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Hypovitaminosis D as a Contributory Factor to Vascular Disease in African-Americans: A graded literature review

James H. Moorman

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Abstract

Background: There is growing concern that chronic hypovitaminosis D at levels below 30ng/ml may negatively contribute to several major diseases of the developed world to include diabetes, cardiovascular disease, and cancer. According to the CDC approximately 80% of African Americans > 1 years of age suffer from vitamin D insufficiency. The clinical question that will be explored in the following literature review is, whether hypovitaminosis D in the African American population contributes to increase incidents of vascular disease.

Methods: An extensive literature search was conducted in the databases of MEDLINE, CINAHL, Web of Science, and Google Scholar. Articles were selected that specifically studied the African American population and assessed the relationship of vitamin D and vascular disease in that group.

Results: All four articles found were cross-sectional in nature and therefore ranked “low” in quality of evidence. Two studies used data from the National Center for Health Statistics and found an independent inverse correlation between vitamin D levels and peripheral artery disease. A third study of ESRD patients looked at the relationship between MMP-9, (a biomarker for vascular disease), and vitamin D levels and found an inverse correlation. There was a positive correlation found in the study by Freedman et al. in regards to vitamin D level and calcified atherosclerotic plaques (CP) in the carotid and infrarenal aorta, with no association found between vitamin D and CP in the coronary vessels.

Conclusion: The findings deduced in this study, suggest that, there is not definitive data that supports as to whether hypovitaminosis D negatively affects vascular health in African-Americans. It is well understood that correlation does not imply causation. There is a need for longitudinal studies as well as random control trials.

Keywords: Vitamin D, African American, Vascular disease, Peripheral Artery Disease, and Cardiovascular disease.

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Hypovitaminosis D as a Contributory Factor to Vascular Disease in African-Americans: A graded literature review



James Moorman PA-S, BSN

A Clinical Graduate Project Submitted to the Faculty of the
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Faculty Advisor: Mark Pedemonte MD

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

[Information redacted for privacy]

Abstract

Background: There is growing concern that chronic hypovitaminosis D at levels below 30ng/ml may negatively contribute to several major diseases of the developed world to include diabetes, cardiovascular disease, and cancer. According to the CDC approximately 80% of African Americans > 1 years of age suffer from vitamin D insufficiency. The clinical question that will be explored in the following literature review is, whether hypovitaminosis D in the African American population contributes to increase incidents of vascular disease.

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Conclusion: The findings deduced in this study, suggest that, there is not definitive data that supports as to whether hypovitaminosis D negatively affects vascular health in African-Americans. It is well understood that correlation does not imply causation. There is a need for longitudinal studies as well as random control trials.

Keywords: Vitamin D, African American, Vascular disease, Peripheral Artery Disease, and Cardiovascular disease.

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List of Abbreviations

25(OH)D.....	25 hydroxyvitamin D
CDC.....	Centers for Disease control and prevention
CP.....	Calcified Atherosclerotic Plaques
ESRD.....	End Stage Renal Disease
MMP-9.....	Matrix metalloproteinase 9
NCHS.....	National Center of Health Statistics
NHANES.....	National Health and Nutrition Examination Survey
PAD.....	Peripheral Arterial Disease
PTH.....	Parathyroid Hormone
UVB.....	Ultra-Violet B radiation

Vitamin D Deficiency as a Cause of Increase Vascular Disease in African Americans

BACKGROUND

Introduction

According to the CDC 2001 to 2006 National Center of Health Statistics (NCHS) approximates that one-third of all Americans aged one-year and over are vitamin D insufficient and of black Americans the number rises to 80%.¹ Over the past 100 years there have been great improvements in nutrition with the fortification of foods with vitamin D and the once common pediatric infliction of rickets as almost been eliminated from the developed world. However, more recently towards the end of the 20th century, scientists have been exploring how vitamin D deficiency may contribute to extra-skeletal health such as cardiovascular disease, hypertension, diabetes, multiple sclerosis, and cancer. This research has led some in the medical community to question whether skeletal health should be the only biomarker for an appropriate vitamin D level should be especially, with the prevalence of vitamin D deficiency in the African American population.

Vitamin D Basics

Vitamin D insufficiency is defined as a concentration of 25-hydroxyvitamin D, (25(OH)D), between 20-30ng/ml (50-75 nmol/L) and deficiency below 20 ng/ml. Hypovitaminosis D is common and may affect more than one billion people worldwide.² Deficiency is known to cause rickets in children, accelerate age related bone loss, and as mentioned earlier, may be associated with nearly all major diseases of the developed world to include, cancer, immune diseases, and cardiovascular disease.^{3,4} Table 1 is from the National Institutes of Health and compares vitamin D with health status.

Recent data from National Health and Nutritional Exam Survey (NHANES) suggest that 77% of the US population have plasma 25(OH)D levels of < 30 ng/ml. The prevalence of vitamin D deficiency is particularly high among African Americans, Hispanics, and Asians.⁵ There is some disagreement within the medical community with The Institute of Medicine's defined parameters for vitamin D deficiency. The concern is that the present recommendation is old with skeletal health the only biomarker and that it falls short in appreciating the effects of vitamin D in extraskelatal health.⁶

The main source of vitamin D is not from diet but rather from cutaneous production as a result of ultraviolet (UV) B photons. More than 90% of the vitamin D requirement for most people comes from casual exposure to sunlight.⁸ UVB radiation with a wavelength of 290–320 nm penetrates uncovered skin and converts cutaneous 7-dehydrocholesterol to previtamin D₃, which in turn becomes vitamin D₃. Anything that influences the amount of exposure to UVB radiation (e.g. cloud cover, clothes, sun-block, etc.), alters the amount of pre-vitamin D₃ being produced from 7-dehydrocholesterol. Latitudes above 37 ° enter a more oblique zenith angle, (angle of the earth in relationship to the sun), during the winter which reduces UVB photons by as much as 80-100% during the winter months.⁹ As Dr. James Dowd puts it, when the leaves change color and begin to fall during autumn, the available UVB is less and your serum vitamin D levels drop. For the places above 37° latitude, vitamin D stores are often depleted by January with diet being the sole source of replenishment.⁶ How much latitude plays a role in vitamin D level is controversial. Hagenau et al¹⁰ published a meta-analysis showing significant decline of vitamin D with latitude in Caucasians but no correlation between latitude and vitamin D deficiency in non Caucasians. Furthermore, as a person ages this situation becomes still more sensitive. Later in life, 7-dehydrocholesterol begins to decline putting older adults at increased risk for developing vitamin D insufficiency. As many as half of older adults in the United States with hip fractures could have serum 25(OH)D levels <12 ng/ml.⁷

Lastly, distribution of melanosomes in skin is one of the largest determinants of vitamin D levels.^{11,12} Melanin evolved as an effective sunscreen, as it absorbs UVB photons. Compared with light skinned people, people with increased melanin pigmentation require longer exposure to sunlight to make the same amount of vitamin D3. The populations with the highest rate of vitamin D deficiency in America are Black Americans.^{7, 9, 11, 12}

Prevalence of vitamin D deficiency in the United States is on the rise despite efforts in food fortification. This decrease may be contributed to the change in lifestyle behavior, increase urbanization, rise in obesity, and dietary habits. In comparing the NHANES there was a marked decrease in serum 25(OH)D levels from the 1988-1994 survey to that of 2001-2004 NHANES data collection. Overall, the mean serum 25(OH)D level in the US population decreased from 30 ng/ml to 24 ng/ml during the 2001-2004 collection.⁵ As described in the Figure 1, non-Hispanic blacks have the highest prevalence of low serum 25(OH)D concentrations.

“As a vascular surgeon, I see more cases of high blood pressure (hypertension), stroke, and peripheral arterial disease (PAD) in African American adults,” said Leila Mureebe, MD, a vascular surgeon at Duke University Medical Center in North Carolina.¹³ African American adults are 40% more likely to have hypertension and are more likely to be diagnosed with coronary heart disease, and they are more likely to die from heart disease.¹³

The link between hypovitaminosis D and vascular disease to include cardiovascular disease is somewhat controversial. In several large cohort studies there seems to be an independent association with hypovitaminosis and cardiovascular mortality.^{14,15,16} There is also evidence of increased vascular disease associated with hypovitaminosis in animal studies.¹⁷ But Rodriguez and colleagues in their cross-sectional study found that the mean plasma 25(OH)D was not significantly different between patients with acute coronary syndrome and the control.¹⁸ Unfortunately, to date, there are no definitive random control trials showing a correlation. Could

chronic hypovitaminosis D in African Americans be contributing to an increase prevalence of vascular disease? This is the question looked at set out in the following literature review.

METHODS

An extensive literature search was conducted in the databases of MEDLINE, CINAHL, Web of Science, and Google Scholar. Terms used during the search were “vitamin D”, “African American”, “vascular disease”, “peripheral artery disease”, and “cardiovascular disease”. The search was limited to English only text with an emphasis on human studies and anything older than 15 years was excluded. Reference lists of found articles were also reviewed to further select relevant articles. The articles were evaluated using the GRADEpro guidelines.

RESULTS

Articles were selected that specifically studied the African American population and assessed the relationship of vitamin D and vascular disease in that group. There were four original research articles found that qualified to address the clinical question; whether hypovitaminosis D in African Americans contributed to an increased incident of vascular disease. Two studies^{19,20} used data from NHANES to evaluate whether there was a statistical association between PAD and vitamin D levels. Both studies did find an association in the general population study population however, in examining the subpopulation of African Americans, this association held for Reis et al²⁰ but fell apart in the Melamed et al¹⁹ study. Association was further supported by the study by Wasse et al,²¹ which found an inverse correlation between vitamin D levels and MMP-9 (a biomarker for vascular disease), and there was also a positive correlation between 25(OH)D and anti-inflammatory IL-10 in African American. Findings differed for Freedman et al²², this study found there was no association between 25(OH)D levels and CP in the coronary arteries and actually an increase in calcified atherosclerotic plaques (CP) in the infrarenal aorta

and carotid arteries with higher levels of vitamin D. See below and table 2 and 3 for further details of relevant studies.

Serum 25-Hydroxyvitamin D Levels and the Prevalence of Peripheral Arterial Disease: Results from NHANES 2001 to 2004

Melamed et al¹⁹ conducted a secondary analysis of the cross-sectional study, NHANES, to assess whether the prevalence of PAD is statistically associated with serum 25(OH)D levels. Subgroup analysis of the study population was conducted. Non-Hispanic blacks were a sample size of 508 participants total with only 60 having PAD.¹⁹

The National Health and Nutrition Examination Survey (NHANES) 2001 to 2004 was a nationally representative cross-sectional survey of the civilian noninstitutionalized United States population performed by the National Center for Health Statistics. Ankle-brachial index (ABI) was measured in NHANES 2001 to 2004 with participants ≥ 40 years of age. Serum 25(OH)D levels were measured for 4839 participants, ≥ 40 years of age, who had complete data on all other study variables. Study procedures in NHANES 2001 to 2004 consisted of an in-home interview followed by a medical evaluation and blood sample collection at a mobile examination center. Self reported race was categorized as non-Hispanic white, non-Hispanic black, Mexican-American, and other. The NHANES 2001 to 2004 examination procedures included measurement of height, weight, and blood pressure.¹⁹

The primary outcome for the study was PAD defined using ABI. Participants with ABI ≥ 1.5 may have severe arterial rigidity and were therefore excluded from analyses (n=10). PAD was defined as ABI < 0.9 . participant characteristics were calculated by PAD status. The statistical significance of differences for these characteristics was determined using least squares and minimum likelihood for continuous and dichotomous variables, respectively. Next, the prevalence of PAD was calculated by quartile of 25(OH)D, with the statistical significance of

trends across quartile assessed using maximum likelihood. Prevalence ratios of PAD associated with quartile of serum 25(OH)D were calculated using log binomial regression models. An initial model included adjustment for age, gender, and race-ethnicity with a subsequent model including additional adjustment for education, current and former cigarette smoking, leisure-time physical activity, diabetes mellitus, total to HDL cholesterol ratio, body mass index, systolic blood pressure, log homocysteine, glycohemoglobin, statin use, antihypertensive medication use, vitamin D supplement use, history of myocardial infarction, elevated CRP, and chronic kidney disease. The multivariable-adjusted association between 25(OH)D, as continuous variable, and PAD was determined overall and for subgroups defined by age, gender, race-ethnicity, BMI, physical activity, diabetes mellitus, a history of myocardial infarction, chronic kidney disease, and vitamin D supplement use. Differences in the association of 25(OH)D and PAD across subgroup were tested by using a multiplicative term in the regression models. Data were analyzed using SUDAAN to account for the complex NHANES sampling design including unequal probabilities of selection, oversampling, and nonresponse.¹⁹

Overall, in the total population, there was a strong, graded association between lower levels of 25(OH)D levels and PAD. However this correlation was not found in the Non-Hispanic black population with the prevalence crossing 1 ranging from 0.81-1.53. Refer to table 2 and 3 for further analysis of the study.¹⁹

Differences in Vitamin D status as a possible contributor to the racial disparity in peripheral arterial disease

A cross-sectional study using data from the NHANES was conducted by Reis et al.²⁰ A total of 3557 white and 1187 black adults aged ≥ 40 years completed a health examination as part of NHANES 2001-2004. Those who did not complete ABI testing or who were missing 25(OH)D information were excluded. The population size was 866 black adults was formed. The study goal

was of establishing whether there is a correlation with PAD and serum 25(OH)D. PAD was determined by an arterial brachial index (ABI) of less than 0.9. Information on smoking, alcohol use, physical activity, vitamin-mineral supplementation, mobility limitation, education, and household income was obtained by self-report.²⁰

All analyses were weighted to the US population to provide nationally representative estimates. SAS-callable SUDAAN statistical software was used to account for the complex survey design, a stratified multistage cluster sample. Because the concentrations of 25(OH)D and the prevalence of PAD differed significantly between the races, they examined predictors of 25(OH)D and risk factors for PAD separately by race. Differences in sample characteristics according to race and presence of PAD were determined with independent sample t test for continuous measures and with chi-square tests for categorical measures. Race-specific odds ratios (Ors) (and 95% CIs) for PAD according to 25(OH)D concentration were estimated by using multivariate logistic regression models. Tests for a linear trend were performed by entering the continuous 25(OH)D variable into the multivariate model as an ordinal term. The researchers found greater association of PAD with lower concentrations of serum 25(OH)D and lower association of PAD with higher serum concentrations. Refer to table 2 and 3 for further analysis of the study.²⁰

25-hydroxyvitamin D concentration is inversely associated with serum MMP-9 in a cross-sectional study of African American ESRD patients

Wasse et al²¹ conducted a cross-sectional study of African Americans with end stage renal disease in the interest of determining whether 25(OH)D is associated with matrix metalloproteinase (MMP) levels (a biomarker for vascular disease). Adult ESRD patients receiving in-center maintenance hemodialysis at one of six Emory University-affiliated Davita dialysis centers in the fall of 2008, were eligible to enroll in the study. The study was limited to

African-Americans. All assessments were conducted at a single baseline visit. Several covariates were analyzed to include, age, gender, self-reported race, length of time on dialysis, body mass index, smoking status, vascular access type (arteriovenous fistula, arteriovenous graft, central venous catheter), season of blood collection, and activated vitamin D treatment. All patients received hemodialysis treatment three times per week. Categorical variables were reported by using the number of percent of observations. Continuous variables were expressed as means with standard deviations. For comparative evaluations, Chi-square tests (Fisher's exact test when appropriate) and student unpaired independent t tests were performed for categorical and continuous variables, respectively. Associations between 25(OH)D and biomarker concentrations were first estimated in univariate analyses using Pearson's correlation coefficients and corresponding P values. To adjust for possible confounding of these associations, multivariate linear regression models were used. Results were stratified by vascular access type. Two-tailed P values $P < 0.05$ were considered statistically significant. All analyses were performed using SAS version 9.2.²¹

There were 91 participants. They found a significant inverse correlation with MMP and 25(OH)D ($p=0.004$). In the univariate analyses and compared to patients with 25(OH)D ≥ 15 ng/ml, MMP-9 and CRP concentrations were significantly greater among subjects with 25(OH)D < 15 ng/ml. The remaining inflammatory markers were not associated with 25(OH)D categories. Difference in MMP-9 concentration between the lowest and highest 25(OH)D groups were compared. Compared to the highest group and after adjustment for smoking, gender, BMI, age, diabetes, season and activated vitamin D treatment, the log MMP-9 concentration was greater in the lowest 25(OH)D group ($P= 0.046$). For every unit increase in 25(OH)D concentration, there was a logarithmic increase in anti-inflammatory IL-10 concentration of 0.02 pg/ml ($p=0.04$). Refer to table 2 and 3 for further analysis of the study.²¹

Vitamin D, Adiposity, and Calcified Atherosclerotic Plaque in African-Americans

Freedman et al²² conducted a cross-sectional study of 340 African Americans with type II diabetes. In this study they examined whether there is a correlation with 25(OH)D and 1,25 dihydroxyvitamin D levels, and calcified atherosclerotic plaque (CP), bone density, and fat volumes. Intact parathyroid hormone (PTH) and C-reactive protein were also examined. African-Americans with type 2 diabetes recruited in the African American-Diabetes Heart Study formed the study population. Examinations were conducted in the General Clinical Research Centers of the Wake Forest University School of Medicine. Calcified atherosclerotic plaque was measured in the coronary, carotid, and infrarenal abdominal aorta arteries with single and multidetector CT systems using a standard electrocardiogram-gated CY scanning protocol based on those currently implemented in the National Heart, Lung, and Blood Institute's Multi-Ethnic Study of Atherosclerosis (MESA). The calcium mass score was used for comparability between vascular territories.²²

Generalized linear models were fitted to test for associations between circulation 25(OH)D, 1,25 dihydroxyvitamin D, hsCRP, and intact parathyroid hormone (PTH) treated separately as predictors with PAD, aorta, coronary, and carotid artery CP. The Box-Cox method was applied to identify the appropriate transformation of each outcome variable that would best approximate the distributional assumptions of conditional normality and homogeneity of variance of the residuals. The natural log of (coronary CP +1), (carotid CP +1), (aorta CP + 1) were analyzed. Analyses were run without adjustment, adjusting for age and gender and adjusting for age, gender, body mass index, GFR, and Hemoglobin A1C. Standard regression diagnostics for collinearity and influence were computed for each model reported.²²

They found no association with 25(OH)D and coronary CP. However, there was a positive association with serum 25(OH)D concentrations and atherosclerotic plaque in the carotid

and infrarenal aorta ($p=0.013$ and 0.014 respectively). Refer to table 2 and 3 for further analysis of the study.²²

DISCUSSION

The clinical question of whether hypovitaminosis D in African Americans contributes to vascular disease is not easily answered but given the present studies there does seem to be a correlation with the strongest evidence coming from the Wasse et al²¹ However, there may also be a harmful association with higher vitamin D levels in regards to vascular health as demonstrated by Freedman et al²² As a clinician, to support vascular health without the significantly increasing the risk of atherosclerotic plaques, there appears to be enough evidence that supports the value of maintaining vitamin D levels at a conservative level between 50nmol/L -75nmol/L in African American patients. It should be emphasized that there is still need for longitudinal studies as well as randomized control trials looking specifically at this population especially to explore the efficacy of vitamin D supplementation on extraskeletal health and appropriate serum levels.

Serum 25-Hydroxyvitamin D Levels and the Prevalence of Peripheral Arterial Disease: Results from NHANES 2001 to 2004

This cross-sectional study¹⁹ found a graded association between lower 25(OH)D levels and a higher prevalence of PAD. This association was present after age, gender, race-ethnicity, and multivariable adjustment. The sample size for African Americans (identified as non-Hispanic black) comprised of approximately 25% of the total population. The prevalence ratio for PAD in the subpopulation of African Americans was 1.11 (0.81-1.53) and since it crosses zero no correlation can be made in this specific group despite the affirmative results of the Caucasian group. Potential limitations most notably, the study was cross-sectional. As any cross-sectional study, one must be cautious interpreting the direction of the association. An additional limitation

is the lack of data in NHANES on sun exposure, geographic location, and the season during which participants attended their study visits a cross-sectional study the quality of evidence is rated low.

Differences in Vitamin D status as a possible contributor to the racial disparity in peripheral arterial disease

Again using data from the NHANES 2001-2004, (nationally representative cross-sectional survey of the civilian noninstitutionalized United States population), Reis et al²⁰ conducted a cross-sectional study and found similar results to that of Melamed et al.¹⁹ Reis et al²⁰ showed that African-Americans are 33% more likely to develop PAD than Caucasians even after adjusting for known confounders. They concluded that their findings suggest that the high frequency of vitamin D deficiency observed in black adults may be an important contributor to higher risk of PAD. As a cross-sectional study the quality of evidence is low. Limitations of the study are similar to that of Melamed et al²⁰ with the study being a cross-sectional. There was no data in NHANES on sun exposure, geographic location, and the season during which participants attended their study visit. As a cross-sectional study the quality of evidence is rated low.

25-hydroxyvitamin D concentration is inversely associated with serum MMP-9 in a cross-sectional study of African American ESRD patients

This cross-sectional study²¹ of 91 African Americans with ESRD was performed with a strong inverse correlation of MMP-9 and 25(OH)D ($r=-0.29$, $p=0.0004$). Secondly there is a dose-response gradient, for every unit increase in 25(OH)D concentration, there was a log decrease in pro-inflammatory MMP-9 concentration of 0.018 pg/ml ($p=0.03$). With the dose-response gradient the study is may be upgraded from a low quality to moderate level (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate) but due to the number of participants and lack of follow up the study

remains at low quality. Limitations include small sample size, cohort limited to ESRD patients, and cross-sectional design of study does not allow for causal inference. As a cross-sectional study the quality of evidence is rated low.

Vitamin D, Adiposity, and Calcified Atherosclerotic Plaque in African-Americans

This cross-sectional study²² most closely met the clinical question by examining calcified atherosclerotic plaques in African Americans and drawing on whether there is a relationship between this vascular disease and vitamin D deficiency. An important observation of the study was that a positive relationship with atherosclerotic plaques in the carotid and infrarenal arteries and serum 25(OH)D levels and, no association found in coronary arteries. This was only a cross-sectional study and as such has limitations. An important limitation of this study was the cross-sectional nature of the CT-derived measurements of CP meaning, that examination of CP was limited to a single plane. Secondly, the population was only that of African American's with type II diabetes. Finally, as a cross-sectional design the study does not allow for causal inference therefore the quality of evidence is rated low.

CONCLUSION

The findings deduced in this study, suggest that, there is not definitive data with strong evidence that supports that hypovitaminosis D negatively affects vascular health in African-Americans. There does seem to be a correlation between hypovitaminosis D and vascular health (especially in the Caucasian population) but to what extent is uncertain. There is a need for longitudinal studies as well as randomized control trials evaluating whether treatment of hypovitaminosis D improves vascular outcomes. It is well understood that correlation does not imply causation. Normal serum concentrations of 25-hydroxyvitamin D may differ based on ethnicity and needs to be determined in the African-American population. Long-term safety studies need to be performed on the effect of supplementing vitamin D in African-Americans

with known deficiency. Vitamin D is an inexpensive supplement that could have a significant role in bridging the health disparity gap between white and black Americans.

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Table 1: Serum 25(OH)D Concentrations and Health¹

nmol/L**	ng/mL*	Health status
<30	<12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30–50	12–20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

* Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL).

** 1 nmol/L = 0.4 ng/mL

Table II. Characteristics of Reviewed Studies

Table 2 Characteristics of Reviewed Studies				Quality Assessment					Importance
Study	Study Design	Sampling	Screening Test	Methodology	Sampling Population	Sampling Process	Indirectness	Quality	
Melamed et al ¹⁹	Cross-Sectional Second Analysis NHANES	White and Black adults. Age ≥ 40 years.	Arterial Brachial index (ABI). Serum 25-hydroxyvitamin D	No Control	Limited to participants of NHANES	Participants of NHANES	Design of study does not allow for causal inference	Low	Similar findings to that of other cross-sectional studies for white Americans. Study lacked power for African Americans
Reis et al ²⁰	Cross-Sectional Second Analysis NHANES	White and Black adults. Age ≥ 40 years.	Arterial Brachial index (ABI). Serum 25-hydroxyvitamin D	No Control	Limited to participants of NHANES	Participants of NHANES	Design of study does not allow for causal inference	Low	These findings suggest that the high frequency of vitamin D deficiency observed in black adults may be an important contributor to their higher risk of PAD.
Wasse et al ²¹	Cross-Sectional	African Americans with End Stage Renal Disease (ESRD).	Serum 25-hydroxyvitamin D and metalloproteinases (MMP's)	No Control	ESRD patients not representative of general population.	Limited to six dialysis centers in Georgia	Surrogate outcome use of MMP biomarker. Design of study does not allow for causal inference	Low	MMP's serve as an important biomarker in extracellular matrix remodeling. 25(OH)D concentration was inversely and significantly correlated with

									MMP
Freedman et al ²²	Cross-Sectional	African Americans with type 2 diabetes. Age median 54.	Vascular imaging with CT Serum 25(OH)D and 1,25 dihydroxyvitamin D.	No Control	Type 2 diabetic patients not representative of gen. population	Limited to Wake Forest University School of Medicine	Design of study does not allow for causal inference	Low	Results contradict what has been observed in individuals of European descent.

Table II. Summary of Findings

Study	Outcome Measurements	Results	Relative Risk	No. of Participants	Quality of evidence
Melamed et al ¹⁹	Peripheral Arterial Disease associated with vitamin D level	Prevalence ratio: 1.11 (0.81-1.53)	n/a	Non-Hispanic black (n=511)	Low
Reis et al ²⁰	Peripheral arterial disease associated with vitamin D level	Excess odds of 33% difference between black and white subjects.	The odds of PAD 2.11 (95% CI: 1.55, 2.87) times as high in black adults	Non-Hispanic black (n=866)	Low
Wasse et al ²¹	MMP-9 association with vitamin D level	Pearson correlation coefficient -0.29, P value = 0.004	n/a	91 African Americans with ESRD	Low
Freedman et al ²²	Calcified atherosclerotic plaque.	Positive association between vitamin D and aorta and carotid artery calcified atherosclerotic plaque (P= 0.013 and 0.014 respectively) but not with coronary artery CP or bone density.	n/a	340 African Americans with type 2 diabetes mellitus.	Low

FIGURES

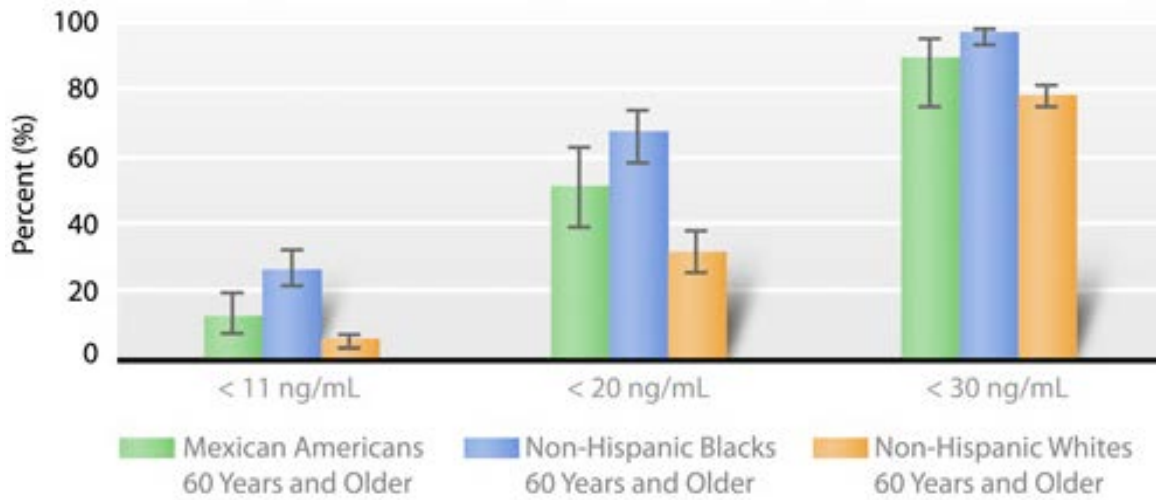


Figure 1: presents the prevalence of insufficiency in the U.S. adults (≥ 60 years) in according to the present parameters.

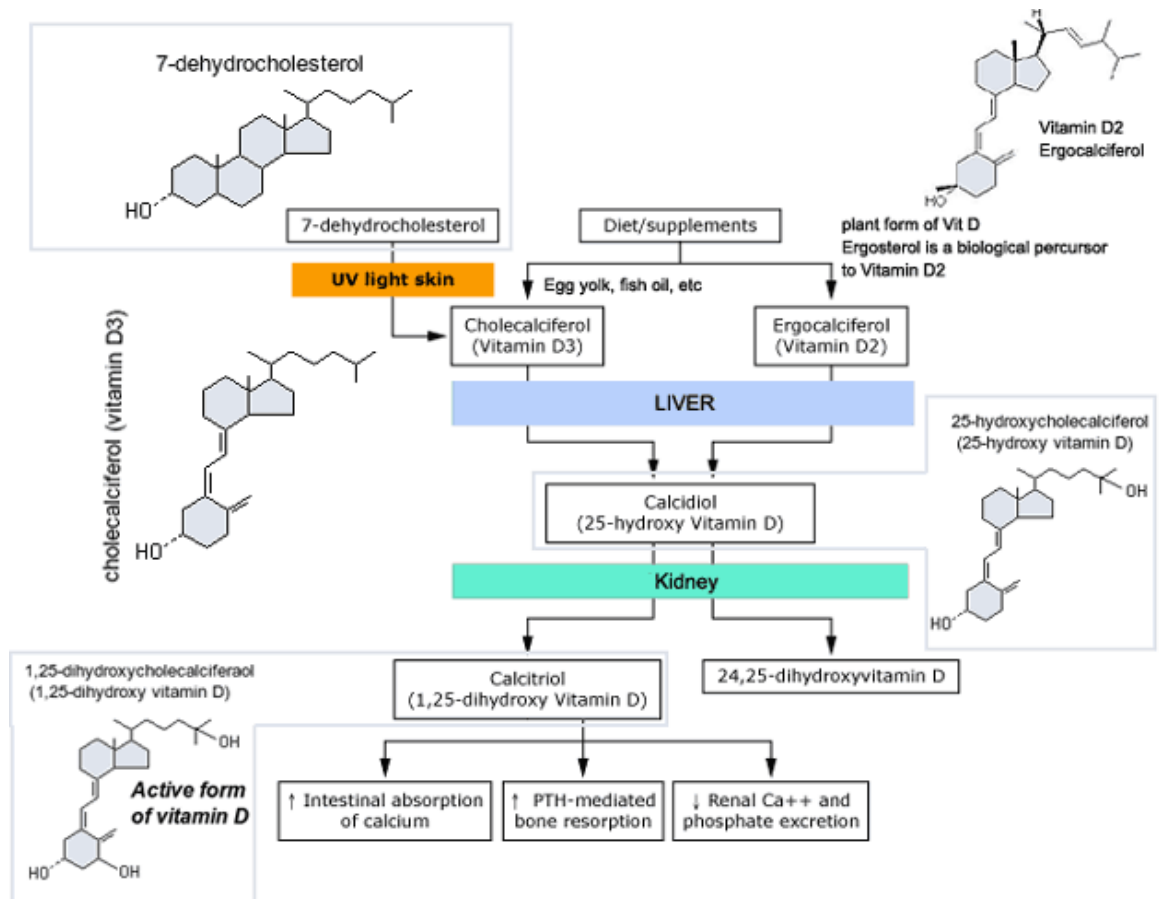


Figure 2. McAuley D. Vitamin D. The clinician's ultimate reference. http://www.globalrph.com/vitamin_d.htm. Last modified September 2011. Accessed January 19, 2012

