Walking Balance in Individuals with Acromegaly

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Studied in partial fulfillment of the requirements

for the degree Master of Science

at

Dalhousie University

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Halifax, Nova Scotia

April 2023

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List of Abbreviations Used

GH: Growth Hormone

IGF-1: Insulin-like Growth Factor 1

AA: Acromegaly arthropathy

OA: Osteoarthritis

PWA: Persons With Acromegaly

PNA: Persons with Non-GH-secreting pituitary Adenoma

ADL: Activities of Daily Living

CoP: Center of Pressure

CoM: Center of Mass

CNS: Central nervous system

MSK: Musculoskeletal systems

BMI: Body Mass Index

TUG: Timed Up and Go test

DGI: Dynamic Gait Index test

SPM: Statistical parametric mapping

W: Walking

OW: Obstructed Walking

H1: Hip extensor energy generation

H2: Hip flexor energy absorption

H3: Hip flexor energy generation

H1F: Hip abductor energy absorption

H2F: Hip abductor energy generation

H3F: Hip abductor energy generation

K1: Knee extensor energy absorption

K2: Knee extensor energy generation

K3: Knee extensor energy absorption

K4: Knee flexor energy absorption

K5: Knee flexor energy generation

A1: Ankle dorsiflexor energy absorption

A2: Ankle plantar flexor energy generation

Abstract

Introduction: Acromegaly is characterized by growth hormone excess. It adversely affects the patients' musculoskeletal and neural systems, consequently impairing physical function. This study explored the walking balance deficits in persons with acromegaly (PWA) in comparison to persons with non-GH-secreting pituitary adenoma (PNA).

Methods: Data (n=8 for each group) was collected using the OptiTrack MoCap and AMTI Forceplate systems. Paired sample t-tests, 2-way repeated ANOVA, and statistical parametric mapping were used to compare outcomes between the groups.

Results: PWA showed longer TUG completion time, but no significant difference in DGI. PWA's supporting limb generated less hip abductor energy when crossing whereas PNA generated more; PWA's crossing limb exhibited less reduction of knee extensor energy absorption whereas PNA exhibited more reduction. However, these differences did not reach statistical significance (p=0.32 and 0.27).

Conclusion: Our study revealed a trend of PWA adopting a different adaptation strategy during obstructed walking.

Acknowledgement

Words cannot express my gratitude to my professor, Dr. Michel Ladouceur, and my committee members, Dr. Kathleen MacLean and Dr. Ali Imran, for their invaluable patience and feedback throughout this journey. Without their guidance and support, I could not have accomplished this.

I would like to express my sincere gratitude to my research partner Michaela for her support and contribution to this project. Her dedication and expertise have been instrumental in the success of this project. Without her help, this research would not have been possible.

Thanks should also go to the study participants, whose contributions impacted and inspired me greatly.

I want to acknowledge Lisa for her significant efforts in reaching out to potential participants.

Lastly, I would be remiss if not mentioning my family and friends around me, who have been a constant source of motivation and encouragement throughout this process. I am grateful for their unwavering belief in me.

Chapter 1: Introduction

Acromegaly, a rare chronic disease, primarily results from elevated circulating levels of growth hormone (GH) and insulin-like growth factor-I (IGF-1) caused by pituitary adenoma (benign tumor) during adulthood (Wennberg et al., 2019). The condition is characterized by enlargement of extremities, increasing soft tissue thickness of hands and feet, and dysmorphic features (Caron et al., 2019). Other clinical features associated with acromegaly range from local compressive effects causing visual-field defects, headaches, and pituitary hormone deficits, to various manifestations of different biological systems (See Section 3.2). Excessive GH stimulates the growth of multiple tissues, including cartilage, synovial tissue, and ligaments, resulting in joint deterioration and the development of arthropathy (Killinger et al., 2012; Pivonello et al., 2017; See Section 4.2 for details). The presence of peripheral nerve hypertrophy has been observed in persons with acromegaly (PWA), leading to impairments in both their sensory and motor nerve function (Jamal et al., 1987). In addition, the mineralization of the attachment of ligaments or tendon to bone (enthesopathy) and calcification of periarticular tissues were observed in PWA, which might lead to abnormal articular afferent information and thus cause proprioceptive deficits (Colao et al., 2004; Pompeu et al., 2012).

Previous studies have concluded that physical function deficit is more pronounced in PWA compared to their peers without the condition (Johnson et al., 2003; Biermasz et al., 2004; Badia et al., 2004; Miller et al., 2008). Multiple studies (Colao et al., 2004; Detendech et al., 1973; Bluestone et al., 1971; Wassenaar et al., 2009) have established arthropathy as the most predominant factor of functional disability in PWA. Moreover, while treatment of acromegaly typically results in self-reported joint pain reduction, a

significant number of patients continue to experience such pain, which appears to have lasting effects on physical function even after remission (Miller et al., 2008; Biermasz et al. 2004). Despite the high prevalence of physical function deficit and joint pain in PWA, arthropathy is often overlooked in clinical practice, with only half of the patients referred to a physiotherapist (Miller et al., 2008). It is notable that no specific treatments have been developed for acromegaly arthropathy, and existing treatments largely rely on approaches used for osteoarthritis (OA) in the general population (for more detailed discussion, see section 4.2).

Recently, there has been growing attention to the impact of acromegaly arthropathy on the ability of PWA to carry out basic and instrumental activities of daily living (ADL). Maintaining balance is a critical aspect of performing ADL without falling. However, there is limited research on the balance abilities of PWA compared to able-bodied individuals, with conflicting outcomes reported in the few studies that have investigated this issue using clinical tests (Lopes et al., 2014; Homem et al., 2017; Atmaca et al., 2013). For instance, while Lopes et al. (2014) did not find reduced dynamic balance in PWA, Homem (2017) and Atmaca (2013) reported otherwise (See Section 5.1 for details).

Most persons with acromegaly exhibit visual impairment and severe headaches when diagnosed (Colao et al., 1998; Russ & Anastasopoulou, 2021). After undergoing adenoma resection surgery, patients may experience complete or partial recovery of visual function, while a small number of patients may experience worsening visual function (Nakao & Itakura, 2011). To investigate the impact of excessive growth hormone on the patients' balance, it is crucial to minimize confounding factors caused by surgery or local compressive effects of the adenoma on visual function, considering the significant role of

visual function in maintaining balance. In other words, the differences observed in balance between PWA, and able-bodied individuals might be attributed to the effect of the adenoma or surgery, rather than excessive GH. Hence, to investigate the impact of GH on balance, it is best to exclude these factors. Besides, despite the importance of walking as a fundamental ADL, there has been no systematic analysis of gait or walking balance in this population, even though there is a higher risk of falls in PWA and a higher odds ratio of fracture despite higher bone mineral density (Title et al., in press; Colao et al., 2004; Mazziotti et al., 2015). Given the mechanical changes found in the joints of PWA, including widened joint space, thickened articular cartilage, altered joint alignment, and the presence of neural function deficiency, there is reason to believe that this population may experience deviated gait and deteriorated walking balance (Horlings et al., 2008; Aydin et al., 2017; Lopes et al., 2014). Therefore, it is crucial to investigate whether the walking balance is indeed impacted by GH excess in PWA, as this information could help promote the development of interventions that can restore balance in these patients.

This thesis is a section of a larger project investigating arthropathy in PWA. Funding was provided by the 2020 UIMRF Special Circumstance Grant. Ethics approval was obtained from Nova Scotia Health Authority Research Ethics Board. The larger project comprises three parts: 1. An assessment of the extent of arthropathy and its functional effect on PWA using a survey, 2. An assessment of changes in standing balance associated with acromegaly, and 3. An assessment of the changes in walking balance associated with acromegaly. This thesis only describes the last part of the project. As mentioned before, GH excess triggers and is associated with joint degenerations and peripheral nervous system modifications, which are considered to impact PWA's walking balance. Therefore,

the specific aim of this study is to establish the effects of acromegaly on walking balance. Eight PWA and eight age-, sex-, BMI-matched PNA were included in our study, named as PWA and PNA (control) group, respectively. The walking balance outcome measures included the timed up and go scores (TUG), dynamic gait index scores (DGI), lower limb joint moments and joint power adaptations during unilateral obstructed walking. Kinematic and kinetic data were collected using an OptiTrack Motion Capture system and AMTI force plate system. Paired sample t-tests were used to determine if there were any significant difference in demographic characteristics and scores from functional tests (TUG and DGI) between the two groups. A 2-way repeated measures ANOVA was used to determine if there was a significant interaction between the effects of acromegaly and obstructed walking on selected lower limb joint power bursts. Statistical parametric mapping (SPM) was used to examine differences in lower limb joint power adaptations between the two groups.

Chapter 2: Literature Review

2.1 Acromegaly

2.1.1 Diagnosis and treatments of acromegaly

Acromegaly is a chronic disease, that primarily arises from the sustained overproduction of GH, a peptide hormone (Lanning & Carter-Su, 2006), and IGF-1, a hormone structurally similar to insulin (National Cancer Institution, n.d.), secreted by the anterior lobe of the pituitary gland.

Acromegaly is typically diagnosed 4 to 10 years after disease initiation, as early clinical features of the disease evolve slowly (Akirov et al., 2021). Blood tests and brain scans are the primary diagnostic tools used for acromegaly. A blood test measures blood IGF-1 level. To further confirm the diagnosis, an oral glucose tolerance test is recommended. An imaging test using MRI is recommended to visualize the size and appearance of the anterior pituitary adenoma after the confirmation of the diagnosis (Katznelson et al., 2014).

Treatments for acromegaly have undergone significant advancements in recent decades and can be broadly classified into three categories: medical therapy, radiotherapy, and surgical management (Barkan, 2001; Colao et al., 2004; Melmed et al., 2005; Gadelha et al., 2019; Adigun et al., 2022). Of these, surgical resection of the adenoma is the preferred and most effective therapy for inherent pituitary defects (Colao et al., 2004; Melmed et al., 1983; Melmed et al., 2005; Gadelha et al., 2019; Adigun et al., 2022). If surgical therapy fails or is not feasible due to high surgical risk, medical management or radiotherapy may be considered (Giustina et al., 2003; Melmed et al., 2005; Gadelha et al., 2019). Medical treatment primarily targets somatostatin level, which is a GH inhibiting hormone (Giustina et al., 2003; Colao et al., 2004; Gadelha et al., 2019; Adigun et al.,

2022), and radiotherapy is used to control the adenoma size but has more side effects than other treatments (Gadelha et al., 2019). Patients receiving radiotherapy have been shown to have significantly lower quality-of-life scores compared to those receiving other treatments (Biermasz et al., 2004).

2.1.2 Pituitary adenoma as the primary cause of acromegaly

GH-Secreting Pituitary Adenoma in the anterior pituitary gland has been identified as the primary cause of acromegaly (Bailey & Cushing, 1928; Davidoff, 1926; Dineen et al., 2017). A pituitary adenoma is the growth of abnormal cells, causing the formation of a solid mass of tissue in the pituitary gland, which is a benign or noncancerous tumor. Inherent pituitary defect (excessive GH secreted by the anterior pituitary adenoma), poor hypothalamic regulation (excessive GH arising from excessive growth hormone releasing hormone), or a combination of both were listed as the major causes of these adenomas (Melemed et al, 1983). These abnormalities arise from the modified DNA of somatotroph cells (GH-secreting cells in the anterior pituitary gland) by irradiation, genetic mutation, virus, or multiple endocrine neoplasias (Medlmed et al., 1983), ultimately leading to the development of adenomas.

2.1.3 Clinical Features of acromegaly

The clinical features of acromegaly are diverse, ranging from local effects, such as pituitary enlargement, visual-field defects, and headaches, to pathological conditions in various biological systems, such as muscle size and mass increase, bone overgrowth in length and width, and cartilage thickness increase, which could disturb the mechanical balance of the joints and eventually develop joint degeneration (Isgaard et al., 1986; Hakeda et al., 1991; Durham et al., 1994; Giustina et al., 2003; Colao et al., 2004; Philippou

et al., 2007; Killinger et al., 2012; Ahmad et al., 2020). Acromegaly can also cause peripheral nerves enlargement, including thickening of the sheath around the nerve fibers bundle (perineurium) and a reduction in axon numbers (Stewart, 1966), which may result in peripheral neuropathy and impaired conduction velocity in the median and lateral popliteal nerve (Jamal et al.,1987).

Persons with acromegaly exhibit deficits in physical function, mobility, and balance, which may be attributed to these pathological changes in their neural system and musculoskeletal (MSK) system resulting from GH excess.

2.2 Physical function

2.2.1 Physical function in Acromegaly

PWA reported decreased quality of life even after achieving remission, due to lingering effects of the disease (Biermasz et al., 2004; Miller et al., 2008; Nunes et al., 2014). Chronic effects of acromegaly may cause a considerable impact on the patient's quality of life, especially on the physical function domain (Johnson et al., 2003; Miller et al., 2008; Biermasz et al., 2004; Badia et al., 2004). Nunes et al. (2014) found that 47.9% of PWA reported having problems carrying out daily activities and 43.7% of patients reported decreased performance at work. Biermasz et al. (2004) included a larger sample size in their investigation and reported similar results by applying five validated, health-related, quality-of-life questionnaires (ACRO-QOL, SF-36, NHP, MFI-20, and HADS). These tools cover a wide range of domains, and the existence of acromegaly was found to be significantly correlated to decreased physical ability, increased physical fatigue, increased role limitation due to physical problems, and increased joint pain.

Acromegaly has also been associated with lower self-confidence to maintain balance although no significant difference was found in the number of falls in the previous

12 months compared with PNA of similar age (Title et al., in press). In addition, PWA showed significantly adverse function on hip, knee, and ankle joints compared with age-, sex-, and BMI-matched patients with PNA (Title et al., in press). Other than age, sex, and ankle functional scores as the predictors of the level of self-confidence in both groups, hip functional score is an additional predictor of self-confidence level to maintain balance in PWA but not in PNA (Title et al., in press).

Though research is limited, it appears as though PWA live with deficits that affect their ability to physically function, perform locomotion, and keep balance. Many of these deficits may be a result of the effect of GH on joint structure and function.

2.2.2 Acromegaly arthropathy

Most individuals diagnosed with acromegaly will also be diagnosed with Acromegaly Arthropathy (AA), a collective term regarding abnormalities occurring in PWA's joints, and the predominant precursor to physical functional disability in PWA (Detendech et al., 1973; Bluestone et al., 1971; Colao et al., 2004; Miller et al., 2008; Wassenaar et al., 2009; Claessen et al., 2017). AA is a highly prevalent condition among PWA (Nunes et al., 2014; Detendech et al., 1973; Barkan, 2002). Signs and symptoms of AA include thickened cartilage, widened joint space, hypertrophied synovial tissues and ligaments, and joint misalignment. Along with psychiatric abnormalities, AA is one of the key drivers of poor quality of life in these patients. Previous studies stated that 50-70% of patients are diagnosed with AA at the time of diagnosis of acromegaly (Killinger et al., 2010; Claessen et al., 2017). Miller et al. (2008) compared the quality of life between PWA with and without joint pain, and concluded that lower quality of life scores, especially in the physical function domain (62.5 vs. 86.3 in SF-36; 59.9 vs. 79.7 in AcroQoL), were

related to the existence of joint pain due to AA. These findings showed that AA is a common and chronic complication in acromegaly and significantly impairs physical function. However, no association was found between the duration of uncontrolled acromegaly and the decline in physical function (Miller et al., 2008), additionally, the period of time from diagnosis of acromegaly to the onset of AA ranges from 0 to 27 years, with an average of 10.5 years (Colao et al., 2004), highlighting the difficulty in predicting and preventing physical function degeneration in these patients.

2.2.3 Regionality of AA

Data on the regional distribution of arthropathy in acromegaly is controversial. Some authors stated that large peripheral joints degeneration (shoulder, knee, hip) was reported less frequently than axial joint degeneration with neck and lower back pain as the most common complaint of these patients (Detendech et al., 1973; Barkan, 2002; Killinger et al., 2010). Layton et al. (1988), Barkan (2002) and Colao et al. (2004) stated peripheral joints were involved in 47-74% of PWA, whereas axial joints were involved in 20-50% of the patients, especially cervical and lumbar spine (Layton et al., 1988). Among all peripheral joints, the knee joint is the most vulnerable to AA due to its unique anatomical tissue structure (double-condyloid hinge joint), which allows it to biomechanically withstand larger shear force produced by constant sliding, rolling, and rotating motions throughout locomotion (Egloff et al., 2012), followed by shoulder, hip, ankle, elbow, and hand joints (Layton et al., 1988; Colao et al., 2004).

2.2.4 Signs and symptoms of AA

The most common symptom of AA is intermittent and chronic joint pain and crepitus with normal joint motion (Detendech et al., 1973; Bluestone et al., 1971; Podgorski

et al., 1988; Layton et al., 1988; Jacobs-Kosmina&DeHoratiusb, 2005). Joint swelling is also a common symptom of AA due to synovial thickness, periarticular tissue hypertrophy, or effusion (Bluestone et al., 1971; Colao et al., 2004; Jacobs-Kosmina&DeHoratiusb, 2005). Furthermore, widened joint space and thickened articular cartilage is common in AA (Wassenaar et al., 2011; Detendech et al., 1973). Formation of osteophytosis, cyst, and bone overgrowth with deformity in both weight-bearing and non-weight-bearing joints can be investigated by radiography and ultrasonography in patients with later-course AA (Kellgren et al., 1952; Bluestone et al., 1971; Detendech et al., 1973; Dons et al., 1988; Podgorski et al., 1988; Colao et al., 2004; Gadelha et al., 2019; Adigun et al., 2022).

2.2.5 Progression of AA

AA starts with an increase in cartilage thickness arising from the hyperfunction and proliferation of articular chondrocytes (increase in matrix synthesis), and the hypertrophy of periarticular tissues (tendon, ligament, synovial) arising from the hyperfunction of connective cells (Colao et al., 2004; Gadelha et al., 2019). These increases are followed by joint space widening and hypermobility of the joints (Colao et al., 2004; Gadelha et al., 2019). The signs are partially reversible and can be alleviated by GH and IGF-1 suppression (Colao et al.,2004; Gadelha et al., 2019). As the disease worsens, fissures will appear on the cartilage surface and increase in size gradually, arising from long-term exposure to abnormal mechanical loading on the joint, possibly leading to calcification of regenerated fibrocartilage and their development into osteophytes between cartilage and periosteum at the margin of the joint (Colao et al., 2004; Gadelha et al., 2019). Fissures could extend to the underlying bone if the disease becomes more advanced and lead to the formation of ulcers of articular cartilage and cyst of subchondral bone (Colao et al., 2004;

Gadelha et al., 2019). Progressive thinning of articular cartilage and narrowed joint space were observed in patients who have the most severe AA (Detendech et al., 1973; Colao et al., 2004; Gadelha et al., 2019). This stage of AA shares similar features to OA and controlling GH and IGF-1 is no longer effective in improving AA for this phase (Colao et al., 2004). AA was usually found to be noninflammatory with symptoms of Osteoarthritis (OA) only developing in the later course of AA (Detendech et al., 1973; Colao et al., 2004).

2.2.6 Osteoarthritis treatment for AA

There is limited research on the function, mobility, and balance deficits of PWA, but most of these patients experience AA, which can be one of the reasons for their impaired joint function, physical function, and balance. Although our understanding of AA is limited, there is extensive research on OA. Considering that OA also affects joint function and balance in patients, along with the fact that the treatment approaches for AA and OA are basically the same, some clues can be obtained by referring to OA.

OA is a disorder caused by degeneration of articular cartilage, risk factors include past injury, female sex, obesity, aging, and genetics (Sinusas, 2012; Egloff et al., 2012). Joint pain and limited range of motion are the most common symptoms in patients with OA, whereas, narrowed joint space, osteophytes, cysts, and joint destruction shown in radiography are common signs of OA (Sinusas, 2012). Thickening of articular cartilage is not typically observed in OA joints; on the contrary, thinning of articular cartilage is more commonly found in OA. The progression of OA is similar to the later course of AA, which starts with changes in the composition of the cartilage matrix resulting in articular cartilage surface peeling off, follows by the appearance of fissures accompanied by osteophytes and cysts (Goldring&Golding, 2016).

Conservative OA treatments have been used to treat AA. The treatment of acromegaly generally could partially improve some joint impairments, like joint pain, cartilage thickness, and joint widening, yet it cannot be cured completely (Dons et al., 1988; Layton et al., 1988; Barkan, 2001; Claessen et al., 2012; Gadelha et al., 2019). The current treatment for residual symptoms of AA is borrowed entirely from the traditional treatment of OA in the general population. These include analgesics, NSAIDS, physiotherapy, corticosteroid or thiotepa injections, aspiration, and surgical intervention (Detendech et al., 1973; Podgorski et al., 1988; Barkan, 2001). Surgical interventions are mainly for hip and knee joints and include cup arthroplasty, intertrochanteric osteotomy, prosthetic femoral head replacement, upper tibial osteotomy, and total joint arthroplasty (Detendech et al., 1973).

The different degeneration processes of cartilage and joint spaces observed in OA and patients with AA suggest that AA and OA joints are subjected to different mechanical loads. It is likely that different joint loading patterns have varying effects on cartilage deformation and chondrocyte viability (Abusara et al., 2011; Guilak, 2011), resulting in diverse impairments to joint integrity and joint function. Consequently, individuals with AA and OA may employ different compensation strategies in balance control while performing ADL.

2.2.7 Mechanical loading on AA and OA joint

The fibers within the articular cartilage are organized in a manner that creates a supportive network, adding structural integrity and rigidity to the articular cartilage, which enables it to withstand mechanical loads by distributing and dispersing compressive forces to the subchondral bone (Neumann, 2016). Additionally, the synovial fluid within the joint

contributes to shock absorbing and friction reduction, which diminishes the load during normal weight-bearing activities within a range that can be absorbed without damaging the underlying bone. In OA, the fibers within the articular cartilage fail to provide sufficient rigidity due to the damage of articular cartilage and the narrowed joint space exposes the subchondral bone to excessive and injurious contact pressure and compressive loading. These changes within the joint could lead to increased joint pain, reduced joint mobility, and gradual decline in the ability to walk (Ornetti et al., 2010; Li et al., 2013; Neumann, 2016).

The impact of the thickened articular cartilage and widened joint space in PWA on joint function has not been investigated yet. The first part of our project provided some initial insights into the joint function in PWA. Higher levels of joint pain and worse hip, knee, and ankle joint function score were observed in PWA in comparison to matched PNA (Title et al., in press). However, the extent to which the observed significantly impaired joint function affects walking ability and balance in PWA remains unclear.

2.2.8 Acromegaly functional disability and balance

Though understudied, physical functional deficits exist in acromegaly. These may be predominantly driven by the existence of joint dysfunction in the form of AA, such as joint hypermobility and reduced joint proprioception. The true impact of decreased joint function on the walking ability and balance in PWA is not well defined but considering that patients with OA experience a decline in balance, it is highly likely that the deterioration of joint function in PWA could challenge their walking ability and balance and lead to risk of falls.

2.3 Walking balance

2.3.1 Why balance is critical

Balance, also known as postural stability, is one's ability to keep or return the projection of the center of mass (CoM) within the base of support (the area between the limbs touching the ground) (Winter et al., 1990). Balance is fundamental to the completion of ADL in a safe manner, as individuals with balance deficits demonstrate increased susceptibility to falls (Cumming & Klineberg, 1994). Falls pose a significant public health concern, especially in the elderly and those with neurological and musculoskeletal disorders, as impaired balance and restricted mobility can severely impact one's health, ADL performance, and overall quality of life (Tinetti, 2003; Rubenstein & Josephson, 2002).

2.3.2 Balance in walking

The transition from a dual-limb stance phase to a single-limb stance phase introduces a period where the CoM briefly moves outside the base of support (MacKinnon & Winter, 1993). During that period, the system is not in a state of static balance. Achieving balance during walking involves swiftly repositioning the CoM back to within the base of support. Failing to promptly restore the CoM within the base of support can result in a loss of balance and increase the risk of falls (MacKinnon & Winter, 1993).

As mentioned before, walking is comprised of two phases, the double-limb stance phase, and the single-limb stance phase, associated with the swing phase on the contralateral limb. The stance phase can be further divided into three sub-phases: heel strike/loading response (initial stance phase), midstance, and push-off phase (later stance

phase). The swing phase can be further divided into three sub-phases: early swing, mid swing, and late swing phase.

The trajectory of the CoM, particularly in the mediolateral direction, is a typical technique to assess one's balance when walking (Tesio & Rota, 2019). The CoM is a single point in space that represents the average of the mass of the entire body. When people walk on a treadmill with no forward displacement, the CoM oscillates from side to side with the trajectory looking like a "bow-tie (∞)" towards the supporting side (Tesio & Rota, 2019). Furthermore, people with balance deficits always show a greater mediolateral shifting of the CoM (Tesio & Rota, 2019). This analysis of the CoM trajectory can only assess the balance impairment. Instead, it is imperative to investigate how the MSK system contributes to the CoM movement to uncover the underlying segmental function deficits responsible for the observed balance impairment. Since unaffected or disturbed human walking requires the movement of all body segments (Tesio & Rota, 2019), comprehension of the kinetics of each joint is crucial to gain a deeper understanding of the adaptive movements throughout the entire body to maintain balance.

Control of the pelvis, which necessitates the cooperation of hip musculature, is crucial for preserving overall body balance because the weight of the head and trunk acts downwards via the pelvis. To illustrate, when the heel strikes the ground, the pelvis of the heel striking side rotates forward in the transverse plane, accompanied by internal rotation of the thigh (Neumann, 2016; Lewis et al., 2017). To keep the toe pointed forward throughout the stance phase, the hip external rotators are activated to counteract the internal rotation moments. In addition, during the transition from the double stance to the single stance phase, the pelvis of the swing side tilts downward (drop) in the frontal plane, which

leads to adduction of the thigh of the supporting side (Neumann, 2016; Lewis et al., 2017). This downward drop of the swing side arises from the action of gravity on the trunk, which is controlled by pliometric contraction of the ipsilateral hip abductors (Neumann, 2016). Therefore, hip abductors (gluteus medius, gluteus minimus, and tensor fasciae latae) play an important role in keeping the pelvis level and keeping the trunk upright (MacKinnon & Winter, 1993; Neumann, 2016). If the hip abductors are not strong enough to provide enough abduction moment, there may be excessive sideways motion during the stance phase with the pelvis maintaining a drop on the side of the swing side. To compensate for this, one with weakened hip abductors may lean the trunk to the same side as the weakened side (stance side) to minimize the external moment demands on the hip abductors of the stance limb (Neumann, 2016). Additionally, the swing side's quadratus lumborum is also activated to level the pelvis and help stabilize the trunk on pelvis. Hip extensors are also activated to control from a forward lean of the body (Neumann, 2016).

These pelvis movements occurring during human walking serve to reduce the displacement of the body's CoM in both vertical and lateral directions, and excessive lateral movement of the pelvis could result in an amplified side-to-side displacement of the body's CoM (Neumann, 2016).

2.3.3 Loss of balance in Acromegaly

Dynamic balance deficits are commonly observed in acromegaly. Most of the previous studies applied clinical balance tests to measure PWA's dynamic balance (Table 1). To illustrate, Lopes et al. (2014) and Homem et al. (2017) used the Berg balance scale (BBS), relying on the interpretation of 14 ADL-simulating tasks, and found no significant difference in the dynamic balance between the two groups ($p=0.06$ and 0.05 respectively).

However, Atmaca et al. (2013) reported significantly lower BBS scores in PWA ($p=0.008$), indicating a higher risk of falls in PWA. The Falls Efficacy Scale – International was also applied by Homem et al. (2017) and Atmaca et al. (2013), where a significant difference was only observed by Atmaca et al. ($p=0.21$ vs. $p<0.001$), meaning higher concern to complete daily activities. Homem et al. (2017) also applied the Performance Oriented Mobility Assessment (POMA: a useful tool to assess one's balance and gait, consisting of 16 ADL-simulating tasks), the DGI (an instrument composed of 8 tasks related to gait modification to assess one's ability to modify their gait in response to different commands), and the TUG (an instrument to assess one's risk of fall) to study balance in PWA and able-bodied individuals. The study found significantly different POMA ($p=0.009$), DGI ($p=0.027$), and TUG scores ($p=0.031$) between the two groups. The discrepancy in the offset of acromegaly on BBS scores may be partially explained by either the difference in the statistical power (Lopes et al. n=28; Homem et al. n=17; Atmaca et al. n=48) or the differences in the ages of the sample population studied (Lopes et al. mean age=52 (43-61) years, no difference; Homem et al. mean age=67 (63-73) years, no difference; Atmaca et al. [49 (25-75) years, lower). Atmaca et al. (2013) included younger participants, and the gap in the balance between younger able-bodied individuals and younger PWA might be greater than the gap in the balance between older able-bodied individuals and older PWA. Homem et al. (2017) proposed that PWA have reduced dynamic balance due to declining peripheral muscle function, visual abnormalities, and increased use of medications. In addition, one study by Haliloglu et al. (2019) applied the Prokin device, which requires the participants to stand on a tilting board and maintain balance. Larger anterior-posterior Center of Pressure (CoP) shifting distance and front/right CoP shifting distance were

observed in PWA compared to healthy control, meaning impaired dynamic balance in PWA.

Table 1. Previous Literatures on dynamic balance in acromegaly.

	Berg Balance Scale (BBS)	**Performance Oriented Mobility Assessment (POMA)**	**Timed Up and Go (TUG)**	**Dynamic Gait Index (DGI)**	**Falls Efficacy Scale-International (FES-I)**	**Walking speed**
Homem et al. (2017)	No significant difference 50 (45–56) vs. 55.5 (50.5–56) P = 0.05	Lower in PWA Lower score, worse function P = 0.009	Higher in PWA Higher score, higher risk of falls P = 0.031	Lower in PWA Lower score, worse function P = 0.027	No significant difference 26 (20.5–39) vs. 26 (19–29.5) P = 0.21	
Lopes et al. (2014)	No significant difference 55.4 ± 1.12 vs. 54.9 ± 1.51 P = 0.06					
Atmaca et al. (2013)	Lower in PWA Lower score, higher risk of falls P = 0.008				Higher in PWA Higher score, high concern to complete daily activities P < 0.001	Slower in PWA P < 0.001

The disagreement in the results from these previous works of literature as to whether the dynamic balance is affected in PWA highlights the need for applying laboratory measurements to assess PWA's dynamic balance. However, no study was conducted to measure the balance during walking in PWA. Given the impaired joint function and neurological modifications in PWA mentioned before, these patients might experience deteriorated walking balance due to the role of the nervous system and MSK system in maintaining balance.

2.3.4 Biological systems contributing to balance

Good balance requires coordination between the sensory, motor, central nervous system (CNS), and MSK systems. The sensory system, which comprises visual, vestibular, and proprioceptive systems, provides humans with information about the body and the environment to maintain postural stability during body sway (Winter et al., 1990). The

visual system helps perceive stimuli from the environment as well as the orientation and movement of the body relative to the visual world. The vestibular system provides information on head orientation and acceleration in space by sensing the shifting of endolymph (fluid fills in the canal) within each semi-circular canal plane (Winter et al., 1990). The semi-circular canals in the inner ear include anterior, posterior, and lateral canals, which are orthogonal to each other. The shifting (magnitude and flow) of the fluid allows humans to sense the head rotation plane and magnitude of displacement. Furthermore, the otolithic organ situated in the inner ear is another organ assisting in sensing head positioning and spatial orientation by detecting the gravity-induced movement of calcium carbonate crystals. The proprioceptive system is composed of muscle, joint, and cutaneous receptors (Winter et al., 1990). The muscle spindle and Golgi tendon are the two main mechanoreceptors responsible for proprioceptive acuity, which provide information on local muscle mechanics, such as the position of each body segment and level of muscle effort (Macefield, 2009). The muscle spindle reacts to muscle lengthening, whereas the Golgi tendon reacts to muscle tension.

The summation of information from all three channels can be transferred to the CNS via afferent nerves where the optimal mechanics pattern can be identified, and motor commands be sent away to the MSK system via efferent nerves. The proportion of afferent information is not evenly distributed across different channels, the sensory contribution of different channels varies depending on the stimuli condition (Goodworth & Peterka, 2012). For instance, when standing on a tilting surface, one would reduce reliance on the proprioceptive system and use information from the other channels as compensation, as the proprioceptive system is most affected by the stimuli, relying too much on this system

would cause inefficiency of the CNS system to make a corrective motor command. It has been experimentally demonstrated that this sensory re-weighting strategy is applied in perturbed standing, steady gait, and perturbed gait (Goodworth & Peterka, 2012).

2.3.5 Neuromuscular control during walking

Walking, unlike standing, is under a continuous condition of imbalance due to the exchange of support from one limb to another (single stance phase). Good postural control during walking should meet two conditions: good neuromuscular control generating proficient motor patterns to complete propulsion, and the ability to produce the optimal response within a situation that includes both internal constraints (disturbances coming from within the body, such as segments' inertial properties and internal forces generated by muscle contractions) and external constraints (conditions imposed by the environment in which the action takes place, such as gravitational forces, imposed accelerations, or obstacles) (Barbeau et al., 1999; Massion, 1992). The process of postural control can be generally divided into two components, the first is keeping given segments in their original position against disturbances, and the second is controlling the trajectory of given segments (Massion, 1992). An example of this is the switching to single limb stance during walking, the base of support area becomes smaller and in order not to topple towards the swing side, the trunk and the supporting limb should be maintained as stable as possible to provide postural support for the movement as well as the trajectory of the passing limb should be controlled.

Ankle joint moments generation (to pull the leg into a vertical position) of the supporting limb and hip moments generation (to pull the whole body into a vertical position) are the two main strategies for postural control in the mediolateral direction (Kuo, 1999).

However, postural control is far more complicated than this, where precise locomotion pattern adjustments are required to meet intricate environmental demands (MacLellan, 2017). As stated by Massion (1992), the motor act is like an iceberg, where the visible aspect is the movement itself, and the concealed part, which is often more critical, involves the neuromuscular control to provide postural support to counteract the destabilizing effects initiate by the movement or by the environment. For instance, postural muscles would be activated in a feedforward manner prior to the onset of the intended movement, and this is called anticipatory postural responses (Binder et al., 2009). An example of this is that when raising an arm during standing, leg and trunk muscles are activated before the activation of the shoulder abductors (Cordo & Nashner, 1982). This anticipatory response reduces or disappears when one's upper body leans on a horizontal bar at chest height. Anticipatory postural control adjustments also appear during gait initiation, these adjustments include accelerating the CoP backward and toward the swing side due to the relaxation of plantar flexors and activation of dorsiflexors (Jian et al, 1993; Lepers & Breniere, 1995). The movements of the CoP induce the acceleration of the CoM moving forward and towards the stance side to preserve balance and reach a steady-state gait (Lepers & Breniere, 1995). These adjustments end at the onset of the swing foot leaving the floor.

The anticipatory postural responses observed in these scenarios suggest that the human neuromuscular system possesses pre-programmed responses to deal with various scenarios instead of relying on an improvised action plan (Winter et al., 1990). In summary, balance control is a result of the cooperation of the neuromuscular system and the MSK system, CoM measurements can indicate if one has good or impaired balance but cannot

indicate how one controls balance, and why balance is impaired. Investigating the coordination of the hip muscles is essential to understand how one maintains balance by controlling the pelvis.

2.3.6 Gait kinetics analysis

Joint moments and power adjustment play a major role in correcting imbalance during both steady gait and disturbed gait. Joint moments are the capability of a force generated by all internal structures around a joint to cause rotation of the segment around the joint. Joint power refers to the net rate of energy generation or absorption, energy generation happens when a muscle generates force by shortening (miometric contraction), while energy absorption happens when a muscle generates force by lengthening (pliometric contraction) (Sloot & Krogt, 2017). Joint moments and power are measurable variables of kinetics analysis, kinetics is an analysis investigating causes of changes in movement patterns and potential muscle dysfunction, it could provide information on the underlying MSK problems (Sloot & Krogt, 2017).

In contrast to joint moments, which are consequences of a force generated by surrounding tissues, joint power is a variable that exhibits the transfer of conservation mechanism (energy flows) between muscle groups (Winter, 1990). Energy flows are the cause of the movements, without them, no motion can occur (Winter, 1990). Due to the valuable insights provided by joint power into how individuals regulate and adjust energy flow to maintain balance, joint power is considered a more informative and discriminative factor in distinguishing various aspects of pathological gait (Winter & Robertson, 1978; Winter, 1990).

2.3.6.1 Joint moments and power in gait

Gait deviations in certain populations can be identified by comparing them with normative data from able-bodied individuals. The first two columns of Figure 1 show net external joint moments from a normative dataset of 13 healthy adults (Robertson et al., 2013) and joint powers (the third column) from a normative dataset of 20 healthy adults (Bovi et al., 2011). The gait cycle is divided into the stance phase and swing phase, the standing phase can be further divided into the heel strike phase (initial stance phase), midstance phase, and push-off phase.

The heel strike phase starts when the heel contacts the floor to foot flat on the floor, during this process, the ankle joint starts with a neutral position followed by a 15-degree plantarflexion, accompanied by an internal dorsiflexion moment arising from the pliometric contraction of ankle dorsiflexors to control plantarflexion caused by gravity. The knee joint starts with a brief internal flexion moment generated by a pliometric contraction of the knee extensors to control weight acceptance when the heel touches the ground, resulting in energy absorption (K1). The hip joint starts generating power through a miometric contraction of the hip extensors to control the forward acceleration of the thigh, resulting in energy generation (H1).

The midstance phase starts from foot-flat to prior to heel-off. At the ankle, the acceleration of the shank is controlled by a pliometric contraction of the dorsiflexors, resulting in energy absorption (A1). The knee joint starts with an extension moment exerted by the miometric contraction of the knee extensors, resulting in energy generation (K2). The hip joint continues extending until a flexion moment is exerted by a pliometric

contraction of the hip flexors just before the push-off phase to control the backward acceleration of the thigh, resulting in energy absorption (H2).

The push-off phase consists in the period from heel-off to toe-off. An ankle plantarflexion moment generated by the miometric contraction of the ankle plantar flexors to propel the whole body upward and forward results in energy generation (A2). A pliometric contraction of the knee extensors exerts a knee extension moment that inhibits the collapse of the knee and results in energy absorption (K3). At the hip joint, hip flexion moments are exerted by miometric contraction of hip flexor, resulting in energy generation (H3).

During the swing phase, it can be seen from Figure 1 that small moments are exerted in all three joints except during the end of swing. At that time, a knee flexion moment is exerted through a pliometric contraction of the knee flexors to control the forward acceleration of the shank (energy absorption, K4). Furthermore, a hip extension moment is exerted by a pliometric contraction of the hip extensors to control the forward acceleration of the thigh, resulting in a slight energy absorption. In the frontal plane, both hip and knee joints exert abduction moments to stabilize the joint.

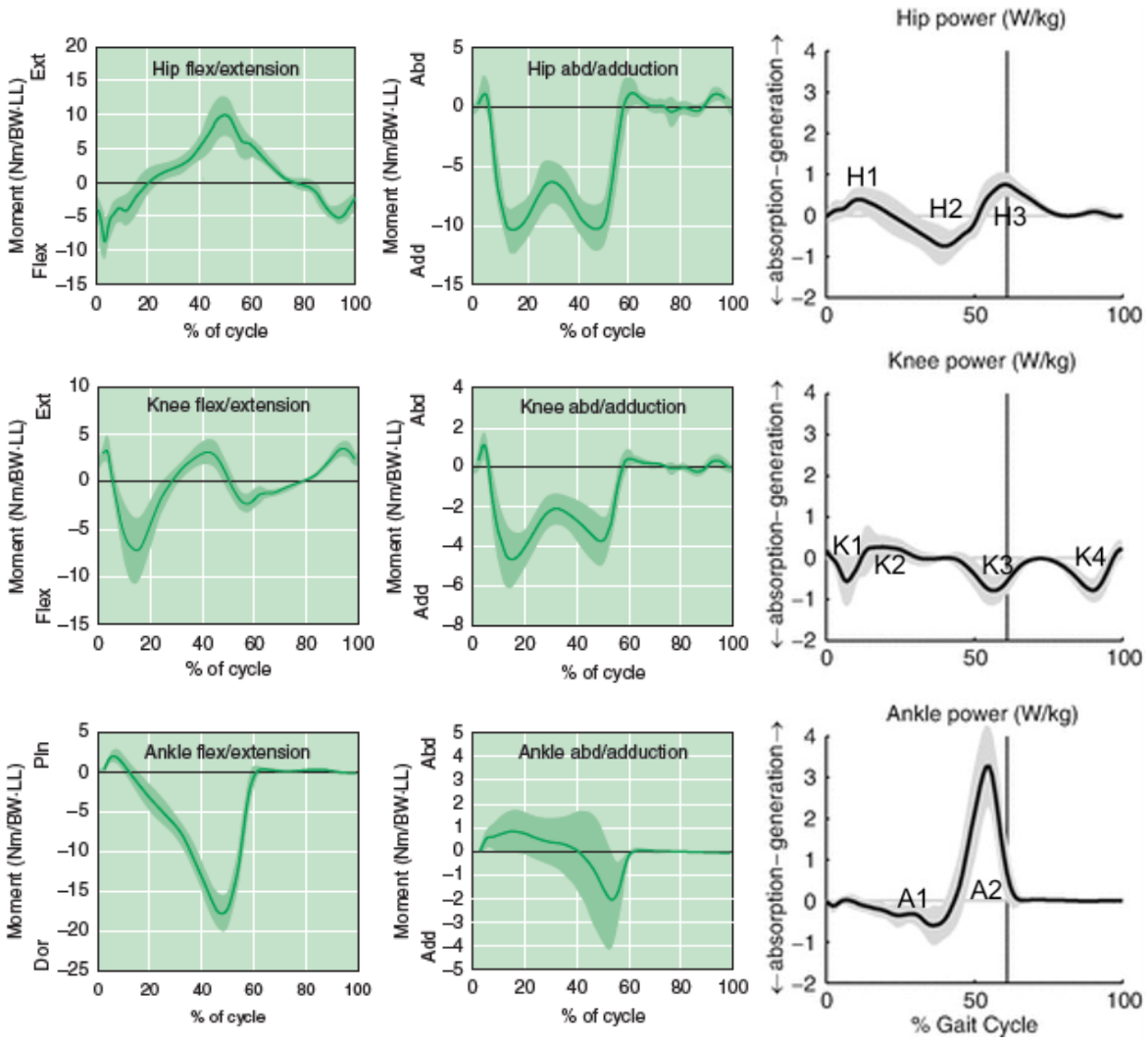


Figure 1. Net external joint moments curves and joint power curves of the hip, knee, ankle during a stride cycle of walking.

From a normative dataset of 13 and 20 healthy adults (Adapted from Robertson et al., 2013; Bovi et al., 2011). The solid line represents the mean value, the band represents standard deviation.

2.3.6.2 Clinical interpretation of joint moments and joint power

Determining the joint moments is critical in assessing the overall load on the tissues around a joint, such as muscles, ligaments, or bones. Higher joint moments may result from excessive loading of any of these components (Sloot & Krogt, 2017). To localize the underlying problem, electromyography (EMG) can be used to determine if higher joint moments are exerted by muscles. Higher joint moments are generally accompanied by

higher muscle activity, but if no significant muscle activation is detected, it may indicate a passive force generation by muscle or ligaments. Conversely, if muscle activity is detected on the antagonists, it suggests an even greater joint load due to the co-contraction of both agonist and antagonist. The factors contributing to lower joint moments can be broadly categorized as either muscle weakness or muscle function inefficiency (Sloot & Krogt, 2017). Muscle weakness can result in an insufficient generation of force required to rotate the segment. In contrast, muscle function inefficiency can occur when the moment arm decreases due to joint morphology changes or an abnormal point of rotation, which forces muscles to exert more effort to complete the movement.

Joint power plays a crucial role in efficient propulsion movements while minimizing energy dissipation. Positive and negative joint power refers to energy generation and absorption, respectively. During gait initiation, the hip joint is the primary contributor to generating energy for the propulsion of the first leg, while ankle push-off (A2) is the main energy source for accelerating the second leg upon the first leg's ground contact (Zhao et al, 2021). Ankle push-off is important as it reduces energy dissipation in the contralateral leg during foot-ground contact. An insufficient A2 power burst due to muscle weakness, or spasticity, results in greater energy dissipation in the contralateral limb, requiring increased muscle activity, specifically by the hip flexors (H3), to ensure proper propulsion (Judge et al., 1996). Research has shown that using hip flexors as the primary energy source during push-off is four times more energy-intensive than relying on ankle plantar flexors (Kuo, 2002). This can lead to overuse injuries and negative impacts on hip musculature. Weak ankle plantar flexors can potentially cause hip pain, therefore, the combined analysis of joint moments and joint power around each joint is necessary to

identify the underlying cause of gait abnormalities, as symptoms in one joint may not necessarily result from local abnormalities.

2.3.6.3 Kinetic Deviation in Patients with Hip OA

As previously mentioned, controlling the pelvis is crucial for minimizing the movement of the CoM during walking and maintaining balance. Furthermore, hip muscles coordination plays a vital role in pelvis control. Individuals with hip OA have been observed to adopt a compensatory gait pattern to reduce the load on the hip joint and alleviate pain. Typically, when the affected side serves as the supporting limb, these patients exhibit a lateral bending of the trunk towards the affected side, known as Duchenne limp, due to hip abductor muscle weakness (Reininga et al., 2012). This compensatory mechanism reduces the demand for generating hip abduction moments (Reininga et al., 2012). Since the coordination of hip muscles and pelvis control in PWA remains unknown, a comparison of gait kinetics in patients with hip OA might be more instructive.

Early-stage hip OA is associated with smaller hip flexion moments in midstance and peak hip extension, a larger peak ankle plantarflexion and peak ankle dorsiflexion moments (Eitzen et al., 2012). Whereas late-stage hip OA is associated with decreased hip abduction, flexion, and external rotation moments (Meyer et al., 2018) as well as reduced hip adduction, extension, external and internal rotation moments (Hurwitz et al., 1997). The decreased joint moments can convey decreased joint loading. This decrease in joint loading might result from decreased force produced by muscle or ligament, the inefficiency of producing force, or shortened force arm due to osteophytes. These findings were in line with McCrory's study (McCrory et al., 2001). They used vertical ground reaction force to quantify abnormal limb loading and found that patients with hip OA present bilateral

asymmetry in limb loading even after hip replacement surgery and rehabilitation regime, with reduced loading on the affected side. Long-term use of an abnormal load pattern can affect other joints and counteract the surgery effect. Diamond et al. (2020) also indicated lower limb loading in patients with hip OA when compared to healthy controls. The asymmetry of limb loading in patients with hip OA is consistent with the asymmetry of joint power in patients with hip OA. These patients present with reduced hip joint power bursts on the affected side and with more power produced by the knee and hip on the unaffected side (Queen et al., 2019). This is similar to Meyer et al. (2018)'s finding of reduced hip flexor power absorption (H2) and hip flexor power generation (H3) in patients with hip OA compared with healthy controls. Except for the knee flexors, patients with hip OA have significantly reduced muscle strength on the affected side for almost every muscle group (knee extensor, hip flexor, extensor, abductor, and adductor) compared to healthy controls (Arokoski et al., 2002; Rasch et al., 2010; Zacharias et al., 2016; Diamond et al., 2020).

When the muscle weakness pattern is combined with the walking kinematic deviations, patients with hip OA seem to apply two strategies to avoid pain. First, the hip reduced range of motion and reduced hip flexor power absorption is compensated by increased pelvic anterior tilt and lumbar lordosis in patients with hip OA (Murray et al., 1971; Hurwitz et al., 1997). Second, the decreased hip adduction angle (Meyer et al., 2018) is thought to increase mediolateral postural stability during locomotion by decreasing the demand on the weak abductor muscles. Gait retraining should be applied with caution in patients with hip OA with weak hip abductors since imposing normal walking kinematics would result in excessive joint contact forces (Valente et al., 2013). Therefore, hip abductor

strengthening seems to be the first and foremost intervention to restore normal gait patterns in patients with hip OA. This understanding of the walking kinetic deviation in patients with hip OA can help in the understanding of the gait pattern modification in patients with AA. Therefore, it could potentially improve the quality of life for patients with AA and help clinicians tailor their treatments accordingly.

2.3.7 Human Gait Adaptation in Stepping Over Obstacles

Studying walking when the pattern needs to be adapted might be a more sensitive way to detect balance deficits. As such, walking over obstacles requires higher demands in pelvis control by controlling the trajectory of the greater trochanter (GT) of the limb going over the obstacle side as well as modifying the normal patterns of muscle energy status (generation, transfer, and conservation).

Current research in the field has largely centered on the study of steady-state gait. However, it is important to acknowledge the limitations of exclusively analyzing steady-state gait in our efforts to comprehend the intricacies of locomotion control (Patla et al., 1991). To gain a more comprehensive understanding of the complex interplay between various systems involved in postural control, it is imperative to study transitory changes in locomotor patterns under disturbed conditions (Patla et al., 1991). Many rehabilitation professionals proposed that assessing balance during multitasking (doing more than one activity at the same time, such as walking forward while concurrently looking up, or walking and crossing an obstacle) is a more sensitive indication of balance loss than assessing balance while doing a single task (Chiu et al., 2006) as it requires higher levels of balance and pelvic obliquity control, thus a higher level of demand for coordination and cooperation of each system. As mentioned above, the ability to adapt movement patterns to human behavioral purposes and disturbed environmental stimuli is also required to

perform good postural control during walking, as when we navigate the physical world, we encounter obstacles and uneven terrain. Therefore, in order to analyze comprehensively the effect of acromegaly on walking balance, it is necessary to explore the performance of PWA in both walking and obstructed walking.

Unilateral and bilateral obstacles are usually used in experimental setups. The difference is that the demands of energy generation and absorption, adjusting foot trajectory, support of body weight, and postural control of the upper body increase when crossing bilateral obstacles as well as when the obstacle height increases (Barbeau et al., 1999; Ladouceur et al., 2005). The term "cross" and "supporting" limbs are used to describe unilateral obstacle avoidance, while "lead" and "trail" limbs are used for bilateral obstacle avoidance. Ladouceur et al. (2005) observed that different motor strategies were applied when an obstacle was placed unilaterally at mid-swing, unilaterally at late swing, and bilaterally at late swing. The toe height changed proportionally with the obstacle height, regardless of whether it was unilateral or bilateral, at mid-swing or late-swing, with an adaptation slope equal to one. However, there was a significant difference in greater trochanter height adaptation when crossing unilateral obstacle at mid-swing compared to other obstacle placements, with a smaller increase in greater trochanter height (Ladouceur et al., 2005).

Anticipatory postural responses are planned prior to the initiation of crossing (McFadyen et al., 2018) and rely on visual guidance. The planning process is largely controlled by the posterior parietal lobe which guides the necessary movement adaptations (Lajoie & Drew, 2007). When an obstacle is presented in a random delay, the latency to react to an obstacle has been shown to be shorter than voluntary stride adjustments. This

indicates the involvement of the autonomic nervous system, the activation of subcortical structures, and the pre-established contingency adjustments at an unconscious level during obstructed walking (Weerdesteyn et al., 2004; Zgaljardic et al., 2010).

In addition to the anticipatory adjustments generated when walking over an obstacle, a distinct reorganization of lower limb energy was also found during obstructed walking compared to walking, with an emphasis on increasing both hip and knee flexion through biarticular muscle activation, instead of focusing on increasing knee flexion through knee flexors during walking (Winter et al., 1991). MacLellan (2017) investigated the muscle activation during obstructed walking of healthy young adults by using EMG. Increased activation of erector spinae (spine extensor), gluteus medius (hip abductor), biceps femoris, and semitendinosus (hip extensor and knee flexor) was observed during the stance phase of trail limb compared to normal walking. An active knee flexor strategy (K5: energy generated by miometric contraction of knee flexors in the cross (lead/trail) limb) is unique for obstacle avoidance to increase the elevation of the limb (McFadyen et al, 1994). McFadyen and Prince (2002) compared the gait between 20 young and elderly males during level walking, bilateral obstacle crossing, and stepping. Figure 2 shows net muscle powers in the sagittal plane for the trail limb knee joint. Figure 3 shows net muscle powers in the frontal plane for the trail limb hip joint. From the two figures, decreased knee extensor energy absorption (K3) and decreased hip abductor energy absorption (H1F) followed by the appearance of knee flexor energy generation (K5) and increased hip abductor energy generation (H2F) were observed while crossing the obstacle. The decreased K3 and H1F to the extent of a reversal to K5 and H2F is an anticipatory motor adjustment to avoid an obstacle (McFadyen et al., 1994).

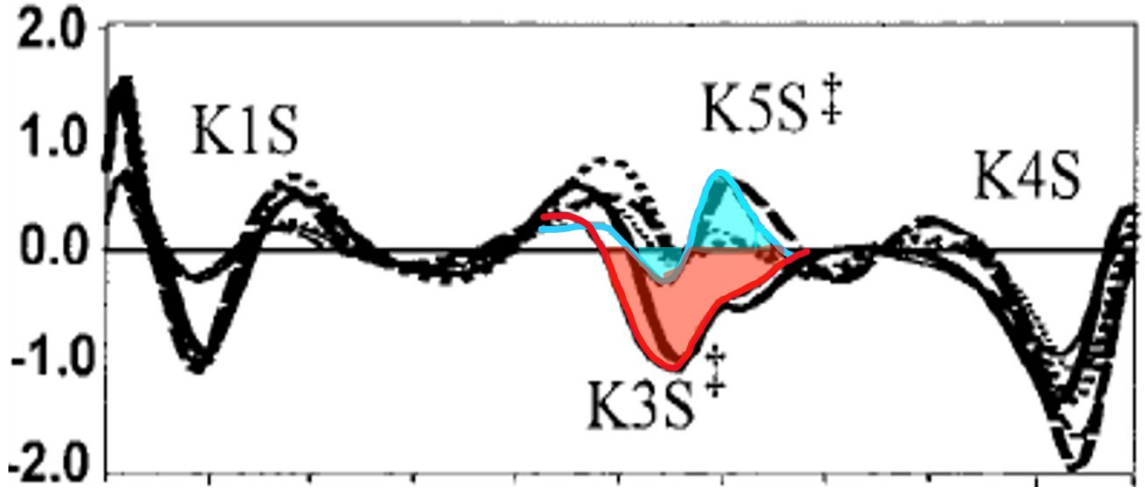


Figure 2. Net muscle powers in the sagittal plane for the trail limb knee joint.

X: Gait cycle; Y: Joint power. Blue: Obstacle crossing; Red: walking. Data are presented across the young (thick curves) and elderly (thin curves) subjects for the unobstructed (solid curve), obstacle (dashed curve), and platform (dotted curve) conditions. Main effects are shown for age (†) and for environment (‡). Positive power indicates generation and negative power indicates absorption (Adapted from McFadyen & Prince, 2002).

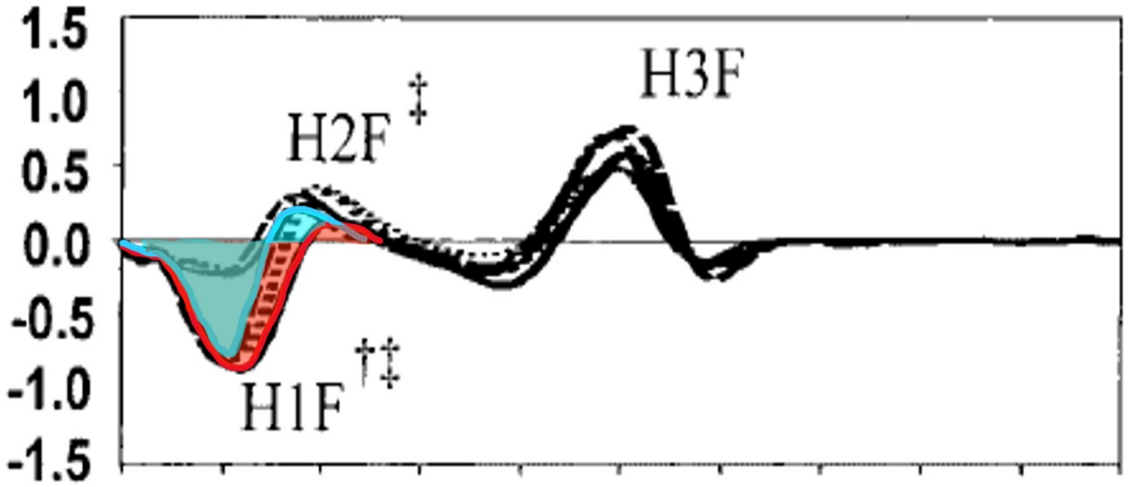


Figure 3.Net muscle powers in the frontal plane for the trail limb hip joint.

X: Gait cycle; Y: Joint Power. Blue: obstacle crossing; red: walking. Data are presented across the young (thick curves) and elderly (thin curves) subjects for the unobstructed (solid curve), obstacle (dashed curve), and platform (dotted curve) conditions. Main effects are shown for age (†) and for environment (‡). Positive power indicates generation and negative power indicates absorption (Adapted from McFadyen & Prince, 2002).

2.4 Gaps in the literature

To date, most studies assessed general dynamic balance in acromegaly, no study systematically assessed the walking balance in this population, even if these patients showed deficient dynamic balance and higher odds ratio of fracture. Besides, no study analyzed if different strategies were used during walking by these patients to maintain balance given the impaired joint function and deteriorated nerve function in PWA. In our experiment, a kinetic gait analysis was used to quantify the gait pattern and evaluate these patients' walking balance.

2.5 Specific aims and hypotheses

The goal of this whole project is to study the severity of arthropathy and the regional disparities of the functional impact of arthropathy symptoms on different joints of PWA (Appendix A) and analyze changes in the standing and walking balance of PWA.

2.5.1 Specific Aim

Acromegaly triggers and is associated with peripheral nervous system modifications and joint degenerations, which are considered to impact PWA's walking balance. Therefore, to better understand if these systematic degenerations impact the transitory adaptations in locomotor patterns of these patients, this study aims to establish the walking balance deficits of PWA and compare them to PNA. Given that PWA exhibited longer distal motor latency of the median and lateral popliteal nerve (Jamal et al., 1987), they might react differently to the obstacle. Besides, the prime mover muscles (knee flexors of crossing limb) and postural synergies (muscles of supporting limb and trunk) were activated before the onset of crossing, therefore, this study focused on the late stance phase of the swing limb and the early stance phase of the supporting limb.

2.5.2 Hypotheses

1) PWA will spend more time to complete the TUG test.

2) PWA will have lower DGI scores compared with PNA.

3) PWA will exhibit different walking balance outcomes (supporting limb H1, H1F, K1 and crossing limb K3, K5) from PNA.

Chapter 3: Methods

This thesis is a section of a larger project investigating arthropathy in individuals with acromegaly. This thesis mainly focused on the assessment of the changes in walking balance associated with acromegaly. The walking balance outcome measures included the TUG scores, DGI scores, lower limb joint moments, and joint power during normal walking and unilateral obstructed walking. Kinematic and kinetic data were collected using an OptiTrack Motion Capture system and AMTI force plate system. Paired sample t-tests were used to determine if there is any significant difference of demographic characteristics and scores from functional tests (TUG and DGI) between the two groups. A 2-way repeated measures ANOVA was used to determine if there is significant interaction between the effects of acromegaly and obstructed walking on lower limb joint power. SPM was used to examine differences in lower limb joint power adaptations between the two groups.

3.1 Participants

Participants with confirmed diagnosis of acromegaly (PWA group) and participants with non-secretory pituitary adenoma (PNA group) were recruited from the Endocrinology clinic in Halifax, NS. The study was approved by the Nova Scotia Health Authority research ethics board. Informed Consent was obtained both during the recruitment phase for the initial survey measure (online consent) and prior to the movement analysis data collection. Participants received the informed consent document by email following the scheduling of their laboratory appointment. The document was thoroughly reviewed and signed upon the participants' arrival at the laboratory.

PNA as a control group that had undergone pituitary surgery was used to avoid confounders caused by the tumor or surgery, such as visual disturbance, and ensure the outcomes arise purely from GH excess. For each PWA (n=8), a sex, age (+/- 4 years), BMI

(+/- 6 kg/m^2) matched PNA was included in the study, except for one pair with the 11-year difference in age and 9 kg/m^2 difference in BMI. Those matching criteria were selected to control for confounding factors, as sex, age, and BMI have been shown associated with OA (Keefe et al., 2000; Anderson & Loeser, 2010; Hartz et al., 1986). The exclusion criteria for this study included: the inability to finish a 10-meter walk independently, a physical disability not related to acromegaly, neurological or vestibular disorders, drug or alcohol abuse, an amputation, and a diagnosis of inflammatory arthritis.

A priori power analysis, and previous studies, determined that an appropriate sample size of the number of participants would range from 15 to 20. However, external circumstances (time limitation and limited list of participants) were factors in some of the recruiting challenges. This thesis is reporting the results from our first 8 pairs of participants that were recruited.

3.2 Equipment

Physical tools included an OptiTrack Motion Capture system, AMTI force plate system (Figure 5), timer, unilateral obstacle with adjustable height (Figure 6). Two clinical balance tests were also applied, which were the TUG test and the DGI test.

3.2.1 OptiTrack Motion Capture system

Calibration and walking trials were captured using a 14-camera OptiTrack Motion Capture system, at a sample frequency of 200Hz. A frame rate of 200Hz, which is higher than the most used sampling rate (Nagymate & Kiss, 2018), was employed in this study to ensure the accurate capture of any rapid movements that occur within the higher frequency range.

This system contained three components: retroreflective markers, which can be attached to certain bony landmarks of the participant's body; 14 cameras, which can

receive the signals reflected from the markers and transfer data to the computer; and software that can record the trajectory of the markers and provide us a file containing the 3-dimensional position of each marker. The motions of body segments were tracked by 20 retroreflective markers placed on specific bony landmarks, namely ASISs, PSISs, medial and lateral femoral epicondyles, medial and lateral malleolus, 1st metatarsal heads, 5th metatarsal heads, big toes, heels, and 4 markers on each rigid body attached on right and left thighs and shanks (Figure 9).

The OptiTrack system is used to collect, analyze, and evaluate human motion. The accuracy of a 12-camera OptiTrack system at 100 Hz on dynamic linear accuracy and gait kinematics was performed by Thewlis et al. (2013). The system was compared to a 12-camera Vicon system and a comparable accuracy was observed between the two systems with deviation less than 1% from the known length, and less than 4° from gait angular parameters. Aurand et al. (2017) also proved that this system had high validity and reliability. It was found that a system consisting of 42 cameras had an error in marker motion of < 0.02mm in 97% of the measurement volume. In addition, it was found that a system consisting of 21 cameras had an error in marker motion of < 0.2mm in 91% of the measurement volume. It was explained that the only position where the error was above this threshold was at the most distant margin of the measurement volume.

3.2.2 AMTI Force plate system

The AMTI force plate system (6-Degree of Freedom dimensions; x,y,z – pitch, roll, yaw; Watertown, MA) with two force plates was used to measure kinetic data in 2000Hz. This is above the recommended sampling frequency (Gudavalli et al.,2013, 1000Hz), for

walking for ground reaction force data collection, but was needed to be used for EMG data collection required by other projects using the same software.

The AMTI force plate system contained three components: the force plate, the amplifier, and the software. The force plate involved four 3-axial force sensors enclosed in the plate, the analog signals are collected via these sensors. Then signal amplification is required before data from the force plate can be used, the raw voltage from the force plate was amplified by the amplifier (MSA-6 Mini Amp, AMTI, Watertown, MA) with a predetermined gain value set to 1000 and sent to the A/D converter (National Instruments 6341 X Series Multifunction DAQ), which was used to convert the analog signal to digital signal. This conversion into a digital signal was done using a software called Mr. Kick that provided a file containing the raw digitized data. These digital signals were converted to force and moments by a pipeline embedded in Visual3D using the calibration matrix in the AMTI force plate manual. The CoP was calculated by Visual3D automatically. The force plate is considered to be the gold standard for the measurement of ground reaction force (GRF) in 3 axes (X, Y, Z), which enables us to calculate the joint moments of force and joint power (Sgrò et al., 2015). The OptiTrack system and Force plate system data collection was synchronized through a TTL pulse from the force plate data acquisition system, data collection continued for 10 seconds onwards.

3.2.3 Timed Up and Go Test

TUG is a tool to assess one's risk of falls, which quantifies the finished time to perform given tasks (Homem et al., 2017). A strong correlation between one's risk of falls and dynamic balance level was stated by Lopes et al. (2014); therefore, we can get a rough estimation of one's dynamic balance from TUG scores. In this test, participants were asked

to start in a seated position, then stand up, walk straight for 3 meters, then turn around, walk back, and sit down (Figure 4). The time it took to complete the whole process was recorded. The equipment includes a standard chair (46cm seat height and 63-65cm armrest height), tape measure, colored tape to mark off the 3-meter path, and a stopwatch to time the performance.

This test has been shown to be valid and reliable enough to assess older adults' ability to maintain dynamic balance and perform normal gait (Podsiadlo & Richardson, 1991). The TUG was described as correlated with log-transformed scores on the Berg Balance Scale (r=-0.81) and gait speed (r=-0.61) (Podsiadlo & Richardson, 1991). Besides, Gautschi et al. (2016) stated that the TUG has excellent intra-rater and inter-rater reliability with ICC equal to 0.97 and 0.99, respectively.

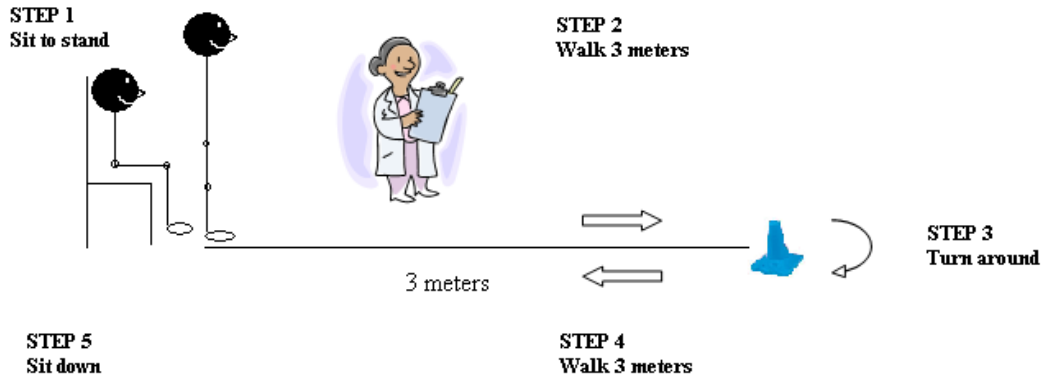


Figure 4. The procedure of the TUG test.

3.2.4 Dynamic Gait Index

The DGI is a tool utilized to assess an individual's capacity to modify their gait and the risk of falls. The test requires the participants to smoothly adjust their gait while maintaining balance in response to eight distinct instructions, including gait on a flat surface, change in gait speed, gait with horizontal and vertical head turn, gait and pivot turn, step over and around obstacles, and climbing up and down stairs. Each task is rated

on a scale of 0 (lowest level of function) to 3 (highest level of function), and the total score ranges from 0 to 24. A lower score indicates a more severe disability, and scores $\leq$ 19 suggest an increased risk of falls.

In a study conducted by Shumway-Cook et al. (1997), the sensitivity and specificity of the DGI were assessed using 22 community-dwelling older adults with a history of falls and 22 without a history of falls. Results indicated that 59% of those with a history of falls and 64% of those without were correctly classified based on a score of 19 or less. The intra-rater and inter-rater reliability of the DGI were tested by Jonsson et al. (2011), with the ICC for intra-rater and inter-rater reliability for the total DGI score calculated at 0.90 (95% CI, 0.76-0.96) and 0.87 (95% CI, 0.73-0.95), respectively. Furthermore, Chiu et al. (2006) conducted a study to retrospectively retrieve clinical records of 84 community-dwelling veterans who were over 64 years old using the Rasch measurement model to evaluate the psychometric properties of the DGI. The average logit measures for the four rating scales (normal, mild impairment, moderate impairment, severe impairment) showed a monotonic increase from -1.32 to -0.37 to 0.66 to 2.16 logits, indicating that the DGI can distinguish between subjects of different ability levels. Additionally, the item difficulty order was determined by utilizing the Rasch logit measures. Gait on a flat surface was the easiest item with the lowest logit measures, whereas gait with horizontal head turn was the most challenging task with the highest logit measures, which demonstrated a clear hierarchical order in difficulty that is consistent with clinical expectations.

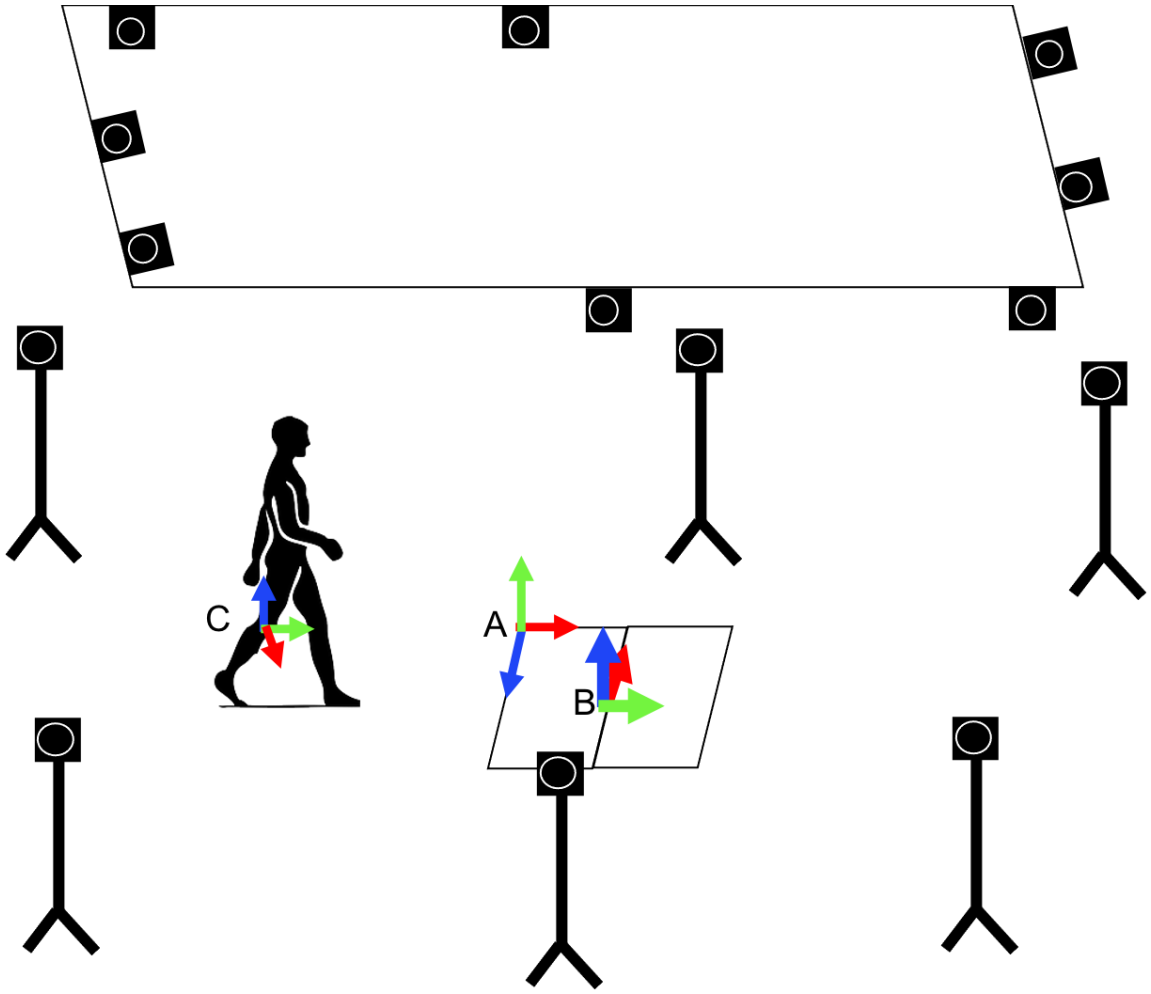


Figure 5. The OptiTrack Motion Capture system and the AMTI force plate system.
A: ISB/Global/MoCap coordinate system; B: Force plate coordinate system; C: joint coordinate system. Red: x axis; green: y axis; blue: z axis.

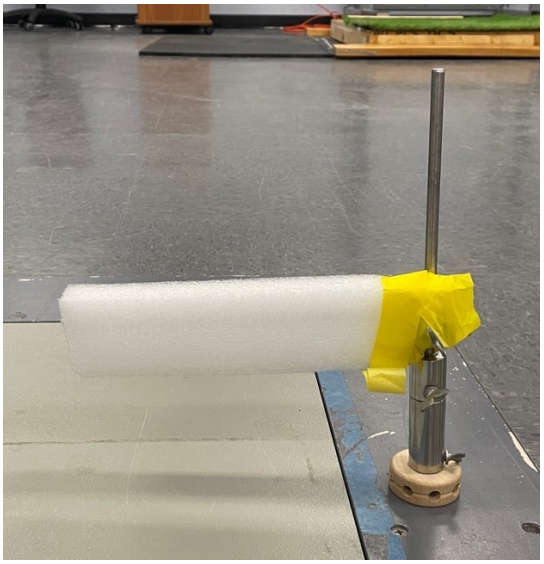


Figure 6. Obstacle with adjustable height.

3.3 Experimental protocol

3.3.1 General Procedures

Figure 7 shows the general flow of the whole project. Only the 2nd, 3rd, 6th, 7th, 9th, and 10th step were reported in this thesis, which was the walking balance part.

1. Prior to the laboratory visit, participants answered the initial survey on their computers.

2. Upon arrival at the laboratory, informed consent was obtained, and participants changed into the required clothes (tight-fitting/sleeveless tops, sports shorts, or yoga pants).

3. The first measurements done in the laboratory were the participants' mass and height.

4. Following these measurements, and to measure standing posture, retro-reflective markers were attached bilaterally on selected bony landmarks based on the model used by Lopes to measure joint alignment (Appendix E).

5. Once the retro-reflective markers were applied, the participants were asked to stand in the anatomical position (with the palms facing forward) for 3 seconds.

6. Upon completion of the standing posture measurement, the marker positions were modified to represent a Six Degrees of Freedom (6DoF) model (Figure 9) (Collins et al., 2009; Buczek et al., 2010).

7. The anthropometric properties (length and circumference) of each segment were then established using a tape measure as per (Figure 8).

8. Following these measurements, the participants completed a Romberg test which aimed to measure standing/static balance.

9. Following the standing/static balance assessment, the participants were asked to walk across a 10-meter walkway with and without obstacles 10 times each. The height of the obstacle was set to 10% of the participant's leg length. The limb used to cross the obstacle

(cross leg) was selected by the subjects. The criteria for a successful trial consisted of not touching the obstacle and having the soles of both feet land on the force plate in respective. 10. Finally, the participants completed the TUG test and DGI test after the obstructed walking assessment.

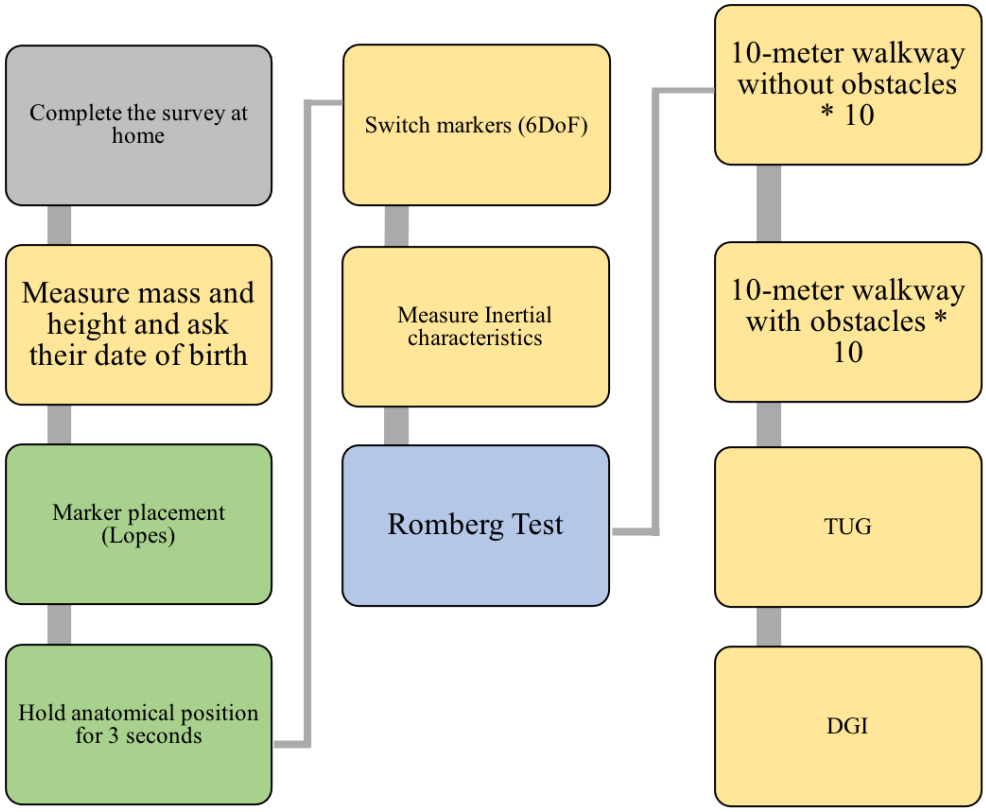


Figure 7. The general procedure of the experiment.

Grey: First part of the whole project (Appendix C); Green: Posture assessment (Appendix E); Blue: standing balance assessment; Yellow: walking balance assessments used in this study.

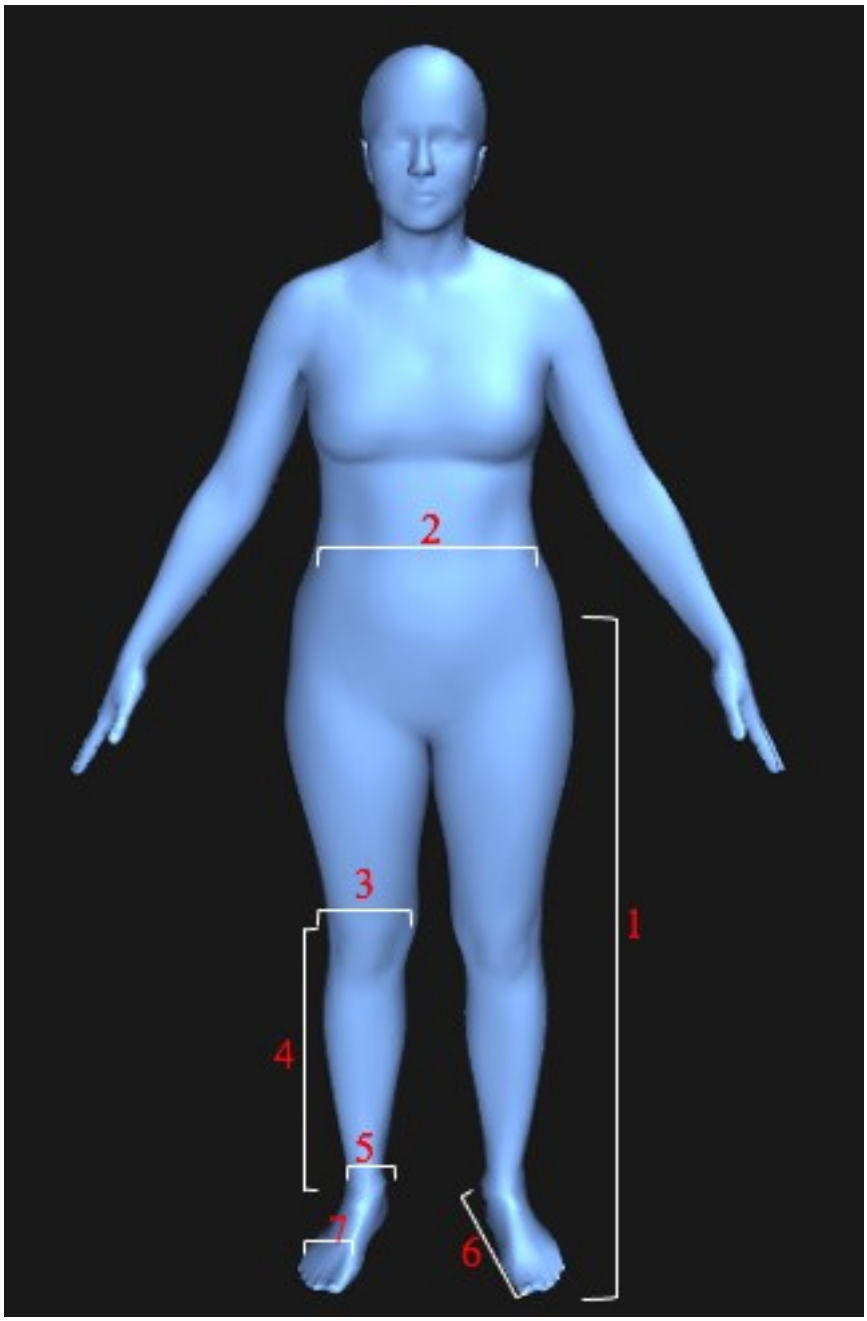


Figure 8. Inertial properties measured to establish the inertial characteristics of the body segments.

1: Leg length (Height – Seat height); 2: RASIS → LASIS; 3: Diameter of distal thigh (RFME → RFLE); 4: Shank Length (RFLE → RFAL); 5: Diameter of distal shank (RFAL → RTAM); 6: Length of foot (RTAM → RTOE); 7: Diameter of distal foot (R5MH → R1MH). ASIS: Anterior Superior Iliac Spine; FME: Femoral Medial Epicondyle; FLE: Femoral Lateral Epicondyle; FAL: Lateral Malleolus; TAM: Medial Malleolus; 5MH: Fifth Metatarsal Head; 1MH: First Metatarsal Head. See Appendix A for details.

3.4 Data Processing

3.4.1 Data uploading and processing

Marker position and ground reaction force data were uploaded to Visual3D (C-Motion, Germantown, MD), and a lowpass Butterworth filter with cutoff frequencies of 6 Hz was used to filter the digitized signals. Four rigid bodies were used to track the participants' motion during walking, each of them containing four markers. Cappozzo et al. (1997) stated that the number of markers on each rigid body should be equal to or larger than four, because the axes of the bone-embedded frame are defined by a plane determined by three non-collinear points. To illustrate, one axis is defined along the line connecting two markers, the plane established by the three markers is taken perpendicular to the second axis, and the cross-product of the first two axes gives rise to the third axis. Therefore, at least three markers are required to construct the bone-embedded frame. However, the markers may be hidden during motion capture, to prevent this from happening, four markers are the minimum requirement for accurate model construction. After filtering the data, a model could be created according to the position of the markers from a static trial, then the linked segments can be defined based on the 6DoF Model (Figure 9). Afterward, joint angles, joint moments, and joint powers were calculated.

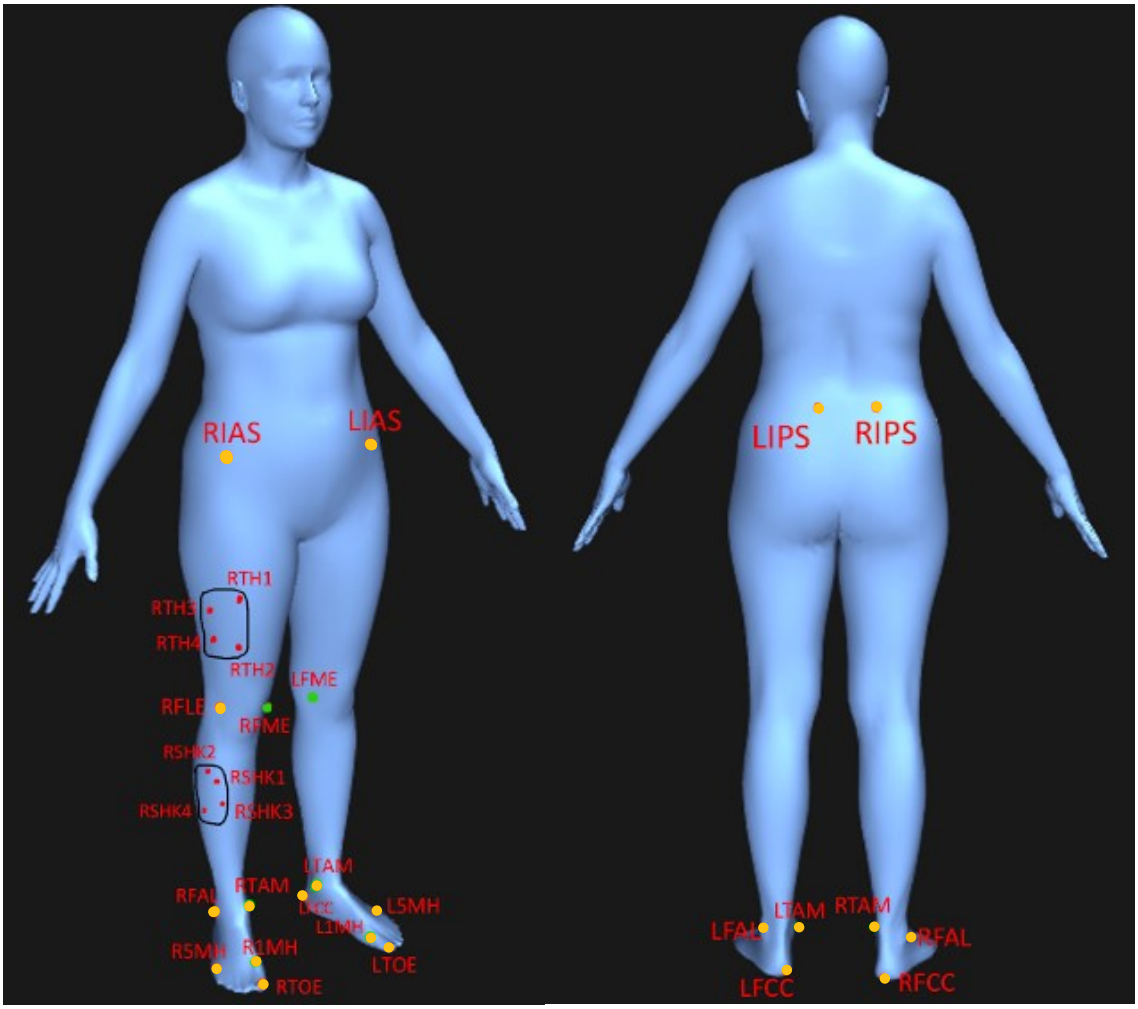


Figure 9. 6DoF model.

Yellow dots: Anatomical markers; Red dots with black frame: Tracking markers; Green: Calibration markers, will be removed after static trial. Definitions for each marker were listed in Table 2.

Table 2. Definitions for the 6DOF set.

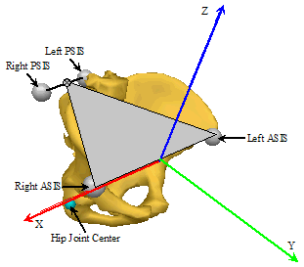
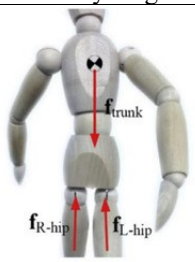
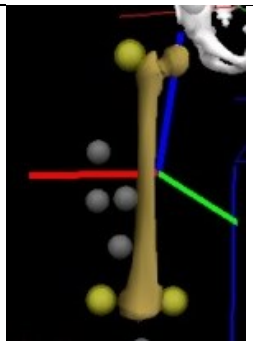
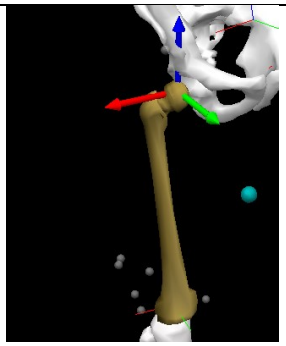
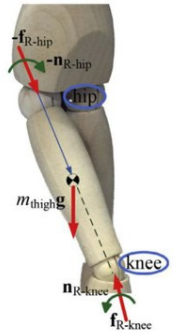
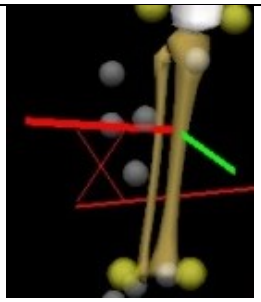
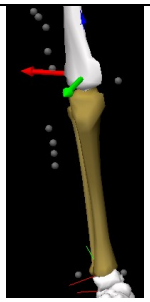
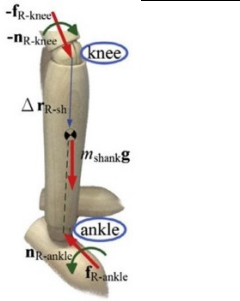
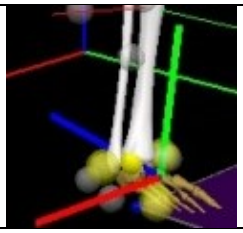
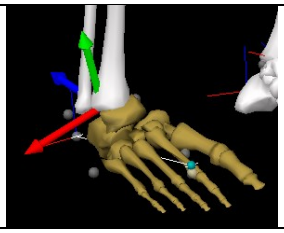
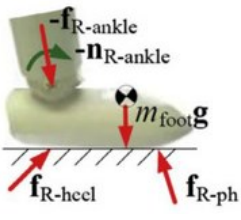
Anatomical sets	Description	Identification
L/RIAS	Most prominent point of left and right ASIS	Anatomical marker
L/RIPS	Most prominent point of left and right PSIS	Anatomical marker
L/RFLE	Most prominent point of lateral femoral epicondyle	Anatomical marker
L/RFME	Most prominent point of medial femoral epicondyle	Calibration marker
L/RFAL	Most prominent point of lateral malleolus	Anatomical marker
L/RTAM	Most prominent point of medial malleolus	Anatomical marker
L/R1MH	Most medially prominent point of 1st metatarsal head	Anatomical marker
L/R5MH	Most laterally prominent point of 5th metatarsal head	Anatomical marker
L/RTOE	Left and right toe	Anatomical marker
L/RFCC	Most prominent point of calcaneus	Anatomical marker
Thigh(L/RTH1-4)	Rigid cluster of four markers, placed laterally with over wrap	Tracking marker
Shank(L/RSHK1-4)	Rigid cluster of four markers, placed laterally with over wrap	Tracking marker

Anatomical sets are used to define the segment coordinate systems (internal virtual landmarks are also required for some segment definitions). Separate clusters are used for tracking. Calibration markers are used to calibrate joint center and will be removed after the static trial.

3.4.2 Model Building in Visual3D

Table 3 indicates the segment coordinate systems, joint coordinate systems, and free body diagrams of pelvis, thigh, shank, and foot segment.

Table 3. Segment coordinate systems, joint coordinate systems, free body diagrams of each segment included in the biomechanical model (Adapted from Ancillao et al., 2018).

	Segment coordinate systems	Joint coordinate systems	Free body diagrams
Pelvis			
Thigh			
Shank			
Foot			

X axis: red; Y axis: green; Z axis: blue. The direction of the arrow is positive; the opposite direction is negative. Ground reaction forces are the forces from the ground to the foot (fR-heel, fR-ph). The Ankle, Knee, Hip joints all have joint forces (fjoint) and moments (njoint).

3.4.2.1 Pelvis segment

The pelvis was modelled with the CODA pelvis model within Visual3D. The Anterior Superior Iliac Spine (ASIS) and the Posterior Superior Iliac Spine (PSIS) anatomical positions were used to define the pelvic segment. Table 3 (first column, first row) shows that the midpoint between left and right ASIS is the origin of the pelvis segment coordinate system. The plane in grey travelling though right and left ASIS, as well as the mid-point of the right and left PSIS, is specified as the x-y plane of the segment coordinate system. From the origin to the right ASIS is the X axis (red). The Z axis (blue) is defined as the axis perpendicular to the x-y plane. The cross product of the X axis and the Z axis is the Y axis (green). The pelvis joint coordinate system was the hip joint coordinate system, which will be discussed in section *3.4.2.2*.

3.4.2.2 Thigh segment

The thigh segments were created using the hip joint center as the proximal end of the thigh, the knee joint center as the distal end of the thigh. The right and left hip joint center (R/LHJC) landmarks were established automatically when the pelvic segment was created, the landmark's location was specified as follows (Bell et al., 1989; Bell et al., 1990):

RHJC=(0.36*ASIS Distance,-0.19*ASIS Distance,-0.3*ASIS Distance)

LHJC=(-0.36*ASIS Distance,-0.19*ASIS Distance,-0.3*ASIS Distance)

The knee joint center, as defined by Hanavan (1964), was located at the lower end of thigh, on the center line, which was halfway between the medial and lateral epicondyle of the knee. The radius of the proximal thigh was set to half of the distance between left and right anterior superior iliac spine (ASIS). Four markers on the thigh cluster were defined as the tracking targets.

The left and right hip joint coordinate system (Table 3, second column, second row) originated at the left and right hip joint center, respectively. The axis passing from the knee joint center to the hip joint center was defined as the Z axis (vertical). Vector v from the medial to the lateral femoral epicondyle was then calculated. The cross product of the Z axis and vector v was defined as the Y axis (anterior). The cross product of the Z and Y axes was defined as the X axis (lateral).

The direction of the axes of the thigh segment coordinate systems was the same as the hip joint coordinate systems. The thigh segment coordinate system originated from the location of the COM of the thigh, which will be discussed in section *3.4.2.5*.

3.4.2.3 Shank Segment

The knee joint center was used to identify the proximal end of shank. The ankle joint center was used to identify the distal end of shank. The ankle joint center was located at the lower end of shank, on the center line, which was the midpoint between the medial and lateral malleolus of ankle. The radius of the proximal shank was half of the distance between medial and lateral epicondyle. Four targets on the shank were selected as the tracking targets.

The knee joint coordinate system (Table 3, second column, third row) originated at the midpoint between medial and lateral knee epicondyle. The axis from the distal end (ankle) to the origin was defined as the Z axis (vertical). Vector v from the medial to the lateral epicondyle was calculated, the cross product of the Z axis and vector v was defined as the Y axis (anterior), the cross product of the Z and Y axis was defined as the X axis (lateral).

The direction of the axes of the shank segment coordinate systems was the same as the knee joint coordinate systems. The shank segment coordinate system originated from the location of the COM of the shank, which will be discussed in section *3.4.2.5*.

3.4.2.4 Foot Segment

The proximal end of the foot was defined by the ankle joint center. The toe target was used to define the distal end of the foot. The radius of the proximal end of the foot was defined as half of the distance between the medial and lateral malleolus. The radius of the distal end of the foot was defined as half of the distance between the first and fifth metatarsal.

The ankle joint coordinate system (Table 3, second column, fourth row) originated at the ankle joint center. The Z axis was defined as the axis from midpoint of the first and fifth metatarsal head to ankle joint center. Vector v was defined as the axis passing from the medial to lateral malleolus. The cross product of the Z axis and vector v was defined as the Y axis. The cross product of the Z and Y axis was defined as the X axis. The Z axis was no longer vertical and was not a convenient representation for joint angles calculation. Therefore, a virtual ankle joint coordinate system was also built for kinematics use only.

The virtual ankle joint coordinate system originated from the heel target. The Y axis was defined as the axis from the origin to the toe target. Vector v was defined as the axis passing from the medial to the lateral malleolus. The cross product of the Y axis and vector v was defined as the Z axis. The cross product of the Y and Z axis was defined as the X axis.

The direction of the axes of the foot segment coordinate systems was the same as the ankle joint coordinate systems. The foot segment coordinate system originated from the location of the CoM of the foot, which will be discussed in section *3.4.2.5*.

The joint and segment coordinate systems built in Visual3D were different from the ISB coordinate system, which X axis as anterior, Y axis as vertical, and Z axis as lateral.

3.4.2.5 CoM location

The origin of each segment coordinate system was located on the CoM location of each segment. The CoM of a segment is the location representing the concentrated mass of the segment. Visual3D approximates the shape of a segment using frusta of right circular cones (Figure 10) to calculate the CoM position, as outlined by Hanavan (1964). Three parameters define this shape: the length (L), the proximal radius ($R_{proximal}$), and the distal radius (R_{distal}). The CoM sits along the vector going between the proximal and distal ends of the segment at a proportional distance, c, from the proximal end of the segment. The value of c can be calculated using:

$$x = R_{distal}/R_{proximal}$$
$$R_{distal} < R_{proximal}: c = (1+2x+3x^2)/4(1+x+x^2)$$
$$R_{distal} > R_{proximal}: c = 1 - (1+2x+3x^2)/4(1+x+x^2)$$

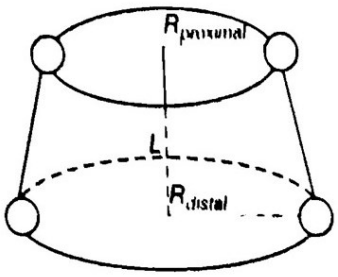


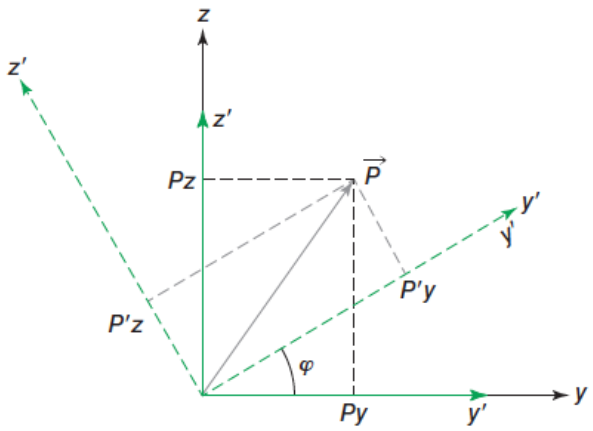
Figure 10. A frustum of right cones. Created by cutting the top from a cone such that the cut is parallel to the base of the cone.

3.4.2.6 Segment mass

Visual3D's default segment masses are based on Dempster's body segment parameters (Dempster, 1955; Robertson et al., 2013). The default segment masses (as a percentage of total body mass (kg)) are Foot (1.45%), Shank (4.65%), Thigh (10%), and Pelvis (14.2%).

3.4.3 Calculation of Joint Angle

Hip angles, knee angles, ankle angles of the right limb during walking were calculated in Visual3D using 6 degrees of freedom pose estimation and a Cardan XYZ sequence of rotations (X: flexion/extension; Y: abduction/adduction; Z: axial rotation, equivalent to joint coordinate system). The right-hand rule was used to determine the sign of joint angles and joint internal moments of force, with positive values referring to hip flexion, adduction, internal rotation, knee extension, adduction, internal rotation, ankle dorsiflexion, inversion, internal rotation. The proximal segment was used as the reference segment. Joint angles consisted in the transformation from one joint coordinate system to another joint coordinate system with the same origin. A simple 2D explanation can be found below:



The green and black are two coordinate systems, the green coordinate system (x'y'z') rotated by an angle ø, the rotation matrix can be written at $R_x = \begin{pmatrix} cos\text{ø} & sin\text{ø} \\ -sin\text{ø} & cos\text{ø} \end{pmatrix}$. The vector $\vec{P}$ can be transformed into $\overrightarrow{P'}$ by $\overrightarrow{P'} = R_x\vec{P}$, $\begin{pmatrix} y' \\ z' \end{pmatrix} = R_x\begin{pmatrix} y \\ z \end{pmatrix}$.

3.4.4 Calculation of Internal Joint Moments

Ground reaction forces and moments caused by the ground reaction force can be measured using AMTI force plate system. Internal joint moments of force were calculated

using standard 3D inverse dynamics methods, which is a technique to calculate the net joint moments using measured kinematics and ground reaction force. Moment of force can be calculated as the cross product of a force and the position vector from the application of the force to the pivot, M = r x F. The joint force is the reaction force between adjacent segments. From Newton's 3rd Law, every force has an equal and opposite reaction force. The ground reaction force is the force exerted on the human body by the ground as a result of contact with the ground (See Table 3 for details). Taking foot as example, the ankle joint force could be calculated as:

$\Sigma F_{foot} = m_{foot}a_{foot}$ $F_{ankle} + m_{foot}g + F_{GRF} = m_{foot}a_{foot}$ $F_{ankle} = m_{foot}a_{foot} - m_{foot}g - F_{GRF}$

where m is mass, a is acceleration, g is gravity acceleration, F_{ankle} is ankle joint force, which can be derived from resultant force on the foot minus weight minus ground reaction force.

The proximal couple moments could be calculated by Visual3D as:

$M^{i}_{foot} = I_{foot}a_{foot}' + \omega_{foot}' \times (I_{foot}\omega_{foot}')$

where I=moment of inertia, a=angular acceleration, ω=angular velocity.

$\sum M_{foot} = M^{i}_{foot}$

$M_{ankle} + M_{GRF} - r_{ankle\ to\ foot} \times F_{ankle} + (r_{ankle\ to\ grf} - r_{ankle\ to\ foot}) \times F_{GRF} = M^{i}_{foot}$

where $r_{ankle\ to\ foot}$ refers to vector from ankle to foot CoM, $r_{ankle\ to\ grf}$ refers to vector from ankle to the CoP.

$M_{ankle} = M^{i}_{foot} - M_{GRF} + (r_{ankle\ to\ foot} \times F_{ankle}) - [(r_{ankle\ to\ grf} - r_{ankle\ to\ foot}) \times F_{GRF}]$

$= M^{i}_{foot} - M_{GRF} + [r_{ankle\ to\ foot} \times [m_{foot}(a_{foot} - g) - F_{GRF}]] - [(r_{ankle\ to\ grf} - r_{ankle\ to\ foot}) \times F_{GRF}]$

$= M^{i}_{foot} - M_{GRF} - [r_{ankle\ to\ grf} \times F_{GRF}] + r_{ankle\ to\ foot} \times [m_{foot}(a_{foot} - g)]$

3.4.5 Calculation of Joint Power

Power is defined as the rate of work, the quantity of energy created or transmitted per unit time (van der Kruk et al., 2018). The measurement of work includes direct method and indirect method. The direct method used force times displacement, or moments of force times angular displacement. The indirect method calculated the sum of kinetic energies (the rate of change of kinetic energy) and potential energies (frictional power (due to air resistance), environmental power (due to external forces and moments), gravitational power). Point Mass Method is one of the indirect methods using the sum of gravitational potential energy (mass*g*height) and the translational kinetic energy (1/2 mass*velocity^2). However, this method was too simple for human movement analyses, because the human body comprises multiple segments, a better way is calculating the sum of each segment's energy. Each segment's energy can be calculated as the sum of gravitational potential energy, translational kinetic energy, and rotational kinetic energy (1/2 mass moment of inertia about CoM*angular velocity^2). The drawback of this method is that if a person stands still with no height or velocity change, the external work will be zero. Joint power analysis is the most commonly used analysis for human walking (Winter, 1991), which used the sum of force power (net force times velocity) and moment power (moments of force times joint angular velocity). Joint power analysis was used by using a pipeline embedded in Visual3D. Energy was calculated by using the trapz function in Matlab.

3.5 Outcome Measures

The outcome measures of the study consisted of: 1. Two functional tests (TUG and DGI, explained in the next paragraph) scores that are used to assess the risk of falls of the participant, and 2. Selected power burst of the supporting limb (H1, H2, H1F, H2F,

K1, K2) and crossing limb (K3, K5) (Table 4). These power bursts were compared between the two groups (PWA vs. PNA) and two walking conditions (walking vs. obstructed walking). In addition, the mean difference of the power curve between walking and obstructed walking (Joint power during obstructed walking – joint power during walking) of the two groups was compared.

Table 4. Outcome Measures.

		Outcome Measures	
Dynamic gait balance	Function tests	TUG Score	
		DGI Score	
	Walking vs. Obstructed walking	Supporting limb	H1, H2
			H1F, H2F
			K1, K2
		Crossing limb	K3, K5

Additional biomechanical measures were also recorded, including spatiotemporal, joint angles, and moments. These are not considered as primary outcomes. However, they may provide some additional information regarding differences between groups in joint power. Therefore, some of this data is presented in the results section. Specifically, these include walking speed, stride length, joint angles, and joint moments.

3.6 Statistical Analyses

Statistical analysis was performed using the SPSS Statistics Premium for Mac. Z-score (±1.96) transform of skewness/standard error of skewness was used to determine normal sampling distribution. Paired sample t-tests, Chi-square tests, and Fisher's exact tests were applied for group comparison of parametric and non-parametric demographic characteristics. Paired sample t-tests were applied to compare the TUG scores, walking speed, and stride length. Wilcoxon signed rank tests were applied to compare the DGI scores due to the abnormally distributed sampling distribution. The repeated-measures 2-way ANOVA was used for evaluation of the 2 groups (PWA vs. PNA) x 2 conditions

(Walking vs. Obstructed Walking) factorial design on H1, H2, H1F, H2F, K1, K2 of supporting limb, K3, K5 of crossing limb. Time series differences between PWA and PNA of selected variables were analyzed using Statistical Parametric Mapping (SPM). The selected variables for the walking condition were for joint power in the sagittal plane (hip, knee, ankle joint power) and the frontal plane (hip power). The selected variables for the obstructed walking condition was the difference in the means of joint power between obstructed and unobstructed conditions (joint power during obstructed walking – joint power during walking) in the sagittal plane (hip, knee, ankle joint power) and frontal plane. The SPM was calculated using the spm1d toolbox (www.spm1d.org). SPM is a technique to compare time series data (a complete waveform) instead of discrete data (a mean, maximum, or minimum). Significance was set to $p<0.05$.

Chapter 4: Results

4.1 Demographic characteristics of study participants

Of the 25 patients with acromegaly initially recruited, 10 patients refused to participate, 4 patients agreed to participate but were unable to travel, 2 patients could not be reached, and 1 patient passed away. Therefore, the PWA group eventually had 8 patients. Tables 5 and 6 outline the general demographic characteristics of the two groups. The PWA group comprised 5 males and 3 females with an average age of 54.9 ± 10.7 years, and BMI of 34.1 ± 6.5 kg/m^2 (Table 5). 1 patient was excluded from the analysis of obstructed walking because of the inability to finish the task. The disease is controlled in 7 patients (87.5%), 8 patients (100%) underwent pituitary adenoma removal surgery, 3 patients (37.5%) underwent pituitary radiation, 2 patients (25%) were taking acromegaly medication, and 2 patients (25%) underwent joint replacement surgery (Table 6). Of the 21 patients with non-GH-secreting pituitary adenoma initially recruited, 9 patients refused to participate, 2 patients agreed to participate but were unable to travel, 1 patient passed away, and 1 patient was excluded due to missing a match. Therefore, the PNA group eventually had 8 patients (5 males and 3 females) with an average age of 56.1 ± 9.5 years, and BMI of 33.6 ± 6.8 kg/m^2 (Table 5). All patients underwent pituitary adenoma removal surgery (Table 6). Table 5 indicates no significant difference in age, BMI, and sex distribution between PWA and PNA with p-values of 0.46, 0.84, and 1.00, respectively.

Table 5 also presents the results of the previous survey about joint function scores, which indicates no statistically significant difference in joint function between PWA and PNA. However, given the statistical power of the analysis, our findings suggest a trend towards adverse joint function scores from the questionnaires (Appendix C) in PWA for weight-bearing joints, such as the hip (HOOS scores: 69.8 vs. 88.37), knee (KOOS scores:

70.4 vs. 83.4), and ankle (FAAM scores: 0.7 vs. 0.9), as well as lower confidence in maintaining balance (ABC-6 scores: 0.6 vs. 0.86). Table 7 presents the demographic characteristics of each matched pair. For each PWA (n=8), a sex, age (+/- 4 years), and BMI (+/- 6 kg/m^2) matched PNA was included in the study, except for one pair (the first row) with the 11-year difference in age and 9 kg/m^2 difference in BMI.

Table 5. Demographic characteristics and previous functional survey results of PWA and PNA.

	PWA (n = 8)		PNA (n = 8)		t-stat	p-value	Cohen's d
	Mean	SD	Mean	SD			
Age (y)	54.9	10.7	56.1	9.5	-0.78	0.46	-0.27
BMI (kg/m^2)	34.1	6.5	33.6	6.8	0.22	0.84	0.08
Age at diagnosis (y)	42.6	10.7	50.1	9.1	-2.03	0.08	-0.72
Years since diagnosis (y)	12.3	10.7	6.0	2.7	1.52	0.17	0.54
HOOS	69.80	28.10	88.37	15.83	-1.63	0.15	-0.58
KOOS	70.36	21.51	83.38	18.32	-1.35	0.22	-0.48
FAAM	0.70	0.34	0.90	0.23	-1.06	0.33	-0.40
ABC-6	0.60	0.31	0.86	0.19	-2.32	0.05	-0.82
Paired sample t-test (df=7)							

HOOS: Hip dysfunction and Osteoarthritis Outcome Score for Joint Replacement (0-100, higher score, better hip function); KOOS: Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (0-100, higher score, better knee function); FAAM: Quick-Foot and Ankle Ability Measure (0-100%, higher score, better ankle function); ABC-6: The Shortened Activities-specific Balance Confidence scale (0-100%, higher score, higher confidence level to maintain balance) (Appendix C).

Table 6. Non-parametric demographic characteristics of PWA and PNA.

	PWA (n = 8)		PNA (n = 8)		p-value
	n	%	n	%	
Female[2]	3	37.5	3	37.5	1.00
Acromegaly controlled	7	87.5			
Pituitary surgery[1]	8	100.0	8	100.0	1.00
Pituitary radiation	3	37.5			
Acromegaly medication use	2	25.0			
Joint replacement surgery	2	25.0	0	0	

[1]Chi Square test
[2]Fisher's Exact Test

Table 7. Demographic characteristics of each matched pair.

Pair	PWA					PNA				
	Age	BMI	Sex	Hip/knee replacement	Crossing limb side	Age	BMI	Sex	Hip/knee replacement	Crossing limb side
1	37	20.77	M	NA	R	48	29.68	M	NA	L
2	58	29.75	F	NA	NA	62	24.52	F	NA	R
3	74	38.06	M	NA	R	75	32.10	M	NA	L
4	56	38.16	M	left right knee	L	53	35.14	M	NA	R
5	49	34.94	F	NA	R	50	37.98	F	NA	L
6	59	32.43	M	NA	L	58	33.22	M	NA	R
7	58	37.79	M	right hip	L	58	29.12	M	NA	R
8	48	40.91	F	NA	L	45	47.22	F	NA	L

NA: Not applicable. One patient in pair 2 did not complete the obstructed walking.

4.2 Functional tests results

4.2.1 DGI scores

Figure 11 and Table 8 show the participants' DGI test scores. No significant difference was revealed among with DGI score between PWA and PNA with p-value = 0.18, only two participants in PWA did not get full marks.

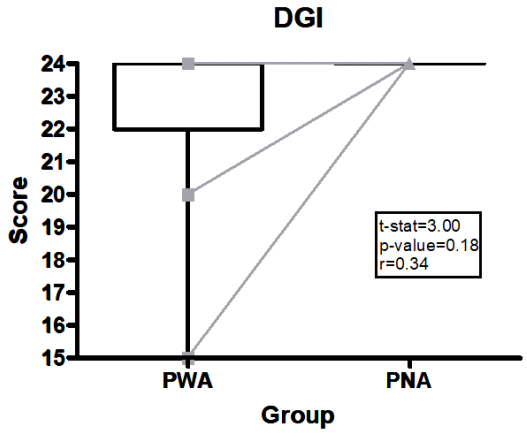


Figure 11. DGI scores of PWA and PNA.
The boxplot includes Maximum, 75th percentile (Q3), Median, 25th percentile (Q1), and Minimum (arranged from top to bottom). In the PWA group, the Maximum, Q3, and Median were coincident since six out of the eight participants achieved full marks. Similarly, in the PNA group, the Maximum, Q3, Median, Q1, and Minimum were coincident as all participants in this group attained full marks. The Grey squares represent the scores of each participant, with squares coinciding when participants achieved the same score. The grey lines in the plot represent the comparison between the two participants within the same pair.

4.2.2 TUG scores

Figure 12 and Table 8 show the participants' TUG test scores. A significant difference in TUG scores was observed with a longer time to complete the task in PWA (PWA: 10.42 ± 2.97s; PNA: 8.00 ± 0.84s; p-value = 0.04). The grey lines represent the comparison of the scores between the two participants within the same pair. The upward-sloping grey line indicates that two participants in the PWA group took less time to complete the TUG test compared to their match in the PNA group (represented by the bottom two grey squares in PWA). Furthermore, only one participant in the PWA group

(corresponding to the grey square on the maximum line in PWA) was classified as a high risk of falls, with a score exceeding 14s.

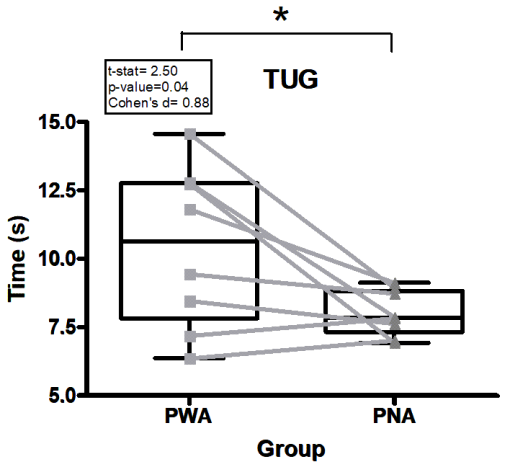


Figure 12. TUG scores of PWA and PNA.
The boxplot includes Maximum, 75th percentile (Q3), Median, 25th percentile (Q1), and Minimum (arranged from top to bottom). The Grey squares represent the scores of each participant, with squares coinciding when participants achieved the same score. The grey lines in the plot represent the comparison between the two participants within the same pair.

Table 8. Patients' functional tests scores, walking speed and stride length.

	PWA (n = 8)		PNA (n = 8)		t-stat	p-value	Cohen 's d
	Mean	SD	Mean	SD			
TUG score (s)[1]	10.42	2.97	8.00	0.84	2.50	0.04	0.88
Walking speed (m/s)[1]	1.07	0.23	1.22	0.12	-1.54	0.17	-0.54
Walking stride length (m)[1]	0.77	0.19	0.95	0.09	-2.28	0.06	-0.81
Obstructed walking speed (m/s)[1]	0.93	0.23	1.07	0.11	-1.45	0.20	-0.55
Obstructed stride length (m)[1]	0.78	0.20	0.88	0.13	-1.13	0.30	-0.43
	Median		Median		t-stat	p	r
DGI[2]	24		24		3.00	0.18	0.34

[1]Paired sample t-test (df = 7)
[2]Wilcoxon Signed Rank Test

4.3 Walking in PWA

4.3.1 Lower limb joint angles during level walking

Although kinematics was not our primary objective, we include the joint angles of PWA and PNA across hip, knee, and ankle joints during walking in Figure 13 to provide a baseline for future studies. No statistical analyses were conducted on these data. The joint angle curves of both groups showed similar patterns, except for some notable differences. During the stance phase (red bars were used to better visualize the range of the gait cycle), PWA demonstrated increased hip flexion angles (first row), knee flexion angles (third row), and decreased hip adduction angles (second row). During the stance phase just prior to the swing phase, PWA exhibited smaller maximum hip extension angles (first row). During the push-off phase, PWA demonstrated reduced ankle plantar flexion angles (fourth row).

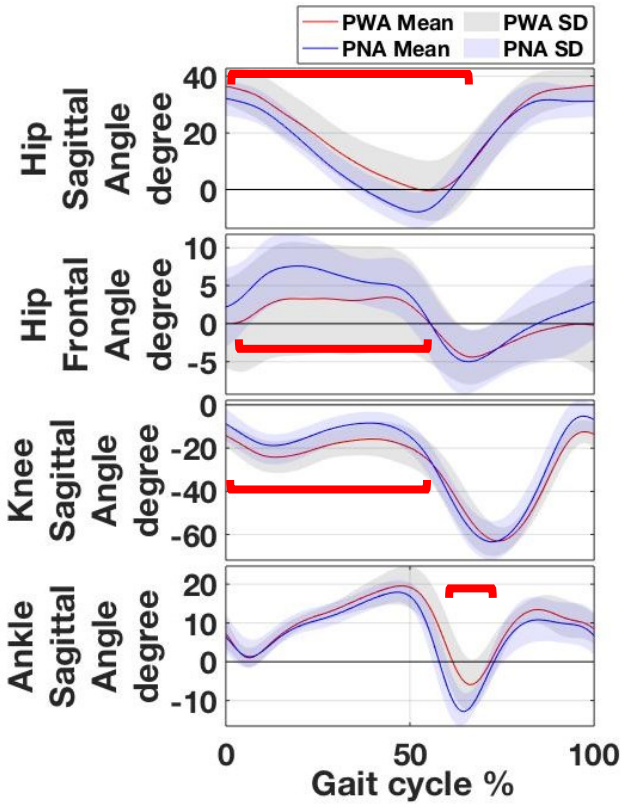


Figure 13. Right limb joint angle during walking (Mean ± SD).
From top to bottom: Hip angle in sagittal plane, hip angle in frontal plane, knee angle in sagittal plane, ankle angle in sagittal plane. A complete gait cycle is defined as right foot heel strike on force plate to right food heel strike on ground. Positive Y: hip flexion, hip adduction, knee extension, ankle dorsiflexion.

4.3.2 Lower limb joint moments during level walking

Figure 14 represents the average net joint moments of the right limb during walking for both PWA and PNA groups. Similar findings were observed for the right and left sides of all analyses. The results reported are for the right side only (Refer to Table 9 for comprehensive details). During the stance phase following initial contact (12-60% gait cycle, a red bar was used to better visualize this range), the PWA group demonstrated reduced hip flexion moments, as depicted by the top left figure in Figure 14. Conversely, the PWA group exhibited increased hip abduction moments in between 20 to 50% of the gait cycle (this range is represented by a red bar), as shown by the top right figure in Figure 14. Similarly, the PWA group exhibited higher knee extension moments in between 20 to 50% of the gait cycle (this range was represented by a red bar), as shown by the left middle figure in Figure 14. Moreover, the PWA group demonstrated elevated knee abduction moments in between 15 to 50% of the gait cycle (the range was represented by a red bar), as shown by the right middle figure in Figure 14. However, no prominent difference was observed at the ankle joints between the PWA and PNA groups.

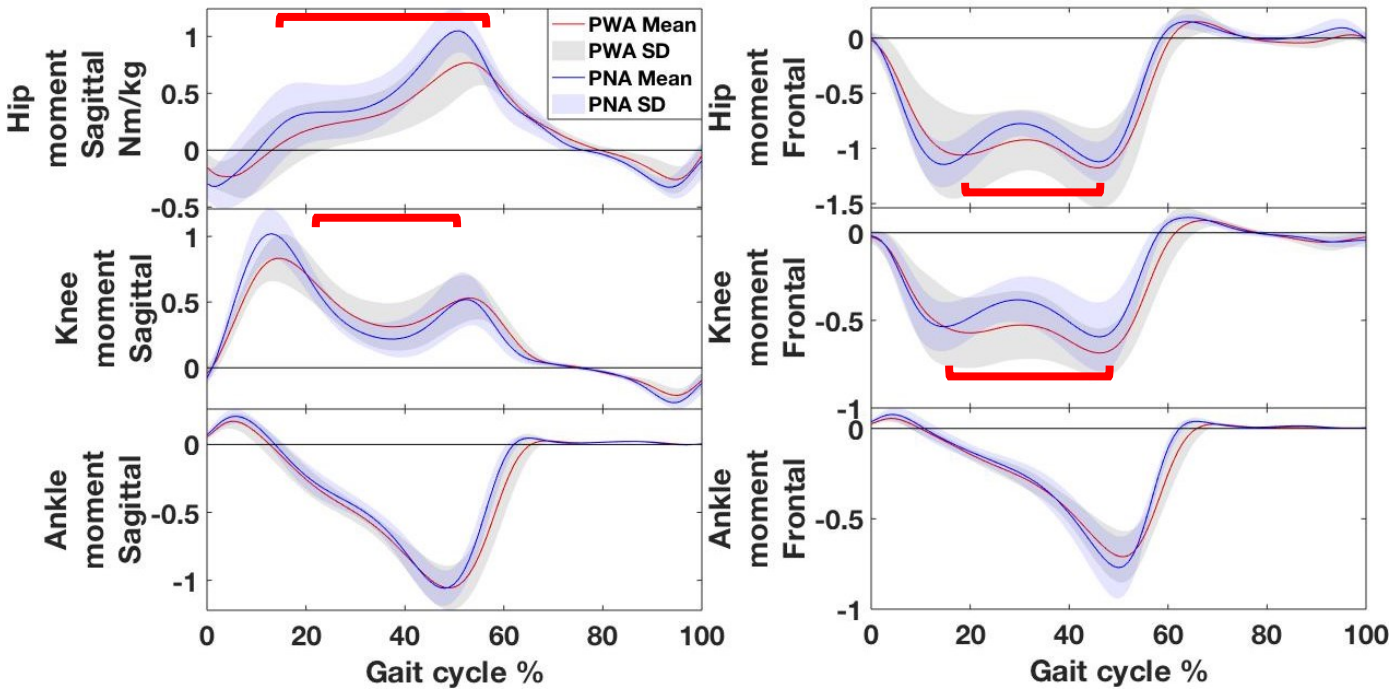


Figure 14. Mean net joint moments curves during walking in sagittal plane (left) and frontal plane (right) for the right limb across hip, knee, ankle joints from top to bottom (Mean ± SD).
PWA data are presented in red (grey band), PNA data are presented in blue (blue band). Positive moments indicate hip flexion, adduction, knee extension, adduction, and ankle dorsiflexion and inversion.

4.3.3 Lower limb joint powers during level walking

Figure 15 represents the average net joint powers of the right limb during walking in the sagittal (first column) and frontal (second column) planes, specifically focusing on the hip (first row), knee (second row), and ankle joints (third row). During the initial stance phase, the PWA group exhibited a higher generation of energy by the hip extensors (H1) but a lower absorption of energy by the hip abductors (H1F) and knee extensors (K1) in comparison to the PNA group (2.89 J/kg; -2.86 J/kg; -5.20 J/kg vs. 2.58 J/kg; -5.28 J/kg; -6.94 J/kg, respectively). In the midstance phase, the PWA group demonstrated a lower absorption of energy by the hip flexors (H2) in comparison to the PNA group (-14.10 J/kg vs. -24.50 J/kg). Furthermore, the PWA group demonstrated a lower generation of energy

by the hip flexors (H3), absorption of energy by the knee extensors (K3), and generation of energy generation by the ankle plantar flexors (A2) during push-off compared to the PNA group (10.28 J/kg vs. 15.16 J/kg; -19.32 J/kg vs. -24.17 J/kg; 15.15 J/kg vs. 16.81 J/kg, respectively). However, none of these differences were statistically significant. Although the p-value for H2 was 0.045 (Table 9), it was larger than the Bonferroni adjusted p-value of 0.001. The SPM analyses also indicated no significant difference in joint powers across the hip, knee, and ankle joints between the two groups.

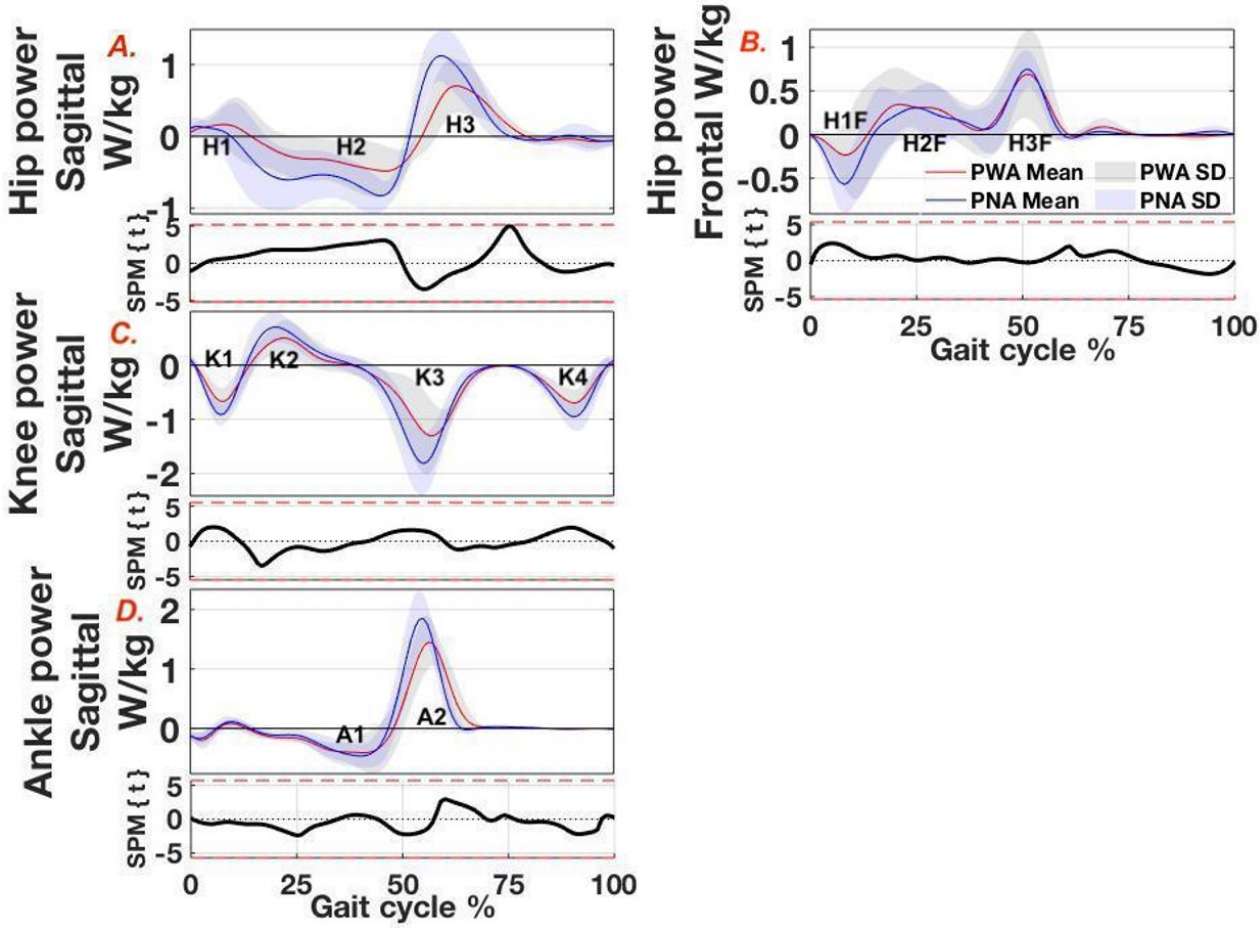


Figure 15. Mean net joint power during walking for the right limb of PWA and PNA across hip, knee, ankle joints (Mean ± SD).
A. hip power in sagittal plane; B. hip power in frontal plane; C. knee power in sagittal plane; D. ankle power in sagittal plane. PWA data are presented in red (grey), PNA data are presented in blue (blue). Positive power indicates power generation and negative power indicates power absorption.

Table 9. Two-way ANOVA results of selected energy burst during walking.

	PWA (n=8)				PNA (n=8)					p-value	Partial Eta squared
	Mean	SD	95% CI		Mean	SD	95% CI				
H1	2.89	3.49	0.47	5.31	2.58	4.10	-0.26	5.42	Group	0.34	0.13
									Side	0.75	0.02
									Interaction	0.44	0.09
H2	-14.10	9.96	-21.01	-7.20	-24.50	12.45	-33.13	-15.88	Group	0.045	0.46
									Side	0.37	0.12
									Interaction	0.91	0.002
H3	10.28	4.93	6.87	13.70	15.16	5.99	11.01	19.31	Group	0.36	0.12
									Side	0.74	0.02
									Interaction	0.33	0.14
H1F	-2.86	4.09	-5.69	-0.02	-5.28	2.65	-7.11	-3.44	Group	0.08	0.38
									Side	0.07	0.40
									Interaction	0.79	0.01
H2F	7.10	8.36	1.31	12.89	5.96	5.29	2.29	9.63	Group	0.46	0.08
									Side	0.25	0.19
									Interaction	0.69	0.02
H3F	8.25	6.68	3.62	12.88	7.64	3.20	5.43	9.86	Group	0.56	0.05
									Side	0.05	0.45
									Interaction	0.86	0.005
K1	-5.20	2.61	-7.01	-3.39	-6.94	1.64	-8.07	-5.80	Group	0.26	0.17
									Side	0.55	0.05
									Interaction	0.83	0.007
K2	6.54	4.99	3.08	10.00	9.89	4.94	6.46	13.31	Group	0.36	0.12
									Side	0.07	0.39
									Interaction	0.47	0.08
K3	-19.32	8.29	-25.07	-13.58	-24.17	8.80	-30.27	-18.08	Group	0.37	0.12
									Side	0.05	0.45
									Interaction	0.48	0.08
K4	-8.10	2.85	-10.08	-6.12	-10.53	2.57	-12.30	-8.75	Group	0.43	0.09
									Side	0.45	0.08
									Interaction	0.22	0.20
A1	-9.03	3.89	-11.73	-6.34	-8.42	3.80	-11.05	-5.78	Group	0.70	0.02
									Side	0.47	0.08
									Interaction	0.78	0.01
A2	15.15	2.14	13.67	16.63	16.81	3.25	14.56	19.06	Group	0.47	0.08
									Side	0.58	0.05
									Interaction	0.80	0.01

SD: Standard deviation; CI: Confidence interval. Two-way: Group (PWA vs. PNA) x Side (Right vs. Left). Highlighted number refers to the "non-significant" difference mentioned in previous paragraph.

4.4 Adaptation to obstacle

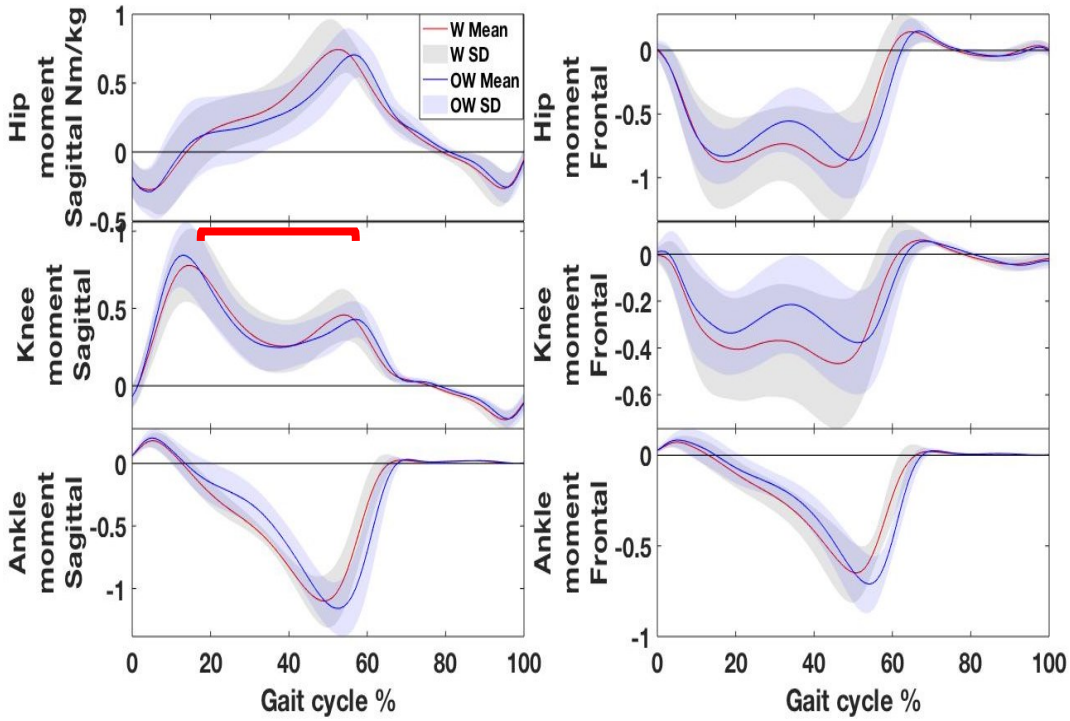
4.4.1 Gait characteristics during obstructed walking

Table 8 indicates that there was no significant difference found in walking speed (p-value = 0.17), walking stride length (p-value = 0.06), obstructed walking speed (p-value = 0.2), and obstructed walking stride length (p-value = 0.3) between the PWA and PNA groups. However, there was a trend towards slower walking speed and shorter stride length in the PWA group.

4.4.2 Lower limb joint moments during obstructed walking

Figure 16 illustrates the average net joint moments of the supporting limb of the PWA (A) and the PNA (B) groups across the hip, knee, and ankle joints when adapting to obstacle. Both groups demonstrated lower hip and knee abduction moments at midstance (Figure 16AB row 1 & 2, right column, blue line) when adapting to obstacle. Additionally, the PNA group exhibited lower knee extension moments at midstance when adapting to obstacle (Figure 16B row 2, left column, blue line), while no prominent difference was observed in the PWA group (Figure 16A row 2, left column). Both groups generated higher ankle plantar flexion and eversion moments during the push-off phase of obstructed walking (Figure 16AB row 3, blue line).

A.



B.

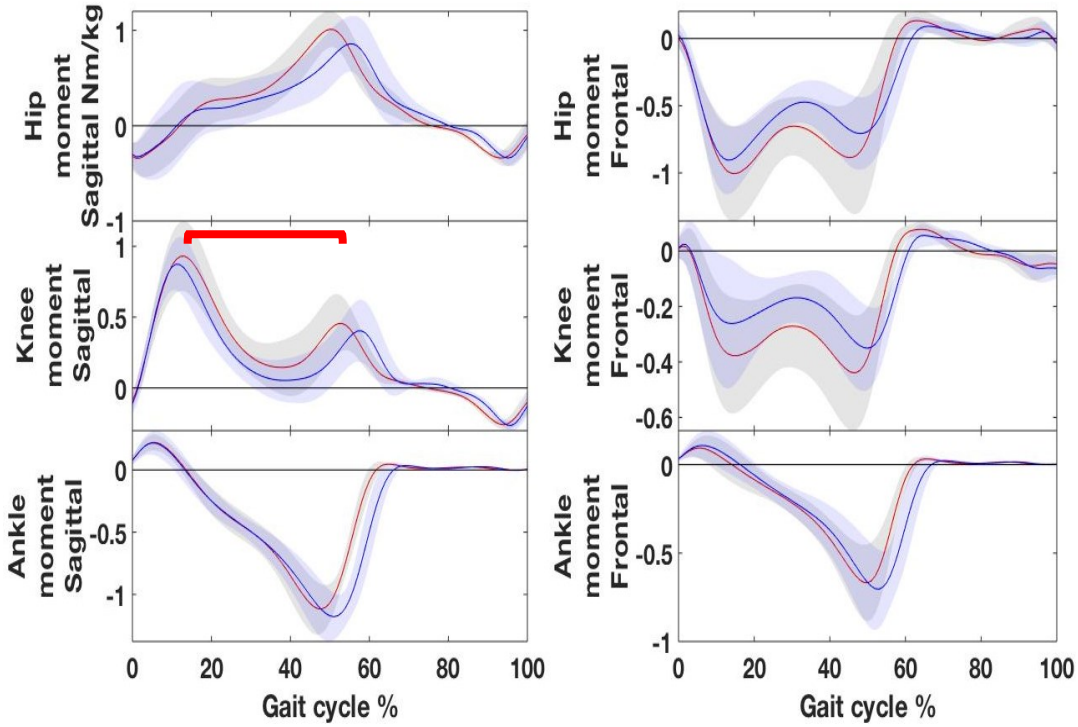


Figure 16. Joint moments across hip (top), knee (middle), ankle (bottom) joints in sagittal (left) and frontal (right) plane of supporting limb during walking (red) and obstructed walking (blue).

A. Joint moments of PWA. B. Joint moments of PNA.

4.4.3 Lower limb joint power during obstructed walking

Figure 17 indicates the mean net joint power of PWA's during walking (red) and obstructed walking (blue) across the hip, knee, and ankle joints (Top: crossing limb; Bottom: supporting limb). Figure 18 indicates the mean net joint power of PNA's during walking (red) and obstructed walking (blue) across the hip, knee, and ankle joints (Top: crossing limb; Bottom: supporting limb).

For the supporting limb (bottom figures), row 1 of the bottom figures of Figures 17 and 18 (blue line, 15-55% gait cycle) indicate that both groups' supporting limbs absorbed less energy through hip flexors during the rest of the stance phase (H2) when adapting to obstacle. Row 2 of the bottom figures of Figures 17 and Figure 18 (blue line, first 15% of the gait cycle) indicate that both PWA and PNA's supporting limb absorbed less energy through hip abductors at the beginning of the stance phase (H1F) when adapting to obstacle. Besides, both PWA and PNA's supporting limbs absorbed less energy through knee extensors during the push-off phase (K3) when adapting to obstacle (Bottom figures of Figures 17 and 18, row 3, blue line, 50-70% gait cycle).

For the crossing limb (top figures), the top figure of Figures 17 and 18 indicate that PWA and PNA's crossing limbs exhibited less energy generation through hip flexor (H3) (row 1, blue line, 45-60% gait cycle) and less energy absorption through knee extensor (K3) (row 3, blue line, 40-55% gait cycle) just before the swing phase. Besides, both of the groups exhibited less energy generation through ankle plantar flexor (A2) during push off (top figures of Figures 17 & 18, row 4, blue line, 40-60% gait cycle).

Figures 19 and 20 present the SPM results on the mean difference of joint power during walking and obstructed walking (joint power during obstructed walking – joint power during walking), with Figure 19 indicating crossing limb, Figure 20 indicating

supporting limb. Figures 19 and 20 indicate no significant difference in the mean difference of joint power of both crossing and supporting limb during walking and obstructed walking (obstructed walking minus walking) between PWA and PNA.

Figure 21 indicates the interaction between the effect of acromegaly and obstacle on supporting limb H2F and crossing limb K3. Table 10 indicates that no interaction was found to be significant. PWA generated less energy through the hip abductor of the supporting limb (H2F) during obstructed walking (W: 5 J/kg vs. OW: 4.85 J/kg), whereas PNA generated more H2F during obstructed walking than normal walking (W: 5.52 J/kg vs. OW: 6.42 J/kg). Further, PWA exhibited less reduction of crossing limb K3 when adapting to obstacle (W: -18.13 J/kg vs. OW: -12.69 J/kg), whereas PNA exhibited more reduction of K3 (W: -21.19 J/kg vs. OW: -12.31 J/kg).

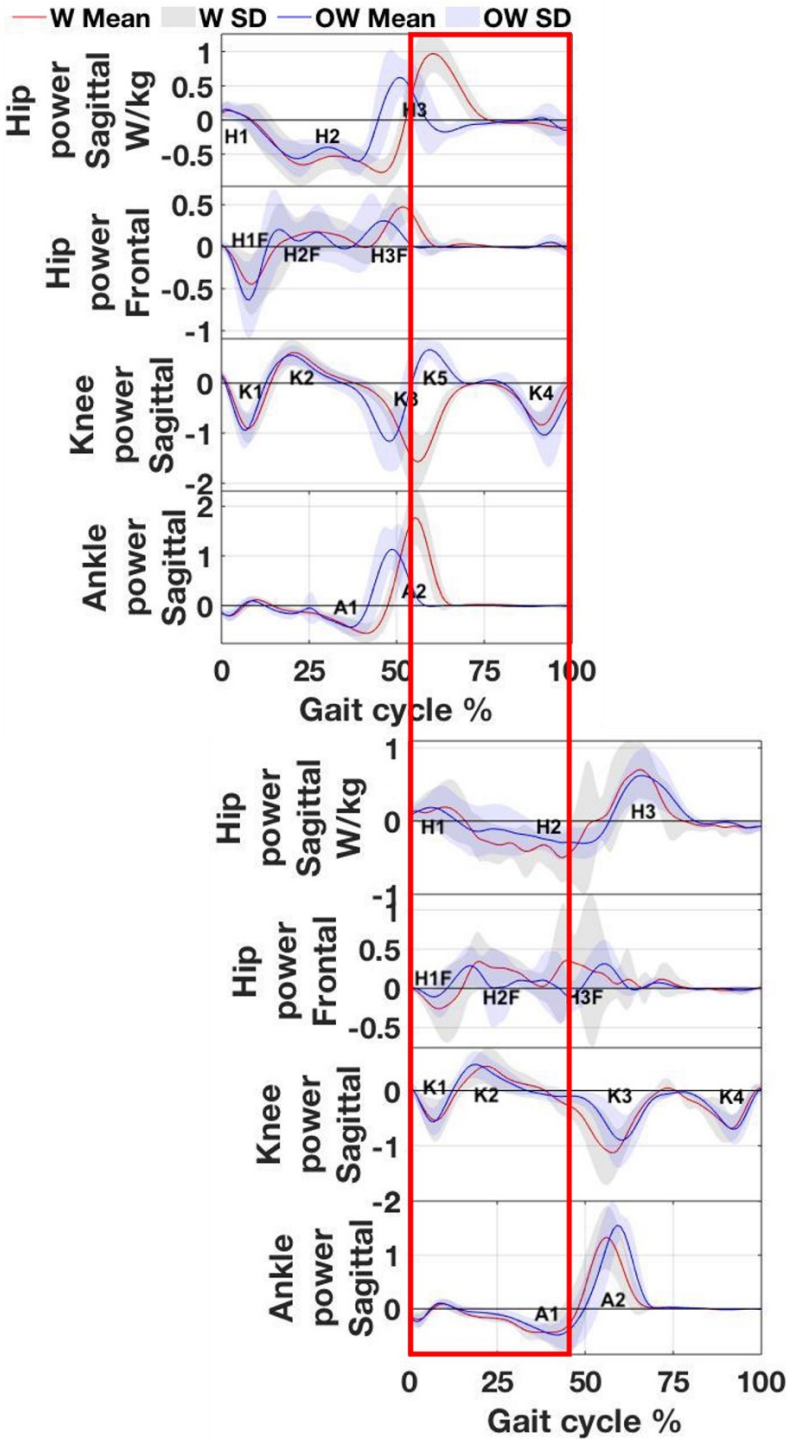


Figure 17. Mean net joint power of PWA during walking (red) and obstructed walking (blue) for the crossing (top) and supporting (bottom) limb across hip, knee, and ankle joints. From top to bottom are Crossing limb hip power in sagittal and frontal plane, Crossing limb knee power in sagittal plane, Crossing limb ankle power in sagittal plane; Supporting limb hip power in sagittal and frontal plane, Supporting limb knee power in sagittal plane, Supporting limb ankle power in sagittal plane. Positive power indicates power generation and negative power indicates power absorption. Red frame means the first half gait cycle (stance phase) of supporting limb happens concurrently with the second half gait cycle (swing phase) of the crossing limb.

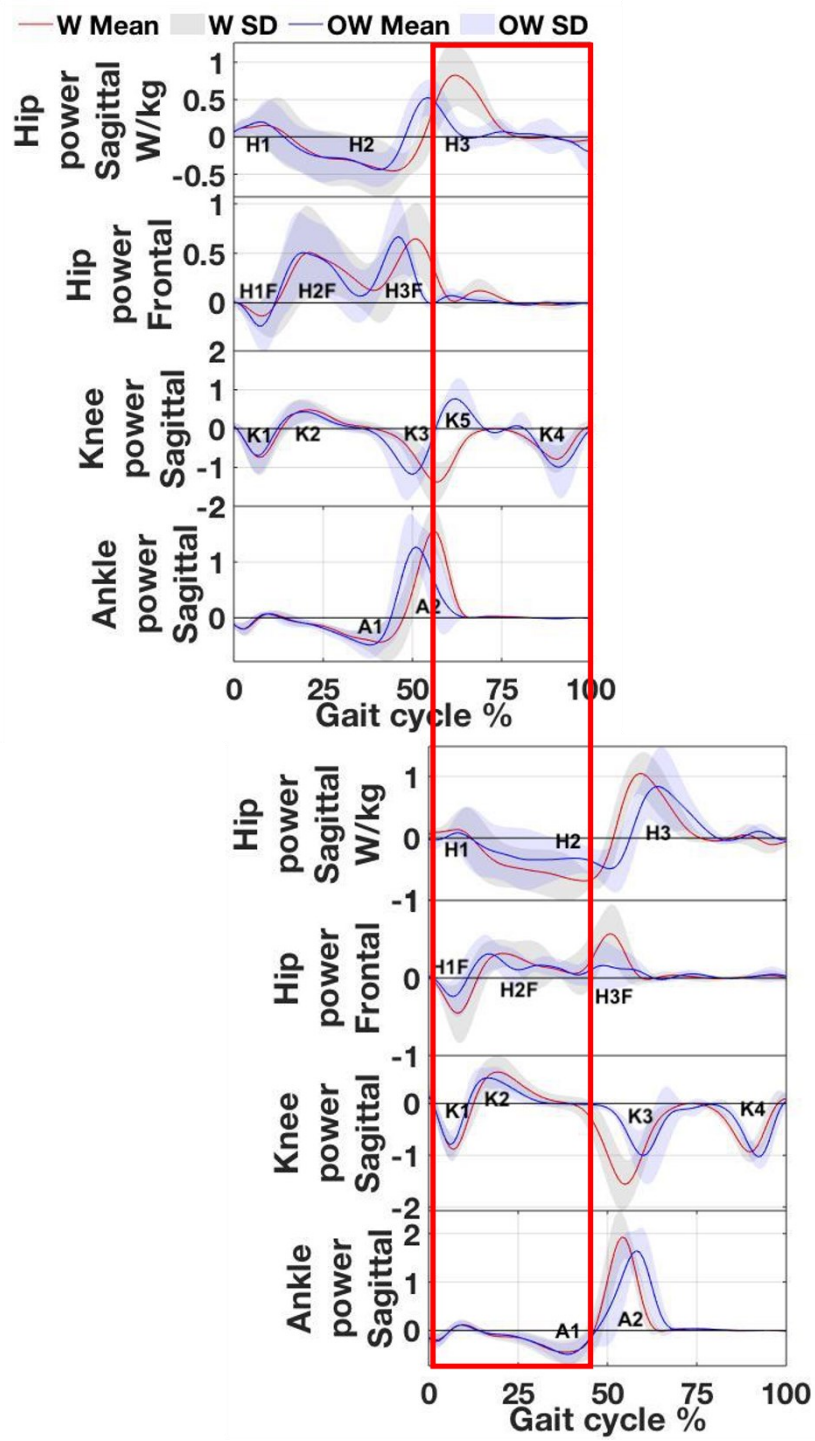


Figure 18. Mean net joint power of PNA during walking (red) and obstructed walking (blue) for the crossing (top) and supporting (bottom) limb across hip, knee, and ankle joints. From top to bottom: Crossing limb hip power in sagittal and frontal plane, Crossing limb knee power in sagittal plane, Crossing limb ankle power in sagittal plane; Supporting limb hip power in sagittal and frontal plane, Supporting limb knee power in sagittal plane, Supporting limb ankle power in sagittal plane. Positive power indicates power generation and negative power indicates power absorption. Red frame means the first half gait cycle (stance phase) of supporting limb happens concurrently with the second half gait cycle (swing phase) of the crossing limb.

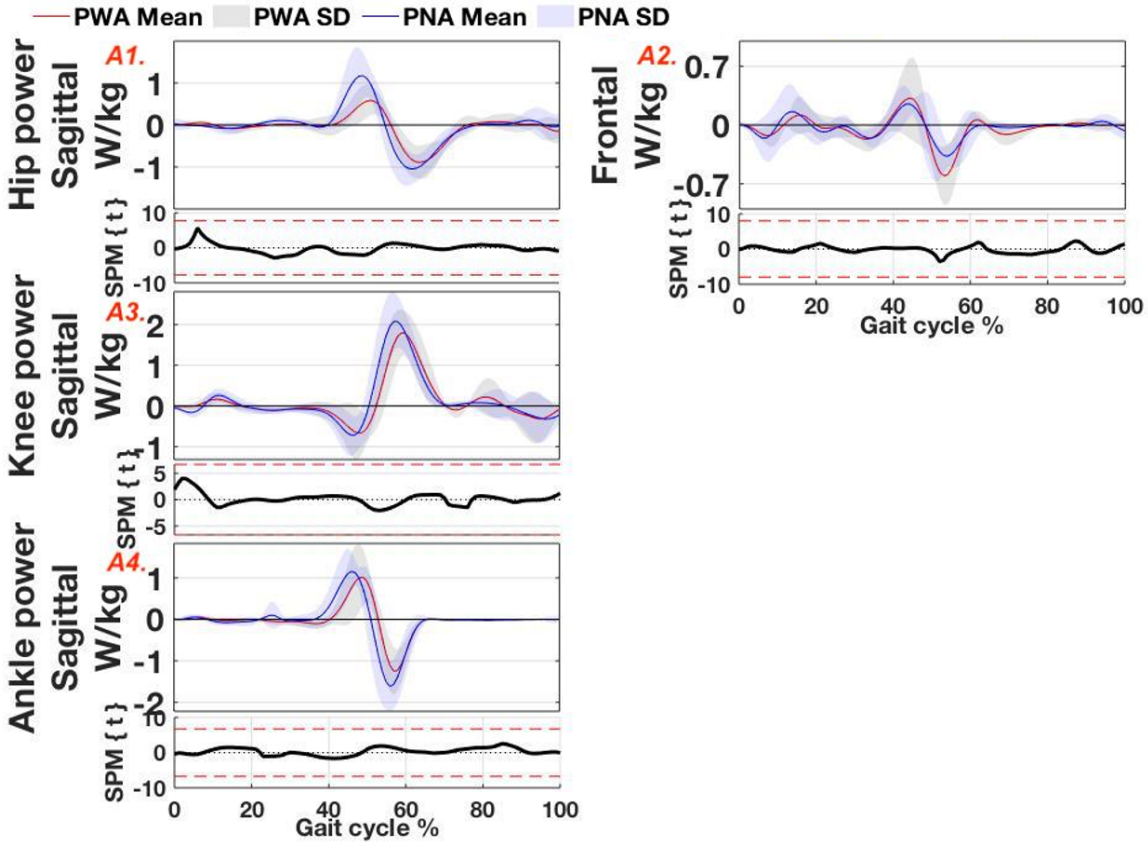


Figure 19. The mean difference of joint power of crossing limb during walking and obstructed walking (joint power during obstructed walking - joint power during walking) between PWA (red) and PNA (blue).
A1-4: Hip power sagittal, hip power frontal, knee power sagittal, ankle power sagittal.

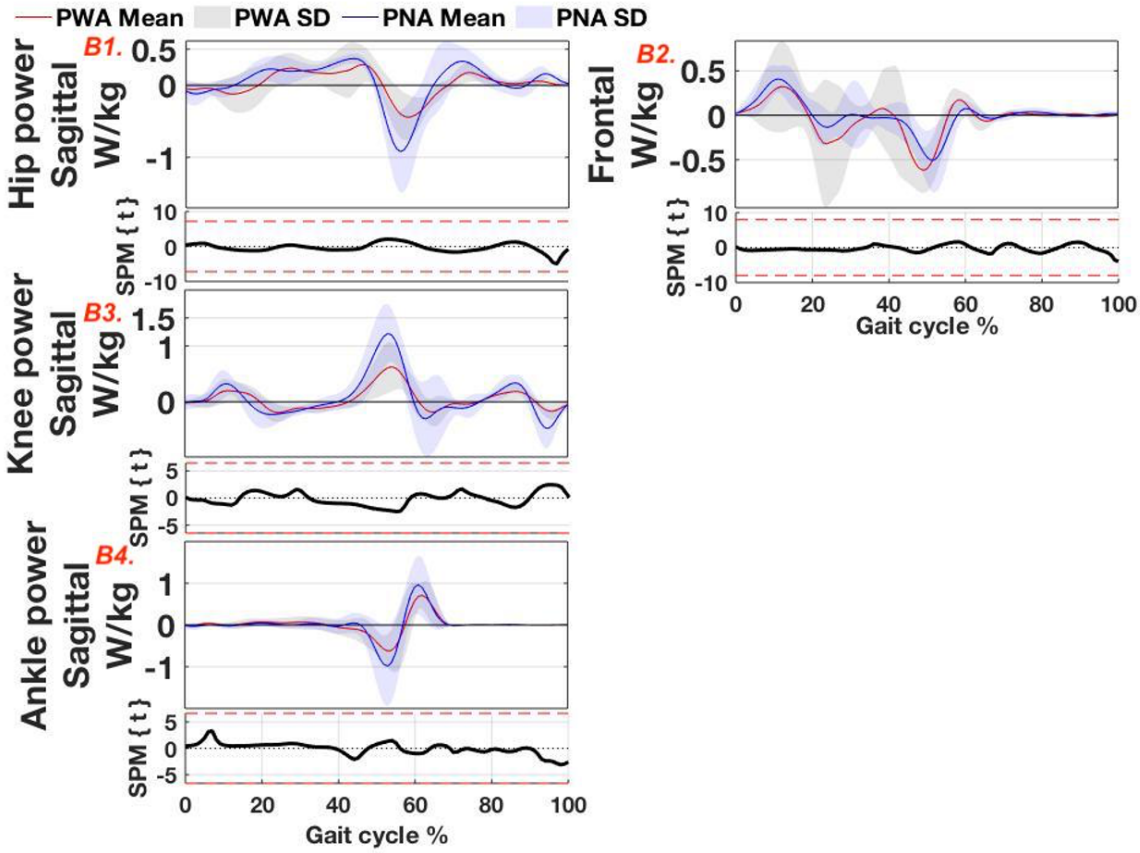


Figure 20. The mean difference of joint power of supporting limb during walking and obstructed walking (joint power during obstructed walking - joint power during walking) between PWA (red) and PNA (blue).
B1-4: Hip power sagittal, hip power frontal, knee power sagittal, ankle power sagittal.

Table 10. The effect of group and condition on selected energy burst.

		SS	df	MS	F	p	Eta squared
H1	Group	7.35	1	7.35	0.11	0.76	0.02
	Condition	2.30	1	2.30	0.73	0.43	0.13
	Interaction	0.75	1	0.75	0.15	0.72	0.03
H2	Group	168.13	1	168.13	0.77	0.42	0.13
	Condition	99.51	1	99.51	12.16	0.02	0.71
	Interaction	0.41	1	0.41	0.05	0.83	0.01
H1F	Group	1.50	1	1.50	0.09	0.77	0.31
	Condition	37.17	1	37.17	5.82	0.06	0.54
	Interaction	0.17	1	0.17	0.03	0.87	0.01
H2F	Group	0.30	1	0.30	0.02	0.90	0.004
	Condition	0.41	1	0.41	0.26	0.64	0.05
	Interaction	5.51	1	5.51	1.25	0.32	0.20
K1	Group	6.14	1	6.14	1.02	0.35	0.15
	Condition	12.39	1	12.39	7.89	0.03	0.57
	Interaction	0.49	1	0.49	0.66	0.45	0.10
K2	Group	3.75	1	3.75	0.13	0.73	0.02
	Condition	22.83	1	22.83	10.64	0.02	0.64
	Interaction	2.91	1	2.91	0.51	0.50	0.08
Cross K3	Group	12.55	1	12.55	0.07	0.79	0.01
	Condition	358.91	1	358.91	53.74	<.001	0.87
	Interaction	20.76	1	20.76	1.45	0.27	0.19
Cross K5	Group	0.21	1	0.21	0.09	0.78	0.01
	Condition	288.96	1	288.96	48.46	<.001	0.89
	Interaction	0.21	1	0.21	0.09	0.78	0.01

Group: Acromegaly vs. Control; Condition: Walking vs. Obstructed walking. Highlighted numbers indicated that all the significant differences in joint power were observed between different conditions, while no significant interaction was found between the effect of acromegaly and obstacle on joint power.

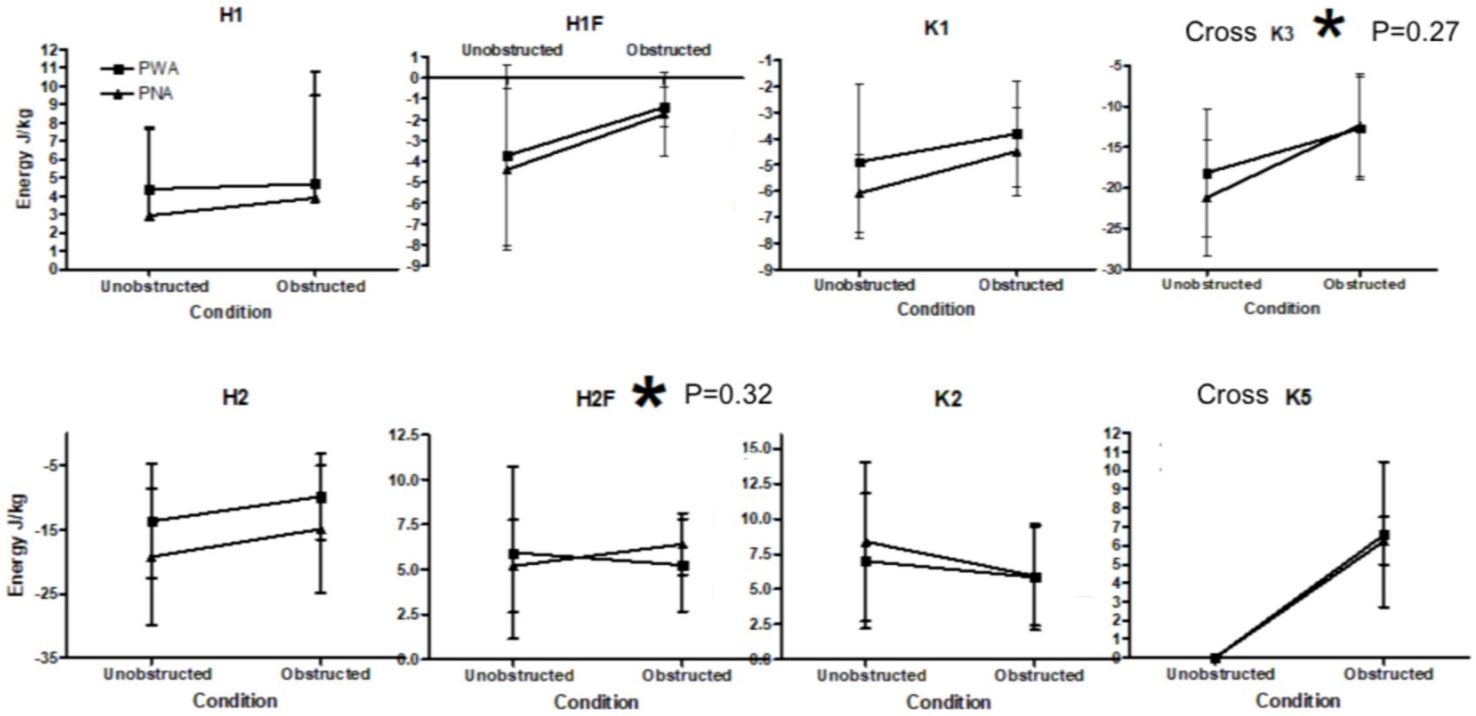


Figure 21. The interaction of the effect of acromegaly and obstacle on selected power burst.

* means there was interaction but not significant.

Chapter 5: Discussion

This study investigated the risk of falls, kinetic gait patterns, and walking balance of PWA during level walking and their adaptation to obstructed walking. Significantly higher TUG scores but comparable DGI scores were observed in PWA in comparison to PNA. The results showed that PWA had greater gait deviations in the hip and knee joints, with a trend towards lower hip flexion moments, but higher hip abduction, knee extension, and knee abduction moments exhibited during the midstance phase. PWA also exhibited a trend towards higher energy dissipation during level walking. With regards to obstacle avoidance, PWA and PNA demonstrated similar patterns of joint moments curves, but PNA exhibited a trend towards lower knee extension moments during midstance when adapting to obstructed walking. In addition, PWA showed a trend towards less supporting limb energy generation by the hip abductor muscles (H2F), more supporting limb energy generation by the plantar flexor muscle (A2), as well as less reduction in crossing limb energy absorption by the knee extensor muscles. These findings suggest that PWA might have different motor strategies and adaptations when faced with obstacles, which may have implications for developing targeted rehabilitation interventions.

PWA included in the current study were able to adapt to the constraints imposed by the environment and complete the obstacle task. Although no statistically significant differences were observed in most of the variables between PWA and PNA, given the statistical power of the analyses, our findings suggest a trend toward altered walking patterns in PWA, that future researchers might wish to explore.

5.1 Unobstructed walking

During level walking, the PWA group exhibited lower hip flexion moments throughout the stance phase as well as a reduced energy absorption by the hip flexors (H2). This finding is consistent with previous studies by Murray et al. (1971) and Hurwitz et al. (1997) that reported lower energy absorption by the hip flexor muscles (H2) and reduced maximum hip extension angle in people with hip OA. In our study, the PWA group also demonstrated smaller maximum hip extension angles compared to the PNA group, suggesting that people with hip OA and AA may employ the same hip extension angle reduction strategy to compensate for the reduced energy absorption by the hip flexors due to muscle weakness or stiffness. This is supported by the findings of Eitzen et al. (2012), who observed highly reduced hip flexion moments at peak hip extension in people with early-stage hip OA, which aligns with our results. The lower energy generation by the hip flexors (H3) in the PWA group further indicates the potential weakness in these muscles, consistent with the findings of Mastaglia et al. (1970). Additionally, Meyer et al. (2018) investigated patients with hip OA prior to total hip replacement surgery, which is considered to be in the later stage of hip OA, and also observed reduced H2 and H3, which are in line with our findings. These findings collectively suggest suboptimal utilization of the hip flexor muscles in both PWA and people with hip OA.

Notably, the PWA group exhibited higher knee extension moments during midstance, despite generating less energy through the knee extensor muscles (K2), which could be attributed to the lower angular velocity of the shank in PWA. However, an alternative explanation for this increase in moments could be the presence of an abnormal traction of the posterior cruciate ligament. During the general stance phase, the anterior

cruciate ligament is loaded due to the anterior shear force transmitted from the patellar tendon (Shelburne, et al, 2004). If there is muscle incoordination during the stance phase, it could lead to posterior traction on the tibia or an anterior traction on the femur, resulting in abnormal traction of the posterior cruciate ligament. Moreover, higher bone-on-bone forces, such as femur compression force and patella compression force, could also contribute to the observed higher moments. It is important to note that this finding differs from that of people with early hip OA, where no difference was found in knee extension moments during midstance (Eitzen et al., 2012).

The PWA group exhibited higher knee abduction moments during midstance, which was not typically observed in individuals with hip OA. However, this finding aligns with the characteristics of knee OA, where increased knee abduction moments with varus malalignment were observed at the knee joint (Sloot & Krogt, 2017). These differences conveyed that PWA share similarities with individuals with knee OA, in addition to those seen in individuals with hip OA.

Neither of the groups in this study exhibited knee flexion moments passing zero during midstance, which contrasts with observations in the healthy population. The presence of knee flexion moments in the healthy population is a result of a biomechanical mechanism that occurs on the supporting limb during the swing limb in the mid-swing phase, where the supporting limb is in an upright position and the orientation of ground reaction force passes through the anterior compartment of the knee. This generates an external knee extension moment, and the gravitational force also causes the thigh to lean forward. In response to these external extension moments, the knee flexor muscles undergo a pliometric contraction to resist the extension. In a healthy population, this contraction

leads to brief absorption of energy between K2 and K3. However, in both study groups, this energy absorption was not observed. One possible explanation for this observation could be a weakness of the knee flexor muscles. Further studies are needed to investigate and understand this phenomenon more comprehensively.

Analyses of the energy burst at the onset of the stance phase revealed interesting findings in the PWA group compared to the PNA group. The PWA group exhibited higher generation of energy by the hip extensor muscles (H1) but lower absorption of energy by the hip abductor muscles (H1F) and knee extensor muscles (K1), indicating an increased dissipation of energy in comparison to the PNA group. This result suggests that PWA may have different energy distribution patterns during the stance phase, potentially indicating altered muscle activation strategies.

It is noteworthy to mention that individuals with hip OA often exhibit a smaller hip adduction angle to compensate for weakened hip abductors reducing the demand on these muscles (Meyer et al., 2018). However, in contrast to people with hip OA, the PWA group demonstrated higher hip abduction moments, along with higher generation of energy by the hip abductor muscles as well as decreased hip adduction angles. This suggests that the hip abductors strength in PWA may not be impaired, and they might have better control over the pelvis to maintain its level position and thereby balance during walking.

The observed differences in hip abductor moments between PWA and people with hip OA could be attributed to factors such as the passive force generated by the ischiofemoral ligament or morphological changes in the hip joints, which may alter the joint center and moment arms. Previous studies have reported weaker hip abductor muscles in people with hip OA (Chamnongkich et al., 2012 and Meyer et al., 2018), but the hip

abductors strength in PWA remains unknown. Strong hip abductors are crucial for maintaining an upright trunk and level pelvis (MacKinnon&Winter, 1993), and hip abductors strengthening has been identified as an effective intervention for restoring normal gait patterns in people with hip OA. However, if PWA do not exhibit hip abductors weakness, rehabilitation programs targeting hip abductors strengthening may have limited benefits for this population.

Gait analyses of the PWA group during level walking have revealed certain gait characteristics that share similarities with individuals with hip OA. Notably, PWA did not exhibit the symbolic sign of hip OA known as Duchenne limp, suggesting that their hip abductors may not be impaired, and that exaggerated bending of the trunk, resulting in excessive movement of the CoM, is not present. However, PWA demonstrated higher knee abduction moments, a characteristic associated with knee OA diagnosis. These findings emphasize the importance of a careful and accurate diagnosis of AA in this population. It is crucial to differentiate between hip OA and other potential causes contributing to the observed gait patterns in PWA. To address these unique gait characteristics, personalized rehabilitation interventions are needed.

5.2 Adaptation with obstructed walking

Hip abductors also play a crucial role in obstructed walking, and their function becomes particularly important for the supporting limb during obstacle crossing. In this study, it was observed that PWA's supporting limb generated less energy through their hip abductors (H2F) compared to PNA. This finding suggests that PWA may encounter challenges in restoring balance after experiencing external perturbations. In contrast, PNA demonstrated a potentially quicker restoration of balance when faced with perturbed

imbalance situations. Notably, in the absence of external perturbation such as level walking, PWA did not exhibit a reduction in H2F, which is consistent with their reduced hip abduction moments observed during obstructed walking. PWA exhibited a greater reduction in hip abduction moment during obstructed walking than normal walking compared to PNA. These findings suggest that PWA may employ a different strategy to control hip abduction when adapting to an obstacle compared to PNA. This difficulty in adaptation may be resulting from the impaired conduction velocity of motor nerves reported in PWA (Jamal et al., 1987). This impairment in motor nerve conduction may affect the coordination and activation of hip abductor muscles when adapting to external perturbations.

The anticipatory locomotor response, as indicated by the joint power of the supporting limbs at the beginning of the standing phase (H1, H1F, K1), and the joint power of the crossing limbs right before the swing phase (K3), is important for the control of walking balance. Both PWA and PNA demonstrated comparable adjustments in the joint powers of their supporting limbs at the beginning of the stance phase, indicating comparable initial responses to obstacle negotiation. Additionally, both groups exhibited the utilization of the knee flexor strategy during obstructed walking, as evident from the presence of a generation of energy by the knee flexor muscles (K5). However, notable differences were observed in the crossing limb absorption of energy by the knee extensor muscles (K3) between PWA and PNA when faced with an obstacle. PNA showed a larger reduction in K3, indicating a better preparation for the subsequent generation of energy by the knee flexor muscles (K5). Sufficient K5 is essential to lift the shank to a safe height, preventing tripping over obstacles. This reduction in K3 in PNA corresponds with the

decrease in knee extension moments in PNA during obstructed walking. In contrast, PWA did not exhibit a reduction in knee extension moments when adapting to an obstacle, and the reduction in K3 was also minimal. This finding, along with the level gait analyses, indicates a potential deficiency in knee flexors strength, which could impact their ability to generate sufficient energy for effective obstacle negotiation and increase the risk of tripping over.

Kinetics analysis during obstructed walking hasn't been done on individuals with hip OA, Chamnongkich et al. (2012) conducted spatiotemporal measures of obstacle gait. Slower speed was observed in people with hip OA when adapting to obstacle-existence condition, which was in line with what we found in PWA (W: 1.07m/s vs. OW: 0.93m/s). Although the walking speed in PWA showed no statistically significant difference from PNA, due to the power of the analyses, a trend towards slower speed and smaller stride length was found in PWA.

5.3 Functional tests

PWA took a significantly longer time to complete the TUG 3-meter walking task. A reduction of 2.42 seconds in the PNA group met the clinical meaningful change criterion of the TUG, which refers to a reduction greater than 0.8, 1.4, and 1.2 seconds (Wright et al., 2011). However, among all the participants in the PWA group, only one was classified as high risk for falls (with a TUG time longer than 14s), and this individual was not the one that could not complete the obstacle-crossing task.

The participant classified as high risk of falls in this study is the oldest among the group, with a significant age difference (15 years older) compared to the next oldest participant. This individual exhibited smaller hip abduction moments but a higher

generation of energy by the hip abductor muscles (H2F). A possible explanation for this finding is that the generated H2F was not primarily used for generating hip abduction moments but rather transferred to, and absorbed by, the ankle joint to ensure normal function of ankle dorsiflexors in controlling plantarflexion after heel strike. This compensatory mechanism might be employed because the ankle joint cannot have a sufficient absorption of the energy generated by the knee extensor muscles (K2). The insufficient K2 and reduced knee extension moments could indicate weakness in the knee extensors of this participant. Therefore, although this patient generated sufficient H2F, it was likely used to compensate for the weakness in knee extensors rather than generating significant hip abduction moments. This aligns with the observations in individuals with hip OA, where patients may struggle to control the pelvis level relying on the hip abductors. As a result, the participant may exhibit a Duchenne gait pattern characterized by decreased hip adduction angles to reduce the demand on hip abductors. However, this compensation strategy could lead to increased CoM sway and compromised balance during walking, as indicated by the TUG score, suggesting a higher risk of falls for this participant.

The participant who did not complete the obstructed walking exhibited smaller ankle plantar flexion moments, indicating potential weakness in the ankle plantar flexors. Additionally, during the mid-midstance, this participant exhibited a burst of generation of energy by the knee extensor muscles and higher knee extension moments. As mentioned previously, during midstance, the ground reaction force and gravity exert forces on the leg, leading to an external knee extension moment. The fact that this participant's supporting limb had to counteract both internal and external knee extension moments suggest a potential for muscle incoordination. Moreover, this patient exhibited higher knee abduction

moments, which is a sign of knee OA. The participant's knee function questionnaire score was 76.33, the second highest among the group, with only two participants achieving a perfect score of 100. It should be noted that the survey was completed in April 2021, while the experiment took place in October 2022, indicating that the participant's condition may have changed over time. In the joint pain survey, the participant reported a pain score of 86 for the right knee. This finding suggests that the participant may experience greater difficulty in flexing their knees sufficiently to successfully navigate the obstacle.

No significant difference was observed in DGI scores between the PWA and PNA groups, with most of the participants obtained full marks, suggesting a potential ceiling effect. However, it is important to note that two PWA participants did not achieve a perfect score. One of them was the one who did not complete the obstructed walking task, this participant obtained 15 out of 25 on the DGI and 12.78s for the TUG. This participant was classified as having a high risk of falls based on the DGI test but not the TUG test. The second participant who did not obtain full marks on the DGI scored 20 out of 24 and 11.81s in the TUG test. This participant was not classified as having a high risk of falls based on either test. Surprisingly, the participant who was classified as high risk of falls based on the TUG test achieved a perfect score on the DGI test. These discrepancies between the results of different clinical tests underscore the importance of using objective measures in conjunction with clinical assessments to gain a more comprehensive understanding of the impact of the disease on gait deviations and fall risk.

5.4 Limitations

This study provides valuable insights into the pathomechanical gait strategies adopted by PWA during walking and obstructed walking. The results highlight the need

for further research to elucidate the gait patterns of PWA and develop strategies to improve their mobility and quality of life. Our study introduces an innovative approach by examining the kinetics of PWA during both walking and obstructed walking, which has not been explored in previous literature.

It is important to acknowledge the limitations of this study. The small sample size limits the generalizability of the results. Additionally, the participants within each group exhibited a wide range of age (PWA: 37-74; PNA: 45-75) and BMI (PWA: 21-41; PNA: 25-47), resulting in large standard deviations in the joint moments and joint power curves. The BMI of some participants may have impacted the accuracy of bony landmark palpation, leading to potential inaccuracies in joint center calculations, segments building, and subsequent outcomes calculations, such as CoM of each segment, joint moments, and joint power.

It should also be noted that two PWA participants had undergone joint replacement surgeries, one on the left and right knee and the other on the right hip. This factor could influence joint function and act as confounding factors when comparing balance between the two groups, because joint replacement surgery may affect proprioception and thereby influence balance abilities (Attfield et al., 1996; Onishi et al., 2017; Labanca et al., 2021).

It is worth noting that the participants performed the walking trials without footwear to investigate the intrinsic muscle activation patterns involved in maintaining balance without the aid of external support. However, this condition may not fully reflect the participants' gait patterns during daily activities, where footwear usage is common. Additionally, the completion of the Romberg test before the walking trials may have induced fatigue, potentially influencing gait performance.

It was previously mentioned that the segment mass calculations in this study were based on Dempster's body segment parameters (1955), a commonly used method in biomechanical studies. However, due to abnormal variation in bone density, bone length, and body composition in PWA (Coloa et al., 2004; Katznelson, 2009), the accuracy of the calculated segment mass may be limited, leading to potential inaccuracies in joint reaction force calculation. Furthermore, the normalization of joint moments and joint power by mass, rather than walking speed or stride length, may overlook the potential influence of these factors on the magnitude of joint moments (Buddhadev et al., 2020).

Despite these limitations, we believe that our findings contribute to the development of rehabilitation interventions aimed at preventing or treating joint degenerations in PWA.

5.5 Implications

Future longitudinal studies with larger sample sizes and better matching of participants are needed to confirm these findings with increased statistical power. It would be valuable to target specific populations with narrower ranges of demographic variables to establish more precise and representative average net joint moments and joint power curves for PWA at different stages. Inclusion of upper body markers to calculate the whole-body CoM and normalization of joint moments by walking speed should also be considered in future studies to provide a more comprehensive analysis. Furthermore, alternative methods for segment mass measurement or calculation that are more suitable for PWA should be explored in future studies. Continual investigation and clinical studies are necessary to deepen the comprehension of the gait patterns in PWA and refine the diagnosis and treatment approaches.

The diagnosis of AA/OA was not recorded in either group, as our primary objective was to investigate the effect of GH excess or the history of GH excess on balance. Therefore, we controlled for confounding variables such as age, sex, BMI, and adenoma removing surgery to minimize the potential impact of these factors on the study outcomes. Future studies could compare the balance between individuals with AA and OA to investigate the specific effects of these conditions on balance. Identifying kinetic gait deviations or balance deficits for early diagnosis of acromegaly can help restore biomechanical function in PWA.

Further investigation is needed to clarify the strength of hip abductor muscles in PWA. If hip abductor weakness is not a common problem in PWA, our result may suggest that neurological modifications associated with acromegaly may be a primary issue. The observation of increased knee abduction moments in PWA also highlights a potential area of concern. Healthcare providers should recognize that PWA may exhibit unique gait modifications and functional limitations, and interventions should be tailored based on individual symptoms rather than treating as generalized cases of hip OA or knee OA. Future studies should also explore neurological modifications in PWA, in addition to joint and muscle abnormalities, and investigate if the treatment for enlarged peripheral nerves improves balance in these patients. Furthermore, the effectiveness of different balance and proprioceptive rehabilitation programs in improving balance in PWA should be examined.

Targeted rehabilitation programs that address specific balance deficits can help mitigate the risk of falls and improve mobility and stability in PWA. The findings of this study have important implications for the management of patients with acromegaly. A better understanding of the specific needs of PWA and the implementation of

personalized interventions can ultimately lead to more effective treatment and improved quality of life for this population.

Chapter 6: Conclusion

This study showed individuals with acromegaly had different joint moments and joint power in both sagittal and frontal plane during walking, more pronouncing in hip joints, besides, these patients generated different anticipatory locomotor responses. Although more research is required given the nature of our findings, our data implied that the gait of individuals with acromegaly should be assessed in clinical practice to supplement self-reported and clinical outcome measures.

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Appendix A: Inertial properties measured to establish the inertial characteristics of the body segments

Weight (kg)	
Height (m)	
Leg length (m) = Height – Seat height	
RASIS → LASIS (m)	
Circumference of distal end of Thigh (m) LFME → LFLE	L:
RFME → RFLE	R:
Length of Shank (m) LFLE → LFAL	L:
RFLE → RFAL	R:
Circumference of distal end of Shank (m) LFAL → LTAM	L:
RFAL → RTAM	R:
Length of Foot (m) **LTAM** → LTOE	L:
RTAM → RTOE	R:
Circumference of distal end of Foot (m) L5MH → L1MH	L:
R5MH → R1MH	R:

Appendix B. Peak joint moments during walking and obstructed walking

Table 1. Joint moments during walking.

	PWA (n = 8)			PNA (n = 8)				t-stat	p-value	Cohen's d
	Mean	SD	95% CI	Mean	SD	95% CI				
Ankle dorsiflexion moment[1]	0.19	0.06	0.14	0.24	0.22	0.06	0.16	0.29	-1.14	0.29	-0.40
Ankle inversion moment[1]	0.08	0.04	0.05	0.11	0.11	0.06	0.05	0.16	-1.08	0.32	-0.38
Ankle eversion moment[1]	-0.66	0.16	-0.80	-0.53	-0.68	0.21	-0.85	-0.50	0.26	0.80	0.09
Knee Extension 1st peak[1]	0.80	0.24	0.60	1.00	0.95	0.24	0.73	1.20	-1.02	0.34	-0.36
Knee Extension 2nd peak[1]	0.47	0.17	0.33	0.61	0.47	0.21	0.25	0.65	-0.01	1.00	-0.00
Knee Extension in midstance	0.24	0.17	0.09	0.38	0.12	0.17	-0.06	0.27	1.24	0.26	0.44
Knee Flexion moment[1]	-0.23	0.06	-0.27	-0.18	-0.27	0.03	-0.30	-0.23	1.75	0.12	0.62
Knee Adduction moment[1]	0.08	0.04	0.04	0.12	0.09	0.02	0.06	0.11	-0.44	0.68	-0.16
Knee Abduction 1st peak[1]	-0.41	0.25	-0.65	-0.23	-0.42	0.20	-0.60	-0.24	0.07	0.95	0.03
Knee Abduction 2nd peak[1]	-0.47	0.27	-0.70	-0.25	-0.45	0.20	-0.65	-0.24	-0.23	0.83	-0.08
Knee Abduction in midstance	-0.32	0.25	-0.58	-0.15	-0.25	0.16	-0.40	-0.10	-0.65	0.54	-0.25
Hip Flexion moment[1]	0.78	0.19	0.63	0.98	1.04	0.19	0.86	1.23	-2.65	0.03	0.94
Hip Extension 2nd peak[1]	-0.28	0.12	-0.41	-0.17	-0.36	0.06	-0.43	-0.30	1.49	0.18	0.53

Hip Abduction 2nd peak[1]	-0.92	0.42	-1.36	-0.53	-0.92	0.39	-1.33	-0.60	-0.04	0.97	-0.01
Hip Adduction[1]	0.19	0.09	0.12	0.28	0.16	0.07	0.09	0.24	0.49	0.64	0.17
Contralateral Hip Extension 1st peak[1]	-0.32	0.15	-0.46	-0.17	-0.32	0.18	-0.50	-0.15	0.09	0.93	0.03
Contralateral Hip Extension 2nd peak[1]	-0.25	0.11	-0.36	-0.15	-0.35	0.09	-0.43	-0.30	1.97	0.09	0.70
Contralateral Hip Abduction 1st peak[1]	-0.99	0.33	-1.33	-0.79	-0.99	0.25	-1.22	-0.73	-0.07	0.95	-0.02
Contralateral Hip Abduction 2nd peak[1]	-1.02	0.35	-1.38	-0.78	-0.93	0.20	-1.10	-0.71	-0.54	0.61	-0.19
Contralateral Hip Abduction in midstance	-0.83	0.27	-1.06	-0.61	-0.66	0.18	-0.83	-0.47	-1.52	0.17	-0.54

	Median	95% CI		Median	95% CI		t-stat	p-value	r
Ankle plantarflexion moment[2]	-1.07	-1.3	-0.95	-1.11	-1.31	-0.92	18.00	1.00	0
Hip Extension 1st peak[2]	-0.34	-0.49	-0.19	-0.30	-0.61	-0.20	12.00	0.40	-0.21
Hip Abduction 1st peak[2]	-0.79	-1.28	-0.59	-1.04	-1.39	-0.78	13.00	0.48	-0.18
Hip Abduction in midstance	-0.66	-1.02	-0.42	-0.61	-0.83	-0.47	19.00	0.89	0.04
Contralateral Hip Flexion moment[2]	0.72	0.44	1.05	1.07	0.83	1.25	33.00	0.04	0.53
Contralateral Hip Adduction[2]	0.15	0.10	0.28	0.12	0.10	0.18	14.00	0.58	-0.14

[1]Paired sample t-test (df = 7)
[2]Wilcoxson Signed Rank Test

Table 2. Joint moments during obstructed walking.

	PWA (n = 7)				PNA (n = 7)				t-stat	p-value	Cohen's d
	Mean	SD	95% CI		Mean	SD	95% CI				
Ankle DF moment[1]	0.21	0.07	0.14	0.27	0.21	0.09	0.13	0.28	0.04	0.97	-0.01
Ankle Inversion moment[1]	0.10	0.05	0.05	0.15	0.11	0.06	0.05	0.17	-0.65	0.54	-0.25
Ankle Eversion moment[1]	-0.72	0.16	-0.87	-0.57	-0.74	0.25	-0.97	-0.51	0.33	0.75	0.12
Knee Extension 1st peak[1]	0.87	0.21	0.67	1.06	0.88	0.20	0.69	1.07	-0.11	0.91	-0.04
Knee Extension 2nd peak[1]	0.45	0.12	0.33	0.56	0.42	0.24	0.20	0.64	0.20	0.85	-0.08
Knee Extension in midstance[1]	0.23	0.14	0.10	0.36	0.04	0.15	-0.10	0.18	2.61	0.04	0.99
Knee Flexion moment[1]	-0.22	0.06	-0.28	-0.16	-0.28	0.03	-0.30	-0.25	2.07	0.08	0.78
Knee Adduction moment[1]	0.08	0.04	0.11	0.04	0.08	0.03	0.06	0.11	-0.43	0.68	-0.16
Knee Abduction 1st peak[1]	-0.35	0.18	-0.52	-0.18	-0.30	0.21	-0.49	-0.11	-0.51	0.63	-0.19
Knee Abduction 2nd peak[1]	-0.38	0.22	-0.59	-0.18	-0.38	0.15	-0.52	-0.24	-0.05	0.96	-0.02
Knee Abduction in midstance	-0.21	0.21	-0.41	-0.01	-0.18	0.08	-0.25	-0.10	-0.38	0.72	-0.14
Hip Flexion moment[1]	0.75	0.17	0.59	0.91	0.92	0.24	0.70	1.15	-1.84	0.12	0.70
Hip Extension 2nd peak[1]	-0.26	0.11	-0.37	-0.16	-0.35	0.09	-0.44	-0.27	1.27	0.25	0.48
Hip Abduction 2nd peak[1]	-0.87	0.31	-1.15	-0.59	-0.78	0.27	-1.03	-0.52	-1.09	0.32	-0.41
Hip Abduction in midstance	-0.54	0.25	-0.78	-0.31	-0.46	0.16	-0.62	-0.31	-1.07	0.33	-0.41
Hip Adduction[1]	0.18	0.09	0.09	0.26	0.12	0.08	0.05	0.19	1.00	0.36	0.38

Contralateral Hip Extension 1st peak[1]	-0.33	0.12	-0.45	-0.22	-0.28	0.17	-0.44	-0.13	-0.68	0.52	-0.26
Contralateral Hip Abduction 1st peak[1]	-1.16	0.35	-1.49	-0.84	-1.13	0.29	-1.40	-0.87	-0.25	0.81	-0.09
Contralateral Hip Abduction 2nd peak[1]	-1.17	0.39	-1.53	-0.81	-0.96	0.31	-1.25	-0.68	-1.07	0.33	-0.40
Contralateral Hip Abduction in midstance	-0.96	0.30	-1.25	-0.68	-0.76	0.22	-0.96	-0.56	-1.56	0.17	-0.59
Contralateral Hip Adduction[1]	0.18	0.08	0.10	0.26	0.13	0.08	0.06	0.20	0.98	0.37	0.37

	Median	95% CI	Median	95% CI	t-stat	p-value	r
Ankle PF moment[2]	-1.13	-1.40— -0.98	-1.19	-1.41— -1.05	10.00	0.50	-0.18
Hip Extension 1st peak[2]	-0.32	-0.49— -0.17	-0.34	-0.65— -0.21	8.00	0.31	-0.27
Hip Abduction 1st peak[2]	-0.78	-1.06— -0.64	-0.93	-1.18— -0.70	11.00	0.61	-0.14
Contralateral Hip Flexion moment[2]	0.65	0.43—0.98	0.94	0.73—1.06	20.00	0.31	0.27
Contralateral Hip Extension 2nd peak[2]	0.27	0.15—0.52	0.35	0.02—0.51	10.00	0.50	-0.18

[1]Paired sample t-test (df = 6)
[2]Wilcoxon Signed Rank Test

Appendix C: Questionnaires used in the first part of the study

Hip dysfunction and Osteoarthritis Outcome Score for Joint Replacement (HOOS, JR.), English version 1.0

HOOS, JR. HIP SURVEY

INSTRUCTIONS: This survey asks for your view about your hip. This information will help us keep track of how you feel about your hip and how well you are able to do your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Pain

What amount of hip pain have you experienced the **last week** during the following activities?

1. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

2. Walking on an uneven surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your hip.

3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

4. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

5. Lying in bed (turning over, maintaining hip position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

6. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

KOOS, JR. KNEE SURVEY

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to do your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Stiffness
The following question concerns the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

1. How severe is your knee stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain
What amount of knee pain have you experienced the **last week** during the following activities?

2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

4. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

5. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living
The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

6. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

7. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Subject/Patient:_____ Date:_____

Quick-Foot and Ankle Ability Measure (Quick-FAAM)

Please answer every question with one response that most closely describes to your condition within the past week. If the activity in question is limited by something other than your foot or ankle mark not applicable (N/A).

	Side	4 No Difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do 0	N/A
Walking up hills	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Walking down hills	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Walking on uneven ground	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Stepping up and down curbs	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Recreational activities	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Running	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Jumping	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Landing	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Starting and stopping quickly	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Cutting/lateral movements	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Ability to perform activity with your normal technique	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Ability to participate in your desired sport as long as you would like	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐

Reset Save As

R Quick-FAAM:_____ _____%

L Quick-FAAM:_____ _____%

Martin R, Irrgang J, Burdett R, Ped C, Conti S, Van Swearingen J. Evidence of Validity for the Foot and Ankle Ability Measure (FAAM). Foot Ankle Int. 2005;26(11):968-983.

The Shortened Activities-specific Balance Confidence (ABC-6) Scale*

Instructions to Participants: For each of the following activities, please indicate your level of confidence in doing the activity without losing your balance or becoming unsteady from choosing one of the percentage points on the scale from 0% to 100%. If you do not currently do the activity in question, try and imagine how confident you would be if you had to do the activity. If you normally use a walking aid to do the activity or hold onto someone, rate your confidence as if you were using these supports.

For each of the following activities please indicate your level of self-confidence by choosing a corresponding number from the following rating scale.

0% 10 20 30 40 50 60 70 80 90 100%

No confidence Completely confident

How confident are you that you will not lose your balance or become unsteady when you...

1. ...stand on your tiptoes and reach for something above your head? _____%
2. ...stand on a chair and reach for something? _____%
3. ...are bumped into by people as you walk through the mall? _____%
4. ...step onto or off an escalator while you are holding onto a railing? _____%
5. ...step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing? _____%
6. ...walk outside on icy sidewalks? _____%

ABC-6 Score: _____ Date: _____

* Peretz C, Herman T, Hausdorff JM, Giladi N. Assessing Fear of Falling: Can a Short Version of the Activities-specific Balance Confidence Scale Be Useful? *Movement Disorders*. 2006 Dec;21(12):2101-5. doi: 10.1002/mds.21113.

Appendix D: Consent Form

Informed Consent Form Non-Interventional Study

STUDY TITLE:	Exploring the impact of arthropathy in acromegaly patients and the associated changes in joint biomechanics compared with able-bodied individuals (Part 2).
PRINCIPAL INVESTIGATOR:	Dr. Syed Ali Imran Department of Medicine Division of Endocrinology and Metabolism Dalhousie University Phone: (902) 473-2952 QEII Health Sciences Centre, Victoria Building 7N-Room 047, 1276 South Park Street, Halifax, NS B3H 2Y9
SUB-INVESTIGATOR:	Dr. Michel Ladouceur School of Health and Human Performance Dalhousie University Phone: (902) 494-2754 Yuqi Wang School of Health and Human Performance Dalhousie University Phone: (902) 401-6753 School of Health and Human Performance Dalhousie University Stairs House, P.O. Box 15000 6230 South Street Halifax, NS B3H 4R2

Introduction

You have been invited to take part in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide,

you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study. The research team will tell you if there are any study timelines for making your decision.

Please ask the research team to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

The researchers will:
Discuss the study with you
Answer your questions
Be available during the study to deal with problems and answer questions

You are being asked to consider participating in this study because you are an adult (age 18 or older) and have been diagnosed with acromegaly. You may also be asked if you have a nonfunctioning pituitary tumour and have undergone pituitary surgery; in this case, we are recruiting you in order to compare against patients with acromegaly.

If you decide not to take part or if you leave the study early, your usual health care will not be affected.
2. Why is there a need for this study?
The purpose of this study is to study the mechanical changes associated with joint disease in acromegaly, such as differences in standing posture and walking patterns.

Posture and balance are necessary for normal walking and activities of daily living, and play an important role in preventing falls and injuries. It is important to explore whether the standing posture and walking patterns are significantly different between acromegaly and non-acromegaly individuals. Knowledge in this area is important for the development of better physiotherapy interventions to help prevent and/or treat joint disease in acromegaly patients.

There has been limited research investigating posture, balance, and walking patterns in acromegaly patients. Several previous studies have suggested possible mechanical changes in acromegaly patients, such as impaired balance, altered joint alignment, and weaker muscle function. However, these previous studies used more subjective methods for assessing walking patterns. Our laboratory is equipped with a force plate system and motion capture system to obtain more objective data. In addition, there is limited studies exploring joint laxity (i.e., the "looseless" of your joints) on posture, balance, and walking in acromegaly patients. In this study, we will examine your lower joints (ankles, knees, hips) for joint laxity, in the same manner that physicians examine joints in the clinic.
3. How Long Will I Be In The Study?
This study can be completed in just one in-person session. The total duration from the time of entry into our lab at the Dalplex building to the end of the tests will be no longer than 150 minutes. The results should be known in 1 year.
4. How Many People Will Take Part In This Study?

We hope to recruit at least 50 acromegaly patients and a similar number of non-acromegaly patients for comparison, for a total of at least 100 patients.

5. How Is The Study Being Done?

If you are interested in this study after reviewing this consent form, we will arrange for you to visit the Dalplex building at Dalhousie University (where the kinesiology laboratory is located). There, you will undergo a series of tests involving standing, balance, and walking. The entire visit will take no more than 150 minutes.

6. What Will Happen If I Take Part In This Study?

If you agree to take part in this study, you will be asked to do the following tests in our kinesiology laboratory at the Dalplex building of Dalhousie University:

You will be asked to hold still for 10 seconds while our camera system records your standing posture.

You will stand still on a force plate system (embedded in the floor) as it detects and records the forces under your feet, with eyes closed and then eyes open.

You will walk along a 10-metre path as our camera system records your walking pattern. This will be performed 10 times each, with and without obstacles.

You will walk while modifying your movements according to 8 different instructions (such as change in speed, turning your head to the side, or stepping over an obstacle).

We will record the time it takes for you to stand up from a chair, walk 10 feet and back, and sit back down.

Finally, a member of the study team will examine your lower joints (ankles, knees, hips) for laxity (i.e., looseness), in the same manner that physicians examine patients' joints in the clinic.

Detailed instructions will be provided at the time by a member of the research team on site.

You may choose not to continue participating in the study at any time. If you decide not to take part in the study or if you leave the session early, your data will automatically be withdrawn from the study. Additionally, you may choose to withdraw after participating in the study, but this will not be possible after the data has been analyzed. We will hold off analyzing data for 1 week following collection from the final participant to allow you to withdraw after you have participated.

7. Are There Risks To The Study?

The foreseeable risk in this experiment include muscle fatigue. If this happens, you are encouraged to keep stretching and moving the muscle and apply mild heat. There is minimal chance of muscle injury. Some people may experience personal discomfort in the form of irritated or itchy skin due to marker placement. If this happens, apply a topical moisturizer and cold compresses. To diminish personal discomfort due to the site of marker placement, a research assistant whose gender matches yours will be on hand to apply these markers. The risk of falling is low since these tests are simple activities (e.g., standing still, walking short distances) and are comparable to everyday when you walk around at home or outside. To minimize the risk of falls, you will be supervised by staff during the testing.

Any study that involves collecting data from patients has the theoretical risk of accidental breaching confidentiality, but we will take many precautions to prevent such a breach, including storing electronic data in a secure password-protected drive on hospital computers, storing physical data in a locked office with controlled access, and limiting access to such data only to members of the study team. All participants will be assigned anonymous study numbers to "de-identify" them, and data will be reported collectively so that individual patients cannot be identified.

8. Are There Benefits Of Participating In This Study?

We cannot guarantee or promise that you will receive any benefits from this research. Participating in the study might not benefit you directly, but there is benefit in advancing our knowledge regarding joint disease in acromegaly patients, paving the way for the development of better treatments.

9. What Happens at the End of the Study?

It is anticipated that the results of this study will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your express permission. Please let us know if you are interested to see the study results after it has been published (although the publication process can be long, and may take months or even years).

10. What Are My Responsibilities?

As a study participant you will be expected to:
Follow the directions of the research team;
Report any major changes in your health to the research team;
Report any problems that you experience that you think might be related to participating in the study;

11. Can My Participation in this Study End Early?

Yes. If you chose to participate and later change your mind, you can say no and stop the research at any time. If you wish to withdraw your consent, please inform the research team. If you choose to withdraw from this study, your decision will have no effect on your current or future medical treatment and healthcare.

Also, the Nova Scotia Health Authority Research Ethics Board and the principal investigator have the right to stop patient recruitment or cancel the study at any time.

Lastly, the principal investigator may decide to remove you from this study without your consent for any of the following reasons:

You do not follow the directions of the research team;
There is new information that shows that being in this study is not in your best interests;

13. What About New Information?

You will be told about any other new information that might affect your health, welfare, or willingness to stay in the study and will be asked whether you wish to continue taking part in the study or not.

14. Will It Cost Me Anything?

<u>Compensation</u>

You will be covered for parking for your in-person visit at our lab in Dalhousie University. Your travel costs will be reimbursed depending on your distance from Halifax: $20 for 100 km or within, $50 for those living beyond 100 km of the city.

Research Related Injury

If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. Your signature on this form only indicates that you have understood to your satisfaction the information regarding your participation in the study and agree to participate as a subject. In no way does this waive your legal rights nor release the principal investigator, the research staff, the study sponsor or involved institutions from their legal and professional responsibilities.

15. What About My Privacy and Confidentiality?

Protecting your privacy is an important part of this study. Every effort to protect your privacy will be made. If the results of this study are presented to the public, nobody will be able to tell that you were in the study.

However, complete privacy cannot be guaranteed. For example, the principal investigator may be required by law to allow access to research records.

If you decide to participate in this study, the research team will look at your personal health information and collect only the information they need for this study. "Personal health information" is health information about you that could identify you because it includes information such as your;

Name,
Address,
Telephone number,
Age or month/year of birth (MM/YY),
Information from the study interviews and questionnaires;
New and existing medical records, or
The types, dates and results of various tests and procedures. >>

Access to Records

Other people may need to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines. These people might include:

The Nova Scotia Health Authority Research Ethics Board (NSHA REB) and people working for or with the NSHA REB because they oversee the ethical conduct of research studies within the Nova Scotia Health Authority;

Use of Your Study Information

Any study data about you that is sent outside of the Nova Scotia Health Authority will have a code and will not contain your name or address, or any information that directly identifies you.

Study data that is sent outside of the Nova Scotia Health Authority will be used for the research purposes explained in this consent form.

The research team and the other people listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

The research team will keep any personal health information about you in a secure and confidential location for 7 years and then destroy it according to NSHA policy. Your personal health information will not be shared with others without your permission.

After your part in the study ends, we may continue to review your health records for safety and data accuracy until the study is finished or you withdraw your consent.

You have the right to be informed of the results of this study once the entire study is complete.

The REB and people working for or with the REB may also contact you personally for quality assurance purposes.

Your access to records
You have the right to access, review, and request changes to your study data.

16. Declaration of Financial Interest

This study is funded by the Special Circumstances Grant from the University Internal Medicine Research Foundation (UIMRF). The PI has no vested financial interest in conducting this study.

17. What About Questions or Problems?

For further information about the study you may call the following team members listed below:

Dr. Ali Imran. Telephone: (902) 473-2952
Dr. Michel Ladouceur. Telephone: (902) 494-2754

18. What Are My Rights?

You have the right to all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction before you make any decision. You also have the right to ask questions and to receive answers throughout this study. You have the right to withdraw your consent at any time.

If you have questions about your rights as a research participant, and/or concerns or complaints about this research study, you can contact the Nova Scotia Health Authority Research Ethics Board manager at 902-473-8426 or Patient Relations at (902) 473-2133 or 1-855-799-0990 or healthcareexperience@nshealth.ca.

In the next part you will be asked if you agree (consent) to join this study. If the answer is "yes", please sign the form.

19. Consent Form Signature Page
I have reviewed all of the information in this consent form related to the study called: "Exploring the impact of arthropathy in acromegaly patients and the associated changes in joint biomechanics compared with able-bodied individuals (Part 2)."

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

I authorize access to my personal health information, and research study data as explained in this form.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time without affecting my future care.

E-messaging (email and texting) can be used by a member or members of the research team to communicate with you while you are in this study. All communication done with you will be done only through a NSHA Webmail account, or text by a phone issued to a research member through NSHA. All efforts are made to keep information sent or received private, but it is possible other people may be able to see, read, and change messages sent to or from NSHA.

☐ I give my permission to be contacted by a member or members of the research team from an NSHA Webmail account or an NSHA cell phone by research staff to communicate during this study. _____ (initials and date).

Email yes ☐ no ☐ Text message yes ☐ no ☐

☐ I do not wish to be contacted by email or text message, unless I otherwise give permission at another time during this study _____ (initial and date).

☐ Not applicable.

_____ _____ _____
/ _____ / ____
Signature of Participant Name (Printed) Year Month Day*

_____ _____ _____
/ _____ / ____
Signature of Person Conducting Consent Discussion Name (Printed) Year Month Day*

_____ _____ _____
/ _____ / ____
Signature of Principal Investigator Name (Printed) Year Month Day*
I will be given a signed copy of this consent form.

Appendix E: Posturography

Parameters measured in posturography. Numbers in square brackets refer to points on the diagram below.

Head horizontal alignment: angle between right-left tragus [1] and the horizontal
Acromion-horizontal alignment: angle between right-left acromion [2] and the horizontal
Anterior-superior iliac spine (ASIS) horizontal alignment: angle between right-left ASIS [3] and the horizontal
Angle between the acromion [2] to ASIS [3] and the vertical
Right and left limb-frontal angles: angle between greater trochanter [4] to lateral projection of knee joint line [5] and [5] to lateral malleolus [8]
Leg length difference: difference between right and leg lengths as measured from ASIS [3] to medial malleolus [9]
Tibial tuberosity-horizontal angle: angle between right-left tibial tuberosities [7] and the horizontal
Hip angles: angle between ASIS [3] to the centre of the patella [6] and [6] to the tibial tuberosity [7]
Scapula-T3 horizontal asymmetry: horizontal asymmetry of the scapular angle [11] relative to T3 vertebra [10]
Leg-heel angle: angle between the lower leg [12] to intermalleolar line [13] and [13] to heel [14]
Head-horizontal alignment: angle between tragus [1] to scapular angle [11] and the horizontal
Head-vertical alignment: angle between tragus [1] to acromion [2] with the vertical
Trunk-vertical alignment: angle between the acromion [2] to greater trochanter [4] with the vertical
Hip angle: angle between acromion [2] to greater trochanter [4] with [4] to lateral malleolus [8]
Body-vertical alignment: angle between acromion [2] to lateral malleolus [8] with the vertical
Pelvis-horizontal alignment: angle between ASIS [3] to posterior-superior iliac spine (PSIS) [15] with the horizontal
Knee angle: angle between greater trochanter [4] to projection of the knee joint line [5] with [5] to lateral malleolus [8]
Ankle angle: angle between the projection of the knee joint line [5] to lateral malleolus [8] with the horizontal

Diagram of key anatomical landmarks used in posturography. Figure obtained from Lopes et al (ref 5).