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EFFECTIVENESS OF A 12- MONTH DIABETES PREVENTION PROGRAM IN REDUCING CARDIOVASCULAR DISEASE RISK IN PREDIABETICS

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EFFECTIVENESS OF A 12- MONTH DIABETES PREVENTION PROGRAM IN REDUCING CARDIOVASCULAR DISEASE RISK IN PREDIABETICS

By Aidan Donahoe

We recommend acceptance of this thesis in partial fulfillment of the candidate's requirements for the degree of Clinical Exercise Physiology.

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ABSTRACT

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The purpose of this study was to evaluate the relationship between obesity and cardiovascular biomarkers in physically active prediabetic participants who completed 12 months of the DPP. The obesity paradox was also studied, which suggests that obese and overweight individuals may have a protective survival benefit when compared to normal weight individuals. Subjects (N=20) ranged from 50-83 years of age and were participating in a structured exercise program at least 2-3 days/week. Cardiovascular risk factors including BMI, HbA1C, weight, WC, SBP, DBP, cfPWV, MVC, GS, and OLBT were examined at baseline and at 3, 6, 9, and 12 months. The CDC-approved curriculum included education of healthy eating habits and the importance of achieving a minimum of 150 minutes of weekly physical activity. Significant improvements were observed in BMI, weight, and WC from pre-to-post. Criteria for classification of the obesity paradox was also studied to determine if the paradox was present in our sample. The obese group experienced greater improvements in WC, SBP, DBP, cfPWV, and GS when compared to overweight or normal weight individuals, but the results explaining the obesity paradox were inconclusive.

ACKNOWLEDGMENTS

With the completion of this research paper, I would like to express my gratitude towards those who have helped me along the way. To begin, I would like to thank Kim Radtke, Ph.D candidate, for her constant attention to detail in this study, her superb work ethic, and assistance when putting the data together. Kim is a mother, wife, academic instructor, advisor, and Executive Director of LEHP, all while finishing her doctoral degree. There are those who make excuses during the busiest times of our lives, but Kim has proven that academic and professional success can be achieved by finding your passion and keeping your foot on the accelerator. I would also like to thank Dr. Salvador "Cha" Jaime for his expansive knowledge on the mechanisms behind cardiovascular disease. Cha challenged me on a weekly basis to think more deeply about the topics we studied, while also helping to steer me in the right direction when it seemed as if this research would get the best of me.

Next, I want to acknowledge Dr. Richard Mikat, who devoted his time to ensuring this paper was comprehensive while also asking the "big-picture" questions. As I buried myself into pages of data and spread sheets, Dr. Mikat helped simplify things and he gave me a new perspective on how the data was analyzed. Lastly, I would also like to thank my friends and family, both in Wisconsin and back home in Illinois. Without their constant support, I do not believe that my mental health would have been as good as it was throughout this process. As I submit this paper in a very unsettling and unprecedented time due to a global pandemic, I am still eager for my future in a clinical setting and grateful for those who have helped me get this far.

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INTRODUCTION

Over the last 30 years, obesity rates have continued to rise and may soon impact up to 85% of American adults (Wang et al, 2008). Although research has shown that obesity significantly increases ones risk of chronic disease morbidity and may become the most prevalent preventable form of death in the U.S. (Lavie et al, 2009), evidence has been controversial. A paradox exists when obese patients with cardiovascular disease (CVD) experience a more positive prognosis than patients who are at a healthier body weight (Lavie et al. 2009). While the mechanisms behind the obesity paradox are in need of further research, some possible explanations include location of fat distribution (Lee et al. 2007), severity of arterial stiffness (Miyano et al. 2010), and rates of sarcopenia (Ohara et al. 2014).

This trend of excessive weight gain also accounts for the largest percentage of primary hypertension risk (Hall et al. 2015). Obesity-related hypertension is further escalated due to an undesired shift in sympathetic and parasympathetic tone, increasing fluid absorption, and raising pressure (Re, R. 2009). Chronic hypertension damages tissue inside the arteries, allowing Low Density Lipoprotein (LDL) to form plaque along the tears in the arterial wall, also known as atherosclerosis. Plaque buildup narrows the inside of the arteries, raising blood pressure in a harmful cycle that can lead to a myocardial infarction or stroke, if left untreated (De Boer et al. 2006). Arteries also experience a natural loss of elasticity with age due to a buildup of collagen within the arterial wall, which further reduces arterial compliance, as measured by cfPWV (Metsamarttila et al. 2018). Stiffened arteries display a higher cfPWV, are associated with an increased risk of

CVD, and are an independent predictor of cardiovascular morbidity and mortality (Nordstrand et al. 2011). Fortunately, research has shown that participating in a consistent aerobic exercise program can improve arterial stiffness in as little as 3 months, which provides support for the exercise component of the DPP (Mustata et al. 2004).

Obese individuals also have a significantly greater risk of developing Type 2 diabetes (T2D) when compared to those of a normal body weight, with rates of obesity in patients with T2D as high as 80% (Hruby, A and Hu, F. 2014). Prior to receiving a diagnosis of T2D, an individual must progress through a prediabetic stage, commonly diagnosed by a glycosylated hemoglobin (HbA1C) of 5.7%-6.4%. Over 84 million U.S. adults had prediabetes in 2015, and only 11.6% of those individuals were aware of their diagnosis (Galaviz et al. 2015). Unfortunately, it is estimated that the prevalence of prediabetes will significantly increase in the coming decades with advanced age and increased body size of the population (Dall et al. 2014). This will impact morbidity rates, as those with prediabetes are twice as likely to experience CVD when compared to individuals with a normal HbA1c level (Huang et al. 2014).

While an increased prevalence of cardiovascular risk factors such as blood pressure and HbA1C alone can be deadly, physical performance tests including walking speed, grip strength, and standing balance have also been individually linked to mortality in older individuals, while the combined use of all three measures further increased prognostic power (Nofuji et al. 2016). This trend is also seen in studies on grip strength, as a weaker handgrip strength was significantly associated with a higher risk of all-cause mortality (Bae, et al. 2019). Furthermore, a decline in gait speed (GS) can be predicted by a decrease in thigh muscle mass area in both men and women (Beavers et al. 2013). This

association between muscle mass and risk of death may help to provide an explanation to the obesity paradox (Abramowitz et al. 2018). Research has also shown that exercise, specifically resistance training exercise, can improve muscle weakness in diabetic individuals (Strasser & Pesta, 2013).

Lifestyle intervention programs such as the Diabetes Prevention Program (DPP) have attempted to delay or prevent the progression of prediabetes to T2D. The DPP is an approved curriculum from the Center for Disease Control consisting of 25 scheduled education sessions focused on increased physical activity and dietary modifications. The DPP has shown that people who are at a higher risk of T2D can prevent or delay the disease through the implementation of a lifestyle intervention program. Research supports the use of the DPP as an effective method to prevent a T2D diagnosis and decrease cardiovascular risk factors in pre-diabetic individuals. (Diabetes Prevention Program, 2019).

The primary purpose of this study is to evaluate the relationship between obesity and biomarkers in physically active prediabetic participants who completed 12 months of the DPP. The research hypothesis is that the implementation of the DPP will significantly decrease the progression of pre-diabetes to T2D and improve CVD risk factors from pre to post including measurements of HbA1C, systolic blood pressure (SBP), diastolic blood pressure (DBP) waist circumference (WC), body mass index (BMI), carotid-femoral pulse-wave velocity (cfPWV), one-leg balance test (OLBT), maximal voluntary contraction (MVC), and GS. These risk factors will be compared to a 12-week hypothesis generating study to identify any significant changes observed over an extended time-frame.

METHODS

Subjects

A convenience sample consisting of 20 subjects currently exercising at either the La Crosse Exercise and Health Program or the Strong Seniors Program (≥ 60 years of age) were recruited. It was assumed that all subjects were currently participating in a structured exercise program at least 2-3 days per week prior to study. Inclusion criteria included at least one of the following: BMI ≥ 25; fasting glucose of 100 to 125 mg/dl; HbA1c of 5.7-6.4 mmol/L; greater than a nine-point score on the DPP questionnaire, or a positive screening for prediabetes. Smokers and Type I and II diabetics were excluded from participating.

Table 1. Descriptive characteristics of the subjects (N = 20)

	Male (n = 7)	Female (n = 13)
Age (yr.)	73.6 ± 6.1	66.5 ± 7.6
Height (cm)	178.0 ± 7.4	163.7 ± 7.1
Weight (kg)	93.6 ± 9.7	76.6 ± 13.6
BMI	29.5 ± 2.0	28.8 ± 5.9

Values represent mean ± standard deviation.

Procedures

Participants were screened at baseline to determine eligibility and placed in the treatment group. Approval from the Institutional Review Board for the Protection of Human Subjects at the University of Wisconsin-La Crosse was obtained prior to testing. Verbal and written explanations were provided for subjects with the opportunity to ask questions before signing the informed consent form. Subjects were informed participation

was voluntary and they could withdraw at any time. On the morning of each screening, subjects were informed to come to the scheduled appointment fasting for at least 12 hours (no food, alcohol, or caffeine). Morning medications were not allowed prior to screening, and subjects were advised to bring prescribed medications that could be taken immediately after testing.

On screening day, each subject completed paperwork, including an informed consent and a DPP questionnaire. Subjects then had anthropometric measurements taken. Height was measured with a stadiometer, measuring to the nearest 0.5 centimeters. Body weight was measured to the nearest tenth of a kilogram using a calibrated scale (Certified Fitness Scale, Rice Lake Weighing Systems, Rice Lake, WI). These measurements were used to calculate BMI (kg/m^2). Waist and hip circumference were obtained following the American College of Sports Medicine guidelines. Waist circumference (WC) was taken at the narrowest part of the torso, between the last rib and the iliac crest, using a cloth tape measuring to the nearest 0.5 cm. Standing with feed together, hip circumference was measured at the largest part of the hips and at the largest protuberance of the gluteus to the nearest 0.5cm (Riebe,D., Ehrman, J. K., Liguori, G., & Magal, M. 2018).

Following a 12-hour fast, blood samples were collected using a lancet (Unistik 2 Normal, Owen Mumford, Marietta, GA) and capillary tube (Cholestech LDH Collection Tube, Abbott, Chicago, IL). Blood was entered into a test cartridge (Afinion HbA1c, Abbott Laboratories, Chicago, IL) and tested using an analyzer (Afinion™ AS100, Abbott Laboratories, Chicago, IL) to obtain fasting measurements of HbA1. This measurement analyzed the percentage of hemoglobin coated with glucose over the past three months (the average lifespan of a red blood cell). Prediabetes HbA1c levels range

from 5.7-6.4%, whereas any amount greater than 6.5% results in the diagnosis of diabetes. Subjects rested in a supine position for five minutes prior to testing, with eyes covered, wearing noise cancelling headphones, and a femoral and brachial cuff. A resting brachial blood pressure measurement was performed on the bare right arm with a brachial cuff and tonometer which also measured arterial pulse-wave velocity in meters/second (SphygmoCorXCEL PWA & PWV, AtCor Medical Pty Ltd., Naperville, IL). The average of the second and third blood pressure measurements were used to determine brachial systolic blood pressure (bSBP), brachial diastolic blood pressure (bDBP), central systolic blood pressure (aSBP), central diastolic blood pressure (aDBP), central pulse pressure (aPP), central mean arterial stiffness. Transit time was measured by using the time from reaching the carotid artery to the femoral cuff. Prior to the resting period, measurements were taken of the carotid artery to the sternal notch, sternal notch to femoral cuff, and from femoral artery to femoral cuff. Carotid-femoral pulse-wave velocity (cfPWV) was measured by using the difference in time (m/s) of the pulse wave reaching the tonometer to the femoral sensor (Figueroa et al. 2016).

Three physical performance tests were also performed, consisting of MVC, GS, and OLBT. The MVC test used a hand dynamometer (microFET Grip Hand Dynamometer, Hoggan Scientific LLC, Salt Lake City, UT) to measure grip strength (kg). Following a continuous inhale, the subject was instructed to exhale and produce a full contraction of the dynamometer. The GS was marked with tape on the floor of a tile hallway at eleven, eight, and three meters apart. The subject was instructed to walk from the starting tape through the eleven meter mark, while the researcher recorded the time taken to walk from the three meter mark to the eight meter mark. The purpose of this test

was to measure normal 5-meter GS as accurately and consistently as possible. Lastly, the OLBT required subjects to stand on one foot while focusing on a black dot on white paper placed at eye level. The best of three balance attempts was recorded on each leg and subjects were asked to stop at 60 seconds.

Subjects were tested at baseline and at 3, 6, 9, and 12 months, respectively. The same order and protocol was used for each subject. The intervention group attended weekly education classes from the CDC-approved curriculum that included dietary modifications and increased physical activity (at least 150 minutes of moderate intensity physical activity). Body weight in pounds was obtained at weekly meetings using a calibrated scale (Certified Fitness Scale, Rice Lake Weighing Systems, Rice Lake, WI). Total physical activity minutes for the previous week were also recorded.

STATISTICAL ANALYSIS

A one-way ANOVA with repeated measures was used to determine if significant changes between subjects occurred over the course of the 12-month study. The alpha level was set at 0.05 to achieve statistical significance for this study. A Pearson Product-Moment correlation was used to determine coefficients of determination in order to find clinical significance between risk factors. An estimation of an appropriate sample size was conducted using a power analysis with data from previous research investigating the effects of DPP vs. usual care in older adults (Xiao et al. 2013). HbA1c, systolic and diastolic blood pressure, pulse-wave velocity, BMI, weight, and WC were the primary variables being used to investigate the effects of a 12-month DPP on CVD risk factors.

RESULTS

Upon completion of the study, a decrease in cardiovascular risk factors including weight, WC, BMI, SBP and DBP, PP, cfPWV, and HbA1C were noted. Subjects experienced the most significant changes from pre-to-post in their BMI (5.9%, $p < .01$), weight (5.8%, $p < .01$), and WC (7.9%, $p < .05$). Specific values of cardiovascular risk factors at 0, 3, 6, 9, and 12 months are indicated in Table 2. There were significant decreases from 0-to-12 months in average BMI (5.9%, $p < .01$), weight (5.8%, $p < .01$) and WC (7.9%, $p < .05$). There were also significant decreases from 0 to 6 months in weight (6.2%, $p<0.01$), WC (7.0%, $p < .05$), SBP (5.3%, $p < .05$), DBP (4.9%, $p < .05$), and PP (18.0%, $p < .01$). Although there was a beneficial change in all risk factors from 0 to 12 months, only the changes in BMI, weight, and WC were significant.

Table 3 displays the coefficients of determination of the relationship between each cardiovascular risk factor. The following correlations met the minimum criteria of $r^2 = 0.50$ to show clinical significance; BMI and weight ($r^2 = 1.00$), BMI and WC ($r^2 = .67$), BMI and SBP ($r^2 = .64$), BMI and DBP ($r^2 = .68$), BMI and cfPWV ($r^2 = .95$), weight and WC ($r^2 = .67$), weight and SBP ($r^2 = .64$), weight and DBP ($r^2 = .67$), weight and cfPWV ($r^2 = .95$), WC and cfPWV ($r^2 = .66$), SBP and DBP ($r^2 = .54$), SBP and cfPWV ($r^2 = .74$), SBP and PP ($r^2 = .91$), DBP and cfPWV ($r^2 = .54$), cfPWV and PP ($r^2 = .60$), PP and HbA1C ($r^2 = .74$), MVC and BMI ($r^2 = -.75$), MVC and weight ($r^2 = -.75$), MVC and SBP ($r^2 = -.92$), MVC and DBP ($r^2 = -.69$), MVC and cfPWV ($r^2 = -.76$), MVC and PP ($r^2 = -.74$) GS and WC ($r^2 = .67$), and OLBT and HbA1C ($r^2 = - .69$). Of those correlations that were clinically significant, the following risk factors were highly significant ($r^2 =$

0.81 – 1.00); BMI and weight (r^2 = 1.00), BMI and cfPWV (r^2 = .95), weight and cfPWV (r^2 = .95), SBP and PP (r^2 = .91), and MVC and SBP (r^2 = -.92).

Table 2. Changes in cardiovascular risk factor from 0-12 months (mean ± SD).

Variables	Pre	3 Months	6 Months	9 Months	Post
BMI	29.0 ± 4.8	27.8 ± 4.8[a]	27.2 ± 4.5[a]	27.2 ± 4.4[a]	27.3 ± 4.5[a]
Weight (kg)	82.5 ± 14.7	79.1 ± 14.8[a]	77.4 ± 13.9[a]	77.3 ± 13.6[a]	77.7 ± 13.4[a]
Waist (cm)	99.1 ± 14.7	90.8 ± 11.7[a]	92.2 ± 12.4[b]	93.7 ± 13.0	91.3 ± 11.5[b]
SBP (mmHg)	138.5 ± 17.0	136.3 ± 13.4	131.6 ± 14.1[b]	128.8 ± 12.5[a]	134.0 ± 14.3
DBP (mmHg)	80.3 ± 10.4	77.6 ± 9.0	76.4 ± 7.8[b]	74.7 ± 6.7[a]	78.1 ± 8.6
cfPWV (m/s)	8.59 ± 1.89	7.88 ± 2.19	7.81 ± 1.78	7.73 ± 1.30	7.78 ± 1.40
PP (mmHg)	59.2 ± 12.2	58.5 ± 10.3	48.6 ± 10.9[a]	54.3 ± 11.0[b]	56.7 ± 10.5
HbA1C (%)	5.50 ± 0.36	5.48 ± 0.29	5.45 ± 0.35	5.46 ± 0.31	5.48 ± 0.37
MVC (kg)	29.3 ± 10.2	29.5 ± 10.7	30.2 ± 10.7	30.2 ± 10.1	29.8 ± 10.1
Gait (sec)	3.93 ± 0.60	3.72 ± 0.46	3.84 ± 0.47	3.77 ± 0.54	3.81 ± 0.63
OLBT (sec)	45.40 ± 21.08	44.15 ± 21.19	48.37 ± 19.36	42.42 ± 21.91	45.54 ± 19.99

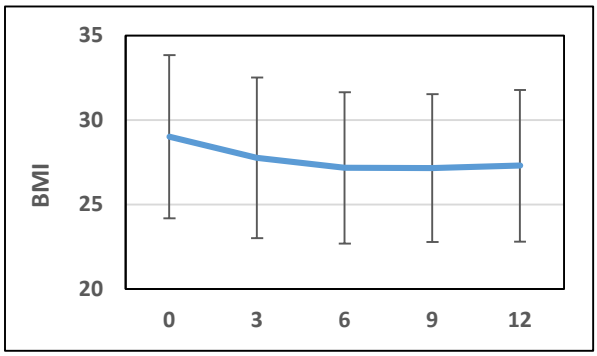
[a] Significantly lower than Pre ($p < .01$).
[b] Significantly lower than Pre ($p < .05$).

Table 3. Coefficients of determination of cardiovascular risk factors.

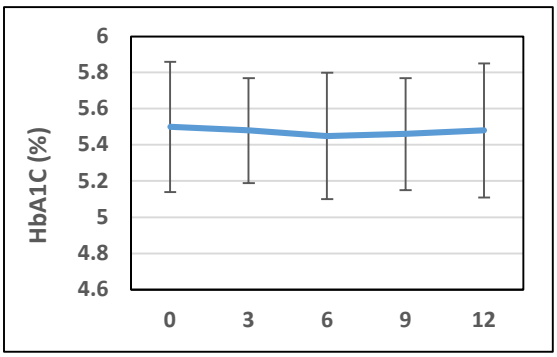
	BMI	Weight	Waist	SBP	DBP	cfPWV	PP	HbA1C	MVC	Gait
BMI	1	1.00[a]	.67[a]	.64[a]	.68[a]	.95[a]	.43	.17	-.75[a]	.41
Weight	1.00[a]	1	.67[a]	.64[a]	.67[a]	.95[a]	.43	.18	-.75[a]	.40
Waist	.67[a]	.67[a]	1	.19	.26	.66[a]	.11	.03	-.20	.67[a]
SBP	.64[a]	.64[a]	.19	1	.54[a]	.74[a]	.91[a]	.49	-.92[a]	.06
DBP	.68[a]	.67[a]	.26	.54[a]	1	.54[a]	.25	.01	-.69[a]	.43
cfPWV	.95[a]	.95[a]	.66[a]	.74[a]	.54[a]	1	.60[a]	.32	-.76[a]	.30
PP	.43	.43	.11	.91[a]	.25	.60[a]	1	.74[a]	-.74[a]	.00
HbA1C	.17	.18	.03	.49	.01	.32	.74[a]	1	-.37	-.12
MVC	-.75[a]	-.75[a]	-.20	-.92[a]	-.69[a]	-.76[a]	-.74[a]	-.37	1	-.08
Gait	.41	.40	.67[a]	.06	.43	.30	.00	-.12	-.08	1
OLBT	.00	.00	.00	-.08	.18	-.05	-.30	-.69[a]	.01	.22

[a] Represents clinically significant differences.
Negative values represent an inverse correlation.

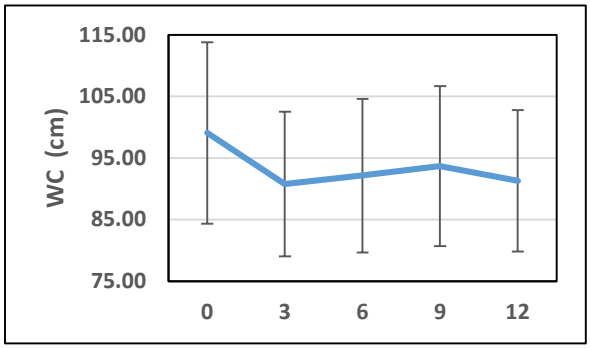
Figure's 1-6. Changes in CV risk factors over 12 months.



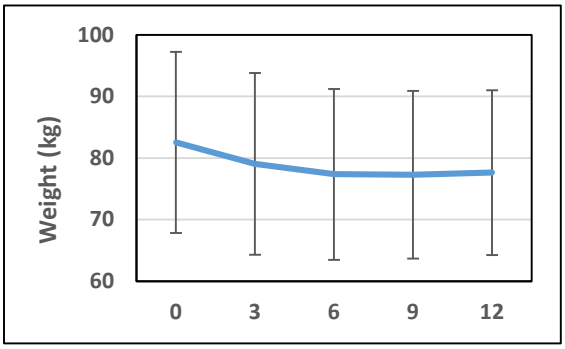
1. Changes in BMI over 12 months.



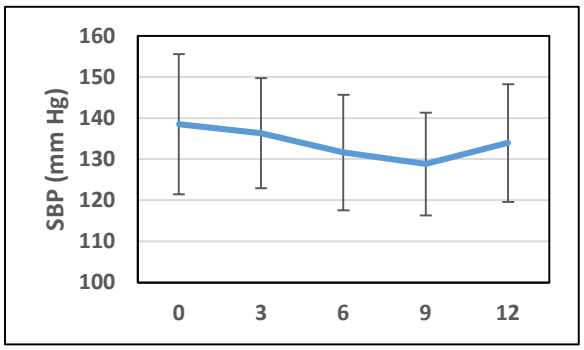
2. Changes in HbA1C over 12 months



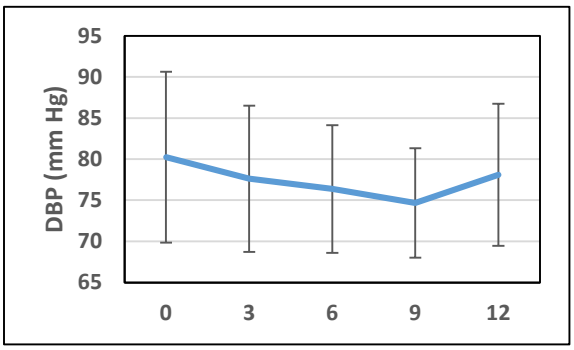
3. Changes in WC over 12 months.



4. Changes in Weight over 12 months

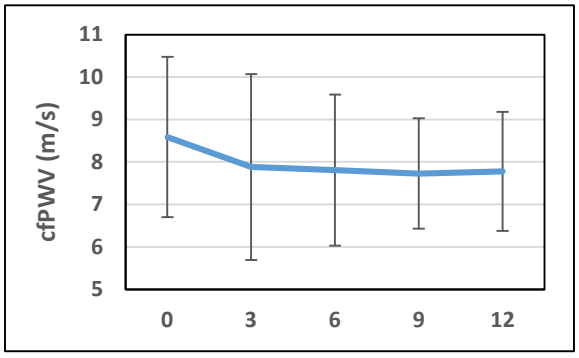


5. Changes in SBP over 12 months.

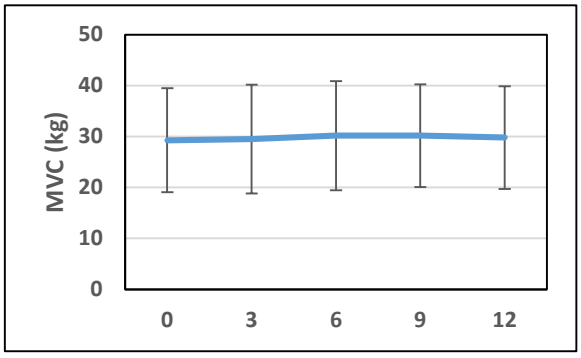


6. Changes in DBP over 12 months.

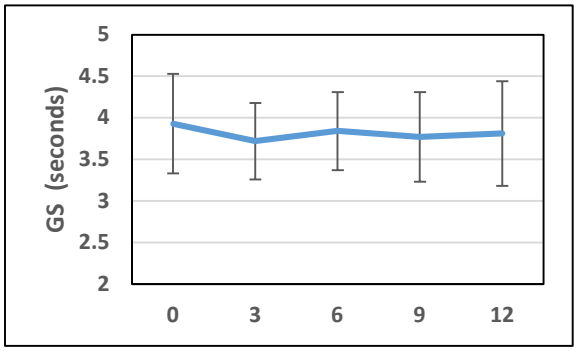
Figure's 7-10. Changes in CV risk factors over 12 months.



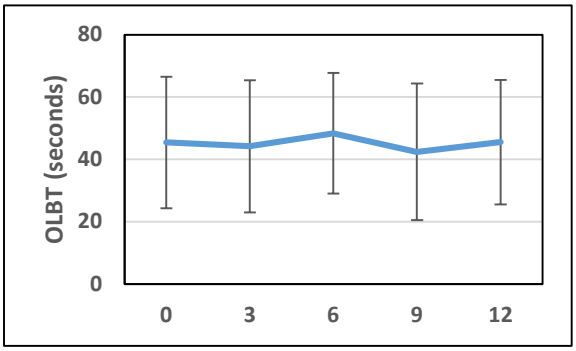
7. Changes in cfPWV over 12 months.



8. Changes in MVC over 12 months



9. Changes in GS over 12 months.



10. Changes in OLBT over 12 months.

DISCUSSION

The main purpose of this study was to evaluate the relationship between cardiovascular biomarkers and obesity in physically active normal and prediabetic participants who completed 12 months of the DPP. As previously stated, the obesity paradox is a phenomenon in which individuals who are classified as obese may have a protective survival benefit when diagnosed with cardiovascular or peripheral artery disease (Lavie et al. 2009). All 20 of our subjects were alive at the end of the study, making it difficult to compare cardiovascular risk factors to the rate of survival.

However, there were differences between healthy, overweight, and obese individuals that are worthy of conversation including differences in both starting values and the rate of change from 0-to-12 months. Of the 20 subjects that completed the study, 4 were classified as normal weight, 7 were overweight, and 9 were obese. After subjects were divided into groups based on their BMI, there was variability in pre-testing values for some cardiovascular risk factors. When looking at HbA1c, the normal weight, overweight, and obese groups each started with a mean value of 5.40, 5.47, and 5.45, respectively. Furthermore, the normal weight group actually increased their HbA1c by 3.3% from 0-to-12 months, whereas the overweight and obese groups experienced a decrease of 0.5% and 2.2%, respectively. Part of this paradoxical shift in HbA1c could be due to the fact that overweight and obese individuals have more weight to lose, or that they may have a greater exercise capacity due to a greater amount of muscle mass, which is required to move their larger body mass (Abramowitz et al. 2018). Furthermore, the cause-effect relationship between prediabetes and mortality in patients with CVD seen in previous studies is why delaying the progression to T2D was a primary goal of this study

(Zand et al 2018). Previous studies have also found that adults with CVD who were classified as normal weight at the diagnosis of T2D had a significantly higher mortality risk compared to those who are obese, further displaying the need to delay the progression of prediabetes (Thomas et al. 2013). Despite only experiencing an improvement of between 0.5% and 2.2%, it is encouraging to know that this study may have been an important factor in slowing the overweight and obese subjects' progression to T2D.

When examining differences in weight between groups, the pre-screening values of the normal weight group were lowest at 62 kg, followed by the overweight and obese groups at 83 kg and 91 kg. The normal weight group only increased slightly by 0.74% from pre-to-post, whereas the overweight and obese groups both decreased by 7.3% and 7.0%, respectively. However, the obese group experienced a significant decrease in weight at 3, 6, and 9 months of 4.7%, 8.2% and 8.1%, respectively. Although the normal weight group did not experience a notable change in body weight, it is important to note that the overweight and obese groups had more weight to lose, and may have presented with greater amounts of lean muscle mass prior to beginning the study, possibly explaining the difference in weight loss between groups. This study did not obtain measurements of body composition, which would have been helpful in comparing levels of lean mass and fat mass to determine if overweight and obese subjects actually had greater amount of lean mass. Due to this limitation, WC was used to estimate the changes in fat distribution experienced by the subjects.

Despite all three groups experiencing a decrease in WC from pre-to-post, specific values varied among different BMI groups. Following analysis of specific pre-to-post

values, the normal weight, overweight, and obese groups experienced a decrease of 3.2 cm, 4.7 cm, and 12.2 cm, respectively. These values may prove to be an important predictor of the mortality rates between groups, as previous studies have shown that a 5 cm increase in WC was associated with a 17% increase in mortality risk in men and a 13% increase in women (Kim et al. 2019). This means that our overweight subjects, who experienced a near 5 cm decrease, may have decreased their mortality rate by up to 17%. Our obese subjects experienced a greater than 10 cm decrease and may have decreased their mortality risk by over 34%, based on research from Kim and colleagues (2019). This pattern of greater change in the overweight and obese groups compared to the normal weight group may be due to the same reasons listed above, such as having more weight to lose or displaying greater amounts of lean mass. However, given the fact that fat located around the waist has been shown to increase mortality by up to 25% in men and women with CVD, these results may serve to increase lifespan in those attempting to decrease their level of central adiposity (Koster et al. 2008). Central adiposity is also associated with an increased metabolic disease risk, regardless of BMI (Shah et al. 2014). Knowing this, the beneficial changes in WC experienced by each group may help to promote the effectiveness of an approved lifestyle modification program in reducing mortality in prediabetic individuals.

Overall, the hemodynamics of each group followed a similar pattern as the weight and WC, with the overweight and obese groups experiencing a more beneficial change in both SBP and cfPWV, while also beginning the study at a higher value. However, the overweight group presented with a lower SBP of over 12 mm Hg when compared to the normal weight group, despite only experiencing a decrease from pre-to-post of 2 mm Hg.

Regardless of the differences in starting values, the obese group experienced the greatest improvement from pre-to-post in SBP of 5.3%, which decreased the average SBP from 148 mm Hg to 140 mm Hg, also known as the minimum criteria for a diagnosis of hypertension. Previous research has also shown that primary preventative blood pressure lowering is associated with reduced risk for death and CVD if the baseline SBP is 140 mm Hg or higher, which was true for obese subjects in this study (Brunström & Carlberg, 2018). Given that previous studies have shown a significant reduction in CVD and coronary artery disease risk following a 10 mm Hg improvement in SBP, the 8 mm Hg improvement in our obese subjects may show similar results in the future (Bundy et al. 2017).

Also of interest in this study was cfPWV, which is an independent predictor of cardiovascular morbidity and mortality in patients with CVD (Nordstrand et al. 2011). For this reason, improvements in cfPWV may not only decrease mortality risk, but may lead to a further improvement in blood pressure regulation due to its positive effects on elastic compliance of the arteries (Lentferink et al 2019). Fortunately, our overweight and obese groups were able to improve their cfPWV from pre-to-post by 8.2% and 15.0%, respectively. These findings may be significant for our obese and overweight subjects, as studies have shown that decreasing aortic stiffness (as measured by cfPWV) could be used as a therapeutic target to improve prognosis (Vlachopoulos et al. 2019). Other studies have also shown that a cfPWV measurement is the type of arterial stiffness measurement that is most robustly associated with CVD, especially with heart failure (Kim et al. 2019). While cfPWV improvements in both the obese and overweight groups follows the pattern seen with other cardiovascular risk factors, the obese group

experienced a change from pre-to-post that was significantly greater than any other risk factor. However, due to the pre-to-post changes in PWV being insignificant, more research is needed to measure PWV in prediabetic individuals to support its validity as a marker of health.

Physical performance tests including MVC, GS, and OLBT were compared to changes in cardiovascular risk factors. Although the improvements in MVC, GS, and OLBT may have been insignificant, they are still worthy of discussion. Previous studies have shown that each of these three factors were significant predictors of all-cause and cardiovascular mortality, thus, even the minor improvements our subjects experienced may have reduced their mortality risk (Nofuji et al. 2016). Despite seeing improvements in all three physical performance measures throughout all five screenings, the greatest improvement was seen in GS from pre-to-post. Research suggests that decreases in GS may be associated with a decrease in thigh muscle area (Beavers et al. 2013). Studies have also suggested that differences in muscle mass between weight groups may help to explain the obesity paradox, which was one goal of this study (Abramowitz et al. 2018). Results from our study support this idea, as the obese weight group displayed greater GS than the overweight group at baseline and at 12 months, although the normal weight group was faster at baseline and following completion of the study. Using this knowledge, our data suggests an obesity paradox may be present in our obese subjects, possibly due to a greater amount of muscle mass. The amount of muscle mass present has been shown to be positively correlated to both MVC and the hemodynamic responses to an MVC test, which may help to explain the average improvement our subjects experienced from pre-to-post (Soares et al. 2019). The OLBT may have also been

influenced by fluctuations in muscle mass, as studies have displayed a positive correlation between muscle mass and balance in elderly subjects (Gouveia et al. 2019). Research has also shown that a higher physical activity level was associated with better static balance and muscular endurance, possibly providing support for the exercise-related benefits of the DPP (Lohne-Seiler et al. 2016). Unfortunately, measures of muscle mass were not taken, thus, more research that accurately measures amounts of muscle mass in its subjects is needed.

Despite the advantage of using 12 months of data, there were some limitations that possibly affected the outcome of this study. Inter rater reliability was slightly inconsistent when measuring WC, and this measurement was performed by a different undergraduate students recruited for research assistance. Each student was taught the proper method of measuring WC, but the primary researchers of the study were unable to monitor every measurement due to shifting their attention to more technical aspects of data collection. Another limitation may be the timing of the study, which started in December of 2018 and ended in December of 2019. Although this prospective cohort study helped to gather data points spread across greater amounts of time, researchers did not require subjects to complete a diet-log to track overall caloric consumption. Total physical activity minutes were self-reported at each of the 25 education sessions but detailed physical activity logs were not required. Both of these detailed logs would have be beneficial to compare with changes noted in cardiovascular risk factors. A larger sample size with the implementation of a control group would have beneficial when comparing changes from pre-to-post.

There were some strengths that should be discussed, including the 12-month time-frame and constant face-to-face contact between researchers and subjects. Between the pre-screening and 6 month screening, subjects were instructed to meet with researchers on a weekly basis in order to attend educational classes on lifestyle modification techniques, dietary advice, and information on the benefits of exercise. This was reflected in the changes from 0-to-6 months, as the most significant change in most risk factors was seen in that time-frame. The level of improvement experienced from 0-to-6 months did not continue to the 12-month screening, which may be explained by the reduced frequency of meetings between researchers and subjects. Meetings did continue every two to three weeks throughout the remainder of the study, which possibly helped to prevent a rebound effect in specific risk factor values. Given the correlation between face-to-face guidance and improvements in all risk factors, this study promotes the use of a guided lifestyle modification program to decrease cardiovascular risk factors.

Based on the results of our study, we support the use of a 12-month DPP in reducing cardiovascular disease risk in prediabetic individuals. Conclusions on the obesity paradox were inconclusive, as all 20 subjects were alive at the end of the study. However, overweight and obese subjects displayed a pattern of greater improvements in WC, SBP, DBP, and PWV cardiovascular risk factors when compared to normal weight individuals.

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APPENDIX A

SCREENING INFORMATION SHEET

University of Wisconsin - La Crosse
Diabetes Prevention Program
Screening Information

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

Have you been fasting for 12 hours? Yes No (Circle One)
Did you take your medications today? Yes No (Circle One)
Have you consumed caffeine in the past 12 hours? Yes No (Circle One)

Height: _____ inches Weight: _____ lbs

Waist Circ. _____ cm Hip Circ. _____ cm

Total Cholesterol: _____ mg/dl LDL Cholesterol: _____ mg/dl

HDL Cholesterol: _____ mg/dl Triglycerides: _____ mg/dl

Risk Ratio= Total Cholesterol/ HDL cholesterol= _____ <5:1 Keep Below
<3:5:1 optimal

Glucose: _____ mg/dl HbA1c: _____

BIA:

Resistance: _____ 5 Meter Walk Time: _____ _____

Reactance: _____ _____

Impedance: _____

Phase Angle: _____ One Leg Balance: _____ _____

_____

Blood Pressure: _____ mm/Hg

MVC: _____ kg _____ kg _____ kg

APPENDIX B

INFORMED CONSENT

1. **INFORMED CONSENT FOR "Effects of a diabetes prevention program on glycemic control, body composition, and vascular function"**

Principal Investigator: **Salvador Jaime, PhD**
UW-La Crosse
142 Mitchell Hall
La Crosse, WI 54601
(608)785-6518

2. I, _____, give my informed consent to participate in this study designed to evaluate the effect of a standardized diabetes prevention recognition program on vascular function, body composition, and physical performance. I have been informed that the study is under the overall direction of Salvador Jaime, Ph.D. who is an Assistant Professor in the Department of Exercise and Sport Science at the University of Wisconsin-La Crosse. I consent to the presentation, publication and other release of summary data from the study which is not individually identifiable.

3. I have been informed that my participation in this study will require 5 total visits to the human performance laboratory (Mitchell 225). Each visit to the lab requires fasting for at least 12 hours (food, alcohol, and caffeine), no strenuous exercise for at least 48 hours, and no morning medication (I will bring to the lab for consumption following the tests). The following measures will be taken at 0, 3, 6, 9, and 12 months:

    a. A finger stick blood draw to evaluate my fasting glucose or HbA1c and lipid levels.

    b. Bioelectrical impedance analysis which involves a small current sent through my body

    c. Laying on my back while there is a pencil-like pressure-sensor on my neck and upper thigh. Following that, the researcher will place a cuff around my upper thigh and arm, both of which will inflate and deflate occasionally.

    d. After the resting measures, a researcher will lower my hand or foot into an ice-bath for 3 minutes while the cuffs mentioned previously will inflate and deflate

    e. Lastly, after sufficient time to rest I will perform the following physical performance measures:
        i. Walking speed – Walk at my usual speed along a straight 11-meter path on a flat floor. ii. Grip strength – The maximal strength of my dominant hand will be measured twice.

iii. Static balance – I will stand on my preferred leg with my eyes open and hands placed on my sides. I will focus on a dot placed directly in-front me during this test. The amount of time I can balance will be measured twice.

4. I have been informed that there are no foreseeable risks associated with this study other than the pain associated with the cold exposure, fatigue associated with grip strength and static balance tests, and the discomfort associated with providing the fingertip blood samples.

5. I have been informed that there are important benefits to myself such as learning about my overall health and how to best prevent type II diabetes mellitus.

6. I have been informed that the investigator will answer questions regarding the procedures throughout the course of the study.

7. I have been informed that I am free to decline to participate or to withdraw from the study at any time without penalty.

8. Concerns about any aspects of this study may be referred to Dr. Salvador Jaime at (608)785-6518. Questions about the protection of human subjects may be addressed to the Chair of the UW-L Institutional Review Board 608 785 6892.

_____ _____

Signature of Participant Date

_____

Printed Name of Participant

_____ _____

Signature of Witness Date

APPENDIX C

PREDIABETES RISK TEST

DO YOU HAVE PREDIABETES?

Prediabetes Risk Test

1 **How old are you?**

Less than 40 years (0 points)
40—49 years (1 point)
50—59 years (2 points)
60 years or older (3 points)

Write your score in the box.

2 **Are you a man or a woman?**

Man (1 point) Woman (0 points)

3 **If you are a woman, have you ever been diagnosed with gestational diabetes?**

Yes (1 point) No (0 points)

4 **Do you have a mother, father, sister, or brother with diabetes?**

Yes (1 point) No (0 points)

5 **Have you ever been diagnosed with high blood pressure?**

Yes (1 point) No (0 points)

6 **Are you physically active?**

Yes (0 points) No (1 point)

7 **What is your weight status? (see chart at right)**

Height	Weight (lbs.)		
4'10"	119-142	143-190	191+
4'11"	124-147	148-197	198+
5'0"	128-152	153-203	204+
5'1"	132-157	158-210	211+
5'2"	136-163	164-217	218+
5'3"	141-168	169-224	225+
5'4"	145-173	174-231	232+
5'5"	150-179	180-239	240+
5'6"	155-185	186-246	247+
5'7"	159-190	191-254	255+
5'8"	164-196	197-261	262+
5'9"	169-202	203-269	270+
5'10"	174-208	209-277	278+
5'11"	179-214	215-285	286+
6'0"	184-220	221-293	294+
6'1"	189-226	227-301	302+
6'2"	194-232	233-310	311+
6'3"	200-239	240-318	319+
6'4"	205-245	246-327	328+
	(1 Point)	(2 Points)	(3 Points)
	You weigh less than the amount in the left column (0 points)		

Add up your score.

If you scored 5 or higher:

You're likely to have prediabetes and are at high risk for type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes (a condition that precedes type 2 diabetes in which blood glucose levels are higher than normal). Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanic/Latinos, American Indians, Asian Americans and Pacific Islanders.

Higher body weights increase diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weights than the rest of the general public (about 15 pounds lower).

LOWER YOUR RISK

Here's the good news: it is possible with small steps to reverse prediabetes - and these measures can help you live a longer and healthier life.

If you are at high risk, the best thing to do is contact your doctor to see if additional testing is needed.

Visit DoIHavePrediabetes.org for more information on how to make small lifestyle changes to help lower your risk.

For more information, visit us at

DoIHavePrediabetes.org

Ad Council · American Diabetes Association. · AMA

APPENDIX D

REVIEW OF LITERATURE

REVIEW OF LITERATURE

This review of literature will evaluate and discuss how the obesity paradox effects cardiovascular disease (CVD) biomarkers in physically active prediabetic subjects who completed 12 months of the Diabetes Prevention Program (DPP). The DPP is an effective 12-month lifestyle intervention program that has been found to improve multiple CVD risk factors and prevent or delay a diagnosis of Type 2 diabetes (T2D). Risk factors including measurements of hemoglobin A1c (HbA1C), systolic blood pressure (SBP), diastolic blood pressure (DBP) waist circumference (WC), body mass index (BMI), and various physical performance measures will be discussed. Pulse wave velocity (PWV) will also be discussed in order to evaluate arterial stiffness in physically active prediabetic individuals who meet the classification for the obesity paradox. The goal of this study will be to further explain why obese and overweight individuals experience a more positive prognosis than their leaner counterparts with the same condition (Lavie et al. 2009).

Introduction

The prevalence of obesity has increased exponentially over the last 30 years, with evidence that rates of overweight or obese adults in the U.S. could reach up to 85% (Wang et al. 2008). Obesity significantly increases the risk of chronic disease morbidities including depression, T2D, cardiovascular disease, and certain cancers (Hruby, A. and Hu, F. 2014).

Recent evidence suggests that obesity is associated with greater morbidity than smoking, alcoholism, and poverty, and may soon surpass cigarette usage as the leading

cause of preventable death in the U.S. (Lavie et al, 2009). Despite pairing these comorbidities with the effects of obesity on a multitude of CVD risk factors, evidence suggests an obesity paradox may be present, stating that overweight and obese patients with established CVD, including hypertension (HTN), heart failure (HF), coronary heart disease (CHD), and peripheral artery disease (PAD) often have a better prognosis when compared to leaner individuals with the same condition (Lavie et al. 2009). BMI is used as a method to determine the classification of obesity by dividing an individual's body weight (kg) by their height (m^2) to classify them into weight categories (underweight <18.5, normal weight =18.5-24.9, overweight = 25 – 29.9, or obese ≥30). One limiting factor in using the BMI calculation is the inability to differentiate between lean and fat mass, which may incorrectly classify individuals with greater amounts of lean mass into a higher weight category (Rothman, 2008).

Also associated with obesity is an increase in arterial stiffness, which is a physiological process where the arteries reduce elastic compliance as a result of aging and can be measured by PWV (Lentferink et al. 2019). As we age, there is an increased amount of collagen in the arterial walls that stiffens the artery, creating an increase in blood pressure during systole and a decrease in diastole due to the early return of the reflected pressure wave impairing coronary blood flow (Metsamarttila et al. 2018). An earlier pressure wave return indicates an increased PWV and also displays a greater amount of stiffness in the artery (Metsamarttila et al. 2018). Recent research has shown that PWV was significantly higher in obese adolescents when compared to their normal weight counterparts (Lentferink et al. 2019). This was further supported by Zebekakis and colleagues (2005) who found that obesity is associated with increased arterial

stiffness from adolescence until old age. Along with being associated with an increased risk of CVD, arterial stiffness measured by carotid-femoral pulse-wave velocity (cfPWV) is an independent predictor of cardiovascular morbidity and mortality (Nordstrand et al. 2011). This was supported by Desamericq (2014) and colleagues who found that cfPWV was significantly higher in patients with CVD risk factors when compared to those without the same risk factors. However, research has shown that an aerobic exercise program of at least 3 months in duration can improve arterial stiffness in patients with impaired renal function (Mustata et al. 2004).

Of all the multiple risks associated with obesity, hypertension and diabetes are two of the most commonly experienced comorbidities (Jiang et al. 2016). Chronic hypertension damages the tissues inside the arteries, allowing LDL to form plaque along the tears in each wall, which further raises blood pressure in a harmful cycle that can lead to a myocardial infarction or stroke if left untreated (Mancia et al. 2001). Other complications of hypertension include heart failure, peripheral vascular disease, renal impairment, hemorrhage, and visual impairment (Singh et al. 2017). These complications of hypertension account for around 12.8% of all deaths worldwide, demonstrating a greater need for effective methods of blood pressure reduction (Singh et al. 2017).

Diabetes, a metabolic condition that is characterized by an elevated blood glucose level due to insulin resistance or lack of insulin production, increases ones risk of CVD, neuropathy, and certain cancers (Wu et al. 2014). The global cost associated with diagnosed diabetes, undiagnosed diabetes, gestational diabetes, and prediabetes exceeded $244 billion in excess medical costs in 2012 (Dall et al. 2014). The prevalence of T2D is projected to grow substantially in the coming decades due to population growth, aging,

and increasing racial and ethnic diversity, which is largely associated with the economic burden (Dall et al. 2014). As these risks and the burden of excess costs continue to rise, there is an increased need to understand prediabetes and effective methods to delay or prevent the progression to T2D.

Although prediabetes is commonly an asymptomatic condition, it always precedes the onset of T2D (Bansal, N. 2015). An estimated 84.1 million adults had prediabetes in 2015, which increased dramatically from 57 million in 2007. Of equal or greater concern is that only 11.6% of those with prediabetes were aware of their diagnosis (Galaviz et al. 2015). The diagnosis of prediabetes is based on the presence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and/or elevated HbA1c levels ranging between 5.7% and 6.4%. Although IFG and IGT tests are more sensitive to changes in blood glucose, the American Diabetes Association and World Health Organization has proposed the measurement of HbA1c as a diagnostic tool for the detection of T2D partly due to the convenience of not being affected by a fasting or timed sample. A HbA1c test is a common and reliable method used to identify glucose regulation, by analyzing the percentage of hemoglobin in the blood that is coated with glucose over the past three months (the average lifespan of a red blood cell (Sherwani et al. 2016).

Prediabetes is considered a reversible condition that significantly increases an individual's risk for developing T2D (Tuso, P. 2014). Prediabetes has been shown to have a cause-effect relationship with CVD and is associated with an increased risk of coronary heart disease, stroke, and all-cause mortality (Zand et al. 2018). If left untreated, 37% of individuals with prediabetes may develop T2D within 4 years, placing them at a greater risk of developing life-threatening conditions such as vascular diseases and

diabetic neuropathy (Tuso, P. 2014). Despite intensive lifestyle interventions, patients who remain prediabetic are at a higher-risk for developing T2D (Perreault, et al. 2012). The current study will focus on participants who meet the prediabetic criteria, based on the CDC Diabetes Prevention Program guidelines, as there is a strong relationship between prediabetes and progressing to a diagnosis of T2D in the future. (Bansal N. 2015). Reducing or preventing the progression from prediabetes to T2D will be an important part of lowering the prevalence of T2D and the economic costs that are associated with it.

One method of slowing this progression is through exercise, which has been recognized as an effective method to prevent or delay the onset of T2D (Bushman, B. 2014). Bushman (2014) has also shown that individuals who engage in at least 2 days of muscle strengthening activity per week were 29% less likely to have an impaired fasting glucose (which can also be used to diagnose prediabetes) compared to those who did not engage in strength training. Similar results demonstrated that moderate-intensity physical activities, such as brisk walking, have been found to significantly reduce the risk of developing T2D (Jeon et al. 2007). Furthermore, when compared to a sedentary population, muscle-strengthening and muscle-conditioning exercises including resistance training and yoga were shown to improve T2D risk in those who incorporated these activities for a minimum of 60 minutes per week along with aerobic exercise (Grontved et al. 2014). Unfortunately, there is a limited amount of evidence in the current literature on the effects of exercise in a prediabetic and sedentary population. One meta-analysis however found a reduction in the progression of prediabetes to T2D for both intensive lifestyle therapy and drug treatments, although the intensive lifestyle therapy proved to be

more beneficial (Hopper et al. 2011). The original DPP clinical trial compared the effects of metformin or a lifestyle intervention program (healthy, low-calorie, low-fat diet and moderate-intensity physical activity for at least 150 $min \cdot wk^{-1}$) to a placebo group in reducing the incidence of T2D. While researchers found that the metformin group reduced the incidence of T2D by 31% compared to placebo, the lifestyle intervention showed a 27% greater reduction than the metformin group (Knowler et al. 2002). Future research that compares rates of T2D in sedentary prediabetics to those of active prediabetics is necessary to further support the use of a lifestyle intervention program in reducing the progression of prediabetes to T2D.

Obesity Paradox

The obesity paradox is a controversial medical condition where individuals who are classified as obese have some type of protective survival benefit when diagnosed with cardiovascular or peripheral vascular disease. One proposed explanation of the obesity paradox is related to fat distribution, as evidence shows that individuals with excess visceral fat do not present with healthy metabolic indices, despite having a normal BMI (Lee et al. 2007). Arterial stiffness may also be overlooked when comparing rates of obesity and mortality as shown by Miyano et al. (2010) who found that older adults with a higher PWV had higher proportions of total deaths, including deaths due to CVD. Visceral obesity and arterial stiffness were also significantly associated with sarcopenia (loss of muscle mass and strength that occurs with aging) which predisposes individuals to the onset of disability, frailty, loss of independence, and an inability to engage in activities of daily living (Cruz-Jentoft et al. 2019). Furthermore, sarcopenia in older adults with T2D has shown that differences in thigh muscle size account for the majority

of effect of normal weight on mortality (Murphy et al. 2014). Lower amounts of muscle mass can impair an individual's ability to participate in exercise, which is often an essential component of a successful lifestyle intervention.

Although this research may help to explain some of the mechanisms behind the obesity paradox, evidence has shown that the relationship between obesity and mortality is not always linear. When looking at the association of bodyweight with total mortality and cardiovascular events in coronary artery disease, Romero-Corral and colleagues (2006) found patients with a lower body weight had an increased risk, overweight patients had a non-significant lower risk, obese patients had no increased risk, and severely obese patients had a significantly higher risk. Study design may also decrease the significance of these results, specifically due to the mean age within each group. Compared to normal weight patients with hypertension and coronary artery disease, overweight and class I to III obese patients were younger and were less likely to be a current smoker or have a history of cancer, previous myocardial infarction, stroke, or peripheral artery disease (Uretsky et al. 2007).

Carbone et al. (2019) recognized that a coexistence of HF/CHD and obesity produced a more favorable prognosis in Class I obese patients, when compared to individuals who were a normal body weight or were classified as underweight. This contradicts their statement that excess adipose tissue produces pro-inflammatory cytokines, which can cause cardiac dysfunction and promote atherosclerosis. One explanation may be the higher amounts of lean mass (LM) that obese patients present when compared to leaner individuals. Lean mass is more metabolically active than adipose tissue, meaning that at rest, those with higher amounts of lean mass will be able

to burn more fat. Vascular Health and Risk Management defines obesity as having excess fat mass that impairs health, which is commonly defined by BMI (Pomeroy et al. 2018). Although BMI is generally a reliable health marker when looking at the general population, its biggest flaw is the lack of attention to LM vs. fat mass (FM) distribution. Over 39% of the U.S. population is defined as being obese through BMI criteria, while only 7.7% meet the criteria for severe obesity, or class 3. The majority of the obese population in the U.S. are below the morbidly obese category, which means a higher percentage of lean mass may be playing a factor in their survival. Of these obese individuals, sedentary persons tend to maintain lower levels of lean mass compared to their active counterparts, which can severely impair exercise capacity and is correlated with the development of skeletal muscle insulin resistance. (Cartee et al. 2016).

The American College of Sports Medicine (ACSM) suggests that WC alone may be used as an indicator of obesity-related health risk. Although WC is not part of the BMI criteria, a high WC has been shown to increase mortality risk by up to 25% in 154,776 men and 90,757 women (Koster et al. 2008). The researchers also stated that fat distribution may be more important than total body fat, in regards to mortality risk. The type of fat also plays an important role, as increased visceral or abdominal fat is positively associated with metabolic disease risk, independent of overall adiposity (Elagazi et al. 2018). Unfortunately, the combined effects of WC and BMI on mortality needs further study and analysis to state that a strong relationship exists (Elagizi et al. 2018).

Although physical performance measures including maximal voluntary contraction (MVC), gait speed (GS) and one-leg balance test (OLBT) are also unrelated

to BMI, they are predictive of future adverse health outcomes and increase their prognostic value when combined (Nofuji et al. 2016). Studies have shown that grip strength measured as MVC was significantly associated with a higher risk of all-cause mortality (Bae et al. 2019). Strength may also play an important role in GS, as decreases in thigh muscle mass area have been show to predict a decline in GS (Beavers et al. 2013). The magnitude of these risks increases in prediabetics and diabetics, as studies have displayed an association between poor lower extremity function and prediabetes and T2D (Zhang et al. 2014), as well as an association between grip strength and prediabetes (Mainous et al. 2016). However, research in diabetic individuals has shown that exercise, specifically resistance training, can significantly improve quality in those suffering from sarcopenia and muscle weakness (Strasser and Pesta, 2013).

While an obesity paradox has been found in previous studies, higher levels of cardiorespiratory fitness (CRF) have been associated with a better prognosis in all populations of CHD and CV patients, which often reduces the effect of an obesity paradox (Schutter et al. 2014). Thus, an improved level of CRF may be more important than lowering BMI or FM in patients with CHD and CVD (Schutter et al. 2014). Increases in CRF can be achieved through structured exercise, such as the DPP, which involves consistent exercise of multiple modalities. Furthermore, The National Institute of Diabetes and Digestive and Kidney Diseases states that people at risk for developing diabetes can prevent or delay the onset of diabetes by losing a modest amount of weight through diet and exercise (Knowler et al. 2009).

Blood Pressure

A SBP reading of ≥120 mm Hg and a diastolic reading of ≥80 mmHg are the current benchmarks for the diagnosis of elevated blood pressure, also known as pre-hypertension. Prehypertension is a precursor to hypertension and is associated with an increased incidence of CVD and an increased risk of cardiovascular mortality compared to normotensive patients (Zhang, W. & Li, N. 2011). Stage 1 hypertension is diagnosed with a systolic reading of ≥130 mm Hg and a diastolic reading of ≥80 mm Hg (Volpe, M. 2005). During 2015-2016, 29% of adults in the U.S. were hypertensive, while over 63% of people aged 60 and over were also hypertensive (Fryer et al. 2017). Due to this age-related increase in blood pressure, our study will focus on reducing both SBP and DBP to normotensive levels.

The National Institute of Health analyzed data from the Framingham study to determine the extent to which diabetic cardiovascular events were caused by hypertension. Of the 1,145 Framingham subjects who were newly diagnosed with diabetes, 58% had hypertension at the time diabetes was diagnosed. According to Chen et al., participants with hypertension at the time of a diabetes diagnosis, exhibited higher all-cause mortality rates and cardiovascular events compared to normotensive subjects. Hypertension was associated with a 72% increase in the risk of all-cause death, and a 57% increase in the risk of any cardiovascular event in individuals with diabetes. While this study does show a relationship between diabetes with hypertension and higher mortality rates, hypertension alone is a deadly CVD risk factor. The ACSM states that hypertension is the most common, costly, but modifiable risk factor for the development of CVD and premature mortality. The ACSM recommends both regular aerobic and

resistance training exercise to lower one's chances of developing CVD, regardless of their diabetic status (Zaleski, 2019).

To determine the effects of exercise on both SBP and DBP in T2D, Dobrosielski et al. examined 140 hypertensive diabetic participants throughout a structured exercise program lasting 26 weeks. Following ACSM guidelines, exercisers attended three sessions per week which included both a resistance and an aerobic component. The aerobic exercise lasted 45 minutes at a target heart rate of 60-90% HRmax, while the resistance component consisted of 2 sets of seven exercises at 10 to 15 repetitions per exercise at 50% of 1-repetition maximum. At the conclusion of the 26-week program, there were no significant differences in either SBP or DBP. One downfall of this study was the lack of dietetic counseling or education on the benefits of physical activity. A future study combining the effects of exercise and proper nutrition counseling may show a greater effect on hypertensive patients with elevated blood glucose levels.

A study by Junior et al. (2018) investigated the effects of a 6-month multicomponent exercise program (MCEP) on functional, cognitive, and hemodynamic parameters of older adults with T2D, while also having an age-matched healthy control group. The MCEP involved mobility, maximal walking speed, lower limb muscle strength, balance, transfer capacity, and executive function exercises. Each group performed the MCEP twice per week on nonconsecutive days, for a total duration of 26 weeks. Not only did the T2D group see a 6% greater decrease in DBP, they also experienced a 4.5% decrease in SBP, as opposed to a 0.1% increase in the control group. SBP is commonly prioritized over diastolic as a marker of health, meaning that a drop of any percentage may have a significant effect on reducing CVD risk. As such, the authors

of this study concluded that a 6-month MCEP may reduce blood pressure in T2D patients.

Although a study conducted by Tsai et al. was not performed on individuals with diabetes, it was able to display findings that may relate to clinicians who are working with diabetics in a clinical setting. Tsai et al. gathered 42 patients, 23 men and 19 women, with white coat hypertension and divided them into two groups, an exercise group and a control group. The control group was not prescribed any exercise, while the exercise group completed three aerobic exercises per week at 60-70% HRmax on a treadmill. Following the 12-week study, those in the exercise group saw a decrease in SBP greater than 10 mm Hg, while the control group saw a less than 3 mm Hg decrease. More research is warranted with diabetic populations as these participants were not diabetic, but our understanding of human physiology suggests an effect on healthy populations may also have beneficial effects on otherwise unhealthy patients.

A previously mentioned study by Mendes et al. (2017) looked at the effect of a long-term, community-based exercise program on glycemic control in older patients with T2D. Although the focus of this study was on glycemic control, participants in the exercise group experienced a significant decrease in SBP of over 11 mm Hg. This number was over three times greater than the decrease in SBP seen in the control group. This is great example of the multitude of benefits that can be seen from a community-based exercise program, especially when education and small dietary changes are made.

HbA1C

Many studies have utilized this simple, reliable, and highly-supported method to determine the effect of exercise on lowering blood glucose levels. One study found that a long-term, community-based, combined exercise program was effective at significantly improving glycemic control (Mendes, R., Sousa, N., Reis, V., Themudo-Barta, Jose, L. , 2017). Mendes et al. (2017) recruited diabetic patients from a local clinic who were assigned to either a control or an exercise program group. The exercise program involved the combination of aerobic, resistance, agility/balance, and flexibility exercises three days per week on non-consecutive days over nine months. Compared to the control group, the exercise group saw a greater decrease in HbA1c percentage by 0.32%. Although this seems small, the difference between being classified as healthy or diabetic is less than 1%. Furthermore, a study including over 100 physicians involved in diabetes care found that a 0.5% change in HbA1c was considered to be clinically relevant (Lenters-Westra et al. 2014). A similar finding was seen in another study, which assigned diabetic subjects to a 9-month exercise program with 12 motivational group meetings focused on physical activity. Compared to the control group, who only underwent usual PA recommendations, the exercise group saw a 0.3% greater decrease in their HbA1c (Galle, F., Di Onofrio, V., Miele, A,. Belfiore, P., Liguori, G., 2018). Both of these studies included community-based exercise groups, which may be an important factor in long-term adherence to structured exercise programs.

Determining which modality of exercise has the greatest effect on lowering HbA1c levels is still debatable. Aerobic and strength training exercise are two types of training that are often compared, especially in regard to diabetes management and

HbA1c. Pan et al. (2018) conducted a meta-analysis of over 37 different studies with 2208 patients diagnosed with T2D. Although there was an improvement in HbA1c in both the supervised aerobic and resistance training groups (0.30% lower, 0.30% lower, respectively), when compared to no exercise, a combination of resistance and aerobic exercise showed a greater decrease than aerobic and resistance training alone by 0.17% and 0.23%, respectively (Pan et al. 2018). More importantly, the supervised aerobic and resistance groups experienced a 0.3-0.6% and 0.2-0.6% greater decrease than the unsupervised group of the same exercise modality, respectively. (Pan et al. 2018). These differences between supervised and unsupervised exercise groups further support the use of a supervised program, such as the DPP, as a method to decrease HbA1c.

Bweir et al. (2009) found contrasting results in his study of 20 inactive subjects with T2D over 10 weeks. Participants were assigned to either an aerobic exercise group (consisting of 20-30 minutes of treadmill walking at 60-75% HRmax, three days per week) or a resistance training group (completed seven exercises of three sets using 8-10 repetitions, three days per week). Although the resistance training group began with a mean HbA1c of 8.9% compared to the aerobic exercise group at 8.7%, 40% of the resistance training group reached a target range of 7%, while none of the aerobic group experienced the same benefit (Bweir et al. 2009). Given that resistance exercise tends to recruit more type 2 muscle fibers, which are more glucose dependent, this could be one reason why the resistance training group saw greater improvements.

Diabetes Prevention Program

The initial DPP study assigned eligible participants to one of three groups: a lifestyle change group, a metformin group, or a placebo group. The lifestyle change group joined a DPP Lifestyle Change Program that provided intensive training, with the goal of losing 7% of their total body weight by eating less fat and fewer calories, along with accumulating a minimum of 150 minutes of exercise per week. Participants met with researchers individually at least 16 times throughout the initial 24 weeks of the program, and again every two months with a phone call between visits. The metformin group took 850 mg of metformin twice a day, and was provided with standard advice about diet and physical activity, while the placebo group only received general diet and physical activity advice (DPP, 2002). During a 10-year follow up, the DPP group showed a delay in the development of diabetes by 34%, as opposed to the metformin group which experienced an 18% delay (Knowler et al, 2009). This study supports the use of a structured intervention program as a method to decrease the progression of T2D when compared to medical intervention alone. Given that our study adheres to a strict, 12-month, CDC-approved intervention curriculum, we expect to see similar improvements in delaying the onset of T2D.

Summary

The purpose of this study was to evaluate how the obesity paradox effects CVD biomarkers in physically active prediabetec subjects who completed 12 months of the DPP. Cardiovascular disease risk factors were measured from pre to post including measurments of HbA1c, SBP and DBP, BMI, and WC. Pulse wave velocity was also measured to evaluate changes in arterial stiffness. Following the completion of data collection and statistical analysis, this study was presented as a Masters Thesis and defended in front of a committee. The goals of this study were to further support the use of a DPP in slowing the progression of pre-diabetes to T2D, attaining a healthier body weight, and preventing hypertension and CVD.

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