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Chemotherapy Induced Peripheral Neuropathy and Foot Posture in Pediatric Cancer Patients

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CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY AND FOOT POSTURE IN PEDIATRIC CANCER PATIENTS

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ABSTRACT

Background

Physical therapists have recognized a potential change in foot structure among pediatric cancer patients undergoing chemotherapy; however it has not been empirically investigated.

Purpose

The purpose of this study was to determine if patients with chemotherapeutic induced peripheral neuropathy (CIPN) develop foot posture abnormalities when compared to gender and age matched controls. We hypothesized that patients with CIPN, especially distal motor CIPN, or ankle ROM limitations demonstrate foot posture abnormalities.

Methods

The medial and posterior foot aspects of pediatric cancer patients (n=38) and age and gender matched controls (n=38) were digitally photographed in a standard position while bearing weight. MMT of great toe extension (GTE) and ankle dorsiflexion (DF), PROM of ankle DF, and peripheral nerve function (using the ped-mTNS) was measured for all subjects. Photographs were analyzed using four aspects of the Foot Posture Index (FPI), calcaneal tilt angle, navicular height, and medial longitudinal arch angle. Independent sample T-test and Mann-Whitney U were used to compare group's foot measures. Spearman correlation statistic was used to determine associations between strength or ROM measures and foot posture.

Results

Subjects' mean age was 11 years (range 5-18) and 37% of the population was male. Children undergoing cancer treatment had higher scores on the ped-mTNS (10.5 vs. 0.7, $p<0.001$), limited

ankle DF PROM (Right 8.3 vs 14.2 degrees, $p<0.001$, Left 8.5 vs 14.3 degrees, $p<0.001$), and decreased strength (right GTE median 3 vs 5 $p<0.001$, right ankle DF 4 vs 5 $p<0.001$). No significant differences were found between groups in foot posture measurements. A modest, but significant, correlation was found between L GTE strength, total FPI on the left foot ($rS=0.29$, $p=0.01$), and left calcaneal tilt angle ($rS=0.27$, $p=0.02$). Right ankle DF PROM was only correlated to right navicular height ($rS=-0.25$, $p=0.04$).

Conclusion

Our data do not support the hypothesis that a difference in foot posture between pediatric cancer patients and healthy controls exists. Although chemotherapy is linked to foot muscular weakness and limited ankle ROM, it was not shown to be strongly correlated to structural changes in foot posture. Limitations of this study include use of a modified FPI and possible impact of PT intervention.

RESEARCH ADVISOR FINAL APPROVAL FORM

The undersigned certify that they have read, and recommended approval of the research project entitled

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in partial fulfillment of the requirements for the Doctor of Physical Therapy Program

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Chapter I: Introduction and Literature Review

Pediatric Cancers

In the year 2015 it is estimated that 1,658,370 people will be diagnosed with cancer, and 10,380 of those will be under the age of 15.[1] Over the past few centuries cancer treatments have greatly improved and more than 80% of children are now surviving cancer.[1] This is a large increase from past statistics. With such a large increase in survivors there needs to be research to document health concerns, and side effects from treatments for these survivors. This is particularly true of the pediatric population as, typically, these cancer survivors will live much longer with possible residual effects from their cancer and the treatment. Additionally, this population will be receiving treatments during one of the most important developmental stages in life.

Described below are several key factors that play into the quality of life of the pediatric cancer population. First, the most common types of pediatric cancers are discussed. Then vincristine and chemotherapy induced peripheral neuropathy are explained in detail as it pertains to pediatric cancer patients and survivors. Lastly, the effect that these treatments have on the structure of the foot and the importance of these changes will be introduced.

Acute lymphocytic leukemia

Acute lymphocytic leukemia (ALL) is the most prevalent form of cancer in the pediatric population. Approximately 2,500 children are diagnosed with ALL each year.[1] This cancer is the result of abnormal mutations in the cells of the bone marrow. ALL occurs most often in children between the ages of two and four. The survival rate is greater than 85%, and is typically treated with chemotherapy and, if necessary, a bone marrow transplant.[1] While the direct cause of leukemia is unknown, it has been shown to be inversely associated with exposure to disease and

infections at a young age. Additionally, ALL has been shown to be related to stimulation of the immune system such as exposure to daycare/childcare settings, birth order, vaccination history, being around others with potential illness, and maternal exposure to infections.[2,3] There is research that also supports that there is a relationship between ALL and a congenital defect resulting in lower level of cytokine IL-10 and a higher need for professional care for infections in childhood. Recently, the incidence of acute leukemia has been increasing in western countries. While the reason for this rise is unknown, there appears to be a relationship between the increased level of toxins children are exposed to such as pesticides on food, pollution from traffic, household chemicals, paint, and familial smoking.[2]

Lymphomas

Lymphoma is a cancer that begins in the lymphatic cells of the immune system, and has two main subtypes: Hodgkin's lymphoma and Non-Hodgkin lymphoma. Hodgkin's lymphoma is uncommon in children under the age of five, and usually affects people between the ages of fifteen and thirty-five. Hodgkin's lymphoma has survival rates above 90% when treated properly. These treatments usually include chemotherapy, radiation, or a combination of both.[4] Non-Hodgkin lymphoma (NHL) is more common in the pediatric population than Hodgkin's lymphoma with approximately 500 new cases each year, containing many different subgroups. Non-Hodgkin accounts for about six percent of pediatric cancers. This cancer is very uncommon in children under the age of three and the risk of obtaining the cancer increases with age.[1] Treatments for NHL include chemotherapy, radiation, bone marrow transplants, or a combination of these treatments. Much like Hodgkin's lymphoma, NHL has high survival rates when properly treated.[4]

Nephroblastoma

Nephroblastoma, also known as Wilms' Tumor, is a cancer of the kidneys most common in the pediatric population. Wilms' tumors typically occur in only one kidney, and may become quite large before they are noticed. This type of cancer is typically found in children between the ages of three to four, and becomes less common as children become older. Wilms' tumors are responsible for approximately five percent of pediatric cancers. The treatments for this cancer include surgical removal of the kidney, chemotherapy, radiation, or a combination of these treatments.[1] While this is a fairly rare cancer with unknown cause, the survival rate remains fairly high. This is made possible by finding clear prognostic indicators. The stage of the tumor and histologic subtypes remain the most important prognostic indicators. More recently studies have shown that patient age, size of the tumor, response to therapy, and other genetic abnormalities have provided additional prognostic indicators.[5] With the addition of more detailed prognostic indicators it has become easier to assign children to the appropriate therapies. It is also argued that since prognostic indicators have helped lead to more beneficial treatment the next step is to minimize the toxicity related to these treatments.[5] Some have thought that screening for Wilms tumors would benefit the pediatric population since these tumors are usually well developed once they are found. However, it has been found that screening does not reduce mortality in children.[6]

Regardless of the type of cancer, children who survive will often need follow up care due to the complications that are associated with the cancer itself and the treatments used to cure the child of cancer. The experiences, or complications, a child has completely depends on the type of cancer they had and the treatments they received.[7] Some of the most common effects of cancer

treatment include: heart or lung problems, delayed growth and development, difficulty learning, peripheral neuropathies and increased risk of other cancers later in life.[1]

Vincristine and chemotherapy induced peripheral neuropathy

One drug that has shown to be damaging to these body systems is Vincristine, a chemotherapeutic agent. One system that is most greatly affected is the peripheral nervous system resulting in chemotherapy induced peripheral neuropathy (CIPN). CIPN is the degeneration of peripheral nerves due to neurotoxic effects of chemotherapeutic agents.[8,9] Different chemotherapeutic agents have varying potential to cause CIPN. Vincristine is one such agent associated with CIPN, even at low doses, and is commonly associated with pediatric cancers.[8,9] Hallmarks of CIPN include stocking-glove pattern of presentation, reduced nerve conduction velocity, pain syndromes, and paresthesias.[8] Sensory afferents are most commonly affected, but motor and autonomic neurons can also be affected depending on the agent. Han and Smith[8] specify three common sensory dysfunctions which include mechanical allodynia, cold allodynia, and reduced sensitivity to heat.

Prevalence of vincristine induced peripheral neuropathy

Vincristine is a chemotherapeutic agent obtained from plant derived vinca alkaloids.[10] It is known to be highly neurotoxic and to induce neuropathies even at low doses. Vincristine's neurotoxic effects primarily involve the distal portion of long sensory afferents and motor axons. The prevalence of vincristine induced peripheral neuropathy is difficult to accurately assess due to the fact that many of its effects are only evident through assessment of nerve conduction velocities. Research by Jain et al 2013[11] attempted to determine the prevalence of vincristine induced peripheral neuropathy in survivors of childhood ALL. Using electrophysiological and

clinical symptom evaluation summarized by the reduced version of the Total Neuropathy Score, the authors were able to determine if CIPN manifested over the course of vincristine treatment in 80 children with no prior history of neuropathy. The authors diagnosed 33.75% of participants with pure motor axonal neuropathy via EMG value assessment whereas only 13.8% of children were diagnosed clinically. In addition, difficulties often arise due to the invasive nature of EMG studies despite the potential for early detection and modification of dosage.[12] Dorchin et al[13] performed a retrospective study of incidence of vincristine induced neuropathy for a total of 51 patients with ALL or NHL, 45% of whom presented with some evidence of neuropathy. The authors further described incidence according to age group. Results showed 31% of patients presented with motor neuropathy, 21.5% had mild sensory neuropathy, and 9.0% had severe sensory neuropathy. Average age of patients with motor neuropathy was 14.5 years which the authors interpreted as incidence increasing with age.

Mechanisms of vincristine induced peripheral neuropathy

Numerous theories exist pertaining to the mechanism of vincristine induced peripheral neuropathy; however the mitochondrial DNA and antimicrotubule theories are most often referenced in the literature.[8,9] For example, an *in vitro* study conducted by Silva et al[14] found that when vincristine was applied to neurons sprouted from rat dorsal root ganglion, there was a loss of growth and shortening of the axon. In addition, when the vincristine was applied to the distal portion of an axon separated from the proximal portion by a barrier, the distal portion degenerated but the proximal segment remained intact. The authors theorized that vincristine caused local metabolic disruption due to disruption of the mitochondrial DNA. Since mitochondria are the primary site of the cellular apoptosis mechanism, disruption of its DNA is thought to activate caspase proteins which mediate pathways of programmed cell death. Han and

Smith,[8] and Jaggi and Singh[9] explain that as a result of mitochondrial dysfunction, there is a decline in the amount of mitochondria and therefore ATP produced in the neuron. The ATP activated sodium and potassium pumps that maintain ion concentrations in the neuron therefore cease to function resulting in the impaired ability of the neuron to maintain its resting membrane potential despite the leakage of ions. In addition, the impaired mitochondria can no longer regulate neuronal calcium levels, resulting in leakage of calcium into the intracellular environment causing further disruption of structure and function. It is thought that because long axons have large metabolic demands for axonal transport, that the distal portions—primarily the terminal endings in the epidermis of the skin—are most affected due to their distant proximity to the neuronal cell body.

Conversely, a study by LaPointe et al[15] investigated the effects of vincristine on microtubule structure and function of microtubule facilitated transport molecules kinesin and dynein which regulate anterograde and retrograde axonal transport respectively. The authors found that unlike other chemotherapeutic agents tested, vincristine inhibited anterograde, retrograde, and the ability of kinesin to travel along microtubules. Although they were unable to observe microtubule depolymerization, they also found that parallel microtubules became disorganized. Without axonal transport, long axons cannot transport essential proteins and molecules to and from the neuronal cell body possibly resulting in degeneration of the most distal portion of the axon.

Lasting effects of vincristine induced peripheral neuropathy

Vincristine induced peripheral neuropathy has also been characterized as having the tendency to worsen after treatment has stopped[16] and its effects can be apparent years post cancer treatment.[17] Verstappen et al[16] found that 25% of children receiving a low dose and 31% of

children receiving a high dose of vincristine over the course of three weeks experienced worsening symptoms of CIPN over the following month post-treatment. Ramchandren et al[17] found that 29.7% of 37 pediatric survivors of ALL (an average of 7 years post treatment with vincristine) had significantly abnormal nerve conduction study results, most noticeably for peroneal motor nerve conduction. Although these children were identified as fitting the criteria for CIPN, all but one did not report symptoms of CIPN in their subjective histories. All 37 children were diagnosed with CIPN according to the Total Neuropathy Score Reduced assessment.

Most concerning of vincristine induced peripheral neuropathy is the potential for muscle weakness as a result of reduced motor neuron conduction, however reducing dosage could impact the effectiveness of cancer treatment. Toopchizadeh et al[18] performed nerve conduction studies and electromyography on children with ALL currently receiving treatment with vincristine. Reduced upper and lower extremity motor nerve conduction values were found in 70.8% of children and 66.7% presented with gait abnormalities as a result. Finally, a significant difference in prevalence of neuropathy was found between children receiving vincristine weekly versus those receiving treatment every three weeks, with those receiving weekly treatment having greater prevalence of neuropathy.

Electrophysiological studies of nerve conduction allow greater insight concerning the effects of motor neuropathy in particular. Changes in nerve conduction velocity can be evident years after chemotherapy treatment is ended and clinical signs and symptoms have diminished. During chemotherapy treatment with vincristine, motor neuropathy and subsequent muscle weakness can be measured and observed. Gomber, Dewan, and Chhonker[19] followed 20 children with various cancer diagnoses over the course of their chemotherapy treatment and additional

follow-up 6 months later. They found that symptoms of areflexia and muscle weakness can manifest as quickly as the second dose of vincristine. Nerve conduction velocity studies were performed on six children with diagnoses of ALL, non-Hodgkin's Lymphoma, Hodgkin's Lymphoma, or neuroblastoma. Of the four nerves tested (median, ulnar, posterior tibial, and common peroneal) the common peroneal nerve was most frequently affected, usually with bilateral lower extremity involvement. All six were diagnosed with grades III to IV motor neuropathy interpreted as severe enough to cause significant disability without foot drop or structural abnormalities, and subsequent modification of dosage after which clinical symptoms greatly improved over the 6 month follow-up period. In addition, this study allows greater insight as to the effects of BMI and malnutrition as risk factors for more severe neurotoxic effects with vincristine. The authors note that the children who were subject to complications of neuropathy were also suffering from malnutrition with BMIs under the third percentile which was significantly lower than the remaining 10 participants who did not develop neurotoxicity. The previous study of prevalence of CIPN of children with ALL by Jain et al 2013[11] similarly show that the peroneal nerve is most commonly involved in cases of electrophysiologically diagnosed motor neuropathy despite not exhibiting any muscle weakness. The common peroneal nerve was affected in 50.7% of participants; upper extremity nerves were less involved, such as the ulnar nerve was affected in only 7.8%. Research by Diaz-Maimes et al[20] further reinforce findings that a reduction in nerve conduction velocity amplitude is greater in motor nerves with the peroneal, followed by the tibial nerve, most commonly affected. In this case 48% of 13 participants exhibited reduction in NCV whereas only 15% had impaired sensory nerves. After 3 months frequency of sensory impairment decreased to 4% whereas motor impairment remained at 48%. Courtemanche et al[12] found pure motor axonal neuropathy in 13 of 17 children all of whom

presented with some form of gait abnormality; noting however, that the participants were largely referred to the authors due to observable foot drop or decrease in walking ability.

Prolonged effects of neuropathy

Although acute symptoms of neuropathy diminish quickly after dose modification or conclusion of treatment with vincristine, it is apparent that underlying effects are prolonged into adolescent years and adulthood in pediatric cancer survivors. Hoffman et al[21] studied various aspects of physical performance among adolescent ALL survivors with an average time of 9.3 years since final dose and compared testing results to their siblings. They found that survivors of childhood ALL treated with chemotherapeutic agents including Vincristine, had lower scores than siblings tested with the 6-minute walk test, Timed Up and Go, and strength measured with dynamometry. This was true even in siblings who maintained similar active lifestyles. Deficits in physical performance continue to persist even through adult years. Ness et al list slowed motor nerve NCV, absent deep tendon reflexes, limited ankle range of motion, and distal muscle weakness among the primary impairments seen in survivors of ALL with an average of 28 years past their final dose and mean age of 35.6 years. Using multiple variate regression models, the authors analyzed aspects of balance, mobility, ankle strength and range, and sensation in a cohort of adult ALL survivors treated previously with various chemotherapeutic agents including Vincristine. Frequency distribution of impairments to note include reduced ankle dorsiflexion AROM of less than 5 degrees in 33.5%, ankle plantar flexion weakness in 24.6%, and ankle dorsiflexion weakness in 16.9%. An association was made between those participants having had a cumulative vincristine dose of >39 mg/m2 and increased likelihood of 1.5 times greater to have reduced dorsiflexion AROM. Furthermore, the authors further investigated the impact these impairments had on participants ultimate physical performance

attributes including walking efficiency as tested using the 6-minute walk test. They discovered that participants with reduced dorsiflexion AROM subsequently had lower scores on the 6-minute walk test compared to the predicted values for healthy individuals with similar age, weight, height, and gender. These authors suggest that those participants who received high cumulative doses of Vincristine and subsequent neuropathic impairments were limited in physical performance measures compared to their healthy peers.

Most research about this topic centers around survivors of ALL, yet as Harman et al[22] mention, Vincristine is the main chemotherapeutic agent used to treat a variety of pediatric cancers such as non-Hodgkin's Lymphoma, Wilms tumor, and malignant mesenchymal tumors. Hartman et al[22] seek to address this deficit in research with their study concerning muscle weakness and ROM deficits in survivors of these cancers an average of 3.3 years after their final dose of vincristine. They found that the average dorsiflexion ROM and strength as measured with dynamometry in survivors was significantly less than those of healthy controls. Passive dorsiflexion ROM deficits were found in 32% of cancer survivors compared to only 14% of controls. Since 5 degrees is considered the necessary range for normal gait, the authors estimate that those survivors with less than 5 degrees, combined with subsequent shortening of the gastrocnemius, will limit overall physical performance.

Prolonged effects of abnormal foot structure

Neuropathy occurs in the general population due to a number of reasons including: Charcot-Marie-Tooth disease, diabetes, chemotherapy, plantar tunnel entrapment, Baker's cyst, and trauma. As previously mentioned, denervation resulting from neuropathy can eventually lead to muscle atrophy. In multiple studies, diabetic feet are compared with controls and the overall intrinsic foot muscle volume is linear to the amount of neuropathy that is taking place, with more

neuropathy leading to weaker intrinsic foot musculature. The cause is predicted to be a result of adipose tissue being deposited beneath the muscle fascia, between muscles, and intramuscularly leading to a reduction in skeletal muscle volume.[23] While this research is for the diabetic population, we hypothesized that a similar process may occur in the pediatric cancer population. Intrinsic foot musculature strength is hard to test or quantify so different methods other than manual muscle testing and dynamometry need to be utilized. However, these tests do not exist in current literature.[23,24,25]

Anecdotally, the physical therapists at Children's Hospitals and Clinics of Minnesota have noted a change in their patient's foot posture. This change in foot posture could indicate weakening of the intrinsic foot musculature. Again, there is no test for intrinsic foot strength, but the physical therapists at this clinic have noted that the children undergoing chemotherapy, particularly vincristine, have poorer foot structure than other children their age.

The intrinsic foot musculature is important in providing additional support to the human foot. The foot is otherwise comprised of ligaments and three arches that aid in holding the foot bones together in a stable position.[26] The arch is designed to provide maximal support, as well as allow some malleability while walking. This unique design allows individuals to complete bipedal postural control tasks involving weight bearing as well as static and dynamic standing balance tasks. Therefore the structure of the foot has great importance and studies have shown that when a small deformation is present, large changes may result.[26]

Additionally, it has been shown that individuals with abnormal foot postures have decreased postural stability.[27] In fact, research shows that foot posture predicts anteroposterior and mediolateral postural stability.[27] This can be explained by the fact that foot arches and toes play an important role in ambulation and support of the foot.[26] If the foot is in the correct

supported position, the rest of the body is allowed to be in its natural position. However if a deformation occurs, the whole body starts to compensate for the change causing problems in other joints such as the ankle, knee, and hip. A study done by Spink et al[28] discovered that foot posture is an independent predictor of postural sway on a foam surface. More specifically, they found that a pronated foot corresponds with poorer performance. Thus they concluded that foot posture affects the rest of the body's balance response.

Similarly, Hagedorn et al[29] discovered that pes planus and a pronated foot posture is significantly associated with hammer toes, overlapping toe deformities as well as hallux valgus. Through this study they concluded that a pes planus and pronated foot posture gives individuals a significantly higher likelihood of developing a foot disorder. These foot disorders increase individuals' likelihood of developing balance difficulties because of muscle imbalances in the foot.[29] In fact, foot disorders and their symptoms have been linked with poor health outcomes and functional limitations. A specific study done by Spink et al[28] discovered that foot posture and the presence of hallux valgus is significantly associated with balance and functional ability. Therefore if an abnormal foot posture exists, individuals are faced with impairments that lead to balance difficulties that can lead to increased fall risk which puts the individual at risk for other injuries. Overall the literature suggests that foot posture affects balance and functional ability and is important to address early on to prevent further foot disorders from developing. There is however limited research on specific long lasting effects of abnormal foot structure in the pediatric cancer population.

Purpose of Study

Upon review of the literature it is made apparent that chemotherapy induced peripheral neuropathy is a common impairment that the pediatric cancer population faces.[11] This is

important to both research and clinical practice as the neuropathy can lead to weakness in foot structure, and this impaired foot structure can alter a person's ability to walk, balance, and perform other functional tasks.[29] The purpose of this study was to determine if patients with CIPN develop foot posture abnormalities when compared to gender and age matched controls.

Our Hypothesis

Our study consisted of comparing participants who were pediatric cancer patients treated with vincristine and healthy gender and age matched controls. All participants had their range of motion, strength, and level of CIPN assessed. Additionally, functional assessments for gait were administered to participants. Lastly, pictures of bilateral feet were gathered for all subjects so that the researchers could measure various aspects of foot structure. With this data, the researchers hypothesized that they would find a difference in foot structure between groups, with the pediatric cancer patients having more pronated feet.

Chapter II: Methods

Participants

Case subjects (n=38) were recruited from the patient population of the pediatric oncology center of Children's Hospitals and Clinics of Minnesota. Age and gender matched controls (n=38) were recruited from siblings of patients attending the cancer and blood disorders clinic and children of staff members. Inclusion criteria for the case group required subjects to be 5 years of age or older and being treated with vincristine or cisplatin for ALL, Hodgkins or Non-Hodgkin lymphoma, or other solid non-central nervous system tumors. This was the same sample population selected by Gilchrist and Tanner[30] for their study of gait patterns in children with cancer being treated with vincristine.

Procedure

Photographs of patients' feet were taken by physical therapists. The physical therapist would palpate to identify the medial malleolus, navicular, 1st metatarsal head, and the bisection of the posterior calcaneus and marked each with a pen. Patients then stood on a rubber mat with equal weight bearing and feet hip width apart for photos of medial and posterior aspects of their feet. The physical therapists also conducted functional testing for all participants including the pediatric modified total neuropathy score, manual muscle testing of bilateral dorsiflexion and great toe extension, bilateral dorsiflexion range of motion, the Bruininks-Osteretsky Test balance and strength subscales, and six-minute walk test.

We used printed and digital copies of the photos to analyze foot posture using a 4-item version of the FPI, the medial longitudinal arch angle, the calcaneal tilt angle, and the navicular height. All raters were blinded to group status of each subject during analysis. Hard copy photo measurements were gathered using a standard 8 inch goniometer and 12 inch ruler.

Prior to gathering experimental data, interrater and intrarater reliability was calculated. Data from 15 subjects were randomly assigned to 4 blind raters, with each rater receiving duplicate copies of each assigned subject. Results showed poor interrater ICC values ranging from -0.991 to 1.0 and high intrarater reliability ranging from 0.866 to 1.0. After method review and retraining, this process was repeated with similar results of high intrarater and poor interrater reliability. Therefore, the decision was made to assign individual measurements to raters to complete in their entirety such that poor inter-rater reliability was mitigated.

Tests and measures

Four foot and ankle musculoskeletal measurement tools were utilized as follows to gather data on foot posture. Photos with missing landmarks or that were incorrectly labeled were omitted from the final sample.

Foot Posture Index (FPI-6)

The Foot Posture Index (FPI-6), defined in the literature as a quantification tool used to assess static foot alignment or posture, was used to analyze foot photographs using the FPI-6 User Guide and Manual.[31] It is traditionally a 6-item test with individual item scores ranging from -2 to +2 where 0 indicates neutral foot alignment, positive values indicate pronation, and negative values indicate supination. The normative value of total FPI-6 score where the highest possible score is 12 for children age 3-17 is 3.7 indicating slight pronation.[32] Our methods were adapted to omit the first criteria of talar head palpation and the fourth criteria of bulging in the region of the talonavicular joint due to the nature of only having photographs to analyze in the study and not having an oblique angle photograph of the medial aspect of each foot. Therefore the FPI was scored by using four out of the six criteria, including supra and infra lateral malleolar curvature, calcaneal frontal plane position, height and congruence of the medial

longitudinal arch, and abduction/adduction of the forefoot on the rearfoot. Printed hard copies of photographs on 8X11" paper and digital photos were used to rate each item under the criteria outlined by Redmond in *The Foot Posture Index 6-Item Version: User Guide and Manual.*[31]

Evidence shows that the FPI-6 has moderate to high interrater reliability with use in the clinic for a pediatric population. Although they did not use the FPI-6 with photographs, a study by Evans et al[33] determined an inter-rater reliability ICC of 0.79 in healthy children. Similarly a study by Morrison and Ferrari[34] determined an inter-rater reliability weighted kappa value of .86 when assessing the pediatric foot. In addition, Terada et al[35] determined a high intra-rater reliability ICC of 0.956 for the left foot and 0.959 for the right foot when using five of the six image-based criteria of the FPI-6. They also found a poor to moderate inter-rater reliability ICC ranging from 0.334 to 0.634. ICC values of the FPI-6 using four image-based criteria are not available in the literature at this time.

Navicular Height

The navicular height (NH), is defined in the literature as the distance from the lowest palpable medial projection of the navicular bone to the supporting surface (Fig 1).[36] This measurement allows researchers to determine the height of the navicular compared to the ground which in turn describes the degree of pronation or supination of the foot. Because the distance of the camera from each foot was not standardized, we used a ratio of the height of the navicular to the length of the foot in the photo to solve for the actual height of the navicular based on the actual length of the foot.

The method used to measure the NH was based on a study by Chang et al and adapted this to measure navicular height based on photographs rather than having subjects present. Chang et al[36] reports that NH is moderately to highly correlated with the index of foot volume with an *r*

of 0.643 and 0.712. This indicated that there is a correlation between the NH and foot arch indicating that NH is an effective measurement of the foot arch in children. A study by Waseda et al[37] found an intra-rater reliability ICC of 0.964 and an inter-rater reliability ICC ranging from 0.980- 0.989. This study however did not look at pictures while making NH measurements and instead used a 3D imaging program. There currently are no ICC values of measuring NH in the pediatric population using photographs.

Longitudinal Arch Index

The longitudinal arch index (LAI), also referred to as the longitudinal arch angle, is defined in the literature as the angle in degrees between a line drawn from the navicular tuberosity to the medial malleolus and a line from the navicular tuberosity to the head of the first metatarsal (Fig 1).[27,38] The method used for measurement of the LAI based on research by Nilsson et al,[38] with the only difference being that the LAI was measured from a photo instead of directly in the clinic on the patient. We were able to use this same method using the boney landmarks indicated by pen markings on each photo to draw the medial arch angle and measure it using a standard goniometer. Nilsson et al[38] reports values of interrater reliability ICC values for this clinical method anywhere from 0.72 to 0.90. In addition, Cobb[27] et al reports high interrater ICC values of 0.95 to 0.96 for a digital photographic measurement method based on a software program and palpated landmarks. However, ICC values for measurement of LAA based on hard copy photographs are not available in the literature at this time.

Calcaneal tilt angle

We defined the calcaneal tilt angle as the angle from the bisection of the posterior calcaneus to the horizontal which we determined to be the line created by rubber-wood interface of the platform. In current research, the calcaneal tilt angle is measured as the angle created by a

line bisecting the gastrocnemius and another bisecting the calcaneus from a posterior view of the foot. Because a line bisecting the posterior gastrocnemius was not included in the photographs, we modified the method to determine the calcaneal tilt angle from the bisection of the calcaneus in reference to the horizontal created by the rubber-wood interface of the platform each subject stood on (Fig 1). By defining a "neutral" foot as exactly 90 degrees between the horizontal and calcaneal bisection, we determined pronation as any angle greater than 90 degrees, and supination as any angle under 90 degrees. We also used these angle measurements to further standardize our ratings of calcaneal frontal plane position for the FPI. For this, we defined 90 degrees as a score of 0, 91-95 degrees as a score of +1, >95 degrees a score of +2, 85-89 as -1, and <85 as -2. To prevent error in measurement, we ensured that the static arm of the goniometer was always pointing towards the medial aspect of the foot.

Statistical Analysis

We used SPSS statistic software to run independent sample T-tests and Mann-Whitney U analyses to compare the case and control groups. Pearson and Spearman correlation statistics were used to determine associations between strength or range of motion measures and foot posture measures.

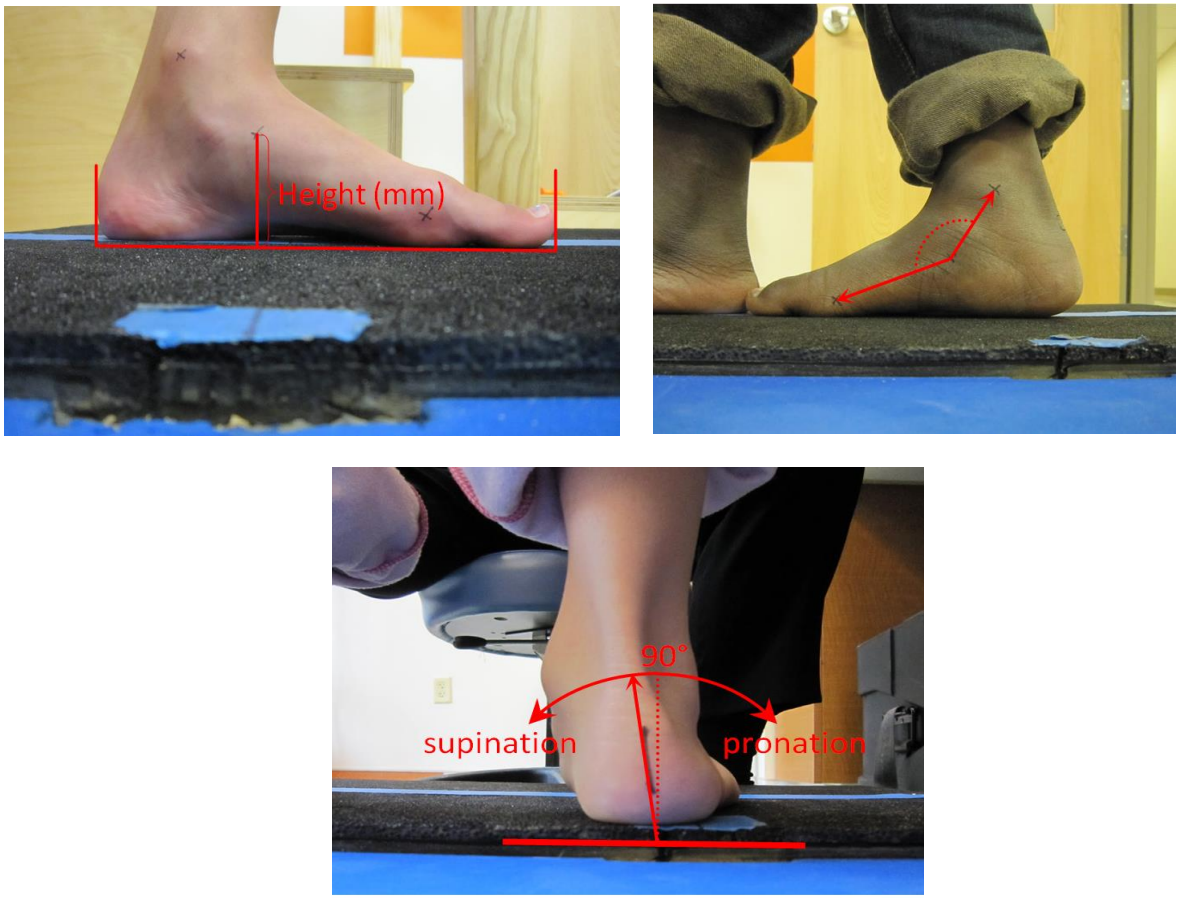

Figure 1: Examples of markings made on hard copy photos in order to measure navicular height (A), medial longitudinal arch angle (B), and calcaneal tilt angle (C).

Chapter III: Results

There were a total of 76 participants in the study, with each group consisting of 38 children. Each group consisted of 34.2% male participants. The mean age of the participants in the case and control groups were 11.08, and 11.34 years respectively. The mean height was 141.91 centimeters and average weight was 43.57 kilograms for the case group. For the control group the mean height was 144.892 centimeters, and the average weight was 42.13 kilograms. The mean body mass index in the case and control groups were 19.39 and 18.82 respectively. The difference between groups in all categories were not significant with p values ranging from .100 to .805 (Table 1).

Table 1: Demographic Characteristics

	Case (n=38)	**Control (n=38)**	**Significance**
Gender (%Male)	34.2	34.2	
Age (yrs)	11.08 (4.69)	11.34 (4.59)	0.805
Height (cm)	141.91 (32.08)	144.892 (20.51)	0.632
Weight (kg)	43.57 (20.29)	42.13 (19.43)	0.753
BMI (kg/m^2)	19.39 (3.91)	18.82 (4.61)	0.561
BMI Percentile (%)	62.21 (29.73)	51.39 (26.72)	0.100

The patient's in this research study were divided into three different categories: Acute Lymphocytic Leukemia (ALL), Lymphomas (including Hodgkin's and Non-Hodgkin's Lymphoma), and other non-CNS solid tumors (including Wilms' tumors). For this research study, 47.7 percent of patients had ALL, 13.2 percent of patients had lymphomas and 18.4 percent of patients had other solid tumors. Patients received a variety of different

chemotherapeutic agents which can be found in Table 2. Out of these chemotherapeutic agents, this research study focused on Vincristine and Cisplatin. Vincristine was received by 37 out of 38 participants in the case group (97.4%), while only one participant received Cisplatin (2.7%).

Table2: Cancer Diagnosis of Experimental Group

	ALL (n=18)	**Lymphomas (n=5)**	**Solid tumors (n=15)**	**Total groups**
Vincristine mg/m^2 (n=37)	25.67 (6.90)	7.446 (3.44)	14.61 (3.81)	17.47 (9.98)
IT Methotrexate (n=26)	138.33 (39.42)	125.63 (46.71)	--	134.42 (41.27)
Cisplatin mg/m^2 (n=1)	--	--	400.00 (--)	400.00 (--)
Etpoposide mg/m^2 (n=13)	600.00 (--)	1550.00 (54.77)	2192.50 (982.82)	1773.46 (794.51)
Asparaginase mg/m^2 (n=19)	21387.50 (42610.56)	5000.00 (--)	0.00 (--)	20525.64 (41580.34)
Cyclophosphomide mg/m^2 (n=33)	2164.71 (1065.92)	2837.50 (1589.19)	6820.00 (1539.35)	2973.64 (1965.27)
Prednisone (n=30)	922.36 (742.83)	1170.00 (827.86)	0.00 (--)	1021.41 (773.73)

Thirty-seven out of thirty-eight patients in the case group had received physical therapy treatment prior to measuring foot posture. Sessions ranged from three to thirty-one sessions with a mean of 11.7 sessions. Similarly, prior to measuring foot posture 17 out of 38 (45%) patients

had received custom bilateral ankle-foot orthoses (AFO) with the goal of helping preserve foot structure.

An independent sample T-test was run in order to determine if there was a significant difference between the mean total ped-mTNS total, light touch, and vibration score for the case and control group. Table 3 illustrates there was a significant difference found between neuropathy scores in the case and control group with each having a p value of < 0.001. These results indicate there is a significant difference in peripheral nerve function and sensation between children with cancer and children without cancer.

Table 3 also indicates the median manual muscle test (MMT) strength scores for ankle dorsiflexion (DF) and great toe extension in the case and control group. As shown, the case group had a median MMT score of 3/5 whereas the control group had a median MMT score of 5/5. These results indicated there was a significant difference in great toe extension strength scores found between groups with a p value less than 0.001. Therefore children with cancer have less great toe extension strength when compared to children without cancer.

When analyzing ankle DF range of motion between groups, Table 3 indicates there was a significant difference found with a p value of < 0.001, These results suggest children with cancer have less passive and active range of motion in their ankle when compared to children without cancer.

Table 3: Range of Motion and Sensation Characteristics Across Groups

	Case (n=38)	**Control (n=38)**	**Significance**
Ped-mTNS total (SD) ● **Light touch** ● **Vibration**	10.45 (4.60) ● 1.32 (1.77) ● 1.13 (1.71)	0.76 (0.75) ● 0.03 (0.16) ● 0.00 (0.00)	<0.001
MMT strength score ● **Ankle DF** ● **Great toe extension**	 L: 4.00 R: 4.00 L: 3.00 R: 3.00	 L: 4.00 R: 5.00 L: 5.00 R: 5.00	 <0.001 <0.001
Dorsiflexion AROM in degrees	L: 3.95 (5.56) R: 3.53 (6.10)	L: 9.79 (5.68) R: 10.47 (5.09)	<0.001
Dorsiflexion PROM in degrees	L: 8.55 (5.50) R: 8.29 (5.57)	L: 14.29 (5.63) R: 14.21 (5.21)	<0.001

When comparing foot posture measures, there was no significant differences found between groups on the FPI-4 total score, medial longitudinal arch angle, calcaneal tilt angle, nor navicular height as all p values were greater than 0.05 (Table 4). However, the left FPI-4 total score was nearly significant with a p value of 0.070.

Table 4: Foot Structure Measures

	Case (n=38)	Control (n=38)	Significance
FPI-4, median	L: 3 R: 3	L: 4 R: 4	L: 0.070 R: 0.307
Medial Longitudinal arch angle in degrees, mean (SD)	L: 148.08 (8.74) R: 145.78 (7.76)	L: 145.92 (8.016) R: 144.44 (9.55)	L: 0.274 R: 0.512
Calcaneal tilt in degrees, mean (SD)	L: 94.92 (5.30) R: 92.24 (4.56)	L: 96.63 (4.52) R: 95.05 (4.11)	L: 0.134 R: 0.415
Navicular height in millimeters, mean (SD)	L: 4.06 (0.84) R: 4.14 (0.92)	L: 4.05 (0.91) R: 4.09 (0.89)	L: 0.939 R: 0.817

Since the significance value for the left FPI-4 total score was 0.07 a histogram was created to visually view the data as shown in Figure 2. As stated earlier a score of zero on the FPI-4 total score indicates a neutral foot. Although there was no significant difference between groups, the histogram illustrates a trend in the data that the case group has more neutral feet compared to the controls who had more pronated feet. This result was opposite of the stated hypothesis.

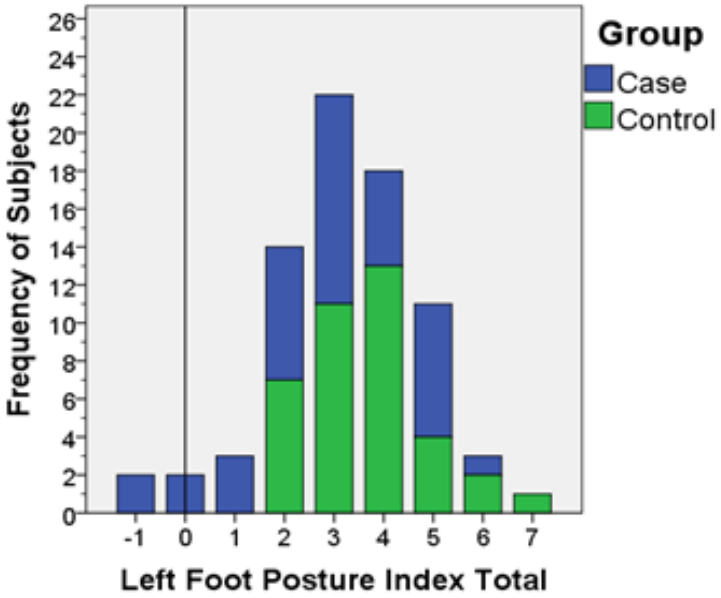

Figure 2: Comparison between L FPI total scores

The Spearman and Pearson analyses that were run indicated three notable correlations within the data. A modest, but significant, correlation was found between L GTE strength, total FPI on the left foot (r_S=0.29, p=0.01), and left calcaneal tilt angle (r_S=0.27, p=0.02). Right ankle DF PROM was only correlated to right navicular height (r_S=-0.25, p=0.04). These correlations indicated that those who have decreased strength have lower scores on the FPI indicating a more neutral foot posture. This also found that those with less strength have a more normal calcaneal tilt angle indicating a more neutral foot posture. Figure 3 illustrates a significant but weak correlation between right DF PROM and right navicular height indicating those with more motion have a lower navicular height and thus a more pronated foot.

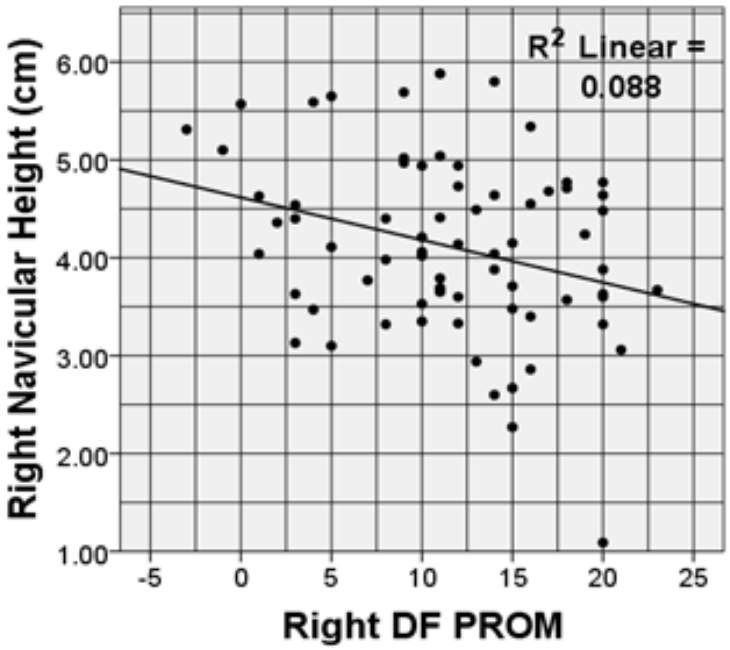

Figure 3: Correlation between right navicular height and right dorsiflexion passive range of motion

Functional measures were analyzed to determine if there was a functional difference between the groups being studied. There was a significant difference found in the Bruininks

Oseretsky Test of Motor Proficiency (BOT) balance section between groups with a p value <0.001 (Table 5). This indicated there was a significant difference in balance between children with cancer and children without cancer. There was also a significant difference found between distance in the six meter walk test (6MWT) as evidenced by a p value <0.001. The last functional measure researched was pain which indicated a significant difference in pain rating between the case and control group with a p value of 0.001, but note that the mean score of 1.32 is indicative of mild pain.

Table 5: Functional Measures

	Case (n=38)	**Control (n=38)**	**Significance**
BOT Balance Score (SD)	8.45 (3.65)	13.63 (3.58)	<0.001
6MWT (SD) ● Distance in meters ● Z-score	507.19 (102.93) -0.397 (11.29)	592.78 (95.21) -0.710 (1.55)	<0.001 0.865
Pain (SD)	1.32 (1.85)	0.22 (0.566)	0.001

Chapter IV: Discussion

Findings Discussed

We hypothesized that pediatric oncology patients with chemotherapy induced peripheral neuropathy, distal motor neuropathy with decreased strength, and decreased ankle ROM limitations would demonstrate foot postures that are over pronated when compared with our gender and age matched control population.

97.4% of our patient population received the neurotoxic chemotherapy drug vincristine. Neurotoxic agents such as vincristine are the root cause of peripheral neuron degeneration, even at low doses.[8,9,16] As a result we found a significant difference, $p<0.001$, between groups on their ped-mTNS[30] total scores, indicating that our case group indeed is a population that has neuropathy.

The extensive amount of diabetic literature has a well-developed description of intrinsic foot musculature atrophy occurring when neurons have limited potential to innervate their targets, and is closely related to motor function.[39] Additionally, vincristine induced peripheral neuropathy has been characterized as having neurotoxic effects not only initially, but also in a chronic manner in motor neuron conduction studies.[16,17] A clinically applicable foot intrinsic muscle volume or strength measure do not exist outside of imaging studies, but it is reasonable to assume that great toe extension and ankle dorsiflexion strength would be closely related. It is reasonable to assume due to nerve conduction studies describing the common peroneal nerve most impacted followed by the tibial nerve.[11,20] The deep peroneal nerve bifurcation innervates the tibialis anterior (ankle dorsiflexion) and extensor hallucis longus (GTE). Distally to these innervations and structures, the deep peroneal nerve bifurcates again into the medial and lateral terminal branches, of which innervate the foot intrinsics. Our patient population had a significant

difference, $p<0.001$, in great toe extension and ankle dorsiflexion strength when compared to our control population. Due to the gap in literature describing foot intrinsic muscle strength, it is reasonable to believe that our patient population had a loss in foot intrinsic muscle volume and strength due to the close association anatomically, and the heightened severity of neuropathy distally.

The relationship between chemotherapy, neuropathy, and losses in range of motion is not fully understood. Our case group had a significant difference, $p<0.001$, in dorsiflexion AROM and PROM when compared to our case group. In our study, it is not clear if the range of motion loss is a direct effect of the chemotherapy, losses in strength, or it is a result of other variables such as decreased activity or function. The loss of muscle function is one of the main contributors in the development of pronation of the foot or Charcot foot among diabetics. The foot intrinsic musculature contribute to the integrity of the medial longitudinal arch in conjunction with the foot extrinsic musculature and other passive plantar ligaments.[40] Maintenance of the integrity of the medial longitudinal arch depends on passive structures through ligaments, and active structures through extrinsic and intrinsic foot musculature. Impairments of active structures have a tendency to lead to over reliance on passive structures, potentially leading to the failure of such structures due to the increased amount of force they are being required to support. Evidence of foot posture abnormalities are well documented through the diabetic literature and have well supported findings related to the underlying implications of neuropathy. Our data did not support a clinical or statistical significance between our case and control groups in any of the foot posture measures utilized in this study. Unexpectedly, our data had a statistical tendency to describe the case group as having

more neutral feet than our control group, meaning that our pediatric cancer patients had better foot posture than our age and gender matched controls.

Methodological Limitations

Pediatric oncology treatment is comprehensive by nature, as the variety of patients and diagnosis are indicated for a variety of therapies beyond chemotherapy. Rehabilitation is a key component of our case group as 97.4% received physical therapy services throughout their plan of care. Children's Hospital of Minnesota uses *The Stoplight Program*,[41] a rehabilitation program developed in-house directed towards improving the quality of life of their patient population. Physical therapy intervention typically addresses strength, balance, activity tolerance, and foot posture as indicated through *The Stoplight Program*[41] and their physical therapist's clinical reasoning. Among our case population, 45% received bilateral Ankle Foot Orthosis (AFO) that were custom fitted to preserve the child's medial longitudinal arch, and improve their functional mobility. Indications for AFO use include ankle dorsiflexion manual muscle test of less than or equal to 3+, ankle dorsiflexion active range of motion less than or equal to 0, or they present with gait abnormalities that would guide their physical therapist's clinical reasoning. The patients who use bilateral AFO's have decreased ankle dorsiflexion strength that is significantly different than the patients who are not indicated for AFO use. This could be significant in our study for a couple of reasons. One explanation is that the patients who were at a heightened risk of developing foot pronation were correctly identified, and their foot architecture was preserved throughout their treatment. This confounding variable could have spared patients from potentially developing foot posture abnormalities, ultimately improving the case population's foot posture scores. Another explanation is that the patients who received bilateral AFO's did not receive any distinct benefit in terms of foot posture preservation. This

could lead one to assume that potential indications for AFO use are not risk factors for developing foot posture abnormalities, and potentially further suggest that a difference does not exist between groups.

Another potential limitation in this study is that the pediatric population as a whole has pronated feet. Normative data on the pediatric population describes them as having pronated feet by scoring an average of 3.7 on the 6 component FPI with a standard deviation of 2.5.[32] This could mean that our case group is representative of the general population, as is the control population.

Pediatric oncology is complex and an abundance of variability it the treatment and the specific patient intrinsically and extrinsically. A cross-sectional study design provides information on a specific subject at that specific moment in time with consideration to variables that the specific subject holds. Different cancer diagnoses are all processes with various progressions and states. Similarly, cancer treatment is a process with variables that are impacted differently along the way. Lastly, children develop at different rates and it cannot be clearly predicted if they have, or when they will reach maturation. To further convolute pediatric oncology, each child has a specific cancer diagnosis that is staged differently and thus they are receiving a cocktail of treatments at various rates and fluctuating degrees. A cross-sectional study design is not the ideal study design to capture the degree of variability present in our study. A longitudinal study design would give the opportunity to measure patient's foot structure throughout phases of their intervention and recovery.

Measurement Limitations

Limitations in measurement were also present in our study. The most impactful limitation exists in the procurement of the digital photographs. Further standardization was

needed in order to decrease the occurrence of excluded data. Standardization of the subjects could have been improved by having more specific foot placements, weight bearing instructions, and further standardizing the child's stance. Landmarks could have been improved by marking them more specifically, more accurately, and inclusion of additional structures to improve measurement utilization. Finally, the presentation of the photograph could have been improved through standardizing the camera placement angle, distance and height, consistent lighting and backdrop, and the presence of a measurement tool in the photograph itself.

Due to the nature of our data, we chose to use a modified version of the FPI by only including 4 out of 6 components. This decreased the validity of our study and limit the data's potential to be generalized. The calculation of true navicular height was done mathematically by extrapolating the height from the true length of the foot that was previously measured and a ratio of height and length that was measured from the photographs. Measurement errors could have taken place either on the digital photographs, or at the time the picture was taken. Calcaneal tilt measurements would have been improved by including additional viewing of the posterior lower extremity and more landmarks to allow reference to the gastro/soleus complex. All of these limitations in measurement could also be significantly impacted with small measurement errors made with the measurement tools utilized, as they could have been more specific.

Poor inter-rater reliability with all of our foot posture measurements limits the potential for consistent and accurate data collection. This would lead to results that are not accurate and cannot be recreated between different raters. Intra-rater reliability was good throughout our study. Due to this, our group chose to have one specific rater generate data on one specific measurement. Although each rater could reliably perform each foot posture measurement, an

entire measurement could have been performed inaccurately. This decreased the validity of our study.

Future Research

This study started with a clinical observation that was developed out of clinical expertise and previous research within the pediatric cancer population. Future research on this topic, or topics similar to this one, could benefit from a longitudinal study design. This would involve taking measurements prior to initiation of chemotherapy and after their final treatment. This can be difficult to complete as many children diagnosed with cancer begin their chemotherapy treatments relatively quickly, leaving a small window of opportunity for initial gathering of data.[1] Another longitudinal study design could utilize measurements taken after final chemotherapy treatment and throughout the patient's remission process. This may provide valuable information on how the effects of the chemotherapy induced peripheral neuropathy changes over time.

Additionally, a cross sectional study design could be improved with use of historical controls who received neurotoxic chemotherapy treatments, but did not participate in any sort of physical therapy. This would allow us to better understand how the pediatric foot structure is affected by current physical therapy interventions.

Lastly, further research on intrinsic foot musculature testing would allow researchers to better track changes in these structures in patients who experience chemotherapy induced peripheral neuropathy. This is important as these are the structures that help determine the shape and functionality of the foot. Currently, researchers are limited to manual muscle testing of nearby structures, such as the great toe and ankle joint, to make assumptions about the strength of the intrinsic foot musculature.

Future research with the pediatric cancer population, specifically in the realm of chemotherapy induced peripheral neuropathy, is important as children are surviving cancer with ever improving success.[1] Additionally, the treatments that these children are enduring, particularly chemotherapy, have been shown to be very taxing on their bodies and ultimately limiting their function. Future research would provide a platform to help improve the pediatric cancer population with improved function and quality of life.

Chapter V: Conclusion

Our data do not support the hypothesis that there is a difference in foot posture between pediatric cancer patients and healthy controls. While no significant data was found between the two groups for foot posture, there was a trend indicating that the pediatric cancer population had a more neutral foot structure. Additionally, although chemotherapy is linked to foot muscular weakness and limited ankle ROM, it was not shown to be strongly correlated to structural changes in foot posture. Limitations of this study include use of a modified FPI and possible impact of PT intervention. As mentioned previously, the modified FPI excludes two measurements. These measurements may, or may not, have allowed the researchers better insight into differences between the case and control groups. Additionally, most of the pediatric cancer participants had received PT for these potential changes in foot structure that the researchers were trying to identify. Therefore the results regarding foot structure may have been confounded by the participation in a PT program. The pediatric cancer population and the effects of CIPN on foot structure and quality of life is an area where further research would continue to be beneficial.

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