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Limb-Specific Comparison of Flow-Mediated Dilation in Abdominal Obese Pre-menopausal Women

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Abstract

Purpose Normal aging can lead to arterial wall stiffening and development of atherosclerosis; however, the effects of overweight conditions can expedite the dysfunction of arterial health. In an earlier study, we identified in a group of abdominal obese pre-menopausal woman that during menses, these women had decreased vascular conductance of the brachial artery during dynamic hand-grip exercise. Endothelial function in abdominal obese (AO) pre-menopausal women could be associated with being highly sedentary which attenuates dilatory responses to FMD of both upper and lower limb vascular function. We hypothesized that the AO women would exhibit limb-specific differences in artery dilation with reduced dilation in the popliteal artery as compared to the brachial artery.

Methods Artery dilatory responses in the brachial and popliteal arteries were assessed using flow-mediated dilation (FMD) in age-matched sedentary controls and AO groups during menses.

Results Significant differences were found between groups including % BF, BMI, weight, waist to hip ratio, fasting blood glucose, and oxLDL. A between-group comparison revealed significantly lower percent dilation of the popliteal artery in AO participants compared to controls ($p < 0.05$) not present in the brachial arteries. Our results also indicate a difference in the time-to-peak (TP) of dilation between the control (33.38 ± 3.232) and AO (62.104 ± 5.813) groups ($p < 0.01$). Following FMD correction with shear rate as the covariate, significant differences in FMD between the brachial and popliteal artery were abolished.

Conclusion We conclude that young, AO women show a limb-specific difference in dilation of the upper and lower extremities when compared to controls. Thus, reductions in FMD of the popliteal artery could be due to impaired dilation of the downstream resistance vasculature preventing increases in shear within the leg conduit arteries not as significantly in the arms.

Keywords Abdominal obese, Women, Flow-mediated dilation, Limb differences

1 Introduction

Overweight and obese physical stature have been associated with increased endothelial dysfunction and the development of cardiovascular disease [29, 35]. Cardiovascular diseases that can develop as a result include atherosclerosis, hypertension, and peripheral arterial disease (PAD), which has an increased deficit upon the vasculature of the lower extremities [8, 18]. The dilatory response of the upper limb brachial artery as compared to the lower limb popliteal artery has been found to be

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equal after a 5-min occlusion in healthy young women [19]. Previous studies of prolonged sitting in sedentary participants have also demonstrated significant deficits in lower limb vascular function [25, 26]. Decreased vascular activity associated with attenuated vasodilator nitric oxide (NO) causing vascular dysfunction has been indicated in both the arms and legs of aging post-menopausal women in addition to conduit artery sheer stress as measured Doppler ultrasound of resting, during exercise and FMD arterial measurements [19–21, 30]. Limb-specific differences have not been investigated among young abdominal obese pre-menopausal women who potentially have a greater risk for developing cardiovascular dysfunction like aging women. Atherosclerotic development within the arteries can additionally develop into the debilitating PAD, which causes a severe damaging effect on the dilatory response in the lower extremities [22].

In pre-menopausal women, estrogen provides a protective role in maintaining proper endothelial function [34]. Overweight and abdominal obese conditions are often linked to disturbances in the menstrual cycle. These menstrual disturbances could potentially lead to decreases in estrogen production and an increased level of androgens in young women who are overweight [23]. Decreased estrogen and potentially higher levels of androgens leave the vascular endothelium susceptible to dysfunction. Additional risk factors that arise from being overweight are analogous to those seen in aging populations, and specifically in conduit artery sheer stress post-menopausal women [30] and decreased vasodilatory function induced by exercise and FMD in obese post-menopausal women [7].

In a recent published study from our lab, we concluded that the overweight abdominal obese pre-menopausal women exhibit a lowered brachial conductance response to dynamic graded small muscle exercise during the menses phase of the menstrual cycle follicular phase. The attenuated vascular response was also resolved upon increases in estrogen during the menstrual proliferative phase [27]. There was a decreased menses estrogen concentration in the AO group potentially leading to elevated oxidative stress as estrogen may have elevated antioxidant effects at the cellular level, thus causing potential vascular dysfunction of the vascular endothelial and smooth muscle similarly seen as an elevated risk among aging post-menopausal women [14, 15, 30, 33].

The aim of this study is to determine potential limb-specific differences in the vascular response to FMD in abdominal obese pre-menopausal women, assessed by Doppler ultrasound. We hypothesized that AO women will show altered vascular function compared to healthy control group women due to increased vascular dysfunction. This endothelial dysfunction could potentially materialize in young AO women even prior to the development of metabolic syndrome and diabetes as identified in a previous study [6]. Thus, we additionally hypothesized that the popliteal artery would exhibit a greater deficit in endothelial function than the brachial artery in the AO population.

2 Methods

2.1 Participants

Twenty women (eleven controls and nine abdominal obese) aged 25 ± 1.29 years were examined in this study. All participants were volunteers and were non-smokers, sedentary (30 min of moderate exercise less than four times a week), and not on any form of birth control as determined by a physical examination form and a personal questionnaire. Participants were screened and separated into two groups based on physical characteristics: healthy sedentary control and sedentary abdominal obese (AO) (having at least two but not ≥ 3 criteria of the NCEP III categorization of the metabolic syndrome including a waist circumference > 96 cm) [9]. The timeline of the participation procedures is outlined in Fig. 1. On study days, participants refrained from exercise, caffeine, aspirin, or ibuprofen ingestion 12 h prior to arrival. All experimental procedures and protocols conformed to the Declaration of Helsinki, and the study was approved by the Human Subjects Committee Institutional Review Board at Eastern New Mexico University.

2.2 Visit 1

Classification of participants in the study groups was based on physical characteristics including body mass index (BMI), percent body fat, waist/hip ratio, resting blood pressure, fasted blood glucose, triglycerides, total cholesterol, and high density lipoproteins (HDL). Anthropometric measurements were taken at a physical screening visit with participants arriving fasted 8–10 h prior to arrival. BMI and percent body fat were measured through bio-impedance using an Omron Fat Loss Monitor (HBF-306C). Triglycerides, HDL and total cholesterol, and fasted blood glucose were measured from capillary blood sample obtained through finger prick (CardioCheck Portable Blood Test System, PTS Panels, for cholesterol; OneTouch Ultra 2 Blood Glucose Monitoring System for glucose measurement). During this visit, the participants were familiarized with the FMD study protocol.

Participants were excluded from continuation in the study if they were using birth control medication, classified as metabolic syndrome or diabetic, diagnosed with polycystic ovarian syndrome, hypertension, or a cardiovascular disease.

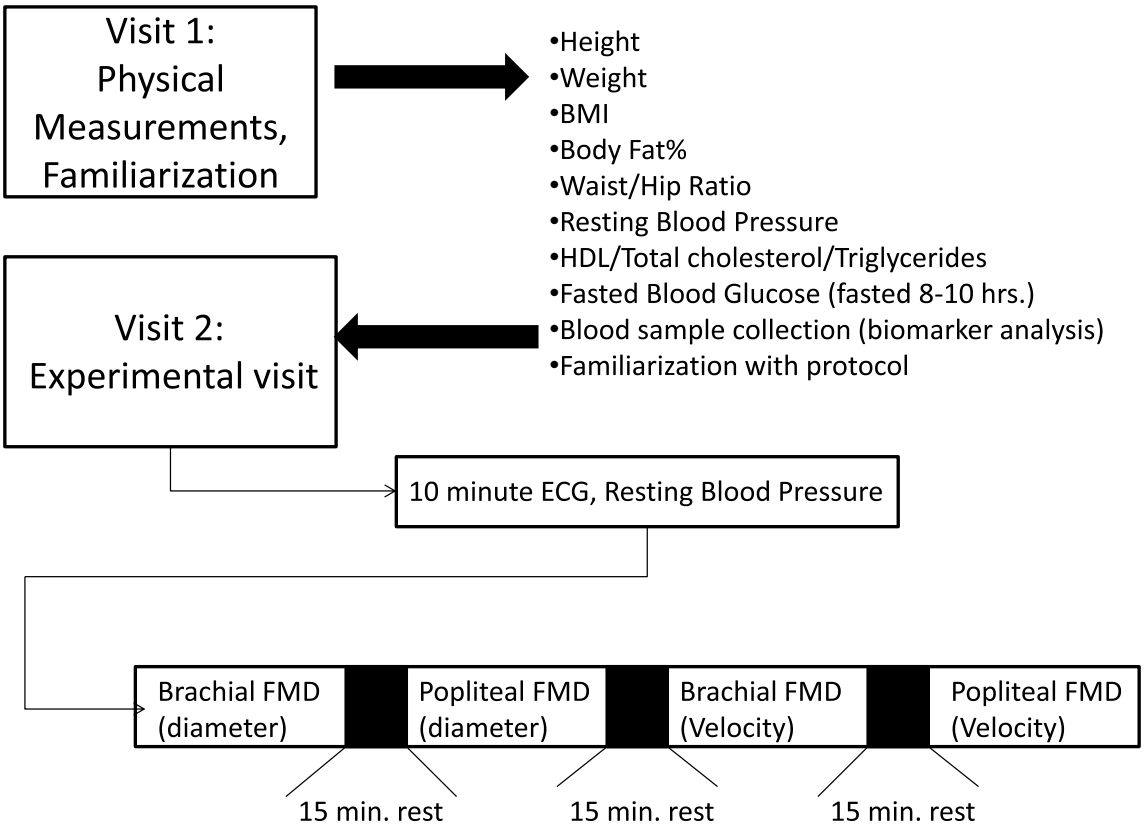

Fig. 1 Overall schematic of study protocol and individual visits of each participant

2.3 Visit 2

Upon arrival, the participants provided both plasma samples for baseline menses estrogen and progesterone and oxLDL quantification, respectively. Venous blood samples were taken from each participant and centrifuged for collection of plasma for biomarker analysis. Blood samples were collected in 10.8-mg EDTA-treated 6-mL vacutainers (BD, Franklin Lakes, NJ); plasma was stored in 3-mL microtubes kept at − 80 °C. Urine was analyzed using commercial pregnancy tests; a positive result was a requisite for exclusion.

Participants were situated in a supine position to record a resting ECG prior to testing. Three lead ECG was recorded for 10 min on a Biopac MP150 data acquisition unit using AcqKnowledge 4.4 data acquisition software (Biopac Systems Inc., Goleta, CA). Resting blood pressure was recorded after ECG using an Omron blood pressure monitor. The brachial artery of the left arm (non-dominant) was imaged with participants in the supine position and the arm extended away from the body at heart level. The popliteal artery of the left leg was imaged with participants in the prone position. Images were obtained using a linear array ultrasound probe operating at 6–12 MHz (GE Vivid E, California, USA). The probe was placed below the biceps brachii ~ 1–3 inches from the olecranon process as previously described by Parker et al. [19]. For imaging of the popliteal artery, the probe was placed behind the knee with the artery imaged just proximal to the bifurcation of the artery as previously described [19]. A blood pressure cuff was placed around the upper forearm distal to the olecranon process for testing of the brachial artery. For testing of the popliteal artery, the blood pressure cuff was placed on the upper gastrocnemius just below the knee. Resting conditions in the arteries were recorded for ~ 1 min prior to occlusion. In both cases, occlusion of the artery of interest was achieved by inflating the cuff to ~ 260 mmHg; this pressure was held for 5 min before release, and during reperfusion imaging continued for an additional 5 min. This test was conducted twice on each of the arteries of interest, once in 2D imaging mode for post-test image analysis of artery diameter and once in Doppler B-mode to record blood velocity during testing to calculate flow and correct the vascular response for shear rate. Doppler velocity measurements were obtained using ultrasound and were collected using the angle of insonation of < 60°. The intra-rater reliability for reproducibility of the Doppler ultrasound measurement was measured by

calculating the coefficient of variation on a control group ($n=10$) of participants and were recorded from a single operator. For measure of sheer rate, velocity was continuously recorded through Doppler B-mode and a custom-built interface audio transducer unit which processed the high-resolution, angle corrected, intensity-weighted Doppler audio information from the ultrasound system into a lower frequency velocity signal (0–20 Hz) [11] that could be sampled in real time by AcqKnowledge 4.4 data acquisition software. Post-processing analysis using yielded mean blood velocities for the 5 min of reperfusion. Each FMD was repeated alternatively between the limbs with 15-min rest between arteries and a minimum of 30-min rest period between occlusion and reperfusion on the same limb. Repeated measurements of FMD in the same limb have been shown to be reproducible in health patients at 10 and up to 30 min between occlusions when the baseline diameter is achieved with a coefficient of variation of 10% [2, 10, 24].

2.4 Artery Diameter and Blood Velocity Analysis

Diameter recordings of each artery of interest were recorded digitally and analyzed post-test using automated edge detection software (Brachial Analyzer, Medical Imaging Applications, Iowa City, Iowa). All measurements of diameter and velocity were completed by a single operator which was blinded to the categorization of the groups during analysis. Intra-rater reliability of the repeated measures by the Doppler ultrasound operator was calculated using a Pearson coefficient of repeated measures of diameter at rest and during peak dilation of the brachial artery. FMD was calculated as the percentage change in diameter during the post-occlusion cuff release peak dilation from the baseline resting state. Similar analysis was used on both brachial and popliteal measurements. Blood flow velocity recordings were analyzed by determining the average (AUC) velocities during rest and during the reperfusion where peak velocity can be found. Values were corrected for shear stimulus if no direct limb-specific difference was seen; shear rate was calculated as 4×mean velocity (cm/sec) /vessel diameter (cm) reported as standard protocol [16, 31]. Time to peak (sec) was calculated as the interval from the point of cuff deflation to the maximum artery diameter [6]. The rate of diameter dilation was determined by a ratio of (%FMD/time to peak).

2.5 Biomarker Analysis

Plasma samples from each participant obtained at visit 1 were used to measure oxidative stress in an oxidized LDL (oxLDL) assay performed according to kit instructions (Cell Biolabs, Inc., San Diego, CA). Two hundred µL of plasma was required from each sample. In addition, 11-keto-testosterone, 17-β-estradiol, and progesterone were also measured from the plasma samples collected from each participant using associated EIA kits (Caymen Chemical Company, Ann Arbor, MI).; absorbance was read at 412, 420, 450 nm, respectively.

2.6 Statistical Analysis

An unpaired t test was used to assess statistically significant differences between groups as well as between the vascular responses of the brachial and popliteal arteries. Values for FMD are presented as the percentage change and corrected for shear rate AUC. The percentage FMD was adjusted for shear rate AUC via ANCOVA to control statistically for the influence of shear stimulus on FMD response [1]. The ANOVAs were completed using SigmaStat software. All data were plotted using SigmaPlot (Sigma Plot version 12.4, Systat Inc., San Jose, CA), and ANCOVA tests were performed using SPSS software (version 22) to determine potential correlation significance accepted at $p \leq 0.05$. Paired t test was assessed on differences of vascular reactivity between arteries within participants. Linear regression analysis was performed to compare the correlation between oxLDL and Waist Circ to the measures of the reactive hyperemia of the FMD in both arteries. All data are expressed as means ± SD.

3 Results

3.1 Anthropometric Measurements

Comparison of the anthropometric data gathered from each group at visit 1 yielded a significant difference in the body composition between the sedentary control and abdominal obese participants. Physical measurements revealed the AO participants had significantly higher body fat percentages (BF%) and body mass indices (BMI) as well as significantly higher fasted blood glucose, weights, and waist to hip ratios (see Table 1). The AO women each had presented with two categories of the defined NCEP ATPII guidelines for metabolic syndrome.

3.2 Limb Comparison of FMD

All FMD data were collected during visit 2 for each participant. A between-group comparison yielded no significant differences in diameters of the brachial or popliteal arteries of control and AO subjects at rest. The intra-rater reliability of the Doppler ultrasound single operator of repeated measures on the brachial artery diameter at rest and during peak dilation has correlation coefficients of 0.856 and 0.937, respectively, with an $n=10$.

After a 5-min occlusion and 5-min reperfusion, the resulting peak dilation was recorded with no percent dilation difference between the groups in the brachial artery (Fig. 2). This overall change was used with resting diameters to calculate traditional FMD percent dilation

Table 1 Physical characteristics of overall experimental groups displayed as averages ± SD; categories statistically different between groups are marked by *

	Control/healthy ($n=9$)	Abdominal obese ($n=9$)	p value
Height (cm)	163.98 ± 1.65	169.29 ± 2.71	0.168
Weight (kg) *	56.53 ± 5.02	97.14 ± 5.57	< 0.001
Waist size (cm)	81.86 ± 6.9	113 ± 19.3	< 0.001
W:H*	0.81 ± 0.01	0.96 ± 0.03	0.002
BMI*	24.1 ± 0.59	33.82 ± 1.94	< 0.001
BF%*	24.47 ± 1.1	35.42 ± 1.86	0.001
Fasted Glucose (mg/dl)	91.57 ± 1.71	99.9 ± 2.78	0.007
SBP (mmHg)	115 ± 3.98	119.7 ± 4.79	0.586
DBP (mmHg)	73.7 ± 2.23	77.2 ± 3.53	0.493
Total Chol mg/dL	140.0 ± 8.6	148.4 ± 11.2	0.544
HDL Chol (mg/dL)	45.83 ± 3.29	40.9 ± 2.27	0.137
Trig (mg/dL)	97.0 ± 8.4	101.8 ± 19.2	0.841
Estradiol (pg/mL)	75.55 ± 10.02	51.86 ± 6.37	0.186
Progesterone (pg/mL)	106.65 ± 63.15	155.2 ± 97.17	0.332
Prog: E2	1.93 ± 1.68	4.28 ± 4.82	0.39
Testosterone (pg/mL)	45.6 ± 5.84	42.45 ± 8.55	0.39
OxLDL (pg/mL)	98.1 ± 40.6	146.06 ± 62.25	0.047

(*W:H* waist to hip ratio, *BMI* Body Mass Index, *BF%* percent Body Fat, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL* high density lipoprotein, *Trig* triglycerides, *Prog:E2* Progesterone to Estradiol ratio, *OxLDL* oxidized low density lipoprotein)

of the arteries of interest in both groups. Limb comparison of percent dilation between groups revealed that percent dilation of the popliteal artery in the AO participants was significantly lower than the percent dilation in the controls ($p<0.05$, Fig. 3). Time to peak diameter presented significant differences between the AO and control participants in both the brachial artery ($p<0.01$, Fig. 2) and popliteal artery ($p<0.001$, Fig. 3). Illustrated in Fig. 3, the rate of popliteal artery increase was significantly higher ($p<0.05$) in the sedentary control (0.1094 ± 0.04% per sec) compared to the AO group (0.0134 ± 0.003% per sec), while no significant difference between the groups was measured in the brachial arteries. Paired t tests of between artery differences within individuals to the FMD indicated a significant difference in the time and rate to peak ($p<0.0001$) with no significant differences in the % dilation of the arteries ($p=0.314$). In the FMD adjusted for shear rate AUC via ANCOVA, the limb-specific differences did not show significant differences between the limbs. The waist circumference was significantly correlated with both the brachial TP ($R=0.829$, $p=0.02$) and popliteal TP ($R=0.755$, $p=0.07$). In addition, as waist circumference increased artery dilation in both vessels decreased but not significantly (popliteal % dilation; $R=0.312$, $p=0.38$ and brachial % dilation; $R=0.477$, $p=0.163$).

3.3 Biomarker Analysis

Plasma analysis of estrogen concentrations in the AO women during menses was not statistically significant ($p=0.556$). Plasma progesterone concentrations in the AO women as compared to the controls yielded no significant difference; however, progesterone was on average higher in the AO group than in healthy controls. Plasma testosterone was measured and compared between groups; there was no statistical difference ($p=0.392$) between the groups. OxLDL concentrations were measured from plasma collected from each participant to assess levels of oxidative stress. Between-group comparisons of oxLDL concentrations yielded a statistically significant difference ($p<0.05$, Table 1) with higher concentrations seen in AO (156.3 ± 17.4 ng/mL) participants compared to controls (98.2 ± 10.5 ng/mL). Across all participants as oxLDL concentration increased, both arteries had correlative declines in % dilation (brachial $R=0.387$ and popliteal $R=0.294$) and TP (brachial $R=0.32$ and popliteal $R=0.182$) but did not reach statistical significance.

4 Conclusion

The findings from this study suggest a vascular dysfunction is present in our local female population prior to other significant clinical diagnoses of disease profiles. The reduced response would signal a condition of advanced

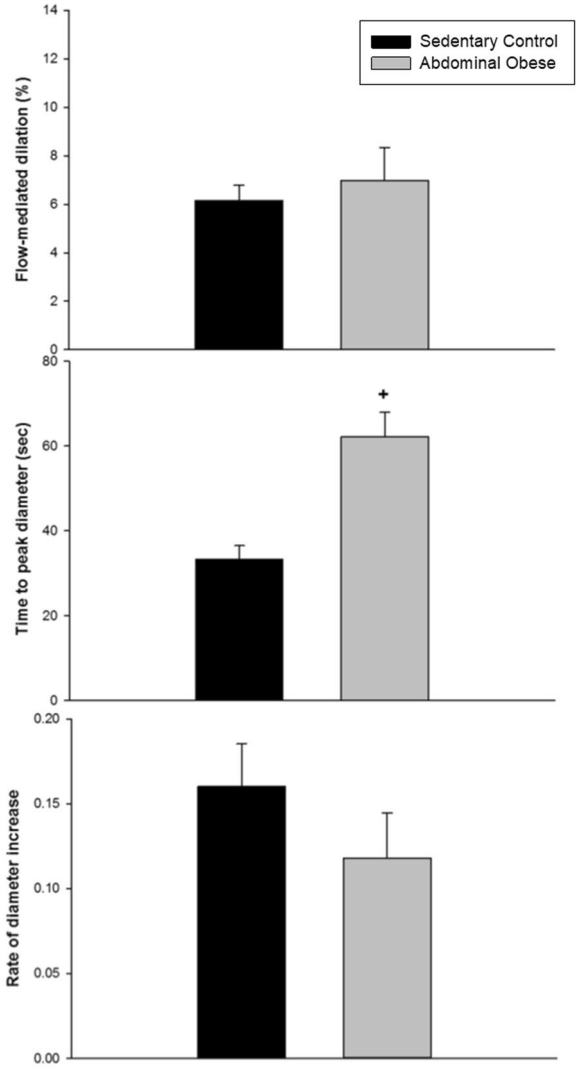

Fig. 2 Vascular responses to brachial FMD in sedentary health controls ($n=9$) and abdominal obese ($n=9$) young women

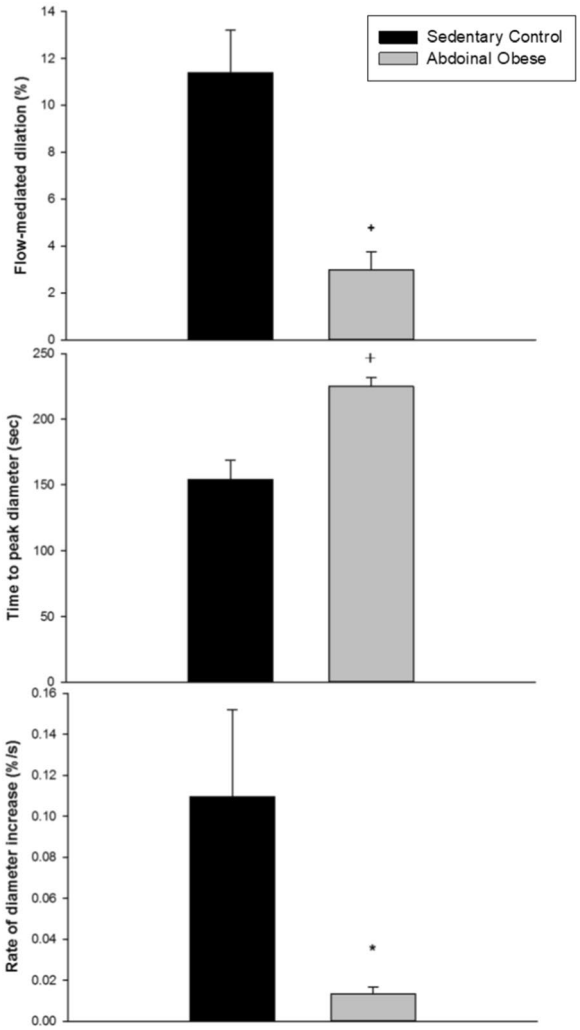

Fig. 3 Vascular responses to popliteal FMD in sedentary health controls ($n=9$) and abdominal obese ($n=9$) young women

cardiovascular aging in abdominal obese women who present reduced arterial function in the legs. This function is comparable to that of advanced age, post-menopausal women [19] and the dilatory responses seen in the presence of metabolic syndrome [6]. Though not in the scope of this study, it cannot be discounted that endothelial function within the resistance arteries downstream of the conduit could be impaired.

4.1 Limb-Specific Comparison

Previous studies have reported that no limb-specific difference in arterial function exists in healthy pre-menopausal women or healthy post-menopausal women [19]. Our results of limb comparison in healthy pre-menopausal women agree with these earlier findings. However, the same comparison in pre-menopausal abdominal obese women revealed a limb-specific difference with lower percent dilation in the popliteal artery as compared to the brachial. Following FMD correction with shear rate as the covariate, significant differences in FMD between the brachial and popliteal artery are abolished. These results are similar to previous work utilizing the former ratio correction method of FMD where alterations in shear the underlying factor for decreases in the dilatory response are limb-specific [16]. Taking this into account, it would appear that reductions in FMD of the popliteal artery could potentially be due to impaired dilation of the downstream resistance vasculature preventing increases in shear within the conduit, as has been previously shown [25, 26]. It cannot be discounted that endothelial function within the resistance arteries downstream of the conduit could be impaired, as these vessels could be more

susceptible to the detrimental effects of abdominal obesity or metabolic syndrome. By measuring the TP during the reperfusion period of the FMD in the brachial artery, there is a significant difference of a much longer period required to reach maximum dilation. These findings are similar to the variability seen by [6] while comparing participants with metabolic syndrome to healthy controls. In addition, the vascular dysfunction seen in the abdominal obese regional population of this study is exaggerated when comparing the temporal changes in dilation by calculating TP diameter from reperfusion beginning at release of ischemic occlusion. Thus, we conclude that the abdominal obese conditions in pre-menopausal women have a negative effect on vascular function in the lower extremities even prior to the onset of diagnosed metabolic dysfunction.

The significance of this result is that the popliteal arteries of the abdominal obese women could be undergoing early development of PAD. AO women in this experiment reported no symptoms or diagnosis of cardiovascular disease including PAD, as determined by individual health history questionnaires. Despite this, the popliteal arteries of these women harbor some level of vascular dysfunction as exemplified by a significantly lower percent dilation as compared to the brachial artery. A potential cause of this limb-specific difference could be increased oxidative stress which was exemplified by significantly higher oxLDL concentrations in AO women as compared to controls (Table 1). Increased oxidative stress could be disrupting normal activity of endothelial nitric oxide synthase (eNOS) leading to increased endothelial dysfunction in the AO women, which in turn could exacerbate existing oxidative stress and cause detrimental effects on overall cardiovascular health.

Previous studies have also described the beneficial effects of estrogen [5] and potential antagonistic effects of progesterone [13] on arterial dilation and changes in blood flow with estrogen blocking sympathetic vasoconstriction and progesterone negating that action. Measurement of sex hormone concentrations yielded no significant difference in the progesterone or estrogen concentrations in the AO women when compared to controls during the menses portion of the menstrual cycle. In this study, all measurements of FMD, estrogen, and progesterone were taken during early menses, when concentrations of each hormone were at their lowest. Future investigations should be aimed at the potential mechanisms of the neurovascular and endothelial dysfunctional development in abdominal obese and metabolic syndrome women with the reduction and potential supplementation of hormones or co-factors for NO and how this can become localized in the vasculature of the lower extremities.

4.2 Potential Limitations

Increased oxidative stress serves as a plausible explanation for the cause of endothelial dysfunction in overweight women. However, more insight is needed into the intracellular cause of endothelial dysfunction in the popliteal artery and the pathogenesis of PAD in overweight premenopausal women. The AO population in this study did have significantly elevated oxidative LDL commonly correlated with an increase in coronary heart disease, atherosclerotic plaques, and even type II diabetes [3, 12, 17, 28]. Future investigations would need to focus on presence and activity of eNOS within the arteries of interest examined in this experiment to assess the associated levels of endothelial dysfunction especially under pathologies associated with oxidative stress. Expression of the enzyme and production of NO and reactive oxygen species as measured by electron paramagnetic resonance [4] or NO metabolites including nitrates using methods of chemiluminescence could be compared between the limbs of each population and between populations to determine the full effect of increased oxidative stress on limb-specific differences.

Other limitations include further examination into the potential effects of sex hormones on dilatory responsiveness and prevention of endothelial dysfunction. Though not significant, discrepancies were seen in the concentrations of estrogen and progesterone in abdominal obese women when compared to controls. When comparing the brachial conductance response in the AO population during dynamic exercise hyperemia, we reported a significant decrease in conduction at all workloads compared to the control groups. As estrogen increased during the proliferative phase prior to ovulation, the group differences in brachial artery conduction were eliminated [27]. Further investigation is needed in the potential differences in sex hormone levels and the possibility of regulatory effects these hormones have on the vascular compliance during menses, proliferative as well as during the luteal phases in the AO and metabolic syndrome populations.

During the FMD, the repeated FMD measurements were recorded with a trained ultrasound technician using the hand-held probe instead of using a probe holder. The skin was marked at the region of interest for repeated measures and the operator is able to adjust if the participant had movement of the upper torso. This movement adjustment might not be compensated for when using a probe holder. These hand-held adjustments could also generate a gain of error and potentially alter diameter or velocity measurements during the trial. In addition, the sheer rate and dilatory responses were compared at repeated measures of FMD within that same artery separated by 30 min and using B-mode and 2D imaging. As

indicated by [32] for further comparison of the sheer stress and assessment of FMD, the analysis of velocity and diameter changes will be measured in a single FMD recording in the B-mode imaging for more accurate comparisons with other research groups.

Finally, future investigation in abdominal obese premenopausal women must include measurement of insulin sensitivity. Insulin resistance has been associated with endothelial dysfunction [29] and can be a common occurrence in an obese population developing metabolic syndrome [8]. Abdominal obese premenopausal women may harbor some level of insulin resistance as compared to healthy controls which in turn may inhibit normal endothelial function. Insulin sensitivity indices correlated with FMD responses would offer a more in-depth view of how endothelial dysfunction is developing. Decreased insulin sensitivity could potentially correlate positively with limb-specific differences leading to increased risk of PAD as well as type II diabetes.

4.3 Overall Significance

The significance of this study is based on the potential development of limb0specific vascular disease at younger ages within these regional and potentially global populations of young AO adults. The disease has not fully developed but this experiment uncovered an early time point at which the dilatory response within the legs is reduced, potentiating a deficit in the time of adaptation to ischemic stress in the AO population. This early time point is prior to the debilitating effects of metabolic syndrome, heart disease or even PAD and because of this, it is prior to the need of any pharmacological intervention. With knowledge that vascular dysfunction can be detected before full development of these debilitating metabolic and cardiovascular diseases, the necessary course of action would be adjustments in lifestyle including regular exercise and diet to improve arterial function.

Abbreviations

AO	Abdominal obese
BMI	Body mass index
BF%	Body fat percentage
ECG	Electrocardiogram
eNOS	Endothelial nitric oxide synthase
FMD	Flow-mediated dilation
HDL	High-density lipoprotein
MAP	Mean arterial pressure
NO	Nitric oxide
OxLDL	Oxidative low-density lipoprotein
PAD	Peripheral arterial disease
RP	Rate to peak
TP	Time to peak

Author's Contributions

R.M.R. and M.A.B. conceived and designed research; R.M.R and M.A.B. performed experiments; R.M.R. analyzed data; M.A.B. interpreted results of experiments; R.M.R and M.A.B. prepared figures; R.M.R. and M.A.B. drafted manuscript; edited and revised manuscript; R.M.R., and M.A.B. approved final version of manuscript.

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Data Availability

The data that support the findings of this study are available from the corresponding author, [M.A.B.], upon reasonable request.

Declarations

Conflict of Interests

The authors declare that they have no competing interests.

Consent for Publication

Not applicable.

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