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Skin Pigmentation and Arterial Stiffness in Young Health Black and White Adults

Zoe R. Lincoln
Georgia Southern University

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An Honors Thesis submitted in fulfillment of the requirements for Honors in Waters College of Health Professions.

By

Zoe Lincoln

Under the mentorship of *Dr. Gregory Grosicki, Ph.D., CEP*

ABSTRACT

Cardiovascular disease (CVD) is currently the leading cause of death worldwide, killing over half a million people in the US every year. This issue is only becoming more prominent, as both the world and US population are experiencing increased rates of CVD risk factors such as hypertension, type 2 diabetes, and obesity. Black Americans specifically are experiencing increased rates of these risk factors, possibly due to lifestyle, socioeconomic, and genetic variables, ultimately leading to a higher prevalence of CVD in this population. One possible mechanism for this health disparity is racial differences in skin pigmentation, which can influence cardioprotective Vitamin D status. To test this hypothesis, we characterized the relationship between skin pigmentation, via melanin content (M-index), and blood pressure (BP) and arterial stiffness in young and apparently healthy Black and White adults. Brachial and central systolic and diastolic BP were significantly greater ($p<0.05$) in Black participants compared to White participants. However, racial differences in BP were abolished after controlling for body mass index (BMI) ($p>0.05$). M-index was not significantly related to any cardiovascular health measures in the sample as a whole ($r=0.05$ to 0.25; $p=0.14$-0.78), or in Black ($r=-0.21$ to 0.13; $p=0.38$-0.74) and White ($r=-0.43$ to -0.31; $p=0.11$-0.23) participant groups. These data suggest that racial differences in body composition may contribute to elevated BP values in Black adults. However, our data suggest that skin pigmentation does not influence vascular health.

Thesis Mentor: _____

Dr. Gregory Grosicki

Honors Director: _____

Dr. Steven Engel

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Honors College

Georgia Southern University

Introduction

Cardiovascular disease (CVD) is currently the leading cause of death worldwide, responsible for one death every 40 seconds among Americans [1]. While this issue is globally pervasive, CVD affects Black Americans to a greater degree than White Americans. Black Americans are 30% more likely to die from CVD compared to White Americans, and over half of this disparity can be attributed to Black Americans developing and possessing CVD risk factors such as elevated BP levels and larger artery stiffening at a greater rate than White Americans [2]. According to the CDC, over half (54%) of Black Americans exhibit hypertension compared to non-Hispanic Caucasian Americans (46%) (2020). This higher incidence of CVD in Black Americans is a "primary cause of disparities in life expectancy" compared to White Americans [3].

Vitamin D may play a role in protecting against CVD. Total serum 25(OH)D is the traditional standard for assessing vitamin D supply in the body [4]. Cardiovascular (CV) benefits derived from 25-hydroxyvitamin D (25(OH)D), the major circulating form of vitamin D, include anti-inflammatory effects, improvements in vascular tone, increased endothelial function, and preventing hypertension [5]. Vitamin D2 and D3 are converted to 25(OH)D in the liver, but it has been shown that vitamin D3 supplementation may be more effective in increasing total serum 25(OH)D than vitamin D2 supplementation [6]. Because of the effectiveness of vitamin D3 supplementation in raising total serum 25(OH)D as well as the CV benefits that 23(OH)D may elicit, vitamin D3 supplementation has been shown to decrease arterial stiffness in overweight Black individuals with vitamin D deficiency [7]. It is well-known that elevated arterial stiffness is an independent risk

factor for CVD and mortality [8]. Thus, decreasing this metric is relevant to the narrative of decreasing overall CVD, particularly in Black adults.

Since vitamin D plays a role in the CV system, factors that limit vitamin D production may be detrimental to CV health. It is suggested that melanin content could play an inhibitory role in vitamin D production because of blunted epidermal exposure to ultraviolet radiation. Those with higher melanin content, such as Black individuals, produce less vitamin D with the same amount of UVR exposure [9].

The purpose of this investigation is to fill gaps in the literature examining the relationship between vitamin D levels, melanin content, and CV measures such as arterial stiffness and how it may be different in Black versus White individuals. This study will provide further evidence to a growing body of literature characterizing factors that may contribute to health disparities been White and Black individuals. Analyzing these relationships, along with socioeconomic and lifestyle factors that may mediate these associations, will provide insight into how clinicians can direct treatment for those with CVD. We hypothesize that compared to White individuals, Black individuals will exhibit elevated melanin content of the skin in a manner that is associated with higher BP and arterial stiffness.

Literature Review

CVD is a term that envelopes many different conditions involving the heart and blood vessels. In 2019, the American Heart Association reported 121.5 million adults are afflicted with CVD in the United States. One contributing factor to the rise in CVD in recent years relates to a definitory change by the AHA and American College of

Cardiology pertaining to what qualifies as high BP in order to reflect the health problems that can occur at lower values.

Prior to November 2017, high BP was defined as a systolic or diastolic value above 140/90 millimeters of mercury (mmHg), respectively. In November 2017, it was updated to include a systolic or diastolic above 130/80 mmHg, respectively. As of 2020, this update increased the prevalence of hypertension from "72.2 to 103.3 million and pharmacological treatment eligibility… from 77.7 to 81.9 million" among US adults [10]. The CDC reports that 108 million people in the United States, 45% of the population, have hypertension. In 2017, there was a greater percentage of men (46%) compared to women (43%) with hypertension, as well as a higher percentage of African Americans (54%) with hypertension compared to Caucasians (46%), Asian (39%), and Hispanic adults (36%) [11].

Of course, a change of definition for hypertension is not entirely responsible for the rise in CVD. It is projected that CVD prevalence will only increase due to other factors such as aging populations, increasing rates of obesity, and contributing lifestyle factors such as inactivity and smoking [12]. Black Americans are more likely to develop CVD at a younger age than White Americans because they have a higher prevalence of CV risk factors such as hypertension, obesity, and diabetes [3]. Hypertension is a leading risk factor for CVD. Closely related, elevated arterial stiffness, measured with pulse wave velocity, is an independent risk factor for CVD and mortality [8]. Since hypertension and arterial stiffness are reciprocally linked, relationships between these variables and health outcomes are often similar [13]. Thus, altering factors that influence one or both of these values could lead to favorable outcomes with CVD. This is especially important in Black individuals

considering that over half of this demographic in the US has hypertension [11]. Black individuals also have higher rates of arterial stiffness, which can be easily and non-invasively assessed using the gold-standard carotid-femoral pulse wave velocity (cf-PWV) technique [14].

Even though Black individuals have a higher prevalence of CVD due to the increased prevalence of traditional CVD risk factors, there exists evidence that Black individuals have impaired vascular function outside of these risk factors. The mechanisms as to why are not entirely understood, but one example where this was found was an estimated reactive hyperemia index (RHI), an indicator of endothelial function, using measures of pulse volume amplitude (PVA) via digital pulse amplitude tonometry (PAT). Black individuals exhibited lower RHI than White individuals, indicating reduced endothelial function even after adjustments for traditional CV risk factors. Furthermore, this trend remained when measuring RHI of healthy individuals (i.e., free of CVD risk factors [14]. A meta-analysis examining racial disparities in arterial stiffness among healthy White and Black Americans showed that the mean difference in pulse wave velocities between African American and White males was significant; “White race was associated with a difference of −0.44 m/s” at a 95% CI [15]. This is significant because a “1 m/s increase in cf-PWV is associated with a 1.12 fold increase in future CVD events” and a 1 m/s increase in brachial to ankle-PWV is associated with a 12% increased risk of CVD [16].

Another potential mechanism of undesirable vascular remodeling and functional decrements in Black individuals could be related to vitamin D status. Vitamin D is produced endogenously when UV rays from the sun trigger vitamin D synthesis. However,

Vitamin D can also be ingested and supplemented via foods or nutritional supplements [17].

Although best known for its role in bone growth, vitamin D may play a critical role in CV health through "effects on the renin-angiotensin system, on glycemic control, inflammatory cytokines, direct effects on the vasculature and regulation of PTH [parathyroid hormone] levels, and calcium deposition in vascular smooth muscle" [18]. In a placebo-controlled randomized trial conducted where vitamin D3 was given to overweight Black individuals with vitamin D deficiency, there was a "demonstrated dose-response increase in serum 25(OH)D," the major circulating form of vitamin D, as well as a dose-dependent decrease in arterial stiffness measured with cf-PWV [7]. Doses in this study ranged from a placebo group, 600 international units (IU)/day, 2,000 IU/day, and 4,000 IU/day. Vitamin D deficiency is a critical issue in Black Americans, with estimations showing that 76% of Black Americans are vitamin D deficient, compared to 40% of the overall adult American population [19].

Evidence suggests that Black individuals may be facing vitamin D deficiency at a higher rate than the overall population due to relationships between vitamin D production and melanin content. Despite inconclusive evidence among existing literature, it is considered that the inhibitory effect of melanin on Vitamin D production is potentially related to racial disparities in CVD and vascular health [20]. Darker-skinned individuals predominantly produce eumelanin, which is the black pigment that provides protection from ultraviolet radiation from the sun [21]. Since individuals with a higher melanin content have natural protection from the sun, they require three to five times more exposure to sunlight in order to produce the same amount of vitamin D as those with lower melanin

content [9]. Since it may require more exposure to UVR for people with a higher melanin content to produce an adequate amount of vitamin D, it is reasonable to suggest that this phenomenon may be related to high rates of vitamin D deficiency or insufficiency in Black adults compared to White.

Currently, many antihypertensive medications cannot adequately control BP. In fact, many individuals need to take a few different medications to control BP [22]. With the disparity that exists between White and Black individuals regarding CVD, it is especially important to determine underlying mechanisms so clinicians can work toward eliminating them as well as improving overall treatment methods for CVD.

Methods

This study is part of a larger study examining racial disparities in CV health, and how different factors such as melanin content, vitamin D in the blood, and inorganic nitrate supplementation via beetroot juice affect cardiac-autonomic and hemodynamic measures in Black and White adults. This information will be used to assess differences in vascular health between White and Black individuals, and analyze the relationship between these measures, melanin content (M-index), and vitamin D (via ELISA) in the blood.

Laboratory Visit 1

Potential participants reported to the Biodynamics and Human Performance Center on the Georgia Southern University Armstrong Campus, where they were given a description of the study along with any associated risks. They then provided informed consent to participate and completed a Medical and Exercise History Questionnaire.

Participants then completed five validated questionnaires to characterize social or behavioral determinants that may account for vascular health differences not attributable to ancestry. The Pittsburgh Sleep Quality Index and the Munich Chronotype Questionnaire were be used to collect data on sleep habits, and the Perceived Ethnic Discrimination Questionnaire and the Socioeconomic State Questionnaire were used to account for socioeconomic status throughout the participants' lifespans. The Family History Questionnaire was used to indicate any ancestral predisposition to disease. Height and weight were then measured on a wall-mounted stadiometer and calibrated digital scale, respectively.

Skin pigmentation was measured as an M-index value by reflectance spectrophotometry (DSM II, Cortex Technology, Denmark). M-index was measured on the inner part of the participant's upper arm because of its low exposure to sunlight and easy access. Lower and higher M-indices reflect lighter and darker skin pigmentation, respectively. The measure was taken three times, the average of which was used for analysis.

Laboratory Visit 2

The second visit to the Biodynamics and Human Performance Center on the Georgia Southern University Armstrong Campus was scheduled between 0600-0900. Participants were asked to present following an overnight fast (no food for >10 hours and no water for >1 hour) and having refrained from exercise, caffeine or alcohol consumption, and over-the-counter medication for 24 hours prior to the visit. Participants were also asked to refrain from eating high nitrate foods and using mouthwash for 72 hours prior to the

visit. In females, the menstrual cycle was not controlled for, but they were asked to report the first day of their last cycle.

The participants were taken to a comfortable medical examination table and asked to complete a resting period of 10 minutes in the supine position. After the resting period was finished, cardiac cycles via electrocardiography and beat-to-beat BP via photoplethysmography were collected for a 10-minute baseline period. Resting central hemodynamics and arterial stiffness were then assessed via pulse wave analysis and pulse wave velocity respectively using the SphygmoCOR XCEL device (At Cor Medical, Naperville, IL).

The participants were then asked to sit in a laboratory-grade blood draw chair, and we collected a venous blood from the antecubital vein in an ethylenediaminetetraacetic (EDTA) tube in accordance with laboratory standard operating procedures. Blood samples were processed in a centrifuge for subsequent vitamin D analysis via enzyme-linked immunosorbent assay (ELISA).

Statistical Analysis

All statistics were run in IBM SPSS (Version 27, SPSS, IBM Company, Armonk, NY) and subject characteristics including age, melanin content, body mass index (BMI), and CV values were calculated using descriptive statistics as means plus or minus standard deviation (SD). M-index and all CV variables were inspected for normality using the Shapiro-Wilks test and box plots. After such, we determined the CV variables were normally distributed ($p > 0.05$), but M-index values were not ($p < 0.05$). M-index values were log transformed but were still nonparametric ($p < 0.05$). Assuming equal variance,

independent T tests were run to analyze the differences in BMI and CV values between White and Black subjects and M-index was compared using the Mann Whitney U-test. Non-parametric Spearman's correlations were used to analyze the relationship between M-index and CV values in all subjects. While M-index of all subjects was not normally distributed, M-index within the self-identified White and Black subject groups was normally distributed. Thus, parametric Pearson correlations were used in discrete White and Black subject groups to evaluate relationships between M-index and CV measures. Given the elevated BMI in Black participants, ANCOVA tests were run to compare CV values in Black and White subjects when controlling for BMI. The statistical significance was set at $P<0.05$.

Results

Included in our sample were 20 White participants (10M/10F) and 17 Black participants (7M/10F). The average age for all participants was 21±3yrs, and the difference in age between White (21±4yrs) and Black (21±3yrs) participants was not significant ($p>0.05$). Average M-index for White participants was 32.53±2.68 and average M-index for Black participants was 59.56±13.35 ($P<0.01$). BMI for White participants was 23.5±2.6 and BMI for Black participants was 26.3±5.8 ($P=0.06$).

Heart rate and vascular health parameters of White and Black participants are summarized and compared in Table 1. Though HR and indices of arterial stiffness (i.e., cf-PWV and AIx75) were comparable between races ($P>0.05$), significantly greater brachial and central BP (systolic and diastolic) values were detected in Black compared to White participants ($P<0.05$).

Table 1. Vascular health measures.

	White		Black		p-value
	Mean	SD	Mean	SD	
HR	62	6	65	9	0.34
cf-PWV	5.7	0.8	6.1	0.7	0.14
B-Systolic	116	7	123	12	0.04
B-Diastolic	67	7	73	9	0.01
C-Systolic	101	7	108	12	0.03
C-Diastolic	68	7	74	9	0.02
AIx75	1.3	8.1	3.8	16.6	0.57

HR, heart rate; cf-PWV, carotid femoral-pulse wave velocity; B, brachial; C, central; AIx75, heart rate corrected augmentation index.

Relationships between M-index and heart rate and vascular health measures are provided in Table 2. Though no statistically significant associations were detected, it is worthy to note that correlation coefficients in Black participants (r = -0.31 to -0.43) were higher than White participants (r = -0.21 to 0.13).

Table 2. Relationships between m-index and vascular health measures.

	All		White		Black	
	Spearman's	p-value	Pearson	p-value	Pearson	p-value
HR	0.05	0.78	-0.16	0.49	-0.38	0.13
cf-PWV	0.13	0.45	-0.11	0.65	-0.43	0.11
B-Systolic	0.22	0.22	-0.21	0.38	-0.31	0.23
B-Diastolic	0.25	0.14	-0.08	0.74	-0.39	0.12
C-Systolic	0.25	0.14	-0.16	0.51	-0.38	0.13
C-Diastolic	0.22	0.19	-0.10	0.68	-0.40	0.11
AIx75	0.11	0.52	0.13	0.60	-0.32	0.22

BMI, body mass index; HR, heart rate; cf-PWV, carotid femoral-pulse wave velocity; B, brachial; C, central; AIx75, heart rate corrected augmentation index.

To evaluate whether racial differences in BP may have been mediated by BMI, we ran an analysis of covariance (ANCOVA) to compare vascular health measures between White and Black participants controlling for BMI. In the models for brachial and central BP (inclusive of systolic and diastolic), significant models were detected ($F=7.4\text{-}11.4$; $p<0.01$ for all). However, BMI ($P<0.05$), but not race ($P>0.05$), was a significant predictor. Regarding cf-PWV and AIx75, no significant models were detected ($p>0.05$) and race and BMI were not independent contributors ($P>0.05$).

Discussion

The original intention for this study was to analyze the relationship between melanin content, vascular measures, and vitamin D status. Due to the time sensitive nature of the project, the vitamin D assays were not completed and only the relationship between melanin content and vascular measures was inspected.

The relationship between melanin content, vitamin D status, and subsequently CV health has not been directly explored in the literature, although studies examining the relationships between vitamin D and CV measures as well as melanin content and CV measures separately have been examined. Vitamin D has been shown to have a dose response relationship with arterial stiffness, where supplementation improves vascular health in overweight Black Americans [7].

The relationship between skin pigmentation and cardiovascular health lacks a consensus. One study showed that although hypertension is more prevalent among Black Americans, this disparity was not associated skin color, but rather was more consistently linked with social class and age [23]. Mosley and colleagues also found mixed results in an Egyptian population where there was no significant relationship between M-index and BP found in men. In women, however, both systolic and diastolic BP increased with increasing M-index, even after controlling for age and BMI [24]. In contrast to these data, Klag and colleagues showed a significant positive association between BP and skin color when measured with a refractometer, although this relationship was only present in a Black population of individuals with low socioeconomic status [25]. Similarly, Ernst and colleagues found that there was a weak, yet statistically significant relationship between skin tone and BP, but this may have been due to gender artifacts [26].

Despite our findings that M-index was not related to CV health measures, previous literature does show a concerning trend in CV health and hypertension amongst Black adults. Supporting our data, racial disparities between White and Black individuals are evident in hypertension among all ages, even though the specific mechanisms are unclear [27]. However, there are other contributors besides our proposed melanin content which

may serve to illustrate the issue of elevated BP in Black Americans, such as health behaviors like smoking and exercise habits [28]. Since higher BP contributes to CVD risk, this issue is crucial to understand from both a whole population and demographically specific perspective [27].

Though we observed elevated BP in Black participants compared to their White counterparts, these differences were extinguished after controlling for BMI. BMI was a significant independent contributor to all BP values, which is relevant because this information adds to the body of literature showing that Black populations are more prone to obesity than other races. Studies cite a plethora of factors such as education, socioeconomic status, emotional well-being, and health habits such as smoking among Black Americans in this multifaceted issue [28, 29]. Knowing that BMI has a correlation with BP values, populations with increased BMI may be at increased risk for CVD, which has been shown to be a more pervasive issue in Black adults [30].

This investigation does have several important limitations. For example, the time sensitive nature of the project prevented the entire investigation from being completed. Specifically, Vitamin D assays were not able to be completed, so we do not have information on the potential relationship between vitamin D status, melanin content, and vascular health measures. Our investigation was also cross-sectional in nature and population size was limited and unequal between Black and White participants. Another important limitation includes the lack of control for the menstrual cycle in women, although previous literature shows a lack of consensus as to whether the menstrual cycle should be controlled for in vascular health studies [31]. Lastly, we were also underpowered to control inspect for gender differences in the relationship between skin pigmentation and

vascular health, though a relatively equivalent number of male and female participants were studied. However, our investigation was highly novel in that we were among the first to examine the relationship between melanin content and vascular health in young adults.

Conclusion

CVD remains a global concern, but has particular relevance for Black Americans, who are 30% more likely to develop the disease than their White counterparts [2]. While it has been postulated that this disparity could be due to differences in skin pigmentation and vitamin D status, supporting evidence is limited. However, there is also compelling evidence for several other factors such as socioeconomic status, education, and health behaviors that could contribute to poorer CV health in Black individuals. Thus, it is likely that a multi-faceted approach to fully eliminate racial disparities in CVD is required.

The data from this investigation implies that while racial disparities exist in cardiovascular health, chiefly in BP, the driving contributor is likely BMI, rather than melanin content. Further research and vitamin D assays should be completed to characterize the relationship between vitamin D and melanin content and how the two affect CV health measures in Black and White individuals.

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