The Mechanisms Associated with Quadriceps Deficits

Having established that significant quadriceps strength deficits can occur frequently in individuals with knee injuries and knee OA, there remains the need to discuss some of the mechanisms that may give rise to muscle weakness in these populations. A number of factors that might contribute to quadriceps weakness have been identified including pain, effusion, muscle activation failure, muscle atrophy and immobilization/disuse. Although these mechanisms are discussed individually in the following sections, it should be recognized that they are likely to be inextricably linked in many individuals with knee injuries and knee OA.

Pain

Pain has been shown to have an inhibitory effect on maximum voluntary muscle contraction. This has been demonstrated by Graven-Nielsen, Lund, Arendt-Nielsen, Danneskiold-Samsøe, & Bliddal (2002) who measured maximal isometric quadriceps muscle torque in 8 subjects before, during and after experimentally inducing muscle pain. The authors reported that experimental muscle pain significantly reduced the quadriceps torque produced during voluntary isometric knee extension. However, when electrical stimulation was applied using a twitch interpolation technique, quadriceps torque was produced at levels similar to the control session, despite the muscle pain. Based on these results, the authors argued that experimentally induced pain can reduce torque without compromising the mechanical capability of the muscle, thus implicating a central inhibitory mechanism.

The findings of a more recent investigation also suggested that pain may operate through a central inhibitory mechanism. Farina, Arendt-Nielsen, Merletti, & Graven-Nielsen (2004) examined the effects of muscle pain intensity on motor unit firing rate and conduction velocity by measuring surface and intramuscular EMG activity in the tibialis anterior (TA) muscles of 12 healthy subjects. The subjects performed submaximal isometric contractions of the right TA muscle both before and after pain was experimentally induced using three incremental intramuscular injections of hypertonic saline. In addition, the subjects performed submaximal isometric
contractions of the left TA muscle both before and after injection of isotonic (non-painful) saline. The authors reported that the experimentally induced pain resulted in a decreased motor unit firing rate that was correlated to pain intensity. In contrast, the firing rate of the active muscle units did not change significantly under the control conditions (i.e. before injection in both legs and following injection of isotonic saline in the left leg). In addition, the authors reported that single motor unit conduction velocities did not differ significantly between any of the conditions which suggested that injection of the hypertonic saline did not alter the muscle fibre membrane properties in the observed motor units. Based on these results, the authors argued that experimentally induced pain may influence submaximal isometric muscle activity through a central inhibitory motor control mechanism.

In a similar experiment, Farina, Arendt-Nielsen, & Graven-Nielsen (2005) provided further evidence implicating a central inhibitory mechanism in the effect of pain on muscle activity. These authors investigated EMG voluntary activity and M-wave properties during electrically elicited and voluntary contractions of the tibialis anterior muscles in 12 healthy subjects. Measurements were performed in the left leg before and after isotonic saline injections and in the right leg after three incremental injections of hypertonic saline. The authors reported that M-wave conduction velocity, amplitude, and spectral content did not change with the injections of painful hypertonic saline. However, surface EMG amplitude decreased during the voluntary contractions as the levels of nociceptive input increased. The authors argued that the unaltered M-wave properties showed that the reduction in muscle activity was not due to changes in muscle fibre membrane properties or impaired neuromuscular transmission, based on the premise that evoked M-waves are affected only by sarcolemma excitability and intracellular action potentials and thus provide a direct indication of the condition of the peripheral muscular system. Instead, the authors suggested that the stimulation of nociceptive afferents by hypertonic saline injection induces a centrally mediated inhibition of muscle activity.

As well as having an effect on isolated isometric muscle contractions, it has been shown that pain can alter motor control strategies during dynamic exercises. Ervilha, Farina, Arendt-Nielsen, & Graven-Nielsen (2005) measured fibre conduction velocity in the biceps muscles and surface EMG activity in the upper trapezius, biceps, triceps, and brachioradialis muscles of 10 healthy subjects while they performed maximum speed elbow flexion/extension movements. Measurements were performed following
injection of (1) hypertonic saline in the biceps, (2) hypertonic saline in both biceps and triceps, and (3) isotonic saline in the biceps muscle. The authors reported that the subjects could perform the exercise with the same mechanical output under all of the conditions, but the presence of pain changed both the relative contribution of the synergistic muscles and the pattern of motor unit activation within the painful muscles. Based on these findings, the authors argued that the muscle activation strategy used to perform and sustain the exercise over time was significantly altered by the presence of pain. Although speculative, it is possible that these findings could be extrapolated to individuals with knee OA or knee injuries. For example, knee pain might lead to diminished quadriceps muscle activity and therefore altered synergistic motor strategies during the performance of physical activities involving the knee.

In conclusion, it is clear from the studies discussed above that pain can have a detrimental effect on voluntary muscle activation, most likely through central inhibitory pathways. Therefore, pain generated by knee injuries or knee OA could potentially contribute to quadriceps strength deficits.

**Effusion**

Another potential source of presynaptic, ongoing reflex inhibition of the quadriceps muscles is the intra-articular knee joint effusion which often accompanies knee injuries and knee OA. Hopkins, Christopher, Jeffrey, & Thomas (2002) argued that an effusion might increase activity in slowly adapting Ruffini endings in the knee joint capsule, which in turn might stimulate Ib inhibitory interneurons, ultimately leading to a reduction in quadriceps alpha motoneuron output. In addition, Palmieri, Weltman, Edwards, Tom, Saliba, Mistry, & Ingersoll (2005) proposed that supraspinal descending pathways involving GABA-ergic interneurons might also contribute to inhibition of the quadriceps muscles following knee joint effusion.

Importantly, some studies have demonstrated that experimentally induced knee effusion can result in significant quadriceps inhibition. For example, McNair, Marshall, & Maguire (1996) investigated the effects of excessive fluid in the knee joint on quadriceps performance and found that isokinetic quadriceps peak torque decreased by 30% immediately following the injection of fluid into the joint.

In a more recent study, Hopkins (2006) also demonstrated decreases in knee extension peak torque and peak power following experimentally induced knee effusion. The
The author reported reductions in knee extension peak torque of 28%, 25% and 23% at 0, 30 and 60 minutes post-injection, respectively. In addition, the authors reported reductions in knee extension peak power of 33%, 23% and 29% at 0, 30 and 60 minutes post-injection, respectively.

However, while the studies described above demonstrated that knee joint effusion is associated with ipsilateral quadriceps muscle inhibition, a recent investigation by Palmieri, Ingersoll, Edwards, Hoffman, Stone, Babington, Cordova, & Krause, (2003) failed to find evidence that knee effusion leads to contralateral quadriceps inhibition. In this study Hoffman reflex (H-reflex) and M-wave measurements were collected using surface electromyography from the vastus medialis muscles of 8 subjects who received an injection of 60 ml of saline into the knee joint of their dominant leg. The authors reported that both maximum H-reflex and maximum H-reflex/maximum M-wave ratios were decreased in the ipsilateral vastus medialis muscles at 10, 20 and 30 minutes post effusion. However, no changes were detected on the contralateral side. Based on the premise that a reduction in the H-reflex indicates an inhibitory action from knee joint afferents on the quadriceps’ motor-neuron pool, these findings appeared to demonstrate that knee effusions resulted in arthrogenous inhibition of the ipsilateral but not contralateral quadriceps muscles. Therefore, Palmieri et al. (2003) suggested that pain-free knee joint effusions are not responsible for the bilateral quadriceps activation deficits which sometimes occur after unilateral joint injury.

In conclusion, it appears that joint effusions may contribute to the significant ipsilateral quadriceps strength deficits that can occur in subjects with knee injuries and knee OA. However, it seems unlikely that joint effusions can explain the bilateral quadriceps strength deficits that are sometimes observed in these populations.

**Voluntary Activation Failure**

While factors such as pain and effusion can cause quadriceps weakness in individuals with knee injuries and knee OA, it has also been suggested that incomplete voluntary activation (VA) of the muscle may contribute to strength deficits, not only in the involved limb but also in the uninvolved limb.

With respect to knee injuries, a number of studies have demonstrated large voluntary activation deficits following ACL injuries. For example, Urbach, Nebelung, Weiler, & Awiszus (1999) used a twitch-interpolation technique to measure quadriceps...
activation failure in 22 male subjects with isolated ACL ruptures and 19 matched controls. The authors reported that the ACL deficient subjects exhibited mean voluntary activation deficits of 16.1% in the involved limbs and 15.3% in the uninvolved limbs. In contrast, the control subjects exhibited mean activation deficits of 8.9%. However, this study had a number of limitations. For example, there was a mixture of acute and chronic ACL deficient subjects included in the sample. In addition, the authors reported that while most of the subjects exhibited a voluntary-activation distribution almost identical to the control group, 23% had voluntary activation deficits of greater than 20% and these individuals were largely responsible for the significant mean deficit. However, in a more recent study Urbach, Nebelung, Becker, & Awiszus (2001) provided further evidence of significant and lasting quadriceps voluntary activation deficits in individuals with ACL injuries. The authors used a twitch interpolation technique to investigate quadriceps voluntary activation in 12 male subjects before and after ACL reconstructive surgery and in 12 matched control subjects. Prior to surgery the authors found that the ACL deficient subjects demonstrated mean voluntary activation deficits of 25.1% on the injured side and 25.4% on the uninjured side, compared to a mean deficit of 9% in the control subjects. At two years post-surgery the mean activation deficits had reduced to 14.7% on the injured side and 16% on the uninjured side, although activation remained lower than in the control subjects (injured side p=0.062, uninjured side p=0.01). Importantly, it should be noted that before surgery approximately two thirds of the ACL deficient subjects exhibited greater voluntary activation deficits than the control subjects. This suggests that large activation deficits were more prevalent in these subjects when compared to those in the Urbach, Nebelung, Weiler, & Awiszus (1999) study. In addition, the results demonstrated that quadriceps voluntary activation failure can persist for long periods following ACL reconstruction, despite participation in a rehabilitation programme and a return to sporting activities.

It should be noted that both of the preceding studies demonstrated that bilateral voluntary activation deficits can occur following a unilateral ACL injury. Importantly, a more recent study by Urbach and Awiszus (2002) has investigated this phenomenon further. In this study the authors used a twitch interpolation technique to investigate the extent of bilateral voluntary activation deficits in 30 subjects with isolated ACL ruptures, 42 subjects with ACL ruptures and accompanying joint damage and 34 matched controls. The authors found that the subjects with isolated ACL ruptures
exhibited mean activation deficits of 16.2% on the injured side and 14.1% on the uninjured side. In contrast, the subjects with ACL ruptures and accompanying joint damage exhibited larger deficits of 23.1% on the injured side and 22.1% on the uninjured side. In comparison, the control subjects demonstrated a mean voluntary activation deficit of 9%. Based on these findings, the authors argued that unilateral knee injuries can cause bilateral quadriceps voluntary activation deficits and that the magnitude of these deficits appears to be related to the severity of injury.

It has been suggested that a major limitation of the preceding three studies is that twitch interpolation techniques can give unreliable results if the contraction effort is not maximal or if the muscle is not fully potentiated prior to testing (Chmielewski, Stackhouse et al. 2004). Therefore, Chmielewski et al. (2004) developed a study which provided practice and familiarization with the procedures, as well as verbal and visual encouragement, in order to ensure that the subjects were exerting a maximal effort. In this study the authors used a burst superimposition technique to assess quadriceps strength and voluntary activation in 100 consecutive subjects at an average of six weeks following isolated ACL rupture. The authors reported that mean quadriceps strength on the involved side (858.5 ± 329.4 N) was significantly lower than on the uninvolved side (989.8 ± 345.7 N). However, activation failure on the involved side ranged from 0-40% and averaged only 7.4%. This was not significantly different from activation failure on the uninvolved side which ranged from 0-42% and averaged 7.2%. In addition, using a definition of inhibition as any voluntary activation value < 95%, the authors reported that fewer than half of the subjects with inhibition exhibited activation deficits of greater than 10%. Interestingly, the authors also found that 12% of the subjects had activation failure in the involved limb only, 21% of the subjects had bilateral activation failure and, somewhat surprisingly, 10% of the subjects had activation failure in the uninvolved limb only. Thus, the cumulative incidence of quadriceps inhibition (defined as < 95% in this study) was 43% for the entire sample. For comparative purposes the authors stated that previous studies have shown the incidence of activation failure in young, healthy subjects was approximately 10%. Therefore, the authors argued that the incidence of quadriceps activation failure was higher in ACL deficient subjects compared to young healthy adults, although the magnitude of the deficits was not large in most cases. In addition, the authors suggested that the smaller activation deficits seen in this study may have
been due in part to the provision of enough practice, encouragement and rest during the testing procedures to ensure that the subject’s efforts were truly maximal.

In a more recent study, Williams, Buchanan, Barrance, Axe, & Snyder-Mackler (2005) also used a burst superimposition technique to investigate quadriceps activation failure in 17 subjects at an average of two months following isolated ACL rupture, although these subjects were all classified as individuals who did not compensate well for the injury. The authors reported that despite participation in a strengthening program, the quadriceps muscles of the ACL deficient limbs \( (1096.85 \pm 279.76 \text{ N}) \) were significantly weaker than those of the uninjured limbs \( (1482.06 \pm 346.65 \text{ N}) \). However, quadriceps activation deficits of only 8-10% were observed and they were not significantly different between the ACL-deficient limbs (VA 90±9%) and the uninjured limbs (VA 92±6%).

Thus, it is apparent that the findings of these two more recent studies (Chmielewski, Stackhouse et al. 2004; Williams, Buchanan et al. 2005) contrasted with previous investigations (Urbach, Nebelung et al. 1999; Urbach, Nebelung et al. 2001; Urbach and Awiszus 2002) regarding the magnitude of quadriceps activation failure in subjects with ACL deficits. These findings may in turn bring into question the relative importance of voluntary activation deficits when considering quadriceps muscle weakness in individuals with ACL deficits. Nevertheless, it appears that voluntary activation deficits play at least some role in both unilateral and bilateral quadriceps strength deficits.

Interestingly, a number of studies have been conducted to investigate a potential cause of quadriceps inhibition in ACL deficient subjects. Based on the premise that joint afferents from the ACL influence quadriceps alpha motor neuron activity (and therefore quadriceps maximum voluntary contraction) via the gamma loop, a number of studies have suggested that interruption of the gamma loop might be a potential mechanism for quadriceps weakness. For example, a succession of studies used patellar tendon vibration to continuously activate quadriceps muscle spindles and consequently reduce activity in Ia afferents (part of the gamma loop) either through neurotransmitter depletion, a heightened threshold of Ia fibres, or presynaptic inhibition of the Ia terminal. It was theorized that this would lead to a decrease in quadriceps maximum voluntary contraction (MVC) and integrated electromyogram (I-EMG) values in subjects with an intact gamma loop. Importantly, it has been
reported that subjects with anaesthetized knees (Konishi, Fukubayashi et al. 2002), ACL deficient knees (Konishi, Fukubayashi et al. 2002) and ACL reconstructed knees (Konishi, Fukubayashi et al. 2002) exhibited abnormal responses to patellar tendon vibration suggesting that gamma loop function was compromised in these populations.

More recently gamma loop dysfunction has also been implicated in bilateral voluntary activation deficits following ACL lesions. Using patellar tendon vibration Konishi, Konishi, & Fukubayashi (2003) observed abnormal MVC and I-EMG values in the uninjured limbs of ACL deficient subjects. The authors suggested that these abnormal values provided evidence of a neurophysiological anomaly affecting the quadriceps muscle gamma loop in the uninjured limbs of ACL deficient subjects. Interestingly, the authors also proposed two possible explanations for bilateral quadriceps gamma loop deficits. The first involved the possibility that ACL lesions could cause inhibitory afferent signals to be sent to the contralateral quadriceps muscle via interneurons in the spinal cord. In contrast, the second explanation was based on studies which suggested that ACL stimulation could cause afferent feedback from mechanoreceptors to be transmitted to supraspinal central nervous system structures (Pitman, Nainzadeh et al. 1992; Valeriani, Restuccia et al. 1996). Based on this premise, the authors argued it is possible that descending inhibitory signals from these structures could attenuate quadriceps muscle function bilaterally.

In conclusion, it appears that there is some disagreement in the literature regarding the size and relative importance of quadriceps voluntary activation deficits following knee injuries. However, it seems that voluntary activation deficits play at least some role in both unilateral and bilateral quadriceps strength deficits. In addition, a number of studies have suggested that altered gamma loop function may play an important role in quadriceps voluntary activation failure following ACL injury.

Importantly, a number of studies have also demonstrated large quadriceps muscle voluntary activation deficits in individuals with knee OA. For example, Hurley, Scott, Rees, & Newham (1997) measured voluntary activation in 103 subjects with knee OA and 25 control subjects by superimposing percutaneous electrical stimulation on isometric quadriceps maximal voluntary contractions. The authors reported that the subjects with knee OA exhibited a significantly (p<0.0001) lower median quadriceps voluntary activation value (72.5%) when compared to the control group (93%).
In another study, Hurley & Scott (1998) used the same protocol to measure quadriceps voluntary activation values in an intervention group consisting of 60 subjects with knee OA and a control group consisting of 37 subjects with knee OA. At baseline both the intervention group (73.5%; [95% CI] 44.5-85%) and the control group (72%; [95% CI] 50.5-90%) exhibited greatly reduced levels of quadriceps voluntary activation.

In a later study, Hassan, Mockett, & Doherty (2001) also superimposed percutaneous electrical stimulation on isometric quadriceps maximal voluntary contractions to measure voluntary activation in 59 subjects with knee OA and 49 control subjects. The authors reported that the subjects with knee OA demonstrated significantly (p <0.001) lower levels of mean quadriceps voluntary activation (66.0%; [95% CI] 58.8-73.2%) when compared to the control subjects (87.4%; [95% CI] 80.7-94.2%). However, it is important to note that all of the subjects with OA were symptomatic and were recruited from a hospital based population, increasing the likelihood that they represented the more severe end of the knee OA spectrum.

Interestingly, Fitzgerald, Piva, Irrgang, Bouzubar, & Starz (2004) found much smaller deficits than those previously described when using a burst superimposition technique to measure isometric quadriceps voluntary activation in 105 subjects with radiographically confirmed knee OA. The reported mean activation deficit for the OA subjects was 3.5% ± 5.0 (SD) with a range of 0-38%. However, it should be noted that a knee flexion angle of 60º was used for the isometric testing, which differs from the 90º angle used in many other studies (Hurley, Scott et al. 1997; Hurley and Scott 1998; Hassan, Mockett et al. 2001; Pap, Machner et al. 2004). In addition, the study lacked a control group for comparative purposes. However, despite the small mean activation deficit observed in this group, the authors stated that their overall results showed a similar profile to those of Hassan et al. (2001) and Hurley et al. (1997) in that the relationship between quadriceps strength and physical function was moderated by the degree of quadriceps voluntary activation failure. The authors argued that these similarities suggested the same phenomena were being measured in these studies, although the variation in the magnitude of the activation deficits highlighted the problem of comparing studies which used different stimulus parameters and testing procedures.
A more recent study by Pap, Machner, & Awiszus (2004) investigated quadriceps voluntary activation in subjects with different levels of OA degeneration. Isometric quadriceps voluntary activation was measured using a twitch interpolation technique in 68 subjects with Outerbridge (1961) stage II (mild) OA, 154 subjects with stage IV (severe) OA and 85 age matched controls. The authors reported that mean quadriceps activation was significantly higher in the control group (89.3% ± 8.0, range 55.4–98%) than in both of the OA groups (p <0.001). However, when the authors compared the OA groups they found that the subjects with stage IV OA actually had significantly higher (p=0.004) activation values (77.2% ± 13.2, range 37.5–97.5%) than the subjects with stage II OA (70.8% ± 16.0, range 4.5–97.3%). This result is somewhat surprising since conventional thinking would suggest that increasing levels of joint degeneration might lead to concomitant reductions in quadriceps voluntary activation. However, Pap, Machner, & Awiszus (2004) argued that these findings do not necessarily conflict with those of previous studies because those investigations did not specifically assess differing severities of joint damage. Instead, previous studies generally examined the associations between activation deficits, strength deficits and differing degrees of disability, which Pap, Machner, & Awiszus (2004) argued do not necessarily correlate with the severity of joint damage. Nevertheless, an explanation of why quadriceps voluntary activation might be greater in individuals with more severe levels of joint degeneration remains elusive. However, based on the premise that knee OA initially causes joint receptors to generate afferent signals which inhibit quadriceps activation, it could be argued that more severe joint degeneration might eventually render these receptors inactive and therefore reduce the flow of inhibitory signals. In addition, it is possible that confounding factors specific to this study may have influenced the results. For example, the number of subjects in the stage II OA group was considerably smaller than the stage IV group and the range of voluntary activation values for the stage II group was wider, with one subject exhibiting a quadriceps activation deficit of 95.5% (Pap, Machner et al. 2004). In addition, the Outerbridge (1961) classifications create specific subsets of OA subjects which may not be representative of those with mild or severe OA as a whole (Pap, Machner et al. 2004).

Finally, in a recent study Molloy (2005) measured voluntary activation using a twitch interpolation technique in 26 subjects with unilateral knee OA (mean age 63.6 ± 12.51 years) and 17 control subjects (mean age 64.69 ± 9.52 years). For the subjects with
knee OA, the author reported mean voluntary activation deficits of 10.6% (± 9.4) and 8.2% (± 7.2) in the affected and unaffected limbs, respectively. In contrast, the author reported a mean voluntary activation deficit of just 1.0% (± 2.1) for the control subjects. Based on these findings, the author stated that the subjects with unilateral knee OA exhibited significant bilateral voluntary activation deficits when compared to the control subjects (p < 0.05).

In conclusion, it appears that a number of studies have demonstrated that quadriceps voluntary activation failure can occur following the onset of knee OA. In turn, these findings may partially explain the quadriceps strength deficits that are so frequently seen in individuals with knee OA.

**Quadriceps Muscle Atrophy**

While pain, joint effusion and activation failure appear to influence quadriceps muscle strength primarily through neural inhibition, it seems likely that if sustained, these phenomena could lead to quadriceps muscle atrophy. This is important because maximum effort muscle torque has been shown to be closely correlated to changes in muscle volume. Therefore, atrophic changes in a muscle could result in concomitant reductions in strength (Fukunaga, Miyatani et al. 2001).

A number of studies have demonstrated that quadriceps atrophy can occur in individuals with knee injuries. For example, Gerber, Hoppeler, Claassen, Robotti, Zehnder, & Jakob (1985) investigated quadriceps atrophy using computed tomography in 41 subjects with chronic, symptomatic instability of the ACL. The authors reported that there was an overall atrophy of approximately 8% in quadriceps cross sectional area (CSA) compared to the uninvolved limb. In addition, they found that the relative decrease in the CSA of the vastus medialis was 2.7% greater than the relative decrease in the total CSA of the quadriceps muscle.

In a more recent study, Williams, Buchanan, Barrance, Axe, & Snyder-Mackler (2005) measured quadriceps volume and CSA in 17 “non-copers” with isolated ACL injuries. The authors reported mean atrophy of approximately 9% in the affected quadriceps muscles, although in this study the vastus lateralis and vastus intermedius muscles were found to be disproportionately affected. The authors suggested that as the largest muscles of the quadriceps group, the vastus lateralis and vastus intermedius muscles may be more vulnerable to the neural disruption that occurs
when the ACL is ruptured. Importantly, the authors also reported that quadriceps strength in the ACL deficient limbs was significantly lower (average 25%) than in the uninjured limbs and that atrophy, along with an average activation failure level of 10%, explained more than 60% of the variance in quadriceps weakness (p = .004).

In a study of meniscal injuries, Akima & Furukawa (2005) investigated thigh muscle atrophy in 32 subjects following meniscal lesions and arthroscopic partial meniscectomy. Using magnetic resonance imaging the authors found that quadriceps muscle volume was significantly lower (approximately 13.5%) in the involved leg compared to the uninvolved leg. However, in contrast to Williams et al’s (2005) and Gerber et al’s (1985) findings, the authors reported that the atrophy seemed to be relatively uniform across the four heads of the quadriceps muscle.

Interestingly, some studies have also suggested that knee osteoarthritis and certain knee injuries may cause preferential atrophy of different muscle fibre types. For example, Nakamura, Kurosawa, Kawahara, Watarai, & Miyashita (1986) used biopsies from the vastus lateralis muscle to investigate muscle fibre atrophy in 51 subjects with isolated ACL injuries, 29 subjects with combined ACL and meniscus injuries, 25 subjects with isolated meniscal injuries and 7 subjects with isolated collateral ligament injuries. The authors reported that atrophy of type 2 fibres occurred in all four conditions, while atrophy of type 1 fibres occurred only in subjects with isolated ACL or combined ACL and meniscal injuries. Based on these results, the authors argued that the atrophy of type 2 fibres could be a non-specific change related to muscle disuse, while the atrophy of type 1 fibres could be a specific adaptation related to disruption of the ACL.

Nakamura & Suzuki (1992) also used vastus lateralis muscle biopsies to compare fibre atrophy in 27 females with knee OA and 16 females with lower extremity fractures. The authors reported that type 2 fibre atrophy was found in both groups but was more frequent in the OA group. In addition, the authors found abnormal mosaic patterns of fibre types (such as fibre type grouping and grouped atrophy of type 2 fibres) more frequently in the knee OA subjects (73.1%) and less frequently in the subjects with fractures (6.3%).

In a more recent study, Molloy (2005) collected surface electromyography (sEMG) data from the vastus medialis muscles of 26 subjects with unilateral knee OA during
an isometric endurance test. The author reported that the initial values for median frequency and mean power frequency were significantly lower in the affected limb compared to the unaffected limb ($p < 0.05$). Importantly, the author suggested that a key contributing factor to these differences might be a decrease in the proportions of type 2 muscle fibres in the vastus medialis of the affected leg. However, the author also cautioned that many factors can influence sEMG values and therefore care should be exercised when making assumptions about fibre type distributions based on sEMG amplitude, spectral and conduction velocity measures alone.

While some studies have suggested that knee OA and specific types of knee injuries may cause preferential atrophy of different muscle fibre types, other studies have suggested that atrophy may be relatively uniform across fibre types. For example, Gerber et al. (1985) examined biopsies from the vastus lateralis muscles of 41 subjects with chronic symptomatic instability of the ACL and reported a similar decrease in fibre size for all fibre types. In addition, Tho, Nemeth, Lamontagne, & Eriksson (1997) examined the quadriceps muscles of 15 subjects at 4 to 24 months post ACL rupture and determined that both type 1 and type 2 fibres exhibited a similar level of atrophy, although these findings were based on EMG frequency analysis rather than muscle biopsies.

In conclusion, it appears that quadriceps muscle atrophy can occur frequently in subjects with knee injuries and knee OA and might therefore contribute to quadriceps weakness in these populations. However, it is less clear whether these pathologies lead to preferential atrophy of different muscle fibre types.

**Immobilization and Disuse**

It has been demonstrated that immobilization or disuse of a limb can lead to muscle weakness (Berg, Larsson et al. 1997; Hortobagyi, Dempsey et al. 2000). This is important because immobilization may be used as part of the treatment regime following a knee injury and because relative disuse of a limb is not uncommon with knee injuries or knee OA. A number of factors may contribute to muscle weakness following immobilization/disuse including alterations in the muscle’s non-contractile and contractile elements and reductions in voluntary activation levels.

Studies using animals by Järvinen, Józsa, Kannus, Järvinen, & Järvinen (2002) and Jozsa, Kannus, Thoring, Reffy, Jarvinen, & Kvist (1990) have demonstrated that
immobilization can cause significant alterations in intramuscular connective tissue including proliferation and thickening of connective tissue, irregular collagen orientation and dramatic reductions in capillary numbers. These studies also showed that increases in connective tissue can occur around the remaining intramuscular capillaries, separating them from individual muscle fibres. In turn, the authors proposed that such a connective tissue barrier, in combination with an overall reduction in capillary numbers, could significantly disrupt blood supply to the muscle fibres and consequently accelerate muscle fibre atrophy.

A number of studies have also described atrophic changes in the contractile elements of muscles following immobilization. These include general muscle fibre atrophy, preferential atrophy of different fibre types and transformations between fibre types.

With respect to general fibre atrophy, Young, Hughes, Round, & Edwards (1982) investigated the number and size of quadriceps muscle fibres in 14 subjects with observable thigh muscle wasting secondary to knee injury. The authors reported that the atrophy seen in these subjects was primarily due to a decrease in muscle fibre CSA. Berg, Larsson & Tesch (1997) also observed reductions in muscle fibre CSA (mean 18% ± 14) in the vastus lateralis muscles of seven healthy males after six weeks of bed rest. In a more recent study, Hortobagyi, Dempsey, Fraser, Zheng, Hamilton, Lambert, & Dohm (2000) described declines in vastus lateralis muscle fibre CSA in 48 healthy subjects following 3 weeks of immobilization at 3° of knee flexion. The authors found that type 1, 2a and 2x muscle fibre areas were significantly and uniformly reduced by 13%, 10% and 10%, respectively. However, while these studies found that atrophy was primarily due to a decrease in fibre CSA, a study by Halkjaer-Kristensen & Ingemann-Hansen (1985) found that quadriceps atrophy following knee collateral ligament rupture and one month of immobilization was due, in part, to a 28% loss in the number of vastus lateralis muscle fibres. In any case, all of these studies may have limitations. For example, it is possible that the biopsied fibres were not representative of those in the other heads of the quadriceps muscle or even in the rest of the vastus lateralis muscle, either at the same level or along the length of the muscle. In addition, atrophic changes in fibre orientation or fibre length may have influenced the biopsy results (Young, Hughes et al. 1982; Halkjaer-Kristensen and Ingemann-Hansen 1985). Nevertheless, these studies appear to have consistently demonstrated that muscle fibre CSA was significantly reduced following a period of immobilization/disuse.
While general muscle fibre atrophy has been demonstrated following immobilization and disuse, it is less clear whether preferential atrophy of different fibre types occurs under these conditions. Preferential atrophy of different fibre types may be important when considering strength deficits because the contractile and energetic properties of type 1 and type 2 muscle fibres differ depending on their myosin heavy chain (MHC) isoform content. Type 1 fibres contain the MHC-1 isoform and have lower maximum shortening velocity, maximum power and ATPase activity than type 2 fibres (D'Antona, Lanfranconi et al. 2006). In addition, the specific tension developed by type 2 fibres has generally been shown to be greater than that of type 1 fibres (Bottinelli and Reggiani 2000).

A number of studies have suggested that type 1 fibres are preferentially affected by immobilization. Sargeant and Davies Edwards, Maunder, & Young (1977) investigated muscle atrophy in the vastus lateralis muscles of seven subjects following unilateral leg fracture and immobilization and found a trend towards greater atrophy of type 1 (46%) than type 2 (37%) fibres. In addition, Häggmark, Jansson, & Eriksson (1981) investigated quadriceps muscle atrophy following knee surgery and five weeks of immobilization and found that there was preferential atrophy of type 1 fibres (26.5%, p<0.0025) but no significant change in the average size of type 2 fibres. Finally, in a more recent study Halkjaer-Kristensen & Ingemann-Hansen (1985) found that there was preferential atrophy of type 1 fibres in the vastus lateralis muscle (21%, p<0.001) following knee collateral ligament rupture and one month of immobilization. However, it should be noted that in all of these studies the subjects had some form of lower extremity injury and therefore the effects of immobilization were not examined in isolation.

In direct contrast to studies that have described preferential atrophy of type 1 fibres, at least one investigation appears to have demonstrated greater atrophy of type 2 fibres following immobilization. Yasuda, Glover, Phillips, Isfort, & Tarnopolsky (2005) examined sex based differences in vastus lateralis muscle morphology by taking biopsies from 27 healthy subjects following 14 days of immobilization in a knee brace (60° knee flexion). The authors reported that the decreases in type 1 (Male = 4.8% ± 5.0, Female = 5.9% ± 3.4), type 2a (Male = 7.9% ± 9.9, Female = 8.8% ± 8.0) and type 2x (Male = 10.7% ± 10.8, Female = 10.8% ± 12.1) fibre areas were similar for both sexes. However, while not explicitly discussed by the authors, these results also
appeared to show that there was greater atrophy of type 2 fibres compared to type 1 fibres under the immobilization conditions used in this study.

Despite the arguments that preferential atrophy of different fibre types occurs, some studies have indicated that type 1 and type 2 muscle fibres may be affected by immobilization in a relatively uniform manner. For example, Veldhuizen, Verstappen, Vroemen, Kuipers, & Greep (1993) examined biopsies from the vastus lateralis muscles of 8 healthy subjects following 4 weeks of cast immobilization and reported no significant difference in the level of type 1 and type 2 fibre atrophy (p > 0.05). In a study described previously, Hortobagyi et al. (2000) also reported that type 1, 2a and 2x fibre areas in the vastus lateralis muscle were uniformly reduced by 13%, 10% and 10%, respectively, following 3 weeks of immobilization at 3° of knee flexion.

As with the lack of agreement regarding the preferential atrophy of different fibre types, there appears to be some disagreement in the literature over fibre type transformations following immobilization. For example, Jankala, Harjola, Petersen, & Harkonen (1997) found that hind-limb immobilization for one week significantly altered the MHC mRNA profile in rat soleus, gastrocnemius, and plantaris muscles towards faster isoforms. In addition, Andersen, Gruschy-Knudsen, Sandri, Larsson, & Schiaffino (1999) observed changes at the mRNA and protein level in the vastus lateralis muscles of 7 male subjects following 37 days of bed rest. The authors reported that muscle biopsies demonstrated a mismatch between MHC isoforms involving an increase in the number of fibres expressing mRNA for MHC-2x and a decrease in the number of fibres expressing mRNA for MHC-1, without significant changes at the protein level. Based on these results, the authors suggested that an increase had occurred in the amount of muscle fibres in a transitional state from phenotypic type 1→2a and 2a→2x. However, in contrast to these studies at least one investigation has failed to find evidence of fibre transformation. In a study described earlier, Yasuda, Glover, Phillips, Isfort, & Tarnopolsky (2005) reported that following 14 days of immobilization in a leg brace, muscle biopsies from the vastus lateralis muscles showed no significant changes in the percentage distribution of type 1, type 2a and type 2x fibres and therefore no evidence of fibre transformation.

Despite the lack of agreement in the literature over the preferential atrophy of different fibre types and the occurrence of fibre type transformations, it is evident from the studies described above that significant atrophy can occur in quadriceps...
muscle fibres following immobilization under a variety of conditions. Importantly, it has also been demonstrated that quadriceps atrophy following immobilization is associated with significant reductions in maximal voluntary strength. For example, Berg, Larsson, & Tesch (1997) reported that after 6 weeks of bed rest a 13.8% (± 4.5%) reduction in quadriceps femoris CSA was accompanied by a 24.5% (± 10.5%) reduction in maximum isometric torque and a 28.9% (± 12.2%) reduction in maximum concentric torque. Hortobagyi et al. (2000) also reported that an 11% reduction in quadriceps CSA was correlated (r=0.75) with a 47% loss of isometric, concentric and eccentric quadriceps strength. Finally, Thom, Thompson, Ruell, Bryant, Fonda, Harmer, De Jonge, & Hunter (2001) found that an 11.8% reduction in quadriceps CSA was accompanied by a 41.6% reduction in 1-RM leg extension strength following cast immobilization from the hip to the ankle for 10 days.

However, while the studies described above demonstrated that a relationship existed between decreased quadriceps muscle CSA and diminished knee extensor strength following immobilization, it should also be recognized that the reductions in strength greatly exceeded those in muscle CSA. Importantly, some authors have proposed that alterations in neural activity following immobilization may explain these discrepancies. For example, Kawakami, Akima, Kubo, Muraoka, Hasegawa, Kouzaki, Imai, Suzuki, Gunji, Kanehisa, & Fukunaga (2001) measured quadriceps activation in 4 subjects who underwent head down bed rest only and in 5 subjects who underwent head down bed rest but also performed a daily bilateral isometric leg extension exercise. While there was no significant difference between the groups before bed rest, the authors reported that quadriceps voluntary activation (VA) was reduced in all subjects in the non-exercise group following bed rest (VA range: 78% to 82%). In contrast, quadriceps activation in the exercise group remained relatively unchanged (VA: range 87% to 96%). Importantly, the authors also reported that the reduction in quadriceps activation in the non-exercise group was correlated with a 10.9% (± 6.9) decrease in isometric quadriceps strength. Based on these results, the authors argued that, in the non-exercise group, the reduction in strength following bed rest was influenced by a decreased ability to neurally activate quadriceps muscle motor units.

In a more recent study, Mulder, Stegeman, Gerrits, Paalman, Rittweger, Felsenberg, & de Haan (2006) also investigated changes in quadriceps CSA, maximal strength and neural activation in 9 subjects who underwent bed rest only and in 9 subjects who underwent bed rest and resistive vibration exercise. The authors reported that
quadriceps CSA (-14.1% ± 5.2) and maximal isometric torque (-16.8% ± 7.4) decreased significantly in the bed rest only group but not in the exercise group. However, maximal voluntary activation (measured seven times) did not change in either group throughout the study. Importantly, the authors suggested that the lack of change in activation might have been due to the repeated testing of muscle function during the bed rest period. The authors supported this contention by reporting that in a subgroup of 5 bed rest only subjects, maximal voluntary torque in the otherwise untested left leg decreased by twice as much compared to the right leg (20.5% vs. 11.1%) and did not equate with the loss of CSA in the left and right legs (11% vs. 9%). Based on these findings, the authors argued that neural activation may have diminished in the more fully immobilized left leg because the decrease in torque could not be completely explained by the reduction in quadriceps CSA.

In conclusion, it is apparent from the studies reviewed here that immobilization or disuse can result in significant reductions in maximal quadriceps strength. In turn, these declines in strength are thought to be largely due to atrophic physiological and structural changes within the muscle, as well as reductions in voluntary activation.

**Summary**

The studies reviewed above have generally demonstrated that factors such as pain, joint effusion, activation failure, atrophy and immobilization/disuse can lead to reductions in maximal voluntary muscle strength. Consequently, these phenomena are likely to contribute to the large quadriceps strength deficits that are often observed in individuals with knee injuries and knee OA. In turn, it seems likely that quadriceps weakness could reduce the prospect of returning to pre-injury activity levels and lead to varying degrees of disability. These issues will be discussed briefly in other subsections of the thesis review.

**References**


