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Compensatory Strategies while Walking in Charcot-Marie-Tooth Disease: Impact and Intervention

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Declaration

I, Gita Mary Ramdharry, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Charcot-Marie-Tooth disease (CMT) is a peripheral neuropathy presenting with distal weakness and sensory loss. This thesis examines the role that proximal activity plays in compensating for distal weakness to maintain functional walking.

Comparative 3D gait analysis showed reduced range of ankle motion kinetics in people with CMT. Additionally, swing phase hip flexion increased, moments and power around the knee altered during preswing and trunk motion increased. These changes were related to the degree of distal weakness. Proximal adaptations were also observed in healthy control subjects following isolated bilateral fatigue of the plantarflexors but did not resemble those of people with CMT.

The role the hip flexors play in compensating for plantarflexor weakness to maintain walking was examined in two studies. When walking on a treadmill people with CMT took an average of 48 minutes to reach level 17 on the Borg perceived exertion scale whereas matched control subjects reached level 8 while walking at the same speed and cadence. After prolonged walking the maximum voluntary contraction of the hip flexors reduced by 20% in the CMT group. Additionally, hip flexor velocity reduced during swing phase and trunk motion increased. A separate study specifically fatigued the hip flexors by 20% resulting in similar kinematic changes to the first study, plus a reduction in walking time to reach Borg level 17 in people with CMT.

The effect of ankle foot orthoses (AFO) was investigated in people with CMT. A variation in the stiffness of the three splints was observed when worn with footwear. During walking all AFOs reduced footdrop during swing phase but did not reduce hip flexion. One of the more rigid devices also reduced the total ankle power generation during preswing.

These studies suggest that proximal compensations are present, they maintain functional walking and may be influenced by orthotics intervention.

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Contents

Abbreviations

1RM	One repetition maximum
AFO	Ankle foot orthosis
ANCOVA	Analysis of Covariance
CIS-fatigue	Checklist Individual Strength
CMAP	Compound muscle action potential
CMT	Charcot-Marie-Tooth disease
CMT1	Type 1 CMT
CMT2	Type 2 CMT
CMTX	X-linked CMT
COM	Centre of mass
deg	degrees
deg/sec	degrees per second
DF	Dorsiflexion
EMG	Electromyography
EVB	Embedded vector basis
FSS	Fatigue severity scale
GLM	General linear model
HMSN	Hereditary motor and sensory neuropathy
HNPP	Hereditary neuropathy with liability to pressure palsy
HSN1	Hereditary sensory and autonomic neuropathy type 1
ICC	Intraclass correlation coefficient
kg	kilogram
MD	Muscular dystrophy
MRI	Magnetic resonance imaging
MVC	Maximum voluntary contraction
NHNN	The National Hospital for Neurology and Neurosurgery
Nm	Newton metres
PF	Plantarflexion
PMP22	Peripheral myelin protein 22
SF-36	Short Form 36
SNAP	Sensory nerve action potential
SPTLC1	Serine palmitoyltransferase, long chain base subunit 1
W	Watts

1 Introduction

People with peripheral neuropathy may present with muscle weakness, sensory loss and musculoskeletal deformities that in turn affects their balance and walking. The presence of such impairments can lead to the adoption of compensatory strategies to maintain function. Understanding exactly how these impairments affect walking, and the role of compensatory strategies in maintaining function, will in turn allow the development of more effective rehabilitation techniques. This investigation focuses on the most common hereditary peripheral neuropathy, Charcot-Marie-Tooth disease.

1.2 Pathology of Charcot-Marie-Tooth Disease

1.2.1 Classification and Genetics

Charcot-Marie-Tooth disease (CMT) is a relatively common hereditary condition that affects 36 in 100 000 people [35]. The hereditary nature and presentation of distal weakness was first described in 1886. In the 1950s improvements in neurophysiological testing revealed differences in the speed of peripheral nerve conduction in individuals with an apparently similar clinical presentation suggesting that variations exist in the underlying pathology. In the 1960s, CMT was renamed hereditary motor and sensory neuropathy (HMSN) and divided into four types depending inheritance pattern, clinical findings and neurophysiology [21]. Confusingly the terms HMSN and CMT have been used interchangeable since then with the patient groups preferring the term CMT. The most common classification now in use reverts back to the CMT label (table 1.1)

The first gene causing the CMT phenotype was mapped in 1989. Since then many more have been identified and an interesting observation has been made. The common CMT phenotype can be caused by as many as a 100 gene mutations that do not have a common theme linking them and the mechanism of cell damage can vary greatly depending on the mutation that occurs [53].

Type 1 CMT (CMT1) has a demyelinating presentation. The most common mutation is of the peripheral myelin protein 22 gene (PMP22) on the short arm of chromosome 17. Duplication of this gene causes CMT1a, that accounts for up to 80% of people with CMT. Rarer point mutations can occur resulting in a more severe form e.g. Dejerine-Sottas syndrome which can often start sporadically [21]. Mutations of the myelin protein zero gene, on chromosome 1, give rise to CMT 1b and accounts for approximately 4% of cases. Mutations of both of these genes affect the stability of the myelin sheath causing demyelination. On neurophysiological examination, people with CMT1

have slowed peripheral nerve conduction velocities (<38 ms^{-1}) due a reduction in saltatory conduction.

Type	Inheritance	Pathology
CMT1 (inc. Dejerine-Sottas syndrome)	autosomal dominant	Demyelination uniformly slowed conduction velocity <38 m/s
CMT2	autosomal dominant	Axonal degeneration conduction velocities >38 m/s [68]
CMTX	X linked	Predominantly axonal condition
CMT4	autosomal recessive	Either demyelinating or axonal neuropathies [21]

Table 1.1: Classification of Charcot-Marie-Tooth disease based on inheritance and pathology.

The axonal forms of CMT cause type 2 disease (CMT2) and are less common but mutation of the mitofusin 2 gene does account for about 10% of cases. Deficiency of the mitofusin protein affects the fast anterograde axonal transport system [67]. Disruption of axonal transport results in degeneration of the distal axon that is initially seen in longer nerves such as those supplying the foot and ankle muscles. The predilection for the disease process to affect longer nerves could reflect the increased energy required to sustain axonal transport to distant regions of the axon. People with CMT 2 have normal conduction velocities but show a reduction in the amplitude of compound motor action potentials (CMAP) and sensory nerve action potentials (SNAP) due to axonal degeneration.

In CMTX there is a mutation of the connexion 32 gene on the X chromosome. This accounts for approximately 10-15% of CMT cases with a mixed presentation of axonal loss and some demyelination. Connexin 32 forms gap junctions between the paranodal areas of the Schwann cells so myelin structure is not as compromised as in CMT1. Nerve biopsy reveals a predominant axonal picture though the exact mechanism is not clear. It has been suggested that cell to cell interactions between Schwann cell membranes and the associated axons are affected [67]

The differences between the two main phenotypes are not strictly distinct. CMT1 may not only show slowed nerve conduction velocities due to demyelination but also secondary axonal loss as reflected by a reduction in the amplitude of the CMAP and SNAP. In CMT1 it is the reduction in CMAP amplitude that most strongly predicts muscle strength and physical disability [72]. This suggests that it is axonal loss rather than primary demyelination that results in clinically identifiable symptoms. How demyelination leads to axonal loss in CMT1 is unclear. It may result in an alteration of axonal ion channels and/or increased energy requirements that lead to disturbances in axonal transport and subsequent axonal degeneration. There are also reports of down regulation of neurotrophic factors in Schwann cells where structural changes in myelin are observed [53]. Further investigation of the cause of secondary axonal degeneration may result in future medical therapies.

How the disease process affects the muscles supplied by peripheral nerves may also vary between the two phenotypes. In CMT 1 there is an increase in the motor unit size, that is, an increase in the number of muscle fibres supplied by one motor axon. This occurs during the chronic, slow denervation process when unaffected motor axons are able to produce collateral sprouts that reinnervate previously denervated muscle fibres. In CMT2 the motor unit size is not increased to the same extent as in CMT1, however muscle biopsies show that the muscle fibres themselves are hypertrophied. Thus, in CMT1 there is collateral sprouting and reinnervation to compensate for gradual denervation whilst people with CMT2 may show a compensatory increase in contractile tissue as reflected by muscle fibre hypertrophy. The reasons for the differences are not clear but it is suggested that in CMT2 there may be a reduced ability to form collateral sprouts [13].

1.2.2 Related conditions

Only the most common gene mutations have been presented in the previous section so far but there are associated genotypes that come under the CMT umbrella. Hereditary neuropathy with liability to pressure palsy (HNPP) is caused by a deletion of the PMP22 gene. The myelin structure is affected but not as profoundly as in CMT1. An asymmetrical pattern of demyelination is observed with transient episodes of weakness and sensory loss often attributable to some type of external pressure or trauma [67].

Recently the gene for hereditary sensory and autonomic neuropathy type 1 (HSN1) has been identified as serine palmitoyltransferase, long chain base subunit 1 (SPTLC1) [27]. It has been suggested that the name HSN1 is in fact a misnomer as it implies a predominant sensory and autonomic presentation. Sensory dysfunction is prominent in this condition with severe loss, painless injuries and neuropathic pain but weakness is also a major symptom similar to the CMT phenotype. Autonomic features are rare though loss of sweating does feature [53]. Recently there has been a call to bring HSN1 back into the CMT classification system [54].

1.3 Clinical presentation

The most common types of CMT show a decline in distal muscle strength and sensation that predominantly affects the longer peripheral nerves.

Muscle strength: The distal lower and upper limb muscles tend to weaken first showing a slow decline in strength over decades. On clinical testing the ankle dorsiflexors muscles may appear to weaken more quickly than the ankle plantarflexors despite being innervated by a shorter nerve. This apparent anomaly is actually because the plantarflexor muscles are much larger so the onset of

weakness is initially not as apparent on clinical manual testing [62]. The proximal limb muscles are less affected but are still weak compared to normative data [9]

Magnetic resonance imaging (MRI) reveals that atrophy of the distal muscles can occur even when an individual appears unaffected on clinical examination [14]. Pes cavus is a common deformity observed in people with CMT where the condition starts early in life and is described as a foot type with an excessively high longitudinal arch and foot supination (figure 1.1). Pes cavus is thought to develop through imbalance between the relatively spared peroneus longus and weakened tibialis anterior causing forefoot cavus. It is further exacerbated by imbalance between the stronger tibialis posterior and the weakened peroneus brevis causing forefoot adduction. Associated hind foot varus is thought to be caused by the unopposed tibialis posterior and long toe flexors [22, 25, 40, 81].

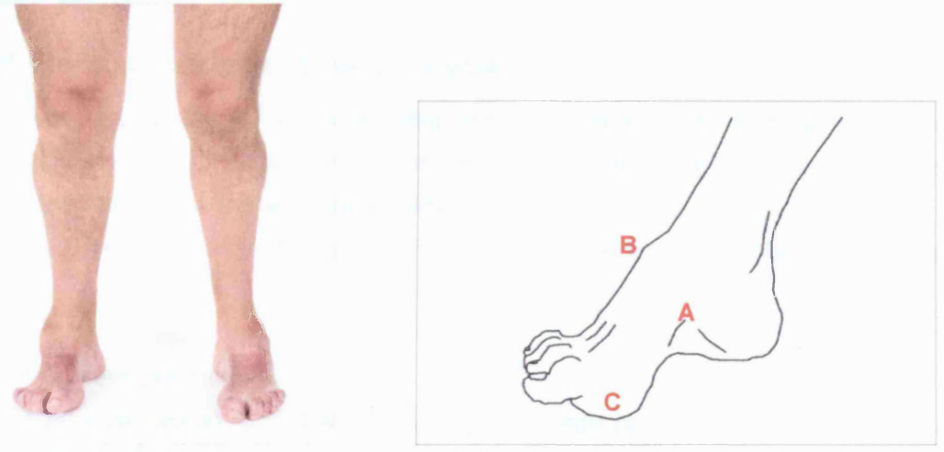

Figure 1.1: Distal wasting and pes cavus. Illustration outlines a high medial arch (A), mid foot supination (B) and dorsiflexed metatarsal phalangeal joints (C).

Toe clawing develops due to gradual wasting of the plantar lumbricals and interossei [25, 62, 40] with wasting and fatty infiltration observed with MRI [14]. This selective wasting of the intrinsic muscles results in unopposed activity of the toe extensors causing dorsiflexion of the metatarso-phalangeal joints. Over time flattening of the transverse arch develops, with tightening of the plantar aponeurosis and Achilles tendon [14]. Where symptoms start later in life foot drop tends to develop rather than pes cavus. In such cases there is a more variable distribution of fatty infiltrate that tends to be higher within the lateral, anterior and superficial posterior leg compartments [14]. Thus, although distal muscle wasting is cited as one of the cardinal symptoms of this condition it does not follow a stereotyped course and variations in the pattern of atrophy can occur that can be observed clinically [75].

Sensory loss: In addition to weakness and wasting, a length dependant gradual loss of sensation occurs. People with CMT1 show a principal impairment of the thickly myelinated large diameter

sensory nerves that mediate the sensations of light touch and vibration [49]. However, sensations that are felt to be conveyed by smaller diameter fibres, such as the ability to detect a painful stimulus like pin prick, may also be reduced [9]. This implies that there is not a clearly delineated pattern of large fibre damage in CMT1. In CMT2 a more general mixed picture of distal sensory loss is seen with both large and smaller diameter sensory fibres affected.

In summary, this section describes various pathological signs observed in people with CMT that could potentially impair movement. Walking requires the co-ordinated execution of lower limb movements so one may expect gait to be altered in people with CMT. Before examining gait deviations in CMT, we should first define normal walking.

1.4 Normal Walking

1.4.1 Definitions of Walking and the Gait Cycle

Walking is defined as an activity where repeated limb movements propel the body forwards while stability is maintained [59, 77]. Bipedal walking is distinguished as having one foot always on the ground with the feet advancing alternately. Although the terms walking and gait are often used interchangeably, the term "gait" will be used in the current context to describe the style or pattern of walking [77].

1.4.1.1 Phases of the gait cycle

Walking is a repeated action (cyclic) so, to simplify the description and observation of gait, it is helpful to split it into individual cycles. One gait cycle starts at the initial contact of the heel (heel strike) and terminates when the heel of the same limb contacts the floor for a second time. Within the gait cycle, distinct phases are identified. Stance phase spans approximately the first 60% of the gait cycle and occurs from heel strike to when the toe of the same leg leaves the floor (toe off), corresponding to the entire period when the foot is on the ground. Swing phase is the period when the foot is off the ground for limb advancement and lasts from toe off to the next heel strike.

To describe the events that occur during stance and swing phase, there are further divisions into smaller sub-phases or segments. Different authors divide stance phase in different ways but for this thesis, the definitions by Whittle will be used [77]. The first sub-phase is the loading response which occurs from heel strike to when the toe of the opposite leg leaves the ground (opposite toe off). It is essentially the period of double support where both feet are on the ground sharing the body's weight and typically lasts for the first 10-12% of the whole cycle. The next segment is mid stance or the single support phase. This spans from opposite toe off to when the heel of the stance leg starts to rise (heel rise). This segment represents about 18% of the cycle and corresponds to when the opposite, swinging leg passes the stance leg. Terminal stance is the segment between heel rise

and the heel strike of the opposite leg. It is the last portion of the single stance phase and leads into preswing. Preswing occurs from opposite heel strike to toe off of the stance leg and is a period when both legs are again in contact with the ground. Swing phase accounts for approximately 40% of the gait cycle and can be further divided into initial swing (toe off to when feet are adjacent), mid swing (from feet adjacent to where the tibia of the swinging leg is vertical) and terminal swing (tibia vertical to the next heel strike). The length of stance and swing phase determines the gait speed with an inverse relationship [59, 77]; the shorter the gait phases, the faster the walking speed.

1.4.1.2 The mechanics of walking

The linear forward progression of the body during walking is achieved through angular motion at joints that connect adjacent body segments. Angular motion of a joint is caused by force acting at a distance from the joint axis resulting in a torque or moment. The direction of joint motion is determined by the summation of all the moments acting on the interconnected limb segments.

During walking, turning moments are normally caused by a combination of external and internally generated forces and moments. External forces include gravity (that acts downward through the centre of mass of the segment); and ground reaction responses (that act through the point of contact of the body with the ground). Internally generated moments are mainly due to the actions of muscles. The torques generated by the ligaments and peri-articular soft tissues are small as their line of action pass close to the joint axis and the structures are normally lax when the joints are not at the end of their range of motion [78].

1.4.1.3 Energetics of walking

For a body segment to move, work must be done on that segment. Much of this energy is derived from muscle activity. All types of muscle contraction will expend chemical energy associated with excitation-contraction coupling. However, the resulting mechanical work done varies depending on whether the muscle contraction is concentric (where the muscle shortens), isometric (where there is no movement) or eccentric (where the muscle lengthens). With a concentric contraction the muscle moment acts in the same direction as the angular velocity of the joint and positive work is done. Energy is transferred from the muscle to the segment and the power, the product of the muscle moment and the joint angular velocity, is positive and is said to be generated. With an eccentric contraction the muscle moment acts in the opposite direction to the angular velocity of the joint. Energy is transferred from the limbs to the muscle. Here the power is negative and is absorbed, either stored as elastic potential energy within the muscle-tendon complexes and ligaments or dissipated in the muscle [82]. In contrast with an isometric contraction no net mechanical work is being done although the muscle still spends chemical energy.

Determining the flow of energy between segments is complicated by the multi-link structure of the body. Energy can be transferred directly between segments with the direction and type of energy flow depending on the relative motion of the two segments [61]. However, energy can also be transmitted to distant segments that the muscle does not directly attach to. For example, the soleus muscle generates force that will control the lower leg (shank) and foot. However, it also influences the more proximal knee and hip joints that it does not span through a process called dynamic coupling. The joints transmit forces from one segment to the other via joint inter-segmental forces (internal joint reaction forces) [82].

The architecture of the muscle also needs to be considered. The example given above is of a uni-articular muscle, but bi-articular muscles may work differently. A bi-articular muscle will simultaneously produce moments at the spanned joints but the muscle may rotate a joint opposite to its muscle moment because the moment of the second joint produces a stronger counter acceleration. As a result of this the energy flow between segments caused by the activity of a bi-articular muscle is the summed energy flow due to the two moments [51, 82].

1.4.1.4 Biomechanical analysis of human walking

Individual human muscle moments cannot be directly measured, instead net moments and forces are often calculated. The net moment is the sum of the individual moments about a joint derived from forces developed by muscles and other structures crossing that joint, such as ligaments. The net force or joint inter-segmental force arises from the acceleration of the body and external forces such as gravity and the ground reaction force. By measuring the body's motion and the application of any external forces it is then possible to calculate these net forces and moments; a process called inverse dynamics. When the joint angular velocity is known it is possible to calculate the net power at different joints. There are some limitations to the inverse dynamics approach that must be considered. Individual joint moments do not reflect the activity of a given muscle group. In particular, the effect if bi-articular muscles are difficult to account for with this approach as is the influence of the proximal segments (pelvis, trunk, upper limbs, head) on the leg segments. It does not account for the energy expended during isometric contractions or to overcome antagonist muscle activity. Thus, although the sum of the individual joint powers should reflect the rate of energy production by the whole body it does not always equal measures of energy consumption estimated by other methods especially in people with pathological gait patterns [79, 82].

More recently forward dynamics models have been produced that simulate the musculo-skeletal system (including the head, arms and trunk as the HAT segment, individual muscle forces using Hill-type muscle actuators) and ground reaction forces. Such muscle-based simulations provide an estimation of the flow of mechanical power that may be generated by individual muscles. An example is the dynamic optimisation model [4]. This model is optimised by varying the muscle

excitation magnitudes and activation times and by kinematic alignment at the beginning and end of the gait cycle. The aim of the optimisation is to minimise the cost function (total metabolic energy consumed/displacement of the centre of gravity). The dynamic optimisation model has been compared with experimental data and was found to reproduce the salient features of normal gait [4]. This method was utilised by Neptune et al [51] to explore which muscles contribute to forward progression of the body during walking [51]. It also has a role in understanding pathological gait when impairments such as weakness or over-activity are simulated and has recently used been used to understand muscle functions related to impairments such as hip stiffness, and clinical gait dysfunction such as in crouch gait or walking with a below-knee amputation [5, 18, 83, 84].

1.4.1.5 Muscle activity during walking

The pattern of muscle activity during walking is complex and concurrently helps to support the body weight, maintain balance and advance the limbs and trunk. The following section will review the muscles active during walking, emphasising the role of the ankle muscles that are often severely affected in CMT. To simplify the description, the task of walking will be summarised into four locomotor functions as described by Perry [59].

Progression: The muscles that progress the body forwards during gait have been explored by a variety of methods. In early stance to mid-stance forward dynamics modelling studies, as described earlier, indicate that gluteus maximus and the quadriceps contribute to the forward progression of the trunk. The vasti muscles of the quadriceps are known to decelerate and slow the leg by acting eccentrically but by mid-stance they also act to accelerate the trunk due to a hip inter-segmental force that is directed upward and forward as they extend the knee [51, 83]. During this time the soleus is active to decelerate the tibia which allows the knee to accelerate into extension thus assisting the vasti [5, 18, 29, 50].

The ankle plantarflexor muscles generate nearly all of the positive work in late stance and early swing. Their contribution is thought to be the body's forward progression but this has been an area of speculation. Early studies contemplated whether the ankle plantarflexors actively pushed down to propel the body upwards against gravity. An investigation of ankle plantarflexors weakened through tibial nerve block found that there was a reduction in the second peak of the vertical component of the ground reaction force, normally associated with plantarflexor push-off, but there was no drop in the body's forward velocity [69]. The authors concluded that this demonstrated that the plantarflexors were involved in forward progression not propulsion vertically. An inverse dynamic study analysed joint powers and mechanical work done [43]. It supported the findings of the first study with reports of plantarflexor contribution to forward velocity of the trunk and not to lifting the trunk up against gravity. They suggest that another mechanism to progress the trunk forwards is the "pull phase" at the end of swing phase i.e. energy transferred from the swing leg to the trunk as the leg is

decelerated through eccentric activity of the hamstrings. In addition they found that at pre-swing there is primarily a transfer of energy to the leg accelerating it into swing phase.

Optimization modelling studies have investigated the role of the plantarflexors in accelerating the leg and trunk [50, 51, 83]. They suggest that the individual plantarflexor muscles work differently.
Soleus, through a concentric action, decelerates the thigh and shank. This redistributes energy to the trunk resulting in trunk forward acceleration. The rectus femoris muscle works in synergy with soleus; when contracting eccentrically it decelerates the leg transferring energy to the trunk. In contrast the gastrocnemius delivers energy to the leg working synergistically with the uni-articular hip flexors to accelerate the thigh, shank and foot segments.

There is some controversy about whether or nor the plantarflexors, mainly gastrocnemius, actually initiate swing. This is based on the timing of activity of the plantarflexors which are active at 52% of the gait cycle whereas toe off occurs at about 60% [19] indicating that it is the hip flexors that are responsible for swing initiation. One study used an alternative method of investigating this approach measuring EMG when stepping and trunk progression was assisted [19]. They found that when swing phase was assisted with a pull forwards on the feet, there was no change in medial gastrocnemius and soleus EMG but a reduction in iliopsoas activity was seen. A change in the plantarflexors was observed when trunk progression was assisted. A problem with this study was that the assistance given to the feet was linear which may have affected the action of the plantarflexors and could have caused them to brake the stance limb if the assistance was perceived as a perturbation. Another modelling study suggests a combined influence on swing initiation with swing phase initiated by a combination of gastrocnemius activity from late-stance to pre-swing and iliopsoas from pre-swing to swing [51].

Upright support: To maintain upright support during walking a combination of anti-gravity muscle activity and balance is required. When the heel strikes the ground at the beginning of stance phase, muscle activity is required to prevent the body's segments from collapsing under the influence of gravity.

The support role of the muscles is shared and varies through the support period. Early in stance phase, the vasti acts eccentrically on the leg to decelerate the thigh segment and prevent collapse at the knee as the centre of mass moves forward (loading response). The ankle plantar flexors and hip extensors also support the limb to control the range of ankle motion during loading [3, 18, 28, 29]. During the single stance phase, soleus and gastrocnemius generate inter-segmental forces that act through the knee and hip to accelerate the trunk upwards [3, 5, 29, 50, 83]. At mid-stance, gluteus medius and minimus support the trunk in the coronal plane. The passive resistance of the joints and bones

also play a significant role at this point. In late stance soleus and gastrocnemius provide the majority of segmental support and contribution to the ground reaction force [3, 50, 50, 83].

Winter (1980)[80] introduced the concept of the support moment which is the sum of the hip, knee and ankle moments. He found that the variance of the support moment is less than that of the individual contributing moments. He further observed that if the ankle moment was low, the hip and/or knee moment would increase keeping the size of the support moment constant. This implies that variations in the moment produced by one joint can be compensated for by the remaining two joints. This model has recently been re-interpreted following a biomechanical analysis using a simple three segment model of the leg. To prevent collapse of the knee in stance phase does indeed require contributions from the hip, knee and ankle moments suggesting that the concept of the support moment is valid. However, in the new model the hip and ankle moments had half the weighting of the knee moment [24, 77]. The implication of these models is that muscle activity around the hip, knee and ankle joint can vary during stance phase providing their sum (support moment) remains the same.

As the muscles are working to maintain upright support and progression during walking the body must remain balanced during these movements and correct any perturbations. The challenge in this situation is that the centre of mass is in motion and the base of support changes its size through the gait phases. The traditional view of balance is that stability is achieved when the centre of mass is within the base of support but when walking this is only true for 20% of the gait cycle [58]. Strategies to maintain or regain balance must be able to adapt to changing environmental and individual contexts and a combination of reactive, predictive and anticipatory strategies are utilised [45, 58].

If the body is perturbed while walking, reactive strategies are employed to preserve stability. They rely on sensory input from the visual, vestibular and proprioceptive systems. Fast acting responses are required to prevent the body from falling but if a person does lose their balance when walking we do not observe local stereotyped responses one may associate with a reflex response. The muscles involved in the response to perturbation can involve the whole body, are context specific and can be biased. For example, if an individual is holding a hand rail, postural responses will be seen in upper limb muscles following perturbation. In contrast, if the arms are constrained any postural responses will predominantly occur in the leg muscles [45]. Following an unexpected perturbation, voluntary responses would be too slow to prevent falling [58]. What seems to happen is that there is an immediate short latency reactive response followed by a subsequent response the timing, magnitude and co-ordination of which are modulated according to the task conditions [58]. Misiaszeck [45] suggests that these fast acting responses are probably mediated by the spinal cord or brainstem. Sensory information is not only used reactively to trigger and modulate postural responses following perturbations. Multi sensory information is constantly monitored and provides

ongoing information about body dynamics, relative limb positions and orientations. Such information is used to plan appropriate future motor responses. Balance control can also be anticipated based on visual information, for example permitting obstacle avoidance. Prior experience of balance perturbation will also influence the motor response [58].

Shock absorption:

At heel strike, the trunk is accelerating forwards and downwards so the impact at foot contact could potentially be high, jarring the joints of the lower limb and trunk. Mechanisms at the foot, ankle, knee and hip help to reduce the magnitude of this impact. The fat pads under the heel serve to smooth the peak forces on impact and dampen vibration [64]. Just after heel strike but before the foot falls flat to the ground, the dorsiflexors and ankle invertors act eccentrically to control plantarflexion and pronation[29]. By delaying the foot contact with the floor the dorsiflexors are acting to reduce the rate that the trunk falls forwards and down thus decreasing peak vertical force [59]. At heel strike, the ground reaction force vector is anterior to the hip and posterior to the knee so creating a flexor torque at those joints. An internally generated extensor moment is required as the trunk moves forward and activity of the vasti and gluteus maximus is observed during this early stance period. The eccentric activity of the vasti muscles absorb the impact and dissipate energy into the muscle [3, 59] so further reducing peak impact forces [17]. As the fore-foot contacts the ground, shock absorption is provided by fat pads over the metatarsal heads but forces are also dissipated through energy storage in the muscles and ligaments of the foot. As weight is taken on the foot, it deforms as the soft tissues are strained. Much of the energy is stored in the plantarflexor muscles and plantar ligaments and can be used to deliver energy by elastic recoil later in the gait cycle [64].

Energy conservation:

During walking the centre of mass (COM) moves vertically and medio-laterally. The total energy of a point mass is the sum of its gravitational potential energy plus its translational kinetic energy. It could be suggested, therefore, that the factors that reduce vertical excursion of the COM could reduce the energy cost of walking. In the 1950s a model of walking described six determinants of gait that were felt to conserve energy while walking [65]. The original model was of two footless rigid limbs with rotation at the hip which described a gait pattern know as 'compass gait'. This pattern of walking describes movement of the COM as an arc, with two depressions per gait cycle. The peak of the arc was mid-stance/mid-swing and the troughs were during the period of double support double support as weight switches from the trail to the lead leg. As each of the six determinants of gait were added on (pelvic rotation, pelvic obliquity, knee flexion in stance, foot rotation, heel rise, lateral displacement of trunk) then the centre of mass motion decreased its displacement [11, 17].

This model was accepted clinically and scientifically for decades but more recently research has taken place to investigate the role of the six determinants. Gard and Childress [16, 17] demonstrated

that the change in pelvic obliquity and knee flexion in stance did not alter the vertical trajectory of the trunk during walking. They suggest that both movements are actually strategies employed for shock absorption at heel strike. An investigation of the effect of heel rise on the centre of mass trajectory showed that the degree of rise contributes significantly to raising the centre of mass height when it is at its lowest point of the trajectory [31]. This group found that the heel rise component accounted for 2/3 of the reduction in centre of mass displacement with pelvic rotation also contributing. Although some of these determinants have some influence of the path of the centre of mass, we must ask whether this indeed represents energy cost during walking. Kerrigan et al [32] found that vertical displacement of the centre of mass reliably predicts oxygen consumption when walking. Other authors point out that it would take a lot of effort to walk with the centre of mass trajectory completely flat and that the up and down motion allows mechanical energy to be stored and released during a cycle [11].

1.5 Altered Gait in CMT

This section will describe gait in people with CMT. Subsequent sections will explore the cause and effect of these changes. Up until the experimental work for this thesis commenced, there were only three small studies describing gait in adults with CMT and one larger study in children. Very recently, two new larger studies of gait in adults with CMT have been published that describe gait deviations using 3D kinetic and kinematic analysis [12, 52]. These studies did not contribute to the formulation of the original hypothesis for this thesis so will not be described here. They will, however, be discussed in the experimental chapters and final overview where they will be compared with the results of this work.

The first of the four studies is a descriptive observation of 12 subjects by Sabir and Lyttle [62]. The second study by Hood and Whittle [26] used kinematic analysis and clinical measurement in nine subjects to investigate gait deviations, compared to normal laboratory values, and related the numbers of deviations observed to clinical measures. A third study by Kuruvilla et al [36] did a more detailed kinetic and kinematic analysis of five people comparing gait deviation in CMT to normative data using grand average graphs but no statistical comparisons were performed. A larger study of children with CMT by Õunpuu et al [57] compared kinetic and kinetic variables to normal laboratory data in 19 subjects. Comparing gait data of children and adults may be problematic in that certain gait deviations may be due to incomplete gait development, though in this study there were no very young children i.e. below five years. In a progressive condition such as CMT, though, one may expect impairments to be more severe in adults due to the extended duration of the disease process. There is also a methodological problem where gait data is compared to laboratory normal data in that there may be differences in gait variables due to faster gait speed of control subjects [37]. None of the studies accounted for this methodologically or statistically.

In all four studies foot drop during swing phase was observed with Kuruvilla et al [36] describing excessive plantarflexion prior to heel strike. Hood and Whittle [26] reported its presence in five out of nine subjects and the study of children by Õunpuu et al [57] noted the variability of presentation with the absence of foot drop in some subjects with distal weakness. The observational study by Sabir and Lyttle additionally describes a small increase in flexion of the hip and knee and an elevation of the pelvis during swing phase [62]. They attribute this finding to a proximal mechanism to keep the toes of the dropped foot from contacting the floor. Hood and Whittle reported that increased hip flexion was not observed in all subjects (four out of nine) and state that the so called 'steppage gait' is not necessarily a common characteristic [26]. They also reported that the most common gait deviations were excessive motion of the pelvis in the horizontal plane (seven out of nine) and the coronal plane (six out of nine) [26]. In contrast, Kuruvilla et al reported a near to normal range and pattern of motion of the hip [36]. The study of children did not report on pelvic and trunk motion.

In addition to foot drop, a lack of propulsive action of the plantarflexor muscles has been described. Ankle kinetics during the propulsive phase (preswing) were significantly less than normal values, in two studies, though these findings should be interpreted with caution due to the lack of account for differences in gait speed as discussed [57 36]. Sabir and Lyttle reported that subjects compensated for the lack of propulsion at swing phase by lifting the trailing foot from floor by elevating the pelvis and flexing the hip and knee. This then necessitated a lateral shift of the trunk over the stance leg to maintain balance [62]. Kurvilla et al [36] also noted this trunk shift but deduced that it was due to hip abductor weakness, despite having no measures of abductor strength to verify this [36]. A further source of disagreement between the studies is over motion of the knee at heel strike. Sabir and Lyttle describe a hyperextension action at the knee [62] and Kuruvilla et al other describe excessive flexion [36]. The study by Hood and Whittle found both deviations with increased stance knee flexion in six out of nine subjects and knee hyperextension in three out of nine. All three studies had small numbers so it is difficult to generalise the findings and but as with other deviations already discussed these differing observations also indicate that there is much variability in gait pattern in people with CMT.

1.5.2 Distal muscle weakness and compensatory strategies

Weakness and wasting in the muscles below the knee is a well recognised feature of CMT causing the classic 'inverted wine bottle' appearance of the lower leg. The ankle plantarflexor muscles are necessary to provide propulsive forces to continue gait progression through acceleration of the trunk and leg. In CMT the plantarflexors are weak and may be unable to provide sufficient force to do this as effectively (plantar flexor failure). Weakness of the anterior tibial muscles prevent sufficient dorsiflexion at mid-swing when the leg is at its longest. If there is inadequate dorsiflexion

at mid-swing there is difficulty with foot clearance and a risk of tripping (foot drop) [59]. Despite these failings, people with CMT are still able to walk and progress forwards without tripping continually. This is because they have adapted their gait to compensate for these problems.

Studies of gait in CMT described in the previous section have suggested that the hip may compensate for distal weakness although they did not explore this in detail. Investigations in other neurological conditions were therefore considered to infer what may be occurring in people with CMT. One study of people with diabetic neuropathy showed a significant reduction in ankle joint moments and power compared to healthy controls. Further, the onset of hip flexion at the end of stance phase occurred earlier in the patient group than in the controls. It was suggested that the less affected hip compensates for the lack of propulsive activity of the plantarflexors at pre-swing by pulling the femur through to achieve limb progression [46].

In people who had a stroke, the "percentage utilisation" for a muscle was measured at normal and maximal gait speeds [47]. The joint moments estimated by inverse dynamics during walking were compared to the maximum torque that could be achieved at the same velocity as extrapolated from direct recordings of applied torque using a dynamometer. While walking, people with a stroke had a higher "percentage utilisation" compared to controls, that is, after stroke the peak ankle plantarflexor moments during walking was close to the maximal that could be achieved using the dynamometer. Although the joint moment during walking does not solely reflect muscle activity this finding was taken to suggest that the plantarflexor was working close to maximum during gait after stroke. The plantarflexor strength after stroke correlated inversely with the walking speed suggesting that weakness in this muscle may strongly influence walking speed as suggested in other studies. There was, however, variability in hip flexor strength in the stroke group that additionally seemed to influence gait speed. Subjects who had low hip flexor strength and were using their plantar flexors maximally tended to walk slower. In contrast, subjects who also used their plantarflexors maximally but had stronger hip flexors tended to walk faster. It was suggested that the stronger hip flexors were able to compensate for the inability of the plantarflexors to produce higher moments at faster walking speeds. Olney and Richards [56] further describe an increased hip flexor moment on the hemiparetic side of people following stroke that is highly correlated with gait speed.

Based on this evidence it is possible that in CMT a similar situation arises where the relatively intact hip flexors compensate for weak plantar flexors to accelerate the leg as swing is initiated. During normal walking, hip flexor muscle activity starts at about 55% of the gait cycle and hip flexor power is generated around this time. If the hip flexors are compensating for inadequate plantar flexor activity a difference in the timing or size of the hip flexor torque could be expected to help progress the limb forward. Further, with prolonged use it could be hypothesised that fatigue of the hip flexors could result in a breakdown in such a compensatory strategy that could limit walking distance.

Indeed subjective reports from people with CMT attending the neuro-genetics clinic at the National Hospital for Neurology and Neurosurgery (NHNN) suggest that people often feel fatigue in proximal muscles around the hip with prolonged walking. Therefore as well as distal weakness, fatigue in proximal compensatory muscle may limit walking distance in CMT. However, there are other factors that may also limit walking endurance and speed that will be discussed in the next section.

1.5.3 Additional factors that may limit walking in CMT

1.5.3.1 Musculoskeletal changes: Biomechanical changes at the foot and ankle are common in CMT and have the potential to limit movement at the joints during the gait cycle either through biomechanical constraints or pain. The most frequent deformity observed is pes cavus characterised by mid and/or forefoot supination, plantar fascia tightness and Achilles tendon shortening. Each of these features can affect motion of the foot during stance phase.

Supination of the foot is often accompanied by calcaneal varus creating a rigid foot structure that has limited shock absorbent properties [7]. The shape of the foot will also alter the initial point of contact at heel strike. It is normal to land on the lateral part of the heel on first contact but people with pes cavus will often land on the lateral border of the mid and forefoot [59], often resulting in excessive callous accumulation on the point of loading. Another consequence is an increased risk of ankle inversion injuries and ankle pain that commonly worsens with prolonged walking.

In addition to problems on initial loading, mid stance foot alignment can be affected due to tightness of the plantar fascia. The foot normally pronates during mid-stance to allow loading of the medial forefoot and first metatarsal but in pes cavus this is inhibited by planter fascial shortening. The changes in loading can lead to secondary problems such as pain. The causes of pain in the pes cavus foot has often been attributed to changes in plantar pressure distribution with the most common complaints being metatarsalgia and plantar fasciitis [7]. A study of subjects with idiopathic pes cavus, neurogenic pes cavus (CMT) and healthy control subjects showed that both of the cavus groups were more likely to report foot pain. Increases in peak plantar pressures at the rear and forefoot were observed due to decreased mid foot loading in both cavus groups. In addition, CMT subjects demonstrated a prolonged foot contact time, due to distal weakness [7], that may also contribute to painful syndromes.

Achilles tendon tightness is very common in CMT and primarily restricts motion during some phases of gait, resulting in a premature heel lift and reduced ankle dorsiflexion during stance [59]. Some authors argue that one benefit of Achilles tendon tightness is an increase in the passive moment at the ankle that could assist with push off. This has been investigated in peripheral neuropathy [63]. Multiple regression analysis revealed that ankle stiffness accounts for a significant portion of the

peak plantarflexor moment at push off when there is weakness of the plantarflexor muscles. In addition, stiffness seemed to help control the forward motion of the tibia in early stance phase. The authors actually recommend stiffening the ankle further to increase to the passive moment at push off recommending caution against overstretching the Achilles in physiotherapy programmes. These recommendations need to be considered with caution, however, as the effect of restricting ankle motion on joint kinetics, in particular ankle power during preswing, was not discussed in the study.

1.5.3.2 Balance and sensation: Balance impairment is another potential influence on walking and gait, though this has mainly been investigated in standing. A study looking at postural sway observed a difference between people with CMT1 and CMT2 with an increase in sway area in CMT2 patients. The proposed explanation was that in CMT2 there is a mixed picture of sensory loss with large and small fibres being affected whereas in CMT1 the larger fibres are preferentially degenerated. It was suggested that the smaller diameter fibres (e.g. type II spindle afferents) have a role in detecting the small, slow changes in muscle length that occur in standing. In contrast, the larger fibres (e.g. type 1a spindle afferents) are more velocity dependant and will not be activated by the small, slow oscillations that occur at the ankle during standing [48]. However, during walking 1a afferents may be of importance. In people with CMT1 a delayed soleus stretch reflex is seen due to the preferential loss of type 1a afferents. This may account for some of the problems seen with dynamic balance. This evidence coupled with experiments pertubating the ankles of healthy subjects during walking suggests that the signals arising from the larger, group 1a nerve fibres are important in the modulation of soleus activity during locomotion [41, 55].

1.5.3.3 Deconditioning and fatigue: The discussion about gait in people with CMT has so far mainly looked at the effect of different impairments on gait kinematics and kinetics. For gait to be truly functional, it must be sustained over time. This can present two problems for people with CMT. Firstly, the compensations that have been developed to maintain locomotor function may require additional muscle activity so increasing the metabolic cost of walking. This has been observed in studies of people with peripheral neuropathy who showed increased aerobic or physiological cost when walking [6, 20]. Secondly, in chronic neurological diseases it is common for people to become de-conditioned due to reduced general activity levels. Indeed, people with CMT demonstrate reduced aerobic capacity during exercise. A bicycle ergometer test protocol demonstrated a 50% reduction in VO_2 max, compared to healthy subjects at 85% of maximum heart rate [9]. A reduction in maximum aerobic capacity in CMT will mean that patients would reach their maximum capacity earlier so making walking effortful and potentially limiting the duration of the activity.

A potential consequence of deconditioning is that 64% of CMT patients report severe fatigue [30]. A study using the Sickness Impact Profile revealed high agreement with statements that come under the 'sleep and rest' and 'alertness' sections. The link between fatigue and deconditioning, however,

has not been examined and fatigue is often caused by multiple factors. The nature of fatigue in CMT was investigated by a study comparing fatigue severity, measured by the Checklist Individual Strength (CIS-fatigue), with general health measured by the short form 36 (SF-36). There were no significant relationships between fatigue and sections of the SF-36 , such as physical functioning, social functioning and body pain [30] though other studies do show a reduction in all sections of the measure when compared with the healthy control subjects [70, 76].

Studies of local muscle fatigue demonstrate that although CMT subjects are initially weaker than control subjects, they do not show an abnormal rate of fatigue when contracting repeatedly to the same percentage of their MVC [39, 66, 73]. It has been suggested that people with a lower maximum voluntary contraction (MVC) at the start of a task may reach a level of fatigue more quickly due to an inverse relationship between the percentage maximal force generated and the time to fatigue when performing repeated contractions to a set force/torque level [42]. In addition, people with CMT will be working at a higher percentage of their maximum force generating capacity in order to perform functional tasks [66, 71]. A recent study has examined fatigue more closely with a comparison of reported fatigue with peripheral fatigue, central activation and central fatigue in people with CMT (n=73) [66]. This study used a twitch interpolation method to ascertain the peripheral and central influences on force degradation before and after a two minute sustained MVC of the biceps. They found that peripheral fatigue was less than control subjects (n=24) which they explained by differences in occlusional blood flow. Interestingly, there was no correlation between peripheral and reported fatigue. In contrast they found that central activation failure and central fatigue was increased in people with CMT and central activation did relate to reported fatigue. This supported the suggestion that impairments of central drive are a key component of fatigability and the subjective experience of fatigue in neurological conditions [42]. The reasons for reduced central activation are not clear but could related to adaptations of the central nervous system.

In people with CMT the sensory disturbance is another major presentation. A reduction in peripheral feedback from type Ia and type II sensory afferents may contribute to reduced central excitation of motor neurons during voluntary contractions [42]. Also, disuse is a common problem in people with neuromuscular disorders that has been implicated in contributing to a reduced voluntary drive. In order to maintain the ability to maximally recruit motor neurons, voluntary use is necessary and this ability will be diminished in a disuse scenario [15, 42, 66]. To overcome fatigue, people must increase the voluntary drive to the motor neurones and this can be perceived as increased effort which may further reduce motivation [71].

As can be seen from the investigations of fatigue in CMT to date, it is a commonly reported symptom that may have multiple causes though central activation appears to be influential. What

remains to be seen, however, is how fatigue impacts the functional abilities of people with CMT and what potential interventions can help to alleviate or manage the symptom.

1.5.4 Current management of gait dysfunction in CMT

There are few good quality intervention trials of management strategies for gait problems in CMT. There are only three randomised control trials of interventions and of the other studies there are methodological problems and a variety of outcome measures making comparison and meta-analysis difficult. This section describes and critiques some of these studies.

1.5.4.1 Orthotic management:

Foot orthoses have been recommended for people with foot deformity to either distribute pressure under the plantar surface or correct flexible pes cavus using lateral posting [2, 81]. One good quality randomised control trial investigated the effects of foot orthoses in painful pes cavus [8]. As such, the main outcome measures were foot pain and function using the Foot Health Status questionnaire. The sample size was powered and the group interventions included a prescribed, custom made foot orthoses and a flat sham insole. Groups were randomised and participants were blinded. The results demonstrated a significant improvement in foot pain and function. Analysis of plantar pressure distribution demonstrated that the customised orthoses reduced plantar pressure particularly at the fore and hind foot. It was concluded that this was the mechanism of the successful intervention. This study looked at a number of different conditions presenting with pes cavus though the majority of subjects had CMT. In addition there was no functional gait measure and it would have been interesting to investigate if the reduction in pain had a positive effect on parameters such as gait speed or maximal distance.

Very few studies have investigated the use of ankle foot orthoses (AFO) in people with CMT. The only study to look at the effect on gait is a single case study which examined perceived exertion, oxygen consumption and cardiac stress for an individual when wearing a basic posterior leaf AFO and a custom made device [6]. The study found improvements in all three variables when the subject wore the custom made AFO. Although this was a good A-B-A single case study design, it was investigating a very specific situation and individualised intervention parameters making generalisation to other people difficult. The only other study of AFO intervention in people with CMT was a study of standing though the group investigated also included people with other lower motor neurone disorders [23]. The intention of this study was to investigate people who were able to walk but not stand still on the spot. They found that people who showed this feature had severe bilateral weakness of the posterior tibial muscles. When ankle foot orthoses were worn, 14 out of 16 subjects demonstrated a significant reduction in the path length of the centre of pressure over 30 seconds. The study did not report a group effect so it is unclear if this was significant and there was no functional measure to see if this extra support assisted the subjects in activities of daily living.

The only other study of external support was actually an investigation of the effect of night splinting to stretch the Achilles tendon [60]. The effect of stretching programmes have been recommended in people with flexible deformity but it is not known if they are effective in assisting gait [2]. The night splinting study recruited 14 adults and children with CMT to a randomised, cross over trial. The intervention phase involved wearing a night splint set into maximum dorsiflexion on one leg for a period of six weeks. The cross over process involved the splint being worn on the other leg so the non-splinted side acted as the control. The main outcome measure was passive dorsiflexion and eversion range of motion and was powered to show a change of 5° dorsiflexion. The study found no significant effects on range of motion. The authors attributed the lack of effect to problems with positioning the foot within the splint that could have affected the efficacy of the stretch applied. They acknowledge that positive subjective reports from subjects were received. This could be because of a change in stiffness of the muscles, rather than passive range but this was not measured in this study. In addition there were no functional measures to see if these subjectively reported benefits carried over into activities of daily living.

1.5.4.2 Exercise and strengthening:

Early studies of strengthening of people with CMT were problematic to interpret in that they were mixed pathology studies and included people with different muscular dystrophies (MD) [1, 33, 34]. CMT and muscular dystrophy, although both under the neuromuscular umbrella, affect different structures so looking at a group effect is difficult. Studies looking at strengthening and muscle fatigue in people with CMT and myotonic dystrophy have shown differences between the two groups [39]. In addition, these studies looked at strengthening the quadriceps muscles. The distribution of weakness in both conditions can be different and people with MD and proximal weakness may have reduced potential to strengthen compared to the CMT group [44]. One randomised control study of strengthening in CMT and myotonic dystrophy actually separated the diagnostic groups [38]. Subjects used weights to strengthen their knee flexors and extensors and hip extensors and abductors using a resistance of 60% of their one repetition maximum (1RM). This was progressed over a 24 week period to 80% of their 1RM with sessions being performed three times per week. The main outcome measure was isokinetic measurement of knee torque but this study also included functional tasks such as timed stair climbing and descent, standing from a chair, standing from supine and two times walk tests. People with CMT showed a significant improvement in knee torques that was comparable with strength training in healthy individuals. There were no significant improvements in the timed functional tests except for self selected gait speed.

A more recent article has investigated resistance training in an exclusively CMT sample [10]. This was a trial of resistance training over a 12 week period with no control group. Twenty subjects trained their knee extensors and flexors and elbow extensors and flexors with a resistance of 40% percent

of their maximum voluntary contraction for the knee and 20% for the elbow. This was progressed over the training period. Outcome measures included fixed myometry for strength measures, body composition and functional tests including timed rise from a chair and timed stair climbing. This study demonstrated improvements in strength and pooled scores for the functional tests. The main drawback to this study was the lack of control group and the improvements observed, particularly with the functional tests, could have been a learning effect. One important outcome of all of these strengthening studies, however, is that there were no reported adverse effects of moderate resistance training in people with CMT which should reassure clinicians prescribing exercise in the face of concerns about overwork weakness [74].

1.5.4.3 Surgical management of foot deformities:

A number of surgical procedures are available to people with CMT. The aims of surgery are to balance forces and relieve symptoms, usually pain, and the procedures are dependent on the disease duration and presentation plus whether deformity is fixed and/or complicated by secondary degenerative changes [2, 22, 25, 81].

One of the earliest surgical options is tendon transfer as a method of distributing forces and addressing muscle imbalance where there is no fixed deformity [22]. Common procedures include the transfer of the peroneus longus and tibialis posterior tendons. There is an argument that early intervention with these types of procedures can stall the progression to fixed deformity and secondary degeneration [81] however this is not supported by any data on longitudinal studies.

Other common procedures are contracture release, e.g. Achilles tendon and plantar fascia [22], and osteotomies. Osteotomies can be performed when problems remain after tendon transfer and there is mild to moderate fixed deformity [81]. For example, where there is calcaneal varus, a lateral osteotomy can be performed to realign the hind foot [2]. Where there is mid foot cavus, osteotomies of the metatarsals can correct this. Joint fusion, often with a triple arthrodesis, is a procedure that is often employed when there are secondary degenerative changes [81] or failure to correct alignment with osteotomies. There is some disagreement as to how aggressively to pursue this approach with some recommending triple arthrodesis as a last resort procedure and others recommending early intervention to prevent secondary problems as the neuropathy progresses [2].

All of the papers presented in this section make recommendations for when to use a particular procedure. However, only one paper attempted to present evidence of surgical outcome. Holmes and Hanson argue that measurement of surgical outcome is difficult due to the highly individualised approach to each patient. They present surgical outcomes from previous papers in terms of percentage success. There is no detail of how this is measured and whether it is the patient or the surgeon who decides a procedure is successful. With the current access to measurement

techniques such as 3D gait analysis, plantar pressure scanning and even simple measures such as functional gait and pain scores, it is disappointing that there are no studies that even attempt to objectively measure the outcomes of these costly and considerable interventions.

1.6 Summary

In summary, CMT is an inherited condition that progresses slowly affecting the longest nerves first. People present with distal weakness and sensory loss as the primary impairments that can lead to secondary problems such as foot deformity, musculoskeletal pain, deconditioning and fatigue. People with CMT are usually able to maintain the ability to walk but with alterations in their gait pattern. Studies of other neurological conditions suggest that people with CMT may have to utilise proximal compensatory strategies to preserve functional walking by maintaining progression of the trunk, leg and foot clearance. To date there is limited evidence for therapeutic interventions to address gait abnormalities in people with CMT.

1.7 Hypothesis

The hypothesis for this thesis was developed from a combination of subjective reports from people with CMT and the research evidence presented. People with CMT often complain that they are unable to walk as far as their friends and unaffected family. There is a suggestion that these people utilise a compensatory strategy using their hip flexors [36, 46, 47, 62] to progress the lower limb when plantar flexor failure is present and allow floor clearance if there is foot drop. If the hip flexor is more active or is working for longer periods of the gait cycle then it may fatigue quicker than normal during prolonged walking. Thus the hypothesis for this thesis is as follows:

People with CMT alter the action of the hip flexor muscles to compensate for reduced ankle muscle activity. Walking for a prolonged distance is limited by fatigue of the hip flexor muscles.

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2 Methods

2.1 Gait analysis

2.1.1 Three dimensional kinematics and kinetics

The CODAmotion CX1 system enabled calculations of 3-dimensional segmental gait analysis when a standardised marker set up is used.

2.1.1.1 Segmental Kinematics

Internal joint centres for the hip knee and ankle were calculated using joint width measurements using callipers and marker positions over the joints (table 2.1).

Joint Centre	Distance	Direction
Ankle	½ inter-malleolar distance	Perpendicular to shank lateral plane (defined by tibial wands)
Knee	½ knee width distance	Plane defined by virtual hip joint and thigh (defined by femoral wands)
Hip	½ inter ASIS distance - $0.19Wu_x$ - $0.36Wu_z \pm 0.3u_y$ Where W is the pelvic width, ASIS is the anterior superior iliac spine, u_x,u_y and u_z are the unit vectors describing the pelvic plane [1, 2]	

Table 2.1: Calculation of internal joint centres

Arrays of markers were used to determine a local coordinate system or embedded vector basis (EVB) for each segment. The EVB consisted of three orthogonal axes (table 2.2) from which unit vectors were defined and is used in the measurement of segmental rotations [2].

2.1.1.2 Joint rotations and kinematics

Relative segment orientation was described in terms of Euler angles. The orientation of the distal segment relative to the proximal segment was described except for the pelvis and foot which was calculated relative to the global co-ordinate frame. Distal segment rotations occurred about the proximal segment axes in the following sequential order: Z (internal/external axial rotation) then X (medio-lateral bending) then Y (flexion/ extension). Once the angles were known, the time derivatives were calculated to give angular velocity and acceleration [2, 5].

EVB	Principal axis	2nd axis	3rd axis
Foot	Line connecting the heel and toe markers that is offset by ½ inter-malleolar distance (u_x)	Line running from the heel marker to ankle marker and orthogonal to the principal axis (u_z)	Orthogonal to 1st and 2nd axes (u_y)
Shank	Ankle joint centre to knee joint centre (u_z)	Tibial wand orientation orthogonal to principle axis (u_x)	Orthogonal to 1st and 2nd axes (u_y)
Thigh	Knee joint centre to hip joint centre (u_z)	Thigh wand orientation orthogonal to principle axis (u_x)	Orthogonal to 1st and 2nd axes (u_y)
Pelvis	Line between right and left ASIS markers (u_y)	Line connecting mid PSIS to mid ASIS and orthogonal to the principal axis (u_y)	Orthogonal (u_z) to 1st and 2nd axes

Table 2.2: Derivation of Embedded vector basis (EVBs) for each segment.

2.1.1.3 Joint forces and kinetics

A inverse dynamics approach was used to calculate the forces, moments and powers at each joint. The joint inter-segmental forces and net joint moments were calculated for the ankle as follows:

The linear (translational) equations of motion were:

$$\sum \vec{F} = \vec{F}_a + \vec{F}_{GRF} + W_{foot} = m_{foot}\vec{a}_g \quad (2.1)$$

Solving for $\vec{F}_a$:

$$\vec{F}_a = m_{foot}\ \vec{a}_g - \vec{F}_{GRF} - m_{foot}g \quad (2.2)$$

Where:

ΣF = sum of all the forces applied to the segment;

$\vec{F}_a$ = the unknown ankle inter-segmental force;

$\vec{F}_{GRF}$ = the ground reaction force;

W_{foot} = weight of the foot;

m_{foot} = mass of the foot

$\vec{a}_g$ = linear acceleration of the foot centre of mass (COM)

g = gravitational constant

Taking moments about the centre of mass the rotational equations of motion were:

$$\sum \vec{M}_g = \vec{M}_a + (\vec{r}_1 \vec{F}_a) + (\vec{r}_2 \vec{F}_{GRF}) + \vec{T}_{GR}$$
$$= I_{foot} \vec{\alpha}_{foot} \qquad (2.3)$$

Where:

$\sum \vec{M}_g$ = the sum of the moments of force acting about the centre of mass,

$\vec{M}_a$ = the vector of the unknown net ankle moment;

$\vec{F}_a$ = the vector of the joint inter-segmental force

$\vec{r}_1$ = the vector of the distance from the ankle joint centre to the COM;

$\vec{F}_{GRF}$ = the vector of the joint reaction force;

$\vec{r}_2$ = the vector of the distance from the point of application of the centre of pressure to the centre of mass

$\vec{T}_{GR}$ =the vertical ground reaction torque vector that normally acts to resist turning about the vertical axis

I_{foot} = the centroidal mass moment of inertia of the foot

$\vec{\alpha}_{foot}$ = angular acceleration of the body segment

Solving for $\vec{M}_a$

$$\vec{M}_a = (I_{foot} \vec{\alpha}_{foot}) - (\vec{r}_1 \vec{F}_a) + (\vec{r}_2 \vec{F}_{GRF}) - \vec{T}_{GR} \qquad (2.4)$$

Joint centre positions were calculated as described previously and the centre of mass was located along the principle axis (tables 2.1 and 2.2). The segment mass, centre of mass locations and the radius of gyration (expressed as a proportion of the segment length) were estimated from anthropometric data based on the subjects' height, weight and gender. Each limb segment was assumed to be rigid and have a uniform distribution of mass around a longitudinal axis connecting the joint centres, to simplify its' inertial properties [4].

The ground reaction force and ground reaction torque was measured using Kistler force plates that were embedded into a walkway (type 9286A Kistler Instruments Ltd, Alton, UK). The force plates

measured the force in the x, y and z plane and the resultant ground reaction force vector at a sampling rate of 200 Hz and sensitivity set at 50 N/V for the X and Y plane and 0.5 kN/V for the Z plane force. Data collection was synchronised to the kinematic data and the position of the force plates within the global co-ordinate reference system defined.

The point of application of the COP was calculated as:

$$COP_x = \frac{[b(\vec{f}_z 1 + \vec{f}_z 2 - \vec{f}_z 3 - \vec{f}_z 4)] + (\vec{F}_x A_z)}{\vec{F}_z} \quad (2.5)$$

$$COP_y = \frac{[a(\vec{f}_z 1 + \vec{f}_z 2 + \vec{f}_z 3 - \vec{f}_z 4)] + (\vec{F}_y A_z)}{\vec{F}_z} \quad (2.6)$$

Where:

b= (inter-sensor distance in the x direction) /2

a= (inter-sensor distance in the y direction) /2

$\vec{f}_z$ *1..4* = vertical force measured by sensor 1..4

$\vec{F}_x$ = Antero-posterior force

$\vec{F}_y$ = Medio-lateral force

$\vec{F}_z$ = Vertical force

Calculation of joint kinetics proceeded in a distal to proximal direction with the net inter-segmental joint forces and net joint moments calculated for the more distal segment being used in the calculation of the next more proximal segment These moments and forces were expressed in the local co-ordinate system (EVB) of the proximal segment.

2.1.2.4 Joint Power

Joint power vectors were calculated from the vector product of the joint moment vectors and the relative inter-segmental velocity [4].

$$\vec{P} = \vec{J}_m(\vec{\omega}_p - \vec{\omega}_d) \quad (2.7)$$

Where:

$\vec{P}$ = the joint power vector;

$\vec{J}_m$ =joint moment vector

$\vec{\omega}_p$ =proximal segmental angular velocity

$\vec{\omega}_d$ =distal segment angular velocity

2.2.2 Two dimensional kinematics

Kinematic or motion data was collected using CODAmotion motion analysis system (Charnwood Dynamics, Leicestershire, UK). This system consisted of two scanners containing three infrared cameras and active infrared emitting diode markers. The scanners were aligned to a global co-ordinate frame where the X axis was defined as the travel (antero-posterior), the Y axis ran in the medio-lateral direction and the Z axis was vertical and orthogonal to the X and Y axes.

	1st vector	**2nd vector**
Sagittal trunk angle	Acromion to ASIS markers in XZ plane	Z axis
Sagittal hip angle	Acromion to ASIS markers	Upper to lower femoral markers
Sagittal thigh angle	Upper to lower femoral markers in XZ plane	Z axis
Sagittal knee angle	Upper to lowers femoral markers	Fibular head to malleolar markers
Sagittal ankle angle	Fibular head to malleolar markers	Heel to toe markers
Coronal trunk angle	Left to right acromial markers in the YZ plane	Y axis
Coronal pelvic angle	Left to right ASIS marker motion in the YZ plane	Y axis
Horizontal trunk angle	Left to right acromial markers in the XY plane	X axis
Horizontal pelvic angle	Left to right ASIS markers in the XY plane	X axis

Table 2.3: Vectors forming the 2D joint angles identified from the marker set up.

Markers were placed on the lower limb and trunk to represent the segments of the subject i.e. foot, leg, thigh, and trunk. The markers were tracked by the motion analysis system, which measures their linear displacement. The data was AD converted at a sampling rate of 200 Hz (Winter 2005). Linear velocity and linear acceleration of the individual markers were calculated as first and second derivatives of displacement with respect to time [6]. Infrared markers were applied bilaterally to the acromion, midway between the anterior superior iliac spines (ASIS) and posterior superior iliac spine (PSIS), upper femur, lower femur, fibular head, lateral malleolus, lateral heel and base of the 5th metatarsal. Trunk and lower limb angles were identified (table 2.3). Angular displacement in the

X-Z plane was calculated and angular velocity and angular acceleration were computed as time derivatives of the angular displacement measure [6].

During off-line analysis of walking heel strike, heel rise and toe off were identified to allow the definition of periods of the gait cycle. Heel strike was defined from the displacement of the heel marker in the Z direction, heel rise from the linear acceleration of the heel marker in the X direction and toe off from the linear acceleration of the toe marker in the X direction.

One cycle was identified from the initial heel strike to the second heel strike of the same leg. The first three cycles of the trial were identified in this way and averaged, as recommended in previous studies [3, 7]. Data from the first minute of the walking test was discarded to allow for the subject settling on the treadmill. The left cycle was used to normalise the data so each cycle duration was 100%. The gait cycle was divided into phases and the maximum, minimum and peak to peak of the pertinent variables were found within each period (table 2.4).

Phase	*Stance*			*Swing*
	Initial heel contact → toe off			Toe off → second heel contact
Period	*Loading*	*Mid-stance*	*Pre-swing*	
	Initial heel contact → opposite toe off	Opposite toe off → opposite heel contact	Opposite heel contact → toe off	

Table 2.4: Definitions of the phases and periods of the gait cycle

2.2 Measurement of ankle stiffness

Ankle stiffness into dorsiflexion and plantarflexion was measured using ramp and hold stretches delivered via a dynamometer (Biodex Medical Instruments Inc., New York, USA). Subjects lay supine, with their knee in extension, and placed their foot in a manipulandum set at plantigrade. The foot, ankle and proximal leg were secured using straps. The manipulandum was rotated through 5° with a peak velocity of 15° per second, as specified by a positional data file (Biodex System3 Researchers Toolkit). Subjects remained relaxed during the test and six stretches in each direction were collected.

Muscular activity was recorded using a telemetry surface electromyography (EMG) unit (MIE Medical Research Ltd, Leeds, UK). Skin was prepared with alcohol rub and bipolar silver/silver chloride surface electrodes were placed longitudinally over the belly of the muscle of interest. Surface EMG was recorded from the tibialis anterior (TA) and medial gastrocnemius (GAS) to confirm muscle relaxation. A real time display of the raw signal allowed monitoring of relaxation during the test. Torque, velocity and position were collected via the Biodex remote access port. Signals were AD converted using a Power 1401. Data was sampled at 2000Hz and collected using Spike2 software (Spike2 version 5.06, Cambridge Electronic Design).

Stretch data was collected using Spike2 software and exported as spreadsheet text files for analysis using Matlab programmes written in house (MATLAB, Mathworks Inc). The last 5 stretches were averaged. The mean torque (Torque $_{Total}$) and position was measured over a 300ms period just prior to the stretch and 725ms post stretch onset when the ankle had stopped moving.

The torque due to the weight of the foot ($Torque_{foot\ weight}$) was estimated as:

$$Torque_{footweight} = mg\sin\theta d \qquad (2.8)$$

Where θ = ankle angle relative to vertical, g = acceleration due to gravity, m = mass of the foot estimated from anthropometric data based on the subject's mass and gender, and d = the manipulandum length.

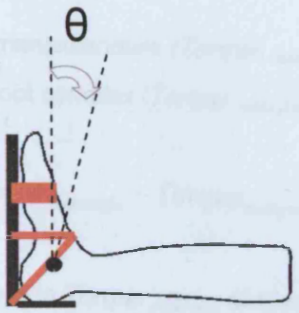

Figure 2.1: Position of foot in manipulandum. Θ = angle relative to vertical.

The change in torque due to the manipulandum ($Torque_{manipulandum}$) was measured directly. The torque due to stiffness in the ankle-foot complex ($Torque_{ankle\text{-}foot}$) was defined as:

$$Torque_{ankle-foot} = Torque_{total} - Torque_{footweight} - Torque_{manipulandum} \qquad (2.9)$$

Stiffness was calculated as the change in $Torque_{ankle\text{-}foot}$ divided by the change in position. This method has been used previously to measure stiffness of the ankle [6] and the glenohumeral joint [9].

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3 Investigation of Proximal Strategies in CMT

3.1 Introduction and Hypothesis

The primary hypothesis for this thesis states that in people with CMT, weak ankle muscles lead to increased muscle activity around the hip to compensate for reduced limb progression and foot drop during swing.

Distal muscle weakness is well described in CMT and will affect the motion, moments and power produced at the ankle during the gait cycle, particularly at the end of stance phase. Prior to this study, a detailed description of any proximal changes that may compensate for distal weakness had not been reported in CMT. However, from previous work in other conditions[22,23] we would expect that weak plantarflexors would be compensated for by an earlier onset and/or increased magnitude of hip kinetics at the end of stance phase to maintain leg progression whilst dorsiflexor weakness and foot drop may be compensated for by an increase in hip flexion during swing phase to allow foot clearance.

In this study we will compare the gait pattern in people with CMT to healthy control subjects. Based on previous work in other types of neuropathy, predictions were constructed for this study from the primary hypothesis:

People with CMT will show

- **Decreased ankle plantarflexor range, moment and power generation during preswing.**
- **The distal plantarflexor changes will be accompanied by a change in the magnitude and timing of the hip flexor moment and power generation normally seen during preswing.**
- **Decreased dorsiflexion during swing phase.**
- **The distal dorsiflexor changes will be accompanied by an increase in hip flexion during swing phase (a high stepping gait)**

3.2 Methods

People with CMT were recruited from the genetic peripheral neuropathy clinic at the National Hospital for Neurology and Neurosurgery. People with clinically definite CMT, regardless of type, and the ability to walk 100m in at least 10 minutes were included. People were excluded if they had a history of other neurological impairment, orthopaedic lower limb impairment unrelated to CMT and lower limb or back pain exceeding 7 out of 10 on a visual analogue scale. Healthy control subjects were matched for age, gender, weight and height and the same exclusion criteria were applied to this group.

Gait analysis: Three dimensional segmental analysis of gait was performed (CODAmotion, Leicestershire, UK) (figure 3.1). Infrared markers were applied in clusters that allowed the calculation of 3D lower limb kinematics via CODA motion software, (see methods, chapter 2). Subjects were asked to walk along a 10 metre walkway. An additional segment for the trunk was defined using markers on the anterior superior iliac spines (ASIS) and acromion processes of the shoulders. Two force plates were embedded in the walkway and used for the 3D kinetic analysis.

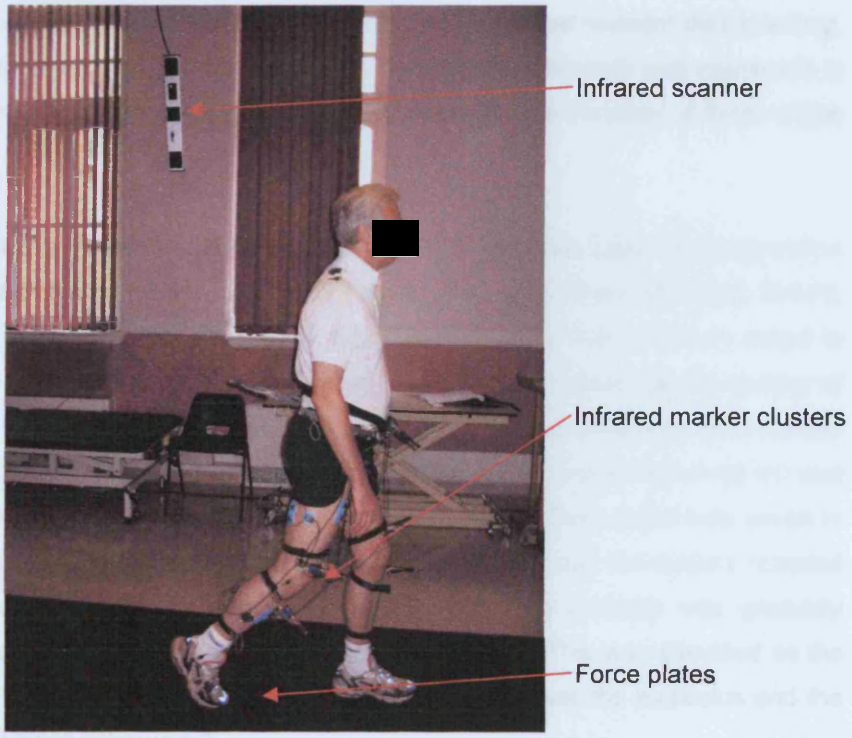

Figure 3.1: Three dimensional gait analysis set up

People with CMT were asked to walk along the walkway at a comfortable speed. Six seconds of synchronised motion and force data were collected per trial (sampling rate 200Hz). Trials were accepted if a single foot landed fully on a force plate. Three footfalls per leg were collected. Subjects walked in shoes but without the aid of any ankle-foot orthoses. Walking aids were used if necessary for safety. Control subjects were asked to walk at the same rate and step length as the CMT subject they were controlling for. Marks were drawn at the beginning of the walkway, to indicate the desired step length, and a metronome was used to cue the subject to the correct cadence. Practice sessions were given until the control subject was consistent in both parameters. Data was collected in the same way as with the CMT subjects.

Strength measures: Measures of isometric maximum voluntary contraction (MVC) of the ankle dorsiflexors, plantarflexors, hip flexors and extensors were recorded using a dynamometer (Biodex Medical Instruments Inc., New York, USA). For measures of ankle strength, subjects lay supine with their ankle in plantigrade. The foot was placed in a manipulandum and the axis of the dynamometer motor was aligned to the ankle joint axis. The foot, ankle and proximal leg were secured using straps and a manual restraint was applied at the shoulders. Hip strength was recorded with the hip at 40° flexion, with the subject supine and the femur secured to a manipulandum with straps. An extra strap was placed across the pelvis and this was reinforced by manual restraint during testing. The axis of the dynamometer motor was aligned with the hip joint axis. Strength was expressed in Nm per Kg of body weight. Contractions were held for three seconds and the peak of three values was taken.

Sensory testing: Two sensory modalities were tested in the CMT subjects. Light touch sensation was measured on the sole of the foot using 10g monofilaments (Neuropen, Owen Mumford, Oxford, UK). Ten standard areas of the plantar surface were tested (appendix 3). Subjects were asked to close their eyes and state "yes" when they felt the filament. The result was scored as the number of positive responses out of ten. Vibration threshold was tested using a biothesiometer (Bio-medical Instrument Co, Newbury, Ohio, USA, 120 Hz). The probe of the biosthesiometer was held still and at a constant pressure over the lateral malleolus and then the great toe. The subject was asked to close their eyes. The intensity of the vibration was gradually increased until the subject reported feeling it. This was identified as the appearance threshold. Then the intensity was gradually decreased until the subject reported that the vibration had disappeared. This was identified as the disappearance threshold. The appearance threshold was established over the malleolus and the great toe from the mean of three measures [6].

Passive ankle joint stiffness:

Ankle stiffness into dorsiflexion and plantarflexion was measured using a dynamometer (Biodex Medical Instruments Inc., New York, USA). (see chapter 2 for full description). Subjects lay supine, with their knee in extension, and placed their foot in a manipulandum set at plantigrade. The foot,

ankle and proximal leg were secured using straps. The manipulandum was rotated through 5° with a peak velocity of 15° per second, as specified by a positional data file (Biodex System3 Researchers Toolkit). Subjects remained relaxed during the test and six stretches in each direction were collected.

Surface EMG was recorded from the tibialis anterior (TA) and medial gastrocnemius (GAS) to confirm muscle relaxation. Torque, velocity and position were collected via the Biodex remote access port. Signals were AD converted using a Power 1401. Data was sampled at 2000Hz and collected using Spike2 software (Spike2 version 5.06, Cambridge Electronic Design).

Joint alignment: Subjects were screened for a scoliosis using Adam's forward bend test [7] (appendix 3). The presence of pes cavus or planus, toe flexion deformities, plantar fascia tightness and calcaneal valgus or varus was noted. In the presence of calcaneal varus the block test was used to ascertain whether this was due to a fixed deformity (appendix 3).

3.2.1 Analysis

Three trials for the left and right legs were exported as text files for analysis using Matlab programmes written in house (Mathworks). A single gait cycle was identified from the heel marker acceleration traces and vertical forces. Cycle duration was normalised, and three cycles were averaged (appendix 2) [10, 19]. The data from the left and right legs were combined. Temporal and spatial gait parameters were recorded.

The primary analysis was based on the four predictions introduced at the beginning of this chapter.

- Peak ankle plantarflexion angular displacement, moment and power generation were measured during preswing (see methods, chapter 2).
- Peak hip flexion angular displacement, angular velocity, moment and power generation were measured during preswing (see methods, chapter 2).
- Foot drop was measured from the dorsiflexion angle in swing when a foot marker (toe or heel) was at its lowest vertical point i.e. at foot clearance.
- The maximal hip flexion angular displacement was measured during swing phase
- The relative timing of the onset of hip and ankle power generation during preswing

This gave a total of ten comparisons for the primary analysis. Consideration was given to correction for the multiple comparisons to decrease the chance of type 1 error. Bonferroni correction was considered too conservative as the correction does not account for dependency among the data which would be the case in this study [2, 29]. In addition there is also the potential to increase type 2 errors giving a false null result [21, 34]. A modified Bonferroni procedure was used as it is less conservative and has a type 1 error probability equal to α (see appendix 1 for calculation) [38].

Although attempts were made to match the walking speed between the two groups, significant group differences in walking speed were still found (see results, section 3.3.2). As many kinetic and kinematic gait parameters can vary with walking speed [18] the effect of this variable was taken into account by performing a univariate analysis of co-variance with gait speed as a covariate (ANCOVA).

A secondary analysis was performed that did not directly relate to the predictions of this study but aimed to see if:

- There were other changes in the motion and kinetics of proximal joints and segments to compensate for distal weakness e.g. the hip, knee, pelvis or trunk.
- There were changes in the ankle, knee and hip kinematics and kinetics during stance related to support.
- There were distal and proximal changes in ankle, knee and hip motion in the coronal and horizontal planes.

The variables analysed were:

- Maximum and minimum ankle kinematics and kinetics in the loading and stance phases
- Maximum and minimum sagittal knee kinematics and kinetics in preswing and hip velocity, moment, power generation in swing
- Peak to peak pelvis and trunk kinematics in all three planes
- Lower limb angular displacement in the coronal and horizontal planes in stance and swing phase

A modified Bonferroni adjustment was made to this data from the secondary analysis (appendix 1) but none of the group differences were significant due to the large number of comparisons. It was decided, however, to still look for patterns in the data using $p<0.05$ as a guide. Data were compared with findings of previous studies to evaluate whether or not a consistent and logical finding was real, and not a false positive result. It was acknowledged, however, that strictly the results of the secondary analysis gave an indication of group trends only.

Impairment measures, such as strength, sensation and stiffness, were compared using 2-tailed unpaired t-tests for interval data and the Mann-Whitney test for nominal data. Gait speed and other temporal and spatial measures were tested using a one way analysis of variance (ANOVA) comparing the CMT group, controls at a matched walking speed and controls at their normal walking speed. Significance was taken as $p<0.05$, with means reported ± the standard deviation unless indicated [29].

Variability in presentation has been described in previous studies of gait in people with CMT [14, 31] so relationships were tested between:

- Temporospatial gait parameters and distal impairments
- Distal gait parameters and impairment measures
- Proximal changes and measured gait variables

Pearson's correlation for parametric data was used for this analysis. If there was more than one significant correlation then a stepwise multiple regression was performed using up to two predictors together to see whether either or both remain statistically significant. Variables were entered into the model if $F < \text{or} = 0.05$ and excluded if $F > \text{or} = 0.1$. Correlations for non-parametric data were tested with Spearman's rank correlation test.

Finally, an intra-group comparison was made by separating the CMT group into people with type 1 demyelinating CMT and type 2 axonal CMT. Unpaired t-tests were used to compare the two CMT groups as there was no difference in gait speed with significance taken as $P<0.05$.

3.3 Results

3.3.1 Subjects

Fourteen people with CMT and 12 matched control subjects participated in the study. Six of the subjects with CMT had type 1 disease and eight had type 2 CMT. There were no significant differences observed in their matching criteria (table 3.1). One person with CMT used a single walking stick. The two groups demonstrated differences in the maximum voluntary contraction of the distal limb muscles but not the proximal groups (table 3.2). It was not possible to get strength measures from one person with CMT due to their individual time constraints.

	Age (years)	Gender	Height (m)	Weight (kg)
CMT subjects N=14	38 ±14	9 male; 5 female	1.67 ±0.9	74 ±14
Control subjects N=12	40 ±10	6 male; 6 female	1.70 ±0.9	68 ±14

Table 3.1: Mean age, gender, height and weight data for both subject groups (± standard deviation).

MVC (Nm/kg)	Hip flexion	Hip extension	Plantarflexion	Dorsiflexion
CMT subjects N=13	1.19 ±0.49	1.21 ±0.68	0.55 ±0.57 *	0.07 ±0.06 *
Control subjects N=12	1.45 ±0.54	1.39 ±0.69	1.73 ±0.66	0.45 ±0.16

Table 3.2: Mean maximum voluntary contraction measures for the CMT and control groups (± standard deviation). * $p<0.05$

None of the subjects had a scoliosis but over half of the people with CMT had foot deformity associated with the condition (table 3.3). Only one person had a fixed ankle varus. Testing of sensory modalities over the foot and ankle demonstrated a decrease in vibration and light touch sensation in the CMT group (malleolus $t = 2.45$, $P=0.03$; toe $t = 2.7$, $P=0.02$; light touch $z = -2.76$, $P=0.003$). Although the control subjects appear to have stiffer ankles when they are stretched into dorsiflexion, the difference between the two groups was not significant. While walking none of the subjects with CMT reported lower limb pain.

	CMT subjects	Control subjects
Percentage of subjects with scoliosis	0	0
Percentage of subjects with pes cavus	57%	0
Percentage of subjects with calcaneal valgus	50%	0
Stiffness of ankle into dorsiflexion (Nm/radians)	49.01 ±13.1	55.24 ±23.48
Sensation: Light pressure (scores out of 10)	5.25 ±3.24 *	10 ±0
Vibration (microns) Malleolus	8.0 ±9.2 *	1.3 ±1.5
Great toe	7.4 ±8.9 *	0.4 ±0.28

Table 3.3: Comparison of distal sensation, ankle stiffness, spinal and foot alignment (mean ± standard deviation for stiffness and sensation data). * $p<0.05$

3.3.2 General Gait Comparison

The temporal and spatial comparison of walking is shown in table 3.4 including control data for the matched pace trials and normal pace trial.

Variable	CMT subjects	Control subjects (matched pace)	Control subjects (normal pace)
Gait Speed (m/s)	1.03 ±0.18* †	1.26 ±0.24	1.37 ±0.18
Cadence (steps/minute)	100.6 ±10.8†	108.5 ±12.6	112.8 ±9.8
Step length (m)	0.62 ±0.08* †	0.71 ±0.069	0.74 ±0.07
Stride time (s)	1.21 ±0.13	1.12 ±0.14	1.07 ±0.1
Double support time (s)	0.19 ±0.03* †	0.14 ±0.02	0.13 ±0.02

Table 3.4: Summary of temporal and spatial data for people with CMT, control subjects walking at a matched pace and control subjects walking at their normal pace (mean ± standard deviation). * $p<0.05$ people with CMT versus controls at a matched pace; † $p<0.05$ people with CMT versus controls at a normal pace.

Gait speed was slower in people with CMT compared to control subjects walking at both their normal speed and the matched speed (ANOVA: $F=10.04$, $P=0.0004$; post hoc: CMT v controls matched: $t=2.78$, $P=0.01$; CMT v controls normal: $t=-4.83$, $P<0.001$). This implies that the methods used to constrain the control subjects did not successfully match the speed. Cadence, however, was better matched with no significant difference between people with CMT and controls at a

matched pace. Controls walking at their normal pace had a higher cadence (ANOVA: F=4.08, P=0.03; CMT v controls matched: t =1.68, P=0.11; CMT v controls normal: t =-3.03, P=0.006).

Step length was longest in the control subjects walking at a normal pace and shortest in people with CMT (ANOVA: F=6.63, P=0.004; CMT v controls matched: t =1.72, P=0.005; CMT v controls normal: t =-4.82, P<0.001). There was no significant difference in stride time but the double support time was longer for people with CMT compared to controls walking at a matched pace and a normal pace (ANOVA: F=15.68, P<0.0001; CMT v controls matched: t =-4.51, P<0.001; CMT v controls normal: t =-5.43, P<0.001).

3.3.3 Kinematic and Kinetic Comparison

3.3.3.1 Primary comparison

Distal differences: There were significant differences in the plantarflexor moment and ankle power generation during preswing (table 3.5; figure 3.4 and 3.5). No significant differences were observed in the plantarflexor angle during preswing or the dorsiflexor angle at foot clearance (table 3.5; figure 3.2).

Variable	CMT subjects	Control subjects	F statistic	P value
Peak PF angle preswing (deg)	6.44 ±9.52	17.26 ±7.58	2.78	0.11
Peak PF moment during preswing (Nm/Kg)	0.89 ±0.37	1.34 ±0.15	7.25	0.01 †
Peak ankle power generation preswing (W/Kg)	1.36 ±0.90	3.04 ±0.65	14.99	0.001 †
Peak DF angle at foot clearance in swing (deg)	-4.35 ±9.04	3.56 ±3.19	2.50	0.1

Table 3.5: Results of ANCOVA for distal gait variables for people with CMT and control subjects walking at a matched pace (mean values ± standard deviation). Deg: degrees; Nm: Newton metres; kg: Kilogram; W: Watts. † significant following modified Bonferroni procedure.

Proximal differences: No significant differences were seen in the motion, moment and power generation at the hip during preswing. During swing phase people with CMT demonstrated a significant increase in hip flexion angle (table 3.6; figure 3.2). There was a trend towards increased hip flexor velocity during preswing in people with CMT that was not significant post modified Bonferroni correction.

Timing of kinetic data

As can be seen in figure 3.5, people with CMT showed a marked delay in the onset of ankle power generation relative to toe off (ANCOVA: F =10.26, p=0.004) with a decrease in total power produced during the push off period (ANCOVA: F =17.11, p<0.0001).

Although there was no significant difference in the onset of hip power generation, people with CMT tended to generate power at the hip before the ankle in contrast to the control subjects who all generated power at the ankle first (relative power onset between hip and ankle ANCOVA: F =5.9, p=0.02). This group difference was significant post modified Bonferroni correction.

Variable	CMT subjects	Control subjects	F statistic	P value
Peak hip flexor angle preswing (deg)	4.42 ±8.55	-1.76 ±7.31	2.11	0.16
Peak hip flexor angle swing (deg)	36.83 ±8.06	27.86 ±7.53	8.21	0.009 †
Peak hip flexor velocity preswing(deg/s)	103.75 ±31.94	98.23 ±42.38	4.92	0.037
Peak hip flexor moment preswing(Nm/kg)	0.15 ±0.23	-0.01 ±0.12	1.63	0.22
Peak hip power generation preswing(W/kg)	0.70 ±0.43	0.94 ±0.49	0.014	0.91

Table 3.6: Results of ANCOVA for proximal gait variables for people with CMT and control subjects walking at a matched pace (mean values ± standard deviation). † significant following modified Bonferroni procedure.

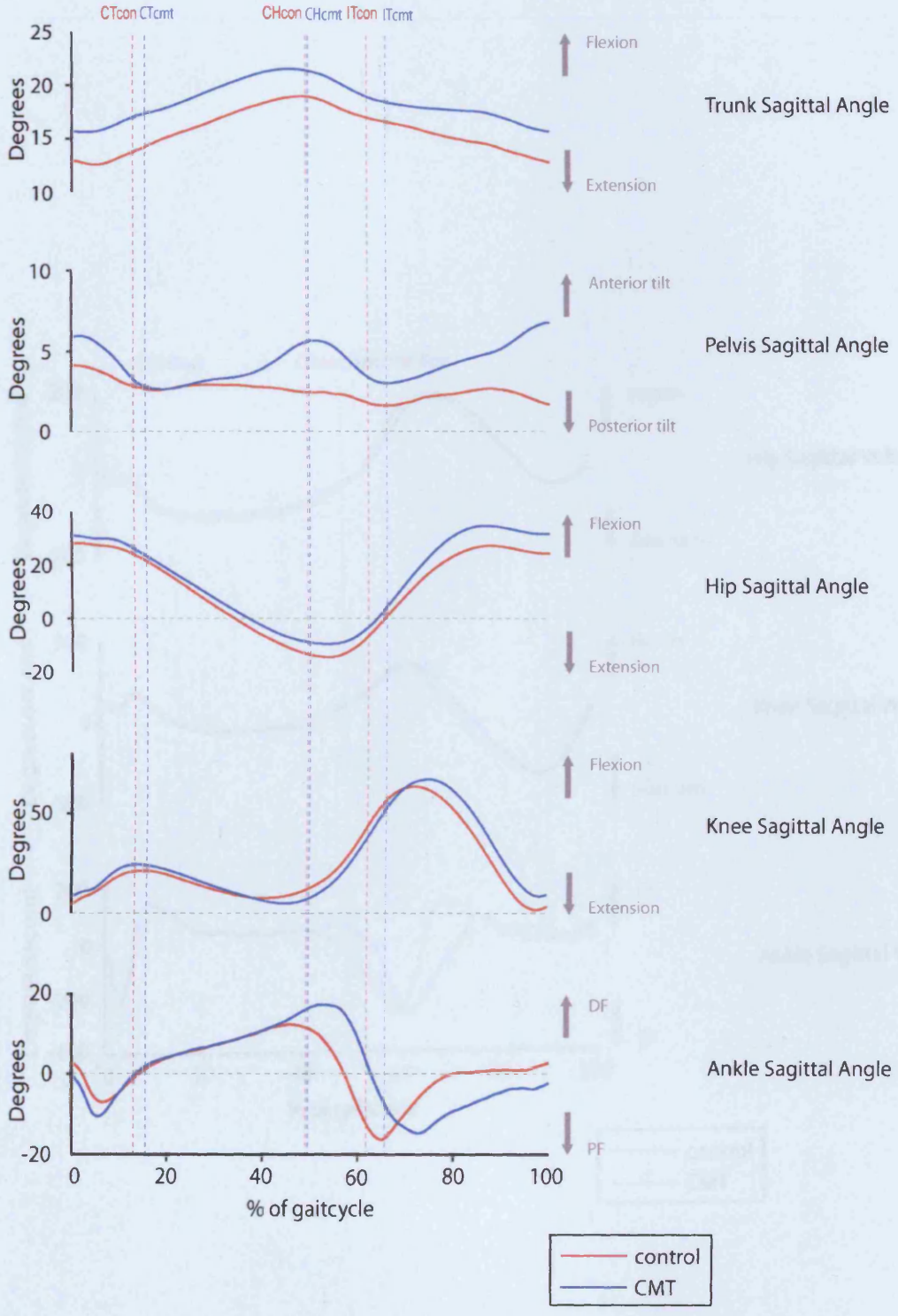

Figure 3.2: Grand average angular displacement in the sagittal plane over one gait cycle for the ankle, knee, hip, pelvis and trunk (average of left and right sides). Comparison of people with CMT and controls walking at a matched pace. CTcon: contra-lateral toe off control subjects; CTcmt: contra-lateral toe off CMT subjects; CHcon: contra-lateral heel strike control subjects; CHcmt: contra-lateral heel strike CMT subjects; ITcon: ipsilateral toe off control subjects; ITcmt: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

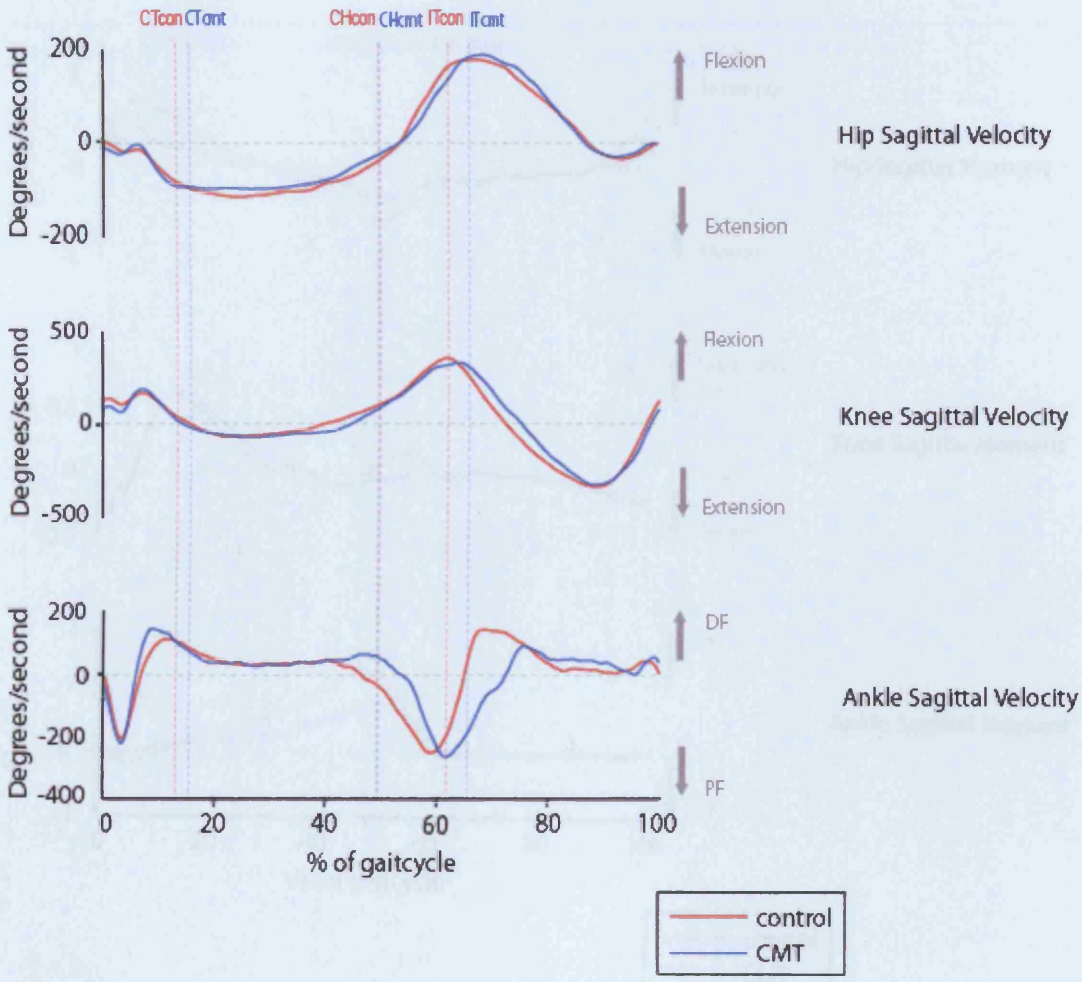

Figure 3.3: Grand average angular velocity in the sagittal plane over one gait cycle for the ankle, knee and hip (average of left and right sides). Comparison of people with CMT and controls walking at a matched pace. CTcon: contra-lateral toe off control subjects; CTcmt: contra-lateral toe off CMT subjects; CHcon: contra-lateral heel strike control subjects; CHcmt: contra-lateral heel strike CMT subjects; ITcon: ipsilateral toe off control subjects; ITcmt: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

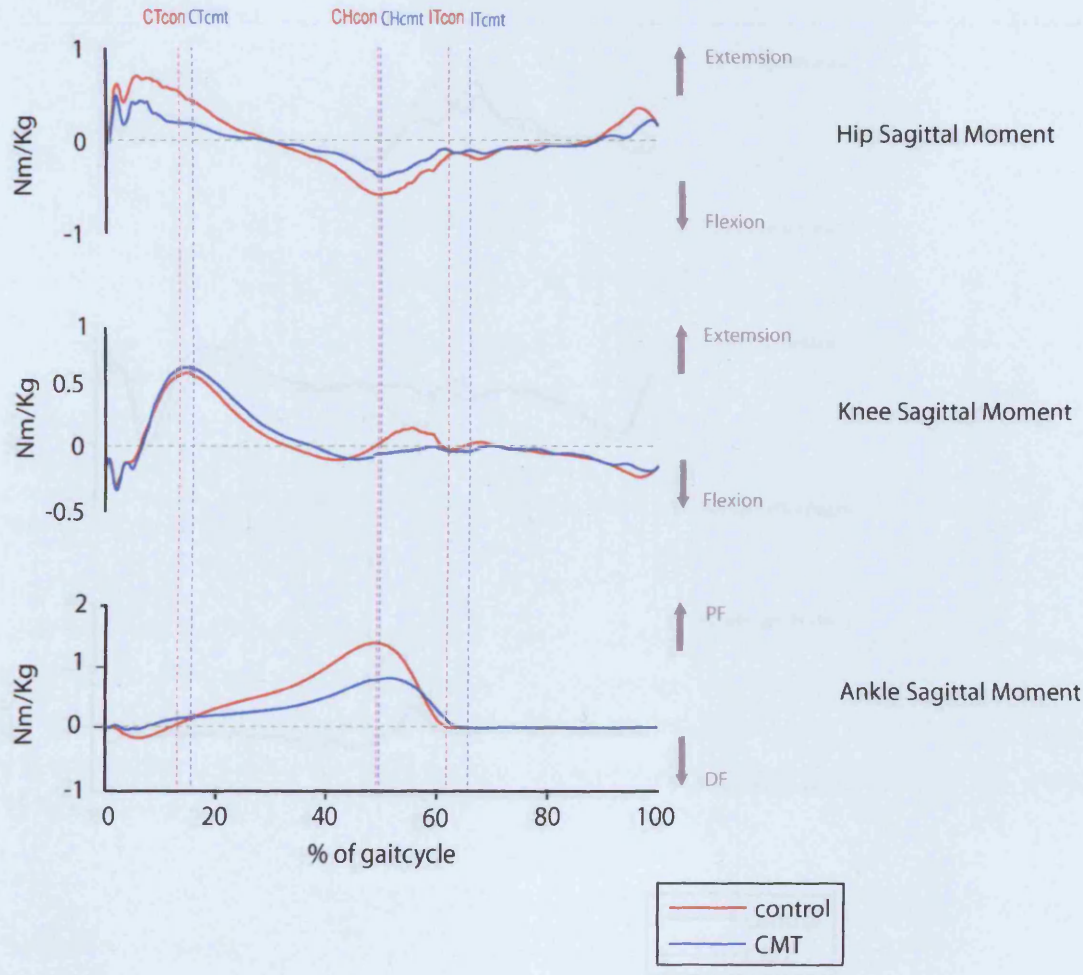

Figure 3.4: Grand average joint moments in the sagittal plane over one gait cycle for the ankle, knee and hip (average of left and right sides). Comparison of people with CMT and controls walking at a matched pace. CTcon: contra-lateral toe off control subjects; CTcmt: contra-lateral toe off CMT subjects; CHcon: contra-lateral heel strike control subjects; CHcmt: contra-lateral heel strike CMT subjects; ITcon: ipsilateral toe off control subjects; ITcmt: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

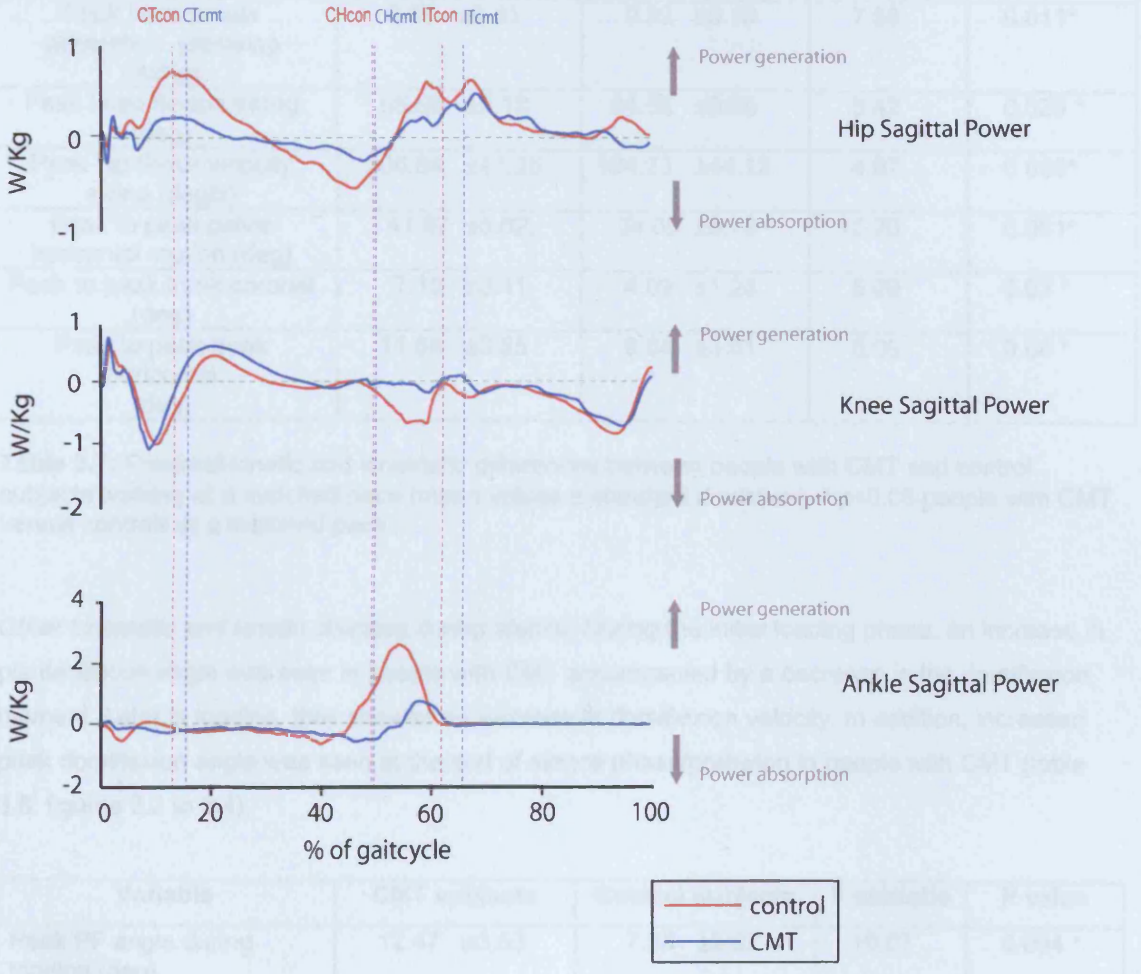

Figure 3.5: Grand average joint powers in the sagittal plane over one gait cycle for the ankle, knee and hip (average of left and right sides). Comparison of people with CMT and controls walking at a matched pace. CTcon: contra-lateral toe off control subjects; CTcmt: contra-lateral toe off CMT subjects; CHcon: contra-lateral heel strike control subjects; CHcmt: contra-lateral heel strike CMT subjects; ITcon: ipsilateral toe off control subjects; ITcmt: ipsilateral toe off.

3.3.3.2 Secondary comparison

Other proximal differences: Proximally, people with CMT had a reduction in knee extensor moment in pre-swing but showed an increase in knee power generation at the end of preswing compared to controls. Later in swing there was an increase in peak knee flexion in people with CMT. They also showed significant increases in horizontal rotation at the pelvis and trunk. This was accompanied by increased trunk rotation in the coronal plane (table 3.7; figures 3.2, 3.4 to 3.7).

Variable	CMT subjects	Control subjects	F statistic	P value
Peak knee extensor moment preswing (Nm/Kg)	0.12 ±0.07	0.22 ±0.12	6.35	0.019 *
Peak knee power generation preswing (W/Kg)	0.60 ±0.31	0.32 ±0.19	7.58	0.011*
Peak knee flexion swing (deg)	68.56 ±5.13	64.56 ±6.68	5.42	0.029 *
Peak hip flexor velocity swing (deg/s)	206.84 ±41.25	194.23 ±44.12	4.87	0.038*
Peak to peak pelvis horizontal motion (deg)	41.97 ±5.62	34.69 ±6.70	15.70	0.001*
Peak to peak trunk coronal (deg)	7.10 ±3.11	4.09 ±1.25	5.09	0.03 *
Peak to peak trunk horizontal (deg)	11.88 ±3.55	8.84 ±3.51	5.09	0.04 *

Table 3.7: Proximal kinetic and kinematic differences between people with CMT and control subjects walking at a matched pace (mean values ± standard deviation). * $p<0.05$ people with CMT versus controls at a matched pace

Other kinematic and kinetic changes during stance: During the initial loading phase, an increase in plantarflexion angle was seen in people with CMT accompanied by a decrease in the dorsiflexion moment. Later in loading, they showed an increase in dorsiflexion velocity. In addition, increased peak dorsiflexion angle was seen at the end of stance phase/preswing in people with CMT (table 3.8; figures 3.2 to 3.4).

Variable	CMT subjects	Control subjects	F statistic	P value
Peak PF angle during loading (deg)	12.47 ±3.53	7.98 ±2.92	10.07	0.004 *
Peak DF velocity during loading (deg /s)	189.74 ±37.85	134.25 ±37.14	15.74	0.001 *
Peak DF moment during loading (Nm/Kg)	0.09 ±0.05	0.21 ±0.07	13.77	0.001 *
Peak DF angle at preswing (deg)	19.87 ±4.87	11.35 ±5.90	8.98	0.006 *

Table 3.8: Results of ANCOVA for distal gait variables for people with CMT and control subjects walking at a matched pace (mean values ± standard deviation). * $p<0.05$ people with CMT versus controls at a matched pace.

Differences in the coronal and horizontal planes: The ankle was also more supinated in people with CMT during loading phase and through the rest of stance. They also showed changes at the knee in the other planes of motion with increased valgus and decreased external rotation in swing (table 3.9; figures 3.6 and 3.7).

Variable	CMT subjects	Control subjects	F statistic	P value
Peak supination during loading (deg)	6.82 ±8.5	-1.04 ±5.17	4.90	0.04 *
Peak supination during stance (deg)	8.79 ±8.42	1.22 ±6.61	4.47	0.05
Peak knee valgus preswing (deg)	9.20 ±5.70	2.62 ±4.06	7.59	0.011 *
Peak knee external rotation swing (deg)	0.91 ±18.81	18.72 ±4.99	6.53	0.018 *

Table 3.9: Results of ANCOVA for coronal and horizontal angular displacement for people with CMT and control subjects walking at a matched pace (mean values ± standard deviation). * $p<0.05$ people with CMT versus controls at a matched pace.

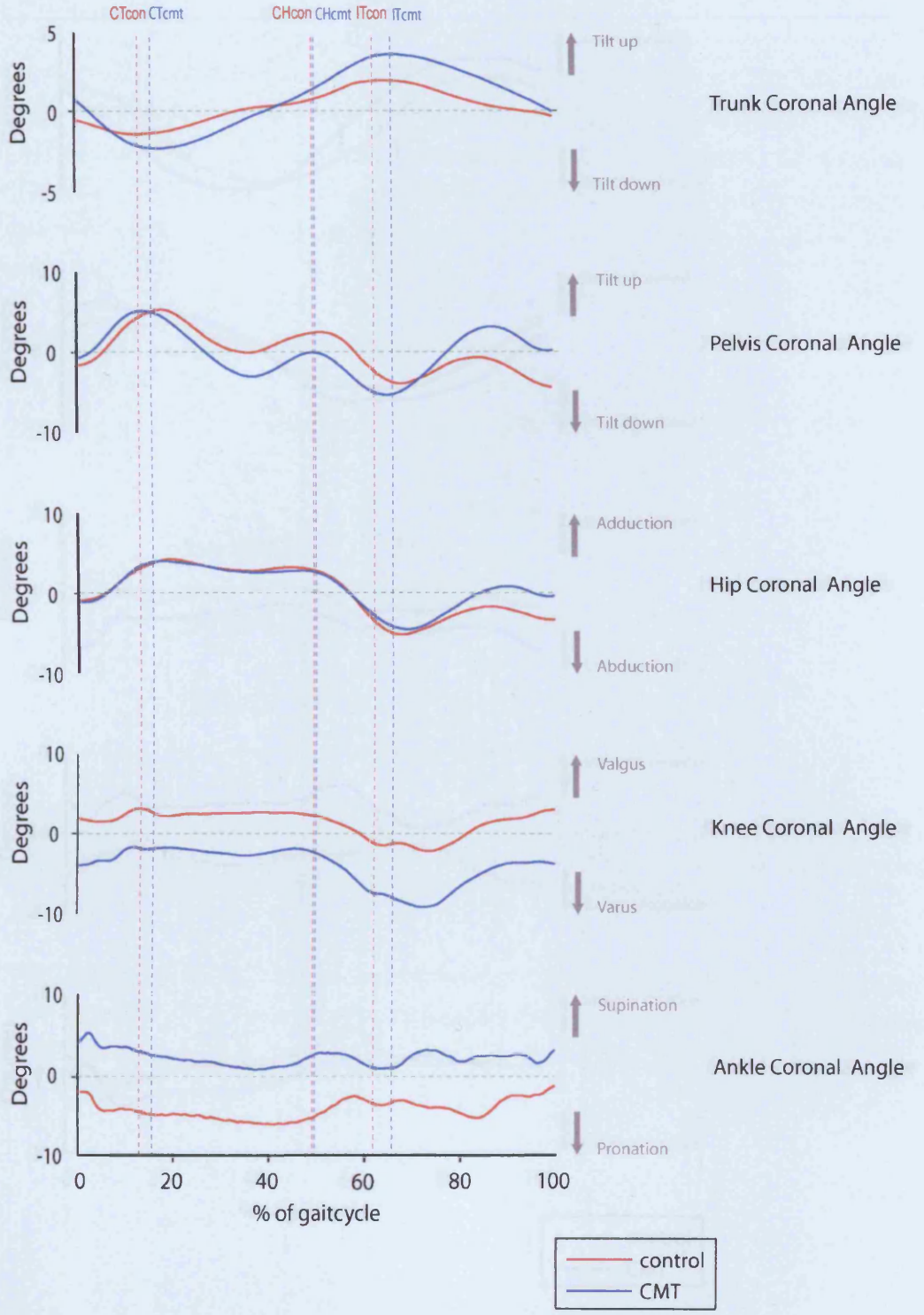

Figure 3.6: Grand average angular motion in the coronal plane over one gait cycle for the ankle, knee, hip, pelvis and trunk (average of left and right sides). Comparison of people with CMT and controls walking at a matched pace. CTcon: contra-lateral toe off control subjects; CTcmt: contra-lateral toe off CMT subjects; CHcon: contra-lateral heel strike control subjects; CHcmt: contra-lateral heel strike CMT subjects; ITcon: ipsilateral toe off control subjects; ITcmt: ipsilateral toe off.

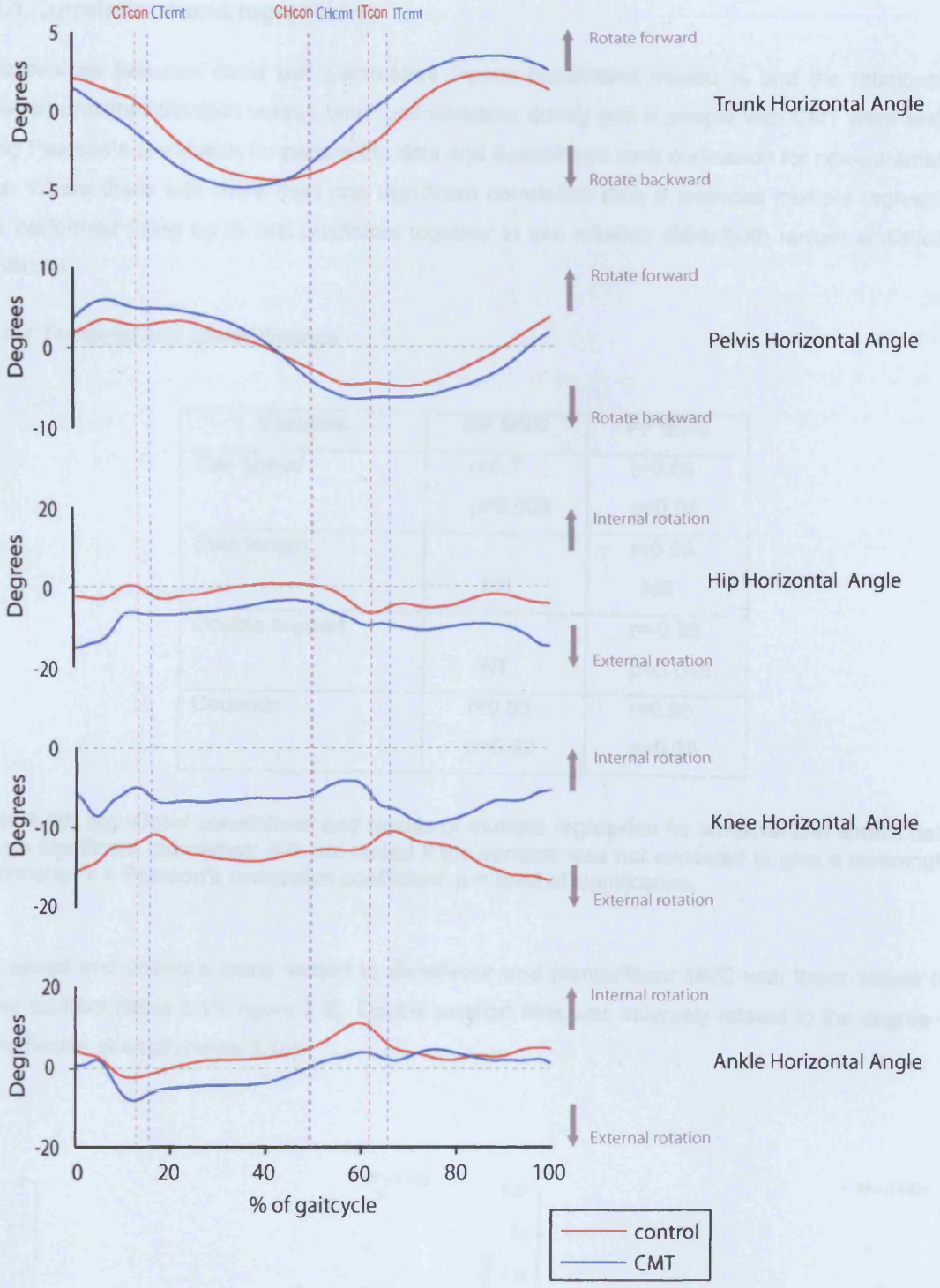

Figure 3.7: Grand average angular motion in the horizontal plane over one gait cycle for the ankle, knee, hip, pelvis and trunk (average of left and right sides). Comparison of people with CMT and controls walking at a matched pace.CTcon: contra-lateral toe off control subjects; CTcmt: contra-lateral toe off CMT subjects; CHcon: contra-lateral heel strike control subjects; CHcmt: contra-lateral heel strike CMT subjects; ITcon: ipsilateral toe off control subjects; ITcmt: ipsilateral toe off.

3.3.4 Correlations and regressions

Relationships between distal gait parameters versus impairment measures and the relationship between proximal changes versus other gait variables during gait in people with CMT were tested using Pearson's correlation for parametric data and Spearman's rank correlation for non-parametric data. Where there was more than one significant correlation then a stepwise multiple regression was performed using up to two predictors together to see whether either/both remain statistically significant

3.3.4.1 Temporal and spatial findings

Variable	DF MVC	PF MVC
Gait speed	r=0.7 p=0.008	r=0.66 p=0.01
Step length	NS	r=0.53 NS
Double support	NT	r=-0.56 p=0.045
Cadence	r=0.63 p=0.02	r=0.56 p=0.05

Table 3.10: Significant correlations and results of multiple regression for temporal and spatial data. NS: no significant correlation; NT: not tested if the variable was not expected to give a meaningful relationship. r = Pearson's correlation coefficient; p = level of significance.

Gait speed and cadence were related to dorsiflexor and plantarflexor MVC with lower values for slower walkers (table 3.10, figure 3.8). Double support time was inversely related to the degree of plantarflexion strength (table 3.10).

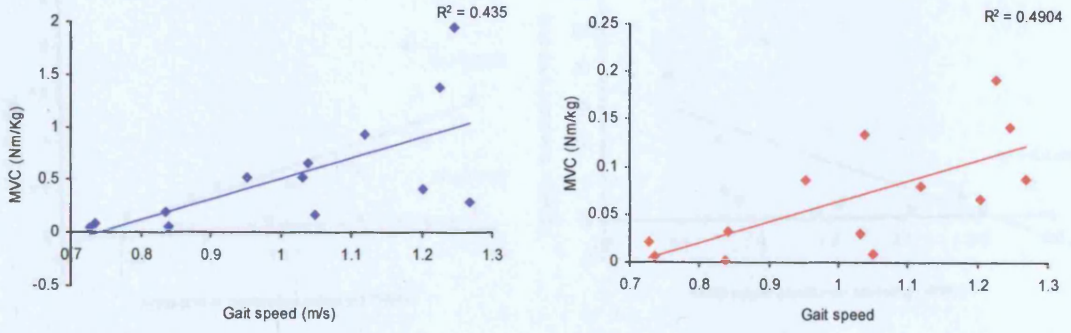

Figure 3.8: Correlation between gait speed and plantarflexor MVC (♦) and dorsiflexor MVC (■).

3.3.4.2 Relationship between distal gait changes and impairments

Distal findings: Variables that were significantly different between the two groups, described in the previous section, were related to primary impairments of weakness and sensory loss (table 3.11).

The ankle plantarflexion moment and power generation during preswing were correlated with the degree of plantarflexor weakness and distal sensory loss (table 3.11). Stepwise multiple regression revealed that plantarflexor MVC and malleolar vibration threshold together accounted for 81% of the variance in ankle power and 82% of the variance in peak PF moment (ankle power: PF MVC plus malleolar vibration threshold F=18.53, P=0.001; PF moment: PF MVC plus malleolar vibration threshold F=20.05, P<0.0001) (figure 3.9). Dorsiflexion angle at preswing was greatest in subjects with distal weakness (table 3.12). No significant correlations were seen between distal coronal changes and impairments

Related Impairments	Peak ankle power generation preswing	Peak PF moment at preswing	DF angle preswing
DF MVC	r = 0.83 p = 0.0005	r = 0.83 p = 0.0004	r = -0.84 p = 0.0003
PF MVC	r = 0.83 p=0.0004	r = 0.84 p = 0.0004	r = -0.79 p = 0.001
Vibration threshold toe	r = -0.62 p = 0.03	r = -0.65 p = 0.02	NS
Vibration threshold malleolus	r = -0.65 p = 0.02	r = -0.66 p = 0.02	NS

Table 3.11: Correlations for distal sagittal kinetic and kinematic data. NS: no significant correlation; r = Pearson's correlation coefficient; p = level of significance.

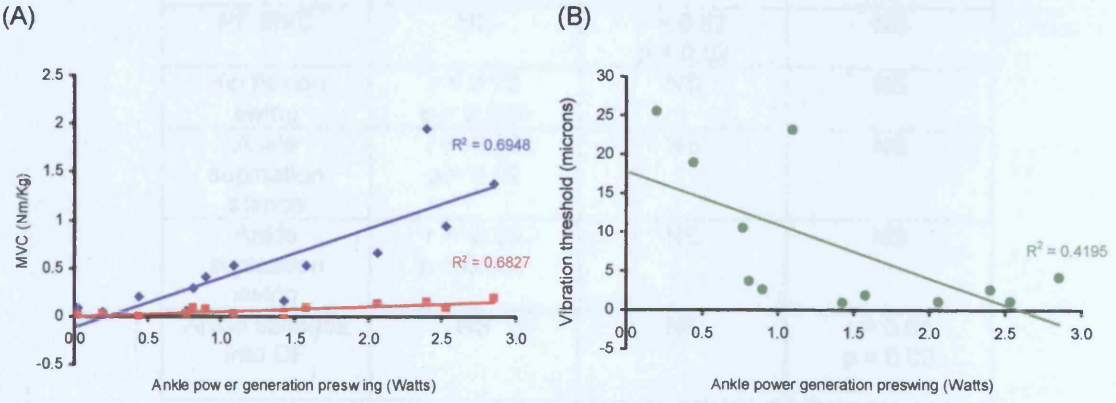

Figure 3.9: Correlation between (A) ankle power generation in preswing and plantarflexor MVC (♦) and dorsiflexor MVC (■); (B) ankle power generation and malleolar vibration threshold (●).

3.3.4.3 Relationship between proximal gait changes and other gait variables

The increase in hip flexion during swing was significantly related to decreased peak dorsiflexion during swing phase (table 3.12). Increased hip flexor velocity in preswing and swing was related to knee power absorption in preswing. Additional changes were found with the knee kinetics during preswing. The knee extensor moment was reduced in people with CMT and was related to the ankle power generation and hip flexor moment in preswing (figure 3.10). Higher knee power generation observed in people with CMT at the end of pre-swing correlated with higher hip power generation in swing.

Related Gait Variables	Hip flexor angle swing	Hip flexor velocity preswing	Peak knee extensor moment	Peak knee power generation
Ankle power generation preswing	NS	NS	r = 0.64 p = 0.01	NS
Peak DF angle swing	r = - 0.56 p = 0.04	NS	NS	NS
Knee power absorption preswing	NS	r = 0.70 p = 0.005	r = 0.76 p = 0.002	NT
Hip flexor moment preswing	NS	NS	r = 0.59 p = 0.03	NS
Hip power generation swing	NS	NS	NS	r = 0.73 p =0.003

Table 3.12: Correlations for knee and hip sagittal kinetic and kinematic data. NS: no significant correlation; r: Pearson's correlation coefficient; p: level of significance.

Related Gait Variables	Horizontal pelvis rotation	Horizontal trunk rotation	Coronal trunk rotation
PF MVC	NS	r = 0.62 p = 0.02	NS
Hip flexion swing	r = 0.72 p = 0.007	NS	NS
Ankle supination stance	r = -0.63 p = 0.02	NS	NS
Ankle supination swing	r = -0.69 p = 0.007	NS	NS
Ankle stiffness into DF	NS	NS	r = 0.62 p = 0.02

Table 3.13: Correlations for pelvis and trunk sagittal kinematic data. NS: no significant correlation; r: Pearson's correlation coefficient; p: level of significance.

Increased trunk horizontal rotation related to plantarflexor MVC and coronal motion related to ankle stiffness into dorsiflexion (table 3.13). Higher sagittal hip flexion during swing was associated with a larger range of horizontal pelvic motion. Additionally, supination of the ankle was inversely related to increased horizontal pelvic motion On stepwise multiple regression only swing phase sagittal hip flexion remained a significant predictor (table 3.13).

3.3.5 Intra-group comparison

3.3.5.1 General comparison

	Age (years)	Gender	Height (m)	Weight (kg)
CMT type 1 N=6	41 ±10	2 male; 4 female	1.61 ±0.1	69 ±11
CMT type 2 N=8	36 ±17	6 male; 2 female	1.71 ±0.07	77 ±16
Control subjects N=12	40 ±10	6 male; 6 female	1.70 ±0.09	68 ±14

Table 3.14: Mean age, gender, height and weight data for the three groups (± standard deviation).

The CMT group was split into two sub groups. Six subjects with the demyelinating CMT1a condition were placed in the group *type-1*. Eight subjects with the axonal condition were put into the *type-2* group. The type-2 group consisted of 3 people with CMT2 of unknown gene, 4 people with CMTX and 1 person with HSN1 (see chapter 1). The type-1 group were older, shorter and lighter than group type-2 probably because two thirds of the type-1 group were female and thee quarters of type-2 were male (table 3.14). The differences, however, were not significant on testing.

MVC (Nm/kg)	Hip flexion	Hip extension	Plantarflexion	Dorsiflexion
CMT type 1 N=6	1.00 ±0.12	1.38 ±0.81	0.86 ±0.79	0.12 ±0.06 *†
CMT type 2 N=8	1.31 ±0.60	1.11 ±0.63	0.36 ±0.30 †	0.04 ±0.03 *†
Control subjects N=12	1.45 ±0.54	1.39 ±0.69	1.73 ±0.66	0.45 ±0.16

Table 3.15: Mean maximum voluntary contraction measures for the two CMT and control groups (± standard deviation). * $p<0.05$ CMT type 1 versus CMT type 2; † $p<0.05$ CMT type 1 or 2 versus controls

	Type-1	Type-2	Control subjects
Percentage of subjects with scoliosis	0	0	0
Percentage of subjects with pes cavus	66%	38%	0
Percentage of subjects with calcaneal valgus	50%	50%	0
Stiffness of ankle into dorsiflexion (Nm/radians)	47.62 ±18.9	60.96 ±26.1	55.24 ±23.48
Sensation: Light pressure (scores out of 10)	5.5 ±2.5†	5.1 ±3.9†	10 ±0
Vibration (microns) Malleolus	4.4 ±3.6	10.6 ±11.3	1.3 ±1.5
Great toe	4.2 ±3.4	9.8 ±11.1	0.4 ±0.28

Table 3.16: Comparison of distal sensation, ankle stiffness, spinal and foot alignment (mean ± standard deviation for stiffness and sensation data). † $p<0.05$ CMT type 1 or 2 versus controls

The type-2 group were significantly weaker than the type-1 group in the DF muscles (type-2 v type-1: $t = 2.67$, $P=0.04$) and tended to be weaker in the PF muscles (type-2 v type-1: $t = 1.38$, $P=0.2$) (table 3.15).

Pes cavus was present in a higher percentage of the type-1 group but calcaneal varus featured equally in both groups. Non-significant trends towards greater ankle stiffness and higher vibratory thresholds in the type-2 group can be seen from the mean values (table 3.16).

Variable	Type 1	Type 2	Control subjects (matched pace)
Gait Speed (m/s)	1.12 ±0.16	0.96 ±0.18†	1.26 ±0.24
Cadence (steps/minute)	104.9 ±9.04	97.42 ±11.4	108.5 ±12.6
Step length (m)	0.64 ±.0.05	0.60 ±0.08	0.71 ±0.07
Stride time (s)	1.15 ±0.11	1.25 ±0.14	1.12 ±0.14
Double support time (s)	0.18 ±0.03†	0.19 ±0.03†	0.14 ±0.02

Table 3.17: Summary of temporal and spatial data for people with CMT type-1, type-2 and control subjects walking at a matched pace (mean ± standard deviation). † $p<0.05$ CMT type 1 or 2 versus controls

No significant differences were seen between the type-1 and type-2 groups in temporal and spatial gait parameters though there was a tendency for the type-2 group to walk slower with a reduced cadence (table 3.17).

3.3.5.2 Kinematic and kinetic comparison

Variable	Type-1 group	Type-2 group	Control subjects
PF angle at toe off (deg)	12.82 ±7.2 *	1.66 ±8.4 *†	17.26 ±7.6
Timing of ankle power onset (% gait cycle)	50.8 ±4.8 *	58.9 ±4.9 *†	46.0 ±3.3
Peak DF velocity preswing (deg/s)	44.73 ±34.7 *†	120.6 ±32.1 *†	-19.19 ±60.9
Peak DF angle in swing (deg)	3.31 ±1.8 *	-1.81 ±4.5 *†	3.19 ±3.1
Peak DF angle at foot clearance in swing (deg)	2.24 ±3.2 *	-9.29 ±8.9 *†	3.56 ±3.2

Table 3.18: Distal kinematic and kinetic differences between the type-1 CMT group, type-2 CMT group and control subjects (mean values ± standard deviation). Deg: degrees. * $p<0.05$ CMT type 1 versus CMT type 2; † $p<0.05$ CMT type 1 or 2 versus controls

Distal Differences: In keeping with the greater peripheral involvement in the type-2 group distal changes were observed during walking between the groups (table 3.18, figure 3.10). In the type-2 group there was a significant reduction in PF angle at toe off (type-2 v type-1: t = -2.68, P=0.02) with a greater delay in ankle power onset (type-2 v type-1: t = -3.09, P=0.01). Dorsiflexion velocity was higher in the type-2 group during the initial part of preswing (type-2 v type-1: t = -4.17, P=0.002) and in swing phase there was a reduction in the peak dorsiflexion angle (type-2 v type-1: t = 2.96, P=0.02) (figure 3.11) and dorsiflexion angle at foot clearance (type-2 v type-1: t = 3.38, P=0.008).

Proximal differences: Subjects in the type-2 group showed significantly greater trunk rotation in the horizontal plane compared to type-1 (type-2 v type-1: t = -2.26, P=0.04). Non-significant trends were seen for the type-2 group to increase hip flexion in swing, greater peak to peak coronal trunk motion and higher range of horizontal pelvic rotation (table 3.19).

Variable	Type-1 group	Type-2 group	Control subjects
Peak to peak trunk horizontal (deg)	11.48 ±4.37 *	12.19 ±3.07 *†	8.84 ±3.51
Peak hip flexor angle swing (deg)	34.63 ±9.6	38.5 ±6.8†	27.86 ±6.9
Peak to peak trunk coronal (deg)	6.08 ±2.33	7.87 ±3.54†	4.09 ±1.25
Peak to peak pelvis horizontal (deg)	39.91 ±6.12	43.53 ±5.06†	34.58 ±6.74

Table 3.19: Proximal kinematic and kinetic differences between the type-1 CMT group, type-2 CMT group and control subjects (mean values ± standard deviation). Deg: degrees

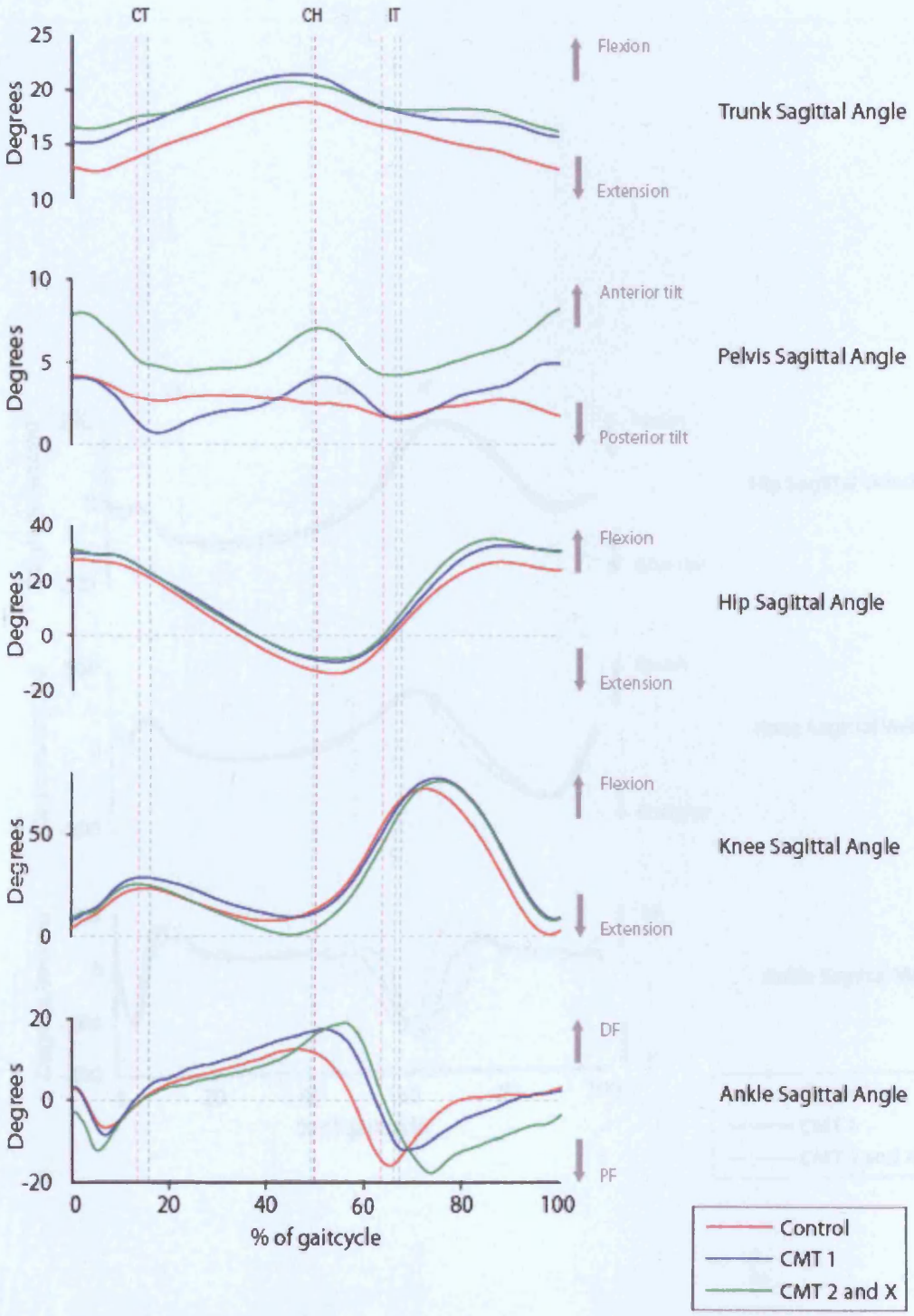

Figure 3.10: Grand average angular displacement in the sagittal plane over one gait cycle for the ankle, knee, hip, pelvis and trunk (average of left and right sides). Comparison of people with CMT, types 1 and 2, and controls walking at a matched pace. CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

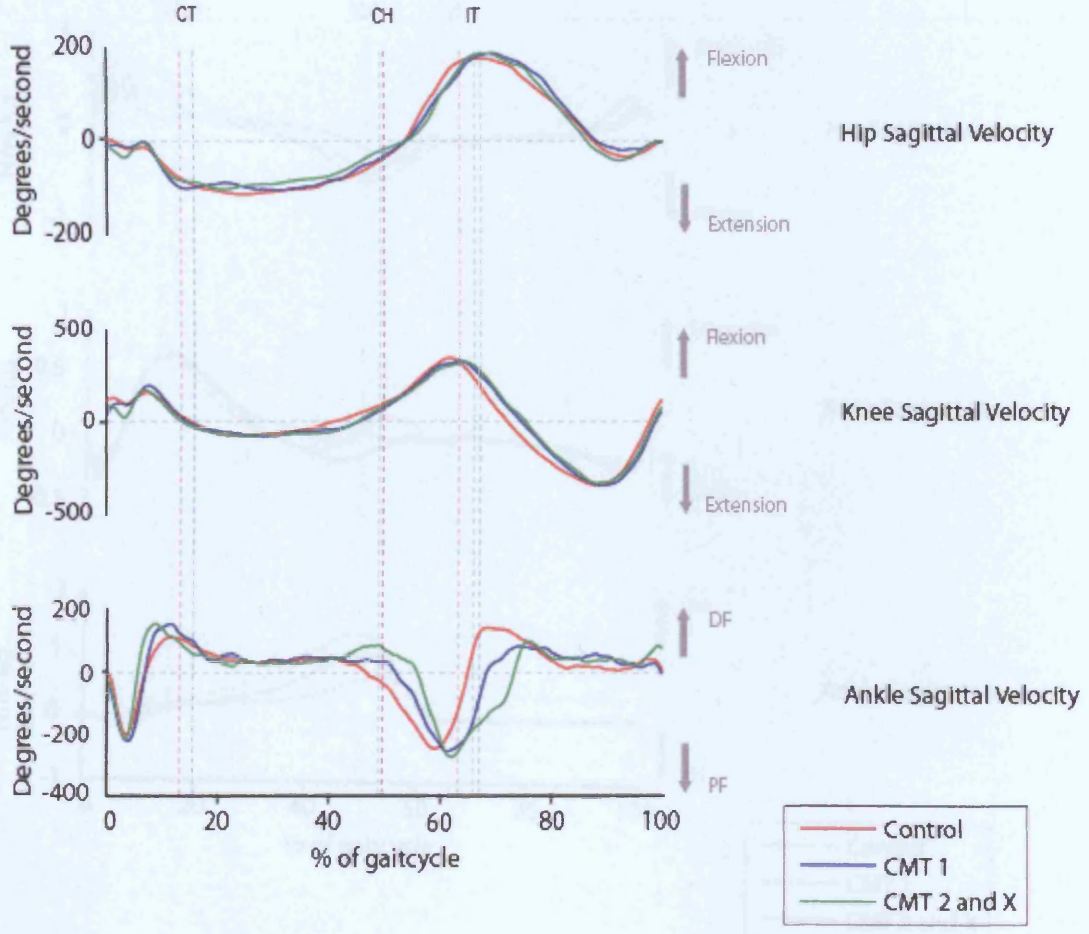

Figure 3.11: Grand average angular velocity in the sagittal plane over one gait cycle for the ankle, knee and hip (average of left and right sides). Comparison of people with CMT, types 1 and 2, and controls walking at a matched pace. CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

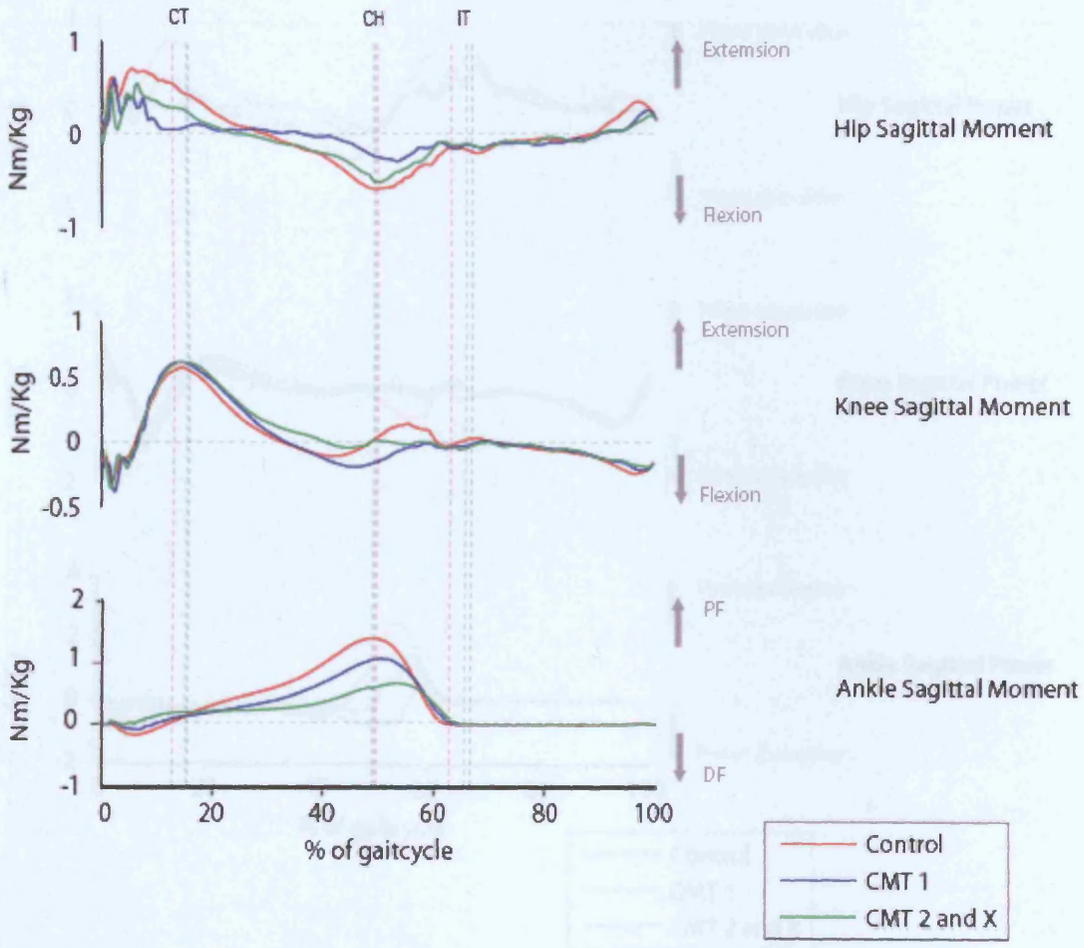

Figure 3.12: Grand average joint moments in the sagittal plane over one gait cycle for the ankle, knee and hip (average of left and right sides). Comparison of people with CMT, types 1 and 2, and controls walking at a matched pace. CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

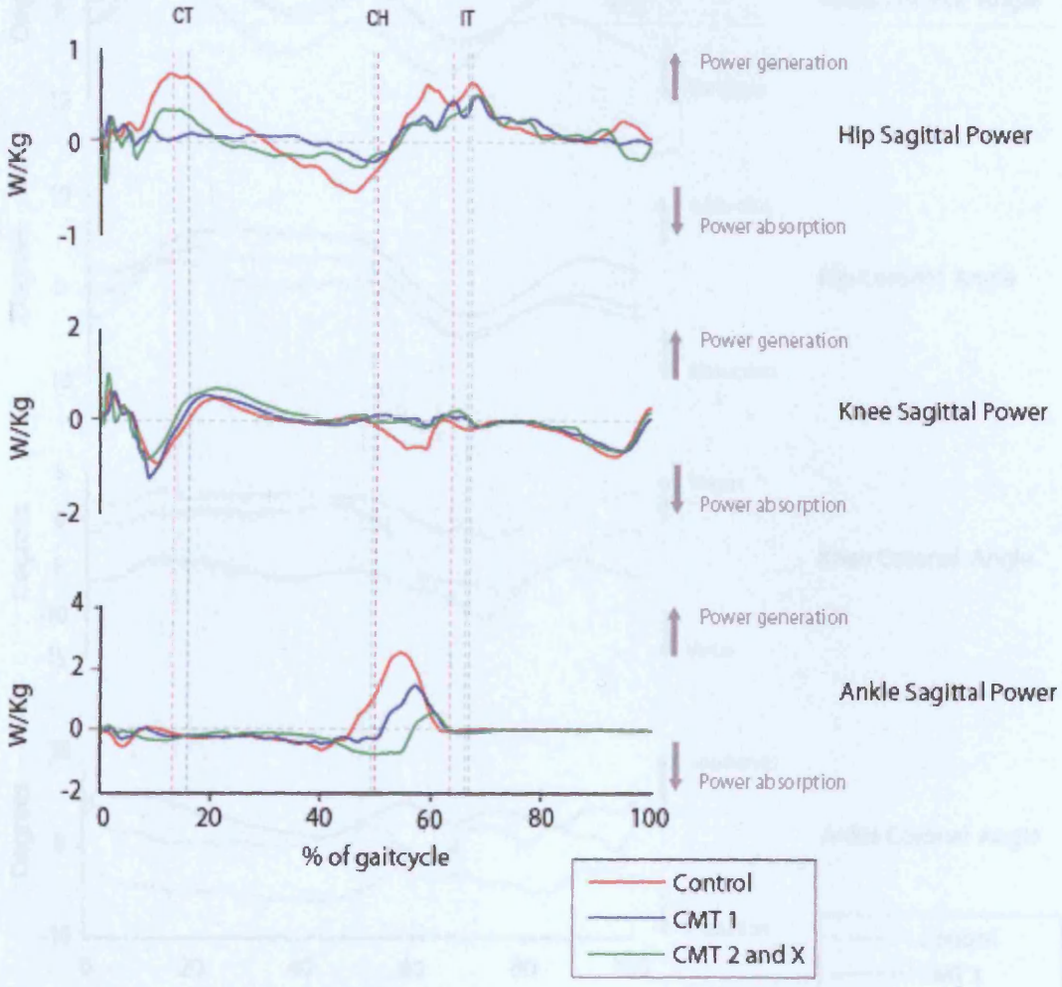

Figure 3.13: Grand average joint powers in the sagittal plane over one gait cycle for the ankle, knee and hip (average of left and right sides). Comparison of people with CMT, types 1 and 2, and controls walking at a matched pace. CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off;

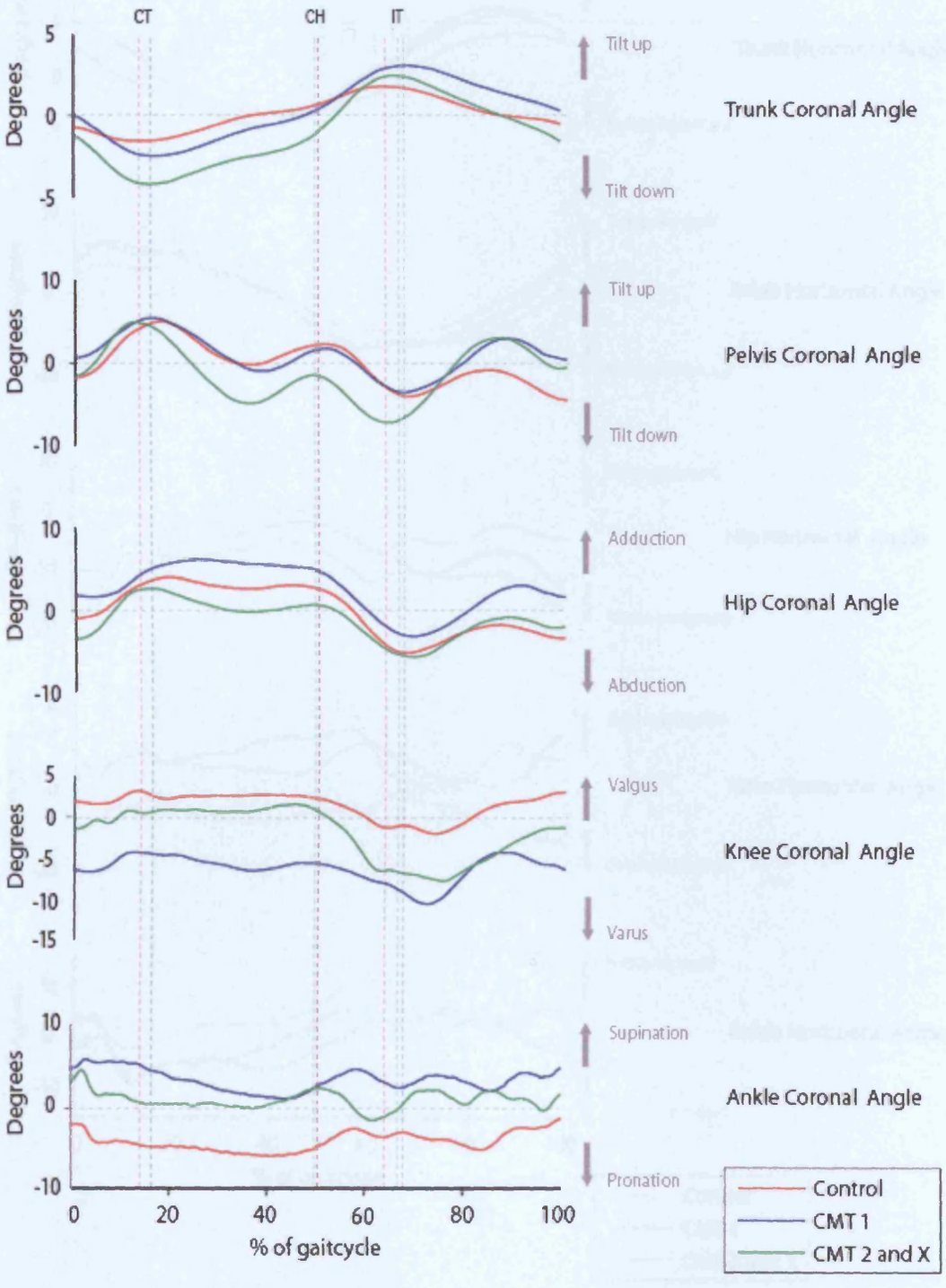

Figure 3.14: Grand average angular motion in the coronal plane over one gait cycle for the ankle, knee, hip, pelvis and trunk (average of left and right sides). Comparison of people with CMT, types 1 and 2, and controls walking at a matched pace. CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off;

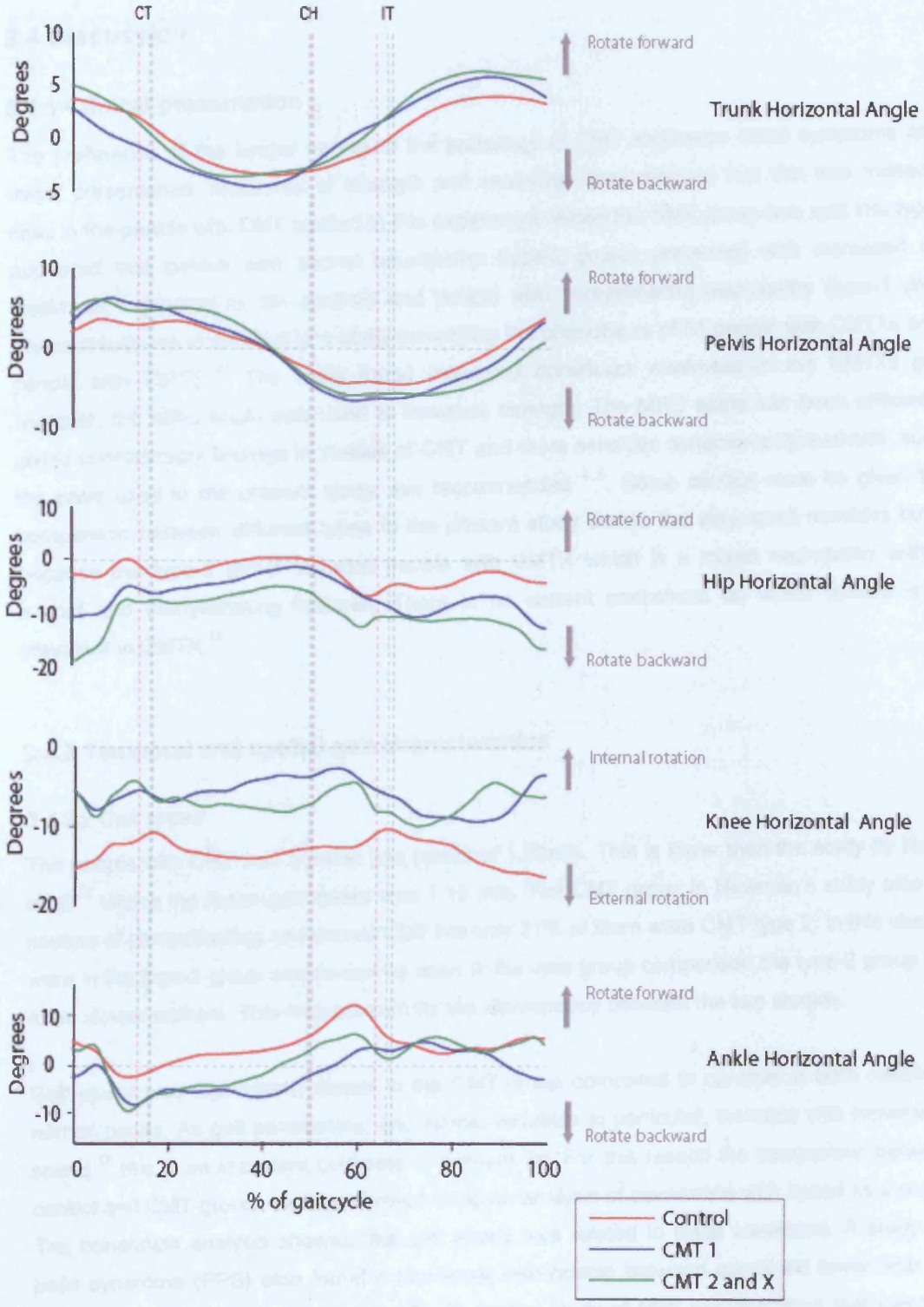

Figure 3.15: Grand average angular motion in the horizontal plane over one gait cycle for the ankle, knee, hip, pelvis and trunk (average of left and right sides). Comparison of people with CMT, types 1 and 2, and controls walking at a matched pace. CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off;

3.4 Discussion

3.4.1 Clinical presentation

The preference of the longer nerves in the pathology of CMT implicates distal symptoms as the major presentation. Measures of strength and sensation demonstrated that this was indeed the case in the people with CMT studied in this experiment. When the CMT group was split into types, it appeared that people with axonal neuropathy (type-2 group) presented with increased distal weakness compared to the controls and people with demyelinating neuropathy (type-1 group). These results are in contrast to a study comparing the phenotypes of 51 people with CMT1a and 61 people with CMT2 [3]. The study found increased dorsiflexor weakness in the CMT1a group, however, the MRC scale was used to measure strength. The MRC scale has been criticised for giving contradictory findings in studies of CMT and more sensitive dynamometry methods, such as the ones used in the present study, are recommended [4 5]. Some caution must be given to the comparison between different types in the present study due to the very small numbers but also because the type-2 group included people with CMTX which is a mixed neuropathy with both axonal and demyelinating features. There is no current consensus on which feature is most prevalent in CMTX [13].

3.4.2 Temporal and spatial gait characteristics

3.4.2.2 Gait speed

The people with CMT had a mean gait speed of 1.03m/s. This is lower than the study by Newman et al [27] where the mean gait speed was 1.12 m/s. The CMT group in Newman's study also was a mixture of demyelinating and axonal CMT but only 31% of them were CMT type 2. In this study 66% were in the type-2 group and as can be seen in the intra group comparison the type-2 group tended to be slower walkers. This may account for the discrepancy between the two studies.

Gait speed was significantly slower in the CMT group compared to controls at both matched and normal paces. As gait parameters, and kinetic variables in particular, increase with increasing gait speed [18] this is an important covariate to account for. For this reason the comparison between the control and CMT groups were performed using an analysis of covariance with speed as a covariate. The correlation analysis showed that gait speed was related to distal weakness. A study of post polio syndrome (PPS) also found a non-linear relationship between combined lower limb muscle strength and maximal walking speed [40]. An earlier study of PPS demonstrated that plantarflexor strength was the best predictor of walking speed [35]. Studies of people with stroke have also demonstrated the important role of the plantarflexors in determining gait speed [23, 32].

3.4.2.3 Gait parameters

This study showed a reduction in step length, cadence and double support in people with CMT. Although this has not been reported before in CMT, studies of people with diabetic peripheral neuropathy and older people reported a similar finding when compared with matched healthy subjects [20] [15, 22] . The reduction in step length may be a strategy to increase stability and has been described by some authors as part of a "conservative gait pattern". Alternatively the step length may be reduced in this group of people with CMT because lower ankle power generation did not propel the body and swing limb sufficiently. The prolonged double support phase in stance may also reflect the adoption of a conservative gait strategy [8]. In people with diabetic neuropathy the double support time was associated with reduced lower limb sensation. This was not seen in the present study where it was associated with distal weakness.

3.4.3 Kinematic and kinetic characteristics

3.4.3.1 Progression

Primary analysis: The plantarflexor moment at preswing and peak ankle power generation were reduced in the people with CMT. This finding was in agreement with other studies of gait in CMT [27] [16] and both variables correlate strongly with plantarflexor strength. In addition a stepwise multiple regression showed that both ankle plantarflexor strength and malleolar vibration threshold are independent predictors of ankle power and plantarflexor moment, together accounting for over 80% of the variance for both variables. Newman et al [27] also felt that the reduced ankle power generation was associated with reduced muscle strength but they did not consider the role of sensory input. Vibratory thresholds measure the perception of the larger diameter sensory fibres involved in awareness of joint position. It is possible that reduced perception of the ankle motion during preswing could influence the velocity or forces produced.

No significant differences were seen in the magnitude of the hip kinetic variables in preswing. Recent investigations of gait in people with CMT have had contrasting results. Newman et al [27] also showed no significant increase in hip flexor moment or power generation during preswing when comparing a heterogeneous group of 16 subjects with control data. A study by Don et al [11] used a different kinetic variable to describe proximal compensations. They measured the *angular impulse* which was calculated from the area under the moment graph for a defined period i.e. preswing. A significant increase in the angular impulse of the hip was described between 21 people with CMT and 21 age and gender matched controls. They did not report a comparison of the peak moment or any joint powers so the results cannot be directly compared to the Newman et al [27] study or the data presented in chapter 3 due to the differing variables. Angular impulse was not formally measured in the present study but the grand average graphs do not indicate that there would be a difference (figure 3.4). In addition, there were no differences in the timing in magnitude of the

moment in preswing, so angular impulse is was unlikely to be dissimilar with this data set. Neither study statistically or methodologically took account of the influence of gait speed on gait variables. Don et al [11] justified the use of the angular impulse variable as it accounted for changes in gait speed more accurately than peak values. They do not explain why this is and the paper they quote as evidence for this does not mention gait speed but discusses adaptations such as changes in the duration or magnitude of force [9].

In people with stroke, Olney and Richards [30] demonstrated an increase in hip flexor moment in late stance/early swing phase. Nadeau et al [23] observed a positive relationship between hip flexor strength and gait speed in people with plantarflexor weakness post stroke. The observation is less clear in people with CMT despite both conditions presenting with distal weakness. This could be due to differences in other presenting symptoms, for example, one is a unilateral disorder, the other is bilateral. People with stroke are more likely to present with proximal weakness of both the lower and upper limb which will affect the gait pattern. Another pertinent factor is disease progression. In stroke, compensatory strategies develop quickly in response to the acute onset of impairments. CMT is an insidious, slowly progressing condition where compensatory strategies develop over time. Diabetic peripheral neuropathy is a more comparable, slow progressing condition and gait analysis also does not show an increase in the magnitude of hip kinetics [22].

In the present study, there were some changes in the timing of activity. Although people with CMT did not generate hip power earlier than control subjects, they did generate power at the hip before the ankle due to a delay in ankle power generation. This suggests that they rely wholly on the hip flexors to initiate swing rather than the synergistic action of the ankle plantarflexors and hip flexors as with healthy subjects. The question remains, however, as to why there was no increase in hip kinetics at preswing [25].

When looking at hip kinetic variables consideration must be given to the increased error in the calculation of hip variables using inverse dynamics [19]. CODAmotion still uses the traditional method of locating hip joint centres described by Bell et al [1]. This is based on external bony landmarks and has been criticised for its inaccuracy as a method that introduces error to the inverse dynamics calculation. Apparent discrepancies between studies could also be a product of this methodological problem.

Secondary analysis: Hip flexion velocity will be related to acceleration of the leg during swing. It was increased during swing compared to the control group, when walking speed was accounted for, and the primary analysis suggested a trend towards an increase in hip velocity during preswing. Hip flexion velocity is a variable one would expect to decrease with reduced speeds as the limb segments slow. This was not the case in the CMT group and could be a strategy to maintain

sufficient limb progression where there is reduced synergistic activity distally. There was, however, no corresponding increase in hip kinetics that could cause this or correlations with distal variables.

Changes were also seen in the knee kinematics and kinetics. Figures 3.4 and 3.5 show that CMT subjects had a lower knee extensor moment in preswing and the knee extensor muscle most likely to be active at this time is the rectus femoris [24]. This has also been observed in the hemiparetic limb of people with stroke [32]. An electromyographic (EMG) study demonstrated that in healthy subjects there is an increase in rectus femoris activity at late stance/early swing whereas the other vasti muscles became active later in swing [24]. Previously it was thought that the main role of rectus femoris was to control excessive knee flexion in early swing [24]. More recently it has been suggested that rectus femoris decelerates the whole leg and re-distributes energy to assist with trunk acceleration through its eccentric action [26]. Therefore the reduced knee extensor moment at preswing in people with CMT may reflect reduced activity of rectus femoris. If the acceleration of the leg is reduced through lower ankle power generation, rectus femoris may not need to decelerate the leg so much during preswing. A positive correlation between the knee extensor moment and ankle power generation at preswing support this hypothesis. If there is a reduction and delay in leg acceleration from the diminished action of gastrocnemius the iliopsoas may have to work alone to initiate swing. A reduction in rectus femoris activity could in turn reduce the opposition to the action of the iliopsoas. This may explain why an increase in the hip flexor moment is not observed in people with CMT but changes in the hip velocity are observed.

The difference in pelvic horizontal rotation was not reported in a previous gait analysis study [27]. The difference between the groups seems to mainly relate to hip flexion in swing. It is possible that the two strategies are used together to maximize stride length and therefore assist with limb and/or trunk progression, though there are no significant correlations to support this. More difficult to explain, though, is the relationship with ankle supination because it is a negative correlation i.e. subjects with CMT who supinated least rotate the pelvis more but this relationship is not seen in control subjects. It is possible that pronation assists horizontal rotation of the pelvis and subjects with pes cavus, who have a stiffer foot and ankle, may not be able to facilitate the range of pelvic motion in this way.

An interesting and previously unreported finding was the difference in range of trunk motion between the groups. Increased horizontal rotation was seen in people with CMT that related to distal impairments. Horizontal trunk motion correlated with plantarflexor strength suggesting that it may be a strategy used to compensate for a reduction of plantarflexor /activity at preswing. It has been suggested that horizontal motion of the lumbo-pelvic area is related to step length [37]. If step length is limited by reduced propulsion from the plantarflexors, this may be why trunk rotation is employed as a strategy.

The main focus of this study was compensation to maintain limb progression but plantarflexor weakness is also implicated in progression of the body. Previous modelling studies suggest that hip and knee extensor activity in early stance also contributes to progression of the trunk's forward acceleration. An increase in such activity could be anticipated in this study but this was not observed. This could be because people with CMT used another strategy such as increased trunk and pelvis rotation. It is also possible that the variability of this group masked differences in weaker individuals. A recent study of gait in people with CMT separated the group according their ability to raise their heels of the ground more than 2 cm when standing i.e. defining plantarflexor failure [11]. Increased knee extensor kinetics were observed in stance in the weaker subjects.

3.4.3.2 Foot clearance

Primary analysis: In the main comparison, people with CMT showed only a trend towards reduced dorsiflexion at foot clearance. This result was surprising as foot drop is well described in people with CMT [39] and there was a significant difference in dorsiflexion MVC. This finding also disagreed with the study by Newman et al [27] who found a difference of 5.6° between people with CMT and controls though this could be because differences in gait speed was not accounted for statistically. The intra-group comparison could provide another explanation. The type-2 group show decreased dorsiflexion variables compared to the type-1 group. The type-1 group were not significantly different to the control subjects and must have influenced the combined group result. Although it is not clear whether this observation is typical for either the type-1 or type-2 group it does indicate variability within the group of people with CMT investigated in this study.

Although performing the ANCOVA was important to account for differences due to gait speed, the functional predicament of people with CMT must not be ignored. People with CMT frequently report tripping and demonstrate reduced dorsiflexion at foot clearance when walking at the speed they are limited to by their impairments. Correlation analysis showed a relationship between dorsiflexor MVC and gait speed so it is possible that foot drop limits speed in this group, though the converse could also be true. Because of this, interventions to address foot drop are still valid.

Increased hip flexion in swing was seen in people with CMT that relates positively to dorsiflexion angle in swing. High stepping gait is has been described in this group [14] and in healthy subjects with weak dorsiflexors following tibial nerve block [17]. An increase in hip flexion could be a strategy to avoid tripping in the presence of foot drop. This suggested strategy could be supported by the increase in hip flexion velocity during swing discovered in the secondary analysis (section 3.4.3.1). The lack of change in hip kinetics in both preswing and swing, however, imply that another mechanism may be responsible for the increase in motion.

Secondary comparison: In preswing, a significant increase in knee power generation in people with CMT was noted prior to toe off. This feature was not present in the control subjects but a similar

event has been described in studies of healthy subjects stepping over obstacles. A study of walking over varying heights of obstacle showed an increased knee power generation that increased with higher obstacles [28]. The authors deduced that the increase in knee power generation was a knee flexor strategy to elevate the limb. Another study of walking over obstacles attributed the knee power generation to a flexor control of the knee joint that increased limb elevation by modulating the passive inter-segmental forces. Hip and knee flexion to clear higher obstacles was achieved through this strategy, not active control of the hip flexors [33]. It is possible that this is the strategy adopted by the people with CMT in the present study. In keeping with this, the hip flexor and knee flexor angles were increased in swing phase and knee power generation does correlate with the peak hip power generation in swing phase (table 3.12). It is, however, unclear whether the change in knee power generation is adopted to compensate for the lack of preswing propulsion or to clear a plantarflexed foot in swing. A dropped foot may be considered a trip hazard by an individual in the same way an obstacle would.

Increased coronal trunk motion in people with CMT was related to stiffness of the ankle into dorsiflexion, i.e. stiffness of the plantarflexor muscles. Although there was not a clear relationship with dorsiflexion angle it is possible that stiffness of the plantarflexors would either reduce or slow the motion of the ankle into dorsiflexion during swing phase. Coronal trunk motion could be an additional way of assisting foot clearance through pulling the swing foot off the floor as the trunk leans away from it.

3.4.3.3 Support

Deficits in eccentric plantarflexor control were evident in people with CMT. Control subjects reached peak ankle dorsiflexion angle and velocity just prior to heel strike of the opposite leg which was when the plantarflexor moment reached its peak. In people with CMT the ankle continued to dorsiflex even after contra-lateral heel strike and the peak plantarflexor moment was delayed (figure 3.4). This period of the gait cycle is sometimes described as the ankle rocker [36] where the leg advances over the fixed foot. In healthy subjects the plantarflexors are thought to prevent forward motion of the shank during the ankle rocker [41] [25]. Peak dorsiflexion angle seemed to relate to plantarflexor MVC and this would fit the possibility that excessive dorsiflexion occurs due to lack of eccentric control of the plantarflexors. The intra-group comparison supports this with the weaker type-2 group demonstrating greater dorsiflexion and velocity.

The loading phase was not part of the main analysis for this study but showed some interesting differences between the groups. People with CMT showed increased plantarflexion angle in this phase compared to controls. This finding has been described as a failure of the heel rocker where either the initial contact is with the forefoot or there is reduced dorsiflexion on heel strike [36]. Intuitively one would expect this finding to be due to either reduced ankle dorsiflexion range of motion or weak anterior tibial muscles. A decrease in the dorsiflexor moment of the ankle was also

seen in loading which in turn is correlated with the dorsiflexor MVC. This would fit with the theory of excessive plantarflexion due to reduced eccentric dorsiflexor activity. The difference in dorsiflexor moment was also observed in another study of gait in CMT where the authors relate this finding with excessive plantar flexion on loading [27].

3.4.3.4 Coronal and horizontal lower limb motion

Differences in motion in the coronal plane were observed. People with CMT showed increased ankle supination compared with controls throughout the gait cycle. No correlations were found with the variables measured in this study. The cause of foot supination and pes cavus, however, is still undecided. The development of pes cavus has been related to weakness of the intrinsic foot muscles but other authors implicate the long muscles of the leg and foot, particularly the imbalance between the peroneus brevis and tibialis posterior [4]. None of these muscles were tested in the present study. In this study the type-1 group were more supinated than the other groups on loading which can be explained by a higher incidence of pes cavus in CMT1a [3]. Some caution must be given to these findings and their interpretation because subjects walked in footwear. Motion within the shoe and inaccurate placing of markers on the shoe over bony landmarks may reduce the accuracy of these findings. The decision to wear footwear was made partly to protect feet if tripping occurred on the rubber surface of the walkway and partly because this study was run concurrently with a comparison of three ankle foot orthoses (chapter 5) which are worn within footwear. The gait analysis and impairment measures took a long time so extra barefoot trials were not added to reduce the impact of fatigue. Because comparisons were done with subjects in footwear, distal findings should be treated with caution. The differences seen in the sagittal plane are probably large enough not to be too affected by this but comparisons in the coronal plane may be prone to more error.

An increase in knee varus was observed that was significantly different during preswing but appeared to be present throughout the gait cycle (figure 3.6). This could be a secondary problem of alignment related to loading feet with pes cavus and calcaneal varus, present in 50% of the subjects with CMT. People with CMT also presented with internal rotation of the knee during the gait cycle which was significantly different from controls during swing. Newman et al [27] observed this feature and suggested that rotation of the knee was adaptive allowing weight to be transferred medially on loading in the absence of pronation.

3.4.5 Future work

A larger CMT group would allow a more meaningful comparison of the two main types of CMT perhaps including a CMTX group because it is a more mixed neuropathy. It has been acknowledged that there are differences in impairments between the two main types of CMT [3] but

understanding the gait deviations particular to each group would be helpful in directing problem orientated interventions perhaps using care pathways.

One area of gait analysis that is missing in this study is electromyography. A comparative study of the timing of muscle activity would be interesting. Relating to the hypothesis for this study, it may be possible that proximal changes in the timing or duration of activity are apparent in the absence of changes in kinetics. One of the difficulties with an EMG study relating to proximal compensation would be the difficulty in recording from the hip flexors. Recording from rectus femoris would not be sufficient because as discussed this bi-articular muscle works differently to the hip flexors. The optimisation methods used in modelling studies investigating the role of individual muscles may be valuable tools to investigate pathological gait patterns. By excluding the action of muscles known to be impaired in a condition, proximal changes may be revealed by the model. This method is being used in other groups e.g. amputee walking [42] and elderly people [12].

3.5 Summary

- People with CMT present with distal impairments of weakness of the ankle muscles, foot deformity and reduced sensory perception when compared with control subjects.

- They walk with a slower gait speed, reduced cadence and step length but increased double support time.

- Distal kinetic and kinematic variables are altered in people with CMT with increased dorsiflexion angle in late stance and reduced plantarflexor moment and ankle power generation at preswing

- Proximal differences were observed between the two groups with increased hip flexion angle and velocity during swing. In addition there was a decrease in knee extensor moment and increased knee power generation during preswing.

- People with the axonal type of CMT were weaker distally. When compared to people with demyelinating CMT, they demonstrated reduced plantarflexor angle at toe off, a greater delay in the onset of ankle power and reduced peak dorsiflexion angle in swing and at foot clearance.

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4 The effect of plantarflexor weakness on gait in healthy subjects

4.1 Introduction and Hypothesis

The primary hypothesis for this thesis states that in people with CMT, weak ankle muscles lead to increased muscle activity around the hip to compensate for reduced limb progression.

Distal muscle weakness is well described in CMT and will affect the motion, moments and power produced at the ankle during the gait cycle particularly at the end of stance phase. Prior to this study, a detailed description of any proximal changes that may compensate for distal weakness has not been reported in CMT literature. However, from previous work in other conditions we would expect that weak plantarflexors would be compensated for by an earlier onset and/or increased magnitude of hip kinetics at the end of stance phase. Further clarification is also required as to which proximal compensations are solely due to plantarflexor weakness and not other distal impairments such as those seen in people with CMT.

In this study the plantarflexor muscles were weakened in healthy subjects through a fatiguing exercise task. Gait was compared before and after plantarflexor fatigue. A prediction was constructed for this study from the primary hypothesis:

Following fatigue of the plantarflexor muscles, healthy subjects will demonstrate

- **Reduced ankle plantarflexor moment and power generation during pre-swing**
- **Increased hip flexor moment and hip power generation during preswing**

4.2 Methods

Healthy subjects were recruited from the staff and students of University College London and the National Hospital for Neurology and Neurosurgery. Subjects were excluded if they had any neurological disease, musculoskeletal condition, any recent lower limb injury or participation in competitive sports around the time of the experiment.

The sequence of events in this study was:

- Initial 3D gait analysis
- Measurement of plantarflexor maximum voluntary contraction (MVC)
- Plantarflexor fatigue task
- Second measurement of plantarflexor MVC
- Second 3D gait analysis
- Third measurement of plantarflexor MVC

4.2.1 Gait analysis

Three dimensional segmental analysis of gait was performed (CODAmotion, Leicestershire, UK). Infrared markers were applied in clusters that allowed the calculation of 3D lower limb kinematics via CODA motion software, (see methods, chapter 2). An additional segment for the trunk was defined using markers on the anterior superior iliac spines (ASIS) and acromion processes of the shoulders. Two force plates were embedded in the walkway and used for the 3D kinetic analysis. Subjects were asked to walk along the 10m walkway at a comfortable speed. Six seconds of synchronised motion and force data were collected per trial (sampling rate 200Hz). Trials were accepted if a single foot landed fully on a force plate. Three footfalls per leg were collected.

Marker sites on the shoulders, pelvis and legs were marked to ensure correct replacement post fatigue test. Markers mounted on the skin and footwear were not removed. The step length and cadence of the subject was recorded from the initial gait trials. The step length was marked out at either end of the walkway. At the second gait measurement subjects were asked to maintain the same step length and cadence using a metronome as an auditory cue. This attempted to replicate the same gait speed for comparison.

4.2.2 Measurement of plantarflexor strength

Plantarflexor MVC was measured in standing. Two strain gauges were attached to an adjustable gantry on a rigid metal frame. A part wood and foam pad was attached to the other end of the strain gauge.

The pad was lowered onto the shoulders of the subject until they were firmly held. This was adjusted and the pads fixed in a position where heel raise was limited but pressure from the pads did not cause excessive discomfort (figure 4.1).

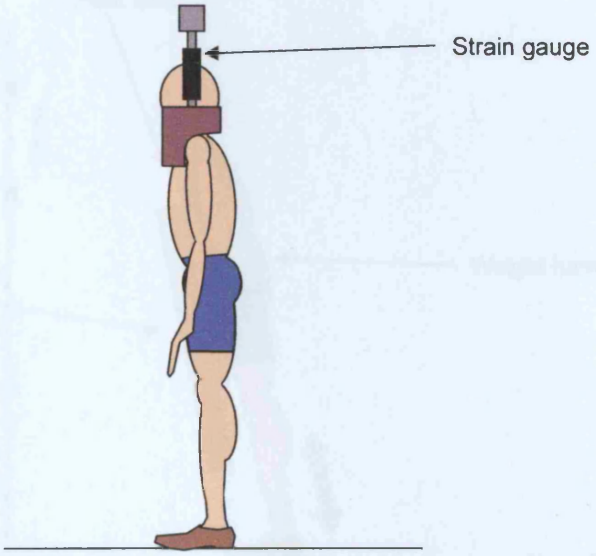

Figure 4.1: Set up for measuring bilateral plantarflexor MVC in standing. Strain gauges were fixed as shown on both shoulders.

Subjects were asked to push against the pads as hard as possible using their plantarflexor muscles. Subjects were monitored to ensure there was no excessive shoulder elevation and verbal encouragement was given throughout the contraction. The output voltage of the strain gauges was summed and the mean of two MVCs calculated. The positions of the strain gauges were marked on the gantry and foot position was marked on the floor. This allowed a consistent set up before and after the fatigue test.

4.2.3 Plantarflexor fatigue task

The plantarflexor muscles were fatigued using a heel raise exercise with the forefoot on a step. To minimise fatigue of the hip, knee and trunk muscles, subjects were asked to rest on a flat support in front of them set at 5° from vertical (figure 4.2). A weighted harness of approximately 10% of the subject's body weight was placed on the trunk. Subjects stood with their forefeet on a non-slip step and were asked to perform through range concentric and eccentric plantarflexion contractions by raising and lowering their heels.

A light was placed on the subject's chest which was projected onto the wall in front. Targets were placed on the wall which corresponded to the position of the light beam when the heels were raised to their highest point and lowered to their lowest point. Another target was placed halfway between the two main targets.

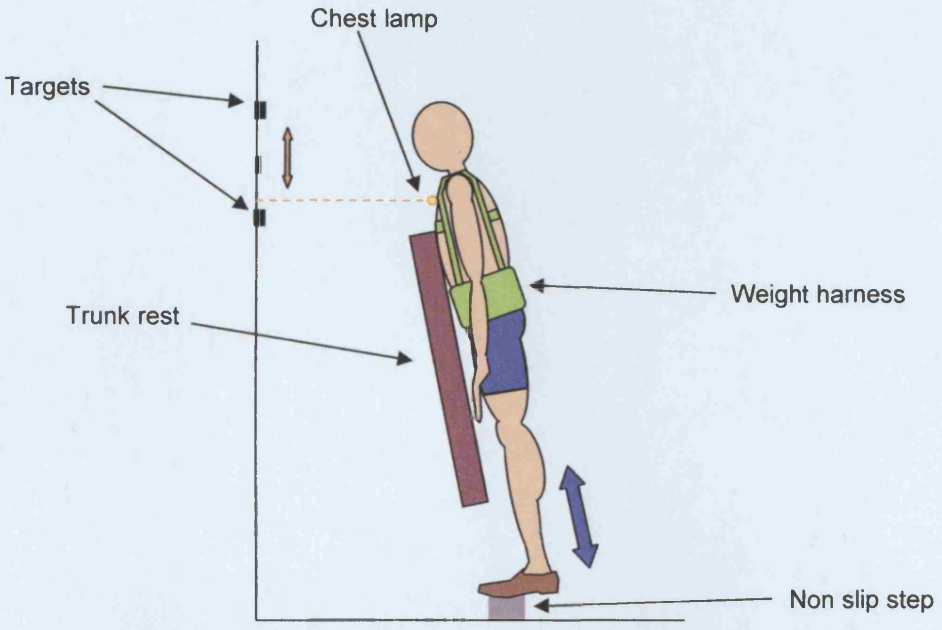

Figure 4.2: Set up for fatiguing the plantarflexors in standing. Repeat full range plantarflexion contractions were performed at a frequency of one per second. A metronome was used to aid timing.

Subjects performed repeated through-range exercises at a frequency of one per second until they were unable to reach the halfway target. A metronome was used to maintain the frequency and the subject was observed to ensure the targets were not reached through excessive knee or trunk extension. It was anticipated that the exercise would be painful so 15 second rests were given as required, the time between rests was at least 2 minutes in all subjects.

As soon as the subject was consistently unable to reach the midway target for 10 repetitions they were removed from the apparatus and the strain gauges immediately placed on their shoulders. As soon as the MVC measures were taken, the gait analysis markers were replaced and walking was measured. The entire process from cessation of the plantarflexor fatigue task to gait analysis took under five minutes.

4.2.4 Analysis

Three trials for the left and right legs were exported as text files for analysis using Matlab programmes written in house (Mathworks). A single gait cycle was identified from the heel marker acceleration traces and vertical forces. Cycle duration was normalised, and three cycles were averaged [3 9]. The data from the left and right legs were combined. Temporal and spatial gait parameters were recorded.

The primary analysis was based on the two predictions introduced at the beginning of this chapter.

- **Reduced peak ankle plantarflexor moment and peak ankle power generation during pre-swing**

- **Increased peak hip flexor moment and peak hip power generation during preswing**

This gave a total of four comparisons for the primary analysis and a modified Bonferroni test was applied to account for multiple comparisons (appendix 1) [23].

A secondary analysis compared:

- Maximum and minimum hip, knee and ankle kinetics and kinematics in loading, mid-stance and swing
- Peak to peak pelvis and trunk kinematics in all three planes

A modified Bonferroni adjustment was made to this data from the secondary analysis but none of the group differences were significant due to the large number of comparisons. It was decided, however, to still look for patterns in the data using $p<0.05$ as a guide. Data were compared with findings of previous studies to evaluate whether or not a consistent and logical finding was real, and not a false positive result. It was acknowledged, however, that strictly the results of the secondary analysis gave an indication of group trends only.

4.3 Results

This section outlines changes in gait before and after fatigue of the plantarflexor muscles. Grand average graphs are presented at the end of this section. Some discrepancy exists in peak values and those presented on the grand average graphs due to variations in the timing of peak variables influencing the average trace.

Ten healthy subjects were recruited, four men and six women. The mean age of the group was 31 (± 5 years). Average height of the subjects was 1.7 m and weight was 65.5 kg.

4.3.1 Changes in MVC

MVC measures were used to indicate how much the plantarflexor muscles fatigued and were expressed as a percentage of the initial pre test reading. Subjects continued with the heel raise exercise for an average of 7.1 ±2.1 minutes. The average drop in plantarflexor MVC after the fatigue test was 25.6%. After the second gait analysis the MVC returned to a level 3.39% less than the initial MVC. A significant correlation was seen between the duration of the exercise and the percentage drop in MVC (r =0.70, P=0.025) (figure 4.3).

	MVC drop (% pre MVC)	T statistic	P value
MVC post PF fatigue test	-25.63 ±13.26	5.49	0.0004
MVC post walking test	-3.39 ±19.87	3.69	0.003
MVC of CMT subjects % of controls	31.79%	-	-

Table 4.1: Changes in MVC before and after the plantarflexor fatigue test. Expressed as a percentage of the initial MVC measure. Percentage of PF MVC for CMT subjects compared to controls (data from chapter 3)

4.3.2 Temporal and spatial gait parameters

Subjects were requested to maintain the same gait speed following the plantarflexor fatigue test with the aid of visual and auditory cues. No significant differences in gait speed, cadence, step length or double support time were observed.

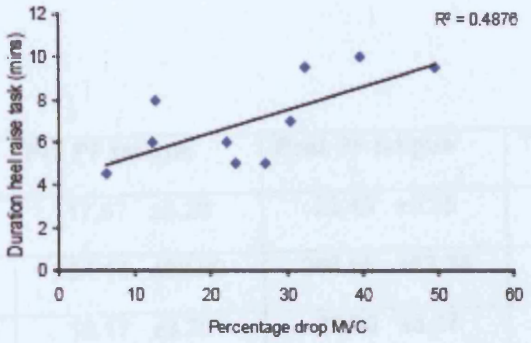

Figure 4.3: Relationship between duration of the heel raise task (minutes) and percentage drop of MVC

4.3.3 Kinetic and kinematic changes

4.3.3.1 Primary comparison: ankle and hip kinetics in preswing

Little change was observed in the variables analysed in the primary comparison. No significant differences were seen in the distal kinetic variables with no change in ankle plantarflexor moment and power generation. Proximally, no significant changes were observed but there was a borderline trend towards increased hip power generation during pre-swing.

Gait variable	Pre PF fatigue	Post PF fatigue	T statistic	P value
PF moment preswing (Nm/kg)	1.51 ±0.18	1.58 ±0.23	-1.14	0.3
Ankle power generation preswing (W/kg)	3.79 ±0.93	3.97 ±1.01	-0.70	0.5
Hip flexor moment preswing (Nm/kg)	0.67 ±0.18	0.83 ±0.31	1.84	0.1
Hip power generation preswing (W/kg)	0.64 ±0.20	0.91 ±0.41	-2.65	0.03

Table 4.2: Changes in primary gait variables after plantarflexor fatigue test.

4.3.3.2 Secondary comparison: kinematics and kinetics in stance

The secondary comparison revealed significant changes in gait variables during loading and stance phase. On loading an increase in the flexion angle and flexion velocity of the knee is observed following fatigue of the plantarflexors (table 4.3, figures 4.4 and 4.5). Proximally there was an increase in hip extensor moment (table 4.4, figure 4.6).

Gait variable	Pre PF fatigue	Post PF fatigue	T statistic	P value
Knee flexion angle loading (deg)	17.57 ±5.28	22.40 ±9.25	-2.95	0.02
Knee flexion velocity loading (deg/s)	234.18 ±53.69	266.66 ±63.34	-3.08	0.01
Peak trunk flexion stance (deg)	18.17 ±3.20	20.50 ±3.07	-2.44	0.04

Table 4.3: Changes in kinematic gait variables in loading and stance after plantarflexor fatigue test.

Following loading, in early stance, an increase in knee extensor moment and power generation was observed (table 4.4, figures 4.6 and 4.7). There was also a corresponding increase in hip power generation in early stance (table 4.4, figure 4.7). Later in stance, just prior to pre-swing, there was a significant increase in hip power absorption (table 4.4, figure 4.7). Trunk flexion was increased throughout the gait cycle with a significant difference during stance phase (figure 4.8). A trend was seen for increased hip flexion velocity during swing phase following fatigue of the plantarflexors (pre: 202 ±36 deg/s; post: 228 ±46 deg/s; t =-1.93, P=0.09).

Gait variable	Pre PF fatigue	Post PF fatigue	T statistic	P value
Knee extensor moment stance (Nm/kg)	0.88 ±0.30	1.05 ±0.37	-2.51	0.03
Knee power generation stance (W/kg)	1.19 ±0.56	1.57 ±0.76	-2.65	0.03
Hip extensor moment loading (Nm/kg)	1.21 ±0.35	1.49 ±0.47	-3.23	0.01
Hip power generation stance (W/kg)	0.98 ±0.24	1.45 ±0.38	-4.53	0.001
Hip power absorption stance (W/kg)	0.98 ±0.56	1.32 ±0.50	2.39	0.04

Table 4.4: Changes in kinetic gait variables in loading and stance after plantarflexor fatigue test.

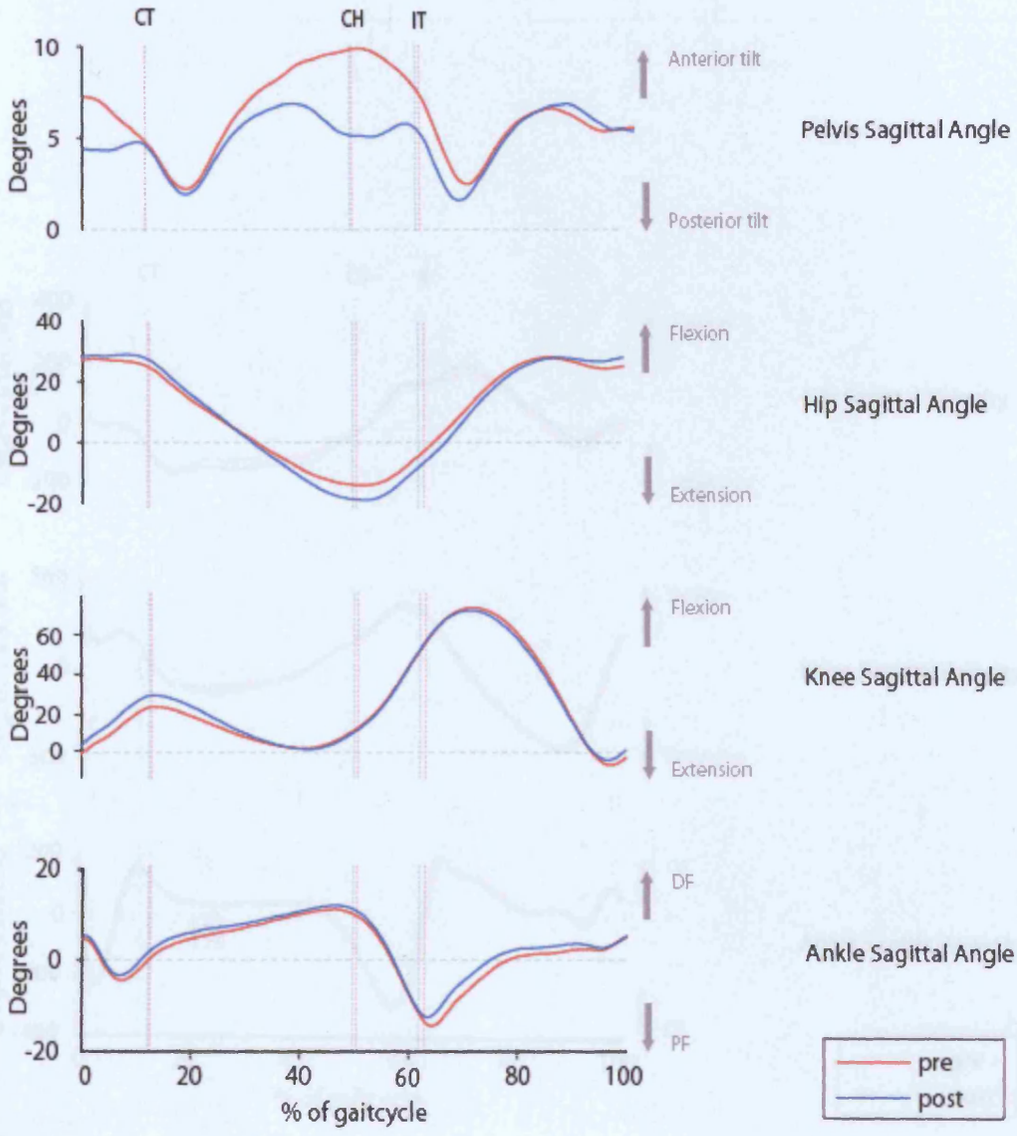

Figure 4.4: Grand average of angular displacement in the sagittal plane over one gait cycle for the ankle, knee, hip and pelvis (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

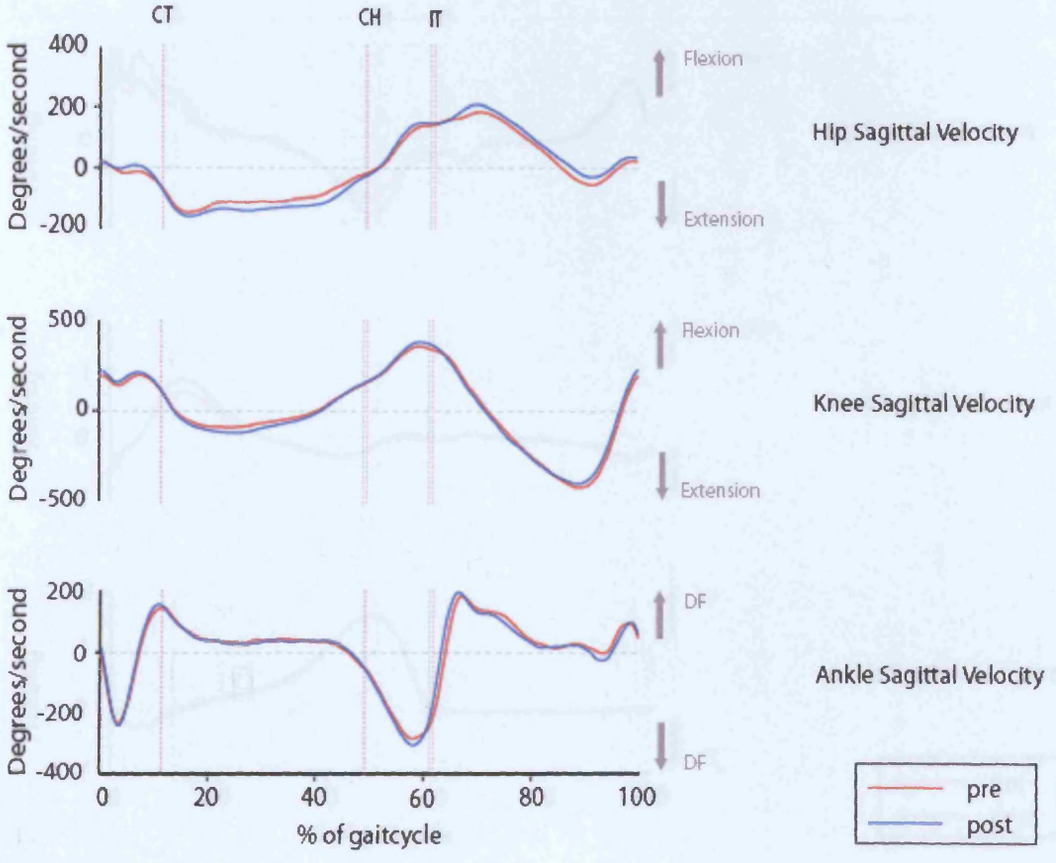

Figure 4.5: Grand average of angular velocity in the sagittal plane over one gait cycle for the ankle, knee, hip and pelvis (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

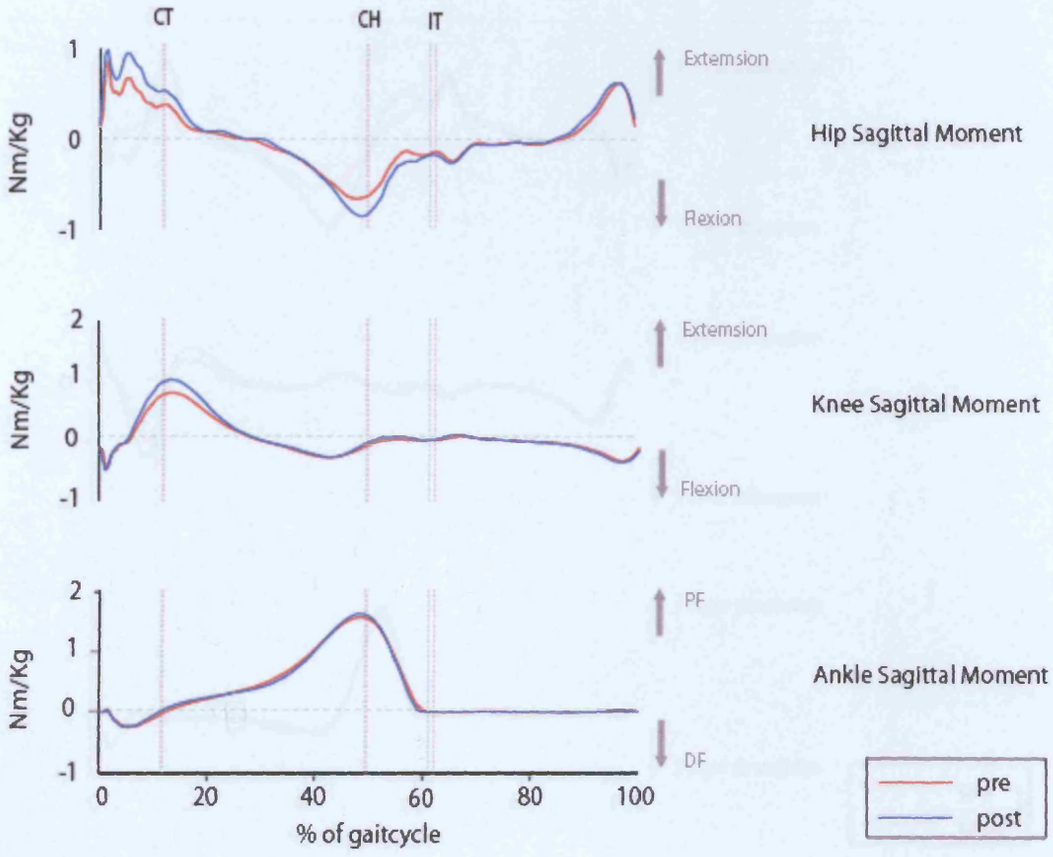

Figure 4.6: Grand average of joint moments in the sagittal plane over one gait cycle for the ankle, knee, hip and pelvis (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

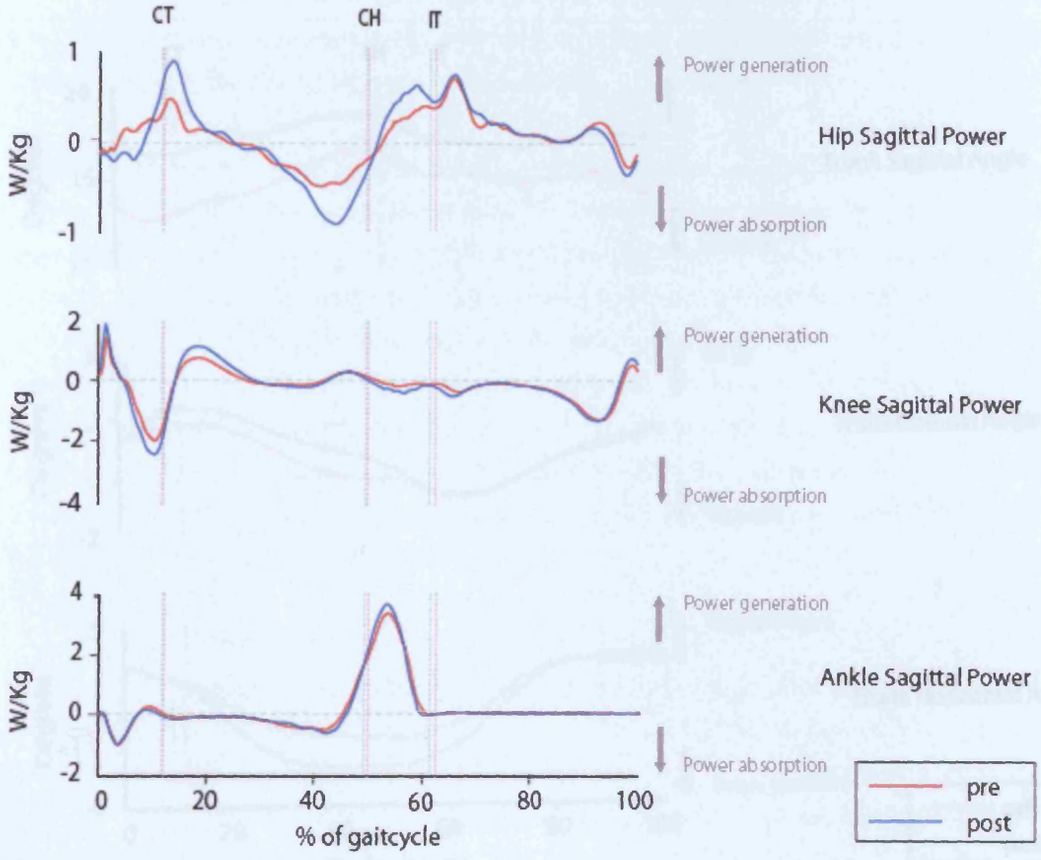

Figure 4.7: Grand average of joint powers in the sagittal plane over one gait cycle for the ankle, knee, hip and pelvis (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

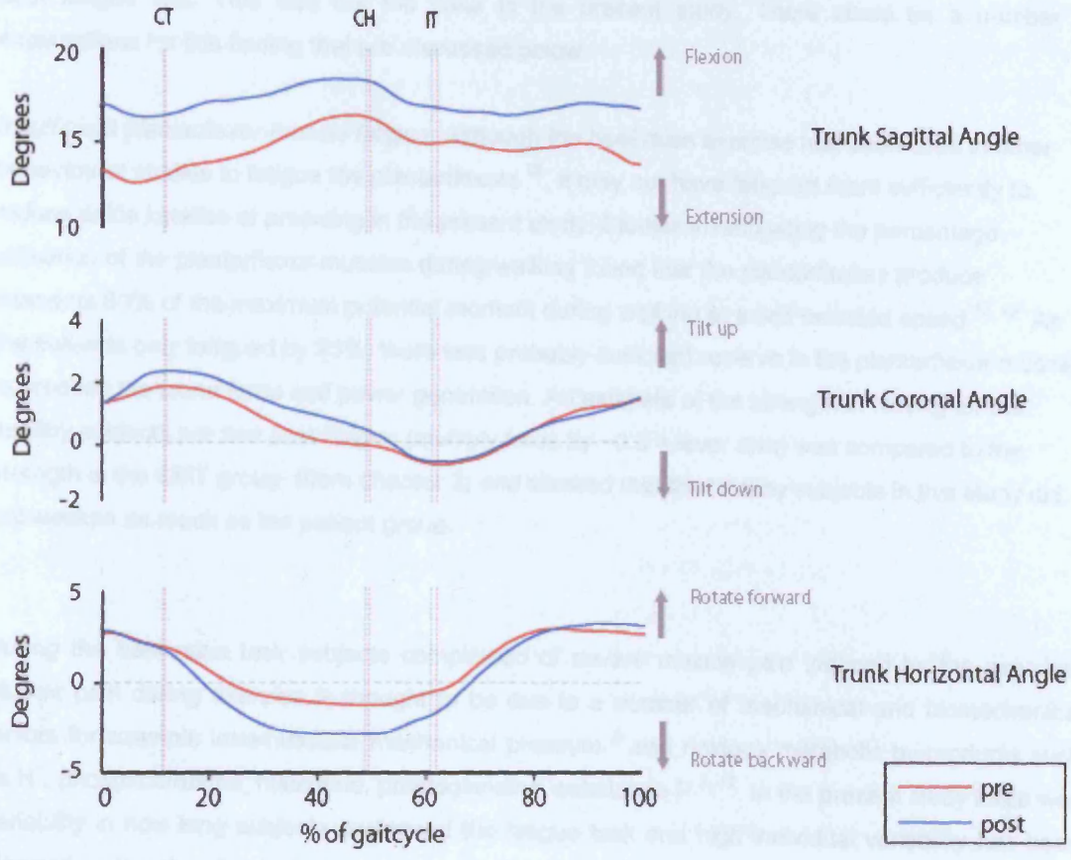

Figure 4.8: Grand average of trunk motion in the sagittal, coronal and horizontal planes over one gait cycle for the ankle, knee, hip and pelvis (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off; DF: dorsiflexion; PF: plantarflexion.

4.4 Discussion

Subjects were successfully constrained for gait speed and cadence before and after the fatigue test as no changes were seen in temporal and spatial gait parameters. This allowed a comparison of gait kinetic and kinematic variables without the confounding influence of gait speed [8].

4.4.1 Distal changes

It was anticipated that a change would be observed in plantarflexor moment and power generation post fatigue test. This was not the case in the present study. There could be a number of explanations for this finding that are discussed below:

Insufficient plantarflexor muscle fatigue: Although the heel raise exercise has been used in other behavioural studies to fatigue the plantarflexors [25], it may not have fatigued them sufficiently to reduce ankle kinetics at preswing in the present study. Studies investigating the percentage utilisation of the plantarflexor muscles during walking found that the plantarflexors produce moments 60% of the maximum potential moment during walking at a self selected speed [13, 19]. As the subjects only fatigued by 25%, there was probably sufficient reserve in the plantarflexor muscles to produce the same force and power generation. An estimate of the strength in Nm/Kg for the healthy subjects pre and post fatigue (multiply force by ~0.3 = lever arm) was compared to the strength in the CMT group (from chapter 3) and showed that the healthy subjects in this study did not weaken as much as the patient group.

During the heel raise task subjects complained of severe muscle pain induced by the exercise. Muscle pain during exercise is thought to be due to a number of mechanical and biomechanical factors for example intramuscular mechanical pressure [2] and noxious metabolic by-products such as H^+, phosphocreatine, histamine, prostoglandins, substance P [2, 12]. In the present study there was variability in how long subjects performed the fatigue task and high individual variability has been reported in the threshold of muscle induce pain in bicycle ergometry tasks [2]. It is possible that subjects with a lower threshold to exercise induced pain limited their performance of the fatigue-task and how long they continued. Self efficacy for tolerating pain was found to correlate with peak pain ratings during bicycle ergometry task [14] indicating central influences on task performance that could account for variability in the present study. Variability in performance has the potential to influence the mean percentage drop of MVC and possibly the mean effects of plantarflexor fatigue on gait.

Increased effort to match gait speed: There is a suggestion that an increase in activation is the primary compensatory strategy when there is weakness of a muscle group [4]. The walking task required the subjects to maintain their cadence and step length post fatigue test to allow

comparison of the gait variables that may vary with differing gait speeds [8]. Constraining the speed may have forced subjects to walk quicker and with a longer stride length than if they were allowed to walk at a self selected pace immediately after the fatigue test. This may have resulted in increased recruitment of the plantarflexors in an effort to achieve the set step length and cadence goals as opposed to just the goal of maintaining walking.

A change in temporal and spatial gait parameters may have been an interesting finding post plantarflexion fatigue as they may have been similar to people with CMT. Unfortunately, this was not investigated with the present protocol. An alternative approach for future studies would be to allow subjects to walk at a self selected speed after plantarflexor fatigue and then use analysis of covariance to statistically adjust for gait speed as in chapter 3. Another approach would have been to look at maximal walking speed to maximise the contribution of the plantarflexors. With reduced strength, effects on ankle kinetics may have been more apparent.

Recovery prior to and during walking test: The goal of the plantarflexor fatigue protocol was to weaken the plantarflexors and to investigate the effect of these changes on a behavioural task i.e. walking. The exercise selected to achieve this had been used in other studies to investigate the effect on behavioural tasks [4]. The heel raise task involves a combination of eccentric and concentric contractions. Concentric and eccentric contraction have been shown to fatigue muscles at different rates and have different recovery times [18, 24]. In the present study, the heel raise task was an intense exercise with a work : rest ratio biased towards work duration. It is possible that some of the fatigue observed was due to depletion of energy stores [21] or local metabolic changes in the muscle leading to activation failure [5, 18]. Fatigue relating to muscle damage brought about by the eccentric contractions would have occurred later and been longer lasting [18, 24]. The subjects in the present study showed a period of recovery from the cessation of the heel raise task to the completion of the gait trials as measured by the plantarflexor MVC. They also reported a subjective sensation of recovery from fatigue as the walking trial progressed which may have affected the consistency of the gait trials. It is probable, therefore, that fatigue measured after the heel raise exercise was due to metabolic changes as the recovery was rapid. A study of the time course of fatigue and recovery from concentric and eccentric muscle contractions of the elbow flexors found that the lowest MVC after concentric exercise was 23 minutes whereas after eccentric exercise it was two hours, taking four hours to achieve recovery to half of the baseline level [24]. Waiting longer to take the gait measurement may have allowed a more stable, sustained level of fatigue induced weakness resulting in more consistent gait trials. There are no studies looking at timing and recovery of fatigue after volitional exercise of the plantarflexor muscles so at present the percentage fatigue cannot be estimated. It would have been useful to trial the heel raise exercise at differing frequencies and numbers of repetitions measuring fatigue during the exercise and post exercise. This would help to ascertain the optimum time to perform the walking trials so it corresponded with the maximum drop in MVC due to long lasting fatigue.

4.4.2 Proximal compensations

Despite the lack of change distally, proximal changes were observed post fatigue test. The changes in the healthy subjects were different to those seen in people with CMT (chapter 3) in that there were no changes in knee kinetics during preswing or in peak-to-peak trunk motion.

4.4.2.1 Limb progression

The primary comparison did not show any significant changes in hip kinetics at preswing. A trend towards increased peak hip power generation was observed, however, that was non-significant post modified Bonferroni correction. Correction for multiplicity for four comparisons was a conservative measure in this study and the chance of a type 1 error was less than 20% [17]. In addition, hip flexor substitution has been suggested as a compensation for weak plantarflexors to assist with limb advancement [4, 10, 27]. Based on this, it is possible that this trend is a real finding.

The secondary analysis showed an increase in flexion at the trunk though the cause of this is difficult to explain as few modelling studies have either included the trunk as a whole segment [6] or considered the effects of the trunk musculature [4]. It is possible that changes at the trunk are a consequence of altered hip muscle activation. It could also be an indication that the trunk and hip muscles, e.g. gluteus maximus, were also affected by the fatiguing task despite efforts to limit this. There were, however, increases observed in hip extensor moments and hip power generation in stance so this may not be the case. A study by Saunders et al [22] found that sagittal lumbo-pelvic flexion was strongly correlated with stride length. It is possible that in the presence of plantarflexor weakness the increase in trunk flexion post fatigue was a compensation to achieve the target step length. The question remains, is this a strategy to accelerate the limb or trunk? It has been suggested that a 'trunk leading' strategy is a way of using the heavy trunk segment to direct movement of the lower body by pulling the leg into swing phase when distal muscle weakness is present [11].

4.4.2.2 Trunk progression

The secondary comparison showed changes at the knee and hip during stance phase. In early stance, as the limb moves into single support, increases in hip and knee extensor moments and power generation are seen. Soleus has been shown to accelerate the trunk to aid progression during its action in preswing [15, 26]. The knee extensors and hip extensors also progress the trunk through their action in early stance [16, 26] so the increased hip extensor moment and power generation following fatigue observed could be a compensation for the reduction in trunk progression at preswing due to soleus weakness. This supposition is supported by findings in optimisation studies that found increased gluteus maximus [4] and knee extensor activity [7] in early stance in the presence of plantarflexor weakness. The increases in hip extensor moment and power generation may also be a strategy to control the increase in knee flexion angle that occurred due to

plantarflexor weakness. Gluteus maximus has a role in accelerating the knee towards extension in single limb support [1, 7]

4.4.2.3 Support

Knee kinematics changed after the plantarflexor fatigue test with an increase in peak flexion and flexor velocity on loading. The ankle plantarflexors have been implicated in control of knee extension during the support phase in stance [1, 6]. The increase in flexion, therefore, seems to represent a failure of the plantarflexors to control the advancement of the shank and exert an extensor moment at the knee. This change may be a consequence of plantarflexor weakness rather than a compensation for it. An optimisation modelling study [4] found that when soleus and gastrocnemius were weakened together, other muscle groups were not able to compensate sufficiently to give normal kinematics. This was also evident in the present study of healthy, neurologically intact adults. Fatigue of the quadriceps during the heel raise exercise cannot be ruled out and could also influence knee flexion. Subjective reports from participants, however, reported localised sensation of fatigue and pain during the exercise in the plantarflexors only.

Later in stance, post fatigue, an increase in hip power absorption and hip flexor moment was seen prior to preswing. This could represent eccentric activity of the hip flexors to control hip extension as there was a trend towards increased peak hip extension ($t=1.87$, $p=0.09$) (figure 4.4). When the knee is almost fully extended just prior to preswing, the limb could be assumed to be a strut. If soleus is not able to control forward rotation of the shank, and hence the thigh, this could lead to an increase in hip extension assuming the trunk remains relatively stable in space due to inertia. The iliopsoas muscle group has been described as working synergistically with the plantar flexors the control the ankle rocker [7]. In this situation, therefore, the hip flexor muscles could be recruited as a compensatory strategy to control hip extension if soleus is weak.

4.4.2.4 Overview

The present study demonstrates proximal changes that are consistent with proposed compensatory strategies investigated in other studies. The obvious question to ask is why do we see these changes when there were apparently no changes in the ankle kinetics? The myometry measure demonstrated that there was a 25% reduction in plantarflexor strength post heel raise exercise showing a significant drop in strength. An optimization study by Goldberg and Neptune [4] looked at combined weakness of the soleus and gastrocnemius by 30%. Their primary investigation was to measure the work done by other compensating muscles to maintain normal kinematics. Although they did not report on ankle kinetics, they found that reduction of the plantarflexion angle at push off was seen and proximally the main compensation was increased net gluteus maximus work in early stance and positive iliopsoas work in preswing/early swing. The proximal findings are very similar to the present study which also showed a trend towards reduced ankle plantarflexor angle after toe off ($t=-1.82$, $P=0.1$) (figure 4.4). Although there was not an overall change in kinetics, the possible

kinematic trend indicates distal changes. The majority of the proximal compensations seen in this study were in stance phase. Although the preswing ankle kinetics were unchanged it appears that impaired activation during loading and stance may have been more influential as maintaining support was considered the primary role of the plantarflexors in other studies [20].

4.5 Summary

- Healthy subjects demonstrated a significant reduction in plantarflexor MVC by 25% with a repeated heel raise exercise, which was terminated when 50% of the full range could not be consistently achieved.

- No significant changes were seen in distal kinetic measures. A trend to a reduction in plantarflexor angle in early swing phase was observed

- There was a trend towards increased hip power generation during preswing that is consistent with significant changes reported in associated literature. This may be a compensatory strategy to assist limb progression in the presence of gastrocnemius weakness.

- Trunk flexion increased significantly during stance phase.

- Increases in knee and hip extensor moments and power generation were observed in early stance, after loading, that may be a compensatory strategy to assist trunk progression in the presence of soleus weakness

- Significant increases were seen in knee flexion angle and velocity on loading that may be due to reduced eccentric control by the plantarflexors.

- There was increase in hip extensor moment observed in loading that may be compensatory activity of the gluteus maximum to control knee flexion.

- Increased hip power absorption was seen in late stance. This may be a strategy to control hip extension in the absence of eccentric control of the plantarflexors over the shank and tibia.

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5 The effect of three foot drop splints on gait characteristics in Charcot-Marie-Tooth disease

5.1 Introduction and Hypothesis

The primary hypothesis for this thesis states that in people with CMT, weak ankle muscles leads to increased muscle activity around the hip to compensate for reduced limb progression and foot drop during swing. Chapter 3 demonstrated some of these differences with increased hip motion and altered timing of power generation relative to the ankle.

People with CMT show a reduced peak ankle dorsiflexion in swing phase compared to control subjects using 3D gait analysis [10]. Traditionally ankle foot orthoses (AFOs) are given to assist the ankle into plantigrade to facilitate foot clearance during swing. As well as this positive benefit, AFOs may also influence other periods of the gait cycle. A study by Salsich and Mueller [13] looked at ankle stiffness in diabetic peripheral neuropathy and the relationship with peak ankle moments. They found that in addition to plantarflexor strength, plantarflexor stiffness contributed significantly to the peak plantarflexor moment during walking. In their conclusions they suggested that stiffening the ankle with an external device, such as an AFO, could increase the passive ankle moment during preswing and in turn improve limb advancement. Improved limb advancement implies improved propulsion at preswing and this may reduce the need to compensate at the hip. This theory was explored in the present study using different commercially available splints with varying designs, materials and rigidity. Based on this theory and the primary hypothesis for the thesis a prediction for this study was proposed:

When wearing AFOs that stiffen the ankle, people with CMT will show:

- **increased in peak dorsiflexion angle throughout swing and at foot clearance**
- **increased peak plantarflexor moment and ankle power generation during preswing**
- **reduced compensatory hip kinematics and kinetics**

5.2 Methods

People with CMT were recruited from the genetic peripheral neuropathy clinic at the National Hospital for Neurology and Neurosurgery. Volunteers were included if they had clinically definite CMT and were able to walk 100m in at least 10 minutes. People were excluded if they had a history of other neurological impairment, orthopaedic lower limb impairment unrelated to CMT and lower limb or back pain exceeding 7 out of 10 on a visual analogue scale.

5.2.1 Ankle foot orthoses

Three commercially available off the shelf devices were compared. The first was called a 'Footup splint' (Somas, Saint Anthonis, Netherlands) which was a cuff worn around the ankle with a detachable elastic strap and a plastic flange at the one end to tie into the laces of a shoe (Figure 5.1a). The material of the cuff did not extend over the ankle joint but the principle of the device was that the elastic strap provided a resistance to plantarflexion which was sufficient to maintain adequate dorsiflexion to allow ground clearance on swing phase.

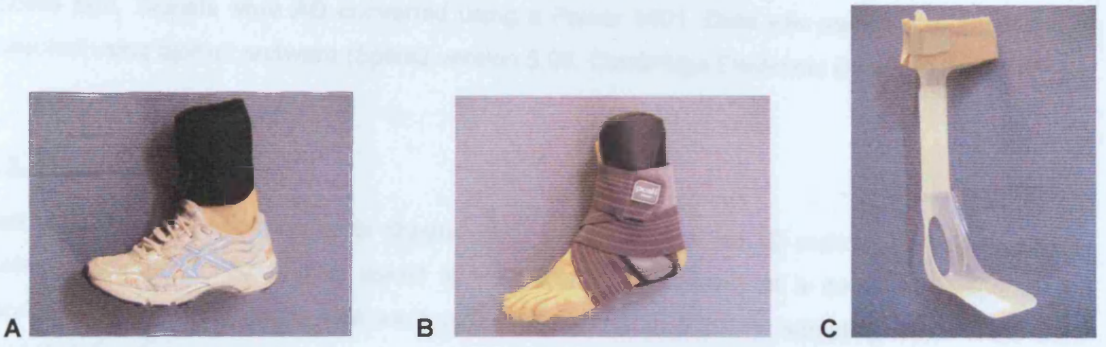

Figure 5.1: A- Footup splint; B- Push brace; C- Multifit Achilles

The second AFO was called a 'Push brace' (Nea International, Maastricht, Netherlands) and was designed as a support for ankle instability following ligament injury (Figure 5.1b). Anecdotal success of the brace in foot drop has lead to its prescription in a number of UK neurological centres. The main brace was made of preformed foam which covers the medial, posterior and lateral aspects of the ankle and extends under the calcaneum. The medial and inferior aspects were reinforced. Three elastic straps further reinforced the brace.

The Multifit Achilles drop foot orthosis (V-M Orthotics International, Halesworth, UK) was the third device investigated (Figure 5.1c). It is a variant of the posterior leaf AFO made of plastic polymer with a half foot plate, a cut out heel section and an adjustable back stem that extended to the calf. As the name suggests it was designed to reduce foot drop during swing phase so improving ground clearance.

Four conditions were tested in all: a shoe only condition (shoe); the shoe and Footup splint (Footup); the shoe and Push brace (Push); the shoe and Multifit Achilles AFO (Multifit).

5.2.2 Measurement of ankle stiffness

Ankle stiffness into dorsiflexion and plantarflexion was measured using ramp and hold stretches delivered via a dynamometer (Biodex Medical Instruments Inc., New York, USA). Subjects lay supine, with their knee in extension, and placed their foot in a manipulandum set at plantigrade. The foot, ankle and proximal leg were secured using straps. The manipulandum was rotated through 5° with a peak velocity of 15° per second, as specified by a positional data file (Biodex System3 Researchers Toolkit). Subjects remained relaxed during the test and six stretches in each direction were collected.

Surface EMG was recorded from the tibialis anterior (TA) and medial gastrocnemius (GAS) to confirm muscle relaxation. Torque, velocity and position were collected via the Biodex remote access port. Signals were AD converted using a Power 1401. Data was sampled at 2000Hz and collected using Spike2 software (Spike2 version 5.06, Cambridge Electronic Design).

5.2.3 Gait Analysis

Gait analysis was performed as in chapter three with synchronised 3D motion analysis and force plate recordings. Subjects were asked to walk along the walkway at a comfortable speed. Six seconds of motion and force data were collected per trial at a 200Hz sampling rate. Trials were accepted if a clean foot fall on the force plate was achieved. A total of three clear trials for each leg were collected.

5.2.4 Analysis

Stretch data was collected using Spike2 software and exported as spreadsheet text files for analysis using Matlab programmes written in house (MATLAB, Mathworks Inc). The last 5 stretches were averaged and stiffness calculated (chapter 2).

A repeated measures general linear model was used to compare stiffness measures for the four conditions and 2-tailed paired T-tests were used for the post hoc analysis. Significance was taken as $p<0.05$.

For the gait analysis, three trials for the left and right legs were exported as text files for analysis using Matlab programmes written in house (Mathworks). A single gait cycle was identified from the heel marker acceleration traces and vertical forces. Cycle duration was normalised, and three cycles were averaged [5, 9]. The data from the left and right legs were combined. Temporal and

spatial gait parameters were recorded. The primary comparison was based on the predictions introduced at the beginning of this chapter and consisted of:

- Peak plantarflexion and dorsiflexion angle in swing and dorsiflexion angle at foot clearance (defined in chapter 3)
- Peak plantarflexor moment and ankle power (max and min) at preswing
- Peak hip flexion during swing phase
- Peak hip moment and power generation during preswing

This gave a total of nine comparisons for the primary analysis which was tested using a general linear model (factor: splints, four levels) and a modified Bonferroni test was applied to account for multiple comparisons (appendix 1) [14]. A priori contrasts were set up comparing the shoe only condition with the three AFO conditions. Significance was taken as $p<0.05$.

A secondary analysis compared:

- Remaining maximum and minimum sagittal hip, knee and ankle kinematics and kinetics in loading, mid-stance and swing
- Peak-to-peak pelvis and trunk kinematics in all three planes

This secondary analysis and temporal spatial data was tested using a repeated measures general linear model (factor: splints, four levels). A modified Bonferroni adjustment was made to the data from the secondary analysis but none of the group differences were significant due to the large number of comparisons. It was decided, however, to still look for patterns in the data using $p<0.05$ as a guide. Data were compared with findings of previous studies to evaluate whether or not a consistent and logical finding was real, and not a false positive result. It was acknowledged, however, that strictly the results of the secondary analysis gave an indication of group trends only.

5.3 Results

This section outlines the comparisons of the four orthotic conditions: shoe only, Footup brace, Push ankle brace and Multifit AFO. Grand average graphs are presented at the end of this section. There are discrepancies between peak values and apparent peaks on the grand average graphs. This is due to alterations in the grand average trace resulting from variations in the timing of the peaks between individual participants.

Fourteen people were recruited to participate in this study. Their details and impairment measures are outlined in chapter 3. Five of the subjects used AFOs prior to this study. Two used the Footup brace, two used the Push brace and one used a supra-malleolar silicon AFO.

5.3.1 Stiffness comparison

The stiffness of the four conditions varied with stretches into both dorsiflexion and plantarflexion (ANOVA dorsiflexion: $F = 6.61$, $P = 0.001$; plantarflexion: $F = 18.11$, $P < 0.0001$). Stiffness into dorsiflexion was greatest when the Push brace and the Multifit AFO were worn, though the Footup brace also increased stiffness compared to the shoe condition (post hoc: shoe v Footup $t = -2.41$, $P = 0.03$; shoe v Push $t = -3.51$, $P = 0.004$; shoe v Multi $t = -2.97$, $P = 0.01$) (figure 5.3). Stiffness into dorsiflexion maybe more relevant to the later part of stance or early part of preswing at the ankle rocker when the ankle moves into maximum dorsiflexion.

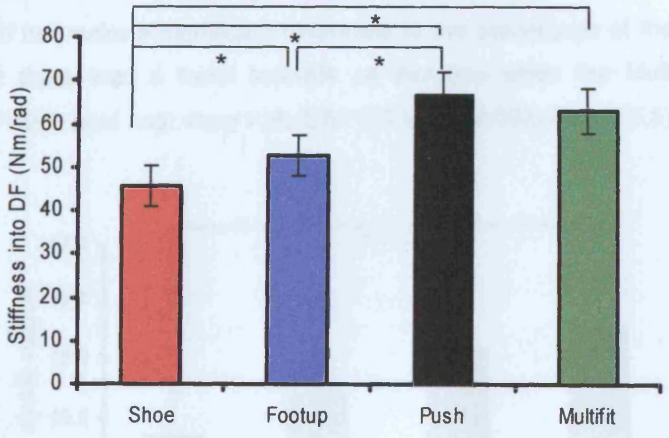

Figure 5.3: Stiffness of the four conditions when worn by the subjects during a 15 °/sec stretch into 5° dorsiflexion. Shoe only, Footup brace, Push ankle brace, Multifit AFO. Error bars: standard error of the mean. Post hoc: * $p < 0.05$

When stretched into plantarflexion, the ankle was stiffest when the Push brace and the Multifit AFO were worn (post hoc: shoe v Push $t = -4.66$, $P = 0.0006$; shoe v Multifit $t = -5.81$, $P < 0.0001$). Again, the Footup brace also increased ankle stiffness compared to just the shoe (post hoc: shoe v Footup

t =-5.50, P=0.0001) (figure 5.4). Stiffness into plantarflexion maybe more relevant to the later part of preswing and swing when the AFO resists plantarflexion during heel raise and after toe off.

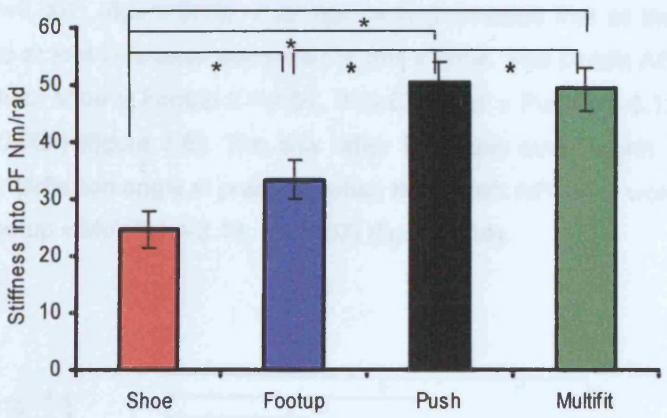

Figure 5.4: Stiffness of the four conditions when worn by the subjects during a 15 °/sec stretch into 5° plantarflexion. Shoe only, Footup brace, Push ankle brace, Multifit AFO. Error bars: standard error of the mean. Post hoc: * p<0.05

5.3.2 Gait analysis

5.3.2.1 Temporal and spatial measures

No significant difference was observed in gait speed, step length and cadence when the AFOs were worn. The AFOs did not make a significant difference to the percentage of the gait cycle spent in double support but there was a trend towards an increase when the Multifit AFO was worn (ANOVA: F =2.21, P=0.1; post hoc: shoe v Multifit t =-3.99, P=0.002) (figure 5.5).

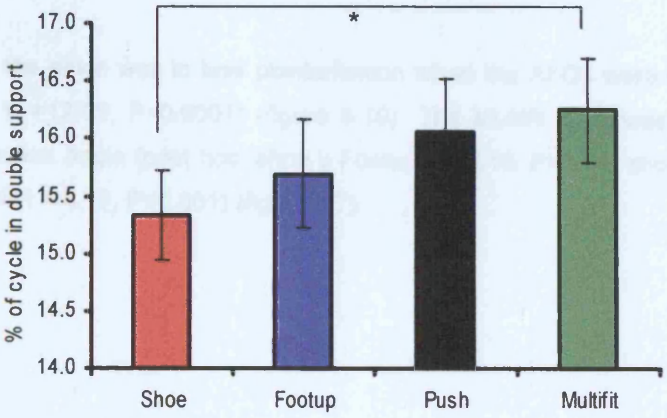

Figure 5.5: Percentage of the gait cycle spent in double support. Shoe only, Footup brace, Push ankle brace, Multifit AFO. Error bars: standard error of the mean. Post hoc: * p<0.05

5.3.2.2 Primary kinematic and kinetic comparison

The foot drop measure defined for this study, the dorsiflexion angle when the foot markers are closest to the floor during swing phase, showed a significant difference between AFO conditions (ANOVA: f =6.35, P=0.001) (figure 5.10). Post hoc testing revealed that all three AFOs improved the dorsiflexion angle at foot clearance compared to just a shoe. The Multifit AFO gave the biggest improvement (post hoc: shoe v Footup t =-2.64, P=0.02; shoe v Push t =-3.12, P=0.008; shoe v Multifit t =-4.37, P=0.008) (figure 5.6). The only other kinematic event worth noting was a trend towards reduced plantarflexion angle at preswing when the Multifit AFO was worn (ANOVA: f =2.76, P=0.06; post hoc: Footup v Multifit t =-3.18, P=0.007) (figure 5.10).

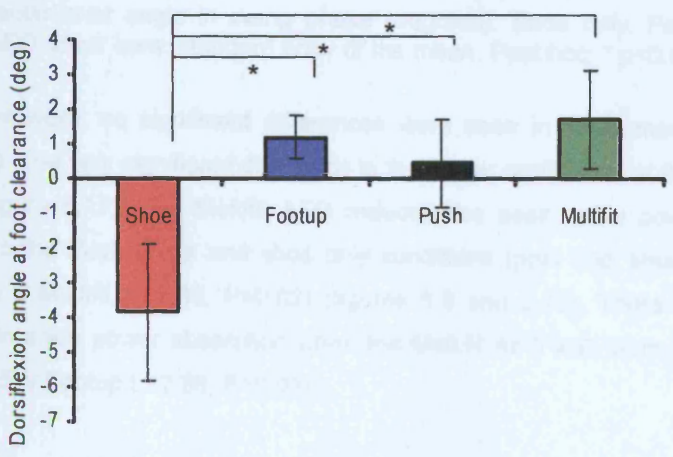

Figure 5.6: Ankle dorsiflexion angle at foot clearance (degrees). Shoe only, Footup brace, Push ankle brace, Multifit AFO. Dorsiflexion: positive values, plantarflexion: negative values. Error bars: standard error of the mean. Post hoc: * p<0.05

In early swing phase the ankle was in less plantarflexion when the AFOs were worn compared to just shoes (ANOVA: F =12.85, P<0.0001) (figure 5.10). The Multifit AFO was most effective at reducing the plantarflexion angle (post hoc: shoe v Footup t =-3.10, P=0.01; shoe v Push t =-3.55, P=0.004; shoe v Multifit t =-4.17, P=0.001) (figure 5.7).

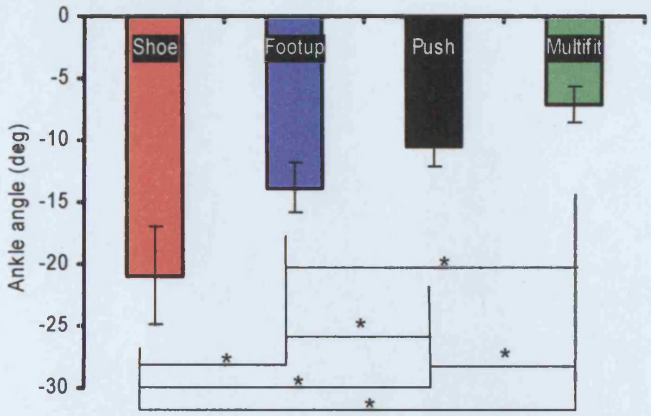

Figure 5.7: Peak plantarflexor angle in swing phase (degrees). Shoe only, Footup brace, Push ankle brace, Multifit AFO. Error bars: standard error of the mean. Post hoc: * p<0.05

When the AFOs were worn, no significant differences were seen in ankle moment produced in preswing (figure 5.12). The only significant difference in the power profile was at the ankle (ANOVA: f =5.39, P=0.003) (figure 5.13). The Multifit AFO reduced the peak ankle power generation at preswing compared to the Push brace and shoe only conditions (post hoc: shoe v Multifit t =3.6, P=0.003; Push brace v Multifit t =2.80, P=0.02) (figures 5.8 and 5.13). There was also a trend towards an increase in ankle power absorption when the Multifit AFO was worn (ANOVA: f =2.18, P=0.1; post hoc: Multifit v Footup t =2.56, P=0.03).

Proximally there were no significant differences in peak values. Although not a planned comparison, a trend was noted toward an increase in total hip power generation in swing phase when the Multifit AFO was worn (ANOVA: f =2.62, P=0.09; post hoc: Push v Multifit t =-3.09, P=0.009) (figure 5.13).

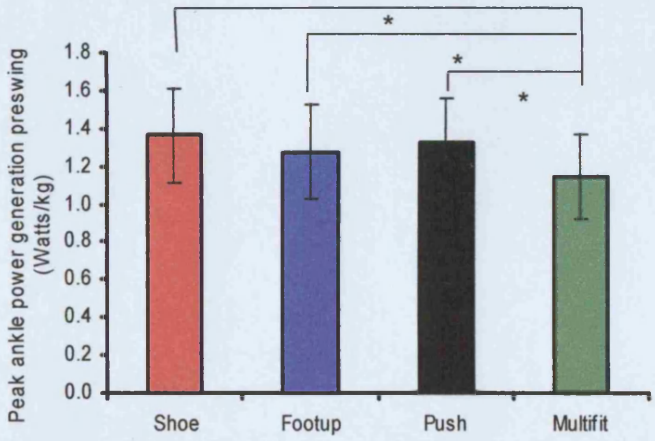

Figure 5.8: Peak ankle power generation at preswing (Watts/Kg). Shoe only, Footup brace, Push ankle brace, Multifit AFO. Error bars: standard error of the mean. Post hoc: * p<0.05

5.3.2.3 Secondary kinematic and kinetic comparison

The secondary analysis revealed no further differences in stance phase or trunk motion. In swing phase there was a difference in the peak dorsiflexion angle achieved (ANOVA: f =3.11, P=0.04) (figure 5.10). The Push ankle brace and the Multifit AFO were the most effective at improving the peak dorsiflexion angle and reducing how far the ankle dropped into plantarflexion (post hoc: shoe v Push brace t =-2.32, P=0.04, shoe v Multifit t =-2.45, P=0.03) (figure 5.9).

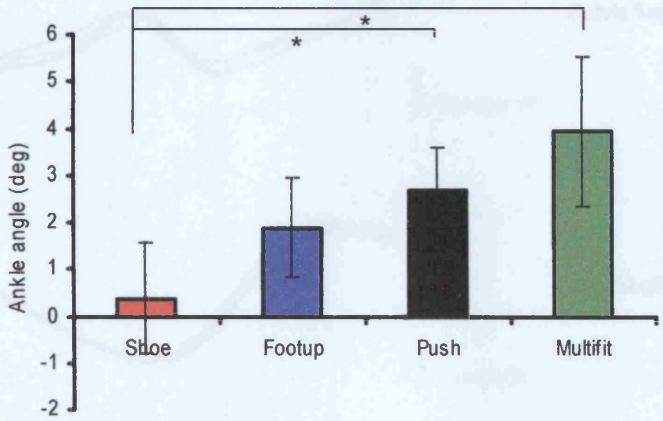

Figure 5.9: Peak dorsiflexor angle in swing phase (degrees). Shoe only, Footup brace, Push ankle brace, Multifit AFO. Error bars: standard error of the mean. Post hoc: * p<0.05

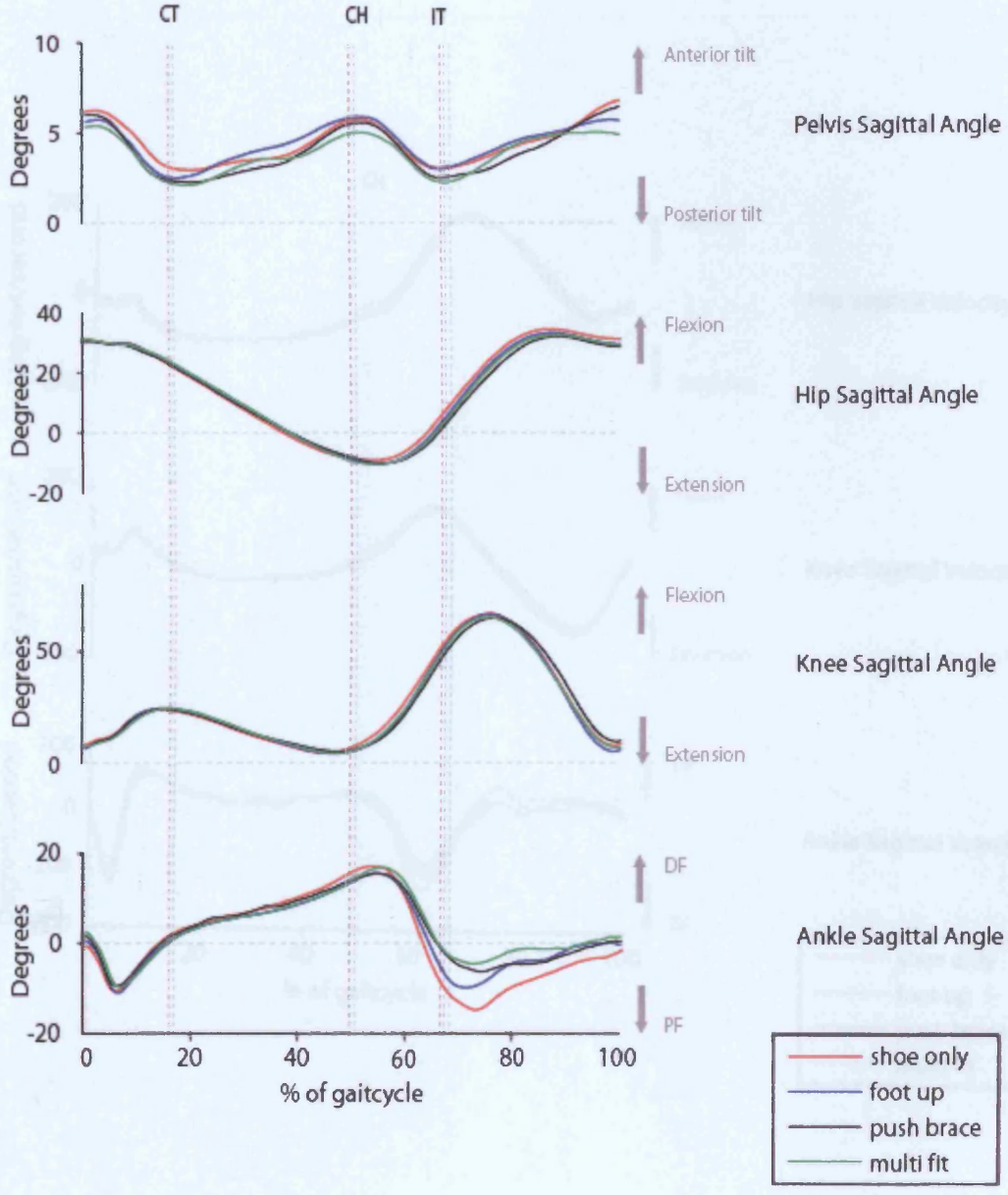

Figure 5.10: Grand average of angular displacement in the sagittal plane over one gait cycle for the ankle, knee, hip and pelvis (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off

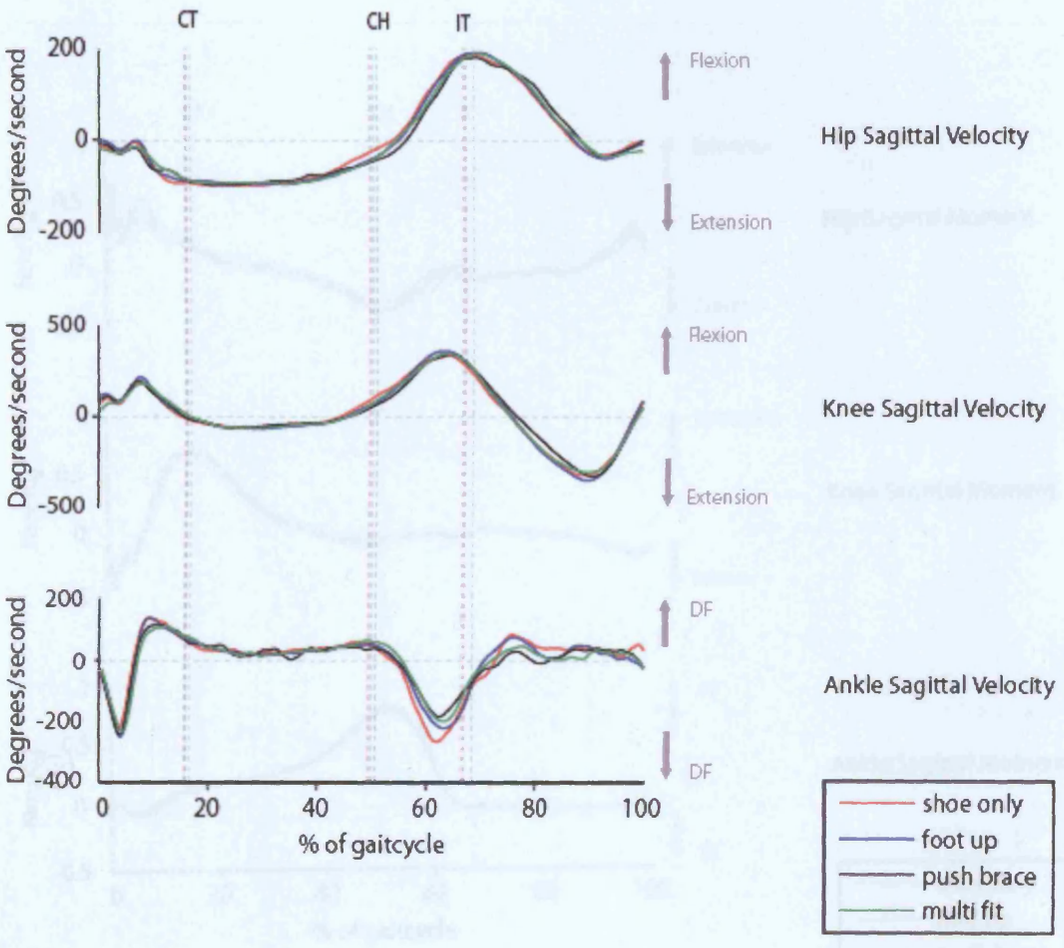

Figure 5.11: Grand average of angular velocity in the sagittal plane over one gait cycle for the ankle, knee and hip (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off

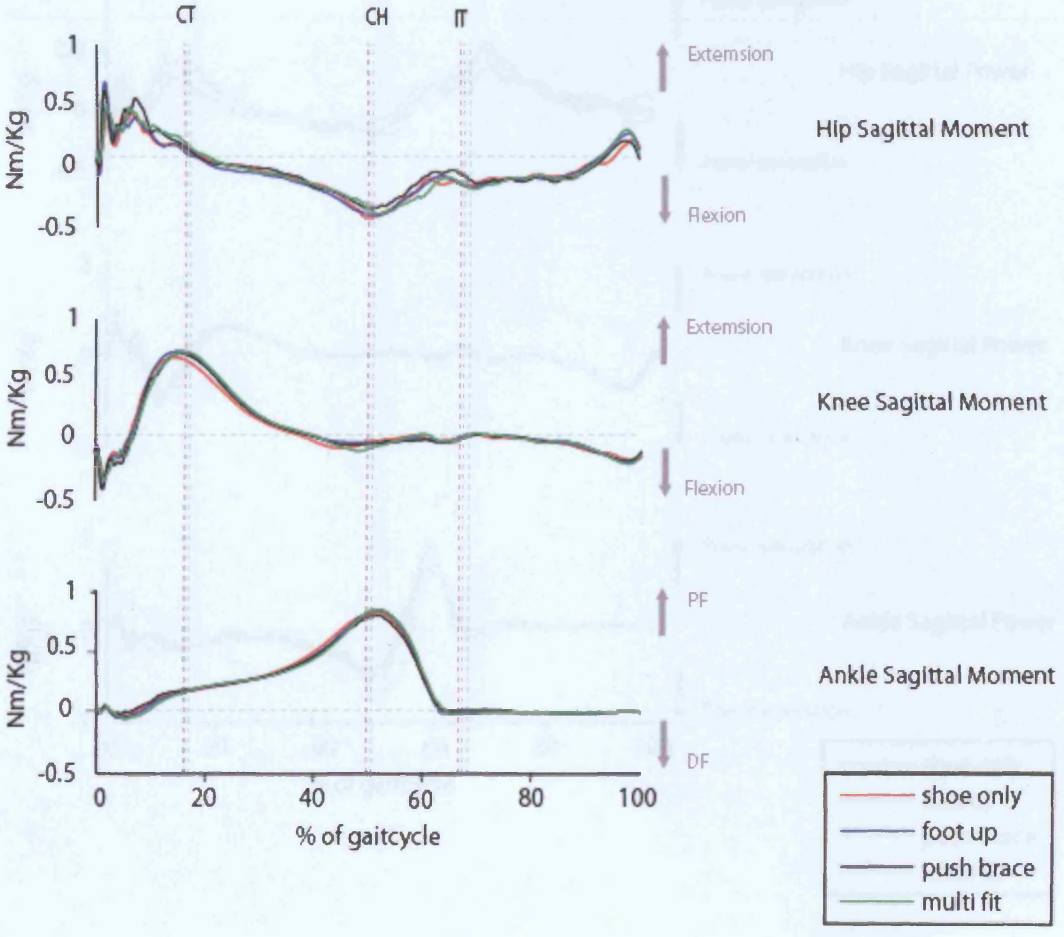

Figure 5.12: Grand average of joint moments in the sagittal plane over one gait cycle for the ankle, knee and hip (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off

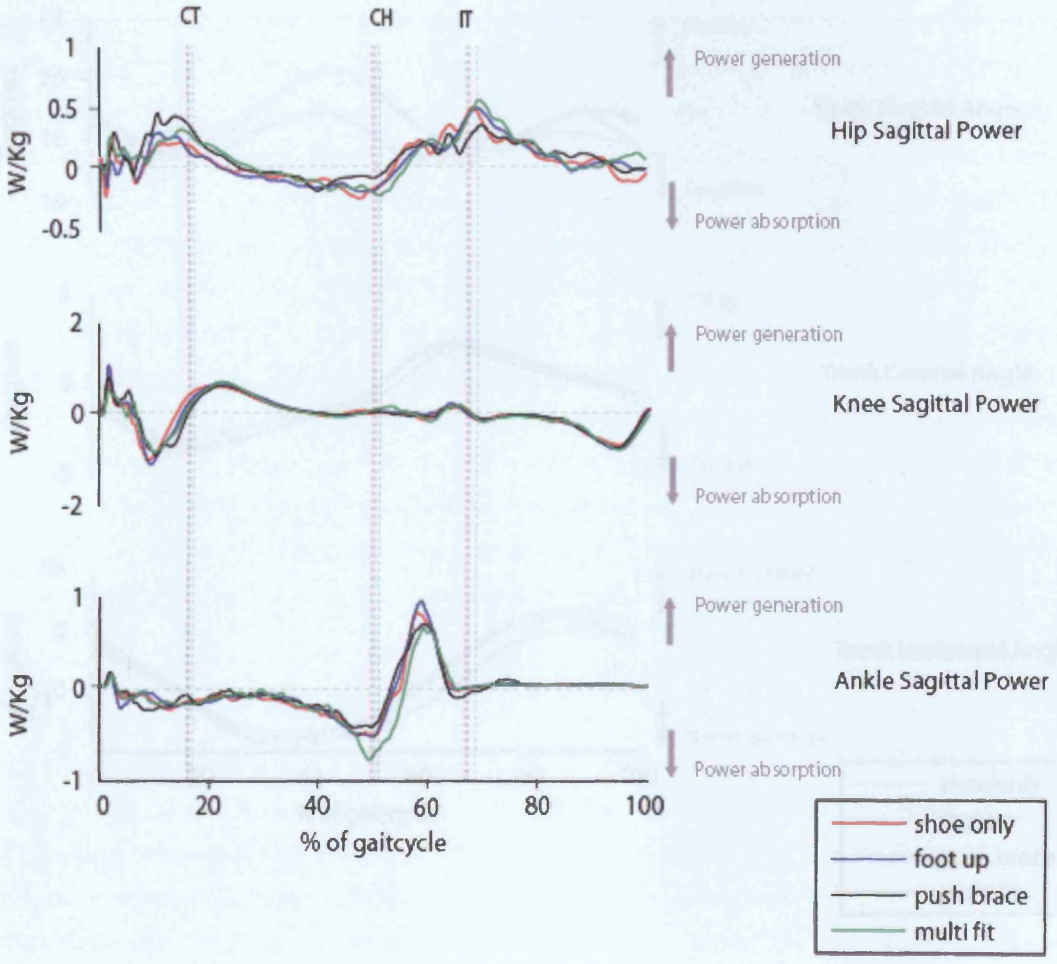

Figure 5.13 Grand average of joint powers in the sagittal plane over one gait cycle for the ankle, knee and hip (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off.

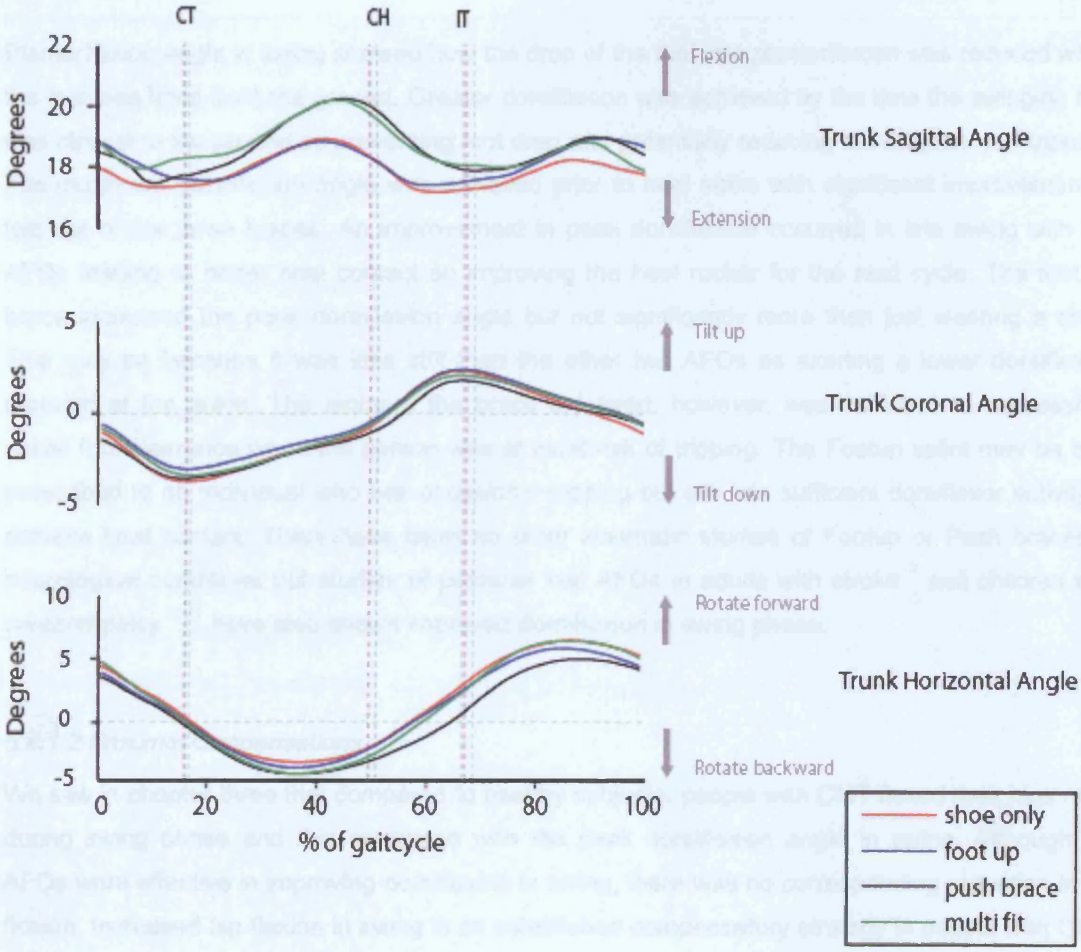

Figure 5.14: Grand average of angular displacement of the trunk in the sagittal, coronal and horizontal planes over one gait cycle (average of left and right sides). CT: contra-lateral toe off; CH: contra-lateral heel strike; CH: contra-lateral heel strike; IT: ipsilateral toe off

5.4 Discussion

5.4.1 Effect of AFOs on foot drop

5.4.1.1 Distal comparison

The three prefabricated AFOs compared in this study are commonly prescribed to improve foot clearance and reduce foot drop in people with neuromuscular conditions. It is reassuring that all of the devices controlled the ankle in swing phase, as they were designed. Three of the variables measured in this study demonstrate this.

Plantarflexion angle in swing showed how the drop of the foot into plantarflexion was reduced when the foot was lifted from the ground. Greater dorsiflexion was achieved by the time the swinging foot was closest to the ground so preventing foot drag and potentially reducing the frequency of tripping. The maximum dorsiflexion angle was achieved prior to heel strike with significant improvement in two out of the three braces. An improvement in peak dorsiflexion occurred in late swing with the AFOs leading to better heel contact so improving the heel rocker for the next cycle. The foot up brace increased the peak dorsiflexion angle but not significantly more than just wearing a shoe. This may be because it was less stiff than the other two AFOs so exerting a lower dorsiflexion moment at the ankle. The moment the brace did exert, however, was sufficient to successfully assist foot clearance when the person was at most risk of tripping. The Footup splint may be best prescribed to an individual who has occasional tripping but still has sufficient dorsiflexor activity to achieve heel contact. There have been no other kinematic studies of Footup or Push braces in neurological conditions but studies of posterior leaf AFOs in adults with stroke [7] and children with cerebral palsy [4, 11] have also shown improved dorsiflexion in swing phase.

5.4.1.2 Proximal compensations

We saw in chapter three that compared to healthy subjects, people with CMT flexed their hips more during swing phase and this correlated with the peak dorsiflexion angle in swing. Although the AFOs were effective in improving dorsiflexion in swing, there was no corresponding reduction in hip flexion. Increased hip flexion in swing is an established compensatory strategy in people with CMT. This study only looked at the immediate effect of orthotic intervention. It is possible that it would take longer to alter an established motor pattern and that hip flexion angle could change over a period of time wearing AFOs. A longitudinal study would be required to see if this is the case. Alternatively, sensory impairment could have reduced the perception of ankle angle so the strategy was not altered. A similar observation was seen in a study of healthy subjects who had undergone peroneal nerve block. Increased hip flexion was seen post block but this was only partly improved by wearing an AFO [8]. The authors deduced that this could be due decreased sensation or a conscious overcompensation to prevent foot drag.

5.4.2 Effect of AFOs on progression

5.4.2.1 Distal comparison

In this study stiffening the ankle did not increase the plantarflexor moment at preswing, as suggested by Salsich et al [13]. Two previous studies have investigated the effect of a posterior leaf AFO in children with cerebral palsy [11] and a solid AFO (i.e. without the cut away around the malleoli) in children with myelomeningolcele [15]. The posterior leaf AFO did not increase the ankle moment at preswing but the more rigid, solid AFO did. These studies were performed by the same research group and were flawed in that the AFO comparison was with barefoot walking and not with a shoe only condition. Footwear can affect lower limb kinetics so this must be considered [4]. Despite this, these papers do offer an explanation as why the AFOs in the present study did not increase the plantarflexor moment as they were not sufficiently stiff.

The present study demonstrated some interesting differences in the three AFOs and how they influenced power generation in pre-swing. Results from chapter three and previous gait comparison studies [10] show that people with CMT generate less power at the ankle than healthy subjects and that this could lead to compensatory changes proximally. The Footup and Push braces did not significantly alter the power profile of the ankle. They did not assist or interfere with power generation despite stiffening the ankle. The Multifit AFO appeared to diminish the generation of power at the ankle despite stiffening the ankle to a similar degree as the Push brace. The prior experience of AFO use must be considered when reasoning why this occurs. Two subjects had used the Footup and two had used the Push brace so the Multifit AFO was new to all subjects. This may have skewed the responses to the Footup and Push brace. Another potential explanation could be other mechanical properties of the AFOs. This study only measured how an AFO stiffens the ankle and not its visco-elastic properties that could account for the difference.

Studies of plastic posterior leaf and solid AFOs also show a reduction in ankle power [11, 12]. Other orthotic devices have been produced and tested to assist with ankle propulsion. Carbon fibre spring splints have proven more successful at increasing ankle power generation in preswing [1, 2]. An increase in ankle velocity during the forefoot rocker was also observed. As ankle power is the product of the moment and angular velocity, it is probably this increase in velocity that contributes to better power generation rather than an increased plantarflexor moment. None of the studies investigated how carbon fibre splints stiffen the ankle or their visco-elastic properties so it is unclear what properties allowed them to work most effectively. More novel devices are also being produced to provide a more active ankle power generation at preswing, for example AFOs with pneumatic "muscles" [6] and variable impedance splints [3]. These devices, however, are still in development and not yet commercially available.

In figure 5.13, the pattern of power absorption in stance was varied with a trend to increased peak power absorption when the Multifit AFO was worn. This could reflect a storage of energy by the Multifit as it was deformed by the ankle rocker. Heel rise was not facilitated at the forefoot rocker so it would appear that the energy stored was either dissipated as heat or, when delivered back to the ankle, was insufficient to exert a sufficient force to assist propulsion of the leg and trunk. During concentric plantarflexion, subjects with CMT may still have had sufficient active plantarflexor strength to push down against the foot piece of the AFO. Both the Footup and Push braces would exert a dorsiflexion moment at this point but it is possible that the Multifit AFO in doing this also significantly absorbed energy as the foot piece deformed so reducing the power generation. After toe off the Multifit AFO lifted the foot into dorsiflexion more than the shoe alone implying an elastic assistance bringing the ankle into dorsiflexion.

5.4.2.2 Proximal compensations

There were no significant differences in proximal motion or kinetics that could be a consequence of the reduction in ankle power generation when the Multifit AFO was worn. There was, however, a trend towards increased total hip power generation in early swing phase when the Multifit AFO was worn, with a significant post hoc result when compared to the Push brace. This result must be regarded with caution but it is possible that the increased total power generation reflects increased overall activation of the hip during swing phase to compensate for the reduction in power generated at the ankle. Although this would fit with the predictions for this chapter, this is not a definite and clear result which may be influenced by the increased error in the calculation of hip kinetics using inverse dynamics [9].

5.4.3 Effect of AFOs on support

The present study demonstrated that the AFOs did not control peak dorsiflexion in preswing. The study of solid AFOs did show a reduction in peak dorsiflexion in stance [15] but posterior leaf AFOs did not [11]. It is possible that the increased plantarflexor moment exerted by a solid AFO contributed to preventing excessive dorsiflexion at the end of stance.

5.4.4 Future work

As this study only looked at the immediate effect of different orthoses, a longitudinal study would be useful to look at any effects over time. As seen in chapter three, people with different types of CMT have a varied presentation so it would be helpful to stratify the groups according to key impairments such as the degree of distal weakness. This would allow us to see if some AFOs are more effective with certain patient characteristics. In addition to 3D motion analysis it would be very useful to look

at functional measures in such a comparative study, for example walking endurance, ambulation over a variety of surfaces, perceived exertion and functional balance scores. Problems with the acceptance of AFOs is a well known issue so comfort scores and subjective opinions on acceptability would also be of interest.

As discussed the only property of the splint materials investigated in this study was stiffness. The net work done during cyclic stretching of the AFOs could be examined by measuring the area inside the torque x angle hysteresis loop. As with the present study it would be useful to look at the hysteresis loop for the AFO/ankle/shoe combination to reflect all of the components influencing ankle motion.

Another approach could be to calculate the visco-elastic properties of the AFO. The leg, splint footwear combination could be stretched using ramp and hold stretches by the dynamometer and stiffness calculated as in the present study. The torque produced during the stretch could be calculated for the AFO combination and a shoe only condition. The viscosity of the AFO could be estimated from the following equations:

$$Torque_{AFO} = Torque_{combined} - Torque_{shoe} \quad (5.1)$$

$$Torque_{AFO} = I\ddot{q} + B\dot{q} + Kq \quad (5.2)$$

Where I is the inertia of the foot (from anthropometric data), B is the viscosity coefficient, K is the calculated stiffness, q is the displacement, $\dot{q}$ is the velocity and $\ddot{q}$ is the acceleration of the manipulandum during the stretch.

5.5 Summary

- Ankle foot orthoses vary in the degree they stiffen the ankle depending on their material and design.
- All three of the AFOs tested improved dorsiflexion in swing
- The Multifit AFO decreased the peak ankle power generation during preswing
- There were no significant proximal changes to compensate for these distal changes but there was a trend towards increased total hip power generation in swing.

5.6 Reference List

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6 Effect of Hip Flexor Fatigue on Walking Endurance in People with CMT

6.1 Introduction and Hypothesis

The primary hypothesis for this thesis states that in people with CMT, weak ankle muscles lead to increased muscle activity around the hip to compensate for reduced limb progression and foot drop during swing. Chapter 3 demonstrated some of these differences with increased hip motion and altered timing of power generation relative to the ankle. Over a short distance these strategies may help to achieve the goal of limb progression. However, when walking for long distances these compensations may cause the muscles to tire prematurely. Subjective reports from people with CMT attending a peripheral nerve clinic support this supposition with complaints of proximal leg weakness when walking for a prolonged distance or time.

Based on the original hypothesis a prediction was made for this study:

People with CMT will be limited in how far they can walk by fatigue of the hip flexors as demonstrated by a reduction in hip flexor strength and alteration in hip motion.

For this study two experiments were performed. The first (session 1) measured the change in hip flexor strength after subjects walked to fatigue. The second experiment (session 2) involved specifically fatiguing the hip flexor muscles and investigating the effect on walking endurance.

6.2 Methods

People with CMT were recruited from the genetic peripheral neuropathy clinic at the National Hospital for Neurology and Neurosurgery. Inclusion requirements were clinically definite CMT and the ability to walk 100m in at least 10 minutes. Subjects were excluded if they had a history of cardiac dysfunction, orthopnoea, other neurological impairment, orthopaedic lower limb impairment unrelated to CMT, and lower limb or back pain exceeding 7 out of 10 on a visual analogue scale. Healthy control subjects were recruited for comparison in session 1 and were matched for age, gender, weight and height. The same exclusion criteria were applied to this group

6.2.1 Session 1: Treadmill Walking Endurance Test

6.2.1.1 Clinical Measures

People with CMT were examined for impairments associated with their condition.

Strength: Isometric strength of the lower limb muscles was measured using strain gauges attached at one end to a custom made rigid frame and to the subjects' limb at the other via canvass straps for most muscle groups and a metal stirrup for the plantarflexors. The proximal segment was secured with extra straps and restraints as necessary. The muscles tested and the subject positions are indicated in table 4.1. Subjects were tested in supported sitting with the knees at 90^{O} except for the dorsiflexors which were tested in supine. The dorsiflexors were not measured at plantigrade as many people with CMT have tight Achilles tendons and restricted dorsiflexion. This would mean that the muscle would be contracting in inner range with possible resistance from the plantarflexor shortening. Therefore a standardised position of 10° of plantarflexion was used. After one practice attempt the maximum voluntary contraction (MVC) was measured. The moment arm from the joint axis to the centre of the strap was measured for each muscle group

Muscle group	Subject position	Joint position
Hip extensors	Supported sitting: chest and pelvis restraint	50° hip flexion
Hip flexors	Supported sitting: chest and pelvis restraint	50° hip flexion
Quadriceps	Supported sitting: chest and pelvis restraint	90° knee flexion
Plantarflexors	Supported sitting: thigh, tibial and ankle inversion restraint	plantigrade
Dorsiflexors	Supine: tibial restraint	10° of plantarflexion

Table 6.1: Standardised joint position for fixed myometry measures.

Range of motion: Subjects were screened for a scoliosis using Adam's forward bend test [4] (appendix 3). The presence of pes cavus or planus, toe flexion deformities, plantar fascia tightness and calcaneal valgus or varus was noted. In the presence of calcaneal varus the block test was

used to ascertain whether this was due to a fixed deformity (appendix 3). Hand held goniometers measured the sagittal ranges of the hip, knee and ankle in standardised positions. The presence and site of ulcers or excessive callous on the plantar surface was recorded

Sensation: Two sensory modalities were tested. Light touch sensation was measured on the sole of the foot using 10g monofilaments (Neuropen, Owen Mumford, Oxford, UK). Ten standard areas of the plantar surface were tested (appendix 3). Subjects were asked to close their eyes and state "yes" when they felt the filament. The result was scored as the number of positive responses out of ten. Vibration threshold was tested using a biothesiometer (Bio-medical Instrument Co, Newbury, Ohio, USA, 120 Hz). The probe of the biosthesiometer was held still and at a constant pressure over the lateral malleolus and then the great toe. The subject was asked to close their eyes. The intensity of the vibration was gradually increased until the subject reported feeling it. This was identified as the appearance threshold. Then the intensity was gradually decreased until the subject reported that the vibration had disappeared. This was identified as the disappearance threshold. The appearance and disappearance thresholds were established over the malleolus and great toe from the mean of three measures [3].

Cardiorespiratory Function: Resting heart rate and blood pressure were taken prior to the walking task (MX3 plus model, Omron-Healthcare, Milton-Keynes, UK). The predicted maximal heart rate was calculated using the formula: max heart rate = 220 – age. Lung function was measured using spirometry (One Flow FVC spirometer, Medisave, Weymouth, UK). Forced expiratory volume (FEV1), forced vital capacity (FVC) and peak expiratory flow rate (PEF) were recorded from the best of three attempts.

Fatigue and health status: Subjects completed the fatigue severity scale (FSS) and the short form 36 (SF-36) questionnaire (appendix 5 and 6). The fatigue severity scale is a nine item scale assessing the functional outcomes of fatigue. It has been used in a variety of conditions including multiple sclerosis, systemic lupus erythematosus [8]. The SF-36 is a questionnaire assessing health status. It consists of eight heath concepts: physical functioning, bodily pain, role limitation due to physical or emotional problems, emotional well being, social functioning, energy and fatigue, and general health perceptions [19].

6.2.1.2 Treadmill test

Prior to the walking endurance test CMT subjects performed a 10m timed walk to ascertain their normal gait speed and cadence. They then walked on a motorised treadmill at the same speed. An auditory metronome was set at the same cadence to cue the subject to maintain a consistent stepping rate. A practice trial on the treadmill followed by 5 minutes rest was performed prior to the test. During the test the subjects wore a safety harness attached to an overhead gantry that was capable of supporting their weight. The tension in the support system was set so that it did not

interfere with treadmill walking (figure 6.1). Two dimensional kinematics were measured during the treadmill test rather than three dimensional because the harness would not allow the subject to wear the pelvic marker frame needed to create the local embedded vectors required for 3D analysis.

Figure 6.1: Harness, marker and EMG set up for the treadmill walking test

Fifteen seconds of motion data was collected every minute the subject remained walking on the treadmill. Prior to the walking test a standing trial was collected to measure the 'neutral' alignment. Angles during walking were expressed relative to this standing trial. Heart rate was measured during the treadmill walking test using a Polar heart rate monitor (Polar Electr Inc. USA).

As this was a test of the subject's everyday walking endurance any orthoses normally worn by the subject were worn during the test. Many of the subjects found walking on the treadmill challenging to their balance so were allowed light upper limb support if required. The Borg scale [1] was used to measure the subject's perceived exertion every minute of the treadmill walking task (appendix 4). Additionally heart rate and pain level, using a 10 point visual rating scale, were recorded every minute during the test. When the subject reached Borg level 17 (very hard) the treadmill test was stopped. Additionally walking would have been stopped if:

1. Pain exceeded level 7 out of 10 on the rating scale
2. If the heart rate exceeds 85% of their maximal heart rate as calculated by 220-age.
3. Chest pain
4. Signs of poor perfusion (cyanosis, pallor)
5. Technical difficulties that prevent the recording heart rate.
6. Subject asks to stop

Points 2-5 include absolute and relative indications for terminating exercise tests as given by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [5]. Following cessation of the test subjects were asked to indicate what made them stop the walking test. Four visual analogue scales were completed to indicate the degree of pain, breathlessness, proximal muscle fatigue and distal muscle fatigue at the end of the test. Control subjects walked at the same speed and cadence on the treadmill for the same duration as the CMT subject they were matching for.

6.2.1.3 Myometry

The primary outcome measure for this study was the change in hip flexor strength with prolonged walking. MVC measures for the hip flexors and plantarflexors were taken before and immediately after the treadmill walking test. The positions of the myometry straps were marked at the initial measurement to aid reliable placement. To calculate the moment, the length of the lever was measured from the greater trochanter to the centre of the strap. For the hip flexor measurement, multi-meters connected to the strain gauges were used to monitor the output voltage of the strain gauges so measurements were all taken from the same baseline tension. Tests of MVC were performed within 2 minutes of the subject completing the treadmill test. To check for motivational influences, a hand held dynamometer was used to measure grip MVC before and after the treadmill test. Repeatability testing of this method demonstrated good agreement between trials with an ICC of 0.83 (appendix 7).

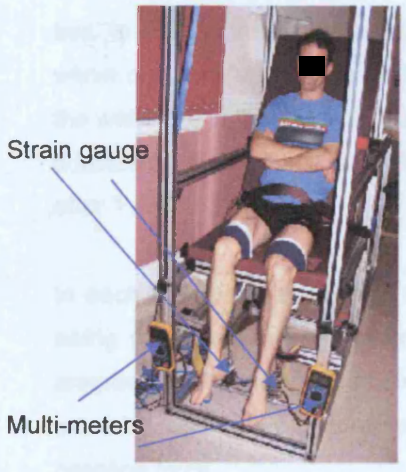


Figure 6.2: Fixed myometry set up for measurement of the hip flexors

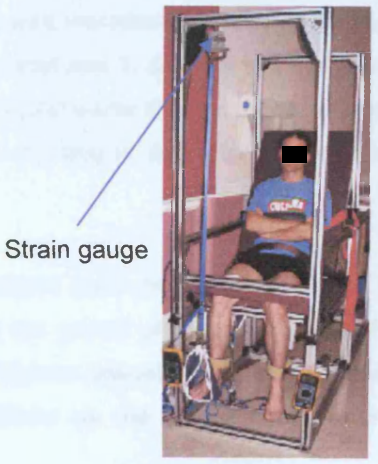


Figure 6.3: Fixed myometry setup for measurement of the plantarflexors

6.2.2 Session 2: Hip Flexor Fatigue Test

At a follow up session the effects of selectively fatiguing the hip flexors on walking endurance were tested. Infrared marker placement was identical to session 1. Subjects initially walked on the treadmill at the same speed and cadence as the first session for three minutes to obtain pre-fatigue kinematic data.

6.2.2.1 Hip flexor fatigue protocol

Subjects sat supported with their hips in 50° flexion, pelvis and chest constrained by straps (see figure 6.2). Straps were placed over the distal thigh and linked to strain gauges mounted on the rigid frame. Bilateral hip flexor MVC recordings were firstly taken. Subjects then performed alternating contractions of the hip flexors to 50% of their MVC at a rate of 40 contractions per minute. Visual feedback of the applied tension was provided by the multi-meters attached to the strain gauge output. MVC measures were taken every two minutes throughout the test. The test was terminated once the hip flexors had fatigued by 20%. Subjects were then immediately transferred to the treadmill and began a treadmill walking test identical to session 1. Kinematics, heart rate, the Borg scale and pain were monitored every minute and the walking test was stopped when the subject reached Borg level 17 or the pain scale exceeded 7 out of 10.

On immediate cessation of the treadmill test a repeat measurement of hip flexor MVC was taken as were the VAS measures of pain, dyspnoea, proximal and distal lower limb fatigue.

6.2.3 Analysis

In session 1 the initial kinematics were compared to the last trial prior to cessation of the treadmill test. In session 2 an initial pre test trial of walking was recorded (pre test) and compared to walking within one minute after the hip flexor fatigue test (post test 1) and the last trial prior to cessation of the walking test (post test 2). Kinematics often changed within the first minute of walking as subjects adapted to the treadmill even in the absence of any fatigue, therefore the first trial was analysed after 1 minute of walking.

In each trial the average of 3 strides were calculated (see chapter 2). Changes in preswing and swing phase were compared as they represent the period of force generation followed by limb progression. Preswing was defined as the time between opposite initial contact and toe off. For the isometric strength measurement, MVC was defined as the difference between the peak and baseline force.

6.2.3.1 Statistical Analysis

Group comparison: clinical measures were compared using 2-tailed unpaired t-tests. Non-parametric data was analysed using a Mann-Whitney test. Significance was taken as $p<0.05$ with means reported ± the standard deviation unless indicated.

Response to treadmill walking test: The response of people with CMT and the control group was compared using a repeated measures general linear model. A factor of *trial* with 2 levels in session 1 (pre and post) and 3 levels in session 2 (pre, post 1 and post 2) was included. A primary analysis was performed based on the prediction introduced at the start of this chapter.

The primary analysis observed:

- hip flexor and plantarflexor MVC
- peak hip flexion velocity during pre-swing and swing phase
- peak hip flexion during pre-swing and swing phase

As six comparisons were made as part of the primary analysis a modified Bonferroni test was applied to account for multiple comparisons (appendix 1) [16]. Changes at other joints were expected to occur so a secondary analysis assessed the changes in:

- peak sagittal ankle, knee and hip amplitude and velocity during preswing
- peak sagittal ankle and knee amplitude and velocity during swing
- peak sagittal trunk flexion and peak to peak changes in coronal and horizontal trunk rotation

Again, a modified Bonferroni test was applied to account for the 19 comparisons. The relationships between the clinical measures and the walking performance were analysed using the Spearman's rank correlation test.

6.3 Results

6.3.1 Session 1: Treadmill Endurance Test

This section outlines the response of people with CMT and matched control subjects to the treadmill endurance test. Grand average graphs are presented at the end of this section. There are discrepancies between peak values and apparent peaks on the grand average graphs. This is due to alterations in the grand average trace resulting from variations in the timing of the peaks between individual participants.

6.3.1.1 Group differences

Eighteen people with CMT were compared to 14 healthy matched controls. Subjects were matched according to age, gender, height and weight with no significant differences found between these variables (table 6.2). Four of the subjects with CMT wore ankle foot orthoses (AFOs). One wore bilateral rigid AFOs, two wore less rigid bilateral ankle braces (neoprene and silicon) and one subject wore an anti-inversion ankle brace on the left leg.

	Age (years)	**Gender**	**Height (m)**	**Weight (kg)**
CMT subjects	37 (± 12.9)	10 male; 8 female	1.69 (±0.7)	70.5 (±12.2)
Control subjects	34 (± 9.7)	8 male; 6 female	1.7 (±0.5)	68.4 (±10.3)

Table 6.2: Age, gender, height and weight data for both subject groups

MVC (Nm/kg)	**CMT subjects**	**Control subjects**
Hip flexors	1.13 ±0.42	1.32 ±0.38
Hip extensors	0.65 ±0.33	1.09 ±0.68
Knee extensors	1.53 ±0.68	2.06 ±0.64
Plantarflexors	0.63 ±0.57 *	1.21 ±0.58
Dorsiflexors	0.10 ±0.08 *	0.39 ±0.17

Table 6.3: Maximum voluntary contraction of lower limb muscles (Nm/kg) for CMT and control subjects. *$p<0.05$

Strength: People with CMT were weaker distally than the control subjects but demonstrated similar strength in the proximal muscles (table 6.3).

Range of motion: Joint range of movement was similar to that of controls subjects in the proximal joints but there was a difference in the range of ankle dorsiflexion. None of the subjects recruited had a scoliosis but a high proportion had foot and ankle deformity associated with CMT (table 6.4).

		CMT subjects	Control subjects
Goniometry (degrees)	Hip flexion	122 ±11	128 ±11
	Hip extension	5 ±3	7 ±4
	Knee flexion	139 ±7	143 ±6
	Knee extension	3 ±4	2 ±2
	Dorsiflexion	-3 ±10 *	14 ±5
	Plantarflexion	62 ±12	62 ±12
Percentage of subjects with scoliosis		0	0
Percentage of subjects with pes cavus		56%	0
Percentage of subjects with calcaneal varus		44%	0

Table 6.4: Range of movement and secondary musculoskeletal complications. *p<0.05

Sensation: People with CMT demonstrated a reduction in the ability to perceive light touch stimuli over the plantar aspect. In addition they showed significantly higher appearance and disappearance threshold for vibration perception compared to control subjects (table 6.5).

Cardiorespiratory Function: There was no significant difference in cardiovascular or respiratory measures between the two groups (table 6.5).

Fatigue and health status: People with CMT had a higher fatigue severity rating compared to the controls (table 6.5). The SF-36 showed lower scores with physical functioning, role limitation due to physical status, energy and fatigue, social functioning, pain and general health (table 6.5). The groups showed no difference in emotional well being and role limitation due to emotional status

Baseline gait differences: Over 10m people with CMT walk at a significantly slower speed and at a lower cadence than control subjects (table 6.5).

Clinical Measures		CMT subjects		Control subjects	
Resting heart rate		74 bpm	(±9)	65 bpm	(±13)
Blood pressure:	Systolic	123 mmHg	(±9)	128 mmHg	(±16)
	Diastolic	78 mmHg	(± 10)	78 mmHg	(±9)
Lung function:	FEV1	3.2 l	(± 0.7)	3.5 l	(±1.0)
	FVC	3.9 l	(± 0.9)	4.3 l	(±1.0)
	PEF	394 l/min	(± 115)	464.5 l/min	(± 163)
Sensation:					
Light pressure		5 out of 10	(± 2.9) *	10 out of 10	(± 0)
Vibration Threshold	Malleolus	AT: 6.1 microns	(± 6.1) *	AT: 0.6 microns	(±0.7)
		DT: 4.9 microns	(± 5.2) *	DT: 1.1 microns	(±1.1)
	Great toe	AT: 8.4 microns	(± 8.5) *	AT: 0.4 microns	(±0.3)
		DT: 6.0 microns	(± 6.3) *	DT: 0.2 microns	(±0.2)
Gait:	Speed	1.13 m/sec	(± 0.1) *	1.59 m/sec	(± 0.2)
	Cadence	108 steps/minute	(± 7.3) *	120 steps/minute	(±10.7)
Fatigue Severity Scale		38.2	(± 14.9) *	16.9	(± 6.6)
SF-36:	Total	998.2	(± 1034.0) *	3227.9	(±183.3)
Physical Function		59.7	(± 24.3) *	97.5	(± 4.0)
Role limitation (physical)		43.8	(± 47.0) *	100	(± 0)
Role limitation (emotional)		68.9	(± 46.2)	94.4	(±19.2)
Energy/fatigue		51.3	(± 21.3) *	72.5	(±14.7)
Emotional well being		78.7	(± 15.3)	85	(±11.1)
Social functioning		68.0	(± 28.1) *	92.1	(±16.1)
Pain		66.1	(± 26.6) *	96.7	(±4.9)
General Health		61.6	(± 21.3) *	83.8	(±11.7)

Table 6.5: Summary of clinical measures for study participants. Mean values are shown with standard deviations in brackets. For FSS, higher value indicates increased severity; for SF-36, higher value indicates better health status. AT- appearance threshold, DT- disappearance threshold. * $p<0.05$

6.3.1.2 Effect of prolonged walking: general comparison

People with CMT walked for a mean time of 48 minutes. Control subjects walked for an average of 44 minutes which although not significantly different, it was slightly less than subjects with CMT. This was because there were four less control subjects.

At the start of the treadmill test, people with CMT reported perceived exertion as 'very light' of level nine of the Borg scale (appendix 4). Control subjects started at level 6.5 or 'very, very light'. By the end of the treadmill test, people with CMT reported a median Borg level of 17, or 'very hard'. For the same speed and time walking, control subjects reported a median score of eight, which was significantly less than the CMT subjects ($Z= -4.93$, $P<0.0001$). In addition, heart rate, expressed as a percentage of the maximum predicted rate, was significantly higher in people with CMT, ($t =3.38$, $P=0.002$) (table 6.6).

		CMT	Controls
Mean walk time	(minutes)	48.3 ±40.5	44.0 ±40.8
Median Borg scale	(start)	9	6.5
Median Borg scale	(finish)	17 *	8 *
% of maximum heart rate	(finish)	60.0 ±10.7 *	57.8 ±11.1 *

Table 6.6: Average walk time, change in Borg scale and heart rate expressed as a percentage of the maximum predicted value (220 – age) on cessation of the walk test. * $p<0.05$

6.3.1.3 Effect of prolonged walking: primary comparison

At the end of the treadmill walking test both the CMT and control groups demonstrated a significant decrease in the MVC of the hip flexors (GLM: trial F =33.76, P<0.0001). People with CMT dropped their MVC by 20% of the initial MVC compared to 14% in the control subjects (figure 6.4). No changes were seen in grip strength indicating that subjects' effort was the same before and after the treadmill test. No change was seen in plantarflexor MVC.

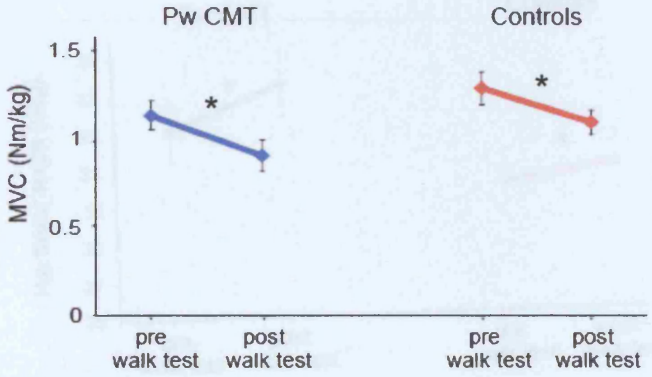


Figure 6.4: Hip flexor MVC measures before and after the treadmill walk test. Error bars are standard error of the mean. * significant difference.

The reduction in hip flexor MVC in the control subjects was unexpected. To investigate this further, five control subjects returned and repeated the treadmill walking test for the same amount of time as they walked in the matched condition. On this occasion they walked at their chosen speed and cadence. Hip flexor MVC was recorded before and after treadmill walking as before. No significant difference was seen in hip flexor MVC before and after walking on the treadmill at a self selected speed (t =0.22 , P=0.84). In the original condition walking at a matched speed, the difference was significant for these five subjects (t =3.25 ,P=0.03).

Both groups also showed a significant increase in hip flexor angle at the end of the treadmill test (GLM: trial F= 10.59, P=0.003) (figure 6.5a). In addition, people with CMT showed a significant reduction in hip flexor velocity during swing whereas control subjects increased the hip velocity (GLM: trial x group F =9.31, P=0.005; post hoc t-tests: CMT t = -2.44, P=0.03; control t =2.76, P=0.02) (figure 6.5b) .

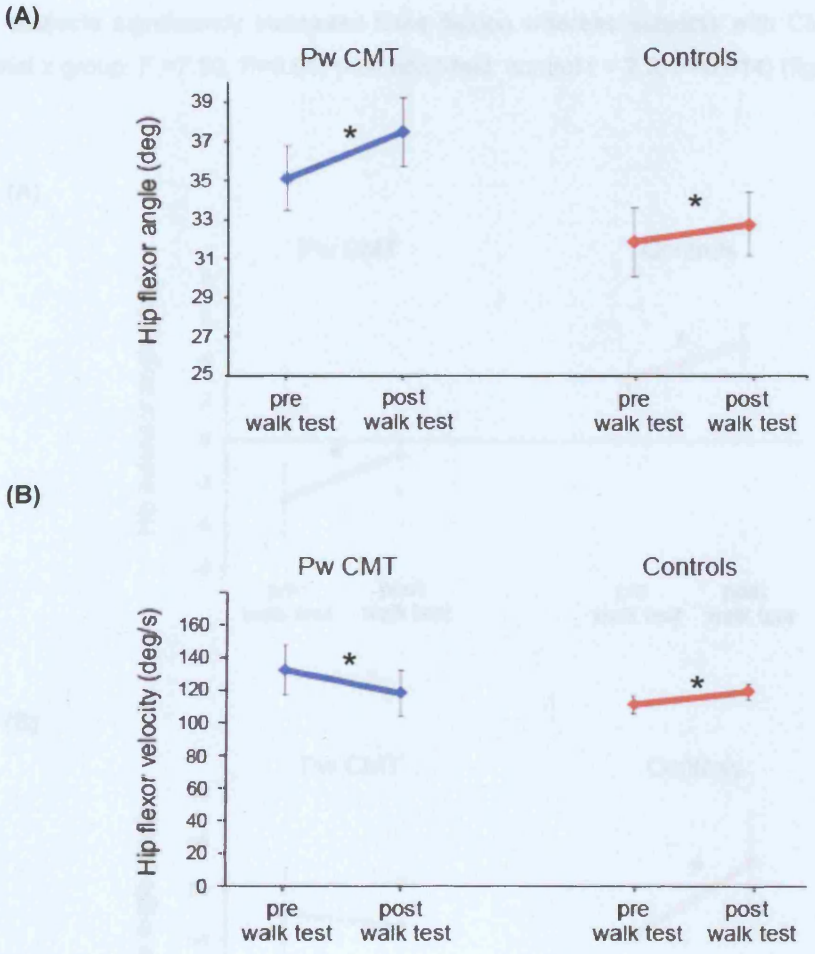


Figure 6.5: Hip flexor angular kinematics at the start and the end of the treadmill walk test. (A) hip flexor angular displacement during swing, (B) hip flexor velocity during swing. Error bars are standard error of the mean. Pw CMT: subjects with CMT; Controls: control subjects. * significant difference.

6.3.1.3 Effect of prolonged walking: secondary comparison

Changes were observed in some of the gait variables analysed for the secondary comparison. At the hip, increased extension was seen during preswing in people with CMT compared to controls at the beginning of the walking test. At the end of the treadmill test, both groups significantly decreased extension at the hip (GLM: trial F =16.94, P=0.0003; post hoc cmt v control pre walking test: t =2.85, P=0.008) (figure 6.6a).

Peak knee flexion angle during swing phase also changed by the end of the treadmill walking test. Control subjects significantly increased knee flexion whereas subjects with CMT did not change (GLM: trial x group: F =7.50, P=0.01; post hoc t-test: control t =-2.8, P=0.014) (figure 6.6b).

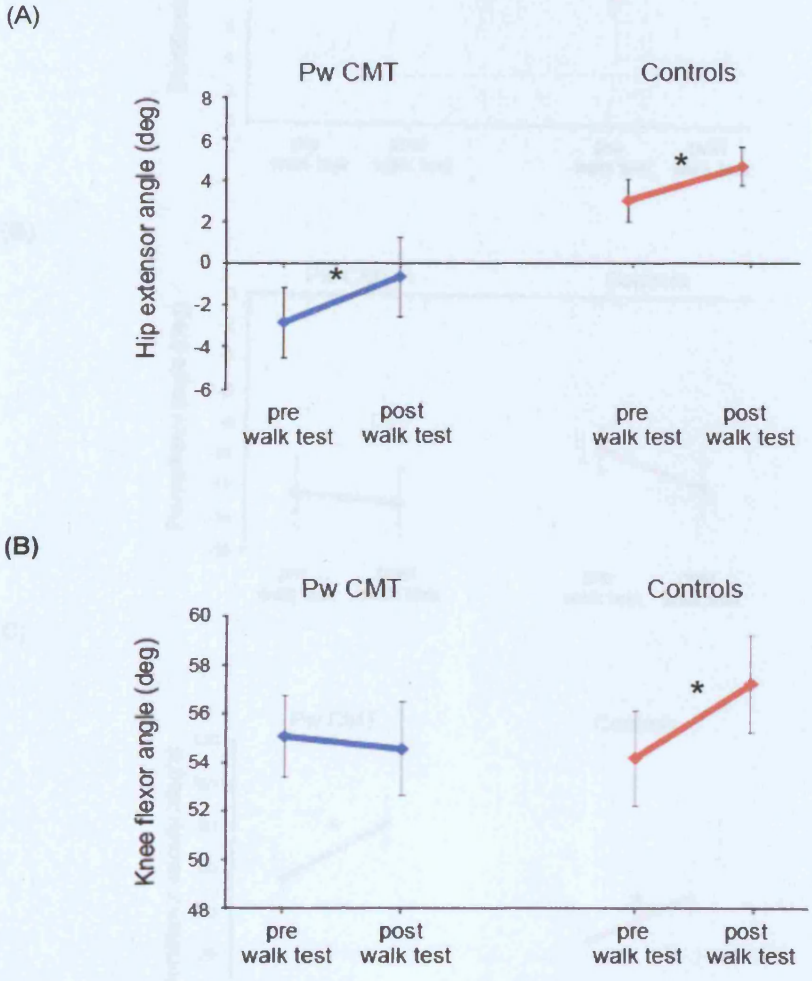


Figure 6.6: Angular kinematics at the start and the end of the treadmill walk test (A) hip extension during preswing. Negative values indicate hip extension. (B) knee flexion during swing. Error bars are standard error of the mean. Pw CMT: subjects with CMT; Controls: control subjects. * significant difference.

The ankle angle did not change in people with CMT but control subjects showed a trend towards increased ankle dorsiflexion during preswing (GLM: trial F =5.34, P=0.03) (figure 6.7a and 6.11). In early swing the control subjects also showed a trend towards increased plantarflexion angle (GLM: trial F =5.13, P=0.03) (figure 6.7b and 6.11). Both groups of subjects demonstrated increased dorsiflexion velocity during preswing (GLM: trial F=26.33, P<0.0001) (figure 6.7c and 6.12).

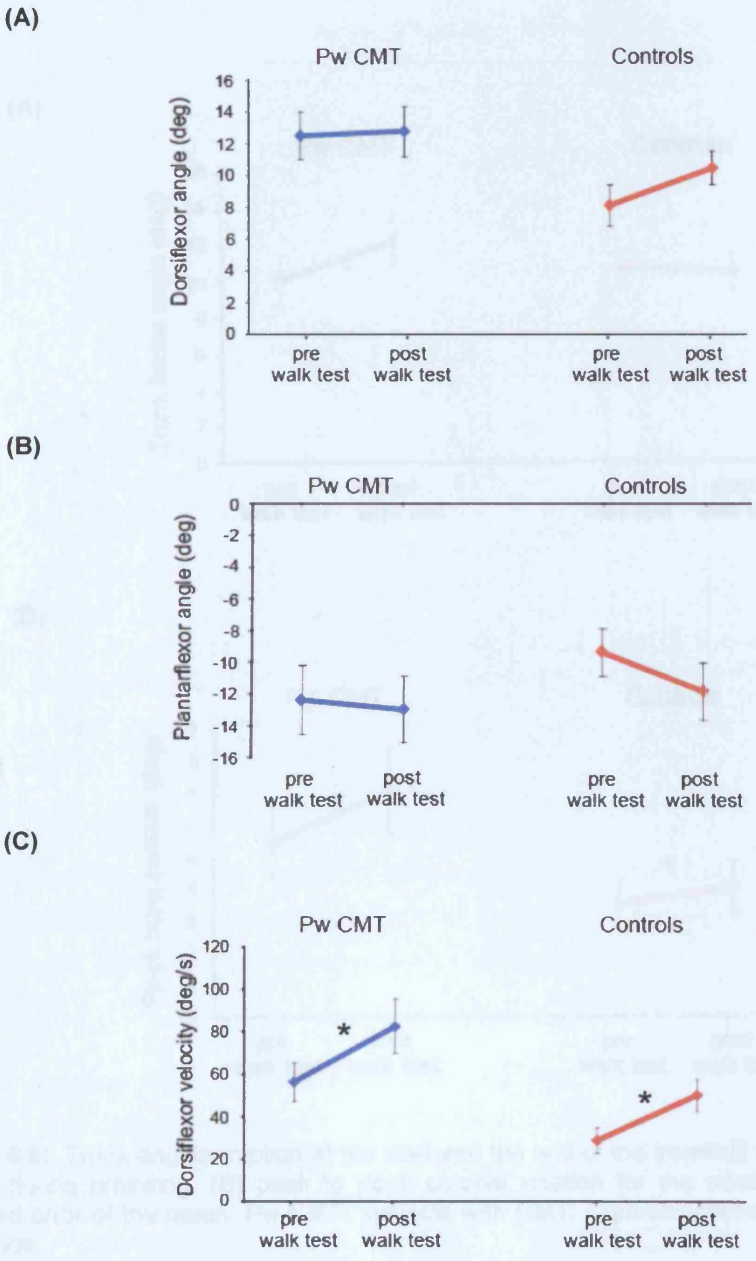


Figure 6.7: Ankle angular displacement at the start and the end of the treadmill walk test (A) dorsiflexion angle during preswing, (B) plantarflexor angle during swing, (C) dorsiflexion velocity during preswing. Error bars are standard error of the mean. Pw CMT: subjects with CMT; Controls: control subjects. * significant difference.

Increased trunk flexion during pre-swing was observed in people with CMT at the end of the treadmill test (figure 6.8a). Peak trunk flexion was reached during pre-swing (GLM: trial x group F =5.31 P=0.03) though this was non significant post modified Bonferroni correction. In addition, greater coronal trunk motion occurred in both groups (GLM: trial F =8.59, P=0.006).

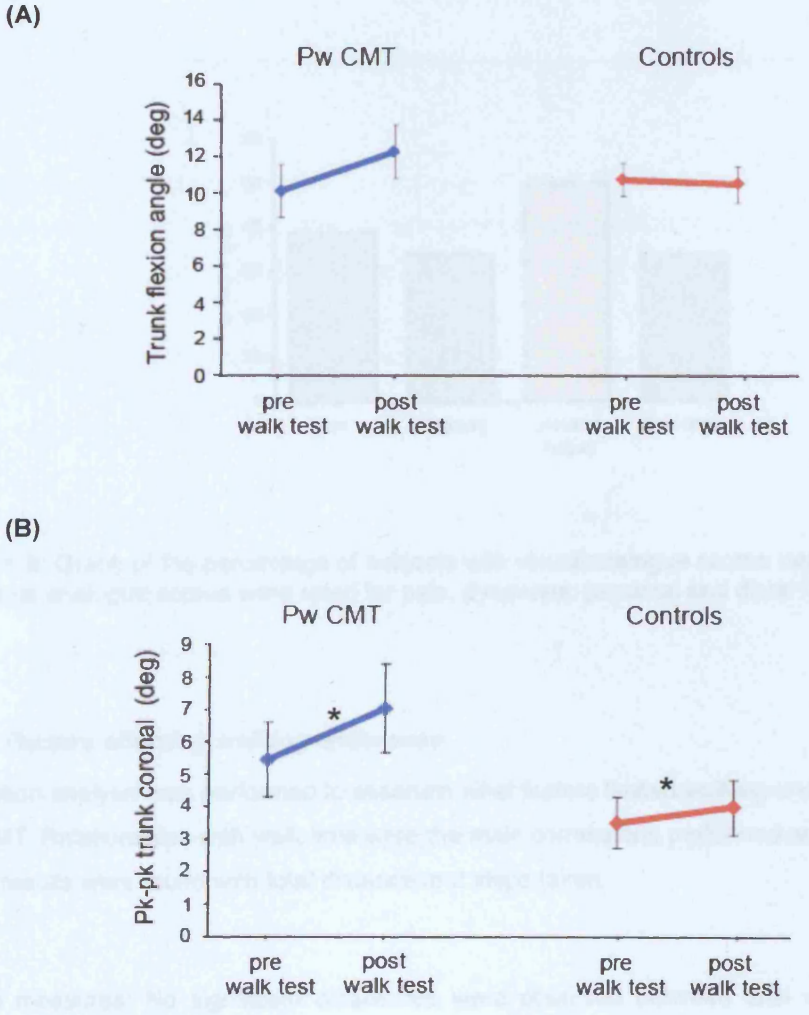


Figure 6.8: Trunk angular motion at the start and the end of the treadmill walk test. (A) peak trunk flexion during preswing, (B) peak to peak coronal rotation for the whole cycle. Error bars are standard error of the mean. Pw CMT: subjects with CMT; Controls: control subjects. * significant difference.

6.3.1.4 Reasons for walking cessation

People with CMT were asked what factors caused them to stop walking during the treadmill test. Sixty seven percent of subjects reported stopping due to fatigue of the legs and a deterioration of their gait pattern. Pain was the reason reported by 22% and 11% stopped because they were breathless.

Visual analogue scores taken after the treadmill walking test showed proximal fatigue was most highly rated symptom with 50% of subjects scoring over five out of ten, i.e. a moderate to severe rating (figure 6.9).

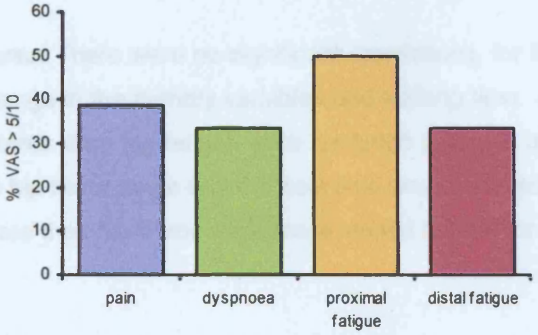


Figure 6.9: Graph of the percentage of subjects with visual analogue scores rated over five out of ten. Visual analogue scores were rated for pain, dyspnoea, proximal and distal fatigue.

6.3.1.5 Factors affecting walking endurance

Correlation analysis was performed to ascertain what factors limited walking endurance in people with CMT. Relationships with walk time were the main correlations performed and presented but similar results were found with total distance and steps taken.

Clinical measures: No significant differences were observed between total walking time on the treadmill and strength, range of motion, sensory impairment and cardio-respiratory measures. Relationships were observed, however, with fatigue severity and sections of the SF-36 relating to physical functioning and fatigue (figure 6.10a and b) (table 6.7).

Walk time versus:	Correlation r value	P value
FSS	-0.68	0.002
SF-36: Physical functioning	0.71	0.002
SF-36: Role limitation due to physical problems	0.65	0.006
SF-36: Energy and fatigue	0.52	0.037

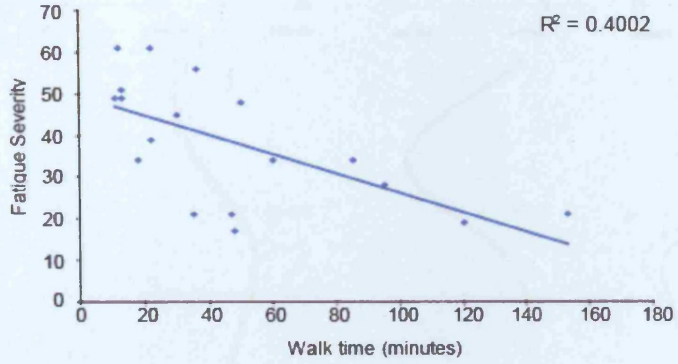
Table 6.7: Significant relationships between walking time and clinical measures.

Primary outcome measures: There were no significant correlations, for the main group of people with CMT, between the change in the primary variables and walking time. However, when subjects who stopped for reasons other than leg fatigue were excluded (i.e. pain or a negative relationship between the change in the hip flexor angle and the walk time was observed (table 6.8, figure 6.10c), That is people who *increased* their hip flexor angle more tended to walk for a *shorter* time.

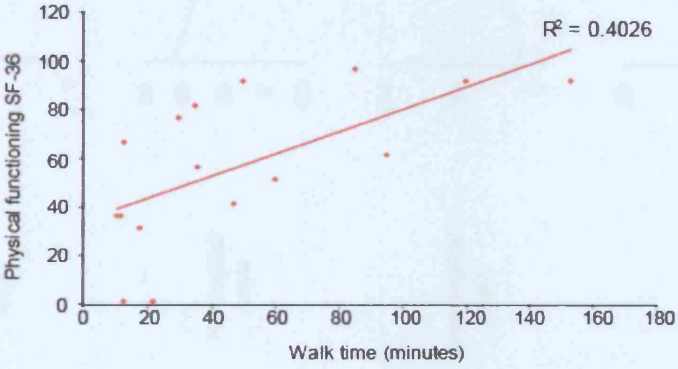
Walk time versus:	Correlation r value	P value
Change in hip flexor MVC	-0.50	0.11
Change in hip flexion angle in swing	-0.65	0.02
Change in hip flexion velocity in swing	-0.17	0.52

Table 6.8: Relationships between walking time and primary outcome measures.

(A)



(B)



(C)

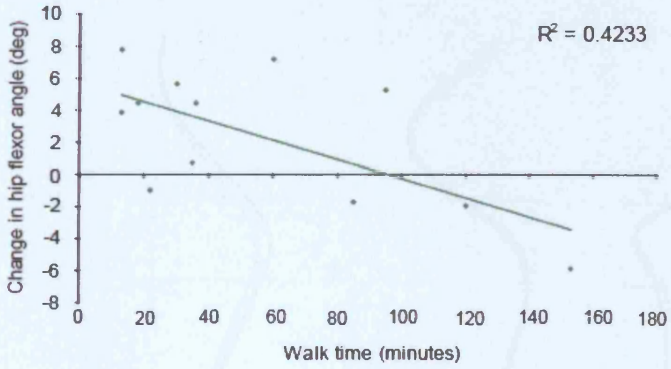


Figure 6.10: Correlations between treadmill walking time and (A) Fatigue Severity Scale (FSS), (B) physical functioning section of the SF-36, (C) change in hip flexion angle post walk - pre walk.

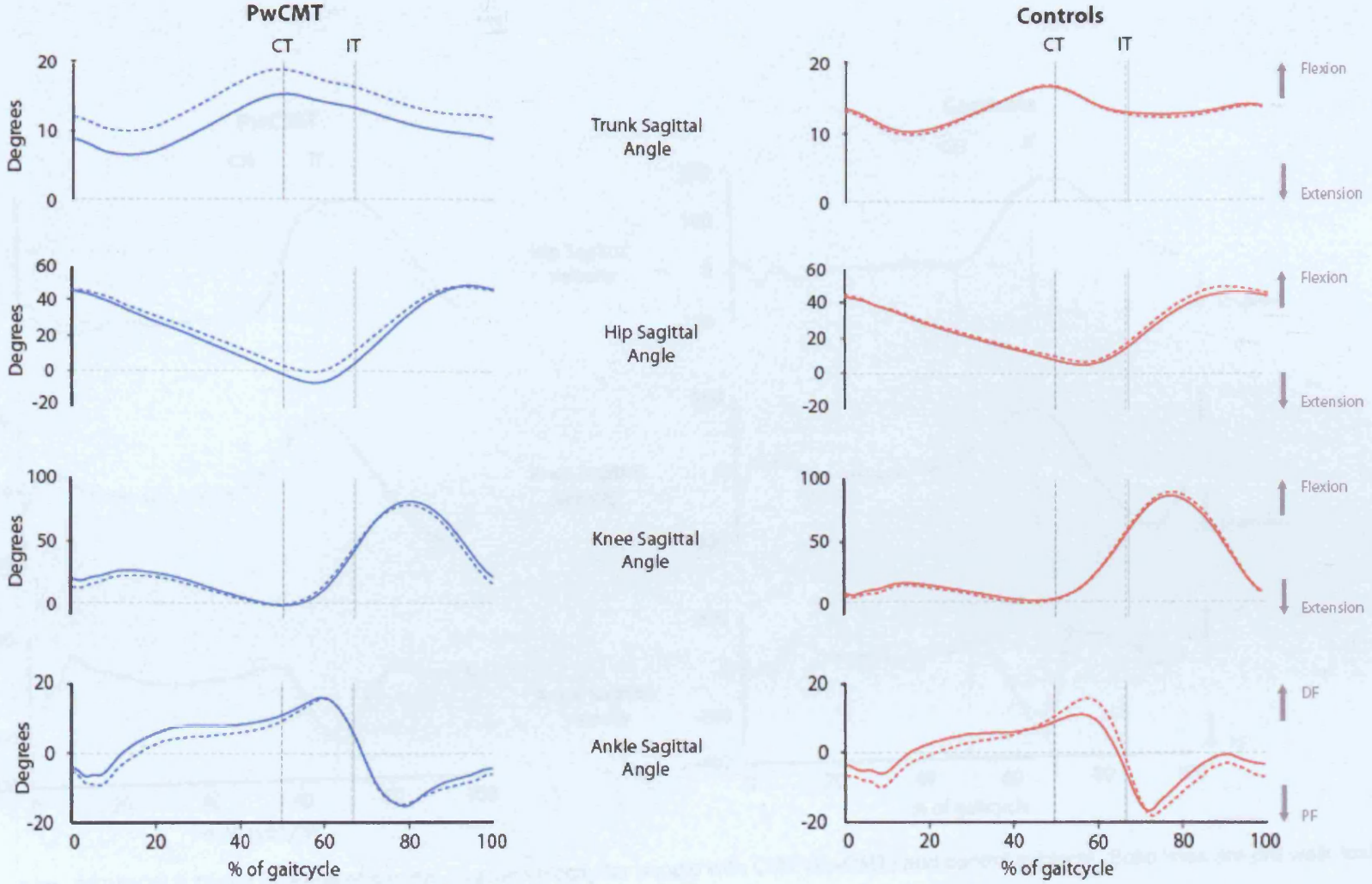


Figure 6.11: SESSION 1: Grand average of sagittal angular displacement for people with CMT (PwCMT) and control subjects. Solid lines are pre walk test and dashes lines are post walk test

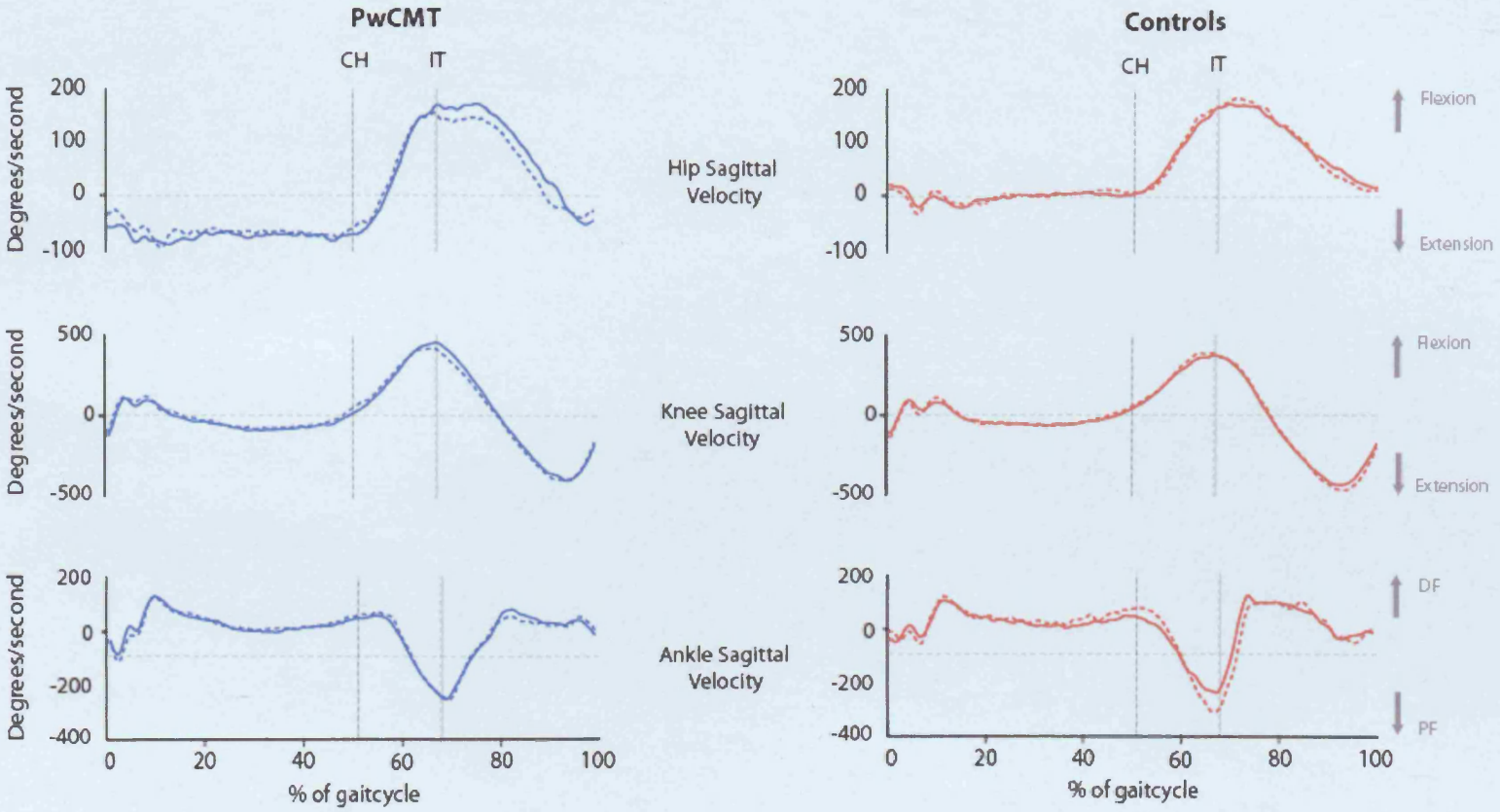


Figure 6.12: SESSION 1 Grand average of sagittal angular velocity for people with CMT (PwCMT) and control subjects. Solid lines are pre walk test and dashes lines are post walk test

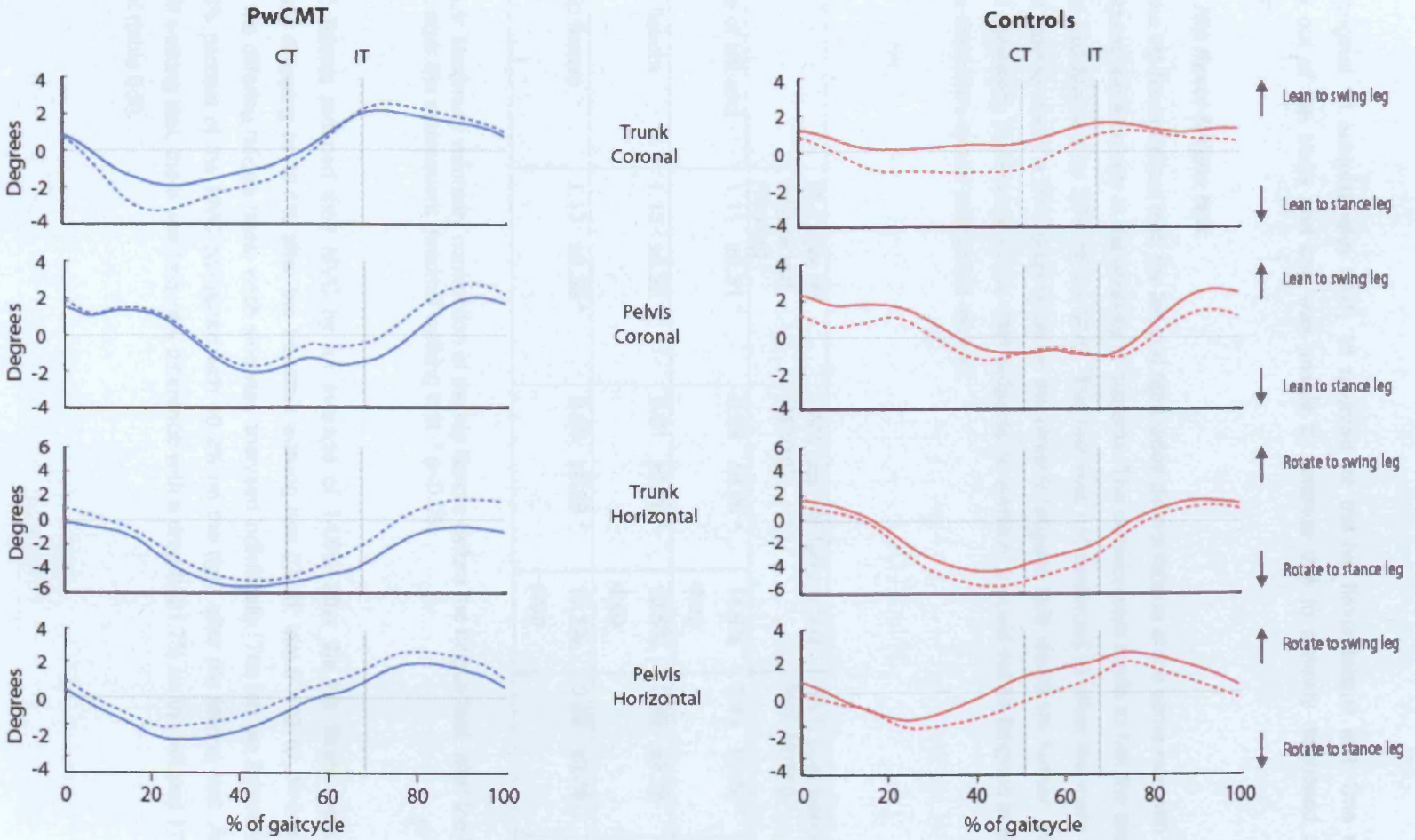


Figure 6.13: SESSION 1 Grand average of coronal and horizontal angular velocity of the trunk and pelvis for people with CMT (PwCMT) and control subjects. Solid lines are pre walk test and dashes lines are post walk test

6.3.2 Session 2: Hip Flexor Fatigue Test

Of the original 18 subjects with CMT, 16 returned for the hip flexor fatigue test. One subject dropped out of the study and one was unable to continue due to a newly diagnosed cardiac condition.

6.3.2.1 Hip flexor fatigue test

During the hip flexor fatigue test, the left and right sides did not fatigue at the same rate with the left side fatiguing more quickly in the majority of subjects. The decision was made to halt the test when one side had fatigued by 20% of the MVC. The test was not continued to allow the more fatigue resistant side to reach a 20% drop because the already fatigued side would tire further. This was deemed potentially detrimental to the CMT subjects. In addition, it could not be fatigued in isolation because the contra-lateral side would recover.

	MVC pre HF fatigue test (Nm/kg)	MVC post HF fatigue test (Nm/kg)		MVC post treadmill test (Nm/kg)	
Average of left and right	1.11 ±0.31 *	0.94 ±0.26 *	14.6% drop	0.86 ±0.28 *	19.6% drop
Left hip flexors	1.13 ±0.32 *	0.91 ±0.29 *	19.5% drop	0.85 ±0.29	21.7% drop
Right hip flexors	1.13 ±0.36 *	0.99 ±0.28 *	10.1% drop	0.88 ±0.36	17.2% drop

Table 6.9: Maximum voluntary contraction of the hip flexors before the fatigue teat, after the fatigue test and after the subsequent treadmill walking test. * $p<0.05$.

The hip flexors reduced their MVC by an average of 14.6% after the hip flexor fatigue test, eventually dropping to 19.6% after the treadmill walking test (GLM: trial $F = 13.16$, $P=0.0002$). In view of the differing fatigue rates, each side was analysed individually. The left hip flexors fatigued by 19.5% percent of the MVC compared with 10.2% on the right after the fatigue test. After the treadmill walking test, there was less of a difference with a drop to 21.7% on the left and 17.2% on the right (table 6.9).

6.3.2.2 General gait comparison

Following the hip flexor fatigue task, people with CMT walked on the treadmill for a mean time of 26 minutes. This was significantly less than the mean time of 48 minutes in session 1 (t =2.077, P=0.047). The median perceived exertion at the start of the walking test was level 11 of the Borg scale. At the end of the walking test it was 17.

6.3.2.3 Primary kinematic comparison

Kinematic hip variables varied according to the trial condition. Peak hip flexion significantly increased when measured immediately after the fatigue test and subsequently during the walking test (GLM: trial F =4.73, P=0.02; post hoc: post test1 v post test2: t =2.29, P=0.04) (figure 6.15). In view of the asymmetrical fatigue rate, the left and right sides were also analysed separately. The left hip did not show a significant change with the trial conditions (GLM: trial F =2.81, P=0.07). The right hip, however, showed a significant increase in flexion after both the fatigue and treadmill tests (GLM: F =6.02, P=0.006; post hoc: post test1 v post test2 t =2.32, P=0.03).

	Pre HF fatigue test	Post HF fatigue test	Post treadmill test
Average peak hip flexion angle swing (degrees)	34.09 ±12.01	39.94 ±12.43	44.54 ±14.93
• Left hip flexion swing	34.03 ±13.29	38.15 ±14.08	44.64 ±20.24
• Right hip flexion	34.16 ±11.76	41.75 ±11.91	44.43 ±13.53
Average peak hip flexion velocity swing (degrees/sec)	154.93 ±29.18	153.20 ±27.93	145.55 ±28.31
• Left hip flexion swing	164.15 ±38.96	147. 38 ±30.82*	141.08 ±32.63
• Right hip flexion	145.72 ±27.91	159.00 ±44.13	150.02 ±33.24

Table 6.10: Change in primary kinetic variables. Average of the left and right hip flexors and mean values for each side ± standard deviation. * significant difference between pre HF fatigue and post HF fatigue test.

The peak hip flexor velocity did not show any change with trial condition (GLM: trials F =1.08, P=0.35) (figure 6.16). Again, in view of the asymmetrical fatigue rate of the hip flexors each side was analysed individually. The left hip showed a significant reduction in hip flexor velocity during swing after the hip flexor fatigue test (GLM: trials F =6.92, P=0.003; post hoc: pre test v post test1 t =-2.18, P=0.046). No further change was seen after the treadmill test and no change was observed with the right hip (GLM: F =0.97, P=0.38).

6.3.2.4 Secondary comparison

The secondary comparison revealed differences in other kinematic variables following hip flexor fatigue or with subsequent walking. Peak knee flexion angle during swing phase increased after the hip flexor fatigue test but did not change any further after the treadmill test (GLM: trial F =3.69, P=0.04; post hoc: pre test v post test1 t =-2.44, P=0.03) (figure 6.15) but the GLM was not significant post modified Bonferroni correction.

	Pre HF fatigue test	Post HF fatigue test	Post treadmill test
Peak knee flexion angle swing (degrees)	54.07 ±11.51	56.71 ±12.83*	57.09 ±13.26
Peak trunk flexion angle pre-swing (degrees)	9.08 ±6.45	11.26 ±5.82*	12.50 ±4.43
Peak to peak coronal trunk (degrees)	4.94 ±5.17	5.59 ±5.55	6.59 ±6.13†
Peak to peak horizontal trunk (degrees)	10.33 ±8.10	10.74 ±8.13	12.55 ±6.90†

Table 6.11: Significant changes in secondary kinetic variables. Average of the left and right hip flexors and mean values for each side ± standard deviation. * significant difference between pre HF fatigue and post HF fatigue test; † significant difference between pre HF fatigue and post walking test.

Increased trunk flexion during pre-swing was observed following the hip flexor fatigue test but did not change after the treadmill test (GLM: F =4.96, P=0.01; post hoc: pre v post1 t =4.34, P=0.0006) (figure 6.15). The GLM was non-significant post Bonferroni correction so this observation was a trend despite the change following the hip flexor fatigue test. There were also changes in trunk coronal and horizontal motion. Coronal trunk motion significantly increased after the fatigue test plus the treadmill test (GLM: F =9.70, P=0.0006; post hoc: post1 v post2 t =2.79, P=0.01). A similar pattern was seen for the horizontal motion of the trunk (GLM: F =7.55, P=0.002; post hoc: post1 v post2 t =2.45, P=0.03) (figure 6.17).

6.3.2.5 Reasons for walking cessation

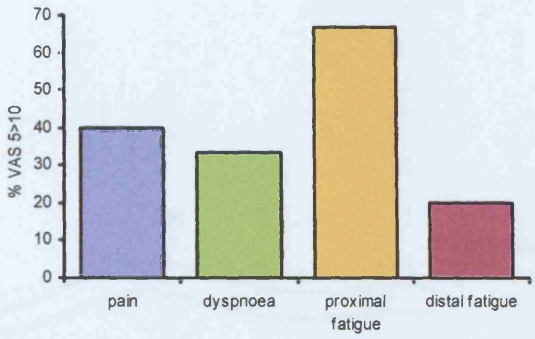


Figure 6.14: Graph of the percentage of subjects with visual analogue scores rated over five out of ten. Visual analogue scores were rated for pain, dyspnoea, proximal and distal fatigue.

People with CMT were asked what factors caused them to stop walking during the treadmill test. Seventy five percent of subjects reported stopping due to fatigue of the legs and a deterioration of their gait pattern. Pain was the reason reported by 19% and 6% stopped because they were breathless. Visual analogue scores taken after the treadmill walking test showed proximal fatigue was most highly rated symptom with 66.67% of subjects scoring over five out of ten (figure 6.14).

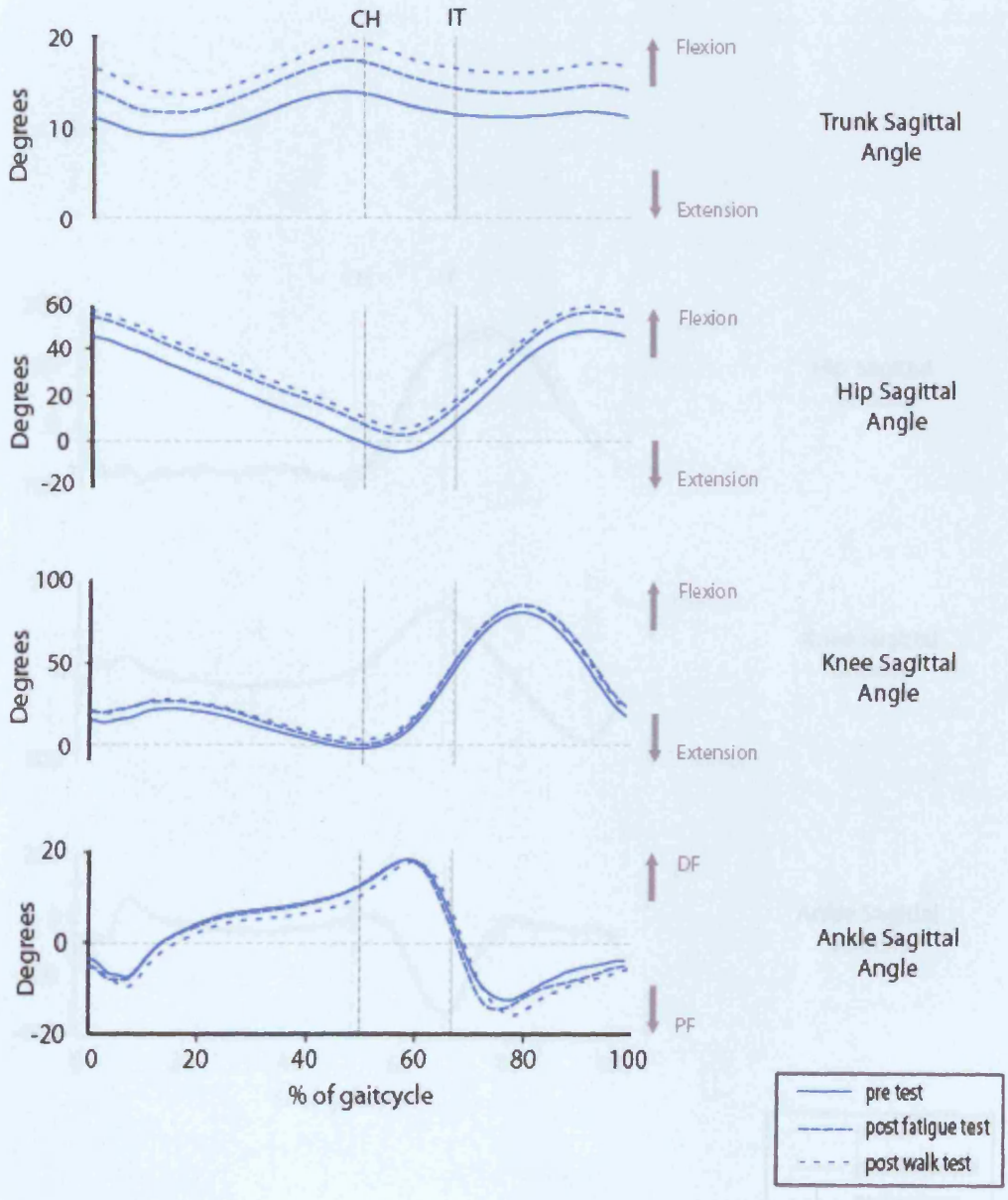


Figure 6.15: SESSION 2 Grand average of sagittal angular displacement for people with CMT. Solid lines are pre walk test and dashes lines are post hip flexor fatigue test, dotted lines are post treadmill walking test

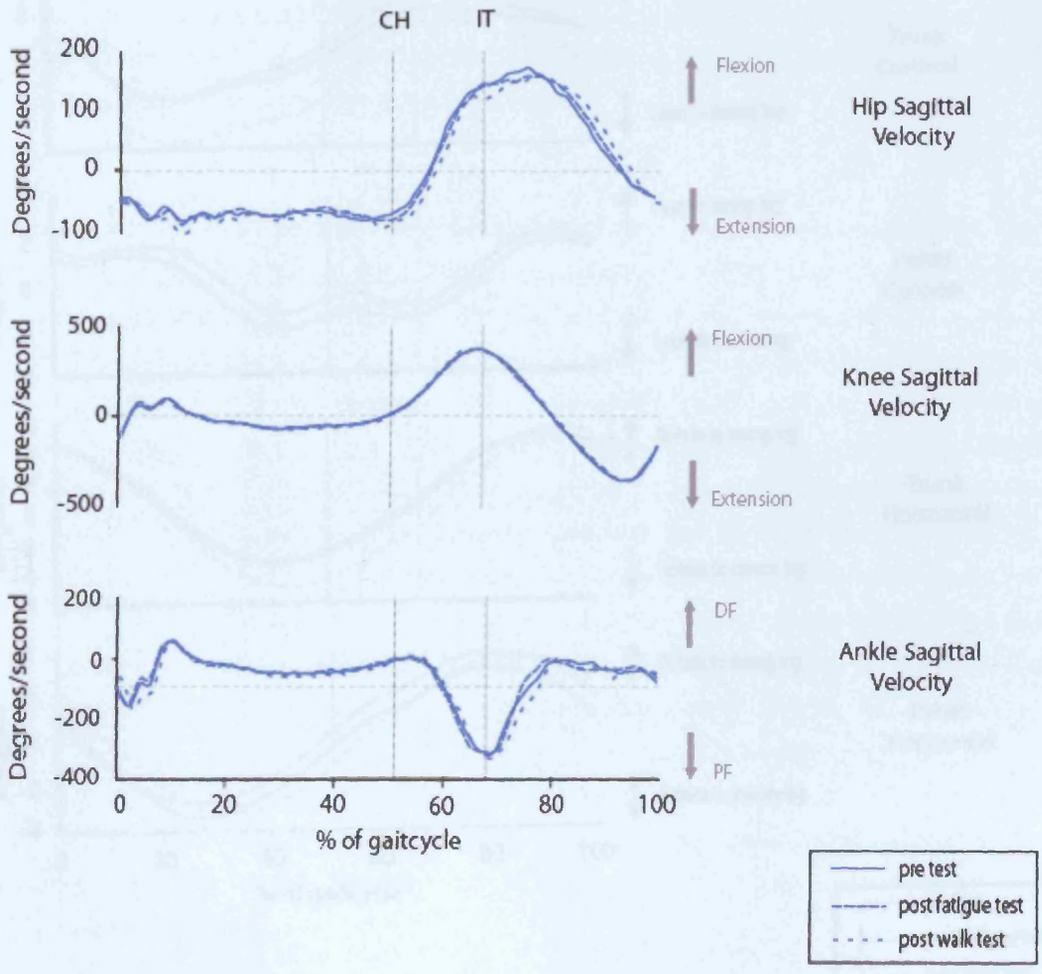


Figure 6.16: SESSION 2 Grand average of sagittal angular velocity for people with CMT. Solid lines are pre walk test and dashes lines are post hip flexor fatigue test, dotted lines are post treadmill walking test

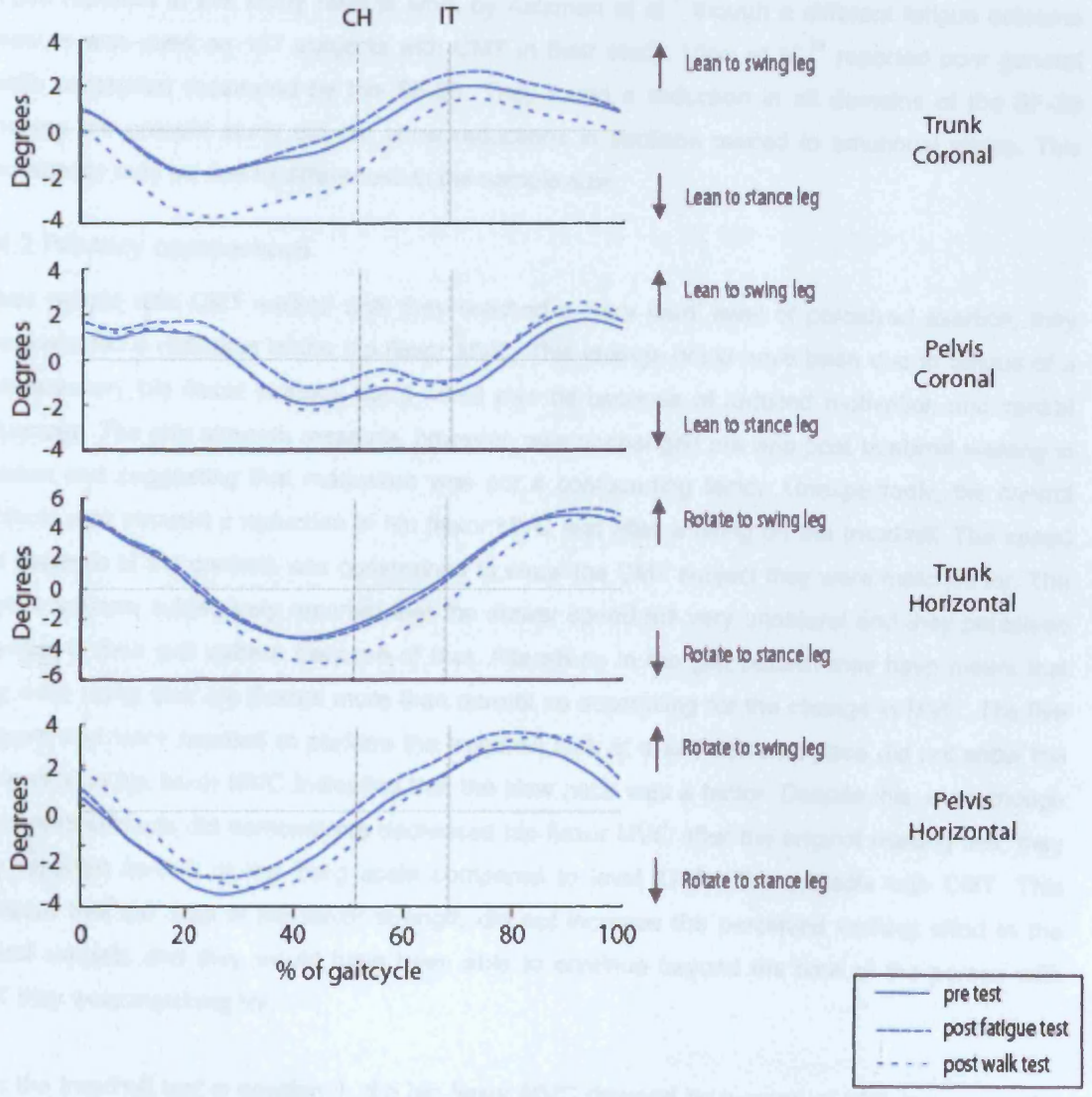


Figure 6.17: SESSION 2 Grand average of coronal and horizontal trunk angular displacement for people with CMT. Solid lines are pre walk test and dashes lines are post hip flexor fatigue test, dotted lines are post treadmill walking test

6.4 Discussion

6.4.1 Group differences

As expected, people with CMT showed greater weakness and sensory loss distally compared to healthy control subjects. Interestingly, despite reports of de-conditioning in CMT in the literature, there were no differences in the cardiorespiratory measures. This probably reflects that the measures used do not give a valid indication of fitness levels. More thorough exercise testing with an analysis of oxygen consumption would be required to make a judgement on differences between the two subject groups.

The fatigue severity scale and SF-36 revealed findings consistent with previous literature. Increased fatigue reported in this study reflects work by Kalkman et al [7] though a different fatigue outcome measure was used on 137 subjects with CMT in their study. Vinci et al [18] reported poor general health perception measured by the SF-36. They found a reduction in all domains of the SF-35 whereas the present study did not show reductions in sections related to emotional status. This discrepancy may be due to differences in the sample size.

6.4.2 Primary comparison

When people with CMT walked until they reached a 'very hard' level of perceived exertion, they demonstrated a reduction of the hip flexor MVC. This change could have been due to fatigue of a compensatory hip flexor strategy but it could also be because of reduced motivation and central influences. The grip strength measure, however, was unchanged pre and post treadmill walking in session one suggesting that motivation was not a confounding factor. Unexpectedly, the control subjects also showed a reduction in hip flexor MVC test after walking on the treadmill. The speed and cadence of the controls was constrained to equal the CMT subject they were matched for. The control subjects subjectively reported that the slower speed felt very unnatural and they perceived changes in their gait pattern because of that. Alterations in the gait pattern may have meant that they were using their hip flexors more than normal so accounting for the change in MVC. The five subjects that were recalled to perform the treadmill task at a self selected pace did not show the same drop in hip flexor MVC indicating that the slow pace was a factor. Despite this, even though the control subjects did demonstrate decreased hip flexor MVC after the original walking test, they only reported level 8 of the Borg scale compared to level 17 for the subjects with CMT. This indicated that the drop in hip flexor strength did not increase the perceived walking effort in the control subjects and they would have been able to continue beyond the time of the person with CMT they were matching for.

After the treadmill test in session 1, the hip flexor MVC dropped by a mean of 20% in people with CMT. In session 2 the asymmetrical fatigue rate of the hip flexors initially was deemed a problem, but analysis of the left and right sides was actually revealing. The left side demonstrated

approximately a 20% drop in hip flexor MVC and also demonstrated some of the proximal kinematic changes observed in session 1. At the end of the treadmill test in the first session, the velocity of hip flexion reduced. This was also seen on the left side after the hip flexor fatigue test in session 2 and did not reduce further with the subsequent treadmill test. These findings implicate fatigue of the hip flexors as the cause of reduced hip velocity. Interestingly, the right side that only fatigued by 10% did not show these changes indicating a possible threshold of hip flexor strength required to maintain hip kinematics over time.

The hip flexor muscles are thought to work synergistically with gastrocnemius to accelerate the limb from pre-swing into swing phase [13, 20]. The control subjects do not show this drop in hip velocity perhaps because the intact gastrocnemius assisted the acceleration of the limb and modelling studies have indeed shown that the plantarflexor muscles may compensate for proximal impairments [6]. Therefore, it is likely that, in healthy subjects, distal compensation prevented a reduction in velocity of hip flexion (see section 6.4.3). If the plantarflexors are weak, as in CMT, the hip flexors may not have the synergistic assistance from gastrocnemius and fatigue prematurely.

During session 1, people with CMT showed an increase in the hip flexion angle during swing phase that was also observed in control subjects. The increase in hip flexion may have been a compensation for foot drop (see chapter 3) that became exaggerated as the person fatigued and tripping was a higher risk. The ankle amplitude graph (figure 6.11) suggests a trend towards a reduction in dorsiflexion in mid to late swing phase that may support this, though the difference was not significant on testing. This increase in flexion, however, seems counterintuitive as a reduction would be expected in view of the reduction in hip velocity. The correlation analysis may offer an explanation. Figure 6.9c shows that although the majority of subjects increased hip flexion others decreased it as indicated by the negative values. The subjects who decreased hip flexion amplitude tended to be those who walked for much longer, i.e. over one hour. The positive correlation between fatigue severity and walking time suggests that subjects that walk for the shortest time are limited by central factors and may still have the capacity to increase hip flexion (e.g. to aid with foot clearance). In contrast the subjects who walk for the greatest time were more likely to be limited by physical factors and show a reduction in hip flexion amplitude. Results from session 2 support this showing that after both the fatigue and treadmill tests, the less fatigued right hip showed a significant increase in hip flexion. The more fatigued left hip showed no change.

6.4.3 Secondary comparison

Distal differences were seen with the treadmill walking test but these changes were primarily in the control group. Changes in ankle motion and velocity could represent distal compensatory strategies employed by the control subjects as the hip flexor muscles fatigued. No change was observed in people with CMT which could be an indication that they are unable to compensate distally due to

weakness of the ankle muscles. Consideration must also be given to possible restrictions in range as four subjects with CMT wore AFOs. While we cannot assume that a lack of change in ankle motion is due to entirely to ankle weakness, the majority of subjects did not wear AFOs and changes were not observed.

Changes at the knee were seen in control subjects. They tended to increase the peak knee flexion angle during swing phase whereas people with CMT did not change significantly. The degree of knee flexion in swing phase is related to the peak knee velocity during preswing. This in turn is determined by momentum from rapid hip flexion and ankle plantarflexion and the activity of the biceps femoris [12]. As was discussed in the previous section, hip flexor velocity increases in control subjects so the increase in knee flexion is probably due to increased momentum from hip flexion. Although not significantly different, there is a trend towards reduced knee angle in people with CMT (figure 6.6b) which could be due to reduced hip velocity and thus reduced momentum. In session 2, however, an increase in knee flexion is seen after the hip flexor fatigue test. It may be that with prolonged walking in session 1 there is not only fatigue in the hip flexors but also in other muscle groups such as the hamstrings. In session 2 only the hip flexors are fatigued so the hamstrings may still able to increase knee flexion. It is possible that the increase in knee flexion during swing phase is to compensate for altered hip motion to assist foot clearance.

In addition to increased hip flexion during swing, people with CMT and control subjects also show a decrease in hip extension during pre-swing. At the start of the test people with CMT show greater hip extension than control subjects. This may be because the dorsiflexion angle at pre-swing is increased in people with CMT due to decreased eccentric plantarflexor control (chapter 3) resulting in a collapse forward of the extended limb at the ankle. This would result in increased hip extension. The change that occurs after the walking test could be due to differences at the trunk rather than the leg as the hip angle is defined by the trunk and thigh segments. An increase in trunk flexion is observed, particularly in people with CMT, which would also be reflected in the hip angle as there was no significant change in the angle of the thigh with respect to vertical.

A trend towards increased trunk flexion is seen in people with CMT following the treadmill test (session 1). In session 2 a similar increase in trunk flexion after the hip flexor fatigue test was observed that did not increase further with the subsequent treadmill test. Although not significant following modified Bonferroni correction the grand average graphs indicate an increase in trunk flexion throughout the gait cycle so supporting this as a real finding and not a false positive result (figures 6.11 and 6.15). Thus an increase in trunk flexion seems to occur when the hip flexors are fatigued. It is possible that this is another level of compensatory strategy employed when the hip strategy fails through fatigue. It could be argued that increased trunk flexion is due to a stooped posture adopted due to general fatigue as the subject reaches Borg 17. Results from session 2

refute this, as the increase in trunk flexion was seen immediately following the hip fatigue test when the Borg was 11.

If we assume that the hip flexor strategy primarily assists limb progression, as discussed earlier, then it is possible that trunk flexion is a secondary strategy that assists limb progression when the hip flexor strategy starts to fail. Studies of trunk motion during walking have suggested that a 'trunk leading' strategy is a way of using the heavy trunk segment to direct movement of the lower body by pulling the leg into swing phase [10]. Due the increased motion of the heavy trunk segment the strategy may be more costly and less efficient than the hip flexor strategy hence the walking time was almost halved in session 2.

An increase in coronal trunk motion was observed after treadmill walking in both sessions, but did not occur after the hip flexor fatigue test in session 2. The analysis in chapter 3 did not definitively reveal why people with CMT have increased trunk motion in the coronal plane though the relationship with plantarflexor stiffness may indicate that it is related to foot clearance. Coronal motion did not increase after specific hip flexor fatigue so it may be a consequence of fatigue of other muscle groups e.g. the dorsiflexors. Horizontal trunk motion also increased in session 2 at the end of the treadmill test. In chapter 3 horizontal trunk motion was related to plantarflexor strength so it is possible that it occurs in session 2 due to distal fatigue, though plantarflexor MVC was not measured in this session to verify this. In view of the synergistic action of the plantarflexors and hip flexors this situation, where the hip flexors are fatigued, may have increased the demand on the weak plantarflexors to maintain limb progression. This may have resulted in increased fatigue by the end of the walking test that was compensated for by an increase in horizontal trunk motion.

6.4.3 Reasons for walking cessation

The changes in hip kinetics may indicate that fatigue of a hip flexor strategy limits walking and indeed the majority of people with CMT reported moderate to severe proximal leg fatigue and stopped because of leg weakness. The correlation analysis, however, indicated that factors other than physical impacted on walking time. No correlation was seen between the drop in hip flexor MVC and the time spent walking on the treadmill. Subjects' perception of fatigue and physical limitation did appear to have a significant influence on walking endurance in people with CMT. Both the FSS and SF-36 are multi-dimensional scales that reflect more than local muscle fatigue. Chronic fatigue that occurs independent of local muscle fatigue has been reported in other long term conditions such as multiple sclerosis and chronic demyelinating polyneuropathy. Increased central activation failure has been reported in a cohort of people with CMT measured by superimposed electrical stimulation during MVC contractions [15]. The central activation failure correlated positively with reported fatigue severity so supporting the assumption that fatigue reported by people with CMT is due to central factors rather than peripheral muscle fatigue.

It is likely that the limitations to walking endurance are due to a number of factors that vary with individuals. There are indications that people who report high fatigue severity are limited by central factors whereas people with low fatigue severity walk further and are limited by local muscle fatigue. These factors should be considered when physiotherapy intervention is aimed at improving walking endurance.

6.4.4 Clinical Implications

A deterioration is seen in hip kinematics and strength with prolonged walking in people with CMT. In order to prolong functional walking distances training the proximal muscles, perhaps specifically the hip flexors, may enable people with CMT to compensate for distal weakness for longer periods of walking.

In view of the link between walking endurance and fatigue severity, approaches that have been shown to influence fatigue in other chronic conditions could be successfully employed, for example general aerobic exercise and drug therapy.

6.4.5 Future work

This study implicates fatigue of the hip flexors as a limiting factor of prolonged walking. Fatigue of muscles will occur simultaneously and could be more influential on walking endurance, e.g. quadriceps or hamstrings, but the present study did not investigate this. The number of muscles that could be measured pre and post walking was limited due to recovery on cessation of walking. In view of the results from chapter 3, which suggest increased activity of the knee musculature, a repeat study focusing on the knee extensors and flexors would be useful.

If, as the present study suggests, hip flexor fatigue is a factor affecting walking endurance, then a training study would be useful. Training regimes could be compared for efficacy e.g. a regime to improve peak strength of the hip flexors versus endurance training. Some caution must be given with resistance training as concerns have been expressed about overwork weakness in CMT [17] though the evidence for this is limited. Previous studies of moderate resistance exercise in CMT have not shown a deterioration in strength measures [2, 9].

The subjects who had the most limited walking endurance were the most fatigued, as measured by fatigue severity scales. The impact of a general exercise approach would be of clinical interest. Aerobic training has been found to reduce fatigue in some studies of people with multiple sclerosis [11, 14]. If aerobic training reduces fatigue in people with CMT who report severe levels of fatigue this may have a greater impact on walking endurance than strengthening proximal muscles. A study investigating the impact on fatigue, general health perception and walking endurance would useful with a post hoc analysis to see if indeed the most fatigued people respond best to this approach.

6.5 Summary

- When walking on a treadmill people with CMT took a mean of 48 minutes to reach Borg level 17. Control subjects performing the exact same walking task only reported a Borg level of 8.

- After the walking test, the maximum voluntary contraction of the hip flexors reduced in both groups. People with CMT also demonstrated a reduction in hip velocity and an increase in trunk motion within the coronal and sagittal planes. Both groups showed an increase in hip extension during pre-swing and hip flexion during swing.

- When the hip flexors were specifically fatigued people with CMT were only able to walk for a mean of 26 minutes. The left and right sides did not fatigue symmetrically. The hip flexion velocity decreased for the more fatigued left side and increased sagittal plane trunk motion occurred. An increase in hip flexion occurred in the less fatigued right hip but did not change in the more fatigued left hip.

- Fatigue severity, physical functioning sections of the SF-36 and the change in hip flexion angle correlated significantly with the total treadmill walking time.

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7 Overview

This chapter gives an overview of the main findings of the four studies presented in chapters 3 to 6. The conclusions of each experiment are examined side by side and compared to the original hypothesis of the thesis stated at the end of chapter 1.

7.1 Aims of the thesis

This thesis aimed to test the theory that during preswing, hip flexor action increases to compensate for weakened plantarflexor activity to continue forward progression of the trunk and lower limb. Until recently, there were no in depth studies of gait in people with CMT and this theory originated from studies of people with stroke and peripheral neuropathy. The hypothesis for this study assumed that such theories could be extrapolated to people with CMT due to the presentation of common impairments such as distal weakness and sensory disturbance.

Four approaches have been utilised to explore the existence and impact of these theorised strategies in people with CMT. Firstly, the kinematics and kinetics of the gait pattern were examined and compared with physically matched controls (chapter 3). Relationships between presenting impairments and gait deviations in people with CMT were considered and an attempt was made to look for potential differences in the two main disease types. The next study attempted to replicate, in healthy subjects, one of the key distal impairments that present in people with CMT and to explore the compensatory strategies employed (chapter 4). In people with CMT, distal gait deviations were altered using external, below knee orthotic devices to see if this caused any change to proximal gait variables (chapter 5). Finally, the impact of the theorised hip flexor strategy on walking endurance was considered with a study of prolonged walking on a treadmill (chapter 6) and the effects of isolated hip flexor fatigue on walking endurance assessed.

The main methods used were biomechanical analysis of gait. The kinematics and kinetics (in chapters 3-5) were analysed to make inferences about muscle contributions to gait variables. This did not include EMG analysis due to difficulty recording from the ilio-psoas muscle group and it was felt that rectus femoris recordings would not represent the action of the hip flexors as it is known to have a different function [31, 33]. In addition to the traditional gait analysis methods, motion of the trunk was also monitored. This has not been considered in other detailed studies of walking in people with CMT but trunk deviations have been described in descriptive studies [41] and some suggest that it is utilised to progress the centre of mass [43 11].

7.2 Summary and interpretation of findings

7.2.1 Temporal and spatial differences

People with CMT demonstrate reduced gait speed, step length, cadence and increased double support time compared to age, gender, height and weight matched controls walking at a self selected pace. These variables correlated with distal muscle strength, particularly the plantarflexors, and compliment the results of other studies of neurological conditions [29, 37, 40, 50].

The experimental designs of chapters 4 and 6 did not allow a comparison of these parameters in healthy subjects with plantarflexor fatigue or people with CMT after prolonged walking. In both studies subjects subjectively reported increased effort to maintain the temporal and spatial constraints after fatigue which was quantitatively expressed in the walking endurance study.
In chapter 4, despite increased effort, healthy subjects were still able to maintain the target parameters. Although this may not have been their maximal speed, if unconstrained, it may have been faster than what they would have adopted as their self selected pace [38].

It was interesting that there was no improvement in these variables with the application of AFOs despite the improvement in dorsiflexion angle. Some authors suggest that reduced gait speed is a compensatory strategy in itself [26, 30]. If this is the case in people with CMT it will be a strategy developed insidiously with the slow deterioration of distal muscle strength over time. As a result, the changes brought about by the AFOs may not have impacted on these compensations immediately but may alter over time. An alternative explanation for the lack of effect of the AFOs is that their main effect is to improve dorsiflexion angle. Dorsiflexion strength is correlated with gait speed, cadence and dorsiflexion angle in swing phase. The correlation with gait speed and cadence, however, could be an incidental correlation rather than causative due to the strong correlation between plantarflexion and dorsiflexion strength. If this is so, changes in dorsiflexion angle by the AFOs would not be expected to alter these variables.

The Multifit AFO, however, did increase double support time. Logically this could be explained by the reduction in ankle power production when this splint was worn supported by the relationship between plantarflexor strength with ankle power production and plantarflexor strength with double support time.

7.2.2 Distal differences related to propulsion

People with CMT presented with increased distal weakness, sensory loss and a high incidence of pes cavus and calcaneal varus. Compared to matched controls they demonstrated reduced peak and delayed ankle power generation that correlated with distal muscle strength. In the weaker group of people with axonal degenerative CMT there was an additional reduction in heel rise. This same reduction in plantarflexor power generation was not observed in control subjects whose

plantarflexor muscles were fatigued by 25% of their MVC, though the ankle did move through less plantarflexion range. This was thought to be because there was still sufficient reserve in the plantarflexors to produce enough power to maintain cadence and step length. In addition, no change in ankle kinematics at preswing were observed when people with CMT walked to fatigue on the treadmill plus no change in plantarflexor MVC when tested after walking. This indicates that plantarflexor fatigue was not key in maintaining walking or limiting walking in these subjects.

When AFOs were applied there was a significant increase in stiffness of the ankle. Increased stiffness did not increase the plantarflexor moment in preswing as suggested by previous authors [28, 40, 42]. In fact one of the stiffer devices had a detrimental effect with a reduction in ankle power generation. This was probably because of the energy storage and release properties of the material it was constructed from.

7.2.3 Proximal differences related to propulsion and progression

The ankle plantar flexors work synergistically with proximal muscles during preswing to progress the trunk and leg. Soleus is the primary muscle involved in forward progression of the trunk but rectus femoris also works eccentrically to transfer energy to the trunk as it decelerates the leg [33, 51]. The gastrocnemius muscle works with the uni-articular hip flexors to initiate swing and accelerate the leg, progressing it from preswing to swing [32, 33, 51]. An increase in hip kinetics has been reported in people with plantarflexor weakness to ensure sufficient trunk and limb progression [13, 28, 29, 35].

People with CMT do not demonstrate a clear increase in preswing hip kinetics as described in other patient populations [28, 36]. Despite no change in hip kinetics in chapter 3, the results from chapter 6 do indicate that the hip flexors are prematurely fatigued by prolonged walking in people with CMT. A reduction in hip velocity is observed and a drop of 20% of the MVC is seen in this group after walking on the treadmill until perceived exertion is "very hard". So why would they fatigue prematurely when there is no increase in hip kinetics? As seen in chapter 3, there is a delay in the onset of ankle power generation which results in generation of hip power before the onset of ankle power generation. In the control group the reverse was true in every subject. Thus in people with CMT, the hip flexors are active in initiating swing phase and progressing the lower limb without the synergistic assistance of the plantarflexors, particularly gastrocnemius [32]. The drop in knee extensor moment indicated a reduction in the decelerating action of rectus femoris on the limb. As a result, less force would be required to accelerate the limb. Normally gastrocnemius assists with initiating and propagating swing but in this situation delayed onset of ankle power generation means that the hip flexors initiate swing alone and have reduced assistance in accelerating the leg. Although less force is required to accelerate the limb, there is less assistance from gastrocnemius so this may be why there is no net change in hip kinetics. Meinders et al [25] supports this relationship between the three muscles by suggesting that the work done by eccentric knee extensor action is the difference between the net work of the leg and the positive work of the plantarflexors and hip flexors .

The other key finding of chapter 3, that has not been described before in people with CMT, was the increased motion of the trunk in the horizontal plane. Increased trunk rotation was inversely related to plantarflexor strength so it may be a compensation for reduced contribution of the ankle plantarflexors to propulsion of the body. Along with the unopposed, but unassisted, action of the hip flexors this may be sufficient for limb progression albeit slower than controls as indicated by reduced speed and step length. In support of this finding, horizontal rotation of the trunk has also been linked to maintenance of step length in studies of healthy subjects [43]. In the treadmill walking study, horizontal trunk motion did not change after specific fatigue of the hip flexors but it did increase after subsequent walking. If the strategy assisted limb progression it would be expected that there would be an increase when the hip flexors were less effective through fatigue. This could support the alternative possibility that this is a strategy to assist the role of the plantarflexors in progressing the trunk forwards, though there is no additional data to support this theory.

Flexion of the trunk was observed in healthy subjects with plantarflexor fatigue and in people with CMT with fatigue of the hip flexor muscles. It was not, however, observed in people with CMT while walking for a short duration at a self selected speed. It is possible that this was employed as a strategy when subjects had to walk at a faster pace than they would select themselves due to constrained gait speed/cadence/step length. Davies and Õunpuu [11] describe a single case of a healthy subject being asked to walk with a flexed trunk. They noted was a forward shift of the centre of gravity and movement of the hip into flexion due to increased anterior tilt of the pelvis. It is possible that when muscles that assist trunk and limb progression are fatigued, this strategy is employed in an effort to keep the trunk anterior of the centre of gravity shifting the onus on other muscle groups to control the 'forward fall'.

In addition to increased hip kinetics, healthy subjects with plantarflexor fatigue also seemed to use hip and knee extension in early stance to assist with trunk progression. The vasti and gluteus maximus have been implicated in facilitating trunk progression in early stance [13 51] and appear to be the main strategy in this case. The same strategy was not seen in people with CMT in this study though the study by Don et al [12] observed some similarities with increased knee extensor angular impulse later in stance in subjects with plantarflexion failure, defined by an inability to raise the heels off the ground more than 2 cm.

So why are the compensatory strategies for plantarflexor weakness in people with CMT and neurologically intact individuals different? In the study on healthy subjects, there was a rapid onset of plantarflexor weakness with the fatiguing task. As discussed, subjects appeared to use hip and knee extensor strategies in stance and a hip flexor strategy in preswing to maintain trunk and limb progression. When requested, the subjects were able to maintain the same temporal and spatial parameters but not the same kinematics post fatigue. All of these findings are remarkably similar to

a modelling study by Goldberg et al [13]. The subjects, however, were not tested over a prolonged period. The strategies may have changed with further walking as they may be inefficient, effortful or quick to fatigue.

In contrast, people with CMT experience a very slow reduction in plantarflexor strength. They show an increase in trunk horizontal rotation and reduced braking by the knee extensors during preswing as implied from a reduction in knee extensor moment. This strategy allows them to maintain the ability to walk but they cannot maintain the same speed, step length and cadence as matched controls indicating that they were unable to progress the trunk as effectively. Although people with CMT cannot walk for as long as intact control subjects, the strategies used may be more efficient and fatigue resistant than the adaptations used by healthy subjects with acute plantarflexor fatigue in chapter 4.

This could be explored with further investigation of healthy subjects. The fatiguing paradigm would not be a useful tool in a study of prolonged walking due to recovery. Plantarflexor action in preswing could be blocked, however, using an external device. We have seen in chapter 5 that certain AFOs have the potential to reduce ankle power generation at preswing so such a device could be used. Alternatively a tibial nerve block could be introduced that would ensure plantarflexor weakness for up to five hours. The other muscles supplied by the tibial nerve would also be affected, i.e. flexor hallucis longus, flexor digitorum longus, and tibialis posterior, and reduced sensation would occur on the plantar aspect. In severe CMT, these muscles are also weak and sensory loss is also present. As the purpose of this experiment would be to replicate CMT, not look at the action of the muscles in isolation, this may be a useful side effect. Another issue with this method is overflow of anaesthetic into the anterior compartment muscles causing foot drop. Again this could be a useful effect to see how long healthy subjects can use their compensatory strategies for the range of impairments found in people with CMT [46]. Healthy subjects could then walk on a treadmill for a prolonged period with monitoring of perceived exertion and either 2D kinematic analysis, as in chapter 6, or a before and after 3D kinetic and kinematic analysis. It would be interesting to see if there is a change in their compensatory strategies over time, how long they can walk for and how their perceived exertion compares to matched people with CMT.

7.2.4 Proximal differences related to foot clearance

Don et al [12] attributed their observation of increased hip impulse at preswing as a compensation for foot drop during swing leading to an increased hip flexor angle. They split their group of people with CMT in to a group with just foot drop and a group with foot drop and plantarflexor failure and found an increase in angular impulse in the former group. Data from chapter 3 of this thesis showed increased hip flexion in people with CMT that indeed correlated with reduced dorsiflexor angle but there was no accompanying increase in hip kinetics. Control subjects in chapter 4 did show a change in hip kinetics at preswing but this was when the plantarflexors were weakened. The

dorsiflexor muscles were not weakened by the fatigue protocol so would not have contributed to the proximal changes at the hip. This finding disputes the suggestion of Don et al [12] and is supported by modelling studies [13] which also surmise that increased hip kinetics at preswing are due to plantarflexor weakness at preswing push off and not dorsiflexor weakness.

So if people with CMT raise the thigh through hip flexion to clear a dropped foot, but no increase in hip kinetics is seen, what strategy is employed to do this? Data from chapter 3 demonstrated a burst of knee power generation at preswing that was not present in control subjects. Studies of healthy subjects walking over obstacles also demonstrate this kinetic feature [34, 39]. The authors attribute this power burst to knee flexor activity causing flexion of the hip and knee through the action of inter-segmental forces. Indeed Don et al [12] reported a burst of biceps femoris EMG activity in people with CMT at around this time which was greater in the group with foot drop and could represent this compensation, though the absence of joint power data does not allow a direct comparison.

Coronal motion of the trunk may be a strategy employed to assist foot clearance in people with CMT. It relates to plantarflexor stiffness which could suggest a link with reduced dorsiflexion range in swing. Prolonged walking on the treadmill revealed an increase in coronal motion when the hip flexion velocity was reduced suggesting that it compensates for a reduction in the hip flexor strategy as a secondary adaptation. With specific fatigue of the hip flexors, coronal trunk motion did not increase when one hip was fatigued to 20% but emerged when they both were.

An interesting finding from the AFO study, chapter 4, was that reducing foot drop did not change the hip flexor angle or any other proximal variables. In a similar argument for the lack of temporal and spatial changes, it was probably because measurement was taken within a few minutes of applying the AFO. People with CMT will have slowly developed their gait pattern as the disease progressed so changing established strategies may require a longer period wearing the AFO. In addition, the clinical measures showed that there was a significant reduction in proprioceptive perception in people with CMT so there may have been reduced awareness of the change in joint angle.

7.2.5 Distal differences related to support

Other distal differences between healthy subjects and people with CMT seemed to relate to support of the lower limb in stance phase. The most prominent distal finding was an increase in the dorsiflexion angle at the end of stance, prior to preswing. This was primarily attributed to decreased eccentric control of the shank by the plantarflexor muscles. Several studies have investigated the role of the plantarflexor muscles in the control of the ankle rocker which support this supposition [2, 13, 15, 16]. Applying splints to stiffen the ankle did not significantly alter that variable but this was probably because the AFOs studied were not rigid enough as it has been described in other studies that investigated rigid AFOs. No increase in forward motion of the shank was observed in healthy

subjects with plantarflexor fatigue despite changes in proximal kinetics during stance. This may be because post fatigue they were not as weak as the people with CMT and were able to control the ankle position sufficiently.

On loading and through stance the ankle was supinated in people with CMT. A modelling study has examined the effect of tibial torsion on the function of the soleus muscle and found a reduction in body centre of mass support and propulsion [44]. In addition to plantarflexor weakness, tibial torsion and knee valgus occurs in people with CMT due to excessive foot supination. Calcaneal deformity may also change the axis of the subtalar joint and foot deformity will also change the length and weight of the shank and foot segments [46]. It is possible that these problems with alignment were also contributing to reduced control of the shank by soleus because of what Schwartz and Lakin [44] term *lever arm dysfunction*.

7.2.6 Proximal differences related to support

On loading there was an increase in knee flexion in healthy subjects with plantarflexor fatigue. A corresponding increase in hip extensor moment was seen that was likely to be a strategy to control this. The finding is in keeping with the findings of Goldberg et al [13]. In people with CMT there was only a trend to this increase in knee flexion and there were no other proximal changes associated with it. This discrepancy could be due to differences in gait speed. As has already been mentioned, slower gait speed could be a primary compensatory strategy in people with CMT that would reduce the destabilisation of the segments as the centre of mass moves over the foot [25] . Conversely, the observation of an increase in knee flexion during loading in healthy subjects with plantarflexor fatigue could be exaggerated due to the goal of maintaining step length and cadence.

7.3 Clinical application and further study

The results of these experiments indicate that in people with CMT, proximal compensatory strategies are used to allow walking to continue when distal impairments are present. The gait adaptations, however, make walking effortful and lead to a reduction in walking distance when fatigue of these strategies occurs. Based on this information, clinicians may choose to intervene in two ways:

1. Improve the ability of the person to utilise their compensatory strategies for longer
2. Reduce the impact of distal impairments so reducing proximal compensations

The results of these studies confirm the link between distal impairments and proximal compensations so adding information to the clinical reasoning process. Chapter 5 also explored the effect of AFOs as an intervention but this was not a randomised control trial. Therefore these results do not provide direct recommendations about what interventions to apply. The following sections

will outline the two approaches to CMT listed above and recommend investigations that will help provide this information.

7.3.1 Utilisation of compensatory strategies

Emphasising the use of compensatory strategies has been recommended in people with diabetic neuropathy [28] by encouraging hip flexion rather than push off from the ankle, even in people who did not primarily do this. This, however, was to reduce the formation of plantar ulcers rather than prolong function and was met with a certain amount of criticism in the literature [9, 24] as others question the encouragement of a strategy without trying other management approaches to reduce ulceration.

The suggestion from the present studies does not encourage the use of a specific strategy as such but recommends increasing how long an established strategy can be used. The results from chapter 6 show that the hip flexors starts to fatigue with prolonged walking with the emergence of other proximal adaptations. Strengthening the muscles that control this, e.g. the hip flexors, may be a way of prolonging walking.

Further investigation is required to see if this approach is effective in increasing walking endurance but also so see what type of strengthening protocol is most effective. Because endurance is the aim of the intervention one assumes that subjects would need to be strengthened with an endurance protocol, i.e. low resistance and high repetition, but increasing their maximum strength may also be useful. A study by Lindeman et al [20] showed that people with CMT fatigued their quadriceps muscles at the same rate as healthy control subjects but started at a lower MVC, that is they had a similar degree of fatigability. If people with CMT have a higher maximal strength this may prolong the time taken to reach the threshold due to the inverse relationship between the percentage maximal force generated and the time to fatigue i.e. around 20% of the MVC when hip flexion starts to fail [23].

It is worth noting, though, that the intention of this approach is not to change the strategies used so no alteration in kinematics is expected during short walks. In addition the subjective impact of fatigue may impact on the results as the correlation between subjective reports of fatigue with walking time was a key finding in chapter 6. This must be a recognised covariate in any study looking at improving walking endurance and should be considered in the design and analysis of any investigation.

7.3.2 Reducing the impact of distal impairments

The most obvious area to try to improve is the strength of the ankle muscles as distal weakness causes the majority of gait deviations seen in people with CMT. Strengthening studies in CMT have to date concentrated mainly on larger muscle groups [1, 10, 17, 19, 21] or upper limb muscles [1, 10, 17]. One study of resistance training in neuromuscular disease found that increases in strength were only found when the baseline values were greater than 15% of normal control data [27]. In chapter 3 the subjects with CMT had a mean strength of the ankle plantarflexors that was 32% of the controls and dorsiflexion strength that was 15%. There may be some potential, therefore, to strengthen the plantarflexor muscles aiming to improve the ankle plantarflexor moments and power generation at preswing. In contrast the more affected dorsiflexor muscles may be too weak to be strengthened. The study of resistance training, however, was performed on subjects with a mixture of neuromuscular pathologies, the majority having muscular dystrophy. Because CMT is a neuropathic condition and not a muscle disease, people could respond differently to strengthening so this finding may not apply.

The other consideration when strengthening the weaker distal muscles is over work weakness. The evidence for this is not conclusive and the pathological process is not fully understood [47] . It is possible that the mechanism of overwork weakness in people with CMT, particularly type 1, is similar to that proposed in people with post polio syndrome where motor units enlarged due to partial denervation are vulnerable to increased oxidative stress [48]. Kilmer et al found that high resistance strength training at a 12 repetition maximum in people with progressive neuromuscular disease resulted in a reduction of the eccentric peak torque of the elbow flexor muscles [17]. This difference, however, was also seen in the contra-lateral elbow that was not trained indicating that this may be a neural adaptation rather then damage to the local muscle tissue, though the authors were unable to explain why there was a negative cross over effect. In addition, there were no detrimental effects seen in the knee extensors with high resistance training or with both muscle groups when a moderate resistance training programme was applied [1]. The main problem with these two studies was that they included people with not only CMT but also muscular dystrophy. Generalising the results to just CMT is therefore difficult.

A study by Vinci et al [49] observed that people with CMT tended to be stronger in the non-dominant hand and suggested this was evidence of overwork weakness because the dominant hand is used more. This study used manual muscle testing as the main outcome measure which has been criticised in studies of muscle strength in CMT [7] In addition, the timescale of deterioration suggested in this paper is over a person's lifetime. Extrapolating this to a study of strengthening larger muscle groups over a 12 week period is difficult although the long term effects of any strengthening program and the presumed increased use of a muscle after strengthening must be considered.

In view of the concerns about overwork weakness an investigation of this in people with CMT would be very useful. Strength changes and motor unit number estimation [4] would ascertain if there has been any detriment through strengthening. Stratifying the subject group into weaker and stronger people would also indicate if weaker muscles can be strengthened safely. Functional and biomechanical analysis of gait would also show if any strengthening effect is enough to improve functional gait and the kinetic and kinematic gait deviations identified in this and other studies.

Another way of intervening distally is through external support. Chapter 5 demonstrated that some distal deviations can be altered with an AFO such as foot drop. As discussed previously longitudinal studies would be required to ascertain if reducing foot drop reduces associated proximal compensations over time. Although chapter 5 was not a randomised control trial and so does not give a definitive recommendation as to the best device to use, the potentially detrimental effects of one type of AFO should be considered when clinically reasoning the prescription of such a device. Only a limited range of devices were tested in this study and the results were not stratified according to subject presentation. More rigid devices may limit ankle power production in some, but people who are severely weakened may benefit from the extra bracing to support the lower limb during the ankle rocker. Also, the potential for carbon fibre AFOs should be investigated because a spring assistance of ankle power would be beneficial to this group. Studies of AFOs should include a stratified subject group and a combination of functional measures and biomechanical measures allowing investigators to see not only whether they work but also how they work and who they work best with. This will allow clinicians to understand the principles of the devices as they reason their use and not just administer AFOs in a prescriptive manner.

Orthoses can assist other distal impairments seen in this group. Pes cavus can be a problematic presentation for a few reasons. Pain is a common complaint due to altered musculoskeletal alignment and altered weight bearing [5]. Also the function of the ankle muscles can be worsened by poor alignment due to lever dysfunction as described by Schwartz and Lakin [44]. A randomised control trial of the use of foot orthoses in people with pes cavus showed improvement in pain, plantar pressure and reported physical functioning [6]. To date there has not been a study using 3D motion analysis as an outcome measure in this type of intervention study. This would be useful to see if foot orthoses alter alignment problems such as tibial torsion and EMG study of soleus would indicate if there is any improvement in activation as has been suggested [44].

7.4 Limitations of methods

The limitations of the design of each study has been discussed in the relevant chapters. This section, however, discusses some of the problems associated with the main measurement tool used, 3D gait analysis. Concern has been raised about error due to skin and marker movement and also the error associated with the linked segment model used for calculations of the hip joint [14]. Maynard et al [22] looked at the reliability of the CODAmotion system and found reduced intra-rater

reliability of hip joint angles that they supposed was due to variability in marker placement. Another source of error could be the estimated location of the hip joint centre. The CODAmotion system uses a method described by Bell et al [3] which involves calculating the hip joint centre from anatomical landmarks and reports estimations within 2.6 cm from the centre of the hip joint when compared with radiographs. The accuracy of this method has been questioned and newer methods have been described that estimate the position of the functional hip joint. This method relies on the subject rotating the hip in two planes during a pre-walking calibration test. As the leg moves, markers on the knee joint trace a trajectory that is then assumed to be the arc of sphere, the centre of which is the functional hip joint centre [18].

More recently another method has been proposed using arrangements of marker clusters to represent two segments, e.g. the pelvis and thigh. The assumption is that as these two segments move relative to each other and the segments intersect at a common point on the axis of rotation which represents the joint centre [45]. New software packages can accommodate these methods while using data from existing motion analysis systems such as CODA. One example is Visual 3D which uses alternative marker arrangements [8]. Marker clusters on rigid plates are used to define a local co-ordinate system for each segment. The position and orientation (PORE) of the segment is calculated and the PORE itself is tracked frame by frame rather than each individual marker as with traditional methods. It also allows the calculation of the joint centres through identifying where the segments inter-connect, as described [45] and is reported to be less vulnerable to error through skin movement. In addition, when marker clusters have to be removed and reapplied e.g. in chapter 4, the position of the marker clusters relative to each other and anatomical bony landmarks and the joint centres can be recalculated after the gait trial so eliminating the concerns that were raised in that chapter about the accuracy of the replacement of markers post intervention. The future use of this type of system would help to clarify the accuracy of particularly kinematic and kinetic data which was crucial to this thesis.

7.5 Overall conclusion

People with CMT demonstrated proximal changes in gait kinematics and kinetics that compensated for distal impairments. The compensatory strategies found in people with CMT differed from those found in healthy subjects with weakened plantarflexor muscles and studies of people with other conditions such as stroke. This difference may be due to the slow adaptation that a person with CMT develops in response to the insidious disease progression.

A role of the hip flexor muscles is hypothesised based on the reduction in strength with prolonged walking and alterations in walking time and kinematics subsequent to selective fatigue. In addition other compensatory strategies were noted. An increase in knee power generation at the end of swing phase may help to elevate the limb whilst an increase in trunk motion may aid limb progression and increase stride length.

With prolonged walking different compensatory strategies may emerge as "first choice" strategies that later fail due to muscle fatigue. Understanding the role and interaction of different compensatory techniques would allow therapists to develop training that specifically aims to optimize and prolong these strategies thus improving walking endurance. Such research should be conducted in parallel with work investigating whether it is possible to reduce the underlying primary impairment and target additional influences on walking and function such as the possible presence central fatigue and the use of ankle-foot orthoses

7.6 References

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Appendix 1: Modified Bonferroni Correction

The modified Bonferroni correction is based on the ordered P-values of individual tests. $T_1,...,T$ is a set of n statistics with corresponding p-values $P_1,...P_n$ for testing hypothesis $H_1,...H_n$. The p-values were ordered as $P_{(1)},...P_{(n)}$ to test the hypothesis $H_0 = \{H_{(1)},...H_{(n)}\}$. The null hypothesis H_0 was rejected if $P_{(j)} \leq j\alpha / n$ for any $j = 1,...n$. Below the procedure is demonstrated with the data from the primary analysis for chapter 3:

Test rank	Variables	P-value	Modified Bonferroni threshold	Modified Bonferroni outcome
1	Ankle power preswing	0.001	0.005	REJECT H_0
2	Hip flexion swing	0.009	0.010	REJECT H_0
3	PF moment preswing	0.010	0.015	REJECT H_0
4	Hip ankle timing	0.020	0.020	REJECT H_0
5	HF velocity preswing	0.037	0.025	ACCEPT H_0
6	PF angle preswing	0.109	0.030	ACCEPT H_0
7	DF angle foot clearance	0.128	0.035	ACCEPT H_0
8	HF angle preswing	0.160	0.040	ACCEPT H_0
9	HF moment preswing	0.215	0.045	ACCEPT H_0
10	Hip power preswing	0.930	0.050	ACCEPT H_0

Table A1.1: Data from the primary comparison in Chapter 3 demonstrating application of the modified Bonferroni test.

Reference

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Appendix 2: Investigating the reliability of the position of the CODA pelvic frame with walking and with repeat application

Introduction

CODA cx1 is a 3D motion analysis system developed by Charnwood Dynamics Limited. The system includes a segmental analysis set up which consists of recommended marker placement to allow the CODA system to calculate gait analysis data. Data is presented in a report relatively quickly which has obvious benefits to the clinical setting.

The gait set up includes a pelvic frame for the placement of the pelvic markers. This was developed to extend some of the markers away from the pelvis due to the tendency for arm swing to obscure markers. The frame consists of two lateral bars and a sacral wand which slot together and attach to the outside of a Velcro belt. The markers correspond to the anterior superior iliac spines (ASIS), the posterior superior iliac spines (PSIS) and the end of the sacral wand.

The frame's location is significant as the CODA software automatically calculates the internal hip joint centre from the marker positions and additional anthropometric data. The location of the hip joint centre needs to be accurate as it is a component of the calculation of hip moments and powers. Several methods of calculating the hip joint centre are described and CODA uses a technique by Bell et al [1]. Charnwood recommend the pelvic frame be tilted so that the plane defined by the PSIS and ASIS markers includes the actual PSIS and ASIS landmarks. The marker set is used to define the local co-ordinate frame of the pelvic segment, the orientation of which is known as the Embedded Vector Basis (EVB). A line linking the PSIS and ASIS is used to define the local X axis as a unit vector. Derivation of the local Y and Z unit vectors is achieved using the Gram-Schmidt algorithm to orthogonalise the axes. The EVB is involved in the calculation of segment rotations using Euler angles. The rotation calculation requires definition of a proximal segment for a distal segment to move relative to. In this situation, the pelvis is the distal segment and the lab co-ordinates represent the proximal segment with unit vectors [1,0,0][0,1,0][0,0,1].

The reliability of the frame placement with repeated applications and during functional tasks, such as walking, is therefore important . The frame sits on the pelvis secured by a Velcro strap rather than the more common method of fixation with adhesive tape. This may make it vulnerable to slippage with movement e.g. walking. Some experimental designs require comparison of gait kinetics and kinematics on different occasions requiring removal of the frame. Any inconsistency in application or slippage of the frame during walking may affect the reliability of measures requiring the hip joint centre e.g. moments. Piazza [5] warns us that there are a number of motion analysis studies suggesting that kinetic and kinematic variables are highly sensitive to errors in hip joint centre location.

Maynard et al [4] report on inter and intra-rater reliability of gait measurement using the CODA mpx30 system. The CODA bilateral gait marker set up was applied to healthy subjects who walked over force plates embedded in a walkway. Kinetic, kinematic and spatio-temporal data was collected twice in one day and again one week later. Results demonstrated generally poor correlation between the three sessions for the intra-rater analysis of 10 subjects. Inter-rater analysis showed good agreement for knee variables and spatio-temporal parameters but hip angle agreement was particularly poor. The authors accounted for the poor agreements by the variability of marker placement. Normal variation of the gait cycle is implicated as another source of inconsistency suggesting that analysis of one gait cycle would be particularly vulnerable to this. Three to ten cycles are recommended for reliable analysis [3].

Methodology

Seven healthy subjects were recruited from staff and clinical students at the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. Two CODA CX1 scanners were used (Charnwood Dynamics Ltd). The bilateral gait marker set up was applied to the subject:

- 6 pelvic markers on the pelvic frame (PSIS, ASIS, sacral wand; left and right)
- 2 hip markers on the greater trochanter
- 2 anterior and 2 posterior femoral markers mounted on thigh wands
- 2 knee markers on the lateral joint line
- 2 anterior and 2 posterior tibial markers on shank wands
- 2 markers on the lateral malleoli
- 2 lateral heel markers
- 2 toe markers on the base of the 5^{th} metatarsal

Tape markers were applied to the ASIS and PSIS to help to visualise the anatomical landmarks when positioning the pelvic frame.

Prior to data collection, subjects were asked to walk on a motorised treadmill for two minutes to find a preferred walking speed. Two marks were made on the treadmill belt, 40 cm apart. Subjects were asked to stand barefoot with the lateral edge of the foot (base of 5^{th} metatarsal) level with the mark (figure A2.1).

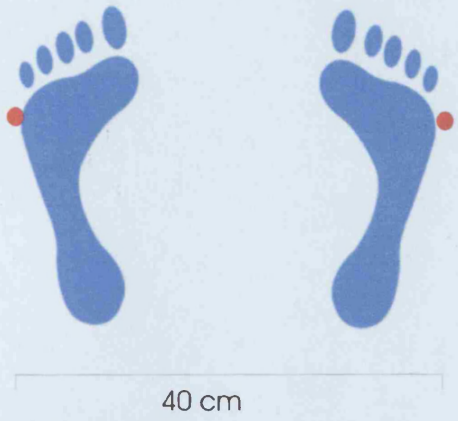


Figure A2.1: Position of the feet and toe markers

Subjects were instructed to stand still for 30 seconds with their arms by their sides. Data was sampled at 200 Hz. Baseline data was obtained by comparing two trials collected consecutively with no alteration in task or set up in between. The effects of walking on the frame position was investigated by comparing trials before and after a 2 minute walk on the treadmill at the subject's preferred speed. For the application repeatability, a standing trial was recorded then the pelvic frame was completely removed and reapplied. A second standing trial followed.

The pelvic segment rotation was calculated via CODAmotion software and exported as text files for subsequent analysis using MATLAB programmes written in-house (MATLAB, Mathworks Inc). The segment rotations obtained from the CODAmotion software were expressed in three directions: **oblique** (medio-lateral rotation), **tilt** (antero-posterior rotation) and **rotation** (rotation around vertical).

Data analysis

Two types of analysis were carried out on the data to test for the repeatability. Interclass correlation (ICC) and the Bland Altman methods were used. For the ICC, model 3 was used for one rater (3,1) as the same rater would be collecting data in the main study. ICCs over 0.75 were considered as demonstrating good agreement. All calculations were done using SPSS.

Although the ICC will give a measure of agreement it does not give us actual measures, indicate bias or clinical importance of any disagreement. In addition, the Bland Altman method was applied [2] in order to obtain the 95% "limits of agreement" to indicate a range of error. The mean difference between the trials should be zero as the same measure is used. The confidence intervals for the limits of agreement were not considered as the sample size was too small. A sample set of at least 50 is required [6].

Results

The two baseline trials showed good agreement for segmental rotation in all directions measures with high ICCs. The limits of agreement for the tilt direction show a wide interval of 11.16 degrees with a higher coefficient of repeatability (table 1).

	Tilt	Oblique	Rotation
Mean difference (deg)	0.66	0.19	-0.32
Standard deviation of difference (deg)	2.80	0.37	1.08
Standard error of difference (deg)	1.06	0.14	0.41
Upper limits of agreement (deg)	6.25	0.93	1.84
Lower limits of agreement (deg)	-4.93	-0.56	-2.48
Coefficient of repeatability	5.59	0.74	2.16
ICC (3,1)	0.9416	0.9970	0.9817
Upper confidence interval	0.9900	0.9996	0.9968
Lower confidence interval	0.6599	0.9865	0.8933

Table A2.1: Results of Bland Altman and Interclass Correlation Coefficient tests for baseline trials.

The trials comparing the effect of walking on the frame position demonstrated excellent agreement as demonstrated by the high ICCs, low coefficients of repeatability and narrow limits of agreement for all directions of movement (table 2). In contrast, the frame repeatability trials did not show such good agreement and had wider limits (table 3).

	Tilt	Oblique	Rotation
Mean difference	0.35	0.13	0.19
Standard deviation of difference	1.54	0.37	2.01
Standard error of difference	0.58	0.14	0.76
Upper limits agreement	3.44	0.86	4.21
Lower limits agreement	-2.74	-0.61	-3.83
Coefficient of repeatability	3.09	0.74	4.02
ICC (3,1)	0.9850	0.9974	0.9499
Upper confidence interval	0.9974	0.9996	0.9914
Lower confidence interval	0.9130	0.9849	0.7084

Table A2.2: Results of Bland Altman and Interclass Correlation Coefficient tests for effect of walking trials.

	Tilt	Oblique	Rotation
Mean difference	1.90	1.67	2.60
Standard deviation of difference	6.66	3.16	4.99
Standard error of difference	2.52	1.19	1.89
Upper limits agreement	15.23	7.99	12.57
Lower limits agreement	-11.43	-4.65	-7.38
Coefficient of repeatability	13.33	6.32	9.98
ICC (3,1)	0.6345	0.4524	0.5641
Upper confidence interval	0.9371	0.9059	0.9251
Lower confidence interval	-1.1271	-2.1868	-1.5367

Table A2.3: Results of Bland Altman and Interclass Correlation Coefficient tests for frame repeatability trials.

Discussion

The baseline results show good agreement according to the ICC but the wide limits of agreement for the tilt direction is of concern. The error is large enough to risk obscuring changes due to an intervention in a study. An explanation could be that while a person stands, there is natural variation in the in antero-posterior pelvic tilt. This is more likely to occur in the tilt direction because the constrained foot position would help to standardise the oblique and rotation components. To standardise the antero-posterior tilt in an experimental situation would be difficult without constraining lumber movement which would restrict more dynamic tasks such as walking.

It is encouraging that walking did not dramatically alter the position of the frame. However, the agreement is better than the baseline trials. This could be because the walking trials were performed after the subject had been relatively active. The second baseline trial was performed straight after the first. A more prolonged stand may have resulted in postural "fatigue" where subjects gradually move to a position of least effort or activity.

The frame repeatability comparison demonstrated that the application of the pelvic frame is not as reliable, even with tape markers on the anatomical landmarks. This has implications for comparative studies using this equipment. If a research design necessitates removal of the apparatus, within a session or comparison on a different day, the measures of segmental rotation may be too variable to detect change due to interventions that may be applied. The segmental rotation measure relies on the accurate position of the pelvic markers. This is also true for the calculation of the hip joint centre when deriving hip moments. This finding implies that the inaccuracy in repositioning the pelvic markers (via the frame) could increase variability and also may explain why particularly poor

agreement in hip angles was found by Maynard et al [4]. As the tilt of the frame is important for uniform calculations of the EVB, repeatability may be improved by marking the position of the arms of the frame with long pieces of straight tape rather than just tape markers on the bony landmarks.

Conclusion

Good repeatability is demonstrated in variables derived from the pelvic markers in baseline trials, and before and after walking. Some variability is seen with the baseline in the antero-posterior pelvic tilt that could be a result of a prolonged stand. The repeatability is diminished when the frame is removed and reapplied.

References

1. Bell AL, Brand RA, Pedersen DR. Prediction of Hip Joint Centre Location from External Landmarks. Human Movement Science 1989; 8:3-16.

2. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1(8476):307-310.

3. Diss CE. The reliability of kinetic and kinematic variables used to analyse normal running gait. Gait and Posture 2001; 14:98-103.

4. Maynard V, Bakheit AMO, Oldham J, Freeman J. Intra-rater and inter-rater reliability of gait measurements with CODA mpx30 motion analysis system. Gait and Posture 2003; 17:59-67.

5. Piazza S, Erdermir A, Okita N, Cavanagh P. Assessment of the functional method of hip joint centre location subject to reduced range of motion. Journal of Biomechanics 2004; 37:349-356.

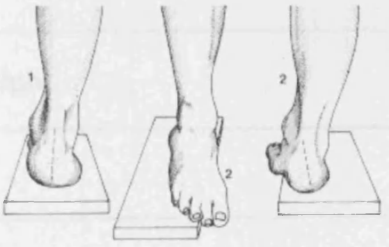
6. Rankin G, Stokes M. Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. Clinical Rehabilitation 2004; 12:187-199.

Appendix 3: Clinical tests

Scoliosis screen: Adam's Forward Bend Test

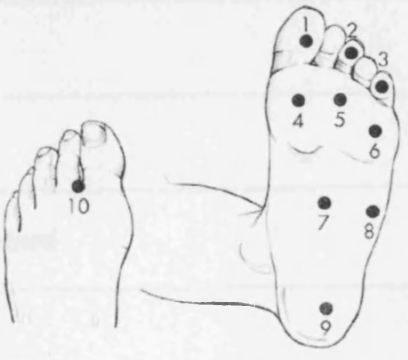
Patients are asked to bend over at the waist as if they were touching their toes.
Instruct the patients to place their feet shoulder-width apart, extend their arms with the hands placed together, and bend forward slowly. The examiner gets their eyes level with the back and looks for one side being higher than the other, or any asymmetry of the back. If this position reveals trunk asymmetry, record forward bend test as positive.

Block Test:



Note the position of the heel when standing on a 2cm block. Then get the patient to stand with the forefoot over the medial edge. If a varus remains then the subtalar joint is fixed. If it corrects to valgus then the joint is mobile.

Plantar areas tested for pressure perception:



Appendix 4: Borg perceived exertion scale

6	
7	Very, Very Light
8	
9	Very Light
10	
11	Fairly Light
12	
13	Somewhat Hard
14	
15	Hard
16	
17	Very Hard
18	
19	Very, Very Hard
20	

Appendix 5: Fatigue Severity Scale Questionnaire

Please read each statement and circle a number from 1 to 7, depending on how appropriate you feel the statement applies to you **over the last week**. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement.

During the past week, I have found that ...							
	Never	Hardly any time	Some of the time	About half of the time	A lot of the time	Nearly all of the time	All of the time
1. My Motivation is lower when I am fatigued	**1**	**2**	**3**	**4**	**5**	**6**	**7**
2. Exercise brings on my fatigue	**1**	**2**	**3**	**4**	**5**	**6**	**7**
3. I am easily fatigued	**1**	**2**	**3**	**4**	**5**	**6**	**7**
4. Fatigue interferes with my physical functioning	**1**	**2**	**3**	**4**	**5**	**6**	**7**
5. Fatigue causes frequent problems for me	**1**	**2**	**3**	**4**	**5**	**6**	**7**
6. My fatigue prevents sustained physical functioning	**1**	**2**	**3**	**4**	**5**	**6**	**7**
7. Fatigue interferes with carrying out certain duties and responsibilities	**1**	**2**	**3**	**4**	**5**	**6**	**7**
8. Fatigue is among my three most disabling symptoms	**1**	**2**	**3**	**4**	**5**	**6**	**7**
9. Fatigue interferes with my work, family or social life	**1**	**2**	**3**	**4**	**5**	**6**	**7**

Appendix 6: RAND 36-Item Health Survey 1.0 Questionnaire Items

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago**, how would your rate your health in general **now**?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
7. Climbing **one** flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking **more than a mile**	[1]	[2]	[3]
10. Walking **several blocks**	[1]	[2]	[3]
11. Walking **one block**	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(Circle One Number)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

21. How much **bodily** pain have you had during the **past 4 weeks**?

(Circle One Number)

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks** . . .

(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

How TRUE or FALSE is each of the following statements for you.

(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Appendix 7: Reliability of hip flexor myometry method

Introduction

Hip flexor myometry was one of the primary outcome measures in chapter 6. The repeatability of the method used was unknown and a repeatability study was undertaken.

Method

The hip flexor measurement was taken from a strain gauges attached to a rigid metal frame. The subject was seated with the hips at 50° and the trunk and pelvis restrained. The strain gauge was attached to the subject via a canvas strap that they were asked to pull against during the MVC test. A multi-meter was connected to the strain gauge to monitor the output voltage so measurements were all taken from the same baseline tension. To calculate the moment, the length of the lever was measured from the greater trochanter to the centre of the strap. In chapter 6, bilateral recordings were taken.

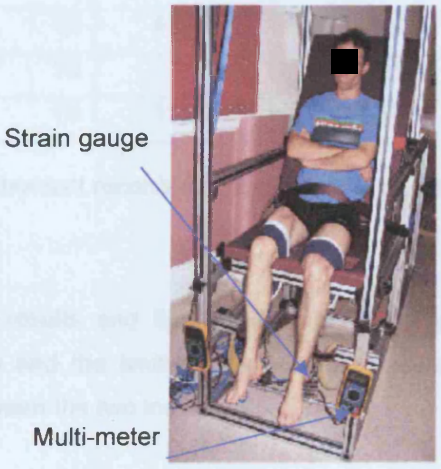


Figure A7.1: Fixed myometry set up for the hip flexors

Repeatability of the hip flexor myometry set up described in chapter 6 was tested on the left hip on different days. Two trials were compared. Intraclass correlation coefficient (ICC), confidence intervals and limits of agreement [1] were calculated to examine repeatability between the two trials. An ICC over 0.75 was considered as demonstrating good agreement. ICC and confidence intervals were calculated using SPSS and the limits of agreement with the formulae suggested by Bland and Altman using Excel to perform the calculations.

Results

Table A7.1 shows the hip flexor moment recorded at the two trials and the difference between them.

	Trial 1	Trial 2	Difference
1	49.64696	76.17342	26.52646
2	100.3834	88.29947	-12.0839
3	45.8934	47.2605	1.3671
4	64.4056	87.36063	22.95503
5	106.9905	114.705	7.714462
6	50.78497	63.36817	12.5832
7	132.7748	95.00688	-37.7679
8	72.9904	70.8665	-2.12391
9	64.03345	57.59289	-6.44056
10	107.3572	110.815	3.457803
11	70.31108	70.10504	-0.20604
12	47.75677	40.20438	-7.55239
13	49.907	44.2557	-5.6513
14	116.7427	107.8757	-8.86701

Table A7.1: Hip flexor moment recorded at trials 1 and 2 plus the difference between them.

Table A7.2 show the results and figure A7.1 shows a Bland Altman plot demonstrating the distribution of the data and the limits of agreement. The results show good agreement in the moment measures between the two trials.

Mean difference (deg)	-0.43
Standard deviation of difference (deg)	15.80
Standard error of difference (deg)	4.22
Upper limits of agreement (deg)	31.17
Lower limits of agreement (deg)	32.04
ICC	0.83
Upper confidence interval	0.94
Lower confidence interval	0.56

Table A7.2: Descriptive statistics, limits of agreement [1], ICC and confidence intervals for the data.

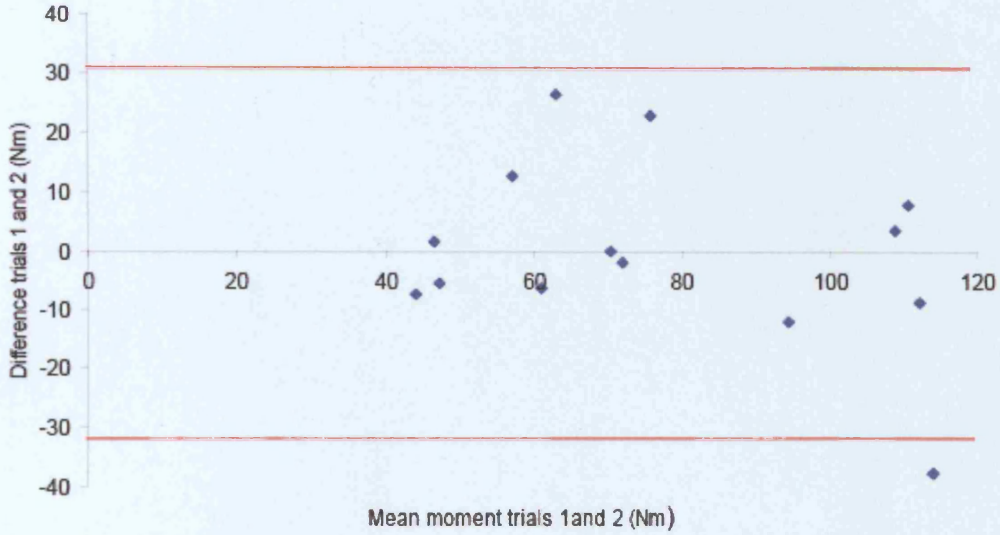


Figure A7.2: Bland and Altman plot demonstrating the agreement of the data and the position within the upper and lower limits of agreement (red lines).

Conclusion

The statistics performed demonstrate good agreement between the trials indicating sufficient repeatability with the method used in chapter 6.

Reference List

1. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1(8476):307-310.