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Cross-sectional and longitudinal associations between serum 25-hydroxyvitamin D and anti-oxidative status in older adults

Alexandra Jungert, Monika Neuhäuser-Berthold*

Institute of Nutritional Science, Justus Liebig University, Goethestrasse 55, D-35390 Giessen, Germany

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ABSTRACT

Objective: Emerging evidence indicates that vitamin D has anti-oxidative properties. The present study investigates whether serum 25-hydroxyvitamin D [25(OH)D] is associated with biomarkers of anti-oxidative status in community-dwelling older adults using cross-sectional and longitudinal data.

Methods: A total of 302 subjects aged 62 to 92 years from Germany (50.6°N) were analysed via cross-sectional approach. For longitudinal analysis, data of 153 subjects were available. Fasting blood samples from 2004 and 2012 were analysed for 25(OH)D concentrations, total anti-oxidative status (TAOS) as well as anti-oxidative enzymes, such as catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD). Multiple regression analyses were performed to examine the associations between 25(OH)D and parameters of anti-oxidative status.

Results: In cross-sectional analyses, 25(OH)D was a significant predictor of CAT ($\beta = -0.166$; $P = 0.010$), lg_{10} GPx ($\beta = 0.136$; $P = 0.037$) and TAOS ($\beta = 0.121$; $P = 0.048$) after adjusting for age, sex, percentage total body fat (TBF), month of blood sampling, smoking behaviour and use of vitamin D supplements. Longitudinal change in 25(OH)D concentration positively predicted change in TAOS ($\beta = 0.224$; $P = 0.006$) after adjusting for sex, baseline TAOS, age, smoking behaviour, use of vitamin D supplements and change in TBF, physical activity level, current time spent outdoors and dietary vitamin D intake.

Conclusion: The maintenance of an adequate vitamin D status may have a beneficial impact on the anti-oxidative defence system in older adults on a long-term perspective.

1. Introduction

Advanced age is associated with oxidative stress, which is characterised by an increased production of reactive oxygen species (ROS) without an appropriate intensification in anti-oxidative defence mechanisms (Cabello-Verrugio et al., 2017). It is anticipated that oxidative stress plays a role in the development of several chronic diseases, such as diabetes, cardiovascular and neurodegenerative diseases (Cabello-Verrugio et al., 2017).

Previous studies indicate that vitamin D has anti-oxidative and anti-inflammatory properties (Argacha et al., 2011; Asemi et al., 2013; Bellia et al., 2013; Ian et al., 2014; Nikooyeh et al., 2014; Bhat and Ismail, 2015; de Almeida et al., 2016; Haas et al., 2016; Farhangi et al., 2017; Hajiluian et al., 2017). However, the underlying mechanisms are not completely understood. Inhibiting effects of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the biologically active form of vitamin D, on the activity of the nuclear factor κB (Ning et al., 2015; Manna et al., 2017) and the expression of pro-inflammatory cytokines, such as tumour necrosis factor-α and interleukin-6 (Marcotorchino et al., 2012), as well as intercellular adhesion molecule-1 and monocyte chemoattractant protein-1 were reported (Ning et al., 2015). Furthermore, 1,25$(OH)_2$D may increase the expression of anti-oxidative enzymes (Dong et al., 2012; Zhong et al., 2014) and may reduce the generation of ROS (Dong et al., 2012; Manna et al., 2017) as well as the formation of advanced glycation end-products (Salum et al., 2013).

Most of the current knowledge originates from in vitro and animal studies and human studies with subjects suffering from vitamin D deficiency or a particular disease. Although vitamin D insufficiency

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D; 95% CI, 95% confidence interval; ABTS, 2,2-azino-bis-3-ethylbensthiazoline-6-sulfonic acid; ANCOVA, analysis of covariance; *B*, non-standardised coefficient beta; *β*, standardised coefficient beta; BMI, body mass index; CAT, catalase; ECLIA, electrochemiluminescence immunoassay; corr. R^2, adjusted coefficient of determination; GISELA, longitudinal study on nutrition and health status of senior citizens in Giessen Germany; GPx, glutathione peroxidase; GSH, glutathione; Hb, haemoglobin; LC-MS/MS, liquid chromatography-tandem mass spectrometry; NIST, National Institute of Standards and Technology; PTH, parathyroid hormone; ROS, reactive oxygen species; SOD, superoxide dismutase; TAOS, total anti-oxidative status; TBF, total body fat

* Corresponding author.
E-mail addresses: alexandra.jungert@ernaehrung.uni-giessen.de (A. Jungert), monika.neuhaeuser-berthold@ernaehrung.uni-giessen.de (M. Neuhäuser-Berthold).

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(Souberbielle et al., 2016) as well as oxidative stress and chronic diseases (Cabello-Verrugio et al., 2017) are frequently associated with advancing age, up to now, no study investigated the associations of vitamin D status with total anti-oxidative status (TAOS) as well as anti-oxidative enzymes, such as catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD), in independently living older adults.

While TAOS is a biomarker of the overall anti-oxidative status, SOD, CAT and GPx provide an insight in the elimination of specific ROS. SOD converts the reactive superoxide anion into hydrogen peroxide, which can be eliminated by CAT or GPx (Weydert and Cullen, 2010).

By investigating the associations between vitamin D and biomarkers of oxidative stress, several confounders have to be considered. For example, smoking was linked to a higher production of ROS on the one hand (Ellegaard and Poulsen, 2016; Niemann et al., 2017) and a decrease in vitamin D status on the other hand (Jungert and Neuhäuser-Berthold, 2015; Jiang et al., 2016). Furthermore, an enlarged total body fat (TBF) was linked to low-grade systemic inflammation and oxidative stress (de Heredia et al., 2012; Bellia et al., 2013) as well as a reduction in circulating 25-hydroxyvitamin D [25(OH)D] concentrations (Jungert et al., 2012; Bellia et al., 2013), the biomarker of vitamin D status (European Food Safety Authority, 2016). Previous studies often failed to consider these confounding factors. Furthermore, longitudinal analyses, which provide an insight into the causality of the observed associations, are not available.

The present study investigates the associations between 25(OH)D and biomarkers of anti-oxidative status in community-dwelling older adults via a cross-sectional and longitudinal approach by taking into account confounding factors, such as body composition, nutrition and lifestyle.

2. Methods

2.1. Study design and population

The present investigation based on the longitudinal study on nutrition and health status of senior citizens in Giessen, Germany (GISELA study). This study was initiated in 1994 and conducted in the Institute of Nutritional Science at the Justus Liebig University of Giessen, Germany. On an annual (until 1998) and a biennial (since 1998) frequency, data on body composition, nutrition and health status were obtained. Inclusion criteria were an age of at least 60 years, physical mobility and a residence in Giessen or surrounding area.

2.2. Ethical standards

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and procedures involving human subjects were approved by the Ethical Committee of the Faculty of Medicine at the Justus Liebig University of Giessen, Germany. Written informed consent was obtained from all subjects.

2.3. Cross-sectional analysis – study subjects

The cross-sectional analysis based on the follow-up 2004 of the GISELA study. In 2004, for the first time data on both vitamin D status and anti-oxidative biomarkers were collected. From the initial cohort in 2004 ($n = 350$), subjects were excluded because of missing data on relevant biochemical measurements ($n = 12$), body composition ($n = 2$), use of medicines/supplements ($n = 12$) and smoking behaviour ($n = 15$). Nine subjects reported a diagnosis of chronic kidney disease and five subjects have declared non-fasting status and were therefore not included in the analysis. Three subjects were excluded because their blood samples showed haemolysis or turbidity. After these exclusions, three subjects were identified as having extreme values: one subject with high SOD (4069 U/g haemoglobin (Hb)), one subject with low SOD (2168 U/g Hb) and one subject with low CAT (108.1 kU/g Hb) and high SOD (4156 U/g Hb). These subjects were excluded from the analyses to avoid distortion and to approximate normal distribution of residuals. Because 25(OH)D and parameters of anti-oxidative status did not differ between subjects with and without reported history of rheumatism, gout, chronic liver disease or respiratory disorders (all $P > 0.05$), subjects who suffered from these diseases were not excluded. Consequently, 302 subjects (210 women and 92 men) aged 62 to 92 years were analysed.

2.4. Longitudinal analysis – study subjects

For the longitudinal analysis, follow-up data from 2012 of the GISELA study were used, in which blood samples for vitamin D status and anti-oxidative biomarkers were analysed with the same methods as the samples in 2004. Of the study cohort in 2004 ($n = 302$), 171 subjects participated in the follow-up 2012, of whom 153 subjects had a complete data set on relevant parameters, reported no chronic kidney disease and their blood samples showed no signs of haemolysis or turbidity.

2.5. Biochemical analyses

Fasting blood samples were collected from the participants in the morning hours (7:00–11:00 a.m.) from August to October in 2004 and from July to September in 2012 and stored at −70 °C until analysed. Blood samples from 2004 and 2012 were analysed on MODULAR ANALYTICS E170 for total serum 25(OH)D concentrations and serum parathyroid hormone (PTH) concentrations by using electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics GmbH, 2011, 2012). These analyses were conducted in the Limbach Laboratory, Heidelberg, Germany, which participated in the Vitamin D External Quality Assessment Scheme. The used ECLIA has been standardised against liquid chromatography-tandem mass spectrometry (LC-MS/MS), which was standardised to the standard of the National Institute of Standards and Technology (NIST) (Roche Diagnostics GmbH, 2011). According to the manufacturer, the 25(OH)D measuring range of the ECLIA was 7.50–175 nmol/l (Roche Diagnostics GmbH, 2011). Based on the scientific opinion of the European Food Safety Authority (2016) and the Institute of Medicine (Ross et al., 2011), vitamin D sufficiency was defined in the present study as 25(OH)D concentrations ≥ 50.0 nmol/l.

Plasma TAOS was assessed based on the inhibition of the 2,2-azino-bis-3-ethylbenzthiazoline-6-sulfonic acid ($ABTS^+$) radical formation by antioxidants (Miller et al., 1993). The $ABTS^+$ radical generates from ABTS in the presence of peroxidase, visible through a colour reaction, which was detected by photometer (Shimadzu UV-160A, Kyoto, Japan) (Miller et al., 1993). The anti-oxidative capacity of the samples was determined in comparison to Trolox, a water-soluble analogue of α-tocopherol (Miller et al., 1993). Therefore, results are presented in mmol Trolox equivalents/l.

Activities of the anti-oxidative enzymes CAT (2004: Shimadzu UV 160A; 2012: Shimadzu UV 1800) (Aebi, 1984), GPx (2004: Shimadzu UV 160A; 2012: Shimadzu UV 1800) (Paglia and Valentine, 1967) and SOD (2004 and 2012: Shimadzu UV 160A) (Marklund and Marklund, 1974) in erythrocytes were assessed by photometric detection. Enzyme activities are expressed as units per 1 g Hb.

2.6. Anthropometric data and body composition

In light clothing without shoes, weight and height of the participants were measured. Body mass index (BMI) (kg/m^2) was calculated by dividing body weight in kg by the square of body height in metre. Body composition was evaluated by a single-frequency (50 kHz) bioelectrical impedance analyser (Akern-RJL BIA 101/S®; Data Input, Frankfurt, Germany) and the equation of Roubenoff et al. (1997).