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Muscle activity during locomotion in various inclination surfaces and different running speeds.

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ABSTRACT

During dynamic activities – walking, jogging and running, muscular function is affected by running techniques and foot strike patterns, inclined surfaces and running speed. In order to assess muscle function during these activities, most studies examine certain muscles such as tibialis anterior, gastrocnemius (lateral and medial), soleus, rectus femoris, vastus (medialis and lateralis), hamstrings (biceps femoris, semimembranosus, semitendinosus), and gluteus. These muscles are commonly selected because they provide supportive and propulsive forces during running. Results of these studies may conclude to special training programs for runners in order to improve their performance.

KEYWORDS: Running; muscle activation; running surfaces; running speeds

Introduction

Running is a popular physical activity and a key element in most conditioning programs. At each running step, when the foot strikes the supporting ground, a ground reaction force (GRF) of two- or three-times body weight is generated [6] inducing shock waves that propagate throughout the locomotor system. The load resulting from ground reaction forces magnitude influences mechanical function of the musculoskeletal system and muscle activation patterns.

During dynamic activities – walking and running, muscular function is affected by running techniques and foot strike patterns, inclined surfaces and running speed. Inclined support surfaces affect the control of movement in terms of the maintenance of an

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upright posture [22], the foot strike patterns used and the related centre of pressure in anterior – posterior direction during stance, and muscles activity [24]. Sasagawa [40] assessed the active stabilization mechanisms on an inclined surface during quiet standing and found that muscle activity changed as a function of support surface conditions.

In order to assess muscle function during running, most studies examine the following muscle groups: tibialis anterior, gastrocnemius (lateral and medial), soleus, rectus femoris, vastus (medialis and lateralis), hamstrings (biceps femoris, semimembranosus, semitendinosus), and gluteus. These muscles are selected because they provide supportive and propulsive forces during running [21].

Effects of foot strike pattern and inclined surfaces on muscle activity

The work performed by muscle groups is partially affected by the foot strike pattern adopted during locomotion [1,16,50]. According to the heel and metatarsal positioning at landing, three foot strike patterns have been identified: rearfoot strike (RFS) in which the heel lands before the ball of foot, midfoot strike (MFS) in which the heel and the ball of foot lands almost simultaneously, and forefoot strike (FFS) in which the ball of foot lands before the heel [17].

Muscle activity differs depending on foot strike pattern. During level running, anterior patterns (MFS and FFS) are associated with greater plantar flexion and knee flexion at initial contact and with higher gastrocnemius lateralis activity and lower tibialis anterior and vastus lateralis activity compared to posterior patterns (RFS) [1,16,42,47,50]. When adopting a forefoot strike running technique, a more compliant ankle and stiffer knee were observed during the stance phase, resulting in a greater negative work at the ankle and a lower negative work at the knee in forefoot strike patterns compared to rearfoot strike patterns [20]. Giandolini [16] reported that adopting a midfoot strike pattern, in order to reduce loading rate during running, resulted in a higher muscular activity of the gastrocnemius lateralis during the pre-activation phase but not during the support phase. It has also been observed that in high – mileage runners the muscular activity of the gastrocnemius lateralis during the support phase was reduced compared to asymptomatic controls [4]. Probably, the pre-activation of the gastrocnemius lateralis is in fact necessary in midfoot strike running technique since the plantar flexors need to counteract the dorsiflexor moment created during the midfoot strike pattern [16].

An earlier, longer and greater plantar flexors (PF) activity, lower dorsiflexor activity, and greater biceps femoris activity have been observed when running with a forefoot strike (FFS) pattern [1,16,50]. Runners adopting a forefoot strike pattern activated their plantar flexors muscles 11% earlier and 10% longer than runners with a rearfoot strike pattern. Specifically, the activation phase of medial gastrocnemius (MG) occurred 7.7-16.3% of the gait cycle earlier and lasted on average 9.7% longer for the forefoot strike runners compared to rearfoot strike runners, at all speeds (2.5, 2.8, 3.2 and 3.5m/sec). A similar trend was observed for the activation phase of lateral gastrocnemius (LG) as well. Forefoot strike runners activated their lateral gastrocnemius muscles 7.7-13.1% of the gait cycle earlier and 6.3-14.3% longer than rearfoot strike runners at all speeds. However, calf muscles deactivation time was not influenced by running technique. This earlier and longer relative activation of the plantar flexors is likely associated with an improved capacity for elastic energy storage [1].

Differences in muscle activity between rearfoot and forefoot strike running patterns were also identified while running on a treadmill at a speed of 4m/sec [50]. Muscle activity was assessed just prior to and after foot contact – an instant with significant kinematic differences between strike patterns [3,29]. In accordance with other studies, results revealed that forefoot strike running pattern was associated with lower tibialis anterior and higher gastrocnemius (MG and LG) muscle activity during late swing phase, compared to rearfoot strike patterns. Additionally, the muscle activity of vastus medialis and lateral hamstrings, during late swing phase, was lower in forefoot strike runners

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compared to rearfoot strike runners. Muscle activity recorded during early stance phase presented no significant differences between forefoot and rearfoot strike patterns. The muscle activity of soleus – during the early stance phase – was lower in forefoot strike runners; however this difference was not significant. Although forefoot strike pattern is related to a greater knee flexion angle at foot contact compared to rearfoot strike pattern, rectus femoris activity during either the late swing or early stance phase presented no significant differences between foot strike patterns [50]. This finding is in contrast with the results of Shih [42] who reported that rearfoot strike runners had greater muscle activity in the rectus femoris during swing phase when adopting a forefoot strike running pattern.

Similar results about foot strike patterns and related muscle activation patterns are reported during running at inclined surfaces. Running at inclined surfaces influences lower limb joint function and muscle activity. Hill running at different slopes and varied surfaces is a commonly used method in training programs for distance runners.

Downhill running is characterized by eccentric contractions with the associated mechanical stress and consequently causes damage within the muscle fiber cytoskeleton, delayed-onset muscle soreness and decreased muscle function [30,35]. Downhill running also influences running economy and running kinematics. Chen [8] reported that running patterns were modified (step frequency was increased, ankle and knee joints range of motion was decreased) up to three days after a downhill run. Kinematic changes observed after downhill running might be due to reduced stretch reflex sensitivity and contractile failure resulting from tissue damage.

During downhill trail run, the more posterior the foot strike (rearfoot strike – RFS), the higher the tibialis anterior (TA) and vastus lateralis (VL) activities but the lower the gastrocnemius lateralis (GL) activity. Conversely, anterior patterns (MFS and RFS) are associated with higher gastrocnemius lateralis (GL) activity and lower tibialis anterior (TA) and vastus lateralis (VL) activities [16,17]. Root mean square (RMS) values from raw electromyography (EMG) signals, recorded during the 6.5km downhill run, were 28.2 ± 14.5% of RMSmax for vastus lateralis, 23.5 ± 10.3% for biceps femoris, 28.1 ± 12.0% for gastrocnemius lateralis and 35.9 ± 18.0% for tibialis anterior [17].

The lower vastus lateralis activity observed with anterior patterns may be associated with less pronounced knee extension at initial contact which may decrease vastus lateralis pre-activation [42] and /or with a negative work developed by knee extensor muscles during the braking phase [20]. In contrast, the higher vastus lateralis activity when rearfoot striking may be related to further alterations in sarcolemma excitability at knee extensors during downhill running [17].

Adopting a forefoot strike pattern during downhill running could induce greater plantar flexors fatigue and damage by increasing their recruitment, and alternatively reduce knee extensors fatigue and damage by decreasing their contribution during the energy absorption phase. Increasing plantar flexors fatigue or damage in downhill sections could affect performance in the subsequent uphill sections, where the work performed at the ankle is substantial [38]. Trail running, which is characterized by large positive and negative inclined surfaces, may mainly cause greater alterations of muscle function in plantar flexors than in dorsiflexors, as has been observed after a 5h hilly run [13].

Changing foot strike pattern could modulate the eccentric work done by knee extensors and plantar flexors during downhill running, affecting this way the severity of muscle fatigue and damage observed in these muscle groups after downhill sections [17]. It is speculated that altering muscle activation patterns by switching between running techniques and foot strike patterns could better distribute the mechanical load and the muscular work done to the lower-limb muscles [1,16,42,47].

While during level running - at a constant speed - the mechanical work required by limb muscles is negligible, uphill running is characterized by increased demands for muscle mechanical work / muscle function in order to increase the body po-

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tential energy [38]. It is suggested that the most of the work necessary to perform uphill running is produced at the hip joint, while the knee and ankle joints performed similar functions at all inclines (0^o, 6^o, 12^o). Mechanical work produced at the hip joint increased significantly with increasing running incline, as a result of either an increase in the moment of muscle force developed by hip extensors or through power transfer by knee extensors to the hip via the hamstrings [38]. Sloniger [43,44] also reported an increased muscle activity (based on MRI) in knee extensors with increasing running incline.

Muscle function during locomotion at different running speeds

Assessing muscle activation profiles during locomotion at different speeds, it appears that many muscles show a similar profile in running as in walking. During running, basic patterns of EMG activity presents an almost simultaneous activation of leg extensors. The onset of activation occurs before foot contact with the quadriceps activation being observed first, followed by the calf muscles, as a function of joint kinematics (maximum knee flexion occurs earlier than maximum ankle dorsiflexion). This part of the extensor activation goes along with a co-contraction of the hamstrings for the knee and of tibialis anterior for the ankle. Muscles activation (burst) end before toe-off, however muscle force continues for sufficient time after the end of activation to cover the complete stance phase [15].

Specifically, Gazendam & Hof [15] assessed averaged EMG patterns during locomotion at different speeds (1.25-2.25m/sec: walking and jogging, 2.5-4.5m/sec: running). EMG profiles were recorded separately for tibialis anterior (TA) and adductor magnus (AM) muscles and for the following muscle groups: 1) a quadriceps group: vastus medialis (VM), vastus lateralis (VL), and rectus femoris (RF), 2) a hamstring group: biceps femoris (BF), semitendinosus (ST) and semimembranosus (SM), 3) a calf group: soleus (SO), gastrocnemius medialis (GM), gastrocnemius lateralis (GL) and peroneus longus (PL), 4) a gluteal group: gluteus maximus (GX) and medius (GD). EMG profiles were determined by the timing (in relation to the gait cycle) and amplitude of activation.

Results revealed that during running at speeds from 2.25m/sec to 4.5m/sec, the EMG activity for the quadriceps group started before foot contact (80% of the gait cycle) and ended at about midstance (115%). Although the profiles were very similar, small differentiations were observed with speed. For the vastii muscles (VM, VL), the EMG amplitude increases for walking and jogging (speeds: 1.25-2.25m/sec), while during running at higher speeds (2.5-4.5m/sec) it presents a more constant form with higher peaks. The amplitude of activation in jogging and running is always higher than in walking. Rectus femoris (RF) presents an earlier onset of activation at about 40 - 70% before foot contact. As speed increases, the onset of activation occurs from 47% at a speed of 2.25m/sec to 37% at 4.5m/sec and EMG amplitude increases as well.

During running the EMG profiles of the hamstring group (BF, ST, SM) present two peaks. The first peak was recorded in the second half of swing, 70-100% of the gait cycle, while the second peak was recorded in stance, 6-30% of the gait cycle. Activation profiles of the three hamstring muscles presented differentiations with speed dependence. In SM both peaks appeared to be constant, while in ST both peaks increased. In BF the first peak increased, while the second peak showed maximum activity at 3m/sec and decreased at higher speeds. During walking, the same two-peaked activation pattern was recorded, with a 10% later onset of activation. The jogging profile presents the same timing pattern of walking, but with higher amplitude.

The EMG profile of the calf group (SO, GM, GL, PL) showed a single activation peak, similar to the quadriceps peak but with 10% later onset of activation. Muscles activity started shortly before stance (86%) and ended before toe-off (125%). It seems that during running, an almost simultaneous activation of quadriceps and calf group is observed which is associated with an energy absorption and production process. In contrast, during walking the activation peak was recorded at the end of stance (26-55%) as such impact absorption and push-

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off are separated in time and done separately by quadriceps and calf. With increasing running speed from 2.25-4.5m/sec, the activation amplitude of soleus and peroneus longus remained constant, while gastrocnemius medialis and lateralis amplitude increased at about 40%.

The gluteus muscles (GX, GD) profile, recorded during running, showed two peaks. The first peak is similar for both gluteus maximus and medius, and its timing occurs from 88% to 118% of the gait cycle. A constant amplitude for GD is appeared, while the amplitude of activation linearly increases with speed in GX. The second peak is observed at mid-wing (60-84% of the gait cycle) for the GX, and at the transition from stance to swing (30-50%) for the GD. Both muscles activation amplitude increased with speed. Walking patterns appeared to be similar with those of running, with the exception of GX second peak which was lower and the amplitude of GD which was lower as well.

The EMG activity of the tibialis anterior (TA) extended over the complete swing phase. During running, it started before toe-off (27%) and ended abruptly at heel contact (100%), with a peak in final swing at 90%. In walking, TA activity started later and extended into stance, with a peak at heel contact.

During running at speeds higher than 3m/sec, the EMG activity for the adductor magnus (AM) shows three peaks: in midstance (18%), in mid-swing (68%) and in final swing (90%). At lower running speeds, EMG activity is low and irregular. The walking profile is different from running, presenting peaks at foot contact (0%) and toe-off (57%).

A study [2] for the hip flexors (iliacus, psoas, sartorius, rectus femoris and tensor fasciae latae) activity during running revealed that all hip flexors were active from about 30-65% of the gait cycle. The rectus femoris activation recorded slightly later (45-65%) which is in accordance with the results of Gazendam and Hof [15], suggesting that RF function is more as a hip flexor than as part of quadriceps (knee extensor). Psoas showed a second peak in late swing, 80-100%. Tensor fasciae latae activity was recorded during stance and early swing (0-50%), supporting the idea of not being a hip flexor. The activation amplitude of iliacus and psoas sharply increased with running speed.

Running speed appears to "interact" with leg muscles contribution to joint and body segment accelerations during dynamic locomotion [9]. Activation patterns of calf muscles (medial gastrocnemius and lateral gastrocnemius) were affected by running speed. When running on a motorized treadmill, runners activated and deactivated both medial (MG) and lateral (LG) gastrocnemius muscles earlier in the step as they run faster (running speed: 2.5, 2.8, 3.2 and 3.5m/sec). Additionally, the activation amplitudes of medial and lateral gastrocnemius increased with increasing running speed (Ahn et al., 2014).

Kyrolainen [26] assessed electromyographic (EMG) activity of the leg muscles (gluteus maximus, vastus lateralis, biceps femoris, gastrocnemius and tibialis anterior) and the ground reaction forces, in 17 elite male middle–distance runners, during running at different speeds. The results showed that the averaged EMG activities of all the muscles increased with increasing running speed, especially in the pre-contact and braking phases.

As running speed increased from 3.5-7 m/sec, the ankle plantarflexors (soleus and gastrocnemius) were mainly responsible for generating higher vertical support forces during ground contact, contributing this way in step length increment. At higher running speeds –above 7m/sec, peak forces developed by soleus and gastrocnemius decreased, while hip muscles – iliacus and psoas combined (ILPSO), gluteus maximus, hamstrings and rectus femoris – generated increased forces and contributed in a vigorous acceleration of hip and knee joints during swing phase, increasing this way step frequency [9].

During level running at moderate speed, hip muscles generate low forces which might reflect a strategy for minimizing metabolic energy cost [38] on the basis of the design of the musculoskeletal system which has been shaped by the need to produce force economically [39,45]. However, during very fast level running (at an exercise intensity equivalent to 115% of peak oxygen uptake), a very high

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level of activity of all of the hamstrings, gluteal and adductor muscles was observed [43]. During uphill running at high speed, the vastus medialis and lateralis and the rectus femoris muscles found to be more active compared to level slow running [49].

Liebenberg [28] investigated how lower extremity muscles are influenced by body weight support during running at different speeds. Muscle activity from the biceps femoris, rectus femoris, tibialis anterior and gastrocnemius was recorded during running on a treadmill, which provided body weight support, at different speed and body weight conditions. Results revealed that muscle activity (average EMG and root mean square EMG) decreased as body weight decreased for all muscles, without however changing muscle activity patterns, and increased across speed for all muscles.

Comparison between treadmill and over-ground running

Treadmills have often been used to investigate human locomotion (walking and running) and to evaluate performance parameters. Treadmill running is a popular training method for distance runners, as it is characterized by decreased ground reaction forces [36] and less stress / load propagated to their bodies compared to over-ground running. When running on a treadmill, the supporting ground (the treadmill belt) is moving relatively to subjects centre of mass (CM), which is opposite to real world bipedal locomotion where subjects centre of mass moves relatively to the supporting ground [33]. As such, many studies have investigated the differences between over-ground / field and treadmill conditions, attempting to answer the question whether over-ground locomotion could be interpreted and related in light of the measurements performed on treadmill.

Comparing over-ground and treadmill running, it was found that in both conditions running step was quite similar. However, differences concerning the kinematic and kinetic parameters were observed [36]. The average speed for instrumented treadmill running (3.80m/sec) was similar compared to the average over-ground running speed (3.84m/sec). The cadence (number of steps / min) was significantly higher and the step time and step length were significantly shorter for the instrumented treadmill running condition. Concerning the angular kinematics, peak knee angles were significantly different between treadmill and over-ground running [36]. The above findings are similar with the results from previous studies [11,41,46]. Elliott & Blanksby [11] reported a shorter unsupported (flight) phase, decreased step length and increased cadence in moderate speeds (3.3-4.8 m/sec) when running on a treadmill compared to over-ground running. Frishberg [14], comparing over-ground (mean velocity 8.54 ±0.09 m/sec) and treadmill (mean velocity 8.46 ±0.13 m/sec) sprinting, found no significant differences in step parameters (frequency, length, support time, flight time) between the two conditions, however, he reported differences in segmental kinematics. When sprinting on a treadmill, the thigh of the support leg was more erect at contact and moved with a slower angular velocity, whereas the shank of the support leg was less erect at contact and moved with a greater range of motion and angular velocity. It has also been reported that when running on a treadmill the foot position at landing is flatter than when running over-ground [34]. McKenna & Riches [31], assessing sprinting kinematics, reported no fundamental differences between field and treadmill conditions.

In contrast, Morin et al. [33] reported that 100m sprint performance parameters were different between treadmill and field conditions, resulting in a lower performance on the treadmill compared to field sprint running. Specifically, the maximal running speed variable was significantly lower on treadmill (Smax = 6.90 ± 0.39 m/sec) compared to the running speed obtained on the track (Smax = 8.84 ± 0.51 m/sec). Nevertheless, the value of treadmill maximal running speed is comparable with the values recorded in previous studies (ranging from 6.10m/sec, [7]), to 11.1m/sec, [48]). Additionally, the variables assessed determining 100m sprint performance – the 100m time and the corresponding mean 100m speed, and the time required for acceleration – are associated with a significantly lower

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performance when running on a treadmill than on the track. However, the time to reach maximal running speed and deceleration time presented no significant differences between field and treadmill.

Differences in kinetic parameters were also observed, comparing treadmill and over-ground running. In treadmill running, the ground reaction forces (GRF) components (peak propulsive force and peak medial force) were significantly reduced, which is associated with the reduced knee moments recorded. Nevertheless, the higher ankle moments and preserved power recorded support the preservation of push-off during treadmill running [36], finding which has been observed in treadmill walking as well [37].

However, Kram [25], attempting to measure the vertical and anterior – posterior ground reaction forces in a treadmill running condition, reported that when running either on a treadmill or overground at the same speed the GRF components were very similar, suggesting that the underlying biomechanics are identical.

It is suggested that familiarity with treadmill running tend to influence biomechanical characteristics of running [27], however, adaptations to treadmill locomotion differ between individuals [34].

As ground reaction forces are decreased while running either on an instrumented treadmill [36] or on a positive - pressure treadmill [23], it is expected some muscles to require less intensities of activation since metabolic cost is reduced [18,19]. According to Hunter's [23] findings, who investigated changes in muscle activation for various lower limb muscles while running on a positive – pressure treadmill at different amounts of body weight support, most of the lower limb muscles showed decreases in activation as more body weight was supported. Specifically, the two vastii muscles (medialis and lateralis) and rectus femoris activities decreased dramatically as more body weight was supported. Peroneus longus activity presented a significantly descending trend with body weight support; however, the amount of this decrease was lower compared to other muscles.

While reduced ground reaction forces may contribute to lower intensity's activation for certain muscles during stance, during the swing phase this decreased activation is not observed for all muscle groups. When using positive – pressure treadmill, compared to a traditional treadmill, some muscle activation patterns may not be altered during the swing phase. During this part of gait cycle, the activity of hip adductors appeared to be relatively unchanged as different amounts of body weight were supported [23], which could be explained by the fact that during the swing phase the function of hip adductors is to keep the swing leg moving in the forward direction [15]. During early stance, the medial and lateral hamstrings remained unchanged as well - independently of body weight condition. Although this phase is related to supporting body weight, it appears that the hamstrings are less involved in body support than expected. However, high muscle activation is necessary in order to produce the appropriate horizontal forces required in running, which were not decreased by the positive – pressure treadmill [23].

It is suggested that when using a treadmill and allowing subjects to accelerate the belt voluntarily, it is possible to interpret – not to reproduce – running performance and evaluate inter-subject differences [33].

Conclusion

During dynamic locomotion, muscular function is affected by running techniques and foot strike patterns, inclined surfaces and running speed. The foot positioning at landing influences running technique and muscle activation patterns. Running at varied inclined surfaces affect lower limb joint function and the corresponding muscle activity. Additionally, it is reported that running speed "interacts" with leg muscles contribution to joint and body segment accelerations during dynamic locomotion, affecting this way muscle activation patterns. Taking into consideration these determinants of running performance and the fact that training adaptation differs between individuals; the above-mentioned parameters should be combined effectively in order to design suitable and beneficial training programs for

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professional and recreational athletes. Many training programs include running on a treadmill which is characterized by decreased ground reaction forces and less stress / mechanical load propagated to athletes' bodies compared to over-ground running, and is speculated that this training method could provide an over-distance running benefit.

Conflict of interest:
The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Κατά τη διάρκεια δυναμικών αθλημάτων τρεξίματος, μικρών ή μεγάλων αποστάσεων, η μυϊκή λειτουργία εξαρτάται από την τεχνική τρεξίματος, το είδος βάδισης του αθλητή, την κλίση των επιφανειών τρεξίματος αλλά και την αναπτυσσόμενη ταχύτητα. Οι σύγχρονες εργομετρικές μελέτες εξετάζουν συγκεκριμένες μυϊκές ομάδες και πως αυτές ανταποκρίνονται στις ανωτέρω μεταβλητές. Σκοπός είναι ο σχεδιασμός εξατομικευμένων προπονητικών τεχνικών βελτίωσης της αθλητικής απόδοσης άρα και επίδοσης ανάλογα με το είδος του τρεξίματος.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: τρέξιμο, μυϊκή δραστηριότητα, επιφάνειες κλίσης, ταχύτητα

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Arthroscopic debridement of minor meniscal lesions: Clinical outcome of three years follow up based on questionnaire and search for causes of failure.

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ABSTRACT

Meniscal debridement of minor lesions remains the most common procedure performed by knee arthroscopy surgeons. Does removing or smoothing the edges of these lesions really alleviate the symptoms? We set up a simple, postal questionnaire in order to let the patients evaluate the outcome of their arthroscopic treatment. We studied 105 patients (78 male and 27 female) with an average of 50,4 years of age, treated in the last 3 years in our department. We recorded the pain, the impairment in daily activities, sports activities and the range of movement, the use of pain killers and the presence of night pain before and after the arthroscopy. We noticed a significant improvement in these parameters in most of the patients (good and excellent results in 80%) but there was also a small percentage that remained unsatisfied (very poor and poor results 13,5%) . The causes of treatment failure in these cases appeared to be coexisting underlying pathology such as lesions of the opposite meniscus and joint instability, patellar instability, end stage chondromalacia, osteoarthritis, elderly age, spinal disease, and hip arthritis.

KEYWORDS: Meniscal tears; arthroscopy trimming

Introduction

The arthroscopic debridement of meniscal tears is a standard technique performed by orthopaedic surgeons. The rationale of removing these small lesions is two-fold; first, to remove, together with the degenerate tissue, the innervation that follows the new vascularization [1,2] after trauma in the meniscus. In the normal meniscus innervation [3,4,5] of the central part is absent. It is only after blood vessels and innervation grows into the central part that symptoms begin [6,7]. The second reason for arthroscopic removal of these lesions is the healing

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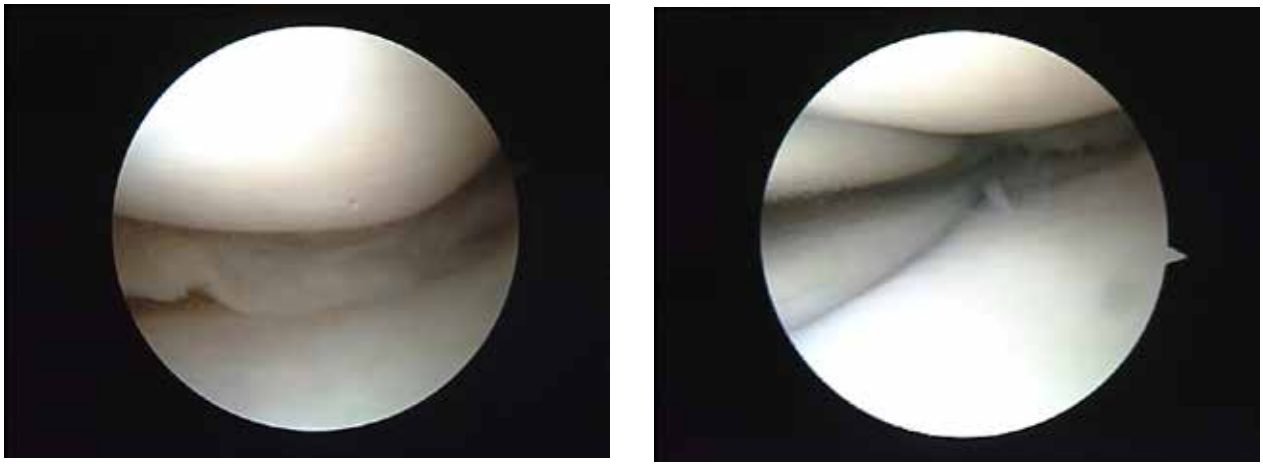

Fig. 1: *Arthroscopic treatment of minor meniscal lesion.*

incapability of degenerate tissue or of tissue in the white on white zone [8]. There are also other causes that generate pain in the knee joint such as plica syndrome [9,10], chondral defect [11], osteoarthritis [12] or more complicated situations such as instability of the knee joint due to anterior cruciate ligament insufficiency [13], patella instability [14] etc. The cause of knee pain can be difficult and can be easily missed. History and careful clinical evaluation are the cornerstones of successful diagnosis, while radiographs and MRI can confirm the final diagnosis.

Despite the thorough diagnostic approach, there is still a percentage of patients that remain unsatisfied after the arthroscopic treatment. The purpose of this study is to evaluate the clinical outcome after arthroscopic debridement of meniscal tears and individualize the possible causes in cases of treatment failure.

Patients and Methods

We studied 105 patients (78 male, 27 female) who underwent arthroscopic treatment of minor meniscal tears in the last tree years in our department (from 1/1/2005 to 1/10/2007). Preoperatively, a meticulous history, erect anteroposterior and mediolateral radiographs and knee MRIs were taken from each patient. The inclusion criteria were a) meniscal symptomatology, b) no radiographic signs of osteoarthritis c) MRI evidence of meniscal injuries, d) small meniscal lesions, affecting less than half the central part of the meniscus, so that removal would not alter the biomechanical stability of the joint e) meniscal cyst that can only be treated arthroscopically f) no other coexisting conditions that could cause joint instability, such as anterior cruciate insufficiency and g) no previous operation on the same knee.

We excluded a) severe meniscal lesions that needed to be repaired b) meniscal cysts treated with open techniques c) cases of anterior cruciate insufficiency and e) previous surgery.

The mean average of patient's age was 50,4 years (range: 23-80). The arthroscopy was performed in 48 right and 57 left knees. The damaged meniscus was medial in 70, lateral in 24 and both in 11 cases. The type of lesion was bucket handle in 12, horizontal cleavage in 6, parrot beak in 2, fibrillation in 8, torn in 14, tear of discoid in 2, flap tear in 2, meniscal cyst in 8, and various tiny lesions in 48 cases (**Fig.1**). The mean follow-up time was 3 years (0.5 – 3).

Arthroscopy was performed under general anaesthesia. The meniscus was approached by the anteromedial and the anterolateral portals in all patients. Eight knee joints were approached by a supplementary third portal (5 high anteromedial and 3 central). We didn't use tourniquet in any patient.

We set up a simple questionnaire (**Fig.2**) that is easy to be completed by the patients, to have their evaluation of the arthroscopic treatment. This

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Questionnaire

		Pre-operatively	Post-operatively	Score
Pain	No pain	☐	☐	2
	Modest pain	☐	☐	1
	Severe pain	☐	☐	0
Daily activities	Not impaired	☐	☐	2
	Slightly impaired	☐	☐	1
	Severely impaired	☐	☐	0
Sport activities	Not impaired	☐	☐	2
	Slightly impaired	☐	☐	1
	Severely impaired	☐	☐	0
Range of movement	Not impaired	☐	☐	2
	Slightly impaired	☐	☐	1
	Severely impaired	☐	☐	0
Pain killers	Never	☐	☐	2
	Intermittently	☐	☐	1
	Regularly	☐	☐	0
Night pain	Never	☐	☐	2
	Intermittently	☐	☐	1
	Regularly	☐	☐	0

Knee score:
Minimum 0 (worst clinical status)
Maximum 12 (best clinical status)

Numeric scale of pain

Pre operative pain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pain score	1	2	3	4	5	6	7	8	9	10
Post operative pain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

No pain **Moderate pain** **Worst Possible pain**

Fig. 2: *Questionnaire, scoring and numeric scale of pain. For each parameter 0 is assigned for the worst, 1 for the intermediary and 2 for the best symptom. Thus, the total knee score could range between 0 for the worst clinical status and 12 for the best, taking into account all 6 parameters that the questionnaire assessed. The questions were answered before and after arthroscopy*

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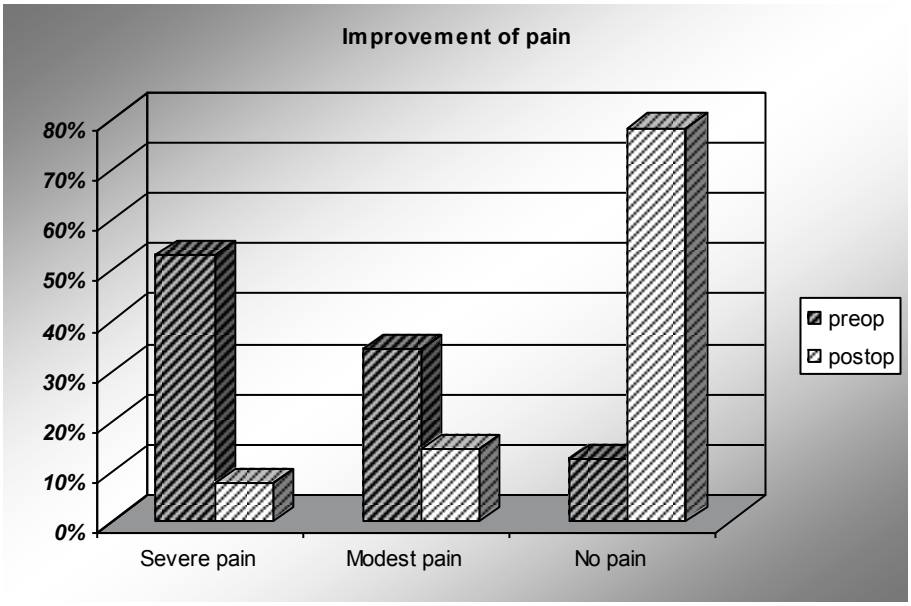

Fig. 3: *Outcome of pain*

questionnaire included: 1) a numeric pain score (0-10), 2) a three grade evaluation of: pain (minor, intermediate, major), daily activities, sport activities and the range of movement (not impaired/slightly impaired/severely impaired), the use of pain killers and the presence of night pain (never/intermittently/regularly). The patient's answers to the questionnaire supplied us with a scoring for further statistical analysis. For each parameter 0 was assigned for the worst, 1 for the intermediary and 2 for the best symptom. Thus, the total knee score could range between 0 for the worst clinical status and 12 for the best, taking into account all 6 parameters that the questionnaire assessed. The questions were answered before and after arthroscopy.

We sent the questionnaire by mail to 210 patients who met the including criteria. After we received their answers, we contacted all patients with complains to obtain further information about it. All data were registered and underwent a statistical analysis with SPSS 10 software.

Results

We recorded one superficial infection treated with antibiotics. We did not notice significant intra-ar-

TABLE 1 *Clinical outcome in 3 years follow up*

		Pre-operatively %	Post-operatively%
Pain	No pain	12,4	78,1
	Medium pain	34,3	14,3
	Severe pain	53	7,6
Daily activities	Not impaired		
	Slightly impaired	3,8	65,7
	Severely impaired	60	28,6
		36,2	5,7
Sport activities	Not impaired		
	Slightly impaired	1	39
	Severely impaired	26,7	42,9
		72,4	18,1
Range of movement	Not impaired		
	Slightly impaired	6,7	53,3
	Severely impaired	54,3	39
		39	7,6
Pain killers	Never	35,2	79
	Intermittently	41	15,2
	Regularly	23,8	5,7
Night pain	Never	21,9	70,5
	Intermittently	45,7	24,8
	Regularly	32,4	4,8

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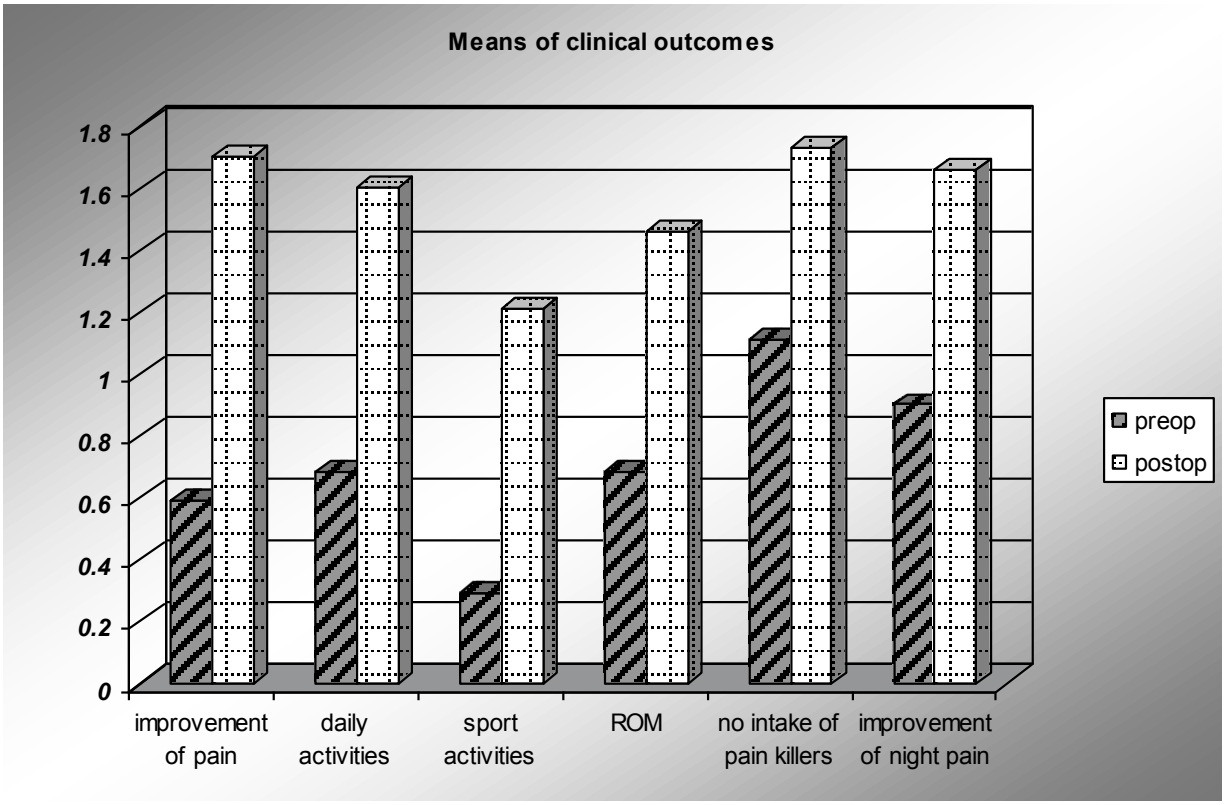

Fig. 4: *Means of clinical outcomes*

ticular bleeding postoperatively in any of the 210 patients who underwent arthroscopy.

The results represent the evaluation of 112 patients (7 questionnaires weren't properly compiled) so we finally had a sum of 105 questionnaires out of 210 asked patients (50%). The mean average of numeric scale pain was 6,28 (range 0-10) preoperatively and 2,20 (range 0-10) postoperatively. Fifty three percent of the patients had severe pain, 34,3% modest pain and a 12.4% had no pain preoperatively. Postoperatively, 7,6% had severe pain, 14,3% moderate pain and 78,1% had no pain (**Fig.3**). Daily activities were severely impaired in 36,2%, slightly impaired in 60% and not impaired in 3,8% of the patients preoperatively. Postoperatively, daily activities were severely impaired in 5,7%, slightly impaired in 28,6% and not impaired in 65,7% of the patients. Performance in sport activities was severely impaired in 72,4%, slightly impaired in 26,7% and not impaired in 1,0% of the patients preoperatively. Postoperatively, performance in sport activities was severely impaired in 18,1%, slightly impaired in 42,9% and not impaired in39,0% of patients. We observed similar results in the range of movement (ROM) that was severely impaired in 39,0%, slightly impaired in 54,3% and not impaired in 6,7% of patients preoperatively. Postoperatively, the ROM was severely impaired in 7,6%, slightly impaired in 39% and not impaired in 53,3% of patients. The daily intake of pain killers was regular in 23,8%, intermittent in 41% and never in 35,2% of the patients preoperatively. Postoperatively, the intake decreased in 5,7% in those who took regular dosages, 15,2% intermittent and 79% never. Night pain was present regularly in 32,4%, intermittently in 45,7% and never in 21,9% of the patients preoperatively. Postoperatively, night pain was present regularly in 4,8%, intermittently in 24,8% and never in 70,5% of the patients (**Table 1**).

The mean overall score of our questionnaire was

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TABLE 2 *Group rating of the clinical outcomes based to our knee score. Evaluation of clinical outcomes*

	Group	Knee score	N. patients	%	
Very poor	I	0-2	5	4,9	13,5
Poor	II	3-5	9	8,6	
Modest	III	6-7	7	6,7	
Good	IV	8-9	20	19,1	80
Excellent	V	10-12	64	60,9	

4,26 (range, 0-10) preoperatively and 9,36 (range 0-12) postoperatively. The mean pain score was 0,59 (range, 0-2) before and 1,70 (range, 0-2) after arthroscopy. The mean score of daily activities was 0,68 (range,0-2) before and 1,60 (range, 0-2) after arthroscopy. The mean score of sport activities was 0,29 (range, 0-2) before and 1,21 (range, 0-2) after arthroscopy. The mean score of the range of movement (ROM) was 0,68 (range, 0-2) before and 1,46 (range 0-2) after arthroscopy. The mean score of pain-killer's intake was 1,11 (range, 0-2) before and 1,73 (range, 0-2) after surgery. The mean score of night pain was 0,90 (range, 0-2) before and 1,66 (range, 0-2) after surgery (**Fig.4**).

Statistical analysis using Pearson's correlation coefficient indicates no significant linear relationship between the time after surgery in neither the numeric scale of pain score r(105)=-0.150, p>0.001, nor the knee score r(105)=0.096, p>0.001 postoperatively. This suggests that we didn't observe the placebo effect, which occurs during the first year, in our series of patients.

The overall scores of our questionnaire ranged between 0 and 12. Based on clinical observations we distinguished five grades of scoring. We considered as very poor results the range between 0 and 2 (group I), poor results the range between 3 and 5 (group II), modest results the range between 6 and 7, good results the range between 8 and 9 and excellent results the range between 10 and 12. Thus, 5 patients had very poor results (4,9%), 9 patients had poor results (8,6%), 7 patients had modest results (6,7%), 20 patients had good results (19,1%) and 64 patients had excellent results (60,9%), (**Table 2**). Nine patients from the first two groups (I and II), (13,5%), had a second operation within 9 months postoperatively. That was an arthroscopy (at 6 of them), a tibial tubercle transfer (patella alta), a medial unicompartmental knee replacement and a total knee replacement. The indication for the second arthroscopy was a missed coexisting lesion in the opposite meniscus in 4 of them, loose bodies intra-articularly and insufficiency of the anterior cruciate ligament. Six of them were treated in our clinic and 3 in other institutes. In groups III-IV the coexisting pathologies that could influence the clinical outcome involved some kind of spinal disease in two patients (spinal stenosis, intervertebral disc herniae), and hip osteoarthritis.

Cartilage lesions, assessed by arthroscopy, were grade II-III in most of the patients (90,4%) and grade IV in 10 of them (9,5%). Six of the 10 (grade IV) had poor results postoperatively (group I and II), three of whom underwent a second operation and more precisely a microfracture treatment of the cartilage damage, a medial unicompartmental knee arthroplasty and a total knee arthroplasty. The other 4 of the 10 patients had modest or good postoperative results (group III and IV) and therefore did not need another surgery in the last 2,5 years. Statistical analysis using Pearson's correlation coefficient indicates a strong association between the grade of cartilage damage and our knee score postoperatively (r =- 0.52). The correlation coefficient is very significant (p < 0.001).

Discussion

The principles of meniscal repair have been described [15,16,17] by many well-established authors. The clinical assessment, before and after surgery, has been described [18,19,20] only for more severe meniscal lesions.

This study claims that there is a clear clinical im-

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provement after the arthroscopic trimming of minor meniscal lesions, when this treatment is based on appropriate indications. In this study we included lesions that occupied less than the central half of meniscus i.e. the white in white region, because such lesions wouldn't make the meniscal structure unstable. Moreover, because in these cases there is no indication for repair due to tissue incapacity to heal. We excluded patients with obvious signs of osteoarthritis in x-ray films or MRI.

Despite the accurate selection of patients without obvious osteochondral signs on imaging studies, we discovered 10 patients (9,6%) with arthroscopic findings of grade IV cartilage damage. The extent of these lesions was limited and for that reason not evident in MRI. Six of these patients had poor results (groups I and II) and the other 4 had good results (groups III and IV). There was strong association between the grade of cartilage damage and our knee score postoperatively ($r = -0.52$, $p < 0.001$).

Following strict including criteria, we had good results (group IV and V) in 80% of the patients. Fourteen patients (13,5%) had poor clinical outcomes (group I and II). The reason behind this failure was a missed concomitant lesion in the opposite meniscus in 4 of them, loose bodies in 1 case, an insufficiency of the anterior cruciate ligament in 1 case, a patella alta in 1 case, and osteoarthritis in 2 cases. In the remaining 5 patients there was not an obvious cause for the persisting pain apart from grade IV cartilage damage and associate synovitis.

Conclusively, this study stresses the good clinical outcome of arthroscopic meniscal trimming of minor lesions, when the appropriate indications are met.

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Ο αρθροσκοπικός γλυφανισμός των ελάσσονων μηνισκικών βλαβών αποτελεί κοινή πρακτική της αρθροσκοπικής αντιμετώπισης παθολογιών του γόνατος. Θελήσαμε να διερευνήσουμε αν η αφαίρεση αυτών των βλαβών και η λείανση της υπολειπόμενης τραυματισμένης περιοχής του μηνίσκου όντως ανακουφίζει από τα συμπτώματα. Χρησιμοποιήσαμε ένα ερωτηματολόγιο αυτό-αξιολόγησης που απεστάλη ταχυδρομικώς στους ασθενείς που υπεβλήθηκαν σε μια απλή αρθροσκόπηση προκειμένου να αξιολογήσουν τα αποτελέσματα της αντιμετώπισης. Μελετήσαμε 105 ασθενείς (78 άρρενες και 27 θήλεις) με μέσο όρο ηλικίας 50,4 έτη, που αντιμετωπίστηκαν στο τμήμα μας τα τελευταία 3 έτη. Καταγράφτηκαν η ένταση του πόνου, η επίδραση στις αθλητικές και στις καθημερινές δραστηριότητες, το εύρος κίνησης της άρθρωσης, η λήψη αντιφλεγμονωδών φαρμάκων και ο νυχτερινός πόνος πριν και μετά την επέμβαση. Από την μελέτη προέκυψε ότι οι περισσότεροι ασθενείς είχαν καλά και εξαιρετικά αποτελέσματα (80%) αλλά όμως ένα μικρό ποσοστό των ασθενών δεν έμεινε ικανοποιημένο (13,5% φτωχά και πολύ φτωχά αποτελέσματα). Οι αιτίες αποτυχίας της αρθροσκόπησης ήταν άλλες συνοδές παθήσεις που υποεκτιμήθηκαν ή διαλάθανε όπως βλάβη και στον απέναντι μηνίσκο, αστάθεια άρθρωσης, αστάθεια επιγονατίδας, προχωρημένη χονδρομαλάκυνση, οστεοαρθρίτιδα γόνατος, μεγάλης ηλικίας ασθενής, παθολογία σπονδυλικής στήλης και οστεοαρθρίτιδα ισχίου.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: Βλάβες μηνίσκων, αρθροσκοπικός γλυφανισμός.

REVIEW ARTICLE VOLUME 69 | ISSUE 4 | OCTOBER - DECEMBER 2018

The role of zoledronic acid in the treatment of post-menopausal osteoporosis.

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ABSTRACT

The purpose of this mini review is to assess the efficacy and safety of zoledronic acid in the treatment of post-menopausal osteoporosis. Osteoporosis is the commonest metabolic bone disease, characterized by decreased bone mass and poor bone quality, resulting in increased risk for fracture. Zoledronic acid is a third-generation nitrogen-containing bisphosphonate used for the treatment of osteoporosis. It is used intravenously once a year and it has been proven to be effective, safe and generally well tolerated. It improves the patient's bone mineral density and reduces the risk for low-trauma osteoporotic fractures. Given the fact that it is given once yearly, intravenously, it is an easy and convenient therapeutic option especially for older patients with polypharmacy who have adherence or tolerance problems with oral bisphosphonates. Its' efficacy and safety are well established in the literature and it continues to be a reliable and safe option, used as a first line treatment in post-menopausal osteoporosis.

KEYWORDS: Zoledronic acid; post-menopausal osteoporosis.

Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue resulting in increased bone fragility and increased danger for fractures [1]. It is the most common metabolic bone disease in developed countries affecting more than 200 million people around the world [2]. It usually affects post-menopausal women and its prevalence increases with age. The most important clinical consequence of osteoporosis is the increased risk for fragility fractures. It is estimated that about 50% of women and 25% of men older than 50 years will suffer an osteoporosis-related fracture in their remaining lifetime [3].

The presence of osteoporotic fractures is associated with increased mortality and decreased quality of life, as many patients fail to return to their previous level of function after an osteoporotic fracture [4]. The high prevalence of the disease and the associated fractures also result in very high economic costs for healthcare systems. Additionally, due to

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the continuously growing number of the aging population around the world, the osteoporosis related fractures pose a great healthcare problem globally and their number is expected to continue to rise [5,6]. It is estimated that the number of people affected by osteoporosis will increase from 44 million to more than 61 million by 2020 in USA and the annual fractures and associated costs will increase by 50%. The worldwide incidence of hip fractures is estimated to be increased by 240% in women and 310% in men between 1990 and 2050 [7].

The clinical importance of post-menopausal osteoporosis.

The main problems caused by osteoporosis related fractures are morbidity, mortality and high health care cost. Therefore, the main goal of any therapeutic intervention is to reduce the incidence of osteoporotic fractures. An age-related decline in BMD can be seen in both men and women but the greater amount of loss happens in postmenopausal women. Age and gender are the two most important predisposing factors for the development of osteoporosis and the majority of patients suffering from this disease are postmenopausal women. The reasons for this are that women have a lower peak bone mass compared to men and also due to the hormonal changes happening after the menopause. Estrogens are very important in preserving bone mass in women and the gradual decline of these hormones after menopause results in increased bone absorption and decline in BMD. Osteoporosis is an asymptomatic disease, meaning that a patient can suffer from it while having few or no symptoms. The disease can exist and progress for years asymptomatically, until its clinical manifestation with skeletal deformities, skeletal pain and osteoporotic fractures. An osteoporotic fracture is defined as a fragility fracture caused after minor force, usually a fall.

The most common osteoporotic fractures are vertebral fractures. In some cases, small vertebral fractures can be asymptomatic but usually they cause great acute or chronic pain and spinal deformity, worsening the patient's quality of life and consisting a great source of morbidity [8]. These fractures usually happen after mild trauma or even simple daily activities like lifting objects or bending. Every fracture is correlated with higher risk for future fractures [9,10,11].

Another common type of osteoporotic fractures are hip fractures which almost always demand surgical intervention and are often considered life threatening conditions in elderly patients. Hip fractures dramatically reduce the patient's quality of life and are correlated with many post-surgery complications including decrease of functional capabilities and increased mortality [12,13]

Long term outcomes are often disappointing regarding patients return to their previous functional status as only one third of patients return to their pre-fracture functional level [14] The main goal of any therapeutic intervention is to reduce the risk for osteoporosis related fractures, mainly using anti-osteoporotic medication, calcium supplementation and lifestyle modifications targeting in fall prevention.

The absolute indications for anti-osteoporotic treatment in the elderly are well studied and documented and include the following categories.

- Patients with fragility fractures.
- Patients with a densitometric diagnosis of osteoporosis (T-score -2.5 or lower at the total hip, femoral neck, lumbar vertebrae, or distal one-third radius)
- Patients with osteopenia and a FRAX® score of >3% or >20% for hip and other major osteoporotic fractures, respectively.

Mode of Action of Zoledronic Acid

Bisphosphonates (BPs) are considered nowadays a first-line treatment against osteoporosis as it is a relatively safe, affordable and very effective category of drugs. The BPs have proven in multiple studies to be able to increase BMD and reduce the risk for osteoporotic fractures [15,16]. They act as anti-resorptives slowing down bone resorption and thus preventing the decrease of BMD. The BPs currently available in Europe are alendronate, risedronate, ibandronate and zoledronic acid. Once BPs

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TABLE 1 *Summarized effect of zoledronic acid on incidence of fractures.*

Study	Endpoint	Absolute reduction in fracture incidence %	Relative risk reduction in fracture incidence %	P value
HORIZON-PFT (Postmenopausal women)	**Vertebral fracture**			
	Over 12 months	2,2	60	<0,0001
	Over 24 months	5,5	71	<0,0001
	Over 36 months	7,6	70	<0,0001
	Hip fracture			
	Over 36 months	1,1	41	P = 0,0024
	Non-vertebral fractures			
	Over 36 months	2,7	25	<0,0001
	Hip fracture			
	Over 36 months	1,1	41	P = 0,0024
	Non-vertebral fractures			
	Over 36 months	2,7	25	<0,0001
HORIZON-RFT (Patients with hip fracture)	**Any clinical fracture**	5,3	35	<0,001
	Clinical vertebral fracture	2,1	46	0,02
	Non-vertebral fracture	3,1	27	0,03
	Hip fracture	1,5	30	0,18

are absorbed, they can be rapidly localized to the skeleton, where they inhibit bone resorption by reducing the creation and activity of osteoclasts and also increasing osteoclast apoptosis. The bisphosphonates mainly act by preventing further bone loss and are connected with minor increases in BMD. Aminobisphosphonates inhibit bone resorption by blocking the action of the enzyme farnesyl pyrophosphate (FPP) synthase in the mevalonate pathway. This reduces osteoclastic bone resorp-

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tion through accumulation of unprenylated small guanosinetriphosphatases within the osteoclast. Bisphosphonates are stable analogues of pyrophosphate, but contain a carbon in the back bone of the molecule (P-C-P in bisphosphonate) instead of an oxygen (P-O-P in pyrophosphate) [17].

BPs have a strong affinity for bone hydroxyapatite. The addition of side chains of different lengths and structures allows many structural variations, producing BPs with a range of potencies and properties, which affects the clinical doses required. Like every other BP zoledronic acid has a high affinity for mineralized bone and binds to the calcium phosphate bone mineral hydroxyapatite mostly at sites with high bone turnover. When compared with alendronate, ibandronate, risedronate, etidronate, and clodronate, zoledronic acid has the highest affinity for hydroxyapatite in vitro [18].

Zoledronic acid has been proved to rapidly reduce the rate of bone turnover, by reducing both bone resorption and bone formation. This is demonstrated by the rapid and marked reduction of biochemical markers of bone resorption and bone formation after the beginning of treatment. These markers were more suppressed after the infusion of zoledronic acid, compared with placebo or weekly oral aledronate [19,20]. Their suppression reached their lower level at 7 days for the resorption markers and at 12 weeks for the formation markers. This well documented reduction at the rate of bone turnover and bone remodeling results in the antiresorptive properties of the drug.

Oral BPs are very effective, but also have important disadvantages. They are poorly absorbed, and are required to be taken on an empty stomach, with no food or drink for the next 30 minutes in order to maximize their absorption. Other disadvantages of the oral BPs are their gastrointestinal symptoms which are very often in the common clinical practice [21,22,23].

Zoledronic acid is a BP which is used once a year intravenously. Its usual dose is 5mg. It has been shown by multiple studies that its use reduces the risk of both hip and vertebral fractures. The fact that the drug is given via intravenous infusion is particularly useful in patients with gastrointestinal symptoms after oral BP administration as it allows to bypass the gastrointestinal system which also deals with the problem of poor gastrointestinal absorption. Its annual iv administration also overcomes the problem of poor patient compliance which is an often phenomenon in oral BPs administration.

Pharmacokinetic properties of Zoledronic acid

The exact pharmacokinetic properties of the drug have not yet been clarified, but it is known that its maximum plasma concentrations are achieved at the end of its infusion. After this, its concentration is rapidly decreased and reaches 1% of its maximal concentration 24 hours after the infusion. This rapid decrease of the levels of the drug in the plasma happens mainly for two reasons. First it is bound to bone very fast due to its high affinity for hydroxyapatite and secondly it is quickly excreted from the kidneys [24]. The drug cannot be metabolized in humans and a great amount of it, estimated about 39% is excreted intact in the urine by the kidneys , in the first 24 hours [24]. The amount of drug bound to the bones can remain there for years and can be released back to the plasma very slowly. The exact rate of release from the bone is not known but it can be detected in the urine even 8 years after the last treatment. Mild or moderate renal failure do not change its clearance compared to normal renal function and the drug can be used safely in these patients. Severe renal failure is the main contraindication for the drug as it is exclusively excreted by the kidneys and there are no data on its use in this population [25].

Therapeutic efficacy of Zoledronic acid

The largest and most important clinical trial considering the use of zoledronic acid for the treatment of postmenopausal osteoporosis was the HORIZON-Pivotal Fracture Trial. It included 7765 postmenopausal women, 65-89 years old which had a femoral neck T-score of -2.5 SD or lower with or without existing vertebral fractures or T-score -1.5 SD or lower and existing vertebral fractures. Patients randomly received 5mg zoledronic acid once a year (n=3889),

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or placebo (n=3876), at the beginning of the trial, 12 and 24 months after. Their follow up continued for three years. The trial proved that patients who underwent treatment with zoledronic acid experienced less vertebral, hip and other osteoporotic fractures and also less days of limited activity because of back pain or fractures, compared to those receiving placebo [26].

Zoledronic Acid and Vertebral fractures.

Vertebral fractures are some of the most usual types of fragility fractures, affecting millions of post-menopausal women. They can be identified either clinically or radiographically. Many new vertebral fractures are identified only radiographically as they are asymptomatic and do not become clinically apparent until multiple fractures occur.

The clinical importance and treatment options of these asymptomatic fractures is not clarified in the literature, nevertheless they are a frequent consequence of osteoporosis and most importantly a good predictor for subsequent fractures. Sustaining numerous vertebral fractures leads to clinically important outcomes, such as changes in height and posture which results in obstructed breathing, increased risk of fall, chronic pain, and functional limitations.

The HORIZON study indicated that there was a relative decrease of 70% in new vertebral fractures after treatment with zoledronic acid, compared with placebo. Regarding multiple vertebral fractures the same study showed a relative decrease of 89% in people treated with zoledronic acid , compared with placebo.

Zoledronic acid and Hip fractures

Hip fractures are considered the most important clinical outcome of osteoporosis because of the associated increase in morbidity and mortality. Many patients suffering a hip fracture are unable to return to their prior level of functioning and independence, resulting in substantial social and financial costs. Treatment with zoledronic acid has proved to be effective as it demonstrated a 1.1% absolute reduction and 41% relative reduction in the risk of hip fractures over a median duration of follow-up of 3 years. The absolute fracture rate was 1.4% after treatment with zoledronic acid versus 2.5% at the placebo group [26].

Zoledronic Acid and Non-vertebral fractures

The HORIZON study reported a reduction of the incidence of overall clinical fractures, including hip fractures. The absolute fracture rates in the zoledronic acid and placebo groups at 36 months were 8.4% and 12.8%, respectively, demonstrating a 4.4% absolute reduction in fracture incidence.

Zoledronic Acid and Risk for second fracture.

The Horizon study estimated the role of zoledronic acid in patients with established osteoporosis or osteopenia and existing vertebral fractures. The drug proved to be very effective, but the study did not consider secondary prevention of new fractures after a first hip fracture. This led to the design of a new phase 3 randomized controlled trial (RCT), the Horizon RFT (Recurrent Fracture Trial), in which 1065 male and female patients were randomized to receive a 5-mg infusion of ZOL and 1062 patients received a placebo infusion within 90 days after surgical repair of a hip fracture, with annual infusions of drug or placebo thereafter until the study end. As in the previous Horizon PFT, all patients received daily oral calcium (1000–1500 mg) and vitamin D (400–1200 IU). The result of the study after a follow-up of 22 months was a significant 35% reduction in any new clinical fracture (8.6% in the ZOL group and 13.9% in the placebo group) [27]. More specifically, any new clinical vertebral fractures (46%) and nonvertebral fractures (27%) were significantly reduced in patients who received zoledronic acid. However, although there was a reduction of second hip fractures in the ZOL group compared with placebo (30%), this did not reach statistical significance. Regarding the safety of this practice there was the expected significant increase in acute phase response (APR) reactions within 3 days of the first infusion in the ZOL group compared with placebo, but not after subsequent infusions. There was no difference in serious adverse events including atri-

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al fibrillation and stroke and during the follow-up there was a 28% reduction in deaths in the ZOL group compared with placebo.

Zoledronic Acid and BMD changes

In the HORIZON-PFT study the BMD was measured at the lumbar spine, femoral neck and total hip and the percentage of change before and after treatment was also used to estimate the efficacy of the treatment. It was proved that the treatment with zoledronic acid significantly increased BMD at the lumbar spine, total hip and femoral neck, relatively to treatment with placebo at time points 12, 24, and 36 months. Specifically it resulted in a 6.7% increase in BMD at the lumbar spine, 6.0% at the total hip, and 5.1% at the femoral neck, over 3 years, compared to placebo.

Zolendronic Acid, Falls prevention and overall quality of life.

Another important aspect of osteoporotic fractures is the danger of fall. BMD is the main factor determining the risk for fracture but falls are the necessary aspect of almost every osteoporotic fracture. More than 90% of osteoporotic hip fractures result after falls. Some studies indicate that falls can have an equally important role as BMD in the pathogenesis of a fracture in the elderly [28].

Recent research indicated that except its already known therapeutic effects, zoledronic acid is connected with a reduced risk of falls. The balance ability and the fall risk before and after two years of treatment was calculated and the results indicated that the risk of falls was reduced at patients treated with zoledronic acid. It was also demonstrated in the same research that therapy was able to improve the overall health related quality of life [29].

Regarding the overall quality of life of osteoporotic patients , treated with zoledronic acid, there are little data, but they suggest that it is beneficial. In an analysis of the HORIZON-PFT trial, patients treated with zoledronic acid were shown to experience less days of limited activity caused by back pain or fracture, compared to those receiving a placebo [30]. It was also reported that treatment with zoledronic acid reduced the number of bed days related to a fracture [31].

Comparison of zoledronic acid with other anti-osteoporosis therapies

The anti-fracture effect of ZOL is impressive but it is hard to directly compare this with other osteoporosis therapies due to differences in study designs. The overall antifracture efficacy is impressive at both vertebral and nonvertebral sites and almost identical to the extremely potent antiresorptive therapy with denosumab. Compared with placebo, denosumab reduced vertebral, nonvertebral, and hip fractures by 68%, 20%, and 40% respectively [32]. These outcomes are very similar to those demonstrated in the HORIZON PFT. Regarding other bisphosphonates, ZOL in a single annual infusion was compared with weekly oral alendronate in women with osteoporosis. In a 24-week trial, 1 week after the first dose of both drugs, ZOL induced a greater reduction in the bone resorption markers urinary N-telopeptide of type I collagen and for serum β-C-telopeptide of type I collagen with the greater reduction continuing through the 24 weeks of observation [33].

In another comparator study, women who had already been taking alendronate for at least 12 months were randomized in a double-blind fashion to 70-mg weekly alendronate or a single infusion of 5 mg of ZOL and followed up for 12 months. The study concluded that there were only small increases in BMD from baseline in both groups and there was no superiority of either drug. This demonstrated that alendronate users could be effectively switched to ZOL but there was no specific benefit over simply continuing with alendronate therapy [34].

Complications related to treatment with Zoledronic Acid.

In general, treatment with zoledronic acid is safe and well tolerated by patients. Complications related with treatment are relatively rare and can be categorized in six main groups: acute phase reaction (APR), hypocalcemia, renal dysfunction, cardiovascular complications, eye inflammation, osteonecro-

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sis of the jaw and atypical subtrochanteric fractures. The commonest complications are acute phase reactions which resemble the symptoms of flu, like fever, headache, myalgia and arthralgia. These reactions usually happen the first three days after drug administration and symptoms usually resolve spontaneously without special treatment [35].

Acute phase reaction becomes apparent within 24-36 hours and consists mainly of fever and musculoskeletal pain. All symptoms considered as acute phase reaction present in the first 2 days after the drug infusion, with their incidence being rare after 3 days. The pathogenesis of these reactions is not fully understood but they are believed to be caused by release of inflammatory cytokines by T cells in the circulation [36].

The most important symptoms consisting the clinical condition of acute phase reaction are: fever, musculoskeletal (pain and joint swelling), gastrointestinal (abdominal pain, vomiting, diarrhea) and general symptoms (including fatigue, nasopharyngitis, edema). The most usual event is fever, which, together with non-specific symptoms such as chills and flushes, occur in about 20% of zoledronic acid-treated patient. About the same proportion of patients can suffer acute musculoskeletal symptoms, mainly pain, which is experienced as a generalized discomfort. Also, the patients can suffer from stiffness of the joints and muscles, and about 10% experience joint swelling. Another common complaint during acute phase reaction is symptoms from the gastrointestinal system. Nausea, vomiting, abdominal pain and diarrhea are the main complaints of patients. Regarding the severity of the symptoms, it was rated by patients as mild or moderate in more than 90% of the events [37].

The acute phase reaction does not pose a serious threat to the patient's health but in some cases, it can cause great discomfort to the patient or even results to absence from work and activity.

The presence of these reactions after a treatment can affect the patient's overall compliance to the anti-osteoporotic treatment plan, as patients can possibly avoid the next programmed drug administration being afraid of the recurrence of symptoms. The danger of acute phase reactions has been found to be reduced by the administration of acetaminophen or ibuprofen before injection of zoledronic acid and three days after that [38]. In general, most of the symptoms of acute phase reaction are easily managed with acetaminophen or NSAIDS.

The possibility of APR should be noted in order to gain informed consent from the patients. It is also important to inform the patient that the risk is for APR is greatly reduced on redosing. The above information is essential, as patients who have already experienced APR are usually very concerned about new APR after redosing.

In conclusion, the APR is by far the commonest side effect from the use of iv amino-bisphosphonates, and all patients should be informed about it. Despite its high incidence, it is usually of mild to moderate severity and lasts only a few days. For the above-mentioned reasons, it usually has minimal impact on long-term compliance to therapy. It is less common in patients who have previously used bisphosphonates. There is evidence that its severity can be reduced by half with co-administration of acetaminophen, so the short-term use of this drug is advised in patients receiving their first iv dose of an amino-bisphosphonate in order to lessen the risk of APR.

Hypocalcaemia is a complication that can occur after any BP treatment if the patient has calcium or Vitamin D deficiency and does not receive a rich in calcium diet or supplementation, as BPs drastically change bone metabolism. The use of calcium and Vitamin D supplementation is a common practice in every osteoporotic patient treated with BP, thus hypocalcaemia in these patients is extremely rare. As the hypocalcaemia can be preexisting before therapy and be rapidly deteriorated with its onset it is advised that all patients should be assessed regarding their calcium and vitamin D levels before initiating treatment with zoledronic acid. Preexisting low calcium levels is a contraindication for treatment with biphosphonates and should be corrected with calcium and vitamin D supplements before the onset of the treatment with zoledronic.

Renal complications are rare and of minor clinical

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importance in otherwise healthy patients. In general, all intravenous bisphosphonates are associated with infusion rate-dependent effects on renal function, such as minor increase in serum creatinine levels or urinary protein. Studies have shown that in long term use, creatinine clearance is not deteriorated and no renal function is affected after zoledronic acid treatment [39]. Serum creatinine monitoring and increased hydration are recommended before every dose infusion only in cancer patients, in which prolonged infusion times and dose reduction are used depending on the creatinine clearance rate. In otherwise healthy patients the use of iv zoledronic acid for the treatment of osteoporosis is only contraindicated if they have severe renal impairment (creatinine clearance<35 ml/min) [40].

Cardiovascular complications are extremely rare and the mechanism connecting them to BP treatment is not known. The HORIZON study found that incidence of atrial fibrillation was increased in patients receiving zoledronic acid treatment compared with the placebo group [26]. On the contrary these findings were not supported by other large epidemiology studies, which did not find increased risk of atrial fibrillation after BP treatment. Regarding the severity of this possible complication and the widespread use of BPs as a first line treatment for osteoporosis, the FDA reviewed all the clinical studies involving BPs and concluded in 2008, that across all studies there was not observed a clear association between overall bisphosphonate exposure and the rate of atrial fibrillation.

Inflammatory eye reactions have been associated with bisphosphonate use, in older research, particularly with iv infusions of pamidronate. In various studies a number of different diagnostic labels were used to describe these symptoms (conjunctivitis, episcleritis, panophthalmitis), and all these represent a similar syndrome. The most common signs of this rare complication are lid edema, conjunctival hyperemia, and chemosis, while common symptomatology includes pain, diplopia, and blurry vision. In the HORIZON study, only one case of iritis presented in the patients receiving ZA treatment, which was successfully treated, resulting in no further problems [41]. A review of the literature in 2012 found fourteen published case reports, regarding this complication [42]. Another more recent review found in 2015 that there was a total number of 29 cases in the literature [43]. The majority of cases (22/29, 76%) were associated with i.v. zoledronic acid infusion and the eye inflammation occurred the first month after infusion. The majority of patients underwent steroid treatment and the vision resolved in all patients except one case, in which anterior ischemic optic neuropathy occurred and caused permanent damage. Despite of its rare incidence, physicians should be aware for this possible complication.

Osteonecrosis of the jaw is probably the most notorious BP treatment complication as despite its extremely low frequency in healthy patients, it receives a great amount of interest from patients and also health care providers such as dentists. Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) can be developed after treatment with both oral or intravenous BPs. This condition manifests as exposed non-vital bone in the maxillofacial area. The main event that triggers the development of this condition is trauma, usually after extended dental procedures. Trauma to the dentoalveolar structures becomes critical as they have a limited bone healing capacity due to the bisphosphonate therapy. The majority of patients developing BRONJ are cancer patients which are treated with high and frequent doses of intravenous BPs [44,45].

Other risk factors for ONJ except cancer and dental trauma, include duration of bisphosphonate exposure, sequential intravenous bisphosphonate therapy (pamidronate followed by ZOL), osteoarthritis or rheumatoid arthritis [46,47]. In 2014 the American Association of Oral and Maxillofacial Surgeons recommended changing the term BRONJ to medication-related osteonecrosis of the jaw (MRONJ), as other antiresorptive drugs, like denosumab have also been related to jaw osteonecrosis cases. Most studies indicate that the use of the recommended dose of 5mg of zoledronic acid once a year, for the treatment of postmenopausal osteoporosis does not affect the frequency of osteonecrosis of the jaw [48].

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Another study demonstrated that even if this problem can occur in up to 5% of bisphosphonate users with cancer of various varieties such as myeloma, it is extremely rare in those receiving lower doses for the management of osteoporosis, estimated as low as 1 in 100,000 [49]. In order to avoid this rare complication physicians can use simple preventive measures, such as screening of the patients dental hygiene and performing any invasive dental procedures before the onset of treatment.

Regarding the atypical subtrochanteric fractures, a number of recent case series have indicated that low trauma subtrochanteric hip fractures are increased in patients who are receiving BP treatment for many years [50,51,52,53,54]. Although the optimal duration of BP treatment is not clarified and the long-term use of BPs is relatively safe, this complication is of great importance for two reasons. First, osteoporosis is a chronic disease demanding long term therapeutic options, for often more than a decade and secondly this type of fracture poses an important complication affecting radically the patient's quality of life. Regarding the risks associated with this complication, in 2009, the American Society of Bone and Mineral Research (ASBMR) convened a multidisciplinary, international task force to clarify the risk of long-term BP therapy regarding atypical subtrochanteric fractures. The task force reviewed all research on this topic and concluded in 2010 that the incidence of atypical subtrochanteric fractures associated with BPs was very low particularly compared to the number of vertebral, hip and other fractures prevented by BPs. It concluded that a causal association between BPs and atypical subtrochanteric fractures could not be established [55].

Another review demonstrated that even if the relative risk of atypical subtrochanteric fractures is high in patients on BPs, their absolute risk is extremely low, ranging from 3.2 to 50 cases per 100,000 patients [56]. Thus, these fractures are extremely rare, particularly compared against the incidence of common osteoporotic fractures of all types, which have been proven to decrease with BP therapy. Despite the rare possibility of atypical fractures, this scenario should be considered among patients receiving long BP therapy and reporting unexplained thigh pain.

Zoledronic acid, patients' compliance and cost-effectiveness

Despite the fact that osteoporotic fractures are one of the commonest reasons for hospitalization in the elderly, connected with high cost, morbidity and mortality, osteoporosis is often underdiagnosed and undertreated. Even when patients are diagnosed with osteoporosis, often after a first osteoporotic fracture, and antiresorptive treatment is started, a great number of patients discontinues therapy.

One important issue to consider is the patient's compliance with long-term intake of a medication for an essentially asymptomatic condition. Poor compliance is a well-documented and well-studied problem in these patients. The effectiveness of anti-osteoporosis treatment is greatly reduced because of poor patient adherence. Some research indicates that only 20% of women with osteoporotic fractures receive treatment, 50% do not take the treatment as prescribed, and 50% discontinue therapy after six months [57]. Another study indicated that only 50% of women with osteoporosis and multiple risk factors, receiving anti-osteoporosis treatment, perceived themselves to be at increased risk of fracture [58].

Some of the most usual reasons for poor adherence include poor patient education, a lack of patient understanding of their condition, patients concern about side effects, dosing intervals, polypharmacy, asymptomatic disease manifestation ('silent disease') and an overall underestimation of the risk for fracture. Poor patients adherence is associated with elevated fracture risk and this underlines the importance of compliance and persistence [59].

Oral BP treatment has a number of disadvantages compared to iv therapy which are responsible for the patient's poor compliance to therapy. BPs are poorly absorbed by the gastrointestinal system due to their large molecular structure,low lipophilicity and negative charge [60]. Less than 1% of oral

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bisphosphonates are absorbed when given per os. This very low bioavailability of orally administered bisphosphonates necessitates a very strict daily or weekly administration routine that often interferes with the patient's regular daily routine. The patient must take the oral bisphosphonate while fasting, with a glass of water, and must not eat, drink, take any other medication or lie down for 30 minutes, in order to increase their poor absorption and decrease the risk of gastro-esophageal reflux. These constraints have raised adherence issues [61,62].

Zoledronic acid is a therapy administered to patients intravenously on a yearly basis and this means greater compliance of patients and guaranteed absorption and bioavailability [63,64]. Patients seem to prefer these less frequent dosing regimens and intravenous (IV) infusion to the oral intake of bisphosphonates [65,66].

Conclusively, treatment of osteoporosis and especially postmenopausal osteoporosis with zoledronic acid is well-documented to increase BMD and reduce the risk for any osteoporotic fracture. It is relatively safe and well tolerated. Considering the fact that patient adherence to oral BPs is relatively low in terms of peptic disorders or frequent intake, the once a year treatment plan with ZA can provide an important and useful treatment option.

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Η οστεοπόρωση αποτελεί την συχνότερη μεταβολική πάθηση των οστών και χαρακτηρίζεται από μειωμένη οστική πυκνότητα και ποιότητα με αποτέλεσμα τον αυξημένο καταγματικό κίνδυνο.Το ζολεδρονικό οξύ είναι ένα διφωσφονικό τρίτης γενιάς που χορηγείται ενδοφλέβια μια φορά τον χρόνο για την θεραπεία της οστεοπόρωσης και έχει αποδειχθεί πως είναι εξαιρετικά αποτελεσματικό και ασφαλές. Βελτιώνει την οστική πυκνότητα των ασθενών και μειώνει θεαματικά τον κίνδυνο για οστεοπορωτικά κατάγματα. Λόγω της ετήσιας ενδοφλέβιας χορήγησής του, είναι μια εύκολη και πρακτική θεραπευτική επιλογή, ειδικά σε ηλικιωμένους ασθενείς με πολυφαρμακία ή σε ασθενείς με πτωχή συμμόρφωση στα από του στόματος διφωσφονικά. Η αποτελεσματικότητα και η ασφάλειά του είναι καλά τεκμηριωμένες και εξακολουθεί να παραμένει μια αξιόπιστη και ασφαλής επιλογή ως θεραπεία πρώτης γραμμής για την μετεμμηνοπαυσιακή οστεοπόρωση.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: Ζολεδρονικό οξύ, μετεμμηνοπαυσιακή οστεοπόρωση

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CASE REPORT

Alveolar rhabdomyosarcoma of the thenar eminence in a 7-year-old child. A case report.

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ABSTRACT

Rhabdomyosarcoma is a highly malignant soft tissue tumor that develops from muscle cells. It is the most common soft tissue sarcoma in children and adolescents and rarely occurs in the hand. Alveolar rhabdomyosarcoma is the commonest histological subtype seen and has the worst prognosis. We report a case of a 7-year-old child, with an alveolar rhabdomyosarcoma of the right thenar eminence, which was treated by wide surgical excision, followed by adjuvant chemotherapy and radiotherapy. Seven years after the operation, no recurrence or metastasis has been observed and the patient remains tumor-free.

KEY WORDS: tumor; soft tissue; rhabdomyosarcoma; hand; thenar eminence

Introduction

Rhabdomyosarcoma (RMS) is a highly malignant tumor that develops from muscle cells. It is the most common sarcoma in children and adolescents, where accounts for more than 50% of all soft tissue sarcomas [1]. RMS can occur in different body areas, most commonly in the head, neck, genitourinary system and retroperitoneum. About 15% of the reported cases involve the extremities and only 7% of them the upper extremity. Primer hand involvement is rare [2].

There are four histological subtypes: embryonal (in infants and young children), alveolar (in older children and adolescents), botryoid (in infants and young children, typically in the vagina) and pleomorphic (older patients 40-70 years old) [2]. It is presented as a rapidly growing, painless mass and a series of tests and procedures are necessary for its diagnosis, including x-rays, ultrasonography (US), computerized tomography (CT), magnetic resonance imaging (MRI) and tumor biopsy (TB) [3].

Alveolar RMS arising in the hand has been associated with poorer prognosis (50% five year survival) than other subtypes. In some cases, its small size and asymptomatic behavior can delay tumor detection and lead to the presence of metastases at

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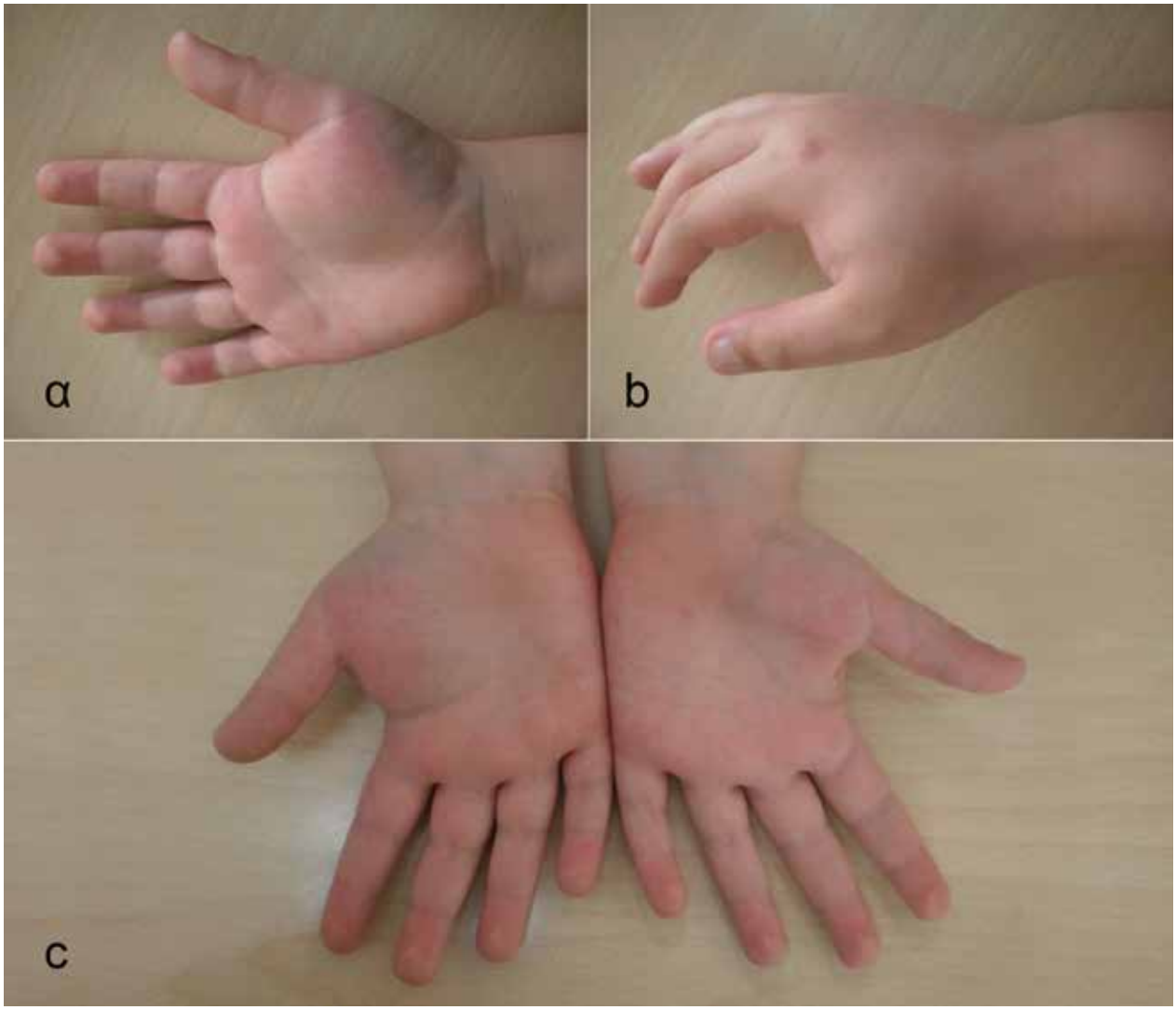

Fig.1: (a-c) *Preoperative pictures of the right thenar eminence.*

the time of its initial diagnosis. Thus, early detection and application of the appropriate treatment of RMS are crucial for patient's survival [4].

We report a case of a 7-year-old child, with an alveolar RMS of the right thenar eminence, which was treated by wide surgical excision, followed by adjuvant chemotherapy and radiotherapy. Seven years after the operation, no recurrence or metastasis has been observed and the patient remains tumor-free.

Case Report

On April 2011, a 7-year-old boy was presented to our department with an enlarging, painless, immobile, hard mass of his right thenar eminence, which was first noticed by his mother about one month earlier. There was no history of trauma, fever, chills or weight loss. Clinical examination revealed a non-tender, fixed, hard, solid mass, with no irritation or changes of the color and trophism of the overlying skin (**Fig. 1a-c**). Local neurovascular elements and the range of motion of the thumb were not disturbed.

During imaging tests, on the anteroposterior and lateral radiographs, a soft tissue shadow was observed in the region of the right thenar eminence (**Fig. 2a-b**). The US examination showed a solid,

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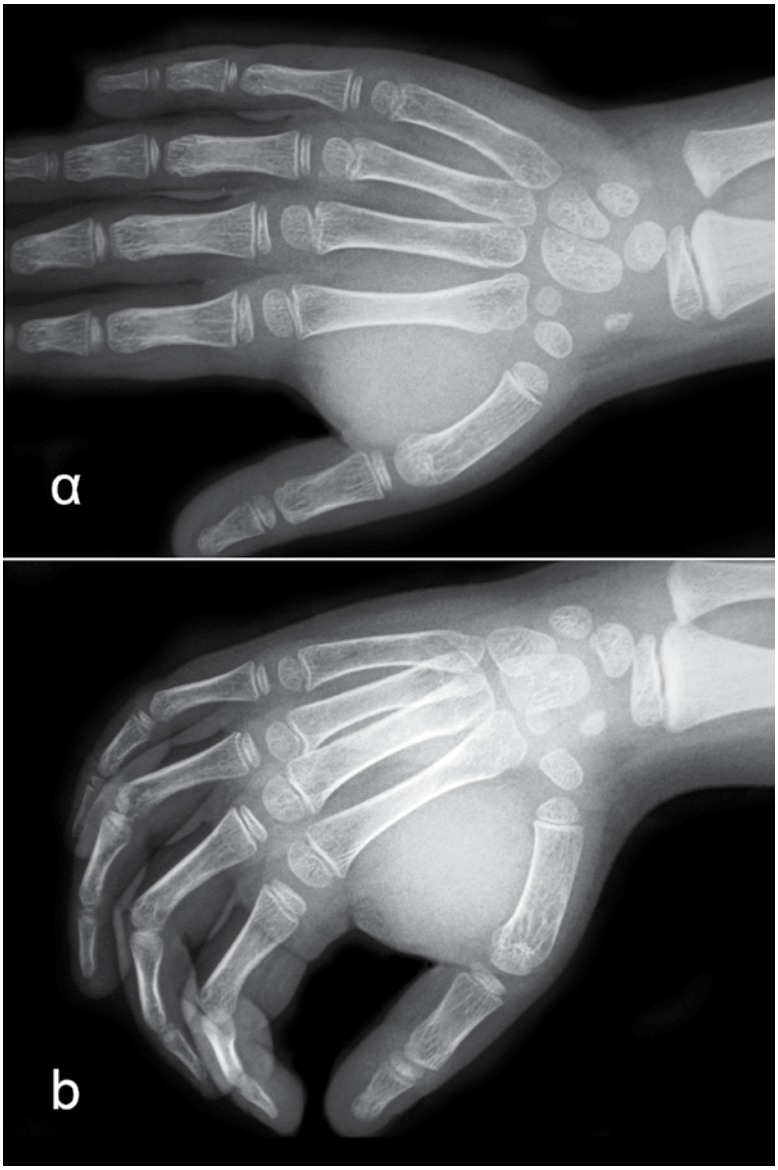

Fig. 2: ***(a)*** *Anteroposterior and* ***(b)*** *lateral preoperative radiographs of the right hand show a soft tissue shadow in the region of the right thenar eminence.*

lobulated mass, with intense vascular flow and no bone infiltration. The MRI scan revealed a heterogeneous, solid, lobular contoured mass, of about 4.5 x 2.0 x 1.5 cm in size, with low signal intensity on T1 images and high signal intensity on T2 images (**Fig. 3a-d**).

A wide surgical excision of the tumor was performed, followed by a histopathological examination (**Fig. 4a-b**). Histologically, the mass was composed of groups of poorly differentiated, small, round cells, which were separated and surrounded by dense fibrous septae. Multinucleated giant cells were also present within the tumor (**Fig. 5a**). Immunohistochemistry showed that the tumor cells were strongly positive for myoglobin, desmin, vimentin, MyOD1 and Myl-4 and focally positive for CD99, CD56, INI-1 and S-100p (**Fig. 5b**). A diagnosis of alveolar rhabdomyosarcoma was confirmed.

Because of negative surgical margins, there was no need for reoperation and radical surgical clear-

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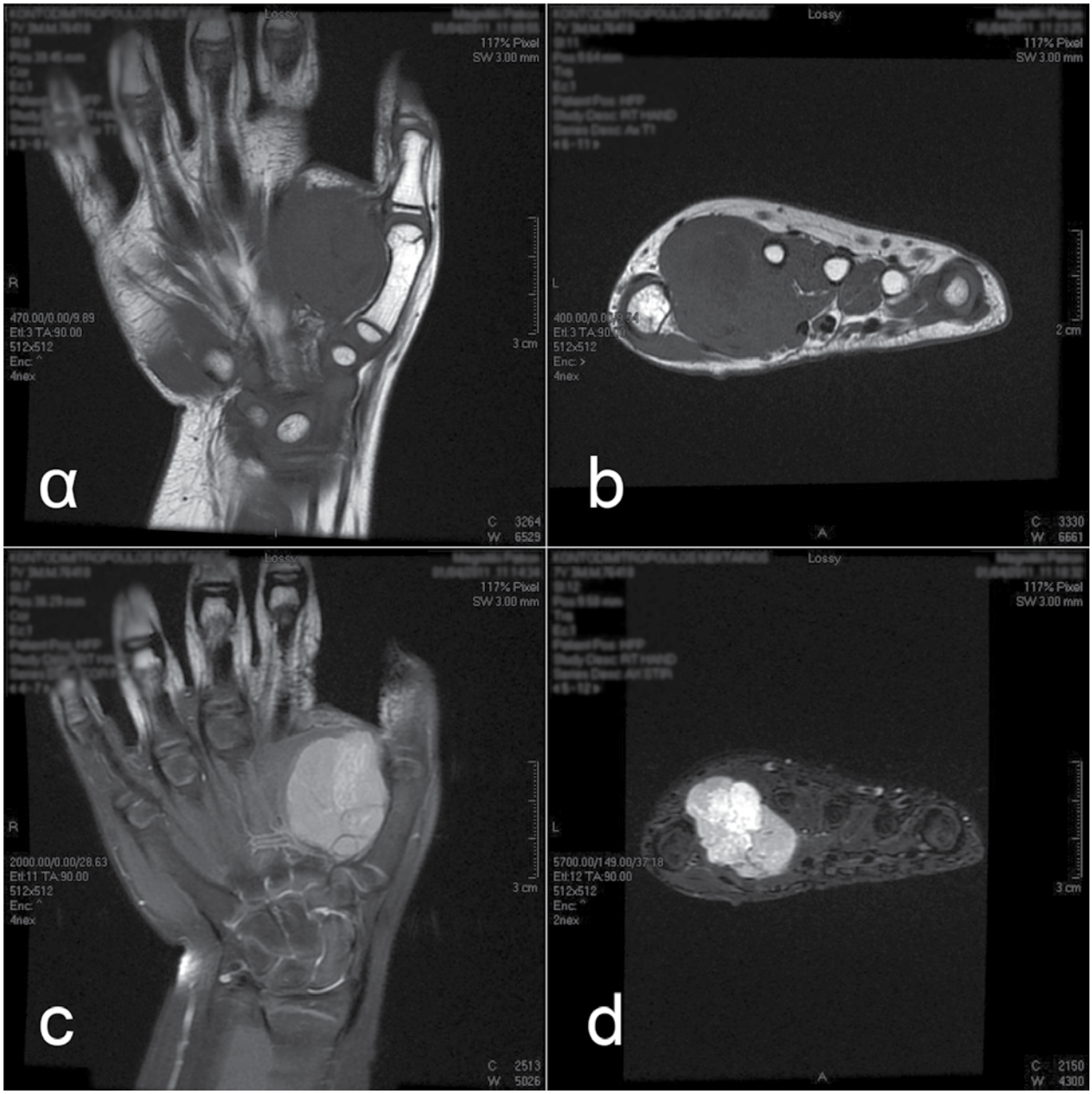

Fig. 3: ***(a)*** *T1 weighted coronal and* ***(b)*** *axial MRI; a solid hypointense mass lesion is observed.* ***(c)*** *Contrast enhanced coronal and (d) axial MRI show dense contrast enhancement.*

ance. A CT scan of the abdomen and chest, as well as a whole body bone scan, were also performed and there was no sign of metastasis. On consultation with an oncologist, it was decided the application of six cycles of external beam radiotherapy (RT) and four cycles of chemotherapy with vincristine and actinomycin.

Sixteen months postoperatively, a full clinical and imaging workup was done and no local recurrence or metastases were found (**Fig. 6a-b**). Seven years after the operation, the boy remains tumor-free, with a full range of motion of his right thumb and no other local disturbances.

Discussion

Rhabdomyosarcoma is the most common soft tis-

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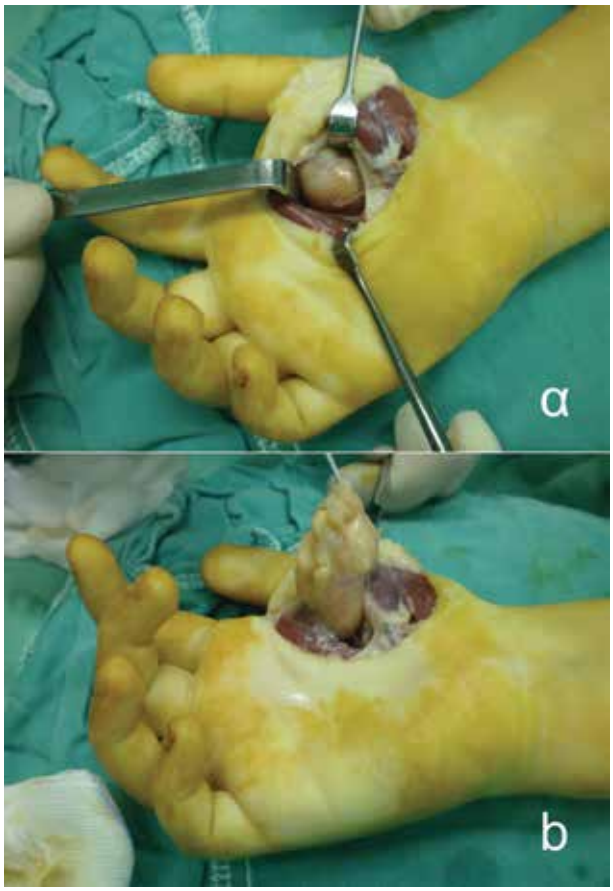

Fig. 4: (a-b) *Intraoperative pictures of wide surgical tumor excision.*

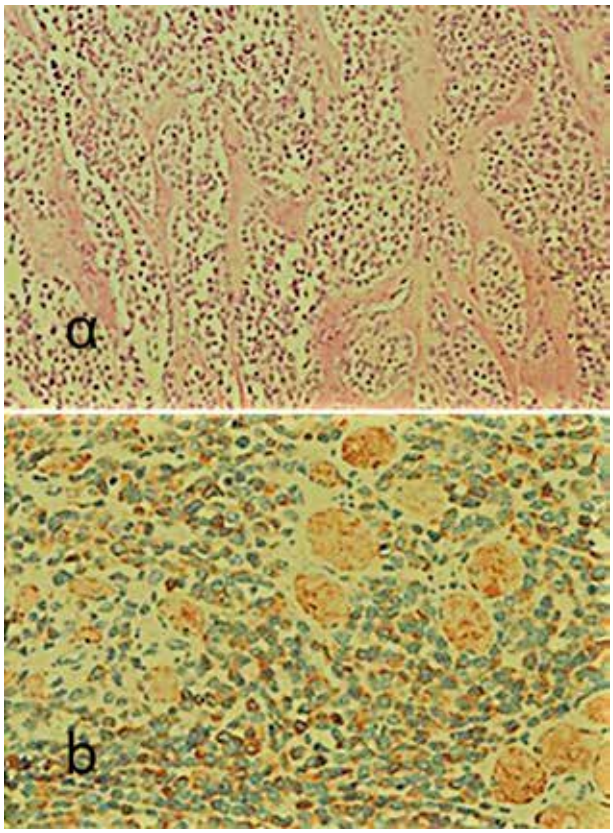

Fig. 5: (a) *Diffusely infiltrating tumor cells loosely attached to fibrous septa peripherally with central loss of cohesion.* ***(b)*** *Diffuse desmin positivity within the tumor cells and the entrapped normal muscle fibers.*

sue tumor in children that accounts for more than 50% of all soft tissue sarcomas [1]. It is a highly malignant neoplasm which can invade the surrounding tissues, as well as to disseminate via lymph and blood flow and metastasize to the lymph nodes, lungs, bones, bone marrow, liver, breast etc [5]. According to the literature, about 15% of all RMS occur in the extremities and have poor prognosis irrespective of the kind of treatment applied. Involvement of the hand seems to be extremely rare and is reported only in a few cases [2]. By the way, despite the fact that the majority of soft tissue sarcomas about the hand are painless, sometimes early detection of RMS primarily occurring in the hand can lead to a good prognosis [4]. Synchronous appearance of multifocal RMS has also been reported [6]. Many of the limb RMS in previous studies, had metastases at the time of initial presentation [5].

Histopathologically RMS is classified in four subtypes: embryonal, alveolar, botryoid, and pleomorphic. This classification is correlated with prognosis [2]. Alveolar RMS is more common in older children and adolescents and accounts for 32% of all rhabdomyosarcomas. It displays a more aggressive clinical course and has worse prognosis than the other subtypes [7]. Microscopically, RMS must be differentiated from other small round blue cell malignant tumors such as neuroblastoma, lymphoma, leukemia, Ewing's sarcoma and metastatic disease [8]. In the differential diagnosis of RMS must be also considered benign tumors like lipoma, neurofibroma and rhabdomyoma and other lesions like hematoma, pyogenic myositis, and myositis ossifi-

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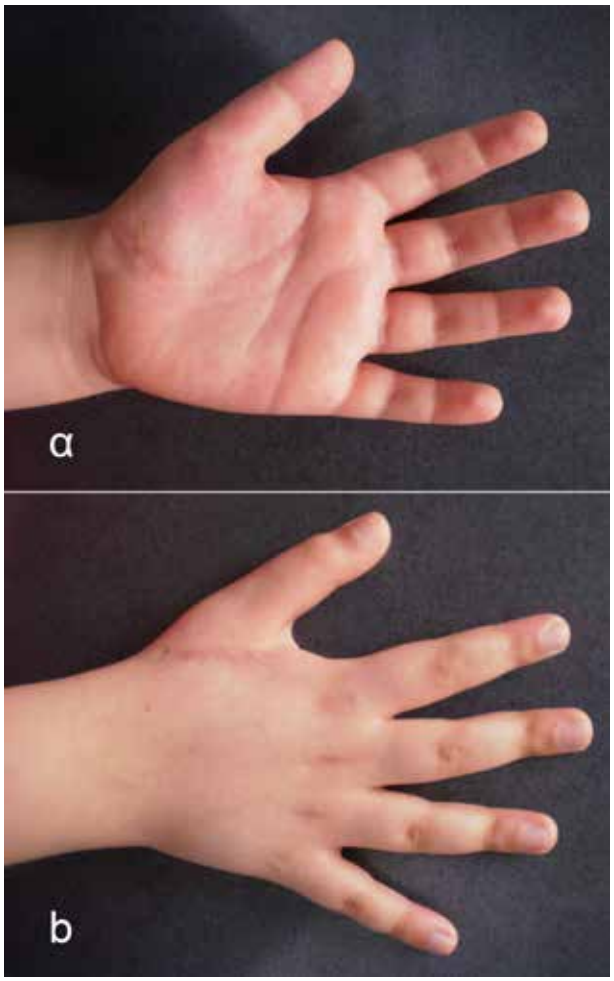

Fig. 6: (a-b) *Pictures of the right hand and thenar eminence sixteen months postoperatively.*

cans. The gold standard in the differential diagnosis of soft tissue tumors is always the histopathological examination [8].

Despite the fact that in some studies authors insist to the radical excision of RMS and partial or complete limb amputation, many other reports claim that patients who were treated primary with amputation had lower survival rates than those treated primary with wide local tumor excision. Therefore, wide local RMS resection is the primary treatment of choice in most of the cases and amputation must be applied only in case of positive surgical margins, or in wide tumor excision failure and recurrence of the tumor. Radical RMS excision may lead to significant functional and cosmetic impairment of the limb. Sometimes, reconstructive surgery can improve limb function at a later stage of treatment [9,10]. Surgical technique is very important. In case of biopsy, a longitudinal excision must be done and be the one which will be used during the final operation. Exsanguination of the limb with tourniquet is prohibited, because there is a chance of tumor dissemination [10].

Chemotherapy must be applied in all RMS cases, because it was proven that improves the overall survival. Response to chemotherapy can be predicted by the identification of gene fusions and chromosomal rearrangement. There is a significantly increased risk of failure and death in patients with metastatic disease if their tumors express PAX3-FKHR [10].

Most authors consider that there is no need of radiotherapy application, in case where radical surgical excision or amputation was done. RT must be used when local wide excision is done, or in cases of close/positive surgical margins and unresectable tumors, in order to enhance local tumor control [10].

In conclusion, RMS is a malignant soft tissue tumor which rarely occurs in the hand, and often presents with disseminated disease at its initial diagnosis. Alveolar RMS is the most common histological subtype seen, with the worst prognosis. In most patients wide tumor excision is the treatment of choice. Radical surgical excision significantly impairs limb function and cosmesis and must be kept in mind in case of wide excision failure or in recurrence of the tumor. Advances in chemotherapy and radiotherapy protocols in selected cases have improved the prognosis of the disease.

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Το ραβδομυοσάρκωμα αντιπροσωπεύει έναν υψηλής κακοήθειας όγκο μαλακών μορίων ο οποίος εξορμάται από τα μυϊκά κύτταρα. Πρόκειται για το συχνότερο σάρκωμα μαλακών μορίων σε παιδιά και εφήβους ενώ σπανίως εντοπίζεται στο χέρι. Το κυψελιδικό ραβδομυοσάρκωμα είναι ο συνηθέστερος ιστολογικός τύπος με τη χειρότερη πρόγνωση. Περιγράφεται η περίπτωση ενός επτάχρονου αγοριού με κυψελιδικό ραβδομυοσάρκωμα στο δεξιό θέναρ, το οποίο αντιμετωπίστηκε με ευρεία χειρουργική εκτομή, συνεπικουρούμενη από χημειοθεραπεία και ακτινοβολίες. Επτά χρόνια μετά την επέμβαση δεν παρατηρήθηκε υποτροπή ή μετάσταση.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: όγκος, μαλακοί ιστοί, ραβδομυοσάρκωμα, χέρι, θέναρ