regarding muscle power during adolescence is provided indirectly by assessments of performance maximal vertical jump with preparatory counter-movement or squat jump due to their simplicity (Viru et al., 1999; Lloyd and Oliver, 2012). It has been reported that short term (4 weeks)-long term training regimes (16 weeks) increased the jump performance in early and late adolescence (14–17 years) (Gorostiaga et al.,1999; Christou et al., 2006; Channell and Barfield, 2008; Gabbett et al., 2008; Santos and Janeira, 2008; Takai et al., 2013). Moreover, direct investigations on muscle mechanical power, reported that heavy resistance training in adolescent professional and college football players (~17 years), as well as in basketball players (14–15 years) promoted their maximal muscle mechanical power in upper and lower body respectively (Baker, 2001; Santos and Janeira, 2008). Thus, it could be concluded that muscle power trainability is feasible in the adolescent population. In fact, Lloyd and Oliver, (2012), "in the youth physical development model: A new approach tolong-term athletic development"; reported that the key period of power development starts with the onset of puberty and continues throughout adulthood. However, even though females exhibit improvements in muscle power due to training, their gains are lower compared to males (Hewett et al., 1996; Weeks et al., 2008). The

muscle power trainability during adolescence could be explained by the improvements in muscle volume due to increased hormone levels of growth hormone (GH), and insulin-like growth factor (IGF-I), which are responsible for the radial and longitudinal muscle fiber growth (Cheek et al., 1971; Allen et al., 1999; Grohmann et al., 2005), as well as from the testosterone responsible for the muscle fiber hypertrophy (Sinha-Hikim et al., 2002). As mentioned above, muscle power can be affected by the contractile quality of the muscle and the muscle fiber topography. Although the specific tension does not change during maturation (O'Brien et al., 2010b), it has been observed that it increases during training (Reeves et al., 2004; Erskine et al., 2010). It is also widely known that some type of training can preferentially promote the area of type II muscle fibers (Costill et al., 1979; MacDougall et al., 1980; Aagaard et al., 2001) and that these muscle fibers increase with maturation, as they are also found in higher percentage and radially bigger in male muscles than females (Glenmark et al., 1992). Testosterone is an androgen hormone that promotes radial muscle growth (Sinha-Hikim et al., 2002), and stimulates the development of muscle power-related fast-twitch muscle fibers (Krotkiewski et al., 1980; Dux et al., 1982; Williams and Amstrong, 2011). Therefore, lower radial muscle growth (Glenmark et al., 1994), and a smaller percentage of fibers type II of females relative to males (Glenmark et al., 1992) can be linked to the gender disparities in muscle power gains during training, due to females lower concentration testosterone levels compared to males (Zatsiorsky and Kraemer, 2006).

So far, it could be concluded that resistance training can promote muscle power during adolescence, which is attributed to the alteration in muscle specific tension and to preferential fiber type II hypertrophy due to mechanical loading. However, growth factors could not be neglected, since androgens and growth hormones can affect the muscle hypertrophy, and length, as well as the muscle fiber distribution, all of which are biomarkers that have a significant effect on muscle power, and could furthermore, link the sex differences regarding the muscle power gains. Interestingly, Gabbett et al. (2008) in 10 weeks preseason strength condition in junior rugby league players, demonstrated that early adolescent athletes exhibited greater relative gains in muscle power compared to late adolescents. These differences may be attributed to the higher coordination of muscle activity characterizing the early stages of adolescence (Viru et al., 1999). Nevertheless, adolescence is a critical period of increased improvements of muscle power, giving a window of opportunity where training can lead to a greater adaptation (Viru et al., 1999; Lloyd and Oliver, 2012).

3.4.3 Training and rate of force development

Besides the significance of maximum strength, the ability to produce force rapidly is an important component for a successful athletic performance. Rapid force production (RFD), a measure of the rate of the increase in force after muscle contraction onset, also referred to as the rate of torque development (Waugh et al., 2014; Maffiuletti et al., 2016), as it is mentioned in chapter **2.4.3**, depends on neural factors, muscle morphology, fiber distribution and tendon stiffness (Maffiuletti et al., 2016; Legerlotz et al., 2016). During prompt maximal voluntary contractions, surface electromyography (EMG) can be used as a tool to evaluate the pace of muscle activation, which is therefore associated with RFD (Maffiuletti et al., 2016). It has been established that heavy resistance training along with explosive-type one can facilitate RFD and more specifically owing to the increase in rapid muscle activation (Maffiuletti et al., 2016). However, even though such improvement is well investigated in adults, the information regarding the effects of training on RFD during adolescence is little. Muehlbauer et al. (2012) investigated the effects of high-velocity strength training on RFD in 28 male and female late adolescents. After a short-term training period (8 weeks), late adolescents exhibited significant improvement in RFD; however, females demonstrated higher gains compared to males. Since the adaptation of rate of force development due to high-velocity strength training can be mainly explained by neural factors (Taube et al., 2007), the authors attributed the aforementioned differences to females' larger potentiality to respond to neural stimuli (i.e., high-velocity strength training). While the effects of training on the rate of muscle development are little investigated in late adolescence, such knowledge is missing in the literature for early adolescence. The training adaptability of RFD can be influenced by the ability of adolescents to experience muscle radial growth due to hormonal effects (Cheek et al., 1971; Allen et al., 1999; Sinha-Hikim et al., 2002; Grohmann et al., 2005). In addition, even though these statements are questionable (Bell et al., 1980), it has been suggested that the percentage of fiber type II increases with age (Lexell et al., 1992; Metaxas et al., 2014), they might exhibit preferential radial growth after a resistance training period (Costill et al., 1979; MacDougall et al., 1980; Aagaard et al., 2001; Winkler et al., 2019) as well as intrinsically could be stronger than type I (Powell et al., 1984; Bodine et al., 1987; Larsson and Moss, 1993); thus, the faster contraction velocity of fiber type II compared to type I, as well as changes in muscle specific tension due to alterations in fiber topography during maturation, and the preferential hypertrophy of fiber type II during training (Winkler et al., 2019), could be some other factors that could explain the RFD increase due to training. Moreover, neurological factors could further contribute to the improvements of RFD during training and link the potential differences

between different ages during adolescence. For instance, the rate of force development is also related to the recruitment of the fast-twitch (Type II) motor units (Williams and Amstrong, 2011), and the ability to employ these motor units increases during adolescence (Dotan et al., 2012). This might indicate that early adolescents would exhibit fewer gains in rate of force development due to training compared to late adolescents. Waugh et al. (2014) stated that the changes in RFD were associated with an increase in tendon stiffness during training. Therefore, the alterations caused in tendon stiffness during maturation and training mechanical loading will contribute to the RFD trainability. On the aforementioned, it could be speculated that training can induce improvements in the rate of force development during adolescence, and factors such as maturation and sex may influence this adaptation.

Even though the connection between hormonal effects on the underlying mechanism of RFD is not investigated, a hypothesis could be made from different studies investigating the hormonal effects on muscle and tendons (Inhofe et al., 1995; Velloso, 2008; Vingren et al., 2010; Murray and Clayton, 2013; Boesen et al., 2014). It is well-known in the literature that growth factors and androgens have a considerable impact on tendon mechanical properties (Inhofe et al., 1995;Boesen et al., 2014), muscle morphology (Kraemer and Ratamess, 2005; Velloso, 2008; Schoenfeld, 2010; Vingren et al., 2010; Franchi et al., 2017), and fiber topography (Krotkiewski et al., 1980; Viru et al., 1999; Praagh and Dore, 2002) indicating that during maturation, the alterations of these hormones concentration levels could impact the adaptation of RFD during training. The lack of literature prevents the extraction of conclusions concerning the effects of training on the rate of force development, as well as the underlying mechanism to be outlined during adolescence, necessitating the need for further investigation.

3.4.4 Training and specific tension

It is well-known as well as clearly stated from the literature that muscle physiological cross-sectional area (PCSA) is the major determinant of its force-generating potential. From a methodological research point of view, when the maximum force produced by the muscle is normalized to its cross-sectional area, the intrinsic muscle strength is obtained, which can also be referred to as specific tension (the SI unit is kN/m^2, Maganaris et al., 2001). Among studies investigating the effects of resistance training on the human body, it is widely accepted that muscle strength increases more than muscle hypertrophy (i.e. muscle radial growth) (Ikai and Fukunaga, 1970; Young et al., 1983; Jones and Rutherford, 1987; Davies et al., 1988; Narici et al., 1989,1996; Ferri et al., 2003), suggesting that the muscle's intrinsic force-generating capacity improves as a result of increasing superimposed mechanical loading. While, it has

been proven that resistance training increases the muscle specific tension (maximal force per unit PCSA) in young and old individuals in *vivo* (Reeves et al., 2004; Erskine et al., 2010), information regarding the effects of training on muscle specific tension during maturation is widely unknown. In literature, there are some suggestions that fiber type could affect the intrinsic muscle strength (Powell et al., 1984; Bodine et al., 1987; Larsson and Moss, 1993); however, there is not a clear view if changes in muscle fiber distribution during maturation could affect muscle specific tension (Wickiewicz et al., 1984; Fitts et al., 1989). There are some speculations, based on scientific evidence, that specific tension is related to myosin heavy chain (MHC), and fast-twitch fibers (type II) are intrinsically stronger than type I (Bottinelli et al., 1996). In conjunction with the notion that the proportion of fiber type II, even though these changes are small, might increase with age (Lexell et al., 1992), the trainability of specific tension would be affected by the maturation changes in fiber type distribution attributed to the testosterone effects (Krotkiewski et al., 1980; Fitts et al., 1989; Viru et al., 1999). Moreover, it might be plausible that specific resistance training protocols could promote preferential hypertrophy gains of fiber type II (Winkler et al., 2019) under the hormonal effects of androgens and growth factors, such as growth hormone (GH) and insulin-like growth factor (IGF-I), which characterize the muscle development during adolescence (Kraemer and Ratamess, 2005; Velloso, 2008; Schoenfeld, 2010; Vingren et al., 2010; Murray and Clayton, 2013; Franchi et al., 2017; Winkler et al., 2019). If so, the preferential fiber type hypertrophy will change the percentage area of fiber type II, which could be further attributed to the changes in muscle specific tension during training. However, other studies failed to support the intrinsic strength superiority and the increased distribution of fiber type II during maturation (Krotkiewski et al., 1980; Bell et al., 1980; Fitts et al., 1989), as well as the training-induced fiber type II preferential hypertrophy (Mero et al., 2013; Bogdanis et al., 2018) and related them to changes in muscle specific tension in MHC concentration during maturation (Canepari et al., 2010), which might be another mechanism attributed to the muscle specific tension trainability. Under the hormonal concept, muscle specific tension trainability might differ between different ages during adolescence, since hormonal and androgens express different concentration levels during maturation (Murray and Clayton, 2013), and it might further indicate that females would exhibit less gains in muscle specific tension compared to males due to their 10 to 20 times lower testosterone concentration levels (Zatsiorsky and Kraemer, 2006). Nevertheless, the aforementioned speculations require further study in order to be proved. In the current literature, there is no information regarding the effects of training on muscle specific tension during adolescence, making the need for investigation a necessity.

3.5 Effects of training on tendon properties in adolescence

Tendons considered to be an important component of the human body; this connective tissue transmits muscle forces to the bone or recoils strain energy to muscle in order to facilitate human movement (McNeill Alexander, 2002). At the same time, the tendon through its compliance contributes to the muscle's capacity to produce force and power by optimizing the muscle's operating range with regard to the force–length, and force–velocity relationship (Hof et al., 1983; Ettema et al., 1990a, b; Roberts, 1997; Kawakami and Fukunaga, 2006). Hence, the tendon properties not only do they have the potential to affect a human's life through their contribution to daily locomotion like walking/running (Lichtwark, 2005; Bohm et al., 2018; 2019b) and stability performance (Karamanidis et al., 2008), but they can also determine athletic performances since they also can influence the skills of sprinting (Stafilidis and Arampatzis, 2007a; Kubo et al., 2011), jumping (Ishikawa et al., 2005; Kawakami et al., 2002; Lichtwark, 2005; Nikolaidou et al., 2017), as well as the running economy (Arampatzis et al., 2006; Fletcher et al., 2010; Albracht and Arampatzis, 2013), which are all an integral part of athletes' pick performance. Tendons are sensitive to their mechanical environment (Kjaer, 2004; Lavagnino and Arnoczky 2005; Heinemeier and Kjaer, 2011; Galloway et al., 2013). For instance, recent research has shown that when the tendon is subjected to repetitive biological loading resulting in an increase in tendon stiffness through an alteration in its material properties (i.e. increase of Young's modulus, Kubo et al., 2001; Arampatzis et al., 2007a, 2010; Malliaras et al.,2013; Bohm et al., 2014), while following long-term tendon loading also leads to tendon stiffness increase, but through another mechanism, that of a radial growth (Rosager et al.,2002; Magnusson and Kjaer, 2003; Arampatzis et al., 2007a; Kongsgaard et al., 2007; Couppé et al., 2013). This mechanical adaptation potential will retain in physiological ranges the strain during locomotion since the ultimate tendon is more or less constant (LaCroix et al., 2013). The changes that occur in both the morphological and material properties of tendons are due to many adaptive mechanisms taking place at the molecular level, such as an increase in collagen synthesis, changes in collagen morphology, as well as changes at the levels of collagen molecular cross-linking (Miller et al., 2005; Kjaer et al., 2009; Heinemeier and Kjaer, 2011). In literature, there is a research 'gap' regarding the tendon plasticity through superimposed mechanical loading by means of training; while similar adaptations have been well investigated in adults (Bohm et al., 2015; Wiesinger et al., 2015), during adolescence the effect of training on the mechanical and morphological properties of tendon remain a scientific mystery.

3.5.1 Effects of training on morphological, material, and mechanical properties of the tendon

As it has been reported in the previous chapter, tendon stiffness increases in response to biologically effective repetitive mechanical loading by changes either in material (i.e. increase of Young's modulus) or morphological properties/cross-sectional area (CSA) (Kubo et al., 2001; Rosager et al., 2002; Magnusson and Kjaer, 2003; Kongsgaard et al., 2007; Arampatzis et al., 2007a, 2010; Couppé et al., 2013; Malliaras et al., 2013 Bohm et al., 2014). During maturation muscle strength as well the weight-bearing during daily tasks increases, imposing a mechanical loading on tendon is sufficient to induce changes in tendon stiffness (Waugh et al., 2012). It has been proven that training is an additional mechanical stimulus that can cause further adaptation in tendon stiffness irrespective of age and sex (Legerlotz et al., 2016; Mersmann et al., 2017b). However, during adolescence, a period in which remarkable bodily growth changes take place (Beunen and Malina, 1988), as well as increases in the strength of the muscle (Asmussen and Heeboll-Nielsen, 1955, 1956), the training effects on tendon properties are widely unknown. Only recently, information has been acquired regarding the trainability of tendon mechanical properties during adolescence. By investigating the stiffness of the tendon in elite late-adolescent volleyball players in a cross-section design, Mersmann and colleagues (2017b) reported that volleyball athletes had higher tendon stiffness compared to recreationally active peers. Further investigation into the same athletic population, demonstrated that sport specific-loading was sufficient enough to promote further gains in late adolescent elite volleyball athletes (Mersmann, et al., 2017c). This indicates that athletic training is a type of mechanical loading that can promote tendon stiffness irrespective of the maturational gains in mass and muscle strength during adolescence. The increased tendon stiffness will serve as a protective mechanism in order for the tendon strain to be remained on physiological levels during muscle's maximum muscle contraction since the ultimate strain of tendon cannot be significantly altered (LaCroix et al., 2013). An effort was also made to understand the adaptation of the underlying mechanisms, such as CSA and Young's modulus, of the training-induced tendon stiffness increase. Studies in adults indicate that alterations in the material properties of a tendon describe the initial phase of loading-induced tendon adaptations, and tendon increased-CSA is considered the key mechanism in the later phase of long-term mechanical loading to improve stiffness (Bohm et al., 2015). When late adolescent elite volleyball athletes were compared with former adults elite volleyball players, there were no differences in tendon stiffness as well as in material properties (Young's modulus), however, CSA was greater in adults, indicating that the main mechanism for the training-induced

adaptation in tendon mechanical properties were the alterations in tendon material properties (Mersmann et al., 2014). In a more recent study, 2 years of survey demonstrated that in late adolescent elite volleyball players, the sport-specific loading increased their tendon stiffness in parallel with tendon CSA with no changes in Young's modulus (Mersmann et al., 2017c). Since tendons adapt to mechanical loading by changing their material properties already at prepubescent age (Waugh et al., 2014) and late-adolescent athletes already feature similar tendon material properties compared with adults who were subjected to years of sport-specific loading (Mersmann et al., 2014), the authors attributed the further increase in tendon stiffness in the longitudinal study of the late adolescent volleyball athletes to the long-term adaptation mechanism of the candidates, which was the enlargement of the tendon CSA (Mersmann et al., 2017c). However, long-term studies on tendon properties proposed, if present at all, a small to moderate tendon hypertrophy (Bohm et al., 2015). It is also likely that tendon hypertrophy could be further promoted during late adolescence by the development of the tendon core that has been assumed to occur during adolescence (Heinemeier et al., 2013). Regarding the aforementioned studies, it could be conclusive, that in addition to maturation mechanical stimulus, tendon stiffness as well as the underlying mechanisms, such as Young's modulus and tendon CSA, are responsive to training during late adolescence irrespective of sex (Mersmann et al., 2014, 2017b, c). However, there might be differences regarding the tempo of adaptation between material and morphological properties during training. It seems that, predominantly, adaptation in tendon mechanical properties due to training will be governed solely by improvements in tendon material properties (Mersmann et al., 2014), and later, under long-term training conditions, tendon radial growth will interfere, as an additional underlying mechanism, in order to achieve further gains in tendon stiffness (Bohm et al., 2015; Mersmann et al., 2017c). However, so far the literature lacks studies regarding the training effects on tendon adaptation during early adolescence.

Growth factors may have a significant impact on tendon properties adaptation. Growth hormone (GH) and insulin-like growth factor (IGF-I) both increase during maturation and athletic training (Velloso, 2008; Murray and Clayton, 2013), and they will affect the morphological and material properties of the tendon by inducing alterations in collagen synthesis and cross-linking (Dahlgren et al., 2002; Choy et al., 2005; Doessing et al., 2010; Heinemeier et al., 2012; Nielsen et al., 2014), which in turn will affect the tendon stiffness. To date, all information of the effects of hormones and growth factors on tendon properties is derived from studies on animals as well as on humans. However, it is difficult to discriminate the effects: a) of the growth-related factors of the endocrine system and superimposed

mechanical loading, b) as well as the interactions between them, on the tendinous tissue during maturation.

4 Imbalances between muscle and tendons

Dissimilar to muscle tissue, it has been proven by the scientists that a considerably lower amount of vascularization (Smith, 1965) and a less active metabolism (Laitinen, 1967) can characterize tendons. While comparing the two tissues on a level of molecular-structural type, it is found that the collagen protein is characterized by a higher half-life, when it is compared to the muscle proteins of both myosin and actin (Lundholm et al., 1981; Thorpe et al., 2010). Its higher half-life is calculated to rise up to ten times higher (Lundholm et al., 1981; Thorpe et al., 2010) and as a result, it can be stated in theory that tendon structural and morphological adaptations might take place at a slower pace due to mechanical loading. The former theory can be illustrated by scientific evidence which depict muscular plasticity in both morphological and architectural properties rather early, that is three to four weeks, through high-intensity resistance training protocol (Seynnes et al., 2007; DeFreitas et al., 2011). However, no analogous findings of quick alterations of both mechanical and morphological properties of the tendon owing to training-induced tendon adaptations are found in current literature. Moreover, because of neural adaptations, it is widely known that gains in muscle strength precede major muscle morphological changes, particularly at the early stage of training (Folland and Williams, 2007). On the contrary, tendon stiffness variations because of superimposed mechanical loading rely on morphological and structural changes ascribed to the tissue metabolism, which as a result strengthens the theory that throughout training the tempo-adaptation between tendons and muscles would vary significantly. To exemplify, Kubo et al., (2010, 2012) estimated the musculotendinous adaptation of the patellar and Achilles tendon in an intervention survey taking up three months. It has been found that in both studies muscle strength gains have emerged well before tendon stiffness changes in terms of one to two months whereas morphological adaptations could only be detected at the muscle and not at the tendon throughout the intervention stage. As well as musculotendinous differences concerning the time-course improvement through training, it is suggested by further investigations that not every type of loading improving muscle strength could be successful in bringing about an improvement in tendon stiffness, which, in accordance with its force–elongation relationship, is the resistance of the tendinous tissue (Arampatzis et al., 2020). To illustrate, although fatigue and plyometric training could improve hypertrophy and muscle strength with relative moderate loads (Sáez-Sáez de Villarreal et al., 2010; Schoenfeld, 2010), the effect of these training

modalities seems to be slighter, less consistent or even to have no impact on tendon stiffness (Arampatzis et al., 2007b; Kubo et al., 2007; Bohm et al., 2014). Unless a rise in the strength-generating potential of the muscle is not paired by an adequate rise in tendon stiffness, at a given comparative intensity, higher strain levels will be manifested through muscle contraction. The fact that the ultimate strain is noticeably unchanged signifies that any increase in tendon operation strain during muscle contraction implies an increase in the mechanical demand imposed on the tendon (LaCroix et al., 2013; Arampatzis et al., 2020).

According to Aramptazis et al (2020), an imbalanced development of the tendon and muscle can bring about implications for "a) the performance of the movement, b) the injury hazard and c) the prescription of training loads". Despite the requirement of a complicated interaction of musculoskeletal (Cormie et al., 2011; Suchomel et al., 2016) so as a movement can be efficient, physiological and neural causes (Raglin, 2001; Yarrow et al., 2009), the relationship of the tendon and muscle is a vital part with reference to how humans create force to move. It is inferred that tendon stiffness and muscle strength must be perfectly balanced for a well-tuned human movement (Lichtwark and Wilson, 2007; Orselli et al., 2018) that is finally regulated by an accurately coordinated neural drive to the muscles (Sawicki et al., 2015). A probable imbalance among the tendons and the muscles could result in a negative impact of the musculotendinous energy exchange as well as larger tendon strain, ultimately reducing the tendon safe factor (ratio of operating strain to ultimate strain) possibly having as a consequence a high risk of injury (Arampatzis et al., 2020). Throughout both cyclic and static loading, the primary strain caused on a tendon at a given load dictates the time of rupture, thus, strain can be thought as a key mechanical factor describing the cause of tendinopathy (Wren et al., 2003). When training plans are adopted for the tendon based on loads of the percent proportion of one repetition of the muscle, further chances of potential imbalances could be brought on. It is explicitly noted that a muscle contraction induced to tendon 4.5 to 6.5% strain is a precondition in order for the tendon properties be enhanced during training (Arampatzis et al., 2007a, 2010; Bohm et al., 2015); yet, needing to achieve these strain levels, the intensity of muscle contraction diverges among individuals (**Figure 17**). Therefore, a valuable tool for target training loading protocols would be a diagnostic procedure allocating tendon properties so as to promote the essential tendon adaptation so that improvement of athletic performance and avoidance of potential injuries could actually take place.

Tendons are considered to be one of the most significant tissues in the human body. Since they are collagenous structures, they have the ability to influence considerably the muscles potential to create force through their compliance. Hence, they can be thought to be an

inextricable aspect of the human musculoskeletal system bringing on the efficient locomotion of the human body (Roberts, 1997; Lai et al., 2014). A range of studies on diverse motor tasks on humans, such as walking (Lichtwark and Wilson, 2007; Lai et al., 2015), running and jumping (Lichtwark, 2005, 2007; Ishikawa and Komi, 2008; Albracht and Arampatzis, 2013), have tried to document the diverse values of maximum tendon strain, because strain is thought to be a kind of mechanical demand opposed on the tendon, from a methodological research point of view. The aforementioned values seem to differ as they were observed to range from 4.3% during walking up to 9.0% during fast running (Kurokawa et al., 2003; Lichtwark et al., 2007; Lai et al., 2018). Furthermore, additional research having investigated the deformation of the quadriceps muscle-tendon unit in addition to the patellar tendon while jumping (Nikolaidou et al., 2017), walking (Bohm et al., 2018), landing and running (Bohm et al., 2018; Hollville et al., 2019), has proved that an ideal amount of tendon deformation is essential so as to accomplish an efficient locomotion throughout daily life and various sports activities. What is of utmost importance is the tendon deformation since it directly affects the potentiality of both the power-velocity and the force-length-velocity of the muscles (Nikolaidou et al., 2017; Bohm et al., 2018, 2019b), and is directly associated with the strain storage and its recoil within the muscle-tendon unit (Lichtwark and Wilson, 2005; Ishikawa and Komi, 2008; Lai et al., 2014). It can be briefly inferred that for the need of an efficient muscle-tendon interaction, muscles have to be sturdy and strong enough to elongate the tendon in proper strain levels so that they are able to utilize sufficiently, as a consequence, the strain energy throughout locomotion. Even though it is implied so far that negative impact being brought about on the tendon by high strain magnitudes, tendon impairments could as well be produced by minor levels of strain.

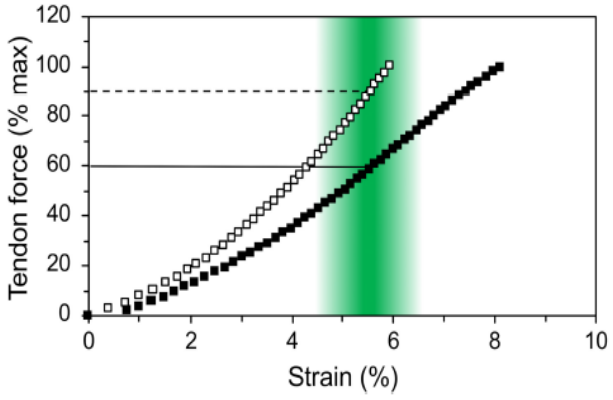

Figure 17 Illustration of the individual relationship of tendon force (in percent of maximum tendon force) and strain in two athletes. The green area represents the range of strain where an optimal mechanical stimulation for training is expected, and the horizontal lines show intensity in terms of force exertion may differ substantially between individuals. (Arampatzis et al., 2020*, Frontiers of Physiology* 11, 1–7, p. 4)

In laboratory conditions in living biological entities (in *vivo*), trying to document with exactness the levels of deformation, which can end up in a rise in the mechanical demand on

the tendon, can prove to be a daunting task. Nevertheless, it seems that the maximum tendon strain could not be changed and remains the same for all species (LaCroix et al., 2013).The adaptability as well as health of the tendon rely on the strain levels to which the tendinous tissue is subjected (Bohm et al., 2015; Wiesinger et al., 2015). To elaborate, it has been shown in research that low levels of deformation of ~3% that were brought on by the mechanical loading cannot promote or further improve tendon properties (Arampatzis et al., 2007a, 2010). Nevertheless, recurring exposure to high levels of strain could provoke overload in a tendon. More specifically, the outcome of Wang et al. (2013) after having subjected the tendon of the rodents with strain values of 9% in a cyclic pattern in the experimental model was tendon deformation in such an extent serves as degeneration on the tissue and weakens its structural integrity. Thus, it can be hypothesized that tendon strain magnitudes which are higher than 9.0% can be disparate during an isometric muscle contraction manifesting an imbalance within the muscle-tendon unit, as a result of greater strength of the attached muscle if compared to tendon stiffness levels which would in turn be minor (Bohm et al., 2019a). Extended investigations on corpses have revealed that the causes on the verge of tendinopathy occurrence take place because of the deterioration of the tendinous tissue at the structural level in consequence of the rise of the local strain brought on by the general increase of tendon strain (Lavagnino and Arnoczky, 2005). Conversely, the same study of Wang et al. (2013) illustrated pathological conditions that may result in the development of tendinopathy, like matrix degradation and catabolic signals which could be caused by low levels of tendon strain as well (~ 3%). During a series of in vivo studies that were conducted in the Department of Training and Movement Sciences of Humboldt University under the supervision of Professor-Dr. Adamantios Arampatzis, there was an effort to classify the levels of deformation, which would prove to be beneficial to the tendon. While the studies were underway and the volume as well as the magnitude of the loading were constantly under control, the participants' tendons underwent a range of intervention protocols of diverse strain magnitude (3% and 4.5–6.5%), strain frequencies (0.17 and 0.5 Hz) and rate (modulated by means of time to climax force of ~130 and ~380ms), in addition to duration (1 s, 3 s and 12 s). It was identified by the research team that the cyclic application of a load yielding a tendon strain, which could in turn promote the tendon mechanical properties, values amid 4.5–6.5% for 3s duration per repetition (Arampatzis et al., 2007a, 2010; Bohm et al., 2014). The early results of Arampatzis et al. (2007a, 2010) seem to have been confirmed later by Wang et al. (2013) that was conducted on rodents, as when Arampatzis et al. (2007a, 2010) implemented an intervention protocol inducing strain values of 3%, there was no progress made regarding the mechanical properties

of the participants' tendons. In reference to the aforesaid findings, Arampatzis et al., (2020) deduced in their review that an exercise providing an optimal tendon strain is essential so as tendon adaptations can be activated and its mechanical properties to be promoted as well. Looking back on previous studies, there was an attempt to identify the load being suitable for applying during training in order to accomplish the preferred levels of tendon deformation. Arampatzis et al., 2007a, 2010; and Bohm et al., 2014, concluded that when exercises' muscles have been trained to maximum loads like 90% of their voluntary maximum isometric strength, it is sufficient to compel the tendon to mechanical properties-promoting strain values, for example 4.5 to 6.5%. Nevertheless, this might not prove to be true, on an individual level.

To this point, having taken into account the previously mentioned information, it is explicitly stated that maximum tendon strain is determined throughout muscle contractions by two components: tendon stiffness, and maximum muscle strength. Nonetheless, when the balance of the last two mentioned is interrupted, the strain can be disarranged, either with too low or too high levels, which as a result can have an impact on the performance competence and the health of the tendon (Mersmann et al., 2017a, 2019). Investigation findings regarding muscle-tendon characteristics during maturation have shown strong correlation between tendon stiffness and muscle strength regardless of the age (Arampatzis et al. 2007b; Stenroth et al., 2012; Waugh et al., 2012; Epro et al., 2017, 2019; Pentidis et al., 2019; Mersmann et al., 2019). Having this observation in mind, the adopted theory is that any tendon stiffness adaptation will come after a proportional increase in muscle strength. On the other hand, a balance in the muscle-tendon unit is not an inevitable result of the strong relationship between tendon stiffness and muscle strength, since a low or high relation could not offer an insight into the margin of the tendon mechanical tolerance throughout maximal muscle contraction. Citing an example, Urlando and Hawkins, (2007) looked into the muscle tendon adaptations at six intervals through eight week span of strength intervention protocol. During maximal voluntary contractions, an increase in tendon force was shown and yet, there was no significant alteration in the strain values, which may be construed as a uniform adaptation between muscle and tendons. Taking a closer look at the given data of the former study, strain values on individual levels exhibited an immense fluctuation between measurement sessions. To give an example, the maximum strain values, which were studied through sessions, diverge significantly from 8.6% to 13.5%. For that reason, and because of the analysis of the group means, imbalances amid tendon stiffness and muscle strength could go unnoticed. Imbalances occurrences between tendon stiffness and muscle maturation through maturation period can be identified by looking at the tendinopathy frequency in the literature, which has been stated to increase (Simpson et al.,

2016). Investigations in late adolescent elite volleyball athletes have detected that they present considerably larger variations as regards muscle strength with non-uniformity in tendon adaptation, evidenced by the lower association and non-uniformity between tendon stiffness and muscle strength (Mersmann et al., 2016). Therefore, not only has the athlete's tendon strain risen chronically in interval of 12 months measurements throughout muscle maximal contractions compared to controls (~7.5% vs. 5.5%, correspondingly), but it also manifested considerably larger variations through the investigation period expressing occurrences of high levels of strain (10–12.5%) contrary to the not active peers (Mersmann et al., 2016). Indications of discordant alterations in tendon stiffness and muscle strength occurring during the period of training have been established in a cross-design study (Mersmann et al., 2017b). Even though there have been signs of higher tendon stiffness in late-adolescent elite male along with female athletes if compared to their inactive equivalents owing to sport-specific mechanical stimuli, tendon stiffness adaptative capability seemed lesser when it was compared to muscle strength in both elite athletic late adolescent genders. According to Mersmann et al. (2016, 2017b) aforesaid data, it serves as an indication that training is a further mechanical stimulus which can additionally bring on musculotendinous system imbalances (Mersmann, et al., 2017a) and could furthermore clarify the increases in the occurrence of tendinopathy during training (Lian et al., 2005; Zwerver et al., 2011; Cassel et al., 2015b; Simpson et al., 2016). In a more recent cross-sectional investigation by Epro et al., (2019), super imposed mechanical loading alterations were studied between the Achilles tendon and the triceps surae (TS) muscle strength in healthy elite track and field jumpers. The consistency of the muscle-tendon unit was evaluated by the authors via the application of a mathematical equation from Robinson et al., (1987) regarding tendon stiffness and muscle strength in swing and takeoff leg, purported symmetry index (SI) The investigation hypothesis lies with the case of intra-limp non-uniformities between tendon stiffness and TS muscle strength, which would be further construed as latent leg-specific dissimilarities in tendon and muscle mechanical properties. The researchers stated the same intra-limp SI between tendon stiffness and muscle strength, contrary to the studies of Mersmann et al., (2016, 2017a, b). The latter was additionally suggested as a balance concerning the muscle-tendon unit per leg. Nevertheless, the last mentioned should not imperatively be considered as a correct notion as, in the case of imbalances regarding the muscle-tendon unit in both legs, a uniform adaptation between tendon stiffness and muscle strength would be construed as well by the equation. The authors supported the consistency in the muscle-tendon unit, as the facts illustrated high relation amid tendon stiffness and muscle strength and intra-limp comparable-similar average strain properties as well. A strong

association, as it has already been mentioned, between tendon stiffness and muscle strength cannot necessarily provide us with a picture of the mechanical demand, which is imposed on the tendon throughout muscle contraction. What is more, the statistic average analysis approach concerning the values of the tendon strain could conceal high strain rates on a personal level.

Having reviewed all the above information within the chapter, it can be deduced that through maturation as well as training, there will be disproportionate adaptations amid tendon stiffness and muscle strength, leading to imbalances in the muscle-tendon unit, resulting in a high risk of tendon injuries.

5 Interaction between maturation and training

Maturation "Timing" referring to the point in time when the spurt takes place and "tempo" concerning the rate or speed at which the person undergoes the spurt, can portray maturation growth spurt. Apart from the chronological age, a point of reference is essential so as to fully appraise individual inconsistencies regarding tempo and timing. Such criteria regarding biological maturity consist of age at the appearance of secondary sex traits, skeletal age and age regarding Peak High Velocity (PHV), the highest growth rate through the period of adolescence spurt (Beunen and Malina, 1988). According to the findings of studies in the populations of North America as well as Europe, PHV arises around the age of fourteen (Malina et al., 2004; Rumpf et al., 2012). Nevertheless, as stated by Malina, 2011, boys playing sports are inclined to mature faintly earlier than their counterparts not playing sports, signaling a possible reciprocal influence between training and maturation. This interaction could be manifested in mechanical as well as muscle morphological properties. It is widely known that muscle strength, along with anatomical cross-sectional area, strikingly grows between 13–15 years in boys (Kanehisa, et al., 1995a, b). The properties of the muscle regarding its function and morphology seem to further develop until adulthood. (Kubo et al., 2001, 2014b). On the contrary, there is proof that there has been an increase in muscle strength in athletes mostly between 12 and 23 years in boys (Degache et al., 2010) and hence, possibly earlier if compared to untrained ones. Taking into consideration the augmented secretion of muscle hypertrophy-mediating hormone levels transpiring at that age (Vingren et al., 2010; Murray and Clayton, 2013) and is of course supported by bodily activity-training (Kraemer et al., 1992; Tsolakis et al., 2004; Zakas et al., 2007), it could be that muscle morphological changes bring the adaptive response to increased mechanical loading. To elaborate, an adult-like morphology of the muscle could well be already manifesting itself in athletes during their mid-adolescent years with just slight changes of the volume of the muscle thereafter (Mersmann et al., 2014, 2017c) in addition

to larger muscle pennation angle related to similar-aged controls (Mersmann et al., 2016). Thus, it is credible that early adolescent athletes have already shown signs of loading-related hypertrophy and muscle remodeling. There is also a maturation and superimposed loading interaction affecting the temporal muscle improvement through adolescence features (in terms of an earlier development) with regard to untrained ones.

Bearing a close resemblance to muscles, the properties of the tendon are influenced by the effect of maturation (O'Brien et al., 2010c; Kubo et al., 2014b), together with its cross-sectional area, Young's modulus (serving as a measure of its material properties founded on the stress–strain relationship) and stiffness (as a system of measurement of its mechanical resilience which is rooted in the force–elongation relationship). Findings of a study carried out on patellar tendon properties, revealed that stiffness of the tendon and its determinants cross-sectional area, material properties and rest length (Young's modulus) rise throughout maturation form nine years old reaching adulthood regarding humans (O'Brien et al., 2010c). As the adaptation of the tendons to mechanical loading occur (Bohm et al., 2015), the growth of muscle strength and mass through the period of maturation might promote the stiffness owing to increased tendon loading throughout the everyday tasks including bearing weight and demanding muscle force (Waugh et al., 2012).

Nevertheless, mechanical loading which is superimposed by sports activities could also advance tendon stiffness during the period of adolescence regardless of the maturation gains in body mass, attesting that the development of tendon mechanical properties throughout maturation can vary in athletes when they are compared to adolescents not training methodically (Mersmann et al., 2017b). Facts regarding the Achilles tendon of untrained youngsters, bearing a resemblance to muscle strength, advocate that what is most pronounced early in adolescence is the increase of tendon stiffness throughout maturation (Kubo et al., 2014a; Mogi et al., 2018). The observations of a more up to date study on adolescent volleyball athletes, however, indicated that under the stimulus of both training and maturation, considerable alterations in tendon CSA and stiffness may take place later on in adolescence concerning muscle strength (Mersmann et al., 2017c). Not having adequate knowledge as regards the development of tendon and muscle during the period of adolescence, there is substantial doubt regarding the way maturation influences the muscle-tendon unit, particularly in interaction with superimposed loading via athletic training.

6 Aim and hypothesis of the thesis

Based on the present literature, data concerning the impact of maturation and superimposed mechanical loading, in relation to partaking in sports and methodical and organized strength training, on the musculotendinous system stems from primarily studies in both children and adults. However, there is not any such knowledge regarding the period from childhood to adulthood. Throughout adolescence, a young person undergoes remarkable changes in both his weight and muscle strength (Asmussen and Heeboll-Nielsen, 1955, 1956), and the continuously amplified mechanical environment is bound to lead up to tendon stiffness (Waugh et al., 2012). Although training is known to be a means of inducing tendon stiffness regarding adults, the double impact of both maturation and superimposed mechanical loading on the tendon is broadly unidentified regarding adolescence. Furthermore, there is not accessible information concerning the consistency of the muscle and tendon adaptation-development throughout adolescence and training, even though inadequate mechanical stimulant is known to result in musculotendinous system disbalances, putting the tendon through larger mechanical demand while opposed by the related muscle and leading, in the end, to a higher risk of injury in the tendon (Mersmann et al., 2017a; Bohm et al., 2019a). The period of adolescence is of utmost importance since growth factors, furthering the overall growth of the body (Vingren et al., 2010; Murray and Clayton, 2013), could be additionally increased all through training (Kraemer et al., 1992; Tsolakis et al., 2004; Zakas et al., 2007), signaling a probable interplay between training and maturation.

There has been an establishment by innovators in studying the human body changes during maturation regarding changes that tendons and muscles experience in their morphological and mechanical properties throughout development (Kanehisa et al., 1995a; Mirwald et al., 2002; O'Brien et al., 2010b; Kubo et al., 2014b). To elaborate, having united information from researchers, it is prevalent that mechanical muscular changes are in balance with those of somatometric alterations throughout maturation as in a cross-sectional study, it was noticed that body weight, muscle strength and weight increased in parallel whereas the increase in muscle strength seems to be more pronounced at the age of 13 to 15 years for both male and female (Beunen and Malina, 1988; Kanehisa et al., 1995a; Degasche et al., 2010), which was followed up then by the muscle anatomical cross-sectional area where the most noticeable increase takes place between ages of 13–15 years in male (Kanehisa et al., 1995a, b). On the contrary, there is a remarkable increase in muscle strength in boys playing football aging between 12 to 13 years, showing the probable impact of training to provoke early maturation when a comparison takes place with the non-playing ones. Because the same hormones rising extremely at that age and

arbitrate muscle hypertrophy (Vingern et al., 2010; Murray and Clayton, 2013) are further improved by bodily activity (Kraemer et al., 1992; Tsolakis et al., 2004; Zakas et al., 2007), and in all probability, the alterations in the morphology of the muscles affect the adaptive reaction to amplified mechanical loading, the aforementioned theory could be supported. To exemplify, by implementing the induction method, as volleyball athletes in their mid-adolescence years displayed a muscle resembling the morphology of the adult, with only slight later on developments in muscle volume (Mersmann et al., 2014, 2017c), they exhibited as well a larger pennation angle measured up to the non-playing equivalents (Mersmann et al., 2016); therefore, in all likelihood, a similar pattern would take place in early adolescent people, signifying that even in the early years of adolescence, remodeling or muscle hypertrophy can occur via training and there is a possibility that an interplay of superimposed mechanical loading with maturation can result in the effect of the muscle growth during early adolescence, no less than temporally, suggesting an early progress of the athletes in comparison to the untrained ones.

Not only does the maturation effect impact muscles, but it also affects tendon together with its morphology (cross-sectional area), Young's modulus (as a gauge of its material properties which derive from the stress–strain relationship), and stiffness (as a measuring 'tool' of its mechanical resilience on the basis of the force–elongation relationship) (O'Brien et al., 2010c; Kubo et al., 2014b). Tendon stiffness is believed to be a significant mechanical property as it affects transmitting muscle force to the skeleton and relies on its material properties and dimensions (Butler et al., 1978). Investigation regarding maturation on patellar growth has revealed that tendon stiffness together with its determinants the length of rest, cross-sectional area (CSA) and Young's modulus (as a measure of the material qualities) rise from 9 years reaching adulthood in human beings (O'Brien et al., 2010c). Aligning with the earlier research Kubo et al., (2014b) and Waugh et al., (2012) stated that Achilles tendon Young's modulus values were poorer regarding children aging 9 to 12 years in comparison to adults. Nevertheless, this growth can attain adult-seeming traits approximately early adolescence as students aging 13 to 15years old displayed analogous material properties in comparison to young-adults. The mechanical alterations which are noticed throughout the period of childhood to adulthood can be arbitrated, to some extent, by a rise in the collagenous network's structural integrity (Rudavsky et al., 2017, 2018).

Throughout puberty development, the tempo growth of the length rest of the tendon seems larger in comparison to its morphology (CSA), indicating that the rises in tendon stiffness are mainly dictated by alterations in the material properties (Neugebauer and Hawkins, 2012;

Waugh et al., 2012). As tendons seem to be influenced by the mechanical surroundings (Bohm et al., 2015), the muscle mass strength rise through the period of maturation could promote tendon stiffness owing to amplified tendon loading throughout the everyday, weight-bearing tasks together with the muscle force increase (Waugh et al., 2012). Reaching the end of adolescence, tendon collagen turnover declines considerably (Heinemeier et al., 2013), tendon plasticity is still preserved, though, mostly regarding loading-induced changes concerning the material properties (Bohm et al., 2015).

Regardless of body mass gains, tendon stiffness during adolescence can be further increased by sports-superimposed mechanical loading (Mersmann et al., 2017b), indicating that the mechanical properties growth of the tendon during the period of maturation could actually vary in athletes in comparison to adolescents not training systematically yet. Information regarding the Achilles tendon of not training adolescents, similar to muscle strength, indicate that the rises connected with the tendon stiffness maturation are most obvious during early adolescence years (Kubo et al., 2014a; Mogi et al., 2018). In contrast, a later study of Mersmann and colleagues (2017c) regarding volleyball athletes in their adolescence stated that considerable developments and improvements in CSA tendon and stiffness might be evident later on during adolescence in comparison to muscle strength under the conjoining stimulus of training and maturation. Because there is not sufficient evidence regarding tendon and muscle development throughout adolescence, hesitation and ambiguity are prevailing concerning the way maturation can influence the unit of muscle-tendon, particularly while interplaying with superimposed mechanical loading via athletic training.

With regards to the most recent evidence, our knowledge of these interactions has increased substantially, supporting the notion that the peril of overuse tendon injury might be augmented by an imbalanced development of tendon stiffness and muscle strength (see Mersmann et al., 2017a). If a tendon is to be healthy and capable of adapting, a sufficient strain applied on the tendon is imperative. For example, mechanical loading, inducing low strain values (~ 3%), could not further progress tendon properties (Arampatzis et al., 2007a, 2010). Nevertheless, a research conducted in rodents has stated that when a tendon is exerted to a cyclic application of 9.0% tendon strain, it acts in a degenerative and debilitating way on the tissue and deteriorates its structural integrity (Wang et al., 2013). As the ultimate tendon strain does not rely on species (LaCroix et al., 2013) and taking into consideration the standard levels of maximal in *vivo* (Hansen et al., 2006; Couppé et al., 2009; Mersmann et al., 2016, 2018), tendon strain found in human beings applying ultrasound methods; strain magnitude bigger than 9% could turn out to be indicative of imbalances regarding muscle-tendon throughout maximum isometric

contraction, marked by tendon stiffness actually being too small in comparison with the related muscle strength (Bohm et al., 2019a).

The aim of this study is to examine and inspect the musculotendinous development throughout adolescence and in what way it is affected by athletic training by comparing athletes and non-athletes as well divided in three different age groups (i.e., early adolescents: 12–14 years, late adolescents: 16–18 years and adults) bearing in mind that the aforementioned groups will differentiate in respect of maturation. This research concentrated on the quadriceps on the quadriceps femoris muscle-tendon unit owing to its significant involvement and contribution to the performance of movement and vulnerability to overuse injury (Zwerver et al., 2011; Simpson et al., 2016; Nikolaidou et al., 2017).

It is hypothesized that:

a) Muscle strength, muscle thickness, pennation angle along with tendon stiffness to be greater in athletes in comparison to non-athletes controls regarding all age groups

b) Furthermore, it is expected that regarding athletes, the major tendon development will be found between late adolescents (LA) and adults, yet more timely clear increases of muscle strength (Degache et al., 2010; Mersmann et al., 2017c), which may augment the mechanical demand of the tendon.

7 Material, methods, and experimental design

Eighty-one male participants consisting of untrained controls (n = 40) and athletes (n = 41) divided in three age groups [EA: early adolescence (n=29), 12–14 years; LA: late adolescence (n = 27), 16–18 years; and YA: young adulthood (n = 25), 20–35 years] in the study (**table 1**). The athletes were recruited from the fields of volleyball, American football, basketball, handball, fencing, judo, kick-boxing, dancing, gymnastics, vaulting, hockey, acrobatics, track and field, decathlon and participated in training sessions no less than three times a week for as a minimum of 75 minutes a session. Due to the fact that the sport-specific low-intensity loading is improbable to be an adequate incentive to substantially alter the mechanical properties of the muscle-tendon unit (Karamanidis and Arampatzis, 2006; Arampatzis et al., 2007c), endurance sports athletes had to be barred. The athletic movement and activity of the non-trained adolescent controls was restricted to doing school sports and no more than a session of leisure sports a week whereas regarding adults there was merely the latter. No participant suffered or underwent any harm or orthopedic abnormality at his or her lower limbs. The research was conducted conforming to the university ethics committee recommendations. Every single participant (along with the respective legal guardians regarding the adolescent groups) has given written informed consent stipulated by the Declaration of Helsinki. The muscle strength measuring (i.e., knee extension moments), patellar tendon stiffness and Vastus lateralis architecture were conducted on the dominant leg (i.e., the one used to kick a ball) focusing on a systematized warm-up comprised of ten submaximal isometric contractions, 2–3 minutes of ergometer cycling and three maximum voluntary contractions (MVC).

Table 1 | Anthropometric characteristics of the non-athletes and athletes in the three age groups (EA, early adolescence; LA, late adolescence; YA, young adulthood; means ± standard deviation).

	Non-athletes			Athletes		
	EA (n = 14)	**LA (n = 13)**	**YA (n = 13)**	**EA (n = 15)**	**LA (n = 14)**	**YA (n = 12)**
Age [years]	12.8 ± 0.6^{b,c}	17.3 ±0.8^{a,c}	29.0 ±3.6^{a,b}	13.0 ±0.8^{b,c}	17.2 ±0.8^{a,c}	26.3 ±3.0^{a,b}
Body height [cm]$^{*\#}$	159.6 ±11.0^{b,c}	175.1 ± 5.3^{a}	179.4 ± 9.6^{a}	168.6 ± 12.0^{b,c}	183.1 ± 8.4^{a}	182.1 ± 8.1^{a}
Body mass [Kg]*	45.4 ± 10.3^{b,c}	70.1 ±15.0^{a,c}	80.7 ± 16.5^{a,b}	56.2 ± 11.2^{b,c}	72.7 ± 10.4^{a,c}	79.5 ± 9.1^{a,b}
Femur length [cm]$^{*\#}$	38.7 ± 2.2^{b,c}	41.0 ± 1.9^{a}	40.6 ± 3.8^{a}	39.8 ± 4.1^{b,c}	43.8 ± 3.8^{a}	42.9 ± 2.9^{a}

$^{\#}$Statistically significant effect of activity ($p < 0.05$).*Statistically significant effect of age ($p < 0.05$). ^{a}Statistically significant difference to EA ($p < 0.05$).^{b}Statistically significant difference to LA ($p < 0.05$). ^{c}Statistically significant difference to YA ($p < 0.05$).

7.1 Assessment of the muscle strength

Because the highest strength that muscles can produce is the decisive factor for most movements and muscle strength of fully activated muscle differs with the velocity (Zatsiorsky and Kraemer, 2006; Knudson, 2007), the partakers were under the instructions to carry out isometric maximum voluntary contractions (MVC) via a dynamometer (Biodex Medical System 3, Shirley, NY, USA, see **figure 21**). Delving deeper, the option of isometric contraction was chosen for the muscle strength assessment, stems from the Force–Velocity relationship, which elucidates the muscle capability to sustain high force rapidly decreases with increases in the speed of concentric–shortening (right to the isometric, Figure 18) and the force prospects of a muscle at a small pace of action is considerably contingent on isometric muscular strength (P0, middle of the graph, **Figure 18**) (Knudson, 2007).

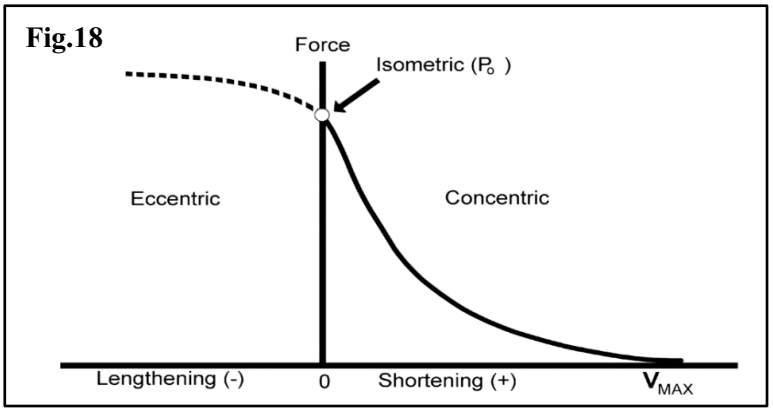

Figure 18 Knudson 2007; (*Fundamentals of Biomechanics;* p. 79); Representation, of the in vitro Force–Velocity relationship of muscle. Muscle force potential rapidly decreases with increasing velocity of shortening (concentric action), while the force within the muscle increases with increasing velocity of lengthening (eccentric action)

Nevertheless, the force of the muscle diversifies at different muscle lengths (Knudson, 2007; **Figure 19**). In accordance with the cross-bridge model or the sliding filament theory (Knudson, 2007), the muscle active isometric force is at its highest point when a greatest number of cross-bridge attachments (overlapping) amid thin and thick filaments can be made (Herzog et al., 1990; Gordon et al., 1966). This, more common than not, matches a point close to the middle of the range of motion, the cited resting length (Knudson, 2007). The potential active muscle tension reduces for longer or shorter muscle lengths since a smaller number of cross-bridges are on hand for binding (Knudson, 2007). Based on this theory, a range of angles were chosen at 65, 79, and 75º of the knee joint (i.e., values at rest calculated by the dynamometer; 0° = full knee extension) throughout the MVC so as the optimum angle is found on the length–tension curve, at which point the greatest number of cross-bridges are attached and the MVC will be the greatest. In a previous study (e.g., Mersmann et al., 2017b), it was found that employing the above resting angles, the participants are able to achieve their approximate optimum angle during contractions. The trunk angle was set to 85°(neutral full hip

extension = 0°) and there was a hip fixation to a dynamometer seat by means of a non-elastic strap.

Fig.19

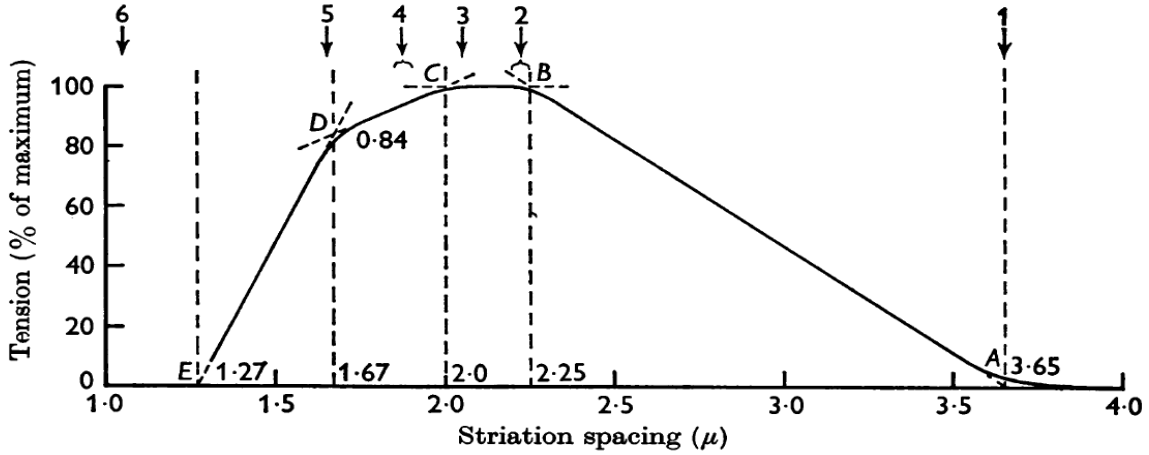

Figure 19 Schematic of the Length–Tension relationship. The arrows along the top (stages) are placed opposite the striation spacings at which the critical stages of overlap of filaments occur. Note, the stage 2 is where the maximal number of cross-bridges are attached (Gordon et al., 1966, *The Journal of Physiology* 184(1), p. 185. Adopted with permission by John Wiley and Sons)

7.1.1 Maximum knee joint moment

Throughout the MVC (Maximal Voluntary Contraction), the calculated moment is diverse from the resultant moment concerning the knee joint. With the intention of having the identical moment between the resultant and the measured one of the dynamometer, the rotation axis of the dynamometer must be brought into line with the knee joint axis (Arampatzis et al., 2004, 2005b). These discrepancies amid moments are attributed to the alterations of the moment arm of the reaction force to the joint of the knee which are induced by the changes of the angle of the knee in relation to the dynamometer axis through the MVC. The variations between the maximum resultant moment and the calculated ones typically range from 3.5% to 7.3%. The latter matches up to absolute values between 7 and 15 Nm (Arampatzis et al., 2004). The deformation of the soft tissue of the leg and the dynamometer compliance, which are challenging to control, are the reasons for these relative knee movements. Arampatzis et al. (2002) stated that "the distortion of the soft tissue of the foot and particularly the motion among rearfoot and barefoot which could account for 7–9° may clarify part of the joint movement and differentiations amid joint angle moments. These disparities might result in not correct calculations concerning the: a) muscle architecture diagnosis, b) muscle forces estimation c)

research of history-dependent properties of the muscle-tendon unit, and (d) evaluation of the strain and tendon hysteresis and aponeurosis (Arampatzis et al., 2004)".

A Vicon (see **figure 21**) motion capture system (version 1.7.1; Vicon Motion Systems, Oxford, UK) was used to record Kinematic data, incorporating eight cameras which operated at 250 Hz, in an attempt to account for these moments variances between resultant moment and dynamometer.Having captured six reflective markers, they were fixed on the subsequent positions: lateral and medial malleolus, the most prominent points of the lateral and medial femoral condyles, trochanter major, and lateral aspect of the spina iliaca (Arampatzis et al. 2004; Mersmann et al. 2017b). Thus, if there is an estimate of the resultant moment at the knee joint to be made, knee joint misalignments and dynamometer throughout the MVC along with the contribution of the gravitational forces must be taken into consideration. Therefore, a reversed dynamics strategy had been followed, being introduced by Arampatzis et al. (2004, **Figure 20**)

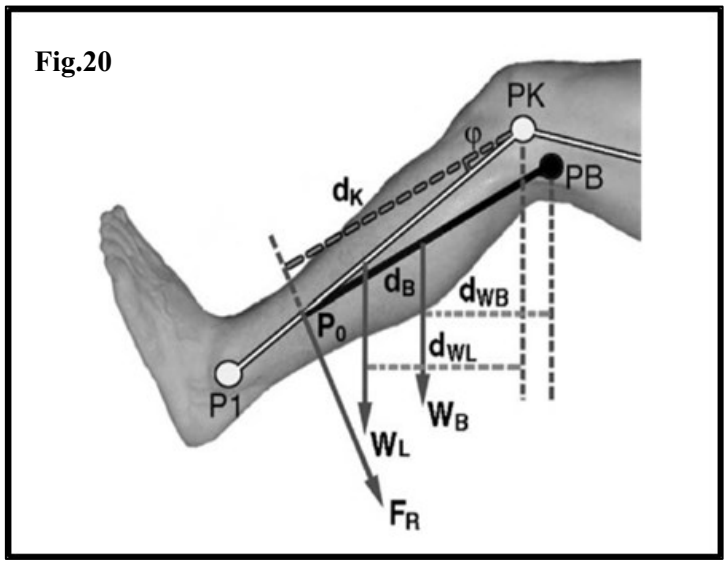

Figure 20 Differences between measured and resultant joint moments during voluntary and artificially elicited isometric knee extension contractions. Free body diagram of the dynamometer arm and the shank-foot segment. $\mathbf{F_R}$: reaction force of the dynamometer lever (defined to be perpendicular to the line defined by points $\mathbf{P_B}$ and $\mathbf{P_0}$); $\mathbf{P_B}$ point on the dynamometer´s axis; $\mathbf{P_0}$: point of application of $\mathbf{F_z}$; $\mathbf{d_K}$: lever arm of force $\mathbf{F_Z}$ to the knee joint (point $\mathbf{P_K}$ is defined as the midpoint of the line connecting the most prominent points of the lateral and medial femoral condyles); $\mathbf{d_B}$: lever arm of the force $\mathbf{F_Z}$ to the joint of the dynamometer (point $\mathbf{P_B}$); $\mathbf{W_B}$: weight of the dynamometer arm; $\mathbf{d_{WB}}$: lever arm of the W_B to the dynamometer axis; $\mathbf{W_L}$: weight of the human shank foot; $\mathbf{d_{WL}}$: lever arm of **WL** to the knee joint; **Φ**: angle between **PK**, **P0** and **P0**, $\mathbf{P_B}$. (Arampatzis et al., 2004, *Clinical Biomechanics.* 19(3), P. 279. Adopted with permission by Elsevier)

Equation 1)$M_{res}=M_B \cdot \frac{d_k}{d_B}$, **Equation 2**) $W_B \cdot d_{WB} \cdot \frac{d_k}{d_B} + W_L \cdot d_{WL}$, **Equation 3**) $I_B \cdot \dot{\omega}_B \cdot \frac{d_k}{d_B} + I_L \cdot \dot{\omega}_L$

$\mathbf{M_{res}}$resultant knee joint moment
$\mathbf{M_B}$moment measured at the dynamometer lever
$\mathbf{d_K}$lever arm of force F_Z to the knee joint
$\mathbf{d_B}$ lever arm of the force F_Z to the joint of the dynamometer
$\mathbf{W_B}$ weight of the dynamometer arm
$\mathbf{d_{WB}}$lever arm of W_B to the dynamometer axis
$\mathbf{W_L}$ weight of the human shank-foot segment

$\mathbf{d_{WL}}$lever arm of W_L to the knee joint
$\mathbf{I_B}$ moment of inertia of the dynamometer about its axis of rotation
$\dot{\omega}_B$angular acceleration of the dynamometer arm
$\mathbf{I_L}$ moment of inertia of the human shank-foot segment about a transverse axis through the knee joint
$\dot{\omega}_L$angular acceleration of the human shank-foot segment

Equation 2 conveys the acting of the gravitational forces, equation 3 portrays the acting of the inertial forces being equivalent to zero as in this study only the isometric contractions were examined. An additional trial was recorded in order for the estimate of the gravitational force ($\mathbf{M_G}$, equation 2) for each angular position to take place. The muscles of the dominant leg was instructed to be relaxed as well as the joint passively rotated around the knee joint at 5°/s all the way through the full range of motion by dynamometer (Mersmann et al. 2017b).

An additional factor that can affect the resultant moment of the knee joint is the antagonist muscles contribution (Biceps Femoris) all through the MVC. The total of this effect amounts to 6–8% of the joint moment (Mademli et al., 2004). "Because the force produced by the contractile muscle elements is reliant on three variables: a) activation of the muscle b) force potential owing to the relationship of the force–length and c) force potential because of the relationship of the force–velocity. If it is so, the antagonistic moment to the resultant moment will be solely dependent on the neuromuscular activation, as the length of the muscle will be invariable throughout isometric contraction and the velocity will be at zero (Mademli et al., 2004)". Thus, if a linear electromyographic (EMG)-activity–knee flexion moment relationship is established, an estimate of the contribution of the antagonistic moment can be considered feasible (Mademli et al., 2004). Concerning that, there has been a recording of two extra knee flexion trial sessions which features an EMG- activity being slightly lesser as well as higher accordingly while being compared to the recorded activity during the maximum knee extension trials.

All through the process of recording the electromyography (EMG, see **Figure 21**) activity of the lateral head of the biceps femoris, two bipolar surface electrodes (Blue Sensor N, Ambu GmbH, Bad Nauheim, Germany) were in use. The latter ones were placed over the mid- portion of the muscle belly, having first cleaned and shaved the skin in for the purpose of decreasing skin impedance, with an inter-electrode distance of 2 centimeters. EMG data were captured at 1,000 Hz (Myon m320RX; Myon, Baar, Switzerland) and passed on to the Vicon system via a 16-channel A-D converter (Mersmann et al. 2017b). Therefore, in the resulting torque of the knee extension estimation, regarding the mathematical equation of inverse dynamics, introduced by Arampatzis et al. 2004, will be added the antagonistic moment of the biceps

femoris, which was first presented mathematically by Mademli et al. (2004): KEM = M_{res} (3) + AM.

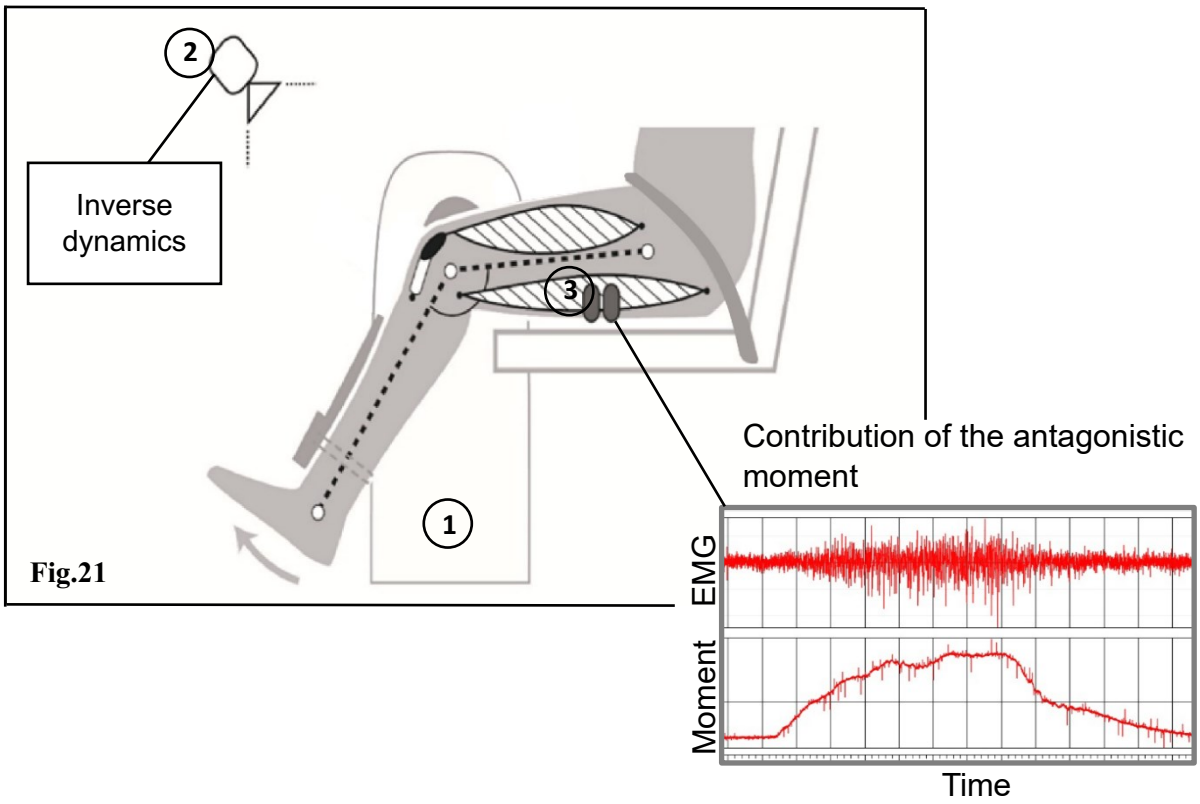

Figure 21| Schematic representation of the experimental setup for the estimation of the resultant moment. A dynamometer (1) was used to measure knee joint moments, while kinematic recordings (2) were used for inverse dynamics and electromyography (3) for the consideration of antagonistic coactivation. (Mersmann et al., 2017, *Frontiers in Physiology*, 8(JUN). Remodified)

7.2 Measurement of vastus lateralis muscle architecture

For the Vastus lateralis architecture assessment (see **Figure 22**), ultrasound images were captured at 60° knee joint angle (measured online using the kinematic model), which has been reported by Herzog et al. (1990) to be the approximate optimum angle of the Vastus lateralis for force production. A 10cm linear ultrasound probe (7.5MHz; My Lab60; Esaote, Genova, Italy; probe: linear array (LA923), depth: 7.4 cm, focal point: 0.9 and 1.9, no image filter) was positioned over the inactive muscle and specifically the belly, in its longitudinal axis at ~60% thigh length, being the assumed anatomical landmark of the maximum anatomical cross-sectional area (Mersmann et al., 2015).

A custom written MATLAB interface (version R2012a; MathWorks, Natick, MA, USA) was used offline so as to analyze the ultrasound images. Three reference points were set to

define the deeper and upper aponeuroses alongside each aponeurosis and a linear least-squares-fit through these points. Subsequently, the discernible features of multiple fascicles were marked manually and a reference fascicle was estimated based on the average inclination of the fascicle portions and the distance of the aponeuroses (Marzilger et al., 2018). The angle between the reference fascicle and the deeper aponeurosis is where the pennation angle refers to. Fascicle length was normalized to femur length. Muscle thickness is defined as the vertical distance between the upper and deeper aponeurosis.

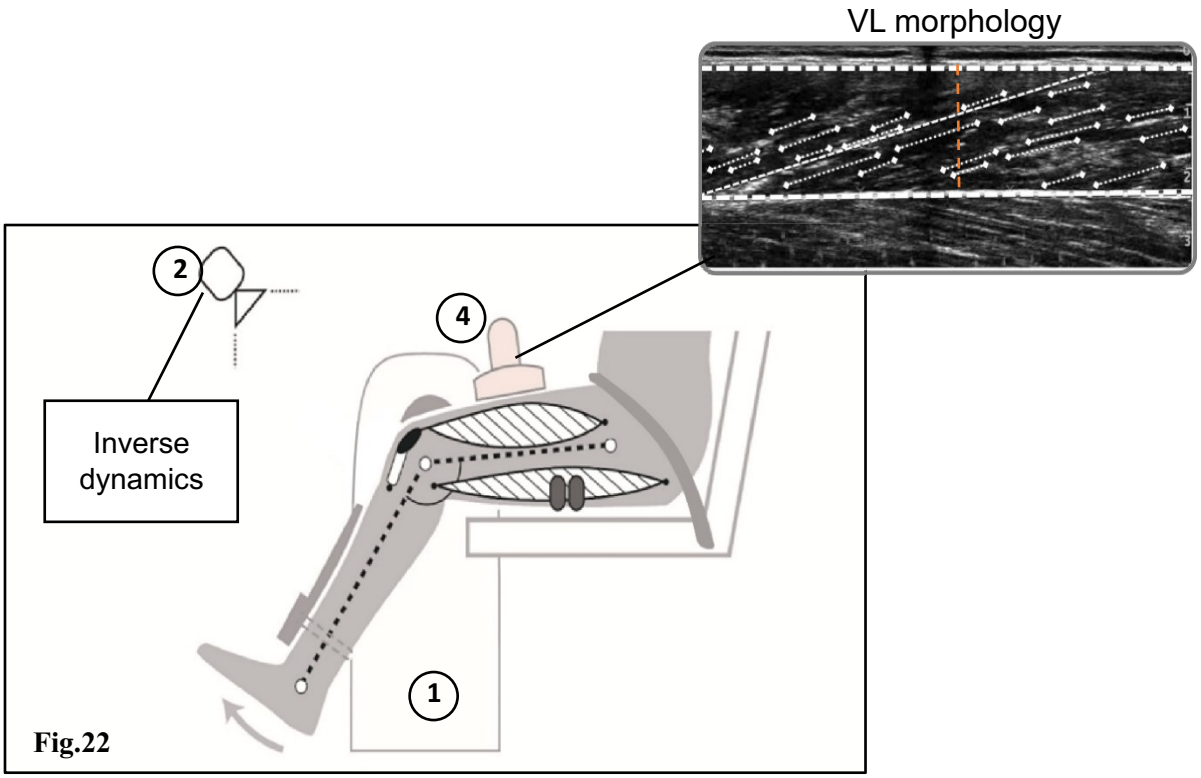

Figure 22| Schematic representation of the experimental setup for the estimation of the vastus lateralis (VL) morphology. A dynamometer (1) was used in fixed angle, while online kinematic recording (2) was used to capture the knee joint angle during no muscle contraction. Ultrasound imaging (4) was integrated to assess VL morphology [4; the digitalization of the aponeuroses and the fascicle portions, indicated by the thick dashed line and pointed lines respectively, the calculated reference fascicle, represented by thin dashed line, are overlaid over the ultrasound image, and the muscle thickness represented as the orange dashed line (Mersmann et al., 2017, Frontiers in Physiology, 8(JUN). Remodified]

7.3 Stiffness of the patellar tendon

For the purpose of shedding light to the relationship of the force–elongation of the patellar tendon, the ultrasound probe (see **Figure 23**; i.e., the probe and settings as illustrated beforehand in chapter **7.1.1** and **7.2**) was set via a customized knee brace, which overlies the patellar tendon in the sagittal plane. The partakers conducted five isometric ramp contractions, steadily intensifying their exertion from rest to maximum in ~5 s while simultaneously the tendon elongation was recorded via the ultrasound at 25Hz. In accordance with the MVC trial, in which the individual partaker accomplished the highest moment, the resting knee joint angle for the ramp contractions was set. Following the same consideration mentioned before, the moments of the knee joint were estimated, by means of implementing the strategy of inverse dynamics and correction for antagonistic activity. As the tendon force, which could be achieved throughout a ramp, is 73% – 95% of that through an MVC, tendon force was calculated by dividing the knee extension moment by the tendon moment arm (Mersmann et al., 2018).

The tendon moment arms (TMA) were predicted according to the regression equation reported by Mersmann et al. (2016) based on sex, body height and mass.

$$TMA=25.88+0.078 \cdot m - 2.242 \cdot s + 0.128 \cdot h$$

- m= mass (kg)
- s= sex (0=males, 1=females)
- h=height (cm)

Since the moment arm of the patellar tendon is significantly influenced by the knee joint angle, it was adjusted to the respective knee joint angle position based on the polynomial regression equation suggested by (Herzog and Read (1993); Journal of Anatomy. 182(Pt2), p.226)

Therefore, the predicted moment arm derived from the equation:

$$\text{Predicted Moment Arm} = (2)\,(TMA/4.71) \cdot (B0 + B1(\Theta) + B2(\Theta)^2 + B3(\Theta)^3 + B4(\Theta)^4)$$

- BO–B4 regression coefficients to predict moment arm of patellar tendon as a function of knee joint angles

B0	B1	B2	B3	B4
0.471D + 01	0.420D – 01	– 0.896D – 03	0.447D – 05	0.000D + 00

*The numbers are given in double precision (D) notation; thus 0.471 D + 01= $0.471 \cdot 10^1 = 4.71$

- Θ optimum angle (angle that achieved during the maximum MVC)
- 4.71 resting length of the Patellar tendon (cm)

The analog and kinematic data were in synchronization with the ultrasound images using and externally induced voltage peak. Patellar tendon elongation during the contractions was determined by manually tracking the deep insertion of the tendon at the patellar apex and the tibial tuberosity frame-by-frame using a custom-written MATLAB interface. To account for tendon slackness at rest, elongation was measured when the distance between the deep insertion points exceeded tendon rest length, which in turn was measured using a spline fit through the deep insertion marks and four additional points along the lower border of the slack tendon. In order to achieve a high reliability (≥ 0.95), the force–elongation relationship of the 5 trials of each participant was averaged using the highest common force of the single trials as a peak force (Schulze et al., 2012). Tendon stiffness was calculated between 50 and 100% of the peak tendon force based on a linear regression because the elongation of the tendon between these two values is located at the linear part of the force–length curve (i.e. area used for calculation of tendon stiffness). As stiffness is influenced by the resting length of the tendon (Butler et al., 1978; Arampatzis et al., 2005a), we further calculated the normalized tendon stiffness (i.e., the product of stiffness and rest length) that represents the slope of the force strain curve.

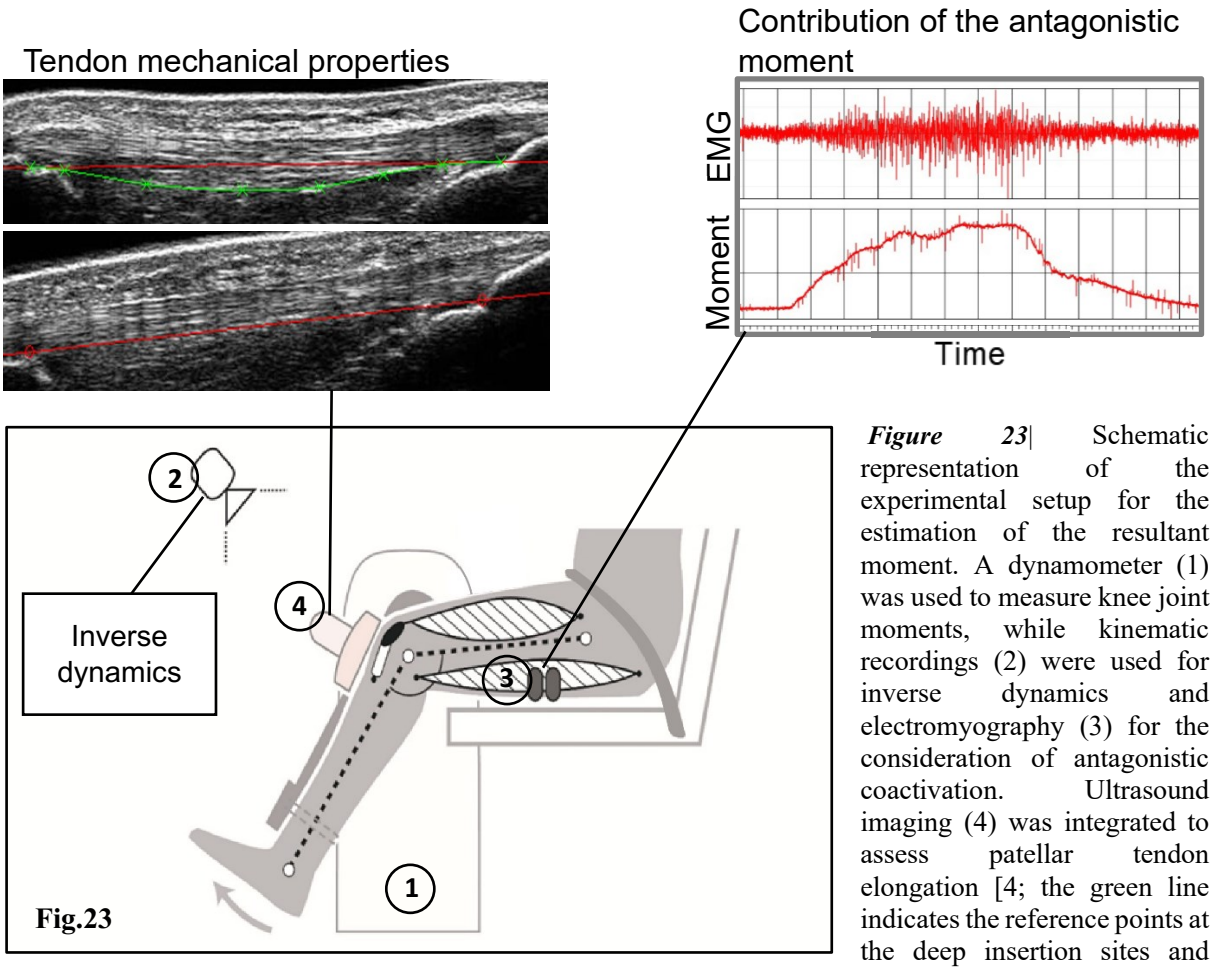

Figure 23| Schematic representation of the experimental setup for the estimation of the resultant moment. A dynamometer (1) was used to measure knee joint moments, while kinematic recordings (2) were used for inverse dynamics and electromyography (3) for the consideration of antagonistic coactivation. Ultrasound imaging (4) was integrated to assess patellar tendon elongation [4; the green line indicates the reference points at the deep insertion sites and lower border as well as the slag of tendon which was taken account during elongation. Red line indicates the elongation of the tendon during muscle contraction (Mersmann et al., 2017, *Frontiers in Physiology,* 8(JUN). Remodified].

8 Statistics

The statistical analysis was conducted in SPSS (version 20.0; IBM, Armonk, NY, USA). A two–way analysis of variance was performed with the fixed factors activity (i.e., non-athletes, athletes) and age (i.e, EA, LA and YA). The Shapiro-Wilk Test was performed to verify the normal distribution of the data and Levene's test to assess the homogeneity of variances. A Bonferroni-corrected *posthoc* analysis was conducted in the case of a significant age effect or interaction of the factors activity and age. The alpha level for all tests was set to 0.05. The effect size f for significant observations were calculated in G*Power (Version 3.1.6; HHU, Düsseldorf, Germany; Faul et al., 2007), based on the partial eta squared or means and pooled standard deviation for non-parametrically tested parameters. The subscript *Activity* and *Age* indicates if the effect size refers to differences between athletes and controls or between age groups, respectively. Effect sizes of $0.1 \leq f < 0.25$ will be referred to as small, $0.25 \leq f < 0.5$ as medium and $f \geq 0.5$ as large (Cohen, 1988). Using the whole sample, the Pearson's r for the correlation of tendon force and stiffness was calculated. Further tendon stiffness was predicted by tendon force using a linear regression model with group-specific y-intercept and slope constants for each age and activity group, respectively, and compared the residuals of the model prediction were with a two-way ANOVA to analyze differences in the association of tendon force and stiffness. The model equation was:

$$y_i = c_0 + \beta_0 F_i + c_1 g_i + \beta_1 g_i F_i + c_2 l_i + \beta_2 l F_i + c_3 g_i l_i + \beta_3 g_i l_i F_i + c_4 a_i + \beta_4 a_i F_i + c_5 g_i a_i + \beta_5 g_i a_i F_i + \varepsilon_i$$

where i *is* index for participant (1,…..,81); g is the activity-group variable (non-athlete = 0; athlete =1); l is late adolescent age variable (EA = 0; LA = 1; YA = 0); a is young adult age variable (EA = 0; LA = 0; YA = 1); c are the intercept constant, β are the slope constants; F is tendon force ε is the residual. Further, it was examined the frequency of individuals that reached strain values greater than 9%, since it has been reported that repetitive strains above 9% can induce catabolic tendon matrix damage (Wang et al., 2013). Though the exceedance of the threshold does not necessarily imply injury, it provides a classification if the mechanical demand for the tendon and risk for fatigue is comparatively high.

9 Results

Considering the anthropometric data (**Table 1**), there was a significant effect of age on body mass ($p < 0.001$, $f_{Age} = 1.04$), but no effect of activity group or activity-by-age interaction ($p > 0.05$). *Posthoc* analysis revealed significantly greater body mass with increasing age of the respective group ($p < 0.05$). There was a significant effect of activity group ($p = 0.003$, $f_{Activity} = 0.36$) and age ($p < 0.001$, $f_{Age} = 0.83$) on body height. Athletes were taller compared to non – athlete controls and EA showed significantly smaller height compared to LA and YA ($p < 0.001$), but there were no significant differences between YA and LA ($p = 1.0$). There was a significant main effect of age and activity ($p = 0.002$, $f_{Age} = 0.43$; $p = 0.007$ $f_{Activity} = 0.32$, respectively) but no activity-by-age interaction ($p = 0.608$) on femur length. EA had smaller femur lengths compared to YA and LA ($p = 0.002$ and $p = 0.028$, respectively), but there were no significant differences between YA and LA ($p = 1.0$).

Considering the absolute and normalized muscle strength (normalized to body mass) of the knee extensors, athletes had higher strength compared to non-athletes ($p < 0.001$, $f_{Activity} = 0.53$ for absolute strength and $p < 0.001$, $f_{Activity} = 0.59$ for normalized strength). There was a significant age effect ($p < 0.001$, $f_{Age} = 1.13$ for absolute strength, and $p < 0.001$, $f_{Age} = 0.64$ for normalized strength) but no activity-by-age interaction ($p = 0.770$ and $p = 0.129$ for the absolute and normalized strength respectively; **Table 2**). EA had lower absolute strength compared to YA and LA ($p < 0.001$, $f = 1.14$ and $f = 0.93$ respectively) and normalized muscle strength ($p < 0.001$, $f = 0.51$ and $f = 0.61$), but there were no statistically significant differences between YA and LA ($p = 0.395$ and $p = 1.0$). There was no significant effect of age ($p = 0.743$), activity ($p = 0.370$) or activity-by-age interaction ($p = 0.532$ **Table 2**) on antagonistic co-activation (i.e. antagonistic moment normalized to maximal resultant moment) and tendon resting length ($p = 0.290$, $p = 0.930$ and $p = 0.505$, respectively). It was found a greater vastus lateralis muscle thickness in athletes compared to non – athletes ($p = 0.001$, $f_{Activity} = 0.4$) and a significant effect of age ($p < 0.001$, $f_{Age} = 0.79$), but no effect of age-by-activity interaction ($p = 0.545$, **Figure 24A**). EA and LA had lower ($p < 0.001$, $f = 0.86$ and $p = 0.001$, $f = 0.48$) muscle thickness compared to YA, and EA lower thickness than LA ($p = 0.007$, $f = 0.41$). There was no effect of activity ($p = 0.473$) or age-by-activity interaction ($p = 0.407$) on pennation angle (Figure 1B). However, there was a significant effect of age ($p < 0.001$, $f_{Age} = 0.6$) on pennation angle (**Figure 24B**). EA, LA both had lower pennation angles compared to YA ($p < 0.001$, $f = 0.65$ and $p = 0.001$, $f = 0.51$), but there were no statistically significant differences between EA and LA ($p = 0.707$). On normalized fascicle length (normalized to femur length), there were no significant

effects of age (p = 0.903), activity (p = 0.299) or age-by-activity interaction (p = 0.935; **Figure 24C**).

Table 2 | Knee joint moments, co-activation (i.e., antagonistic moment normalized to the resultant knee joint moment), tendon resting length, and normalized stiffness of the non-athletes and athletes in the three age groups (EA, early adolescence; LA, late adolescence; YA, young adulthood; means ± standard deviation).

	Non-athletes			Athletes		
	EA (n = 14)	LA (n = 13)	YA (n = 13)	EA (n = 15)	LA (n = 14)	YA (n = 12)
MVC [Nm]*#	145.2 ± 34.6[b,c]	269.9 ± 72.3[a]	288.2 ± 61.0[a]	202.0 ±65.7[b,c]	327.3 ± 69.4[a]	367.0 ± 64.7[a]
Normalized MCV [Nm/Kg]*#	3.20 ±0.42[b,c]	3.84 ± 0.56[a]	3.60 ± 0.54[a]	3.56 ± 0.74[b,c]	4.49 ± 0.63[a]	4.61 ± 0.55[a]
Antagonistic co-activation [%]	8.4 ± 4.3	11.1 ± 6.3	8.9 ± 6.1	8.5 ± 6.3	8.1 ± 5.1	8.5 ± 4.5
Tendon resting length [mm]	49.2 ± 8.5	52.0 ± 4.4	51.0 ± 8.4	50.6 ± 6.9	53.0 ± 7.6	48.1 ± 5.9
Tendon normalize stiffness [kN/strain]*#	41.5 ± 11.6[b,c]	57.2 ± 11.1[a]	63.3 ± 15.7[a]	51.0 ± 15.1[b,c]	65.9 ± 14.7[a]	70.5 ± 14.5[a]

#Statistically significant effect of activity (p < 0.05). *Statistically significant effect of age (p < 0.05). [a]Statistically significant difference to EA (p < 0.05). [b]Statistically significant difference to LA (p < 0.05). [c]Statistically significant difference to YA (p < 0.05).

Patellar tendon maximal force was greater in athletes compared to non-athletes(p < 0.001, $f_{Activity}$= 0.52) and there was a significant effect of age (p < 0.001, f_{Age}= 1.12), but no significant age-by-activity interaction (p = 0.772, **Figure 25A**). EA had significant smaller patellar tendon force compared to LA and YA (p < 0.001, f = 0.93 and f = 1.13, respectively), but there were no significant differences between LA and YA (p = 0.602). Athletes had stiffer patellar tendons compared to non – athletes (p = 0.013, $f_{Activity}$= 0.31, **Figure 25B**) and there was a significant effect of age (p < 0.001, f_{Age}= 0.61). EA had statistically lower patellar tendon stiffness compared to YA (p = 0.015, f = 0.66) and LA (p < 0.001, f = 0.42), but there were no significant differences between YA and LA (p = 0.104). There was a significant effect of age (p < 0.001, f_{Age} = 0.66) and a significant effect of activity (p = 0.01, $f_{Activity}$= 0.32) on normalized patellar tendon stiffness (**Table 2**), but no statistically significant activity-by-age interaction (p = 0.956). EA had smaller normalized patellar tendon stiffness compared to LA (p = 0.001, f = 0.55) and YA (p < 0.001, f = 0.70) but no significant differences between LA and YA (p = 0.592). There was a significant effect of age on patellar tendon maximum strain (p = 0.028, f_{Age}= 0.33; **Figure 25C**). EA had lower tendon strain compared to YA (p = 0.039, f = 0.33), but there were no statistically significant differences between EA and LA (p=0.120) or LA and YA (p = 1.0). There was a tendency towards an effect of activity on patellar tendon strain (p = 0.072, $f_{Activity}$= 0.22), but no age-by-activity interaction (p = 0.389).

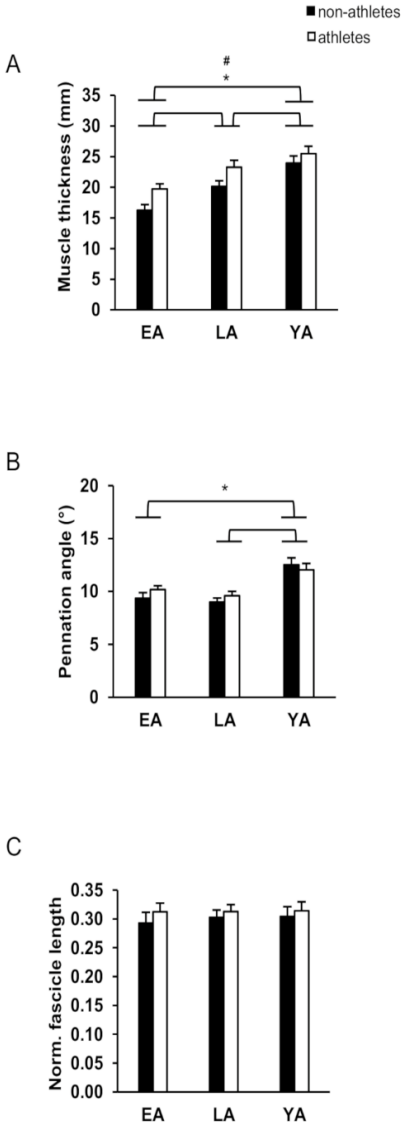

Figure 24 | Mean values and standard error (error bars) of vastus lateralis (VL) muscle thickness (**A**), pennation angle (**B**), and normalized fascicle length (**C**; normalized to femur length) of non-athletes (black) and athletes (white) in early adolescence (EA), late adolescence (LA), and young adulthood (YA).#Statistically significant effect of activity ($p < 0.05$). *Statistically significant effect of age ($p < 0.05$)

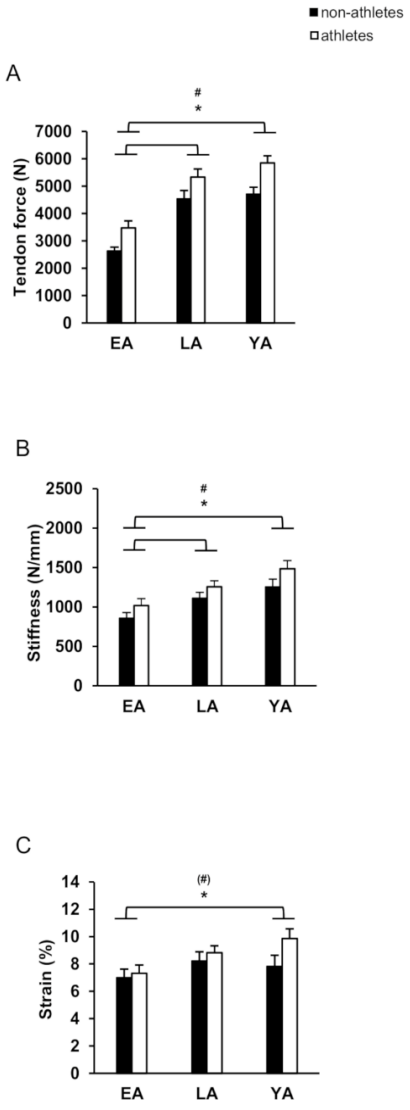

Figure 25 | Mean values and standard error (error bars) of patellar tendon: tendon force (**A**), tendon stiffness (**B**), and tendon strain (**C**) of non-athletes (black) and athletes (white) in EA, LA, and YA #Statistically significant effect of activity ($p < 0.05$). *Statistically significant effect of age ($p < 0.05$)

There was a significant correlation between tendon force and tendon stiffness ($r = 0.631$, $p < 0.001$, **Figure 26A**) for the whole investigated group of participants. The residuals of the regression model that included group-specific terms showed a tendency for an activity effect ($p = 0.098$) and no effect of age ($p = 0.524$) or age-by-activity interaction ($p = 0.536$, **Figure 26B**). Examining the individual tendon strain values during the maximum isometric contractions, it is notable that athletes were more likely to reach strain magnitudes higher than 9% strain compared to non-athlete controls (frequency in athletes: 28–66% and in non-athletes: 15–33%, **Figure 28 see chapter 10.7**). Furthermore, the frequency of individuals that reach strain values greater than 9% increased from EA to YA in both athletes and non-athletes (**Figure 28, see chapter 10.7**).

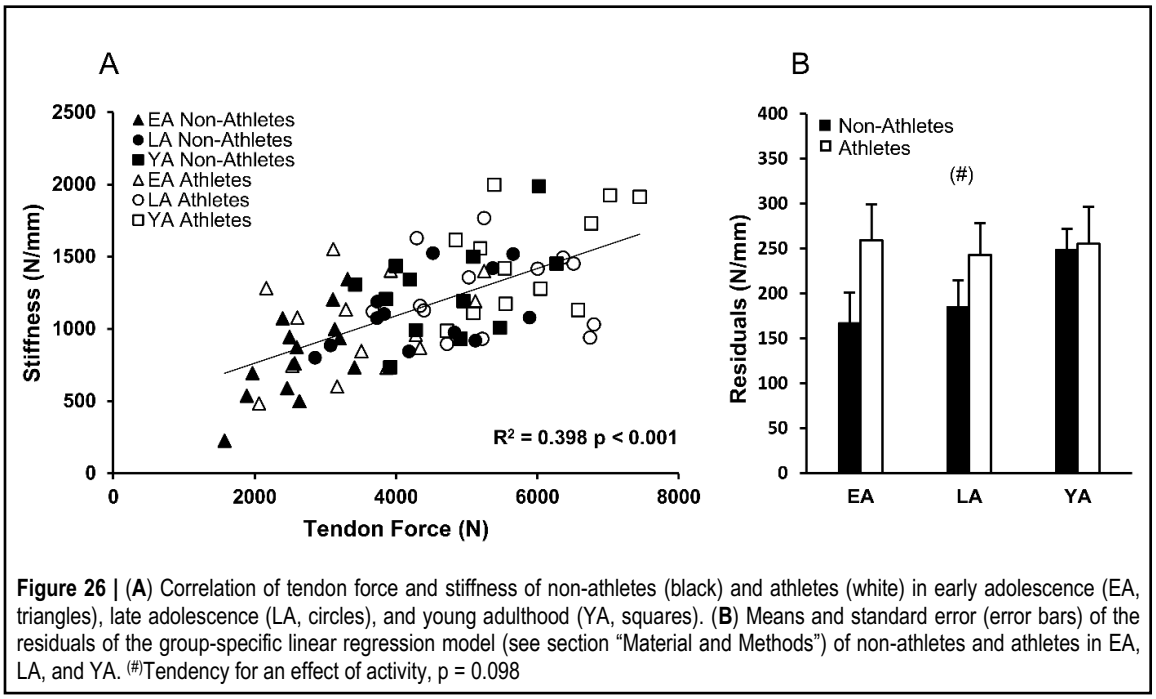

Figure 26 | (**A**) Correlation of tendon force and stiffness of non-athletes (black) and athletes (white) in early adolescence (EA, triangles), late adolescence (LA, circles), and young adulthood (YA, squares). (**B**) Means and standard error (error bars) of the residuals of the group-specific linear regression model (see section "Material and Methods") of non-athletes and athletes in EA, LA, and YA. (#)Tendency for an effect of activity, $p = 0.098$

10 Discussion

This cross-sectional study has delved into the development of quadriceps femoris muscle strength, patellar tendon mechanical properties as well as vastus lateralis (VL) architecture through the period of adolescence and how athletic training can influence individuals and more specifically 81 male subjects covering a maturational variety of time periods, from early adolescence (EA, 12–14 years) to late adolescence (LA, 16–18 years) and later on, young adults (YA, 20–35 years). According to the results, regardless of anthropometric differentiations, athletic training had an impact on both tendon and muscle, manifesting greater tendon stiffness, muscle strength and LV thickness in athletes when they are compared to non-athletes controls. Nonetheless, even though the absolute values differed between controls and athletes, the development of tendon stiffness, muscle strength and VL thickness since early adolescent years until adulthood did not differentiate significantly, displaying an analogous impact of maturation on muscle-tendon properties in both groups.

10.1 Maturation effects on muscle morphological and architectural properties

It is well-known that muscle thickness and angle of pennation are an index of muscle hypertrophy (Kawakami et al., 1993, 1995; Kubo et al., 2001, 2014a; Aagaard et al., 2001; Miyatani et al., 2002, 2004; Mersmann et al., 2017b; Franchi et al., 2017, 2018); however, changes in muscle thickness can be modulated by alterations in muscle architecture, such as fascicle length and pennation angle (see **Figure 27**; Franchi et al., 2017, 2018).

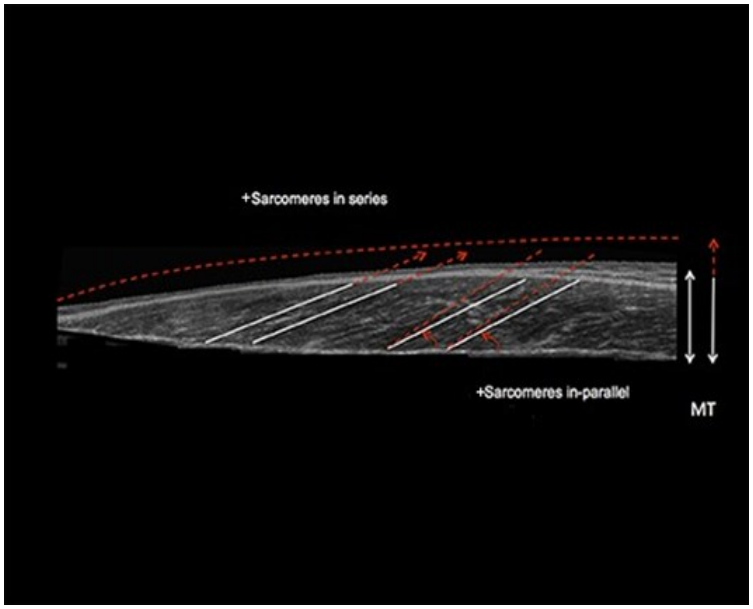

Figure 27 Schematic diagram illustrating the distinct ways of vastus lateralis muscle thickness development (MT, imaging acquired by using extended field of view ultrasound technique): a similar increase in MT can indeed be developed either through an addition of sarcomeres in-parallel with an increase in pennation angle, or through an addition of sarcomeres in series, which is represented by an increase in fascicle length. (Figure adopted and modified by: Franchi et al., 2017, *Frontiers in Physiology,* 8(JUL), 1–16. p. 10)

.

Due to sufficient resolution and good contrast between surrounding tissues, magnetic resonance imaging (MRI) is called the golden standard technique method for measuring muscle size, because it enables the accurate segmentation of transverse plane images over the entire length of the muscle (Mitsiopoulos et al., 1998; Maden-Wilkinson et al., 2013). However, the high costs and limited accessibility of MRI scanners challenge the measurement of muscle size by means of MRI. On the other hand, ultrasonography is an alternative reliable method for the measurement of muscle morphometrics, such as muscle thickness, pennation angle, and fascicle length(Aggeloussis et al., 2010; Giannakou et al., 2011; Marzilger et al., 2018). Several investigations revealed a positive association between muscle morphometric parameters and muscle cross-sectional area (CSA) or muscle volume (Miyatani et al., 2002, 2004;Franchi et al., 2018), underlying that muscle morphometrics are reliable predictors of muscle size. Increments in muscle pennation and fascicle length are indicative of addition in sarcomeres in parallel (radial growth) and series (longitudinal growth) respectively (Franchi et al., 2017; Radnor et al., 2018), which will both eventually result in increased muscle mass. In the present study, even though VL muscle thickness (**Figure 24A**) increased with maturation, the differences during the passage from early adolescence to adulthood were not large. These findings confirm the existing literature which states that the major adaptation in muscle morphology, such as CSA and muscle thickness, take place in early adolescence (Kanehisa, et al., 1995a, b; Viru et al., 1999; Kubo et al., 2001, 2014a). The findings in muscle pennation are contradictory. While data of O'Brien et al. (2010a) and Kubo et al. (2001), obtained from the quadriceps muscle as well, did not indicate significant changes during maturation, in the present study a development of VL muscle pennation towards adulthood was found (see **Figure 24B**). However, there were no differences between the younger groups. This indicates that development in muscle thickness during adolescence is due to the increase of the fascicle length, but towards adulthood, muscle pennation tends to be the muscle thickness-modulation factor. In light of findings on the gastrocnemius (Weide et al., 2015) an increase of muscle pennation with maturation seems well possible. However, lack of muscle pennation development during adolescence does not necessarily mean lack of radial growth and consequently development of muscle thickness due to the addition of sarcomeres in parallel. Muscle thickness is highly correlated to physiological cross-sectional area (PCSA; Copley and Kuipers, 2014), which increases during maturation due to the addition of sarcomeres in parallel without detectible development in muscle pennation (O'Brien et al., 2010a). It is well-known that longitudinal development of the muscle is stimulated by the growth of the length of the skeleton (Nordmark et al., 2009). In the present study, it was found that normalized fascicle

length (fascicle length/femur length, see **Figure 24C**) was similar between all age groups, which is in accordance with earlier reports (Kubo et al., 2001; O'Brien et al., 2010a) and indicates that during maturation fascicle length develops in proportion to bone growth. Thus, the lack of differences between the younger groups could be explained by the muscle lengthening, subsequently creating space for the addition of parallel sarcomeres along the length of the aponeurosis (O'Brien et al., 2010a). However, as the bone growth is already complete during adulthood (Feldesman, 1992), this may indicate, even though it is a speculation, that longitudinal development of the muscle stops and a hypertrophic model is adopted where an additional attachment area on the aponeurosis is acquired by increasing pennation angle (Alexander and Vernon, 1975; Kawakami et al., 1995; O'Brien et al., 2010a). The inconsistencies regarding the findings in pennation angle between this study and O'Brien et al. (2010a) as well as with Kubo et al. (2001) may be attributed to different methodological approaches. Kubo et al. (2001) and O'Brien et al. (2010a) took under their consideration the visible single fiber in order to estimate the pennation angle with the deep aponeurosis. In this study, the visible features of multiple fascicles were marked manually and a reference fascicle was calculated based on the average inclination of the fascicle portions and the distance of the aponeurosis(Marzilger et al., 2018). Then, pennation angle was estimated by the angle between reference fascicle and the deeper aponeurosis.

According to the results of the current thesis, it is revealed that muscle thickness, with regard to muscle morphology, throughout the stage of maturation, considerable increases take place during the early years of adolescence. Moreover, it has been proved that there is divergence between the tempo-development of the morphological properties throughout maturation period, the rise of the fascicle length being attributed to the morphological development of the muscle through the period of adolescence, and past the late years of adolescence towards the period of adulthood, increases in pennation angle will modulate further the muscle morphological development. The results of this thesis in the lack of pennation angle development during the passage from early to late adolescence reveal that adolescence is a period where an individual does not exhibit muscle radial growth since the pennation angle is PCSA's modulation factor attributed to the addition of sarcomeres in parallel resulting in augmentation of muscle fibers and hence in radial muscle growth(Kawakami et al., 1993, 1995; Aagaard et al., 2001; Franchi et al., 2017;). The most reliable morphological property which can best describe changes in sarcomeres in parallel is PCSA (Aagaard et al., 2001; O'Brien et al., 2010a) and can be best assessed by the magnetic resonance imaging (MRI, so-called the golden standard; Mitsiopoulos et al., 1998; Maden-Wilkinson et al., 2013). However, in this

research due to methodological limitations, such an assessment was not plausible. It is well-known that PCSA and muscle thickness are highly correlated (Copley and Kuipers, 2014), and PCSA increases during maturation without detectable changes in pennation angle by ultrasonography (O'Brien et al., 2010a). Therefore, this dissertation data on morphological development during adolescence should be interpreted with caution. For instance, the unchanged pennation angle values during the passage from early to late adolescence may indicate a lack of muscle radial growth, but there is a possibility that during adolescence the addition of sarcomeres in parallel to occupy the empty space created along the aponeuroses or the tendon during the longitudinal development of the muscle without any detectible changes in angles of muscle fascicles by the ultrasound (O'Brien et al., 2010a). Thus, it may be suggestive that muscle thickness/muscle morphology development during adolescence would be accompanied by both muscle fiber radial as well as longitudinal growth due the addition of sarcomeres in parallel and series respectively (O'Brien et al., 2010a; Franchi et al., 2017).

The development of the morphological properties of the muscle is the result of hormonal alteration during growth. The pattern of human growth alters dramatically with the onset of: 1) the activity within the hypothalamo-pituitary–gonadal axis leading to a large increase in the production of androgens (for males), and 2) with the activation of the growth hormone–insulin-like growth factor (GH-IGF-I) axis (Murray and Clayton, 2013). During maturation, the GH-IGF-I axis, which is of major importance for the overall body growth, experiences a marked activation (Murray and Clayton, 2013). It is well-known that radial and longitudinal fiber growth are related with the GH and IGF-I secretion (Cheek et al., 1971; Allen et al., 1999; Grohmann et al., 2005); thus, it seems that there is an association between single fiber CSA and body height (Aherne et al., 1971). In addition to increasing GH secretion, the maturation-related elevation of the sex steroids increase the sensitivity to GH (Vingren et al., 2012; Murray and Clayton, 2013). It has been shown that persons with a deficiency in GH had smaller muscle mass (Hulthen, 2001), while administration of testosterone alone fails to increase circulating IGF-I levels compared to the administration of GH and testosterone which resulted in a greater increase in IGF-I concentrations than where GH was administered as a single agent (Gibney et al., 2005), leading to a greater muscle mass and CSA (Giannoulis et al., 2006). However, it is the locally produced IGF-I, acting in an autocrine/paracrine fashion which is the most important for the muscle growth (Murray andClayton, 2013; Velloso, 2008).

10.2 Maturation effects on muscle strength

Muscle strength is one of the most important muscles' functional properties since there is a close association between muscular strength and speed of the movement (Weyand et al., 2000), as well as between muscle strength and muscular power (Stone et al., 2003; Wisloff, 2004; Tveter and Holm, 2010). It is known that during maturation strength increases from pre-puberty to adolescence with a marked increase in 13–15 years (Kanehisa et al., 1995a, b). Though, after late adolescence, it seems as if no further significant increments of muscle strength take place (Landi et al., 2017). Thus, our findings of a marked increase of the knee extensor strength from EA to LA of the order of 86%, and a greater muscle strength of YA and LA compared to EA as well as the adult-like strength of LA compared to YA are not surprising. It was found a significant relationship between knee joint moment with pennation angle ($r = 0.383$, $p < 0.001$; see **appendix A1**) and muscle thickness ($r = 0.766$, $p < 0.001$; see **appendix A2**). As muscle thickness is a predictor of muscle size and pennation angle an important modulator of the physiological cross-sectional area (PCSA) (Aagaard et al., 2001; Giles et al., 2015), these findings provide evidence that knee extensor strength is strongly dependent on muscle morphometrics and size, whatever the age. Furthermore, the findings of this thesis confirm earlier evidence that during maturation muscle strength increase is strongly dependent on morphological development of the muscle, such as muscle thickness, cross-sectional area (CSA), physiological cross-sectional area (PCSA), and muscle volume (Bamman et al., 2000; Kanehisa et al., 1995a, b; Kubo et al., 2001, 2014a; Tonson et al., 2008). It is well-known that muscle strength is associated with pennation angle (Mersmann et al., 2017a). Though this did not parallel the differences of muscle strength observed between groups in the present study, probably since the other quadriceps muscles, muscle specific tension, moment arms, and activation also greatly determine isometric knee extensor strength (O'Brien et al., 2010b). Radial fiber growth, which is a prerequisite for muscle strength development and muscle hypertrophy, underlies the addition of sarcomeres in parallel and can be best described by the pennation angle which is the modulation factor of PCSA and muscle thickness (Kawakami et al., 1995; Aagaard et al., 2001; Mersmann et al., 2017a). The analysis of the development of muscle architecture suggests that the marked increase in muscle strength from early to late adolescence is primarily due to an increase in muscle thickness attributed to the fascicle length increase, and only later in the adulthood pennation angle as well as muscle thickness underlie the further development in muscle strength. In adolescent groups, the predominant increase of fascicle length indicates a muscle longitudinal growth, which, however, could not explain the development of muscle strength, since longitudinal muscle adaptations are more related with

the maximal shortening velocity and mechanical power of the muscle rather than with the force they can produce (Goldspink, 1985). However, it seems that development in muscle thickness due to radial growth (Copley and Kuipers, 2014), which is the main contributor to the increasing force-generating potential of the muscle (Aagaard et al., 2001; Farup et al., 2012; Johnson and Klueber, 1991), might be plausible during adolescence without being detectable by changes in pennation angle with the ultrasound technique (O'Brien et al., 2010a,see **chapter 10.1**). The findings of this dissertation showed that there are no differences in muscle strength between late adolescents and young adults. However, the morphological parameters related to muscle strength, such as muscle thickness and pennation angle, were higher in young adults compared to late adolescents, suggesting that gains in muscle strength development exceeded those of muscle morphology and architecture during late adolescence. It has been reported that the force-generating potential of the muscle can be influenced by the specific tension (Bottinelli et al., 1996), which may be dependent on fiber type distribution (Bottinelli et al., 1996; Maganaris et al., 2001). The majority of reports from a single fiber, motor unit, and whole in situ muscle experiments indicate that type II fibers are intrinsically stronger by 40–50% compared to type I fibers (Rowe and Goldspink, 1968; Witzmann et al., 1983; Powell et al., 1984; Bodine et al., 1987; Kanda and Hashizume, 1992; Larsson and Moss, 1993; Stienen et al., 1996). It is well-known that late adolescents, apart from their smaller muscle CSA compared to adults, exhibit adult-like fiber type II distribution (Lexell et al., 1992). This adult-like development of fiber type II distribution occurring during late adolescence could be due to testosterone, an androgen hormone that stimulates the development of fast-twitch muscle fiber in puberty, as has been demonstrated in animal experiments (Dux et al., 1982; Krotkiewski et al., 1980), and reaches its adult levels concentration around late adolescence (Vermeulen et al., 1970; August et al., 1972; Khairullah et al., 2014). Therefore, it could be speculated that due to adult-like fiber type II population of late adolescence, this would lead to a corresponding development in their muscle specific tension, which could further explain why in this thesis late adolescents demonstrated adult-like muscle strength development, while the thickness and pennation angle of their muscles, which are morphological factors that correlating with muscle strength, were smaller compared to young adults. Moreover, it seems that the level of androgenic maturation development of testosterone might play a significant role in the adult-like development of muscle strength in late adolescence, since the testosterone levels, which are reported to reach adult levels during late adolescence (Khairullah et al., 2014), are associated with the fiber type II population (Dux et al., 1982; Krotkiewski et al., 1980) and therefore indirectly with muscle specific tension and muscle strength (Rowe and Goldspink, 1968; Witzmann et al., 1983;

Powell et al., 1984; Bodine et al., 1987; Kanda and Hashizume, 1992; Larsson and Moss, 1993; Stienen et al., 1996; Bottinelli et al., 1996). Results from cross-sectional studies demonstrated that children have higher antagonistic co-activation compared to adults (Frost et al., 1997; Lambertz et al., 2003; O'Brien et al., 2010b). Joint stability can be provided by the aid of co-contraction, but the agonistic muscle energy cost of exercise will increase by greater antagonistic co-contraction (Frost et al., 2002), and net force output will be reduced (Radnor et al., 2018). In the present study, the analysis of the data demonstrated that there were no differences among age groups in antagonistic co-activation, confirming the existing literature which states that under maximal isometric contractions there are no age-related differences in antagonistic co-activation (Falk et al., 2009a, b).

The result of this thesis confirms the existing literature, which states that muscle strength increases during maturation with the most prominent increases occurring in early adolescence, while it reaches adult-like levels in late adolescence. However, while muscle strength follows the morphological development of the muscle (VL thickness), architecture changes in muscle pennation, which normally accompany the muscle strength development (Kawakami et al., 1995; Aagaard et al., 2001; Mersmann et al., 2017a), are detectable only in young adults and not in the younger groups. Nonetheless, radial fiber growth which is a prerequisite for the muscle strength development and hypertrophy (Mersmann et al., 2017a), might be plausible during adolescence without detectable changes in pennation angle (see **chapter 10.1**). The lack of muscle strength differences between late adolescents and young adults, despite the muscle morphology differences, might be attributed to adult-like development of the muscle quality (specific tension). Nevertheless, the depiction of muscle architecture by an MRI, would provide a clearer picture of the mechanism of the muscle strength development during maturation. However, in this study, this technique was not used.

As with muscle morphology, even though hormone effects are outside the scope of this research, would have a significant impact on muscle strength during maturation. In the present study, a high correlation between muscle strength and muscle thickness was shown ($r = 0.766$, $p < 0.001$), and these data are following earlier studies that demonstrated an increase in muscle strength in parallel with muscle morphometrics, such as muscle thickness, as well as with muscle CSA, volume and PCSA (Kanehisa et al., 1995a, b; Kubo et al., 2001, 2014a; Tonson et al., 2008). Thus, it is not surprising that during adolescence, muscle strength is consistent with the onset of activity within the hypothalamo-pituitary–gonadal axis leading to a large increase in the production of androgens (for males) resulting in a significant increase in growth GH secretion and an increase in serum IGF-I concentrations (Giustina, 1997; Gibney et al.,

2005; Murray and Clayton, 2013). It is widely known form the bibliography that testosterone, GH and IGF-I secretion are responsible for the radial (addition sarcomeres in parallel) and longitudinal growth (addition sarcomeres in series) (Cheek et al., 1971; Allen et al., 1999; Grohmann et al., 2005; Atkinson et al., 2010) resulting to muscle-morphology augmentation (O'Brien et al., 2010a; Franchi et al., 2017).

10.3 Maturation effects on tendon stiffness

In the literature, there is only sparse information regarding tendon stiffness development during adolescence. The plethora of the information originates from cross-sectional studies comparing younger groups (5–14 years) to adults in order to extract information about the development of the tendon mechanical properties, leaving the in-between maturational passage (adolescence) well unexplored. This study is one of the few that investigates the tendon stiffness development emphasized to the adolescence (12–18 years). It is well-known from the existing literature that tendon stiffness increases during maturation (Kubo et al., 2001, 2014b; O'Brien et al., 2010c; Waugh et al., 2012; Mogi et al., 2018). The data of the present study suggest an increase in tendon stiffness during adolescence; however, the differences between late adolescence and young adults were not significant. The results of this thesis confirm earlier studies reporting that the major development in tendon stiffness during maturation seems to occur from early to late adolescence (Mogi et al., 2018). The principal changes in the femur length, body height and body mass also appeared at this stage, which points to an analogous development of the functional and mechanical muscle-tendon properties with the skeletal system (**Table 1**). Tendon stiffness could be affected by its material properties (Young modulus's), morphology (cross-sectional area: CSA) and resting length. For instance, if a tendon hypothetically had constant values of CSA and Young's modulus, an increase in its resting length would lead to a decrease in its stiffness and vice versa (Butler et al., 1978; Enoka, 2008). Data analysis of the present study demonstrated that there were no differences in tendon resting length among age groups (**Table 2**). These findings are consistent with earlier studies suggesting that tendon resting length does not increase during maturation and that it already reaches an adult-like development in early adolescence (Kubo et al., 2014a, b; Mogi et al., 2018), indicating that the increase of tendon stiffness during maturation observed in this study might be due to tendon morphology and material properties development. In fact, studies by means of ultrasonography suggest an increase in tendon stiffness in parallel with tendon CSA and Young's modulus during maturation(O'Brien et al., 2010c; Waugh et al., 2012). However, it is reported that ultrasound based-assessment does not provide reliable results and objectivity

for the tendon CSA (Ekizos et al., 2013) and, consequently, this would result in erroneous estimation of tendon material properties (Young's modulus). Therefore, this study did not use ultrasound technique in order to investigate the tendon CSA and Young's modulus, hence, questions remain even today regarding the development of the morphological and material properties of the tendon and the link of these properties with the increase of tendon stiffness during adolescence. As tendon adapts to mechanical loading (Arampatzis et al., 2007a, 2010; Couppé et al., 2008; Bohm et al., 2014, 2015), buildups in mass and muscle strength could increase the stiffness due to increased loading during the daily weight-bearing tasks and the augmented muscle force (Waugh et al., 2012). Data analysis of this thesis demonstrates a significant correlation between tendon force and stiffness ($r = 0.631$, $p < 0.001$, **Figure 26A**). In fact, it is widely accepted that maximum muscle strength (Muraoka et al., 2005), or more precisely the force exerted on the tendon during maximum isometric contractions, is associated with tendon stiffness (Arampatzis et al., 2007c; Seynnes et al., 2009) and is an important mediator for tendon adaptation in both adults (Seynnes et al., 2009) and during childhood development (Waugh et al., 2012). Therefore, it seems likely that the similar tendon stiffness between late adolescents and young adults is due to the absence of significant differences in their tendon force. As with muscles, tendinous tissue may also be subjected to hormonal effects. The maturation passage from early to late adolescence is characterized by activation of the hypothalamo-pituitary–gonadal axis resulting in to increase of testosterone, growth hormone (GH), and insulin-like growth factor (IGF-I) (Murray and Clayton, 2013). It has been reported that levels of these hormones are associated with tendon stiffness (Marcus et al., 1990; Inhofe et al., 1995; Boesen et al., 2014), indicating that, in terms of hormonal development, maturation might be a unique factor in tendon stiffness adaptation besides the increase of mechanical loading.

From the findings of this thesis and the existing literature, it could be concluded that the major tendon stiffness development occurs from early to late adolescence. However, as a person matures towards later stages of adolescence, the already developed muscle strength will apply to the tendon a mechanical loading environment high enough to modulate an adult-like tendon stiffness. This development in tendon stiffness, according to ultrasound assessments, will be attributed to changes in tendon Young's modulus and CSA (O'Brien et al., 2010c; Waugh et al., 2012). However, as it was mentioned before, ultrasonography does not provide reliable results for the measurement of tendon CSA (Ekizos et al., 2013), which was the reason why in the present study this specific technique was not used to investigate the underlying mechanisms, such as CSA and Young's modulus, of the increased tendon stiffness during adolescence.

10.4 Training effects on muscle morphological and architectural properties

In the literature, there is no satisfactory evidence regarding the training effects on muscle morphology plasticity during adolescence. The sparse literature of late adolescence is followed by the almost non-existent literature in early adolescence. More importantly, even to this day, information regarding the underlying mechanisms of training-induced muscle hypertrophy in early adolescence is missing from the literature. The adolescence period is crucial because it is characterized by accelerated hormonal changes which can increase the adaptations rates of muscle morphology due to training (August et al., 1972; Martha et al., 1989; Vermeulen et al., 1970; Viru et al., 1999). This is the first study investigating differences in muscle morphology and architecture properties, such as fascicle length and pennation angle, between athletes and untrained controls in early adolescence, and compares the training-induced adaptations during different maturation statuses. As it has been mentioned in the previous chapter (**10.1**), muscle morphometrics by means of ultrasonography are good predictors for the muscle size (Aggeloussis et al., 2010; Giannakou et al., 2011; Marzilger et al., 2018). For instance, muscle thickness can indicate its morphological properties (i.e., volume or ACSA; Miyatani et al., 2002; Esformes et al., 2002; Giles et al., 2015) and there exists an association between the pennation angle and the muscle PCSA (Kawakami et al., 1995; Aagaard et al., 2001), respectively. Analysis of the data revealed higher muscle thickness in athletes compared to untrained counterparts, indicating athletic training-induced muscle hypertrophic results in all age groups (**Figure 24A**). The findings of this thesis confirm the existing literature in which late volleyball adolescent athletes demonstrated greater vastus lateralis (VL) thickness compared to untrained cohorts (Mersmann et al., 2016, 2017b), and 8 weeks of body mass-based squat intervention increased thickness at the thigh anterior in early adolescence (Takai et al., 2013). However, this is the first study investigating the muscle architecture changes due to athletic training in early adolescence. Interestingly, fascicle pennation angle, which is normally in line with the muscle hypertrophy and indicates the addition of sarcomeres in parallel (Kawakami et al., 1993, 1995; Aagaard et al., 2001; Mersmann et al., 2017a), seems not to be affected by the athletic training in all age groups (**Figure 24B**). In the literature information regarding adaptation in muscle pennation due to training is conflicting (Ema et al., 2016). The analysis of the data in the thesis is in line with Albracht and Arampatzis (2013) and Hoffrén-Mikkola et al. (2015) who reported no changes in muscle pennation during the intervention protocol, despite the increase in muscle thickness observed in some cases (Hoffman et al., 2012). However, more recent findings demonstrated greater muscle pennation of vastus lateralis (VL) muscle between late adolescent volleyball athletes and untrained controls (Mersmann et

al., 2016, 2017b). It is well-known, that different kinds of training regimes may result in the different adaptation of the pennation angle. Alegre et al. (2006) reported pennation angle increase in VL after isometric knee extension training at a long muscle length (90° flexion of knee joint) for 8 weeks but did not after training at a short muscle length (50° flexion of knee joint). Thus, it may be suggestive that during training muscle length could influence the adaptations of pennation angle in the athletic groups and could further explain the lack of differences in pennation angle observed between athletes and non-athletes in this thesis (**Figure 24B**). Even though ultrasonography is a reliable method for the assessment of muscle morphometrics, the reliability between them differs. For instance, muscle thickness has higher reliability compared to pennation angle (0.96 vs 0.86 respectively; Aggeloussis et al., 2010; Giannakou et al., 2011; Marzilger et al., 2018). Moreover, in this thesis, the pennation angle estimated by the reference fascicle and the angle of it with the deeper aponeurosis which was delimited manually by 3 reference points in order to define a straight line. Marzilger et al. (2018) observed that variations in the aponeuroses slope could affect the estimation of the pennation angle; indicatively, 1° changes in aponeuroses slope could increase the pennation angle in the order of 8.3%. Therefore, methodologically, due to the slightly lower reliability of pennation angle compared to muscle thickness by the ultrasound assessment, as well as due to the human factor, variations regarding the definition of the aponeuroses slope, which eventually will affect the estimation of the pennation angle, may be some of the reasons that led to lack of differences in pennation angle between athletes and non-athletes observed in this thesis. Further analysis in architecture longitudinal adaptation demonstrated that normalized fascicle length unaltered by the athletic training (**Figure 24B**), confirming the existing literature reported that there were no differences in normalized fascicle length between athletes and no-athletes in late adolescence (Mersmann et al., 2017b), as well as lack of fascicle length adaptation after 14 and 11 weeks of training (Albracht and Arampatzis, 2013; Hoffrén-Mikkola et al., 2015). It is well established that the remodeling of muscle architecture in response to training is load depended (Franchi et al., 2017). For instance, it is well-known that eccentric loading increases the fascicle length (Schoenfeld, 2010; Franchi et al., 2014, 2017), while concentric loading increases the angle of pennation (Franchi et al., 2014, 2017). Therefore, it may be suggestive that training loading stimuli was not the prerequisite that would provide the longitudinal adaptation to muscle fascicle in athletes examined in this thesis. The statistical analysis has shown a lack of interaction between maturation and athletic training in all morphological variables. In simple words, this means that muscle hypertrophy adaptations due to athletic training will be similar between the age groups and will not be influenced by their maturation status. A more detailed

explanation of this phenomenon will be described in the chapter (**10.8**). Therefore, it could be concluded that beside the greater average of the muscle morphology, the course of its development will be similar in athletes compared to non-athletes. However, it seems that the greater muscle morphology of athletes will not be underlying by changes in fascicle length or pennation angle. The lack of muscle architectural adaptation is hard to interpret. However, this thesis findings are in line with studies who reported no architecture changes despite the increments in PCSA, CSA and the muscle thickness observed after the short and long term training protocols (Raj et al., 2012; Scanlon et al., 2014).

10.5 Training effects on muscle strength

In the literature, there is an extensive information about the increase of muscular strength adaptations due to athletic training during adolescence. However, evidence regarding the underlying mechanisms of the training-induced muscle strength gains, such as muscle hypertrophy and architecture properties, is missing from the literature on early adolescence and there is only scarce on the late adolescence. As with the non-athletes, there was a marked increase from early to late adolescence in muscle strength of the athletes by 62%; however, athletes were significantly stronger compared to non-athletes. The findings of this thesis indicate that superimposed loading in the form of athletic training promotes muscle strength gain beyond that of maturation (Naughton et al., 2000; Lloyd et al., 2014), and are consistent with the literature reporting that different types of training regimes induce increases in muscle strength in athletes and non-athletes irrespective of age (Komi et al., 1978; Pfeiffer and Francis, 1986; Ramsay et al., 1990; Faigenbaum et al., 1996; Gorostiaga etal., 1999; Falk and Eliakim, 2003; Kanehisa et al., 2003; Hoff and Helgerud, 2004; Szymanski et al., 2004; Tsolakis et al., 2004; Christou et al., 2006; Channell and Barfield, 2008; Gabbett et al., 2008; Santos and Janeira, 2008; Chelly et al., 2009; Takai et al., 2013; Lloyd et al., 2014; Meylan et al., 2014; Sarabia et al., 2015; Mersmann et al., 2016, 2017b; Moran et al., 2017). As it has been mentioned in the chapter (**10.1**), the morphometrics of muscle thickness and pennation angle are reliable indices of muscle morphology such as muscle volume or cross-sectional area (CSA), and physiological cross-sectional area (PCSA), respectively (Kawakami et al., 1995; Aagaard et al., 2001; Miyatani et al., 2002; Esformes et al., 2002; Giles et al., 2015). In the present study, there was a high correlation between muscle strength and muscle morphology, such as muscle thickness and pennation angle in both athletes and non-athletes ($r = 0.766$ and $r = 0.383$, $p<0.001$ respectively; see **appendix A1 & A2)**. These findings confirm the literature stating that muscle strength is highly associated with muscle hypertrophy (Seynnes et al., 2007).

However, while muscle strength increased in line with muscle thickness in athletes, pennation angle, which has frequently been shown to increase in line with muscle strength and in parallel with muscle thickness (Kawakami et al., 1993, 1995; Ichinose et al., 1998; Aagaard et al., 2001; Mersmann et al., 2017b) or to differ between athletes and untrained controls (Mersmann et al., 2016), was not affected by athletic training in this study. Nevertheless, some investigations have reported an increase in muscle strength after an intervention period with no concomitant changes in muscle architecture (Albracht and Arampatzis, 2013). The findings in this thesis are in line with Raj et al. (2012) and Scanlon et al. (2014) who reported gains in muscle strength in parallel with muscle hypertrophy after a training period, but without any kind of alteration in fascicle length or pennation angle. Antagonistic co-activation has been reported to reduce due to superimposed mechanical loading (Mersmann et al., 2017b), however, this study demonstrated that athletic training did not promote any change in antagonistic co-activation (**Table 2**). As it has been mentioned in the chapter (**10.4**), the reliability of pennation angle by means of ultrasonography is lower compared to other morphometrics, such as muscle thickness (Aggeloussis et al., 2010; Giannakou et al., 2011; Marzilger et al., 2018). Moreover, the pennation angle values could be influenced by the human factor, since the delineation of the aponeuroses slope, which has been done manually (see **chapter 7.2**), can affect the estimation of the pennation angle (Marzilger et al., 2018). Additionally, the length of the muscle where the superimposed mechanical loading was exerted during training might affect the adaptation of pennation angle (see **chapter 10.4**; Alegre et al., 2006). Thus, it may be suggestive that the increase in muscle strength with no such relative changes in pennation angle observed in this thesis is attributed to methodological issues and training conditions.

In conclusion, the increase in muscle strength due to athletic training is related to the corresponding increase in muscle hypertrophy (VL thickness); however, muscle strength will not be followed by the corresponding changes in the architecture of the muscle during training, which may be due to methodological issues and training conditions that could affect the estimation and the adaptations of the pennation angle respectively. Just like with the muscle hypertrophy, there was no interaction between athletic training and maturation, indicating that the course of muscle strength development will be similar in athletes compared to non-athletes. However, the lack of this interaction will be described in more detail in the chapter (**10.8**).

10.6 Training effects on tendon stiffness

A clear impact on athletic training as well as a marked increase from EA to LA without showing any disparities between LA and YA, correspondingly to muscle strength, was found in normalized patellar tendon stiffness and patellar tendon stiffness (**Figure 25A**). It is a well-known fact that via training tendon stiffness regarding adults can be increased by superimposed mechanical loading (Bohm et al., 2014). Taking into account the associated information that exists in the literature, the present study consists the first attempt to investigate the training effects on patellar tendon mechanical properties in EA (12–14 years), via comparison of athletes and non-athletes. There is an agreement between this thesis results and earlier studies stating a greater patellar tendon stiffness in volleyball athletes regarding the stage of late adolescence when they are compared to untrained controls (Mersmann et al., 2017b), and furthermore display the responsiveness of the tendon to mechanical loading at this particular age. It is provided by the present study supplementary proof that tendons actually adapt to augmented mechanical loading and improve their stiffness already in EA. In the present study, it is clear that the average enhancement in patellar tendon stiffness because of training reached ~25% concerning EA partakers, a phenomenon which can be interpreted as an evident and functionally relevant adaptation. Studies employing magnetic resonance imaging (MRI) showed that a probable mechanism of the tendon stiffness responsiveness throughout the period of training, can be ascribed to the growth of tendon cross-sectional area (CSA), and the Young's modulus increase (Arampatzis et al., 2007a; Heinemeier and Kjaer, 2011; Bohm et al., 2014). Nevertheless, the tendinous tissue imaging, in the current thesis, was practicable only via ultrasound, which is prevalent that such technique cannot yield trustworthy results concerning the tendon CSA.

10.7 Imbalances between muscle and tendons

According to the results of this present study, the impact of the age on the tendon strain through maximum contractions with a substantially higher tendon strain values in adults when they were compared to EA, signifies an unbalanced increase in tendon force compared to stiffness with increasing age. Moreover, despite not being statistically significant, the strain values through the maximum isometric contractions in addition to the regression model residuals, which predict tendon stiffness by tendon force, were in tendency greater regarding athletes ($p = 0.072$ and $p = 0.098$, respectively; **Figures 25C** and **26B**, respectively). While analyzing the individual strain values that were reached throughout the maximum isometric contractions in every investigated age group (**Figure 28**), it is noteworthy that athletes rather

than individuals were prone to reach strain magnitudes higher than 9%, suggesting muscle-tendon unit imbalances and consequent high mechanical tendon demand. What is more, the incidence of strain values, which is over than 9%, has risen from EA to YA regardless of activity status. The above interpretations endorse the idea that both maturation along with athletic training could result in the increased prevalence of imbalances between tendon stiffness and muscle strength. Numerous studies (Lian et al., 2005; Zwerver et al., 2011; Cassel et al., 2015b; Simpson et al., 2016) stated an analogous phenomenon of the tendinopathy prevalence in connection with athletic training and maturation (i.e., increased prevalence from EA to YA and in athletes).

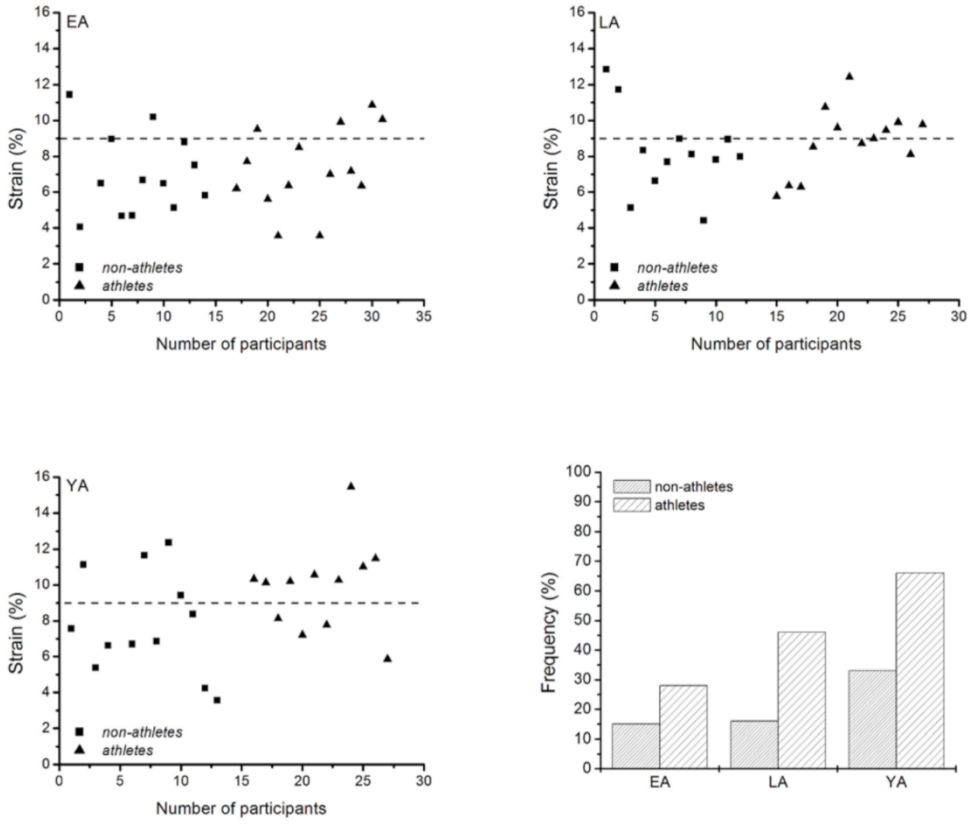

Figure 28 | Individual patellar tendon strain values during maximal isometric contraction of non-athletes (squares) and athletes (triangles) in early adolescent (**A**; EA), late adolescent (**B**; LA) and young adulthood (**C**; YA), and frequency of cases with strain values greater than 9% for each group (**D**)

An overall tendon strain increase has proved to rise the local tissue strains at the common site of structural degeneration in patellar tendinopathy (Lavagnino et al., 2008). Furthermore, an association between the tendon strain and the structural integrity of it has lately been found

concerning basketball players in their adolescence, along with an increased strain and damaged tendon microstructure in a subgroup with tendinopathy (Mersmann et al., 2019). Therefore, between tendon stiffness and muscle strength development during maturation along with athletic training, while tendon repeatedly undergoing high strain levels, imbalances could be a risk factor in the overuse-induced tendinopathy etiology as well as the common background tendinosis or the quite scarce tendinitis. What is more, a hypothesis could be made regarding a tendon strain increase through muscle contraction resulting in maltracking of the patellar, redistribution of loads at the patellofemoral contact area and, consequently, patellofemoral pain (Powers et al., 2017), a phenomenon common in adolescents too (Rathleff, 2016). Although the association of musculotendinous imbalances with mechanisms of overuse injury justifies experimental proof, the incorporation of specialized training, from a precautionary standpoint, which could increase tendon stiffness and help support a balanced adaptation between tendon and muscle, may be a significant approach for practicing athletics. An efficient training stimulus for the adaptation of the tendon has been indicated by former research, which is an amalgamation of high loading magnitude, a suitable loading duration per repetition (i.e., 3 s), and recurring loading (Arampatzis et al., 2007a, 2010; Bohm et al., 2014). As for children, the development of resistance training competency ought to pave the way for the high loads application (Lloyd et al., 2014). However, it has already been indicated that precise tendon training combined with the exercise recommendations aforementioned can be successfully implemented to children so as to induce an improvements in their tendon stiffness (Waugh et al., 2014). The review of Mersmann et al. 2017a provides us with plenty of details concerning tendon trainability. “It has been reported that a training program comprised of five sets of four muscular contractions as well as an intensity of 85% to 90% of the isometric voluntary maximum in addition to muscle contraction through exercise or just a movement, which could induce to the tendon a high magnitude of the strain of 3 s duration can be a sufficient training stimulus to further promote tendon stiffness, hinder any imbalances amid muscles and tendon or tendinopathy, both in adolescents and in children (Mersmann et al., 2017a)”. What is more, in the exact same review, it has been suggested that “the mode of the muscle contraction is not a limiting factor (Kjaer and Heinemeier, 2014; Bohm et al., 2015). However, it must be taken into account that throughout a usual training dynamic protocol enabling eccentric-concentric contraction, the required tendon force to promote tendon stiffness transpires merely between angles 60º and 100º of knee flexion in a parallel squat (0º = full extension) owing to the alteration of gear ration throughout movement (Flanagan et al., 2012; Penailillo et al., 2015). Thus, it is recommended that the movement duration be increased (e.g., to ~6 s) while a large

range of motion is applied during the exercise. Isometric training should be carried out close or at optimal angles so that the contracting muscles are capable of potential force generation (i.e. ~60º knee flexion for patellar tendon training or ~10º ankle dorsiflexion and extended knee for the training the Achilles tendon) and it is considered advantageous as training could be under control rather effortlessly in relation to duration and intensity (Mersmann et al., 2017a).

10.8 Interaction between maturation and athletic training

Concerning present bibliography, this study is thought to be the first one to shed light on the interaction between athletic training and age in both tendon and muscle properties during adolescence. It was put forward as an effect of athletic training on the growth of muscle and tendon properties throughout adolescence owing to the level of androgenic hormones (e.g., testosterone), which stimulates protein synthesis and, hence, muscle hypertrophy (Lundberg, 2017; Murray and Clayton, 2013) is diverse in every phase of maturation and could be further influenced by athletic training (Kraemer et al., 1992; Tsolakis et al., 2004; Zakas et al., 2007). Lack of any age-by activity interaction manifests that regardless of the marked discrepancies of tendon stiffness and muscle strength, the progress of these muscle-tendon unit properties with maturation is parallel to athletes compared to controls. This, however, is contradictory to previous suppositions (Mersmann et al., 2017a), and to the deduction of an earlier met-analysis (Behringer et al., 2010; Moran et al., 2017) suggesting that the muscle strength trainability and the anabolic response of the muscle to mechanical stimuli could rise throughout adolescent maturation, a process which is considered to influence the course of muscle-tendon development with escalating differences between athletes and controls with age. Without a shadow of a doubt, growth hormones and sex affect tendon and muscle protein metabolism (Rooyackers and Nair, 1997; Hulthen, 2001; Doessing et al., 2010; Hansen and Kjaer, 2014) and additionally, it seems that akin to systemic basal levels of the aforementioned hormones (Murray and Clayton, 2013), the endocrine response to exercises increases via maturation too (Vingren et al., 2010). Nonetheless, studies that directly made a comparison to the results and consequences of training in states of low or high concentrations of circulating endogenous hormones came up with no differences concerning the intramuscular anabolic signalling (Spiering et al., 2008), acute protein synthesis (West et al., 2009), or the morphological and local functional reaction to recurring training sessions (West et al., 2010). Though the maturation effects of the endocrine system on tendon plasticity are not widely known, any advantageous impacts of the growth hormone levels and the augmented systemic testosterone could counterbalance other processes which lessen the tissue regeneration of the tendon core

just before the end of the adolescence period (Heinemeier et al., 2013). Having taken the above findings into account, it could be argued that it is highly unlikely that the local responses of the muscle-tendon unit to training are a sole function of the maturation-related changes of the basal levels and load-induces secretion of systemic hormones. However, in view of the fact that there are limits in a cross-sectional comparison, the alterations of the sensitivity of the muscle-tendon unit to mechanical stimulation from childhood to adulthood infer that further research is required.

10.9 Limitations

Lacking in control for biological age could prove to be a curtailment of the current study. Nevertheless, the evaluation of the skeletal age entails exposure to radiation and to the professed invasiveness too, the precision of grading the secondary gender characteristics being quite low (Schlossberger et al., 1992; Taylor et al., 2001; Slough et al., 2013), which could be a particular difficulty regarding small sample comparisons. Evaluation of maturity, which is based on anthropometric data, can serve as a tempting alternative. These predictions, though, could not justify the substantial variation in anthropometry at an analogous period of maturity, nonetheless. Since athletes from sports in which body height is a selection criterion (e.g., basketball and volleyball) were included and consequently the athletes of this study were actually considerably taller if compared to the non-athlete controls, a more advanced level of maturity in athletes would be suggested by any prediction based on anthropometry. Whether or not that could not re-capture in agreement the real differences in the biological age, differences in maturity cannot be excluded. Whereas maturity-related discrepancies regarding physical characteristics are reported to have been mostly eradicated in non-athletes as well as athletes aging 16–18 years (Malina et al., 2004, 2013), the differences noticed between non-athletes and athletes must be construed with caution taking into consideration the EA group. Contrary to that, it is highly unlikely that the specific differences in calendric age between age groups could not illustrate the diverse stages of maturity. Hence, to my way of thinking, the lack of assessment and evaluation of actual maturity cannot affect and influence in any way our conclusions, taking into account the impacts of maturation. To conclude, because of inherent limitations of cross-sectional studies, further longitudinal study and research is mandatory to substantiate the development of the musculotendinous system and its further interaction with mechanical loading shown by data in this thesis. Furthermore, because the acquisition of the MRI scans could not be viable and since it has already been proven scientifically, the valuation of the tendon cross-sectional area (CSA) data that use ultrasound devices, display low reliability

(Ekizos et al., 2013). The current study cannot attend to and address the research question existing thus far on the subject of the underlying mechanism bringing about the increase in tendon stiffness in athletes (maturation) and in non-athletes too. In addition, further information would be provided by an MRI concerning the muscle physiological cross-sectional area (PCSA), a morphological property which can portray in the best possible way the muscle radial expanse because of the adding of sarcomeres in parallel (Aagaard et al., 2001; O'Brien et al., 2010a). Nonetheless, pennation angle and muscle thickness were used in the present study, in which the former ones were in the form of morphometric indexes of muscle hypertrophy (Miyatani et al., 2002, 2004; Franchi et al., 2018) and viable to be given access via ultrasonography (Aggeloussis et al., 2010; Giannakou et al., 2011; Marzilger et al., 2018). In order for the tendon force estimation to be more convenient, several methodological assumptions were applied in a plainer mode. An example is cited to support the previously mentioned theory. The calculation of the tendon force occurred form measurements carried out on joint moments exclusively in the sagittal plane. Thus, the analogous tendon force components having stemmed from the generated-quadriceps moments through contraction in frontal and transverse plane alike must be neglected (Seynnes et al., 2015). However, the consequent underestimated-tendon force is estimated to be small. Last but not least, it is widely acknowledged that the estimate of the total strain using ultrasound devices being appropriate only for use in the single plane, are able to hardly reflect the reaction to complex three-dimensional load allocation of the tendons throughout loading (Lersch et al., 2012; Khodabakhshi et al., 2013). Even though applying the current technique the strain exerted on the tendon at the local level could not be inspected, there is supporting proof in the literature displaying the connection between increased local and total strain, especially in the regions where a tendon is susceptible to injuries (Butler et al., 1990; Pearson et al., 2014). Concerning this matter, it is highly expected that the imbalances between total tendon strain and tendon force being confirmed in the current thesis, may well symbolize the advanced mechanical demand placed on the tendon by the working muscle.

11 Conclusion

To conclude, evidence is provided by the current study that apart from higher levels of muscle strength, tendon stiffness and muscle thickness concerning athletes, the development of the properties of the knee extensor muscle-tendon unit from early adolescence period to adulthood seems to be analogous in athletes and non-athletes controls, observing the most significant changes occurring during the period of early and late adolescence. Even though muscle thickness tends to further increase its size throughout maturation, there are divergences amongst age groups in the muscle morphology development fundamental mechanisms, such as pennation angle and fascicle length. According to the results, it is prevalent that the muscle thickness growth during adolescence is chiefly dictated by the fascicle length alterations and not only when reaching adulthood does pennation angle tend to be a muscle thickness-modulation factor. However, absence of muscle pennation growth through adolescence does not automatically leave out the muscle fiber augmentation, which is accredited to the muscle pennation increase owing to the adding of sarcomeres in series, and therefore resulting in muscle morphology development (Kawakami et al., 1993, 1995; Aagaard et al., 2001;). It could be that throughout adolescence, the muscle longitudinal development following the bone growth (Nordmark et al., 2009), creates space for the addition of parallel sarcomeres along the length of the aponeurosis (O'Brien et al., 2010a). And it is only later leading up to adulthood that the longitudinal development of bone reaches, during the late years of adolescence, adult-like characteristics (Feldesman, 1992) and as a result, muscle length likewise and therefore the muscle pennation may apply a training-induced mode at which point the additional attachment space is acquired by the parallel sarcomeres causing rise in pennation angle (Alexander and Vernon, 1975; Kawakami et al., 1995; O'Brien et al., 2010a). Nonetheless, this particular type of development in muscle architecture during the period of adolescence can be perceptible only by MRI assessment (O'Brien et al., 2010a), and no such technique was applied in the current research. The literature is confirmed by the results that muscle strength relies on muscle morphometrics (Aagaard et al., 2001; Giles et al., 2015). While moving on to the tendon properties, tendon stiffness undoubtedly displayed that, it increases along with maturation. Nevertheless, during a person's process towards maturity and while being at the last stages of adolescence, it obtains adult-like tendon stiffness. As the stiffness development depends on muscle strength, and more specifically on the force which is applied on the tendon throughout maximum muscle contraction (Arampatzis et al., 2007c; Seynnes et al., 2009; Waught et al., 2012; Bohm et al., 2014), the adult-like muscle strength development of the late adolescent would provide a mechanical loading environment which would be adequate to promote their

tendon stiffness analogous to that of an adult. The morphological and material properties of the tendon were not investigated in this thesis due to the fact that ultrasound cannot provide reliable results regarding the assessment of patellar tendon morphology (Ekizos et al., 2013). Therefore, examining and investigating the underlying mechanisms behind tendon stiffness growth was not feasible. It has been established that superimposed mechanical loading, as athletic training is an adequate stimulus, which could promote muscle strength and morphology along with tendon stiffness beyond the ones of maturation. Above all, this current study bridges the current knowledge gap concerning the muscle hypertrophy in the early stages of adolescence as well as its underlying mechanisms. It appears that athletic training did not serve the use of an adequate superimposed mechanical loading stimulus to promote muscle architecture adaptations. While these observations seem hard to interpret, they are in conformity with the studies which stated no architecture alterations notwithstanding the increase in physiological-cross sectional area (PCSA), cross-sectional area (CSA) and muscle thickness detected after a long- and short-term training protocols (Raj et al., 2012; Scanlon et al., 2014). The imbalances frequency in the quadriceps femoris muscle-tendon unit seems to increase along with athletic training and age throughout the stages of adolescence reaching adulthood and leads to an increased mechanical demand for the patellar tendon. Thus, certain intervention protocols regarding athletic training practice are suggested to reinforce a balanced adaptation between tendon and muscle.

12 Practical implications

There are several factors such as the development of the mechanical, morphological along with the functional properties of the muscle in addition to the tendon mechanical properties during maturation period together with the development of myotendinous properties throughout training and the existence on non-uniform adaptation in consequence of highly imposed mechanical load both during athletic training and maturation, affect movement performance and result in the high rate of occurrence risk of injury. The findings proved the lack of interaction between maturation and athletic training, which are in contrast with earlier findings that the trainability of muscle morphological and functional properties increase with age (Behringer et al., 2010; Moran et al., 2017). Consequently, analogous training gains would be anticipated by a trainer regarding muscle strength and morphology throughout adolescence showing no signs of advanced progress of these properties owing to decisive periods "window-period of opportunity" throughout the developmental years, during which time both children and adolescents are more susceptible to training-induced adaptation (Viru et al., 1998, 1999; Lloyd and Oliver, 2012). The muscle strength rise, which is monitored during maturation throughout adolescence period along with its subsequent improvement in adolescent athletes because of training, could be associated with enhanced athletic performance in both groups, as motor skills like sprinting, throwing tasks, jumping and cutting would be positively influenced by such an improved muscle functional property (Weyand et al., 2000; Wisloff, 2004; Hoff and Helgerud, 2004; Chelly et al., 2009; Lloyd et al., 2014; Suchomel et al., 2016). At the same time, the increase of muscle morphology and more specifically, muscle thickness, could allow the larger capacity for the production of power by the muscles (Lee et al., 2018). There have been studies indicating that result of the increase of patellar tendon stiffness, regarding both stages of maturity (e.g., non-athletes and athletes), could, in all probability, facilitate the rate of force development (Waugh et al., 2013). And taking into account the scientifically established association of the improved-tendon stiffness with the increasing muscle strength during movement, the improvement in the mechanical property of the tendon is such that it may permit muscle's fascicle to further function within the optimal range (Stenroth et al., 2015). Nevertheless, the most significant finding of the current thesis is the imbalance regarding tendon loading-capacity and the adaptation of the muscle strength, with the potential of leading, as an overuse syndrome, to an increased risk of tendon injury. The last-mentioned evidence is of utmost importance since if this finding is put into practice in real life situations, it could mean that, through the period of maturation and regarding the athletic population, throughout muscle work during diverse movement tasks at a given relative contraction, will make the tendon prone

to increase to increase mechanical demand. Actually, Wang et al. 2013 illustrated that the exposure of the tendinous tissue to cyclic loading leading to a high magnitude of strain, the peril of the tendon creating cumulative microtrauma, on top of resulting in failure, can be increased. Consequently, it stands to reason that the hypothesis that through training and maturation, the integrity of the tendons is in jeopardy to be compromised by owing to the fact that tendon adaptations, in relation to non-uniformity, do not coincide with those of the muscle. As the fatigue of the tendon can be ascertained by the initial strain, as well as by the cycle of loading (Wren et al., 2003; Fung et al., 2009; Legerlotz, 2013), it seems that during both maturation and athletic training, whether chronic or episodic, because of the imbalances in the muscle-tendon unit, the quadriceps muscles during contraction will subject the patellar tendon to soaring levels of strains resulting in tendon microstructure impairments and deterioration, which can ultimately be a key factor in predisposed overuse-tendinopathy (Mersmann et al., 2019; Lavagnino et al., 2008), in addition to further tendon injuries like tendinitis and tendinosis. An experimental intervention study illustrated that a training protocol which would entail five sets of high intensity muscle contraction and movement–contraction duration providing 3 seconds of high magnitude of strain (Mersmann et al., 2017a), should be the most suitable intervention protocol to put into practice to athletes training as well be implemented to non-athletic population in which a non-uniform muscle and tendon improvement and development is shown.

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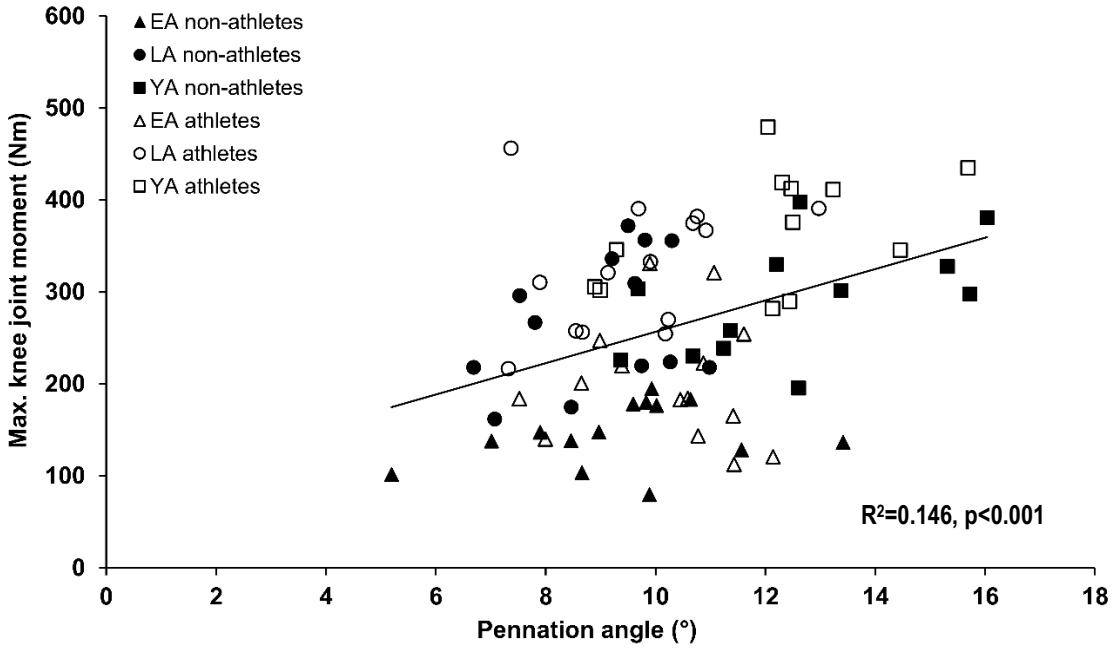
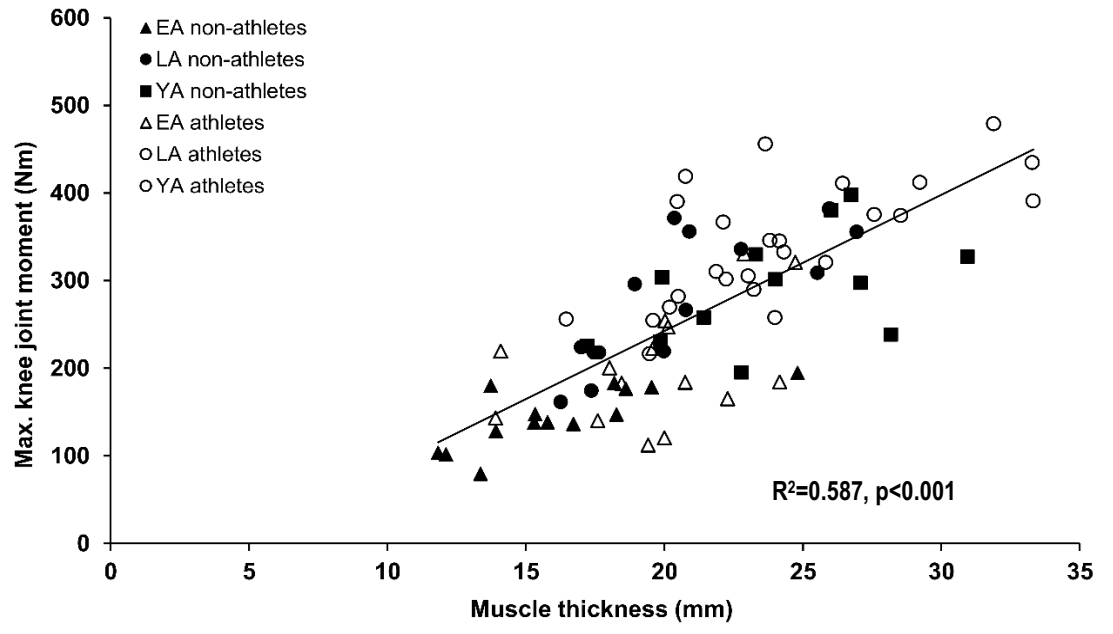
Appendix



A.1: Relationship of pennation angle of the vastus lateralis with the maximum knee joint moment in athletes and non-athletes in EA, LA and YA



A.2: Relationship of muscle thickness of the vastus lateralis with the maximum knee joint moment in athletes and non-athletes in EA, LA and YA

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Eidesstattliche Erklärung | Statutory declaration

Hiermit erkläre ich verantwortungsbewusst, dass diese Dissertation das Ergebnis einer unabhängig-persönlichen wissenschaftlichen Arbeit ohne den Beitrag externer Unterstützung ist. Ich erkläre ausdrücklich, dass ich für die Unterstützung meiner Arbeit keine anderen Quellen als die angegebenen verwendet habe und dass ich das verwendete habe Quellenmaterial, das entweder wörtlich odernach Inhalt zitiert ist. Mir ist bewusst, dass ein Verstoß gegen das Prinzip der wissenschaftlichen Unabhängigkeit einen Betrug ist und entsprechend bestraft wird. Meine Doktorarbeit ist einzigartig und wurde nicht zu Promotionszwecken an anderer Stelle eingereicht, angenommen oder abgelehnt. Darüber hinaus erkläre ich, dass ich in meinem gewählten Promotionsfach inzwischen nicht promoviert habe.

I hereby declare responsibly that this dissertation is the result of independent-personal scientific work without the contribution of any external assistance. Iexplicitly state that I have not used for the support of my work other sources than the declared ones, and the used sources material quoted either literally or by content has been marked. I am aware that violation against the principle of scientific independence is tantamount to deception and is punished accordingly. My doctoral thesis is unique and has not been submitted elsewhere for doctoral purposes, accepted or rejected. Furthermore, I declare that I have not in the meantime been awarded a doctoral degree in my chosen doctoral subject.

Berlin, den 15.12.2020

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Georgios Charcharis