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Research Article

Pulse Wave Analysis of HbA1c Categorized Prediabetes, Type 2 Diabetes and Normo-Glycemic Populations: A Pilot Study

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Received: May 14, 2021 ; **Published:** June 02, 2021

Abstract

Introduction: Arterial stiffness is a significant risk factor for cardiovascular events and early detection is key for intervention and monitoring. This pathophysiological process is accelerated in type 2 diabetes (T2D), yet the onset of this condition has a limited body of research.

Purpose: To evaluate (1) arterial stiffness properties via pulse wave analysis (PWA) across a 4-group spectrum, and (2) determine whether waist-to-height-ratio (WHtR), waist circumference (WC) or body mass index (BMI) serves as the best predictor of early changes in PWA pathophysiology.

Methods: PWA was measured in 52 participants across four groups separated by HbA1c values: 14 normo-glycemic (N, 4.0 % -5.1 %), 15 high normal (HN, 5.2%-5.6 %), 10 prediabetes (PD, 5.7% -6.4 %) and 13 with T2D (T2D, ≥ 6.5%). Brachial, central and peripheral pressures, central and peripheral augmentation index (AIx) data were collected via Sphygmocor using validated methods after overnight caffeine abstinence and a minimum 4-hr fast. Group differences were evaluated via MANCOVAs. HbA1c, WHtR, WC and BMI data were assessed through regression to determine the best predictor.

Results: Significant differences were found between N to T2D and HN to T2D for brachial systolic blood pressure (SBP) [$F(3,46) = 2.743$, $p < .05$], brachial diastolic blood pressure (DBP) [$F(3,46) = 3.329$, $p < .028$] and brachial mean pressures (MP) [$F(3,46) = 4.321$, $p < .009$]. Central DBP and MP differed between N to T2D, and HN to PD and T2D groups [DBP:$F(3,44) = 3.874$, $p < .015$; MP:$F(3,44) = 3.303$, $p < .029$]. Central pulse pressure (PP) and CAIx showed no differences between groups. Peripheral pressures significantly differed between N and both PD and T2D; HN and both PD and T2D groups for peripheral SBP [$F(3,44) = 3.007$, $p < .040$], peripheral DBP [$F(3,44) = 4.316$, $p < .009$] and peripheral MP [$F(3,44) = 3.487$, $p < .023$], but not PP or PAIx. WHtR and WC were identified as the best predictors of CAIx after adjusting for age and height [$R2 = .800$, $F(5,45) = 16.023$, $p < .0005$; adj. $R2 = .640$], while PAIx had no significant predictor.

Conclusion: PWA may be effective for identifying differences in multiple brachial, central and peripheral pressure measures across a novel, pre-defined HbA1c spectrum; however, more research needs to be executed to validate these findings. WHtR and WC, but not BMI, effectively predicts CAIx.

Keywords: *Pulse Wave; Early Detection; Arterial Stiffness; Cardiovascular; Prediabetes*

Abbreviations

BMI: Body Mass Index; CAIx: Central Augmentation Index; CDBP: Central Diastolic Blood Pressure; CMBP: Central Mean Blood Pressure; CSBP: Central Systolic Blood Pressure; DBP: Diastolic Blood Pressure; H: Healthy; HbA1c: Hemoglobin A1c; HN: High Normal; HR: Heart Rate; PAIx: Peripheral Augmentation Index; PD: Prediabetes; PDBP: Peripheral Diastolic Blood Pressure; PMBP: Peripheral Mean Blood Pressure; PSBP: Peripheral Systolic Blood Pressure; PWA: Pulse Wave Analysis; QI: Quality Index; SBP: Systolic Blood Pressure; T2D: Type2 Diabetes; TR: Transfer Function; WC: Waist Circumference; WHtR: Waist-to-Height Ratio

Introduction

Arterial stiffness is a powerful independent predictor associated with cardiovascular events, commonly associated with hypertension, pre-hypertension, stroke and all-cause mortality [1-5]. The concept of arterial stiffness is broad, describing a state of altered endothelial function. This state of decreased arterial elasticity, compliance and distensibility may be detected on a regional or local level of measurement at chosen points of assessment [6,7]. This pathophysiological process is associated with aging, obesity, decreased glomerular filtration rate, and diabetes, giving rise to focus on earlier detection [3,8,9]. Arterial structural properties progressively become stiffer with aging, and type 2 diabetes (T2D) is known to accelerate this dysfunction within vascular tissues [5,10-12]. Inflammation is believed to contribute to mechanistic changes and is likely affected by hyperglycemia, altering properties within endothelial tissues that lead to changes within cellular structures [13-15]. These processes ultimately lead to increases in arterial stiffness and the advancement of cardiovascular disease [16,17]. Elevations in blood pressure (BP), increased abdominal adipose tissue, and elevated body mass index (BMI) status metabolically interact to develop underlying changes in the endothelium, increasing arterial stiffness [12,13,15,18,19]. Such changes are often seen prior to receiving a prediabetes (PD) or T2D diagnosis, giving rise to a need for preventative research.

Pulse wave analysis (PWA) is a simple, non-invasive technique that has been used in studies to measure peripheral pressure at the radial artery and provides central pressure waveform information via a validated transfer function [6,20]. This unique tool allows for assessment of central and peripheral pressures, and estimations of central and peripheral augmentation indexes (CAIx, PAIx), all of which are known indicators of arterial stiffness [6,21-23]. Diabetes biomarker-related research indicates endorsement of PWA as a viable means to evaluate arterial stiffness, allowing earlier detection of central pressure changes, potentially before significant pathophysiological damage impacts existing vascular properties [24].

We hypothesized that individuals possessing early hyperglycemic tendencies, such as our predefined hemoglobin A1c (HbA1c) high normal (HN) group [HbA1c 5.2 - 5.6% (33 -38 mmol/mol)], might also display signs of pathophysiology related to arterial stiffness (increased central pressures, or CAIx and PAIx), or accumulated adipose tissue detectable by waist circumference (WC), BMI and waist-to-height-ratio (WHtR) when compared to healthy (H), thus aligning closer to our PD and T2D groups. Therefore, the purposes of this study were to evaluate (1) central and brachial BP measures for arterial stiffness across a HBA1c defined spectrum of subjects from N to T2D and (2) compare WC, BMI and WHtR as screening measures for potential changes in arterial stiffness.

Materials and Methods

Study population, screening, questionnaires and baseline measurements

A total of 52 adults, ages 18 to 65 years, participated in the study. Exclusionary criteria included type 1 diabetes, pregnancy, smoking, kidney or liver problems, peripheral vascular disease, HIV, hepatitis, cancer, stroke, nerve, or heart related diseases. Individuals were screened prior to obtaining informed, signed consent. This research was approved by the Internal Review Board of Old Dominion University. Study participants filled out screening and lifestyle questionnaires before having their height, weight, WC, and family history of diabetes recorded. Participants abstained from caffeine overnight (8 hours), food (4 hours) and exercise (24 hours) before arriving for testing. Fasting and abstinence from caffeine ingestion and exercise were verbally confirmed prior to testing. Each subjects' height, weight

and anthropometric measurements were recorded according to previously established methods [26-28]. WC, WHtR and BMI were all defined and calculated according to established research [27,29,30]. Individuals were matched by age and sex when placed by their HbA1c into one of the four groups during screening, healthy (H), high normal (HN), PD and T2D [H: HbA1c 4.0 - 5.1% (20 - 32 mmol/mol); HN: HbA1c 5.2 - 5.6% (33 -38 mmol/mol); PD: HbA1c 5.7 - 6.4% (39 - 46 mmol/mol); and T2D: HbA1c 6.5 - 14.0% (48 - 130 mmol/mol)]. A Seimens DCA Vantage 2000 Analyzer (Lenters-Westra and Slingerland, 2010), DCA Vantage HbA1c test kits, standardized procedures and universal precautions were utilized for HbA1c finger-stick testing [31].

Brachial and central pressure measurements

Brachial systolic (SBP) and diastolic (DBP) blood pressures were measured by standard procedures via sphygmomanometer and an appropriately sized cuff after 10 minutes of quiet rest in the supine position, and then PWA measured were acquired [32,33]. Subjects were instructed to lie quietly in the supine position for the duration of PWA measurements as wave forms were developed through non-invasive means utilizing applanation techniques and a tonometer with a piezoresistive transducer. The pen-like tonometer was placed at the site of the radial artery, where data was collected over 10 second time periods, generating a waveform from the captured data in a detailed computer view. The signal was automatically formatted, rescaled, concurrently analyzed through SphygmoCor software (Version 8.0, Atcor Medical, Sydney), which is a validated tool that utilizes a transfer function (TF) to derive central arterial pressures from radial wave form data [34]. The TF gives a full account of data received and transmitted through a detailed window view of the software [35]. Additional procedures for PWA are outlined elsewhere [20,32]. This technique was easily managed in the laboratory setting, enabling diversification of assessments made available to our individuals as part of a larger study. The application itself lasts approximately 20 minutes, including the 10-minute supine resting period, followed by a tonometry reading, which generally lasts under 5 minutes [7,20].

SBP and associated pulse pressures differ at the central and peripheral locations due to peripheral amplification [36-39]. In contrast, regional variation of larger and conduit arteries demonstrates considerably smaller variation in diastolic and mean pressures, allowing for accurate estimations of centralized pressures to be made from limb sites, such as the radial artery and notable differences in waveform between H and T2D subjects (See figure 1) [7,35]. Central SBP, DBP and augmentation index (AI) were derived from the TF within the SphygmoCor device for data analysis, and quality of waveforms was assured by the quality index (QI) software mechanism [32,35,37], which accounts for dependent measures including pulse height, length, and changes in pressure over time. QI was portrayed following each PWA capture, with minimum target goals of 85% [20]. A minimum of one capture was made for each study participant. When more than one capture was taken, the best QI indexed capture was utilized for analysis.

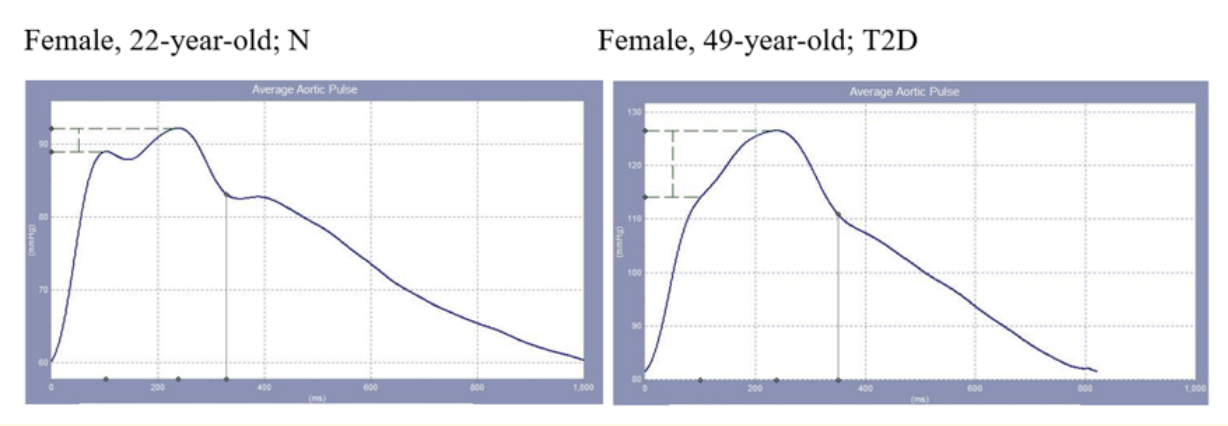

Figure 1

Statistical analysis

Data were expressed as means or medians ± standard deviation (age, BMI, WHtR, WC, BP values). Mean and median values were determined by group (N, HN, PD, and T2D) (See table 1). Variables were checked for normality with Kolmogorov-Smirnov and Shapiro Wilk testing, visual inspection, and calculated z-scores. Differences between groups were evaluated via MANCOVAs with the independent categorical variable operating as HbA1c (4 groups) and dependent variables included central/aortic BP measures (CSBP, CDBP, CMBP, CAIx), brachial BP measures (SBP, DBP, MBP), peripheral/radial BP measures (PSBP, PDBP, PMBP, PAIx). CAIx and PAIx had multiple covariates and were adjusted for age, HR, and body height to evaluate potential confounding factors. A two-sided test value of $p < 0.05$ was considered statistically significant, as a rejection of the null hypothesis that distributions were the same across the four groups. Central and peripheral pressures (CAIx and PAIx) had multiple covariates and were adjusted for age, HR, body height to evaluate potential confounding factors. Screening measures (HbA1c, BMI, WHtR, WC) were evaluated through multiple regression to determine the best predictor of CAIx and PAIx. A hierarchical multiple regression was performed on HbA1c and BMI, WHtR, and WC, accounting for age, body height and weight. All analyses were performed with SPSS version 24.0 software (SPSS, Chicago, IL).

Results

Subject characteristics and overview

Table 1 displays the subject characteristics, including family history of diabetes, regular exercise, and alcohol consumption. Central [CSBP, CDBP, CMBP, heart rate (HR)], Brachial (SBP, DBP, MBP), and Peripheral Pressure (SBP, DBP, MBP) differences are noted.

Variable	Normo-Glycemic (N)	High Normal (HN)	PD	T2D
N (m/f)	14 (7/7)	15 (3/12)	10 (3/10)	13 (3/10)
Age (years)	32.1 ± 11.7	47.7 ± 16.0	49.6 ± 11.0	45.0 ± 11.8
Height (m)	1.7 ± .1	1.6 ± .1	1.7 ± .1	1.7 ± .1
Weight (kg)	80.0 ± 12.0	79.1 ± 17.6	96.1 ± 17.2	102.3 ± 27.9
HbA1c (%)	4.88 ± .2	5.41 ± .2	5.88 ± .3	7.79 ± 2.0
Diabetes Family History	4Y, 7N, 3U	6Y, 7N, 2U	7Y, 3N	11Y, 2N
Regular Exercise (Y/N)	11Y, 3N	12Y, 3N	5Y, 5N	11Y, 2N
Alcohol Consumption	9Y, 5N	8Y, 6N, 1U	6Y, 4N	6Y, 6N, 1U
Central AIx	20.7 ± 2.9	15.6 ± 2.5	14.9 ± 3.1	14.7 ± 2.7
	Non-significant			
Aortic/Central SBP (mmHg)	102.4 ± 9.9	110.1 ± 8.1	116.1 ± 13.0	114.9 ± 7.9
	N - PD, $p < .034$ and T2D, $p < .03$			
Aortic/Central DBP (mmHg)	72.4 ± 7.5	75.1 ± 7.0	80.1 ± 6.2	81.2 ± 6.9
	N - T2D, $p < .02$, HN - PD, $p < .03$ and T2D, $p < .01$			
Aortic/Central MBP (mmHg)	85.9 ± 8.0	90.3 ± 7.4	94.8 ± 7.5	96.2 ± 6.2
	N - T2D, $p < .03$, HN - PD, $p < .04$ and T2D $p < .02$			
HR (bpm)	60 ± 8	60 ± 8	65 ± 11	70 ± 7
Brachial SBP (mmHg)	116 ± 9	119 ± 8	125 ± 11	126 ± 6
	N - T2D, $p < .03$; HN - T2D, $p < .04$			
Brachial DBP (mmHg)	72 ± 7	74 ± 7	80 ± 6	80 ± 7
	N - T2D, $p < .02$; HN - T2D, $p < .02$			

Brachial MBP (mmHg)	86 ± 7	89 ± 7	95 ± 6	95 ± 5
	N - PD, p < .04 and T2D, p < .01; HN - PD, p < .04 and T2D, p < .01			
Peripheral AIx	76 ± 4	70 ± 4	75 ± 4	75 ± 4
	Non-significant.			
Peripheral SBP (mmHg)	115 ± 9	119 ± 9	125 ± 11	121 ± 10
	N - PD, p < .04 and T2D, p < .02			
Peripheral DBP (mmHg)	71 ± 7	73 ± 7	79 ± 6	80 ± 7
	N - PD, p < .05 and T2D, p < .01; HN - PD, p < .03 and T2D, p < .01			
Peripheral MBP (mmHg)	86 ± 8	90 ± 8	96 ± 10	96 ± 6
	N - PD, p < .04 and T2D, p < .023, HN - PD, p < .032 and T2D, p < .020			
Notes: Data are shown as means ± SD; Y = Yes, N = No, U = Unknown; Central AIx was adjusted by age, HR, CMP, and body height; Peripheral AIx was adjusted by age, HR, RMP, and body height				

Table 1: *Subject characteristics, central, brachial and radial pressures.*

Central pressures

An analysis of brachial Central SBP, Central DBP and Central MBP through GLM MANCOVA testing revealed significant differences across multiple measures. No significant differences were found between) groups for Central SBP: [F(3,44) = 2.291, p < .091]. Central DBP and Central MBP differences were found between N and T2D (p < .02), HN and PD, (p < .030) and HN and T2D (p < .00) groups [DBP: F(3,44) = 3.874, p < .015) and between N and T2D (p < .028), HN and PD (p < .039), HN and T2D (p < .019) groups for Central [MBP: F(3,44) = 3.303, p < .029]. CAIx and PAIx were both adjusted for age, HR, associated mean pressures and body height to account for known impacting factors. There were no significant differences across any group combination for CAIx and PAIx in relationship to HBA1c (Table 2). Central pulse pressure (PP) and CAIx showed no differences between groups.

CAIx, Adjusted for Age and Height: [R^2 = .800, F (5,45) = 16.023, p < .0005; adj. R^2 = .640]				
Variable	**Normo-Glycemic (N)**	**High Normal (HN)**	**PD**	**T2D**
BMI (kg/M^2) (Means, SD)	28.4 ± 4.3	29.28 ± 5.6	32.77 ± 2.0	36.12 ± 9.4
	Regression Model, p < .03			
WC (cm) (Means, SD)	92.3 ± 10.9	95.0 ± 14.2	106.4 ± 14.3	114.1 ± 1.1
	Regression Model, p < .00			
WHtR (Means, SD)	.55 ± .1	.58 ± .1	.62 ± .1	.68 ± .1
	Regression Model, p < .00			
HbA1c (%)	4.88 ± .2	5.41 ± .2	5.88 ± .3	7.79 ± 2.0
	Separate Model; Non-significant.			

Table 2: *BMI, WC, WHtR Data and CAIx regression model results.*

Peripheral pressures

An analysis of peripheral SBP, peripheral DBP and peripheral MP through GLM MANCOVA testing revealed significant differences across multiple measures. Peripheral pressures significantly differed for N and PD (p < .035) and N and T2D (p < .017) groups for peripheral SBP [F(3,44) = 3.007, p < .040]. Group differences were found for N and PD (p < .050) and N and T2D (p < .012), HN and PD (p < .025) and HN and T2D (p < .005) groups for peripheral DBP [F(3,44) = 4.316, p < .009] and N and PD (p < .041), N and T2D (p < .023), HN and PD (p < .032) and HN and T2D (p < .020) groups for peripheral MP [MP [F(3,44) = 3.487, p < .023], but not for PP or PAIx.

Brachial pressures

An analysis of brachial SP, DP, and MP through GLM MANCOVA testing revealed significant differences across multiple measures. Significant differences were found between N and T2D ($p < .028$) and HN and T2D ($p < .044$) for brachial systolic SBP [$F(3,46) = 2.743$, $p < .05$], N and T2D, ($p < .016$) and HN and T2D ($p < .017$) for brachial DBP [$F(3,46) = 3.329$, $p < .028$] and N and PD, ($p < .038$), N and T2D, ($p < .007$); HN and PD ($p < .041$), HN and T2D ($p < .008$) for brachial MP [$F(3,46) = 4.321$, $p < .009$].

BMI, WHtR, and WC

Multiple regression testing revealed that WHtR ($p < .003$) and WC ($p < .008$) as the best predictors of CAIx when compared to BMI ($p < .030$) after adjusting for age and height [$R^2 = .800$, $F(5,45) = 16.023$, $p < .0005$; adj. $R^2 = .640$], while PAIx had no significant predictor.

Waveform quality index and waveform quality

The median QI was 92.2%, with 10.7% QI falling under the quality target of 85% [20]. The best waveforms were taken from multiple attempts and used for data analysis. The overall mean of the collected waveforms of QI was 92.2%, with 89.3% of waveforms meeting the 85 QI target.

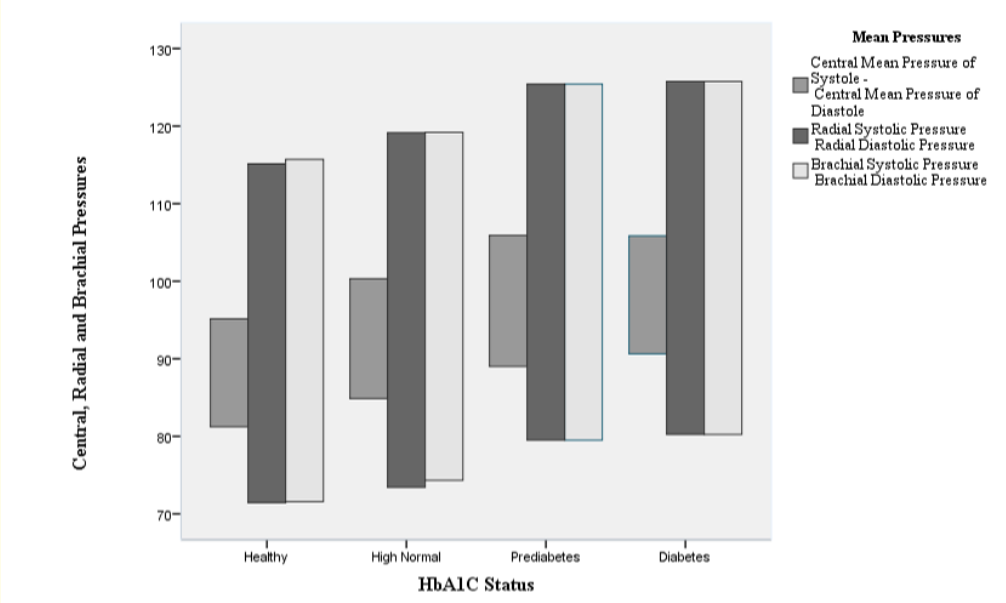

Figure 2: *Pressure by HbA1c status.*

Discussion

It is crucial to continue the advancement of valid, easy to use screening methods that can be employed to detect more serious health problems, as the vast majority of first world countries and developing countries continue the obesity pathway, developing inflammation and associated conditions within their health patterns. Our findings indicate steady increases in weight across our groups, from N to T2D,

with small variation in our HN group, but larger SD, further validating the inflammation pathway that is commonly discussed in prior literature, as in Johnson (2012) [40]. These increases in adiposity are common across literature, giving rise to tissues functioning in "sick fact" ways that contribute to advance disease development [41], ultimately furthering the pathway towards arterial stiffness. This being said, not all relationships are clear, as serum chemerin does not always proportionately relate to the increase in waist circumference size [42], making it difficult to always see how this pathophysiology develops. Thirty-six of our individuals stated that they were physically active at least three times per week, giving opportunity to combat the effects of this "sick fat" syndrome, which Aatola (2014) discusses in great detail [43]. The Young Finns Study discusses physical activity as one of the key components that must be "at goal" along with three others: nonsmoking status, ideal body mass and a diet that favors cardio metabolic health [43]. Our study required non-smoking status, and while we did not control for nutritional status, and BMI was elevated across all groups - starting with physical activity and nonsmoking status helped to favorably address key factors, and these certainly should be submitted as plausible arguments for the inability to detect elevated CAIx and PAIx factors in our population via PWA. Recent research validates that time spent in sedentary postures increases waist circumference and increases cardiometabolic risks [44] yet our individuals had increased waist circumferences with a predominantly active status, overall, as a study. Other favorable factors that are addressed by Aatola include ideal cholesterol, BP and fasting glucose; two of the three were monitored through our measures and are reported. The elevated BMI and enlarged waist circumference were certainly an expected, but also, a potentially confounding factor, as it provides the need for further research, with more balanced groups, in a larger population. While we attempted to age match, the increased waist circumferences created problematic variances.

Typical evaluation of BP relies on sphygmomanometer [45], but looking beyond conventional means of assessment seems prudent given the impact of high BP and endothelial dysfunction on health outcomes [3,8,10]. Elastic properties and compliance of the arterial system are key components of endothelial health, yet they may be disrupted with aging, obesity, diabetes, or key factors such as smoking, ultimately leading to the development of health concerns. Individuals may experience arterial stiffening without overt clinical manifestations, allowing time for pathology to develop silently [13,15,46,47]. Individuals with T2D are at increased risk for accelerated physiological processes associated with arterial stiffness, giving just cause to research efforts aiming to detect indications of arterial damage at earlier stages in subjects experiencing various ranges of hyperglycemia [13,17,22]. Thus, our research fills an important gap addressing individuals who are likely to be facing early physiological changes.

CSBP, CAIx and PAIx are commonly used parameters for evaluating arterial stiffness, but require adjustments for key factors such as HR, age, associated MP, and body height to obtain accurate assessments [37] and previous researchers commonly adjusted for covariates, as our study did. Despite these adjustments, CAIx and PAIx did not reveal significant differences between any of our 4 groups (See figure 1). When comparing our subject data to AtCor reference range data, comparisons reveal that our subjects had little variation from group to group, and were overall, relatively healthy compared to published population means for age. Only our H group seemed to have slightly elevated CAIx compared to norms.

Our study findings include significant differences between our H subjects and subjects with PD and T2D when evaluating central pressures by means of PWA. Our HN group did not significantly differ from other groups on any central or brachial pressure measure tested, potentially indicating some unique things to consider. HN's test results appear to display unique physiological attributes similar to H, PD and type 2 diabetes, as the HN group did not significantly differ from any of these populations on several measures. This group may contain a unique subset of individuals that carry both healthy and less healthy characteristics, or specific individuals may be upsetting the statistical frame of reference. More research in the context of a larger population is needed to determine these matters. Our study differs from some, as our subjects were screened for cardiovascular and other known health issues prior to participation due to other measures being collected for the study, thus allowing a unique perspective of a relatively healthy population [20,33]. We cautiously offer the HN group as a potential new subset population for further research to determine which characteristics may be congruent with H, PD and T2D in a larger, more diversified study.

Previous PWA research has evaluated CSBP, central pulse pressure (PP) and CAIx at the radial artery via applanation with participants engaged in a sitting position, with their arm extended in a resting position on rigid surface [36,48]. This study also utilized the SphygmoCor device (SphygmoCor, Atcor Medical, Sydney, Australia) with a generalized transfer function, collected at a steady HR of 75 beats, much like our research, however, central SBP, but not brachial SBP was independently predictive of PWV and A1x-75. In contrast, our study revealed a mix of significant differences between our N, PD and T2D groups for central, peripheral, and brachial pressure measures. Our small sample size is likely to contribute to this phenomenon, and with larger numbers, it is quite possible that trends would emerge.

Central arterial stiffness has been evaluated by several different types of studies and methods, yet generally non-invasive routes involve PWA or pulse wave velocity (PWV) as means to assess the need for medical intervention, further testing or modeling predictions related to hypertension [35-37,49]. Wittrock., *et al*. [6] analyzed PWA measures of central arterial stiffness in relationship to invasive ratio pulse-to-pressure stroke-to-volume to validate correlation between the measures in 49 patients. These research scientists reported issues with 12% of their cases where applanation was not successful, reportedly due to cardiac arrhythmias or non-detectable radial pulse. In contrast, we had 100% detectability of the radial pulse in 54 subjects when utilizing PWA measures, but also, with utilizing a different tonometry instrument. They employed an HDI/Pulse Wave CR2000 Cardiovascular Profiling Instrument (Hypertension Diagnostics, Inc Eagan, MN), whereas we utilized a SphygmoCor (Atcor Medical, Sydney, Australia). Kotecha, New [20] utilized PWA to evaluate 531 patients who had been referred for coronary angiography and determined that the measure was useful in risk stratifying patients for further procedure. This study evaluated patients with suspected or known history related to heart disease, whereas our study evaluated non-smoking, prescreened "N" individuals, and was able to identify changes in central AP, potentially indicating a more sensitive use of PWA. Koivistoinen., *et al*. 2018 utilized PWV to predict the progression of hypertension development in young adults (N = 1183) by utilizing prediction modeling, with findings suggesting a value for the use of PWV as a tool in hypertension prevention in young adults [49].

Assessing abdominal obesity is part of ascertaining cardio metabolic risk, yet debate remains over which screening methods are the most effective [27,50]. Previous research has compared WHtR and WC as screening tools and indicate a stronger performance of WHtR over WC due to height bias [50]. Shorter individuals were more likely (30%) to be classified with metabolic syndrome if WC was used as the method of grouping. In comparison, taller individuals did not experience the same issue, leading Schneider's team to recommend WHtR, not WC, as a measure for metabolic syndrome. Our study found significant relationships in both WHtR and WC, and in contrast to prior research, our findings are congruent across both variables, with significant differences falling between H and T2D and HN and diabetes, across both measures. A review of table 1 shows steady increase across our four groups, demonstrating this relationship. Our pilot study, however, only examined 52 individuals, whereas Schneider., *et al*. examined 6,971 individuals to justify their recommendations.

Examinations of WHtR in comparison to BMI through research and systematic reviews of literature reported that WHtR performed better overall as a screening tool relating to the detection of cardio metabolic risk [29,30]. This research examined studies covering more than 300,000 adult individuals across a diverse ethnic spectrum and both genders and reported the superiority of WHtR over WC as a screening tool, as did Schneider., *et al* [51]. Our data show support for WHtR, even with a small number of participants. A significant result was indicated for BMI, yet post hoc comparisons revealed that differences in BMI were not strong enough to be significant between groups, whereas WHtR was a strong enough measure to determine differences between our H and HN populations as they relate to PD and T2D.

This study has limitations to consider. Our H group demonstrated increased WC, as this was a female dominant study and WC was 92.3 cm $\pm$ 10.9 cm, and normative values are 102 and 88 cm respectively for males and females [51]. Likewise, WHtR indicates an overall elevation from known and accepted standards, with our H population median beginning at .55 and progressing to .68 for the median of the T2D group (.50 for m, .48 for f). Such elevations in a female dominant study or any deviations from typical anatomy of the radial artery or brachial complex could have affected our waveforms in ways that we are unaware [35].

We focused on healthy, non-smoking individuals; thus, we are not aware of potential applications to HbA1c categorized subjects who might be smokers or experiencing symptoms of known cardiovascular disease. While research literature indicates clear findings for N individuals and those with PD or T2D, clarification is needed regarding individuals experiencing elevated, but not yet clinically diagnosable hyperglycemia, as in the case of our HN group. We do not know the extent that PWA may assist with identifying arterial stiffness in individuals who smoke, and have elevated HbA1c values, but not yet clinically diagnosable PD. Our study was small, and findings should be confirmed in larger studies before generalizations can be made. Future research should include repeated procedures with a larger population, and balanced groups to better facilitate a more robust statistical model.

Finally, our HN group did not significantly differ from other groups on pressure variables, suggesting that our subjects may not have been truly representative of this population. More importantly, PWA identified significant differences in central pressures in non-smoking subjects without a history of major disease or other known pathology beyond hyperglycemia. WC, and WHtR measures effectively identified significant differences between H and HN subjects and subjects with PD and T2D, accurately assessing increases in metabolic risk progressively across the 4-group spectrum.

Conclusion

In conclusion, group differences were found at the central, peripheral pressure and brachial pressure levels in our pilot across a novel, pre-defined HbA1c spectrum. We were able to identify changes in central DBP, MBP, peripheral DBP, SBP, and MP, as well as brachial DBP, SBP, and MP. Our study participants were carefully screened and evaluated as non-smoking participants, including "N" individuals potentially indicating a more sensitive use of PWA for this study and opening the doorway for suggested further study with healthy and early disease populations. WHtR and WC were better predictors of CAIx compared to traditional BMI measures, with PAIx having no impact predictor in our study. Our pilot shows PWA, WHtR and WC as promising non-invasive early detection tools to monitor and determine vascular health changes. Future research should further explore how early changes can be detected in vascular health in healthy and early disease state populations.

Acknowledgement

The authors are grateful to the Human Movement Sciences Department of Old Dominion University for funding and to Dr. Corey Rynders for mentoring with PWA.

Funding Support

This study was supported by Old Dominion University's Department of Human Movement Sciences, Human Performance and Movement Exercise Laboratories.

Declarations of Interest

None.

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