Exploration of Association of 1,25-OH2D3 with Augmentation Index, a Composite Measure of Arterial Stiffness

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Background and objectives: Abnormalities in mineral metabolism [calcium, phosphate, and immunoreactive parathyroid hormone (PTH)] and vitamin D have been linked to increases in central arterial stiffness. Central arterial stiffness can be measured using noninvasive technologies, including augmentation index (AIx), a composite measure of arterial stiffness.

Design, setting, participants, and measurements: In 131 outpatients identified from individual cardiac or kidney disease clinics, we examined conventional demographic and laboratory risk factors, vitamin D levels (1,25-OH2D3 and 25-OHD3), and markers of inflammation or endothelial function [C-reactive peptide (hsCRP), matrix metalloproteinase 2 (MMP-2), matrix metalloproteinase 9 (MMP-9), and IL-6] in relationship to AIx.

Results: The median eGFR was significantly different between clinics (range 25–81 ml/min). Subjects with higher phosphate or MMP-9 levels were found to have a higher AIx (P = 0.02 and 0.07, respectively). Lower 1,25-OH2D3 levels or reduced eGFR were associated with higher AIx (P = 0.002 and 0.005, respectively). The associations between 1,25-OH2D3 and phosphate levels and AIx were observed for values within the normal range. No association was noted for calcium, iPTH, 25-OHD3, or hsCRP and AIx. Adjusting for potential confounders [eGFR, calcium, phosphate, and (log) iPTH] the association of lower 1,25-OH2D3 with AIx remained statistically significant.

Conclusion: This exploratory study demonstrates a significant association between AIx and 1,25-OH2D3 in a diverse group with cardiac, kidney disease, or both. These increasing understanding of the role of vitamin D in vascular health lends a context to these findings and raises questions as to additional modifiable risk factors in complex patients. Further studies are required.


Despite significant advances in the prevention and treatment of cardiovascular disease (CVD) the incidence, prevalence, morbidity, and mortality remain high. While traditional risk factors such as hypertension, diabetes, dyslipidemia, and tobacco use offer targets for therapeutic intervention, they do not account for the entire spectrum of disease. In recent years the focus has turned to emerging nontraditional risk factors as well as the concept of central (aortic) arterial stiffness (CAS). Estimates of CAS using radial tonometry and subsequent pulse wave analysis (PWA) have been validated and shown to predict outcomes as diverse as global CV risk, ischemic threshold, and CAD disease burden, as well as CV and all-cause mortality in the general population as well as the elderly and those with diabetes, hypertension, or chronic kidney disease (CKD) (1–5).

CAS has been shown to vary with various physiologic and pathologic states. Aging has long been associated with a hardening of the conduit arteries. Recently it has been shown that a significant independent association exists between inflammation, as measured by hsCRP, IL-6, or soluble intercellular adhesion molecule-1, and CAS (3,6,7). Likewise an association exists between CAS and the gelatinases [matrix metalloproteinase 2 and 9 (MMP-2 and MMP-9)] that mediate the degradation of collagen and elastin and CAS (8).

Abnormalities of mineral metabolism [calcium (Ca2+), phosphate (PO4), and intact parathyroid hormone (iPTH)] and vitamin D have been implicated as risk factors for CVD in both the CKD and non-CKD populations, being associated with increased rates of myocardial infarction, stroke, and heart failure (HF), as well as an increased all-cause mortality (OR 1.71 for men and 1.85 for women) (9–12). Part of this increased risk stems from the recognition that hyperparathyroidism and vitamin D deficiency result in multiple dysregulatory abnormalities including malignant myocardial and valvular calcification, disturbances in the renin–angiotensin system, and vascular endothelial cell dysfunction leading to increased arterial stiffness and resultant hypertension, left ventricular hypertrophy, and diastolic dysfunction (11,13–16). To complicate matters further, vitamin D deficiency is highly prevalent in unscreened...
populations and is associated with increased inflammation, as well as vascular and myocardial dysfunction (17,18).

**Purpose**

The purpose of this exploratory observational cross-sectional study was to describe the relationship between nontraditional cardiovascular risk factors in outpatient populations identified predominantly as having either cardiac disease or kidney disease.

**Materials and Methods**

**Subjects**

Between the months of March 2004 and April 2006, 131 consecutive consenting patients over the age of 18 yr from two cardiac clinics and one renal clinic at a tertiary care institution in Vancouver, BC, Canada, were enrolled. Forty-one patients with predominantly coronary artery disease (CAD) were recruited from the Healthy Heart Program (HHP), 41 with predominantly NYHA class 1–3 HF from the Heart Function Clinic (HFC), and 49 with predominantly CKD from the Kidney Function Clinic (KFC). At the time of enrollment all of these patients were receiving best evidence standardized care. Recruitment did not vary by season. The study protocol was approved by the institutional ethics board, and all patients provided informed written consent.

**Variables of Interest and Data Collection**

Detailed baseline characteristics, medications, and comorbidities were ascertained by clinical and chart review. All patients had brachial BP measurement, height and weight determination, and a pulse wave analysis (see below) at the time of enrollment. Venous blood samples were obtained for complete blood count (CBC), electrolytes, lipids, creatinine, and parameters of mineral metabolism (Ca2+, PO4, and iPTH) after an overnight fast. Kidney function was estimated by using the four-variable MDRD formula and standardized creatinine values. For the purposes of data analysis, patients with GFR >60 ml/min/1.73 m² are assumed to have normal kidney function.

At the time of initial blood draw, samples for vitamin D levels (1,25-OH2D3 and 25-OHD3) as well as inflammatory and endothelial markers (hsCRP, MMP-2, MMP-9, and IL-6) and NT-proBNP were frozen, stored at -70°C, and later run as a separate batch analysis in a central laboratory. 25-OHD3 levels were determined by Sorin RIA (Stillwater, MN), and 1,25-OH2D3 levels were determined by using a competitive binding assay (13). MMP-9 and MMP-2 were measured by using a quantitative sandwich enzyme immunoassay technique. (Quantikine; R&D Systems). IL-6 was measured by using a multiplex Luminox assay (Human Cardiovascular Disease Panel 3 Linco plex kit). High-sensitivity CRP was measured by using a solid-phase chemiluminescent immunometric assay (Immulite 2000; Siemens Healthcare). All analyses were run in the same laboratory under the same conditions using standard protocols.

**Measures of Central Stiffness: Pulse Wave Analysis**

Pulse wave analysis (PWA) is a validated simple, reproducible, noninvasive, tonometric technique for assessing CAS (2,19). Using a peripheral site, in this case the radial artery, one is able to capture and analyze a composite pulse waveform that consists of a forward traveling pressure wave due to ventricular contraction and a peripherally reflected wave (which normally results in diastolic augmentation). As the central arteries stiffen there is increased conduction with faster translation of the outgoing wave. Eventually the timing of the reflected wave encroaches earlier into systole resulting in increased cardiac afterload (augmented systolic pressure) as well as a fall in coronary perfusion pressure and diastolic BP (3,20).

Data derived from PWA can be used to calculate a validated surrogate of central arterial compliance known as the augmentation index of the central aortic pressure waveform (AIx) (2,19). AIx is a parameter that reflects the degree to which central arterial pressure is enhanced by wave reflection and is defined as the augmentation pressure divided by the pulse pressure. Higher AIx values suggest increased peripheral wave reflection and/or earlier reflected wave return secondary to increased pulse pressure propagation velocity (PWV) (due to increased CAS) (3,20).

Using previously described techniques a trained research assistant performed pulse wave analysis using applanation tonometry of the radial artery. Aortic pulse waveform, central aortic pressure, and augmentation index at an HR of 75 were assessed with the commercially available noninvasive SphygmoCor Aortic BP Waveform Analysis System (AtCor Medical, Sydney, Australia), a validated assessment of CAS (21–21). This technique is simple to apply in an outpatient setting given the use of the radial artery, which is easily exposed.

**Statistical Analyses**

The study cohort’s demographics at baseline, as well as the AIx, measures of mineral metabolism, and inflammatory markers of interest were summarized by the clinic of origin where patients were recruited (see Table 1). We then examined these parameters of mineral metabolism and inflammatory markers by the tertile of AIx. Descriptive statistics such as mean with SD or median with interquartile range, depending on the underlying distribution, are reported for continuous variables. Percentages are used to summarize categorical variables. χ², one-way ANOVA, and Kruskal–Wallis tests were employed, where appropriate, to examine whether the distribution of the aforementioned variables is homogeneous across clinics and across tertile of AIx. All tests were two-sided with P < 0.05 considered to be statistically significant.

If the distribution of any of the mineral metabolism and inflammatory markers was found to be nonhomogeneous among the tertile of AIx, we subsequently examined whether the observed difference was linear in relationship with AIx. To do so, a simple linear regression model was employed. The identified marker was treated as the outcome variable, and the tertile of AIx as a continuous predictor in the model. In the multiple regression model, we further adjusted for eGFR and all other remaining mineral metabolism and/or inflammatory markers.

All analyses were carried out in SAS software, Version 9.1 (SAS Institute, Cary, NC). Graphical presentation of the data was prepared in the statistical software SPLUS, Version 7.0 (Insightful Corporation).

**Results**

One hundred thirty-one subjects were enrolled for investigation. The demographics of the study population are as stated in Table 1. Overall, the cohort had a mean age of 62 yr and was predominantly men (67%). Sixty-six percent (66%) of the patients enrolled were hypertensive, and 29% had type 1 or type 2 diabetes. The average eGFR for the cohort was 51 ml/min/1.73 m². With respect to CVD, 50% had underlying CAD, 36% had HF or left ventricular hypertrophy (LVH), and 5% had a history of stroke or peripheral vascular disease (PVD).

When stratified by clinic of origin the demographic results were similar although those originating from KFC were significantly younger with a higher burden of hypertension (P =
Table 1. Characteristics of study cohort at baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall</th>
<th>HHP</th>
<th>HFC</th>
<th>KFC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>131</td>
<td>41</td>
<td>41</td>
<td>49</td>
<td>—</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>62 (12)</td>
<td>62 (11)</td>
<td>67 (11)</td>
<td>58 (13)</td>
<td>0.002</td>
</tr>
<tr>
<td>Male, %</td>
<td>67</td>
<td>68</td>
<td>79</td>
<td>57</td>
<td>0.08</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>80</td>
<td>80</td>
<td>87</td>
<td>73</td>
<td>0.28</td>
</tr>
<tr>
<td>Body mass index in kg/m² (SD)</td>
<td>27 (5)</td>
<td>28 (4)</td>
<td>28 (5)</td>
<td>27 (6)</td>
<td>0.56</td>
</tr>
<tr>
<td>eGFR in ml/min/1.73m² [IQR]</td>
<td>51 [31-79]</td>
<td>81 [66-90]</td>
<td>64 [44-79]</td>
<td>25 [16-37]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>66</td>
<td>54</td>
<td>54</td>
<td>86</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29</td>
<td>29</td>
<td>23</td>
<td>33</td>
<td>0.61</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>50</td>
<td>80</td>
<td>74</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>5</td>
<td>2</td>
<td>10</td>
<td>2</td>
<td>0.18</td>
</tr>
<tr>
<td>Left ventricular hypertrophy or heart failure, %</td>
<td>36</td>
<td>22</td>
<td>87</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>5</td>
<td>5</td>
<td>13</td>
<td>0</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*HHP, Healthy Heart Program (predominantly CAD); HFC, Heart Function Clinic (predominantly heart failure); KFC, Kidney Function Clinic (predominantly chronic kidney disease); IQR, interquartile range.

A significant difference was found between clinics for MMP-2 (P < 0.001) but not MMP-9 (P = 0.75). With respect to inflammatory markers, no difference was observed in hsCRP or IL-6 levels when stratified by clinic. Patients from the CKD clinic had the lowest NT-proBNP level whereas patients from the HFC, expectedly, had the highest level.

Table 2. Augmentation index, mineral metabolism, and inflammatory markers overall and by clinic type

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall</th>
<th>HHP</th>
<th>HFC</th>
<th>KFC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augmentation index (SD)</td>
<td>20.9 (8.9)</td>
<td>17.6 (9.0)</td>
<td>20.9 (7.8)</td>
<td>23.8 (8.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Calcium in mmol/L (SD)</td>
<td>2.31 (0.12)</td>
<td>2.29 (0.09)</td>
<td>2.33 (0.14)</td>
<td>2.29 (0.14)</td>
<td>0.30</td>
</tr>
<tr>
<td>Phosphate in mmol/L (SD)</td>
<td>1.12 (0.22)</td>
<td>1.04 (0.17)</td>
<td>1.08 (0.21)</td>
<td>1.22 (0.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP in mcg/ml [IQR]</td>
<td>0.92 [0.39-3.04]</td>
<td>0.99 [0.37-2.52]</td>
<td>1.29 [0.64-3.69]</td>
<td>0.81 [0.37-2.03]</td>
<td>0.15</td>
</tr>
<tr>
<td>MMP-9 in mcg/ml [IQR]</td>
<td>0.47 [0.32-0.79]</td>
<td>0.56 [0.32-0.83]</td>
<td>0.42 [0.33-0.91]</td>
<td>0.49 [0.30-0.66]</td>
<td>0.75</td>
</tr>
<tr>
<td>IL-6 &lt; 0.64 pg/ml, %</td>
<td>72</td>
<td>80</td>
<td>59</td>
<td>76</td>
<td>0.07</td>
</tr>
<tr>
<td>NT proBNP in pg/ml [IQR]</td>
<td>244 [60-658]</td>
<td>194 [61-308]</td>
<td>1,021 [443-1,930]</td>
<td>94 [44-265]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Significant differences between clinics were observed for AIx, phosphate, iPTH, 1,25OH2D3, MMP-2, and NT-pro BNP. For AIx, phosphate, and iPTH there was a "gradient" of effect through the three clinics with HHP having the lowest values, KFC having the highest, and HFC sitting in the middle. The opposite effect was observed for 1,25OH2D3. HHP, Healthy Heart Program (predominantly CAD); HFC, Heart Function Clinic (predominantly heart failure); KFC, Kidney Function Clinic (predominantly chronic kidney disease); AIx, augmentation index; CRP, C-reactive peptide; MMP-2, matrix metalloproteinase 2; MMP-9, matrix metalloproteinase 9; IQR, interquartile range.
and 0.005, respectively). Strikingly, with respect to 1,25-OH2D3 function (eGFR) were more likely to have higher AIx (P = 0.005, respectively). Similarly, those with lower 1,25-OH2D3 levels or lower values for renal function (eGFR) were more likely to have higher AIx (P = 0.002 and 0.005, respectively). Strikingly, with respect to 1,25-OH2D3 and phosphate levels, this finding was observed for values that remained in the normal reference range for our laboratory (phosphate normal range 0.65–1.65 mmol/L). No association was noted for calcium, iPTH, 25-OHD3, or hsCRP with respect to the tertile of AIx. These findings remain when AIx was analyzed as a continuous variable (data not shown).

Figure 2 demonstrates linear relationships of eGFR, phosphate, and 1,25-OH2D3 with the tertile of AIx. Phosphatemia was found to increase with AIx tertile (P = 0.008). An inverse relationship was observed between eGFR and AIx tertile and between 1,25-OH2D3 and AIx tertile where lower values of eGFR were associated with higher AIx tertile (P = 0.003). Likewise, lower values of 1,25-OH2D3 were associated with higher AIx tertile (P < 0.001).

Multivariate Analysis

We further examined whether the linear relationship between 1,25-OH2D3 (in logarithmic scale) and tertile of AIx remains after adjusting for potential confounders such as eGFR, calcium, phosphate, and iPTH via logarithmic scale. The observed inverse linear relationship between 1,25-OH2D3 and tertile of AIx remained statistically significant (R² = 0.51; β for AIx tertile = −0.16, P = 0.03). Conversely, the relationship between eGFR and AIx after adjusting for all mineral metabolism markers was no longer significant (R² = 0.45; β for AIx tertile = −0.05, P = 0.08). Similarly, the relationship between phosphate and AIx was also NS (R² = 0.23; β for AIx tertile =

Table 3. Summary statistics for mineral metabolism and inflammatory markers by augmentation index

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall</th>
<th>First tertile</th>
<th>Second tertile</th>
<th>Third tertile</th>
<th>P valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augmentation index (SD)</td>
<td>20.9 (8.9)</td>
<td>[-11, 17]</td>
<td>[17, 25]</td>
<td>[25, 47]</td>
<td>—</td>
</tr>
<tr>
<td>Clinic type, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>HHP</td>
<td>31</td>
<td>49</td>
<td>27</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>HFC</td>
<td>31</td>
<td>34</td>
<td>39</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>KFC</td>
<td>38</td>
<td>17</td>
<td>33</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>eGFR in ml/min/1.73m² [IQR]</td>
<td>51 [31-79]</td>
<td>73 [45-87]</td>
<td>50 [32-73]</td>
<td>40 [21-70]</td>
<td>0.005</td>
</tr>
<tr>
<td>Calcium in mmol/L (SD)</td>
<td>2.31 (0.12)</td>
<td>2.27 (0.10)</td>
<td>2.33 (0.12)</td>
<td>2.30 (0.15)</td>
<td>0.09</td>
</tr>
<tr>
<td>Phosphate in mmol/L (SD)</td>
<td>1.12 (0.22)</td>
<td>1.04 (0.19)</td>
<td>1.14 (0.26)</td>
<td>1.18 (0.21)</td>
<td>0.02</td>
</tr>
<tr>
<td>CRP in mcg/ml [IQR]</td>
<td>0.92 [0.39-3.04]</td>
<td>0.84 [0.38-2.59]</td>
<td>1.08 [0.68-2.42]</td>
<td>0.69 [0.32-2.90]</td>
<td>0.27</td>
</tr>
<tr>
<td>MMP-9 in mcg/ml [IQR]</td>
<td>0.47 [0.32-0.79]</td>
<td>0.36 [0.29-0.63]</td>
<td>0.49 [0.40-0.67]</td>
<td>0.57 [0.31-0.98]</td>
<td>0.07</td>
</tr>
<tr>
<td>IL-6 &lt; 0.64 pg/ml, %</td>
<td>72</td>
<td>68</td>
<td>78</td>
<td>68</td>
<td>0.52</td>
</tr>
<tr>
<td>NT-proBNP in pg/ml [IQR]</td>
<td>244 [60-658]</td>
<td>226 [58-787]</td>
<td>265 [63-1,117]</td>
<td>204 [61-646]</td>
<td>0.70</td>
</tr>
</tbody>
</table>

aWhen categorized by tertile of AIx trends were observed between groups. The most abnormal value of AIx was found to be significantly associated with lower eGFR and 1,25(OH)2D3 levels as well as higher phosphate levels. There was an association towards higher MMP-9 in the most abnormal AIx group. HHP, Healthy Heart Program (predominantly CAD); HFC, Heart Function Clinic (predominantly heart failure); KFC, Kidney Function Clinic (predominantly chronic kidney disease); AIx, augmentation index; CRP, C-reactive peptide; MMP-2, matrix metalloproteinase 2; MMP-9, matrix metalloproteinase 9; IQR, interquartile range.

bBased on one-way ANOVA or Kruskal-Wallis test.
Discussion

This exploratory study demonstrates a significant association between AIx (a composite measure of central arterial stiffness) and 1,25-OH2D3 in a diverse group of individuals with CVD, CKD, or both. To our knowledge this is the first study to describe these associations in subjects with milder CKD (stage 2 to stage 4), a group known to be at highest risk of CVD, and in cardiac patients not followed by nephrologists. Importantly, we believe that this information adds credence to the postulated importance of the role of vitamin D in the maintenance of vascular health.

In addition to other factors, vitamin D is known to exert immunoregulatory properties via the ubiquitous vitamin D receptor, a receptor that is present in almost every organ, as well as the vascular wall and most immune cells. In normal conditions vitamin D has been shown to inhibit antigen-presenting cell maturation, angiogenesis, and smooth muscle cell proliferation, as well as alter the cytokine profile to one that less favors inflammation through interaction with the vitamin D receptor (17). Moreover, on a more phenotypic level, vitamin D deficiency may be associated with obesity, metabolic syndrome, and diabetes, conditions known to be associated with adverse vascular health (22). Given the aforementioned effects of vitamin D on mitigating smooth muscle proliferation and inflammation we postulate that a deficiency of 1,25-OH2D3 would lead to multiple dysregulatory vascular effects, eventually leading to abnormalities in central arterial stiffness, and thus our observed relationship with AIx. It is interesting to note that these data describe a relationship despite the relatively “normal” levels of 1,25-OH2D3. It may be that current definitions of deficiency and insufficiency need to be reexamined.

CAS has been shown to be related to a number of pathologic states. Studies from various populations have shown that AIx and PWV are related to anthropomorphic variables (gender, height, aortic width), smoking status, and BP (systolic, mean arterial, and brachial pulse pressure), as well as various pathologic states. Inflammation, a marker of vascular health, has been linked to abnormalities in conduit artery function. Recent studies have shown a relationship between hsCRP, IL-6, or soluble intercellular adhesion molecule-1 and CAS (1,6,7). Likewise, there is an association between CAS and the gelatinases (MMP-2 and MMP-9) that mediate the degradation of collagen and elastin (8).

In this small exploratory study we were not able to find an association between hsCRP or IL-6 and AIx in our analyses. This is potentially congruent with existing literature, with some studies observing a correlation and others failing to find one.
and our relatively small numbers of subjects a significant asso-
ciation did emerge in patients traditionally considered to be
125O\textsubscript{H}2D3-deficient who were undergoing treatment (CKD
patients) as well as those who were not (cardiac patients).

The observation that vitamin D is associated with measures
of CAS must be interpreted with caution. Although biologic
plausibility exists, it is possible that the observed association
may be the result of residual confounding and does not neces-
sarily indicate a causal link among 125O\textsubscript{H}2D3, deficiency, and
vascular disease. Likewise, our small numbers and the cross-
sectional observational nature of this study limit interpretation;
therefore, this study remains only hypothesis-generating and
should facilitate further studies that examine the degree of
variability in outcomes explained by these newer laboratory
tests in addition to CAS measures. More importantly, once the
biologic relationships are more thoroughly ascertained, large
randomized clinical trials might be undertaken to ascertain
whether treatment with vitamin D supplementation might im-
impact these measures of CAS (surrogates) or hard CV outcomes.

Currently the most widely available clinical estimates of CAS
are derived from applanation tonometry with the resultant
calculation of an augmentation index (AI\textsubscript{x}) as well as measure-
ments of peripheral pulse-wave velocity. Concerns have re-
cently arisen regarding the ability of AI\textsubscript{x} to assess CAS because
of its being a composite measure that is dependent on multiple
factors including PWV, pulse pressure propagation distance,
and incident and reflected wave overlap (left ventricular ejec-
tion time and time to shoulder relationship), as well as a sys-
temic reflection coefficient. Owing to these concerns, recent
investigations into the mechanism of CAS have suggested that
wave reflection (i.e., AI\textsubscript{x}) is not pathogenic but merely an
epiphenomenon. A recent study examining the etiology of CAS
found that the observed increase in pulse pressure is primarily
attributable to increased wall stiffness and reduced aortic di-
ameter rather than premature wave reflection (28). Thus, while
being a composite measure of arterial stiffness, given that mul-
tiple studies have shown AI\textsubscript{x} to correlate closely with direct
measurements of PWV and to be an independent predictor of
adverse cardiovascular events, including mortality, we believe
the findings herein to be of interest. Consensus remains regard-
ing the prognostic utility of this test (3–5).

In summary, we have reported an exploratory study that
examines the role of mineral metabolism parameters and in-
flammatory markers in patients with CVD, kidney disease, and
the combination thereof. In so doing we have attempted to link
an emerging literature on vascular biology, conventional and
nonconventional risk factors for vascular health, and new un-
derstandings about vascular health and disease in CKD pa-
tients. Thus, this simple observational study appears to de-
scribe the complex interaction of multiple aspects of vascular
health and corroborates known relationships. It may be that
nondialysis CKD patients represent a severe subtype of the
CVD population. As such, studies need to be conducted exam-
imining nontraditional risk factors in those with CKD, CVD, or
both. It is imperative that we better understand the complexity
of the pathobiology of vascular disease in a spectrum of pa-
tients so that better therapeutic approaches can be designed
and tested.
Disclosures

None.

References


