# EFFECT OF INTERMITTENT PNEUMATIC COMPRESSION (IPC) ON GLUCOSE REGULATION AND INFLAMMATION IN TYPE 2 DIABETES

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## ABSTRACT

**Purpose:** The purpose of this study is to determine whether the intermittent pneumatic compression (IPC) device improves glucose regulation and inflammation in participants with type 2 diabetes. It was hypothesized that the intermittent pneumatic compression device will have positive effects on glucose regulation and inflammation in individuals with type 2 diabetes. **Methods:** Subjects included 10 individuals diagnosed with type 2 diabetes. Baseline measures of lipid profile and HbA1C were obtained by a finger stick. Plasma and serum were obtained intravenously to analyze insulin, glucagon, Interleukin 6 (IL-6) and C-reactive protein (CRP). The subjects came in a total of 3 times to the laboratory to be measured for the variables previously listed. The subjects completed a total of 35, IPC treatments (5 days/week for 7 weeks) by using the NormaTec recovery system (NT). **Results:** No significant differences found within lipid profile or inflammation. CRP values decreased from the 1$^{st}$ to the 3$^{rd}$ treatment, but no significant difference was found. HbA1C was found significant ($p = .002$, $p = .026$) from 1$^{st}$ to 2$^{nd}$ and 1$^{st}$ to 3$^{rd}$ treatments. **Conclusion:** Previous research has shown an increase in blood flow from the use of the IPC devices. An increase in blood flow to the lower extremities can lead to positive effects in endothelial function, decreased inflammation and with further research, a decrease in HbA1C and other glucose regulators.

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# CHAPTER I

# INTRODUCTION

Diabetes is a disease that has become prevalent among adults and children. Raaijmakers et al., (2015) discussed how diabetes is a chronic illness that requires intense, and constant medical care. The varying types of diabetes, type 1 and type 2 require different forms of care for an individual dealing with this disease. Type 1 can be developed from birth or at an early age and is brought on by the individual not being able to produce insulin to maintain one's blood sugar levels. Type 2 can develop over time from several factors such as, diet or other preexisting health issues. Type 2 is brought on by the individual being insulin resistant, causing the insulin being produced to be non-responsive by the body. Insulin is an important factor when dealing with type 1 and type 2 diabetes. Insulin is a hormone produced by the pancreas that lowers glucose levels within the blood. Monitoring insulin levels is very important in individuals with diabetes. High amounts of cholesterol in the blood and hypertension can also be caused from type 2 diabetes because of the difficulty in metabolizing glucose. If uncontrolled diabetes progresses, other cardiovascular risks may develop over time.

Inflammation is very common amongst individuals with type 2 diabetes. High blood glucose levels can play a role in inflammation in the blood vessels and can cause other diabetic complications. The connection between type 2 diabetes and inflammation is still being researched, but the increased fat tissue seems to have a small connection with inflammation and insulin resistance. C-reactive protein (CRP) and interleukin 6 (IL-6) are the most common markers to test for inflammation within the blood (Singh-Manoux et al., 2017). Insulin resistance can be caused by chronic inflammation among individuals that have type 2 diabetes. Insulin resistance is the body's way of rejecting the insulin that is being produced, which induces blood sugar to rise. Being able to understand how sensitive the body reacts to insulin is important when trying to control or prevent the onset of diabetes.

Intermittent Pneumatic Compression (IPC) is a device used by inflating and deflating varying types of cuffs around the limbs to improve venous circulation in individuals suffering from diabetes, edema, thrombosis, cardiovascular risks, etc. This type of compression treatment has also been used to treat swelling after a traumatic incident and possibly after surgical procedures (Almstedt and Lewis, 2016). Martin and Braith (2012) found significant evidence showing decreases among high sensitivity C-reactive protein while using an EECP device, which has similar effects to an IPC device. Seeing decreases in any compression treatments shows promising evidence that this could be a big step towards controlling and preventing any future cardiovascular risks for type 2 diabetes. IPC has been used in various research studies to help aid athletes in decreasing inflammation and speed up the recovery process. It has been used frequently in the field of sports medicine for the treatment of small injuries (Sutkowska, 2017).

Taking all the necessary measures to try to prevent or control one's diabetes can reduce the risk of other medical complications such as, kidney failure, cardiovascular issues and hypertension (Raaijmakers et al., 2015).

## Purpose

The purpose of this study is to determine whether the intermittent pneumatic compression (IPC) device improves glucose regulation and inflammation in participants with type 2 diabetes.

## Hypothesis

Intermittent pneumatic compression will have positive effects on glucose regulation and inflammation in individuals with type 2 diabetes.

# CHAPTER II

# LITERATURE REVIEW

## Intermittent Pneumatic Compression

Intermittent pneumatic compression is consistently used by medical professionals as it is designed to improve venous circulation or other preexisting conditions. Salek, Bahrpeyma & Mohajeri-Tehrani (2015) studied the effects of IPC on patients with diabetic neuropathy. There is a decrease in neural blood flow regarding this complication. There is a major risk of falling because of the poor balance patients with diabetic neuropathy develop. Diabetic neuropathy is shown among individuals who have had a long-term diagnosis of diabetes and have a loss of motor control and poor limb circulation. There were 39 patients involved within this study, intervention group (n=20) and control group (n=19). The participants were randomized by using a random number table. The age of the patients involved ranged from 40-75 years of age. Each participant completed questionnaires, balance and neuropathy tests. The intervention group participated in IPC for 45 minutes a day for 10 sessions. After the 10 sessions, the questionnaires, balance and neuropathy tests were repeated. The intervention group

showed significant decreases in the neuropathy screening scores after the 10 sessions, along with the balance tests. This study shows that IPC tends to have a positive effect on individuals who suffer from diabetic neuropathy.

A systematic review was done over IPC for individuals with critical limb ischemia. This is an advanced stage of peripheral artery disease which involves the arteries being engulfed with plaque and hardened. Individuals with critical limb ischemia may have many different types of treatments. Some may have to go through amputation and some receive specific medical treatment. IPC is supported to have positive effects and prevent further risks for individuals with critical limb ischemia (Moran, Teljeur, Harrington and Ryan, 2015). This systematic review found studies that are involved with using IPC to help people who are suffering from critical limb ischemia. There were three different types of IPC that were researched in this review, such as ArtAssist device, ArterialFlow device, and another compression device that is involved with ventricular contraction of the heart (Moran, Teljeur, Harrington and Ryan, 2015). This systemic review showed inconsistent research with IPC treatment and individuals with critical limb ischemia who aren't suitable for percutaneous transluminal angioplasty or surgical revascularization.

A similar study, Karvos et al., (2008) discussed intermittent pneumatic compression and its effects on a controlled study with an 18$^{th}$ month follow up for individuals with critical limb ischemia. The purpose of this study was to evaluate IPC in patients with critical limb ischemia, non-healing wounds, amputations and tissue loss. There were two groups within the study; group 1 consisted of 24 patients with a median age of 70 that used the IPC treatment to care for tissue loss and wound healing, group 2

consisted of 24 patients that did not use the treatment of IPC to help with the care of tissue loss and the healing of wounds produced by the critical limb ischemia. Researchers found that wound healing and limb salvage was improved by the use of IPC treatment in group 1 ($p<.01$, with a p value of $<.05$). The treatment group showed significant increases in healing than the control group.

IPC has been researched in multiple studies for finding ways as therapy for peripheral artery disease. Peripheral artery disease (PAD) is an ongoing health concern that effects the lower extremities that hardens and narrows blood vessels making it harder for blood to pump throughout the limbs. This may also cause a decrease in blood flow which may cause the nerves and other tissues in the body to become injured. Individuals with PAD struggle with daily tasks, exercise and have a poor quality of life because of pain and lack of mobility. IPC has been supported through research to help individuals suffering from PAD. Sheldon, Roseguini, Laughlin, Newcomer (2013) discussed the effective point that makes this compression method so easy is that it is able to be done at the individual's home Studies that have researched IPC have found that this method elevates blood flow, reduces risks of negative vascularity and helps with relieving ischemia.

Manfredini et al., (2014) researched oxygenation changes on ischemia foot of a novel IPC device and of an existing sequential device in severe PAD. They discussed that haemodynamics in PAD is positively affected by IPC but there is not a lot of research on perfusion of the foot. Subjects of the study included 12 patients that had PAD, aged: 72.5±10.8 years). They completed 7, 35 minute treatments of either a gradient pump (GP) which compresses the thigh or an SFC (sequential foot-calf compression device)

(ArtAssist) which compresses both calves. The treatment days were split up between 48 hours. Results showed a significant difference ($p<.004$) while SFC treatments showed no significant results. This study concluded that an IPC thigh device showed positive changes in haemodynamics and ischemic foot perfusion. The subjects were also very compliant to the GP treatment.

Venus leg ulcers are a common affliction that may affect individuals throughout their lifetime. A venous ulcer may be caused by either an injury on the lower extremity, poor circulation, obstruction of the vein lumen and incompetence of the valve (Comerota, 2011). This condition can damage blood cells and be very painful. Venous leg ulcers cost the healthcare system a lot of money for treatment options. IPC has been researched in treatment/prevention of venous leg ulcers among individuals. Articles on IPC and venous ulcers were reviewed and the results have shown positive effects on venous ulcers by using the IPC treatment. More than a 16 week compression treatment should be used among individuals suffering from venous ulcers.

Pfizenmaier, Kavros, Liedl and Cooper (2005) researched upper extremity ischemic ulcers as opposed to lower ischemic extremity ulcers. Lower extremity has been widely researched for ischemic ulcers, while upper extremity ulcers do not have as much research to show. The purpose of this study was to see if the use of IPC treatment positively effects upper extremity vascular ulcers. The subjects of the study consisted of 26 patients with a total of 27 upper extremity ulcers. The average of IPC pump use was about 5 hours per day. They measured pain and size of the ulcers before and after treatment, after 25 weeks of IPC, 25 out of the 26 patients within the study felt improvements with pain and size in ulcers. More research needs to be done on the use of

IPC treatment on upper extremity ischemic ulcers. Further research also needs to be done on the effects of IPC compared to standard medical care when treating upper and lower extremity ischemic ulcers.

One group of researchers, Amah, Voicu, Bonnin, and Kubis (2016) examined compression treatment on the lower limbs and abdomen to see if it influenced the amount of blood flow in the forearms. The compression suit was covering the lower limbs and the abdomen and elicited a compression of 65 mmHg, which was aligned with each diastole of the cardiac cycle. Laser Doppler flowmetry (LDF) measured the forearm skin microcirculation before and after compression treatment. Acetylcholine (Ach-test) and hyperthermia (hyperT-test) were measured in response to the LDF. The subjects of the study consisted of 12 women and 12 men (N=24), aged 43±14 years. Significance was set at $p<.05$. The LDF measurement after the compression treatment increased significantly ($p<.01$), while the Ach-test ($p<.001$) and hyperT-test ($p<.001$) also increased significantly. There were no differences within gender in either measurements. The researchers concluded that a low-pressure compression enforced on the abdomen and lower limbs increased forearm blood flow. More research needs to be done to support this conclusion.

Bahadori, Immins, and Wainwright (2017) researched two compression methods such as, IPC and neuromuscular electrical stimulation (NMES) to evaluate its effect on microcirculation of the thigh. There were 10 subjects in the study that had their blood microcirculation measured by using a laser speckle contract imaging (LSCI) method. Both of the devices increased blood flow of the thigh, but the NMES device increased

more in blood flow than the IPC device, but they both still significantly increased blood flow.

One particular study researched IPC on delayed onset muscle soreness (DOMS) in long-distance runners. Draper (2014) measured the effects of IPC on inflammation of the muscle in long distance endurance running. Ten subjects were involved within the study (5 men and 5 female), ages 18-55 years. The intervention consisted of two 20 mile runs at 70% of $VO_{2max}$ for five consecutive days with either no treatment (control) or treatment (IPC). The subjects that received the treatment were treated immediately after the run for an hour and for five days after. The control and intervention groups were measured for C-reactive protein (CRP) pre and post run and daily for the five days. The results showed no significant differences in control and intervention groups for CRP, weight loss, fluid intake, sweat rate, heart rate and percentage of $VO_{2max}$. This research did however find a significant difference in decreased pain on the second run and running times from the control (196.2 minutes) to the intervention (204.8 minutes).

Labropolous et al., (2005) investigated the hemodynamics of patients with critical limb ischemia (CLI) when treated with IPC. They recruited 20 subjects with CLI and sought out to find if IPC influences gastrocnemial, skin and collateral arterial blood flow. Compression cuffs were placed around the calf and foot, while the pressure went to 120mmHg for 3 seconds at 3 cycles per minute. The researchers examined 3 arteries; popliteal, medial gastrocnemial and genicular collateral artery. Results shows a significant increase in flow volumes for all 3 variables ($p \leq 0.02$). This study concluded that individuals with CLI may benefit from IPC with an increased amount of skin blood

flow. Arteriovenous pressure gradient is increased by the increase in blood flow from the intermittent pneumatic compression treatment.

**Mechanical/Biochemical Effects of IPC**

External compression shows changes in the hemodynamics and the structure of individuals suffering from lower extremity conditions. This compression method applies intense pressure that encloses the lumen, causing venous emptying and preventing stasis (Chen, Frangos, Kilaru, Sumpio., 2001). Swelling is caused by the increase in pressure on the extremities and puts 20% more tension on the endothelial cells. The pressurized blood moves through the veins and if the pressure is applied periodically then this could increase peak velocity of blood flow by 200% within the lumen (Chen, Frangos, Kilaru, Sumpio., 2001). Blood is drained at the site of compression, which provides a pulsatile flow through the compressed extremity.

**Alternative Methods of Compression**

Enhanced external counter pulsation (EECP) is a method that has been used to treat patients with coronary artery disease. EECP is very similar to IPC because of the method of using compression to help treat health conditions. This method is noninvasive and uses cuffs that inflate and deflate to increase venous return to the heart and decrease left ventricular afterload (Lawson et al., 1996). EECP can be beneficial for diabetic patients because of the cardiovascular health risks that may lead to coronary artery disease. This method could help with endothelial function, cardiovascular risks and inflammation in patients with diabetes. The following study identified twenty-seven patients with angina and treated them with EECP on exercise hemodynamics and

myocardial stress perfusion (Lawson et al., 1996). There were men (n=26) and women (n=1) that participated in the study with a mean age of 60 (range 46-73 years). They performed a radionuclide stress test before entry into the study. The subjects received 1 to 2 hours daily (35 total hours) of EECP treatment followed by the same radionuclide stress test at the same cardiac workload. The results of the study concluded that the stress test plus the EECP had a positive effect on exercise tolerance in the patients with chronic stable angina. This study showed beneficial for coronary artery patients because of the decrease in cardiac workload and improved myocardial perfusion (Lawson et al., 1996).

Levenson (2006) researched cyclic GMP (cGMP) release by using acute enhanced external counter pulsation. EECP is typically used to help treat individuals with CAD. Arterial function is related to the release of cGMP and regulates vascular smooth muscle and affects growth of cells and division. This study had a one-time treatment of EECP to examine the effects of cGMP levels. There were 55 subjects included within the study. There were 25 subjects with cardiovascular risk factors and 25 subjects with coronary artery disease. The individuals were randomized within two groups; control or active EECP for 1 hour. cGMP platelet and plasma were taken pre and post EECP treatment. Significance was determined at $p<.05$. Results of the study showed a significant increase in cGMP for plasma concentration ($p<.001$) and platelet content ($p<.01$). The EECP showed positive effects with increasing cGMP in patients with CAD and cardiovascular risks.

Feldman et al. (2006) examined EECP on patients experiencing chronic heart failure. EECP has been known to decrease the amount of chest pain and extends time to exercise induced ischemia in patients with coronary artery disease and angina. There

were 187 participants within the study, the subjects were randomized within a 1:1 ratio to EECP treatment or continued physical therapy. Sessions lasted 1 hour and were completed 35 times over 7-8 weeks. The pneumatic cuffs were placed specifically around each lower extremity and the buttocks. The pressure of the cuffs were pumped up to the onset of diastole and were released before the onset of systole. Pressure was set to 300mmHg and was reached within the first five minutes of the beginning of the start of treatment Pulse oximetry and clinical status was monitored throughout the testing. Both groups exercised, but the group that received EECP treatment increased 60 seconds more when exercise was tested after 7-8 weeks. This study suggests that 35, 1 hour treatment of EECP will have a positive effect and benefit patients with heart failure and systolic left ventricular dysfunction.

Endothelial function is important when looking at vascular diseases that may have an imbalance of contraction and relaxation of the endothelium. Many patients that have coronary artery disease (CAD) have endothelial dysfunction. Bonetti et al., (2003) studied the effects of EECP on endothelial function in patients with coronary artery disease. This study consisted of 23 individuals with refractory angina and completed an EECP treatment for 1 hour a day, 5 days a week for 7 consecutive weeks. Each treatment was given at the same time every day for each individual patient to prevent any circadian vascular effects. Peripheral endothelial function was measured by using a reactive hyperemia-peripheral arterial tonometry (RH-PAT) that was obtained from the finger of the patients. These measurements were performed pre, mid and post intervention after the EECP treatment. Results showed significant improvement in RH-PAT measurements

after pre, mid and post intervention. This study showed that EECP treatment can be beneficial for patients who are suffering from CAD.

**Glucose Regulation & Inflammation**

Insulin is a hormone produced by the pancreas that is involved in lowering blood glucose levels. When glucose levels rise, insulin is secreted by the beta cells of the islets of Langerhans inside the pancreas (Wilcox, 2005). If this process is disrupted, glucose will not be able to be taken into the cells and used for energy. Therefore, causes insulin resistance and an increase in glucose within the blood which can have harmful effects on the body.

Individuals with type 2 diabetes are not able to use insulin accurately, which is called insulin resistance. Insulin resistance is caused from the body's cells being un-responsive to insulin and not being able to use it effectively throughout the body. There are many other risk factors that individuals with insulin resistance are predisposed to; cardiovascular disease, hypertension, polycystic ovary syndrome, cancer, sleep apnea, etc. (Wilcox, 2005).

Glucagon is a hormone produced by the pancreas that secretes when blood glucose levels fall too low. For individuals with type 2 diabetes, it is shown that glucagon raises blood glucose levels too high because of the impaired recognition of insulin. Ferrannini et al., (2007) researched insulin resistance by the hyperinsulinaemic clamp in 1,296 non-diabetic subjects. The researchers found that whole body insulin resistance shows an association with increased fasting glucagon levels, as a possible result of alpha

cell insulin resistance. Increased levels of glucagon in the body may have an effect on insulin resistance in type 2 diabetics.

C-reactive protein (CPR) and interleukin 6 (IL-6) are the most common markers to test for inflammation (Singh-Manoux et al., 2017). An increase in systemic inflammation can increase an individual's risk for cardiovascular diseases and insulin resistance (Haffner 2006).

Colwell, J. (1999) examined a large population of individuals who are obese and or diabetic. Their BMI and CRP levels were measured. It was discussed that individuals with these qualifications have a high increase of inflammation within the blood, especially CRP levels. Chronic elevated CRP levels within the blood could have a negative effect on the body and potentially cause more damage to vessels.

Martin and Braith (2012) investigated anti-inflammatory effects of EECP in participants with abnormal glucose tolerance (AGT). The subjects consisted of 18 non-insulin dependent AGT with a plasma glucose concentration of >140 mg/dL after a 2 - hour glucose tolerance test. The participants were randomized into control (N=6) and experimental groups (N=12). The length of the study was 7 weeks, during this the experimental group had to undergo 35, 1-hour EECP treatments with each cuff being at a pressure of 300 mmHg. Following the treatments, laboratory testing was conducted pre and post treatment to determine levels of tumor necrosis factor (TNF-α) and high sensitivity C-reactive protein (hsCRP). Control group did not receive EECP treatment and regular medical care was continued. Results showed significant decreases in both hsCRP ($p \leq 0.01$) and TNF-α ($p \leq 0.02$). Findings within this study show significant

decreases in these inflammatory markers from EECP and can possibly decrease cardiovascular risks and insulin resistance for individuals with AGT.

# CHAPTER III

# METHODS

## Research Design

This is an experimental research study. The independent variable is intermittent pneumatic compression. The dependent variables are glucose regulation and inflammation.

## Subjects

This study will include ten subjects, with an age range between 30-70 years that have been diagnosed with type 2 diabetes. The participants involved within the study will be recruited by word of mouth among the Cleveland State University community and throughout the Cleveland area. Each of the participants will be given an informed consent specifying all the procedures, potential risks and benefits.

## Procedures

Two weeks prior to the study, participants will maintain a normal diet and physical activity pattern. The subjects should be fasted 10-12 hours prior to arriving in

the laboratory. The subjects will come in a total of 3 times during the study for pre, mid and post testing during which plasma and serum blood samples will be obtained. The morning of testing, baseline measures of serum, plasma, body composition, lipid profile and HbA1C will be obtained. Lipid profile, HbA1C and glucose will be obtained by a finger stick and analyzed in the Cholestech LDX. The blood received intravenously from the antecubital space will be spun through a centrifuge to extract the isolated blood plasma and serum, which will be pipetted into tubes and frozen until further analyzed. The pre, middle and post-plasma samples, will be analyzed for C-reactive protein (CRP) RayBiotech), Interleukin 6 (IL-6) (R&D Systems), glucagon (Invitrogen) and insulin (CrystalChem) using commercially available ELISA kits. Quality of life will be measured pre-and post-intervention by using the SF-36 health survey. Body composition will be measured pre-intervention by the BodPod and determine body fat percentage.

The subjects will participate in a 1 hour, at home, pneumatic compression treatment for 5 days a week for 7 weeks using the NormaTec recovery system. This will accrue thirty-five treatments total for each participant during the study. The NormaTec recovery system is a large boot that fits around each leg of the participant and is divided into sections that are called cells. Each cell is around a part of the leg, the first cell (cell 1) is located on the foot and the cells continue up the leg until it reaches the top of the thigh (cell 5). Each subject will receive treatment at the same intensity setting of 10 (90 mmHg for cells 1 and 5 and 100 mmHg for cells 2, 3 and 4) for one hour. Each cell compression has a duration of 30 seconds. During the 30 second compression and duration of the cells, there are 3 techniques, pulsing, gradients and distal release. Each part of these techniques are important for the movement of fluid, forced pressure, and

circulatory flow within the muscles of the lower extremities. The recommendation for the intensity setting is to be at 10 (settings from 1-10) for the best results.

When the subjects arrive halfway through the 7 weeks, they will come in fasted (10-12 hours), lipid profile, glucose, HbA1C and venous blood draws will be obtained, spun through the centrifuge and frozen to be further analyzed.

During the $7^{th}$ week, the participants will come in a final time. They will bring the device with them to return to the lab. Lipid profile, glucose and HbA1C will be obtained and analyzed. Venous blood samples will be obtained. The blood will be spun in a centrifuge and frozen to be further analyzed. The presence of the CRP, IL-6, glucagon and insulin will be analyzed by using the ELISA kit. SPSS version 22 will be used for data analysis. For the conclusion of the study, the subjects will be compensated for their participation in the study.

**Data Analysis**

Descriptive statistics were obtained on all measures. A repeated measures ANOVA was used to assess the different time points of the treatment on the dependent variables (glucose regulation, lipid profile and inflammation) across the 7 weeks. Paired sample t-test was used to specify changes pre and post SF-36 health status questionnaire. SPSS (version 22) was used for all analyses with $p \leq .05$ used as the level of significance for all tests.

# CHAPTER IV

## RESULTS AND DISCUSSION

Ten subjects with type 2 diabetes participated in the study to help determine whether glucose regulation and inflammation are positively affected by the NormaTec recovery system. The subjects performed 35 total pneumatic compression treatments for 1 hour a day, 5 days a week for 7 weeks. Blood measures were taken for the $1^{st}$, $17^{th}$ and $35^{th}$ treatment of lipid profile and HbA1C, which were obtained by a finger stick. Plasma and serum were obtained $1^{st}$, $17^{th}$ and $35^{th}$ treatment intravenously to analyze insulin, glucagon, Interleukin 6 (IL-6) and C-reactive protein (CRP). Repeated measures ANOVA compared the lipid profiles, glucose regulation and inflammation markers during the 3 laboratory visits. The SF-36 health status questionnaire was compared pre and post intervention and analyzed using the repeated measures paired sample t-test. The graphs shown show +/- the standard error for each of the outcomes.

Results from the repeated measures ANOVA showed no main effect of time point on total cholesterol (TC), HDL, LDL or triglycerides (TRG). However, there was a slight decrease in mean values for total cholesterol ($1^{st}$ -$35^{th}$, $17^{th}$ - $35^{th}$), HDL ($1^{st}$ - $17^{th}$, $1^{st}$ –

35th, 17th – 35th), and LDL (1st – 17th, 1st – 35th, 17th – 35th) throughout the 1st through the 35th treatment blood measurement.

**Table 1: Comparison of Lipid Profile for Pre, Middle and Post Treatment.**

| Variable | Mean ± SD | Effect Size |
|---|---|---|
| TC1 | 158.6 ± 43.2 | |
| TC2 | 162.0 ± 56.5 | .089 |
| TC3 | 153.2 ± 39.8 | |
| HDL1 | 49.3 ± 13.9 | |
| HDL2 | 48.7 ± 11.8 | .124 |
| HDL3 | 46.7 ± 10.5 | |
| TRG1 | 142.0 ± 96.2 | |
| TRG2 | 171.0 ± 177.5 | .097 |
| TRG3 | 181.9 ± 185.9 | |
| LDL1 | 74.8 ± 23.5 | |
| LDL2 | 73.6 ± 23.2 | .133 |
| LDL3 | 68.3 ± 25.8 | |

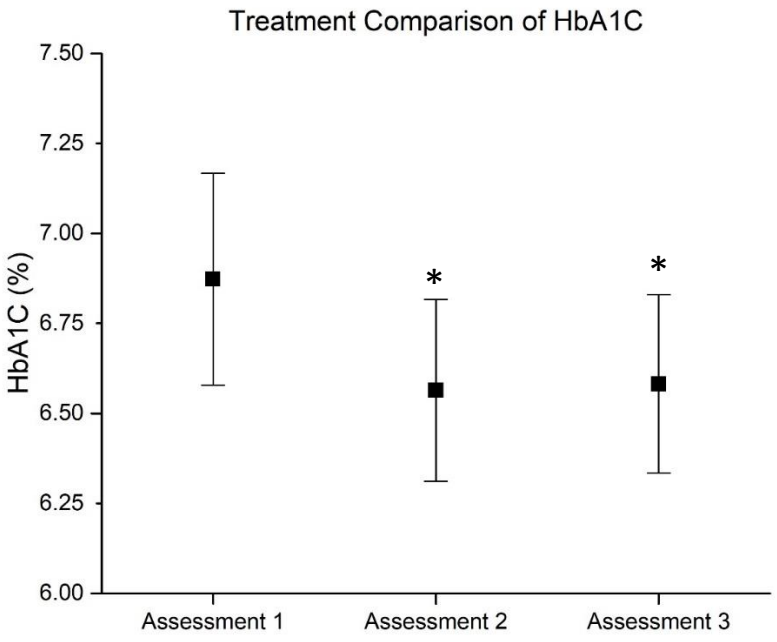
Results from the repeated measures ANOVA showed main effect of time point on HbA1C ($p = .015$) in table 2. Table 2 Post-hoc comparisons showed that HbA1Cs at time points for the 17th ($p = .002$ and 35th ($p = .026$) treatment were significantly lower than time point 1. Mean insulin values showed a slight decrease from the pre (1st) to middle (17th) treatment blood draw and the pre (1st) to post (35th) treatment blood draw, although no significance was found. The slight decrease shown in the other glucose regulators may have an influence on the significant decrease in HbA1C.

**Table 2: Comparison of Glucose Regulation Between the Pre, Middle and Post.**

| Variable | Mean ± SD | Effect Size |
|---|---|---|
| HbA1C1 | 6.9 ± 1.01 | |
| HbA1C2 | 6.5 ± .88 * | .467 |
| HbA1C3 | 6.5 ± .86 * | |
| INSULIN1 | 29.0 ± 64.5 | |
| INSULIN2 | 25.2 ± 38.9 | .08 |
| INSULIN3 | 21.5 ± 38.7 | |
| GLUCAGON1 | 6.6 ± 2.2 | |
| GLUCAGON2 | 6.2 ± 1.8 | .033 |
| GLUCAGON3 | 6.4 ± 1.5 | |
| GLU1 | 136.0 ± 29.3 | |
| GLU2 | 128.1 ± 29.4 | .073 |
| GLU3 | 137.7 ± 34.6 | |

***Indicates significantly different than assessment 1 ($p \leq .05$)*

•*Indicates significantly different than assessment 2 ($p \leq .05$)*




**Indicates significance*

**Figure 1: Pre, Middle and Post Blood Draw for HbA1C**

Figure 1 is showing the significant decrease in HbA1C among the three treatment blood draws throughout the 7 weeks. There was a significant difference in treatments pre and middle (1st and 17th) (p = .002) and treatments pre and post (1st and 35th).

(p = .026).

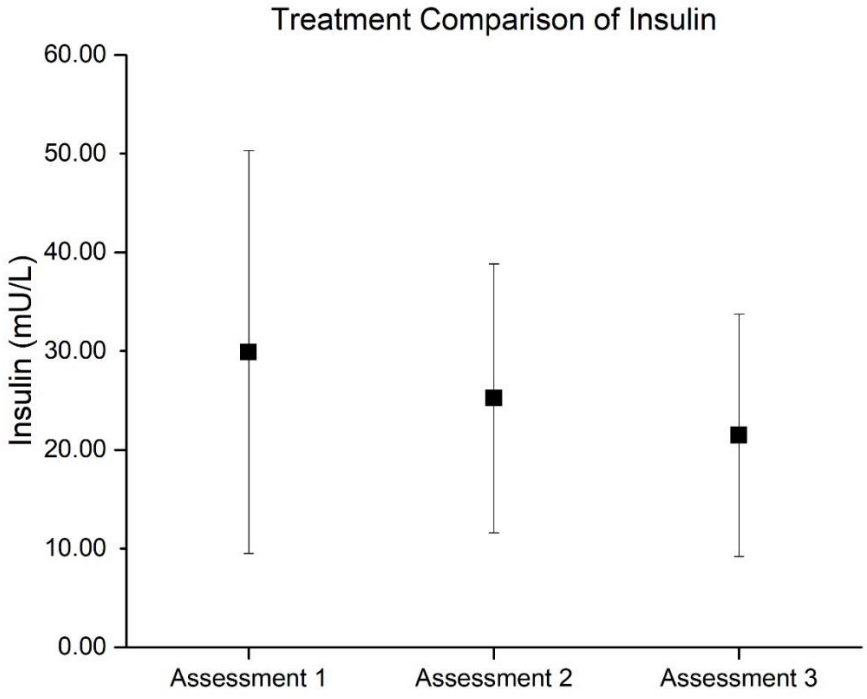



**Figure 2: Pre, Middle and Post Blood Draw for Insulin**

Figure 2 shows a slight decrease in insulin leves from the 1st, 17th and 35th treatment blood draws. There was no significant difference within either of the 3 treatment blood draws. However, there is still a decrease in insulin levels among this diabetic population which could lead to further research being done to show significant findings.

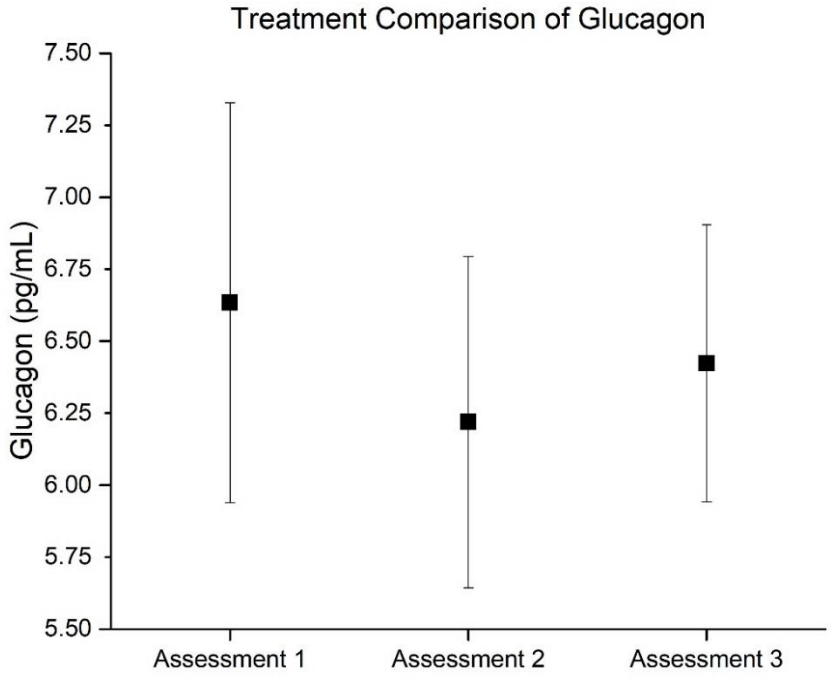



**Figure 3: Pre, Middle and Post Blood Draw for Glucagon**

Figure 3 is showing a decrease in glucagon values from the 1st to the 35th treatment blood draw. Glucagon values showed an increase after the 17th treatment, however still lower than the 1st treatment.

Table 3 shows the comparison between pre, middle and post treatment for CRP and IL-6. Results from the repeated measures ANOVA showed no main effect of time point on CRP and IL-6. There was no significant difference ($p \leq 0.05$) in either variable. There was, however, a slight decrease in CRP and IL-6 values from the 1st to 35th treatments. Although the decrease in inflammation was not significant, this still shows positive effects coming from the pneumatic compression treatment. The slight decrease may also contribute to the significantly lower HbA1C values.

**Table 3: Comparison of CRP and IL-6 on Pre, Middle and Post Treatment.**

| Variable | Mean ± SD | Effect Size |
|---|---|---|
| CRP1 | 13.4 ± 11.6 | |
| CRP2 | 13.0 ± 8.6 | .181 |
| CRP3 | 9.9 ± 6.7 | |
| IL61 | 3.3 ± 1.8 | |
| IL62 | 3.4 ± 2.0 | .066 |
| IL63 | 3.0 ± 1.7 | |

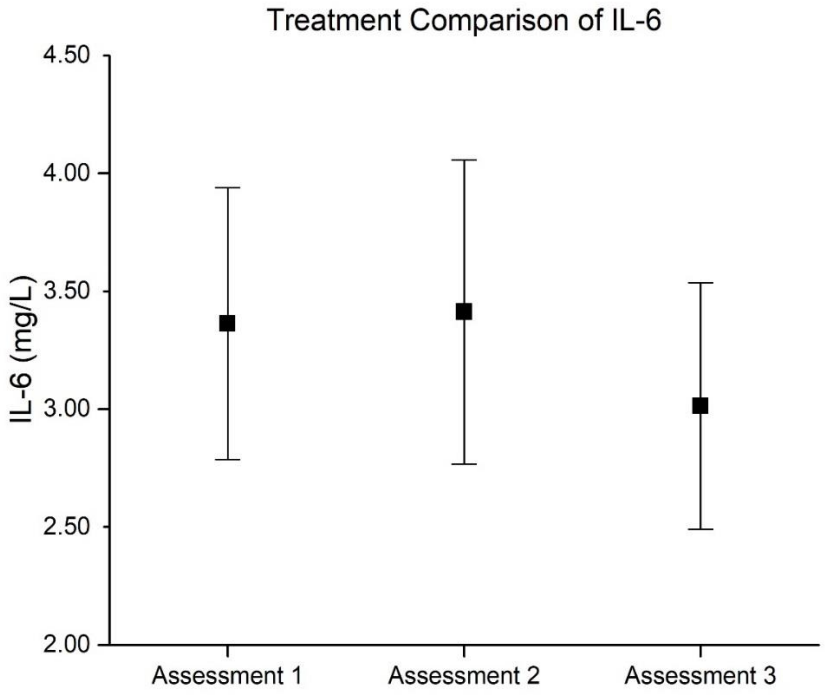



**Figure 4: Pre, Middle and Post Blood Draw for IL-6**

Figure 4 shows that values for IL-6 were slightly lower after the 17$^{th}$ treatment and 35$^{th}$ treatment blood draw. There was a slight decrease in the inflammatory marker IL-6, although no significance found.

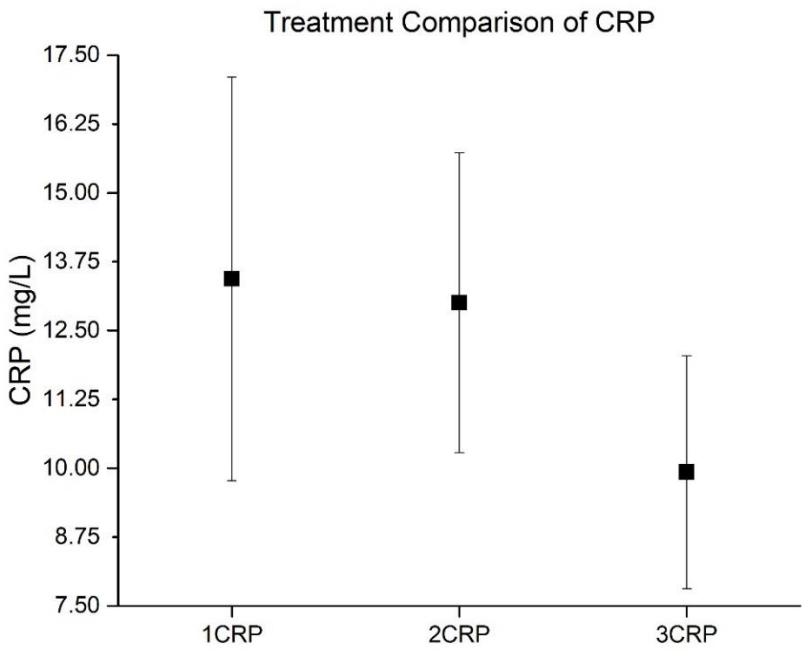



**Figure 5: Pre, Middle and Post Blood Draw for CRP**

Figure 5 is showing a slight decrease in CRP values from all treatment blood draws. There was a larger decrease in CRP values from the 1st to the 35th treatment blood draws. Although there was no significant difference for the decrease in CRP values, the decrease in inflammation that occurred during these pneumatic treatments could potentially lead to more research being done to find a significance.

Table 4 shows no significant difference ($p \leq 0.05$) in any variable of the SF-36 health status questionnaire based on protected paired t-test results. Although no significant values were obtained, there was increase in scores from pre to post survey in physical functioning, role physical, bodily plan, general health and vitality. This shows

that individuals increased in the physical aspects of the questionnaire and felt better about themselves after using the compression therapy.

**Table 4: Comparison of SF-36 Pre and Post intervention.**

| Pair | Mean ± SD | Mean ± SD | Δ | Sig. (2-tailed) |
|---|---|---|---|---|
| PhysicalFunctioning1 – PhysicalFunctioning2 | **PhysicalFunctioning1** 51.4 ± 8.2 | **PhysicalFunctioning2** 52.6 ± 7.5 | -1.3 | .140 |
| RolePhysical1 – RolePhysical2 | **RolePhysical1** 52.4 ± 7.9 | **RolePhysical2** 54.2 ± 7.7 | -1.7 | .191 |
| BodilyPlan1 – BodilyPlan2 | **BodilyPlan1** 53.2 ± 8.1 | **BodilyPlan2** 54.0 ± 6.9 | -.8 | .644 |
| GeneralHealth1 – GeneralHealth2 | **GeneralHealth1** 45.2 ± 10.5 | **GeneralHealth2** 47.9 ± 10.2 | -2.7 | .130 |
| Vitality1 – Vitality2 | **Vitality1** 55.2 ± 10.5 | **Vitality2** 55.8 ± 8.4 | -.62 | .693 |
| RoleEmotional1 – RoleEmotional2 | **RoleEmotional1** 53.5 ± 5.2 | **RoleEmotional2** 53.5 ± 6.1 | .00 | 1.0 |
| MentalHealth1 – MentalHealth2 | **MentalHealth1** 55.5 ± 6.1 | **MentalHealth2** 55.4 ± 5.9 | .09 | .923 |
| MCSScore1 – MCSScore2 | **MCSScore1** 55.5 ± 6.1 | **MCSScore2** 55.0 ± 5.5 | .53 | .526 |
| PCSScore1 – PCSScore2 | **PCSScore1** 49.5 ± 9.1 | **PCSScore2** 51.6 ± 7.8 | -2.1 | .189 |

## Discussion

### Inflammation

Mean values for CRP decreased from the 1$^{st}$ to the 35$^{th}$ IPC treatment. Although, there was no significant difference in the results for CRP and IL-6, the slight decrease in mean values from these treatments have been shown to have a positive effect on an individual's risk factors for cardiovascular disease and preexisting diabetes. This slight decrease shown in CRP values could lead to a clinical meaningful change in CRP while using this pneumatic compression device. Martin et al., (2012) discussed the positive

impact that IPC has on the inflammatory markers (hsCRP, TNF-α) by the significant difference they found in their results. As a result of their study, both inflammatory markers decreased within the 7 week treatment therapy. Decreasing these inflammatory markers in individuals that have abnormal glucose tolerance can possibly decrease their risks for cardiovascular diseases and other possible health concerns that may come from them having increased inflammation in the blood. Another really important factor among this population is potentially decreasing insulin resistance with the decreased inflammation. Bonetti et al., (2003) studied the effects of EECP on endothelial function in participants with coronary artery disease by using RH-PAT. High inflammation levels can have a negative effect on an individual's endothelium and potentially causing detrimental damage. The endothelium is an important tissue encompassing the blood vessels, heart and lymphatic vessels. There can be negative health risks if this tissue becomes damaged, such as heart failure, stress cardiomyopathy and infections. The results found in this study show that compression therapy may help these individuals benefit from any further cardiovascular complications. The results from these studies show positive outcome from the decreased inflammatory markers, along with the slight decrease in inflammation in the present study that examined CRP and Il-6.

Diabetic neuropathy and IPC treatments were researched by Salek, Bahrpeyma & Mohajeri-Tehrani (2015). They found that there may be some positive effects for individuals dealing with diabetic neuropathy. This could be due to the increased blood flow from the compression treatments that will help the nerve damage caused from hyperglycemia. The increased circulation shown could help individuals with type 2 diabetes suffering from a decrease in blood flow to the lower extremeties. There may be

some positive outcomes from the use of IPC for diabetics who are suffering from diabetic neuropathy.

Obese and diabetic individuals tend to have increased inflammation levels according to Colwell, J. (1999). Having these high inflammatory markers can lead to damaging effects of the body. CRP levels have been widely studied as being a potential risk factor for cardiovascular disease. Detrimental vascular injury can be caused from these high inflammatory markers in the blood for an extended period of time. Seeing a decrease in IL-6 and CRP shows promising results from using the pneumatic compression device. The decreased inflammation levels within the blood can lead to an increased blood flow and possibly more of a decrease in HbA1C. More research needs to be done on the effects of IPC on the diabetic population with the regulation of glucose and inflammation.

**Glucose Regulation**

The significant decrease found in HbA1c levels from the 1$^{st}$ to 17$^{th}$ and 1$^{st}$ to 35$^{th}$ treatment can lead to many unanswered questions. This significant decrease may be a product of the decrease in inflammation due to the compression therapy. The decrease in inflammatory markers, insulin and glucagon can potentially be a factor to the significantly low HbA1C levels throughout the 7 weeks. The significant decrease in HbA1C levels could have a clinically meaningful change. This significant decrease in this major marker for diabetic individuals could result in potentially controlling glucose better. The IPC treatments may have led to an increase in blood flow shown by Labropolous et al., (2005) that leads to an increase in circulation which can help with lowering inflammation. The decrease in insulin levels may have something to do with the

body using more glucose and becoming less resistant to the insulin being produced. Chronic inflammation can have a negative impact on the body and has been known to have a relation with increased levels of glucose in the blood. If blood flow is increased, due to this compression treatment, then inflammation may be decreased due to recent studies (Lawson et al., 1996). If inflammation is decreased, then this may have a positive effect on HbA1C levels. More research needs to be done on the effects of chronic inflammation on HbA1C in type 2 diabetics.

Ferrannini et al., (2007) found that high glucagon levels in the body may have a relation with insulin resistance. Glucagon is produced to help blood glucose levels not reach the point of being hypoglycemia. If too much glucagon is found, then there could be a relation to insulin resistance. Furthermore, if glucagon levels in the blood are too high then this may have a correlation to increase blood glucose levels and resistance to insulin in type 2 diabetics that was found with researchers Ferrannini et al., (2007). The slight decreases found in glucagon and insulin levels could play a part in the significant decrease shown in HbA1C.

**SF-36 Health Survey**

There was no significance found with the SF-36 health survey, but there were some slight increases worth noting. The individuals who participated in the study showed slight increased among their general physical health from pre ($1^{st}$) and post ($35^{th}$) treatment surveys. From performing these compression treatments, individuals felt physically better after the $35^{th}$ treatment when compared to when they first started the treatments.

# CHAPTER V

# SUMMARY AND CONCLUSION

There has been previous research on intermittent pneumatic compression devices and its effects on individuals with cardiovascular disease and chronic inflammation. The hypothesis was supported due to the significant decrease in HbA1C. The results obtained showed positive effects relating to glucose regulation and inflammation. Therefore, the hypothesis was supported.

Based on current research, inflammation and glucagon levels may be influenced by these compression treatments, but more research needs to be completed to obtain any significant findings. Research using these compression devices has shown a decrease in inflammation, which can lead to decreased cardiovascular risks and damage to arteries, nerves and vessels. Previous research has found positive effects for increased blood flow with these compression treatments that has led to more research benefiting certain populations decreasing possible risk factors for a number of various diseases. An increase in blood flow to the lower extremities can lead to positive effects in endothelial function, decreased inflammation and with further research potentially a decrease in HbA1C and

other glucose regulators. The fact that there was a significant decrease in HbA1C shows that this can be a promising start to help prevent or control type 2 diabetes. The effects shown from this pneumatic compression device could potentially be an alternative method to the use of medications in the future for individuals with type 2 diabetes. More research needs to be done on how effective IPC treatments are for individuals with type 2 diabetes.

# CHAPTER VI

# APPLICATION, LIMITATIONS AND FURTHER RESEARCH RECOMMENDATIONS

## Application

The use of intermittent pneumatic compression devices has become large among the medical community for leg ulcers, thrombosis, and cardiovascular disease. Individuals diagnosed with type 2 diabetes take medications and are recommended to follow a diet and exercise plan to help control their diabetes. If further research is done using IPC treatments to examine the effects that this can have on type 2 diabetes, then this could potentially be a huge step in aiding individuals with type 2 diabetes to refrain from having to take medications and instead using this compression device to help lower or maintain their glucose levels. More research needs be done on how this device affects the diabetic population, which could potentially be a huge and new step towards preventing and controlling type 2 diabetes.

## Limitations

Limitations of the study were identified as follows:

1. Diet and exercise was not controlled within the study, which could have led to an increase or decrease in the variables measure.
2. Medications taken by the subjects were not controlled.
3. The study conducted contained a small sample size (N=10).

## Future Research Recommendations

1. A larger sample size would be recommended for any future research in this line of study.
2. Controlling for diet and exercise would possibly help with any limiting factors that may have influenced the variables examined.
3. Having the subjects maintain a log of the days that they are performing the treatments may help in any limiting factors that could have influenced the variables measured and help with any future research.

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Appendix A

## The SF-36v2™ Health Survey

**Name:** _____ **Date:** _____

**Instructions for Completing the Questionnaire**

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by marking your response.

1. In general, would you say your health is:

- O Excellent
- O Very Good
- O Good
- O Fair
- O Poor

2. Compared to one year ago, how would you rate your health in general now?

- O Much better now than one year ago
- O Somewhat better now than one year ago
- O About the same as one year ago
- O Somewhat worse than one year ago
- O Much worse than one year ago

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

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| a) Vigorous activities such as running, lifting heavy objects, participating in strenuous sports | O | O | O |
| b) Moderate activites such as moving a table, pushing a vacuum, bowling or playing golf | O | O | O |
| c) Lifting or carrying groceries | O | O | O |
| d) Climbing several flights of stairs | O | O | O |
| e) Climbing one flight of stairs | O | O | O |
| f) Bending, kneeling or stooping | O | O | O |
| g) Walking more than a mile | O | O | O |
| h) Walking several hundred yards | O | O | O |
| i) Walking one hundred yards | O | O | O |
| j) Bathing or dressing yourself | O | O | O |

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

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a) Cut down on the amount of time you spent on work or other activities | O | O | O | O | O |
| b) Accomplished less than you would like | O | O | O | O | O |
| c) Were limited in the kind of work or other activities | O | O | O | O | O |
| d) Had difficulty performing work or other activities (for example, it took extra effort) | O | O | O | O | O |

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

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a) Cut down on the amount of time you spent on work or other activities | O | O | O | O | O |
| b) Accomplished less than you would like | O | O | O | O | O |
| c) Did work or other activities less carefully than usual | O | O | O | O | O |

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

O Not at all

O Slightly

O Moderately

O Quite a bit

O Extremely

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

- O None
- O Very mild
- O Mild
- O Moderate
- O Severe
- O Very severe

8. During the past four weeks, how much did pain interfere with your norma the home and housework)?

- O Not at all
- O A little bit
- O Moderately
- O Quite a bit
- O Extremely

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

| | **All of the time** | **Most of the time** | **Some of the time** | **A little of the time** | **None of the time** |
|---|---|---|---|---|---|
| a) did you feel full of life? | O | O | O | O | O |
| b) have you been very nervous? | O | O | O | O | O |
| c) have you felt so down in the dumps nothing could cheer you up? | O | O | O | O | O |
| d) have you felt calm and peaceful? | O | O | O | O | O |
| e) did you have a lot of energy? | O | O | O | O | O |
| f) have you felt downhearted and depressed? | O | O | O | O | O |
| g) did you feel worn out? | O | O | O | O | O |
| h) have you been happy? | O | O | O | O | O |
| i) did you feel tired? | O | O | O | O | O |

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

- O All of the time
- O Most of the time
- O Some of the time
- O A little of the time
- O None of the time

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

| | **Definitely true** | **Mostly true** | **Don't know** | **Mostly false** | **Definitely false** |
|---|---|---|---|---|---|
| a) I seem to get sick a little easier than other people | O | O | O | O | O |
| b) I am as healthy as anybody I know | O | O | O | O | O |
| c) I expect my health to get worse | O | O | O | O | O |
| d) My health is excellent | O | O | O | O | O |

# THANK YOU FOR COMPLETING THESE QUESTIONS!

Appendix B


**Informed Consent**

**Effect of Intermittent Pneumatic Compression (IPC) on Glucose Regulation and Inflammation in Type 2 Diabetes**

**Introduction and Purpose of this Research**

This study is being completed by students and faculty from Cleveland State University's Health and Human Performance Department. This research in particular is being undertaken by Dr. Kenneth Sparks, and graduate researcher Caitlin Nagy.

The purpose of this study is to determine the effects of intermittent pneumatic compression (IPC) on endothelial function and metabolism in type 2 diabetes and Prediabetes.

The NormaTec device is a type of IPC that was originally designed to help athletes recover from strenuous exercise and improve circulation caused by various diseases. Those with type 2 diabetes and prediabetes could have lower than average blood circulation. This research aims to identify if use of the NormaTec device will have any effects on glucose regulation and inflammation in individuals with type 2 diabetes.

**Risks**

Risks associated with this study include discomfort while using the NormaTec device and giving blood samples. Only qualified personnel will be administering the NormaTec treatment and drawing blood.

**Benefits**

There is no direct benefit or medical benefit and it is not to be considered to be a medical treatment while participating in this study nor should it be used in place of regular medical care. You will however be compensated $200 at the conclusion of the study.

**Procedures and Commitment for Participation**

Subjects will need to respond to the medical history questionnaire and quality of life survey honestly. Subjects will need to be present to receive a one-hour NormaTec treatment for 5 days a week for 7 weeks, a total of 35 treatments. Two weeks prior to the study, subjects will be instructed to keep their typical diet and exercise routines. Baseline

measurements of ankle/brachial index, body composition, and a blood sample for lipid profiles and Hba1c measurements will be obtained. Plasma samples will also be taken to measure insulin, glucagon, IL-6 and C-reactive protein.

**Confidentiality**

All efforts will be made to keep your data confidential, any data and information obtained during your participation will not be disclosed to anyone without your consent. Your data will only be used as group data without any identification of participant's names.

**Freedom of Consent**

Your participation in this study is completely voluntary. You may withdraw from the study at any time, without penalty or consequence.

**Inquiries**

Questions about the procedures used in this research are welcomed. If you have any doubts or questions please contact Dr. Kenneth Sparks at 216-687-4831 or undergraduate student researcher Shana Strunk at 330-317-9448.

**Patient Acknowledgement**

I have read and understand this consent form or it has been read to me and I understand it. The procedures, purposes and known discomforts, risks and benefits of this research have been explained to me. I have had a chance to ask questions and they have been answered sufficiently. I am 18 years or older and I voluntarily consent to participate in this study and I have been given a copy of this consent form.

I understand that if I have any questions about my rights as a research subject I can contact the Cleveland State University Institutional Review Board at 216-687-3630.

Signature of Participant_____ Date _____

Signature of Witness _____ Date _____

Appendix C

Diabetes Data Sheet

Name: _____ Code: _____

Date of 1st Test: _____

Tube Labels: _____

HbA1C: _____

Date of 2nd Test: _____

Tube Labels: _____

HbA1C: _____

Date of 3rd Test: _____

Tube Labels: _____

HbA1C: _____

Appendix D

NormaTec