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25-Hydroxyvitamin D is lower in deprived groups, but is not associated with carotid intima media thickness or plaques: Results from pSoBid

Susan Knox [a,1], Paul Welsh [b,1], Vladimir Bezlyak [c], Alex McConnachie [c], Emma Boulton [b], Kevin A. Deans [d], Ian Ford [c], G. David Batty [e,f], Harry Burns [g], Jonathan Cavanagh [h], Keith Millar [h], Iain B. McInnes [i], Jennifer McLean [j], Yoga Velupillai [k], Paul Shiels [l], Carol Tannahill [j], Chris J. Packard [m], A. Michael Wallace [a,2,†], Naveed Sattar [b,*,2]

[a] Department of Clinical Biochemistry, Glasgow Royal Infirmary, Glasgow G31 2ER, UK
[b] Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, 126 University Place, University of Glasgow, Glasgow G12 8TA, UK
[c] Robertson Centre for Biostatistics, University of Glasgow, Glasgow G12 8QQ, UK
[d] Department of Clinical Biochemistry, Aberdeen Royal Infirmary, Aberdeen AB25 2ZD, UK
[e] Medical Research Council Social and Public Health Sciences Unit, Glasgow G12 8RZ, UK
[f] Department of Epidemiology and Public Health, UCL, London WC1E 6BT, UK
[g] Scottish Government, St. Andrew's House, Edinburgh EH1 3DG, UK
[h] Section of Psychological Medicine, University of Glasgow, Gartnavel Royal hospital, Glasgow G12 0XH, UK
[i] Glasgow Biomedical Research Centre, University of Glasgow, Glasgow G12 8TA, UK
[j] Glasgow Centre for Population Health, Glasgow G2 4DL, UK
[k] Graduate Entry Medical School (GEMS), University of Limerick, Ireland
[l] University Department of Surgery, University of Glasgow, Glasgow Western Infirmary, Glasgow G11 6NT, UK
[m] Glasgow Clinical Research Facility, Western Infirmary, Glasgow G11 6NT, UK

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ABSTRACT

Objective: The association of the circulating serum vitamin D metabolite 25-hydroxyvitamin D (25OHD) with atherosclerotic burden is unclear, with previous studies reporting disparate results.
Method: Psychological, social and biological determinants of ill health (pSoBid) is a study of participants aged 35–64 years from Glasgow who live at extremes of the socioeconomic spectrum. Vitamin D deficiency was defined as 25OHD < 25nmol/L, as per convention. Cross-sectional associations between circulating 25OHD concentrations and a range of socioeconomic, lifestyle, and biochemistry factors, as well as carotid intima media thickness (cIMT) and plaque presence were assessed in 625 participants.
Results: Geometric mean levels of circulating 25OHD were higher among the least deprived (45.6 nmol/L, 1-SD range 24.4–85.5) versus most deprived (34.2 nmol/L, 1-SD range 16.9–69.2; $p < 0.0001$). In the least deprived group 15% were "deficient" in circulating 25OHD versus 30.8% in the most deprived (χ^2 $p < 0.0001$). Log 25OHD was 27% lower among smokers ($p < 0.0001$), 20% higher among the physically active versus inactive ($p = 0.01$), 2% lower per 1 kg/m^2 increase in body mass index (BMI) ($p < 0.0001$), and showed expected seasonal variation (χ^2 $p < 0.0001$). Log 25OHD was 13% lower in the most versus least deprived independent of the aforementioned lifestyle confounding factors ($p = 0.03$). One unit increase in log 25OHD was not associated with atherosclerotic burden in univariable models; cIMT (effect estimate 0.000 mm [95% CI −0.011, 0.012]); plaque presence (OR 0.88 [0.75, 1.03]), or in multivariable models.
Conclusion: There is no strong association of 25OHD with cIMT or plaque presence, despite strong evidence 25OHD associates with lifestyle factors and socioeconomic deprivation.

1. Introduction

It has been widely reported that vitamin D deficiency, as assessed by measuring the major circulating vitamin D precursor 25-hydroxyvitamin D (25OHD), may adversely affect the cardiovascular system [1]. Prospectively, several studies report a link

* Corresponding author. Tel.: +44 (0) 141 330 3419; fax: +44 (0) 141 330 6972.
E-mail address: nsattar@clinmed.gla.ac.uk (N. Sattar).
[1] Joint first authors.
[2] Joint senior authors.
† Deceased.

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between low circulating 25OHD concentrations and higher risk for incident CVD events [2–4], as well as a range of other acute and chronic diseases. Such research has led to recommendations regarding desirable 25OHD levels, and the requirement for vitamin D supplements in large proportions of the population [5]. As such, routine clinical biochemistry departments locally and elsewhere, are reporting vastly increased clinical demand for 25OHD measurements [6].

We have previously argued, as have others, that observational data may be confounded and subject to reverse causality, these limitations being of particular relevance for 25OHD [6–8]. There is no convincing evidence from randomized trials that vitamin D supplements can reduce CVD risk, despite reported observational associations with risk [9]. To advance the literature, we aimed to investigate the association of circulating 25OHD with measures of atherosclerotic burden, whilst also investigating (and therefore adjusting for) any association of 25OHD with socioeconomic status and related characteristics. Carotid intima media thickness (cIMT) and plaque presence are emerging as potentially strong markers of CVD risk in general populations, with plaque presence is perhaps a stronger predictor of cardiovascular events than cIMT [10].

The pSoBid (psychological, social and biological determinants of ill health) study comprises a cross section of men and women from either socially deprived or socially advantaged areas in Greater Glasgow, who had cIMT and plaque presence measured. We hypothesised that 25OHD would be lower in more deprived individuals independently of measured lifestyle factors, and that such associations could at least partially explain a hypothesised association of 25OHD with markers of carotid atherosclerosis.

2. Methods

2.1. Participants

The recruitment procedure for the pSoBid study has been described in detail previously [11]. Briefly, participants were invited to participate in the study at random (via ten general practice lists) from areas known to be at the extremes of the socioeconomic continuum in Glasgow, Scotland, such that approximately equal numbers of males and females across three age categories (35–44, 45–54, and 55–64 years) would be recruited. Socioeconomic selection was based on Scottish Index for Multiple Deprivation (SIMD) 2004 scores which is a small area-based score of deprivation based on data from public records relating to 38 indicators across 7 domains: income; employment; health; education, skills and training; housing; geographic access; crime [12] (see Supplementary data). As an illustration annual household income was <£15,000 among in 60% of the most deprived participants, and >£45,000 among 60% of the least deprived participants. SIMD is currently used for clinical cardiovascular risk assessment in Scotland (the ASSIGN risk score [13]). Those recruited were either most deprived (bottom 5% of SIMD score) or least deprived (top 20% of SIMD). A total of 666 participants recruited between Dec 2005 and May 2007 (616 underwent ultrasound measurements of the carotid artery) [11]. This group comprised 171 males and 171 females in the least deprived group, and 156 males and 168 females in the most deprived group. Only 19 participants (2.9%) were born outside of the United Kingdom or Republic of Ireland. Comparison of participants with non-participants has been reported previously [14]. Participants underwent a routine physical examination (including measurement of blood pressure, body mass index [BMI], and waist hip ratio [WHR]) and lifestyle questionnaire [11]. Dysglycaemia was identified through current treatment for diabetes, and a fasting measure of plasma glucose [11]. Physical activity was assessed using a validated questionnaire and categorised those who were inactive, moderately inactive, moderately active, and active. The study was reviewed and approved by the Glasgow Royal Infirmary Research Ethics Committee; all participants gave written informed consent.

2.2. Carotid intima media thickness and plaque count

Doppler velocity in right and left internal carotid arteries was recorded in order to identify carotid artery stenosis using an ACUSON Sequoia 512 Ultrasound System with an L7 5–12 MHz linear array broadband transducer (Siemens Medical Solutions, Erlangen, Germany). Images of the distal 1 cm of the common carotid artery, the carotid bulb and the proximal internal carotid artery were recorded on the left and right side, and intima media thickness of the far wall of the artery determined (using eTrack software). At the six sites, the number of carotid plaques was determined [15], and counted. Plaque was defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or demonstrating a thickness >1.5 mm as measured from media–adventitia interface to intima–lumen interface. In order to adjust for unreadable images, total plaque count for each subject was divided by the number of readable images present and multiplied by 6 (the maximum possible number of images per subject) [15]. Nurses performing scans were subject to reproducibility checks as detailed [14]. Reading of the scans was performed off-line by a reader who was blinded to the identity of the participants.

2.3. Analytical procedures

Fasting venous blood samples were taken on the same visit as the ultrasound examination. We have a high-throughput method for the measurement of $25OHD_3$ and D_2 using an automated solid-phase extraction (SPE) procedure with liquid chromatography–tandem mass spectrometry [16]. The lower limit of sensitivity was reported as 7.5 nmol/L for $25OHD_2$ and for $25OHD_3$. Within- and between-assay precision was below 10%. Our method is currently in routine clinical use. Results are reported as total 25OHD ($25OHD_2 + 25OHD_3$). Measurements of 25OHD were made by technicians who did not have access to the prior cIMT or plaque measurements, and were therefore blinded. A total 25OHD of <25 nmol/L (10 ng/ml) was defined as “deficiency”, by convention frequently cited in the literature.

2.4. Statistical analysis

Descriptive statistics are presented as mean (SD) and median (interquartile range, IQR) for continuous variables and count (%) for categorical outcomes. Due to skew, 25OHD is presented as a geometric mean and geometric standard deviation (i.e. the square root of the factor the geometric mean must be divided or multiplied by to give the 95% range). Associations between 25OHD and demographic and socioeconomic factors are presented adjusting for age, sex, and month of participation, and again with further adjustment for BMI, physical activity level and smoking status. Linear regression models were used, with log 25OHD as the response variable. Effect estimates are reported as percentage differences associated with a 10-year increase in age, or for categorical variables, relative to a reference category. Associations between 25OHD and cardiovascular risk factors were assessed using linear regression models with the risk factor (or its logarithm – see Table 2 for details) as the outcome, and the logarithm of 25OHD as a predictor (scaled by the standard deviation (SD) of log 25OHD), with adjustment for age, sex and deprivation group. Effect estimates are reported as the regression coefficient,