

Potential role of vitamin D deficiency on Fabry cardiomyopathy

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Abstract Patients with Fabry disease frequently develop left ventricular (LV) hypertrophy and renal fibrosis. Due to heat intolerance and an inability to sweat, patients tend to avoid exposure to sunlight. We hypothesized that subsequent vitamin D deficiency may contribute to Fabry cardiomyopathy. This study investigated the vitamin D status and its association with LV mass and adverse clinical symptoms in patients with Fabry disease. 25-hydroxyvitamin D (25[OH]D) was measured in 111 patients who were genetically proven to have Fabry disease. LV mass and cardiomyopathy were assessed by magnetic resonance imaging and echocardiography. In cross-sectional

analyses, associations with adverse clinical outcomes were determined by linear and binary logistic regression analyses, respectively, and were adjusted for age, sex, BMI and season. Patients had a mean age of 40 ± 13 years (42 % males), and a mean 25(OH)D of 23.5 ± 11.4 ng/ml. Those with overt vitamin D deficiency (25[OH]D ≤ 15 ng/ml) had an adjusted six fold higher risk of cardiomyopathy, compared to those with sufficient 25(OH)D levels >30 ng/ml ($p=0.04$). The mean LV mass was distinctively different with 170 ± 75 g in deficient, 154 ± 60 g in moderately deficient and 128 ± 58 g in vitamin D sufficient patients ($p=0.01$). With increasing severity of vitamin D deficiency, the median levels of proteinuria increased, as well as the prevalences of depression, edema, cornea verticillata and the need for medical pain therapy. In conclusion, vitamin D deficiency was strongly associated with cardiomyopathy and adverse clinical symptoms in patients with Fabry disease. Whether vitamin D supplementation improves complications of Fabry disease, requires a randomized controlled trial.

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Introduction

Patients with Fabry disease frequently develop cardiac and renal complications, including progressive nephropathy, transient ischemic attacks, early strokes, hypertrophic cardiomyopathy with arrhythmias, which can subsequently lead to death (Breunig and Wanner 2008; Weidemann et al 2009; Wanner et al 2010; Weidemann et al 2010). The morphological hallmarks of Fabry cardiomyopathy consist of left ventricular hypertrophy and replacement fibrosis. At the advanced stage of replacement fibrosis, left ventricular function is significantly reduced in the fibrotic segments. This structural damage and functional loss can lead to significant heart failure and even end-stage disease.

Vitamin D is associated with decreased cardiovascular-related morbidity and mortality (Wolf et al 2007; Dobnig et al

2008; Pilz et al 2008a, b; Mehrotra et al 2009; Drechsler et al 2010; Drechsler et al 2011), possibly by modifying cardiac structure or function; however, firm evidence for either remains lacking. Vitamin D status plays a crucial role for the myocardium and vasculature. Experimental studies identified vitamin D receptors and expression of 1α -hydroxylase in vascular smooth muscle, endothelial cells, and possibly cardiac tissue (Somjen et al 2005; Chen et al 2008; Chen et al 2011). These cells and tissues may therefore be able to produce $1,25(\text{OH})\text{D}$ on a local level. Experimental data showed that vitamin D receptor knockout and 1α -hydroxylase knockout mice develop heart failure, despite having normal calcium levels (Bouillon et al 2008; Pilz et al 2010).

Due to symptoms such as heat intolerance and the inability to sweat, Fabry patients tend to avoid sunlight exposure. Often, patients also suffer from malabsorptive gastrointestinal disease. Both conditions may contribute to a deficiency in vitamin D. It is equally important to note that, patients with Fabry disease have been shown to suffer from low bone mineral density, leading to osteopenia and osteoporosis, further linking vitamin D deficiency to the disease (Germain et al 2005; Mersebach et al 2007). Given the link between vitamin D deficiency and abnormalities in cardiac structure and function, we hypothesized that vitamin D deficiency may contribute to the cardiomyopathy observed in Fabry patients. This study investigated the vitamin D status and its association with left ventricular mass and hypertrophy, as well as adverse clinical symptoms in a large cohort of patients with Fabry disease.

Methods

Study population

Between 2001 and 2009, 111 patients with genetically confirmed Fabry disease were seen at the Fabry Centre for Interdisciplinary Therapy in Würzburg and were included into this study upon their first visit. Inclusion criteria for the present study were (1) genetically proven Fabry disease and (2) availability of blood samples for measurement of $25(\text{OH})$ vitamin D. For the analysis, we divided the cohort according to their baseline $25(\text{OH})$ vitamin D levels into groups based on overt deficient <15 ng/ml (<37 nmol/l), moderately deficient 15 – 30 ng/ml and sufficient >30 ng/ml (75 nmol/l) serum levels in line with established categorizations used in the literature (Mehrotra et al 2008; Wang et al 2008). Clinical symptoms and renal parameters were assessed. Parameters of cardiac function were measured by echocardiography and magnetic resonance imaging.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The ethics committee

approved the research protocol. Written informed consent was obtained from all patients for being included in the study.

Data collection

Information on age, gender, smoking status and history of hypertension was obtained through patient interviews. Systolic and diastolic blood pressure was measured in sitting position after 5 min rest. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Comorbidities, including the presence of coronary artery disease, congestive heart failure, and cardiac dysrhythmia were obtained from patient reports and the patients' clinical records. In addition, we asked the patients about specific symptoms of Fabry disease, including the presence of anhidrosis, acroparesthesia, heat- and physical stress intolerance, pain, nausea and diarrhea. A physical examination was performed by a medical doctor who was specifically trained in the care of patients with Fabry disease. We recorded information about kidney transplantation and dialysis. Urinary protein excretion was determined in 24 h urine samples.

Levels of $25(\text{OH})\text{D}$ were measured in serum samples taken at baseline; i.e. prior to any enzyme replacement therapy with galactosidase A. Samples were stored without repeated freeze thaw cycles at -80 °C until measurement. Serum concentrations of $25(\text{OH})\text{D}$ were measured by means of a chemiluminescence assay (IDS, iSYS $25(\text{OH})\text{D}$; Immunodiagnostic systems Ltd, Boldon, UK) on an IDS-iSYS multi-discipline automated analyser. Within-day coefficients of variation were 5.5–12.1 % and inter-day coefficients of variation were 8.9–16.9 %, respectively. Routine haematological and biochemical parameters were all determined in a central laboratory at the Würzburg University hospital. The Glomerular filtration rate was measured by the clearance of Technetium-99m labeled DTPA (^{99}Tc diethylenetriaminepentaacetic acid).

MR-tomography and standard echocardiographic measurements

A routine cine-MRI was performed in 81 patients as part of the standard assessment (LV heart mass and MR-ejection fraction) on a Siemens Sonata-Avanto (Erlangen, Germany) or a Philips Gyroscan ACS-NT (Best, Netherlands) 1.5 T Full-Body-Scanner (Beer et al 2006). Reasons for the missing examinations were claustrophobia, metal implantations or missing consent.

Patients were lying on their left side for the echocardiographic examination. Echocardiography was performed using a GE Vingmed Vivid 7 (Horten, Norway; 3.5 Mhz). LV end-diastolic (LVEDD) and end-systolic dimensions (LVESD), as well as end-diastolic thickness of the posterior wall (LVPWD) and the septum (IVSD), were measured using standard M-mode echocardiographic methods from parasternal LV long axis images.

The Devereux formula, indexed to body surface area and gender, was used to calculate the LV mass. Normal values for end-diastolic wall thickness (both posterior and septal wall thickness) are <11 mm for women and <12 mm for men, respectively. Based on these cut-off values, we determined the presence of hypertrophy of the posterior wall, hypertrophy of the septum, and hypertrophy in general within patients. Hypertrophy in general was documented if either posterior or septal hypertrophy or both were present. Normal values for left ventricular mass include 67–162 g in women and 88–224 g in men. Fractional shortening was measured ($FS=(LVDD-LVSD)/LVDD$). Ejection fraction (EF) was calculated using the modified Simpson method. Blood pool pulsed Doppler of the mitral valve inflow was used to extract the ratio of early-to-late diastolic flow velocity (E/A) and the deceleration time as a parameter to evaluate diastolic dysfunction.

Data analysis

Continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR) as appropriate, and categorical variables were expressed as percentages. Differences between groups were tested using ANOVA for continuous parameters and the chi-square test for categorical parameters, respectively.

The study population was divided into three groups according to their 25(OH)D status at baseline. Patients were grouped into overt vitamin D deficient (≤ 15.0 ng/ml), moderately vitamin D deficient ($>15 \leq 30$ ng/ml), and vitamin D sufficient (>30 ng/ml) (Mehrotra et al 2008; Wang et al 2008). We assessed the association of baseline 25(OH)D with LV mass, cardiomyopathy and adverse clinical symptoms. The patients with sufficient 25(OH)D levels were used as the reference group. By logistic regression analyses, odds ratios (ORs) and corresponding 95 % confidence intervals were calculated. The analyses were adjusted for the following confounders: age, sex, BMI and season (summer/winter). A p-value of <0.05 was considered as indicating statistical significance. All p-values are reported as two-sided. Analyses were performed using SPSS version 16.0.

Results

Patients had a mean age of 40 ± 13 years, and 47 (42 %) of the patients were male. The mean 25(OH)D concentration was 23.5 ± 11.4 ng/ml. Of all patients, 26 % had overt vitamin D deficiency (<15 ng/mL) and 47 % had moderate vitamin D deficiency ($>15 \leq 30$ ng/ml). Patients had on average a normal BMI (mean 23.5 ± 4.2 kg/m²) and normal blood pressure (mean 124/81 mmHg). Regarding comorbidities, about one third (32 %) of the patients had elevated blood pressure ($> 130/80$ mmHg), 34 % suffered from heart failure and 9 % had angina pectoris. The mean glomerular filtration rate was normal

(93 ± 35 ml/min). On average, patients did not have overt proteinuria (89 mg/day). The baseline characteristics of the Fabry patients are presented in Table 1.

Cardiac and renal function by vitamin D status

Of all patients, nine patients (8 %) had a vitamin D level below 10 ng/ml, and 15 patients (14 %) had a vitamin D level below 12 ng/ml. When using 15 ng/ml as a cutoff for severe vitamin D deficiency, a total of 29 patients (26 %) were affected and were used for subsequent analyses. Patients with moderate or overt vitamin D deficiency more often had cardiac hypertrophy than patients with sufficient vitamin D status. General cardiac hypertrophy was present in 72 % of the patients with overt vitamin D deficiency, and in 78 % of the patients with moderate deficiency, while it was present in 35 % of the vitamin D sufficient patients only (Table 2). The mean LV mass was substantially different with 170 ± 75 g in overt deficient, 154 ± 60 g in moderately deficient and 128 ± 58 g in vitamin D sufficient patients ($p=0.01$). Regarding renal status, the percentage of patients with proteinuria (> 150 mg/24 h) was 35 % in the group of vitamin D sufficient patients, and slightly higher with 48 % and 46 % in the groups with moderate and overt vitamin D deficiency, respectively.

We performed logistic regression analyses to evaluate the risks of adverse cardiac and renal symptoms controlling for the following confounders: age, sex, BMI and season (summer/winter). By adjusted analyses, patients with overt vitamin D deficiency (25[OH]D ≤ 15 ng/ml) had a 6 fold

Table 1 Characteristics of Morbus Fabry patients

	Study cohort N=111
Age years	40±13
Sex % female	58
25(OH) vitamin D ng/ml	23.5±11.4
BMI kg/m ²	23.5±4.2
Systolic blood pressure mmHg	124±17
Diastolic blood pressure mmHg	81±11
Arterial hypertension %	32
Cardiovascular disease	
Angina %	9.1
NYHA I-II %	34
Arrhythmia %	14.7
Renal status	
Serum creatinine mg/dl	1.0±0.6
GFR ml/min	93±35
Proteinuria mg/day	89 (23–597)

Values are presented as means and standard deviation or median and interquartile range

BMI Body mass index; GFR Glomerular filtration rate

Table 2 Cardiac, renal status and clinical symptoms by vitamin D category

	25(OH) vitamin D ng/ml		
	≤15 N=29	>15≤30 N=52	>30 N=30
Age years	37±10	43±14	38±12
Male sex %	52	44	30
BMI kg/m ²	24.9±4.9	23.0±3.8	22.9±3.7
Systolic RR mmHg	124±17	129±18	117±14
Diastolic RR mmHg	85±11	80±11	81±11
LV mass g	170±75	154±60	128±58
Hypertrophy septum %	64	69	30
Hypertrophy posterior %	54	69	30
Hypertrophy general %	72	78	35
Ejection fraction %	62	65	60
Proteinuria %	46	48	35
Proteinuria mg/day	118 (30–715)	102 (34–602)	66 (0–416)
Clinical symptoms			
Chronic pain %	52	48	31
Pain therapy %	37	12	11
Depression %	17	6	8
Edema %	35	22	11
Heat intolerance %	69	57	46
Cornea verticillata %	50	53	27
Diarrhea %	39	30	29

Values are presented as means and standard deviation or median and interquartile range or percentages, as appropriate

LV Left ventricular

higher risk of cardiac hypertrophy, compared to those with sufficient 25(OH)D levels >30 ng/ml (HR 6.4, 95 % CI 1.1–38.8, $p=0.04$). Similarly, the adjusted risk of septal hypertrophy was six fold increased (HR 6.1, 95 % CI 1.1–36.5, $p=0.04$). The odds ratio for heart failure was 2.4 (0.6–9.3) in overt vitamin D deficiency and 2.9 (0.9–9.2) in moderate vitamin D deficiency. We did not find any association between vitamin D deficiency, hypertension or arrhythmia. The results of all further logistic regression analyses are presented in Fig. 1.

Clinical symptoms of vitamin D status

Furthermore, adverse clinical symptoms more often occurred in patients with vitamin D deficiency, as compared to those with vitamin D sufficiency. Patients with vitamin D deficiency experienced chronic pain, depression, and were often in need of medical pain therapy. Similarly, the prevalences of edema, diarrhea, heat intolerance and cornea verticillata were higher for patients with vitamin D deficiency (Table 2).

Logistic regression analyses were performed to evaluate the risks of adverse clinical symptoms associated with vitamin

D status, adjusting for confounders including age, sex, BMI and season. The results of the logistic regression analyses for the occurrence of clinical symptoms are presented in Fig. 1.

Discussion

The present study investigated the vitamin D status in patients with Fabry disease. We evaluated the associations of vitamin D status with cardiac and renal complications, as well as with clinical symptoms. We found that vitamin D deficiency was prevalent (73 %) among Fabry patients. Vitamin D deficiency was associated with hypertrophic cardiomyopathy and an increased left ventricular mass. With increasing severity of vitamin D deficiency, the median levels of proteinuria increased, as well as the prevalences of depression, edema, cornea verticillata and the need for medical pain therapy.

In general, vitamin D from either ultraviolet-B induced synthesis in the skin or from nutritional intake is hydroxylated to 25-hydroxyvitamin D (25[OH]D) in the liver, circulating up to 1000 fold higher concentrations than the most potent vitamin D metabolite 1,25-dihydroxyvitamin D (1,25[OH]2D) (calcitriol) (Dusso et al 2005). The renal production of 1,25(OH)2D is dependent on substrate availability when circulating 25(OH)D is low. In patients with chronic diseases, limited sunlight exposure and reduced capacity of the skin to synthesize vitamin D, as well as a loss of vitamin D binding protein in the urine, are mainly responsible for the high prevalence of depressed 25(OH)D levels (Jacob et al 1984; Wolf et al 2007; Wang et al 2008; Mehrotra et al 2009). Fabry patients typically suffer from so-called Fabry crises due to heat intolerance, especially during the summer. Patients systematically avoid outdoor activities and, thus, are potentially at risk of developing insufficient vitamin D levels.

The treatment of Fabry disease today focuses on relieving symptoms, supporting organs and arresting disease progression. Enzyme replacement therapy with alpha or beta galactosidase A is administered to patients with Fabry disease, but some patients do not respond well to the treatment. So-called adjunctive therapies and treatment strategies are currently being discussed to support patients with Fabry disease and improve morbidity, mortality and quality of life. In this context, a sufficient blockade of the renin-angiotensin-aldosterone system is widely advocated, but adequate vitamin D storages or supplementation may also be necessary. However, we do not yet advise vitamin D therapy on the basis of our data, although nutritional vitamin D supplementation is widely recommended. The present findings are observational and cannot prove causality.

Interestingly, anti-hypertrophic and anti-proliferative actions of vitamin D metabolites have recently been reported (Pilz et al 2010). In hypertrophic hearts, an increased expression of the VDR has been found in cardiac myocytes and fibroblasts (Chen et al 2008). Experimental studies have found that cardiac myocytes and fibroblasts express the enzymes 1α -

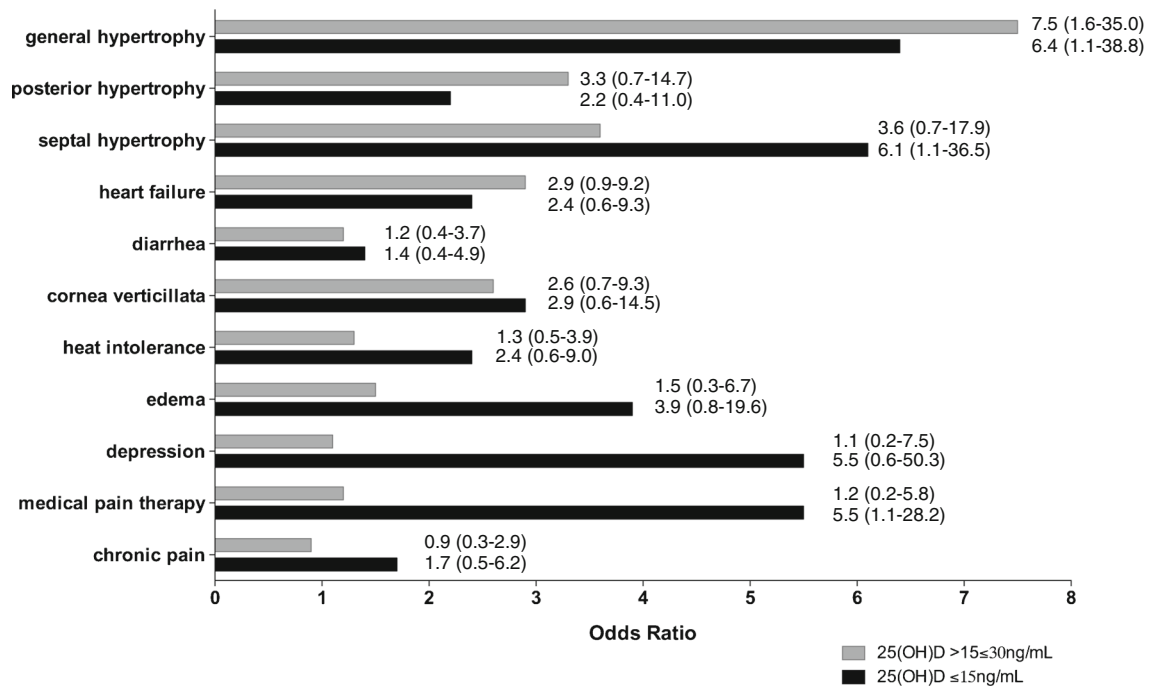


Fig. 1 Odds ratios for the relation between vitamin D status and clinical outcomes, adjusted for age, sex, BMI and season. The odds ratios are presented with 95 % confidence intervals for the patients with overt

25(OH)D deficiency (*black*) and moderate 25(OH)D deficiency (*grey*), as compared to the patients with 25(OH)D sufficiency (reference group)

hydroxylase and 24-hydroxylase (Akeno et al 1997; Chen et al 2008). The conversion of 25(OH)D to 1,25(OH)2D by 1 α -hydroxylase is mainly dependent on substrate availability. Therefore, the concentrations of circulating 25(OH)D may be a significant determinant of vitamin D effects in the myocardium. In addition, vitamin D receptor activation was reported to modulate cardiac calcium flux, thus inducing an accelerated relaxation of cardiomyocytes. This, in turn, may improve the diastolic function of the heart (Pilz et al 2010). Finally, vitamin D deficiency has been found associated with congestive heart failure (Pilz et al 2008a, b) including infants with vitamin D-deficient rickets (Brown et al 2009). In animal studies, calcitriol or related analogs such as paricalcitol attenuated left ventricular hypertrophy (Chen et al 2011), augmented diastolic relaxation and reduced end-diastolic pressures. Furthermore, a reduction of cardiac mRNA expression, blood levels of natriuretic peptides, and episodes of congestive heart failure have been observed (Bodyak et al 2007; Tishkoff et al 2008; Przybylski et al 2010; Bae et al 2011). Despite the encouraging experimental and clinical data from previous studies, we cannot prove causality from our observational data. We, therefore, cannot rule out reverse causation, i.e. that vitamin D deficiency is a consequence of left ventricular hypertrophy and heart failure and thus reflects a cardiac disease’s severity. The most advanced Fabry patients (suffering from heart failure, fatigue, hypohidrosis) may tend to avoid sun exposure most and those with proteinuria are on top losing the vitamin. Therefore, vitamin D may be merely a marker with low levels reflecting disease severity.

With increasing severity of vitamin D deficiency, the median levels of proteinuria in our patients increased. Knockout of the vitamin D receptor in diabetic mice was associated with severe albuminuria and glomerulosclerosis from increased thickening of the glomerular basement membrane and podocyte effacement (Zhang et al 2008a, b). Moreover, combined treatment with paricalcitol and an angiotensin receptor blocker in models of diabetic nephropathy prevented the development of albuminuria, maintaining the structure of the glomerular filtration barrier, and reducing glomerulosclerosis, in association with a reduced renal expression of renin (Zhang et al 2008a, b). A recent randomized controlled trial demonstrated a reduction of residual albuminuria in patients with diabetic nephropathy (de Zeeuw et al 2010), whereupon 2 μ g/day paricalcitol were added to a sufficient inhibition of the renin-angiotensin-aldosterone system.

Conclusion

In conclusion, our study shows that vitamin D deficiency is associated with the development of complications in patients with Fabry disease, to include progressive Fabry nephropathy, hypertrophic cardiomyopathy and adverse clinical symptoms. It remains to be proven whether vitamin D deficiency is a risk factor for these complications or merely a marker of disease severity. This is important for the development of novel strategies as additional treatment interventions for patients with Fabry disease. Adjunctive therapeutic strategies can help to support

patients with Fabry disease and improve morbidity, mortality and quality of life. In this context, novel studies are needed to validate the potential use of vitamin D status as a marker for disease progression. Importantly, further research is required to establish the role of vitamin D status as potential intervention target. A randomized multicenter controlled trial is required to clarify if vitamin D supplementation improves the complications of Fabry disease.

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Competing interest Christiane Drechsler, Benjamin Schmiedeke, Markus Niemann, Daniel Schmiedeke, Johannes Krämer, Irina Davydenko, Katja Blouin, Andrea Emmert, Stefan Pilz, Barbara Obermayer-Pietsch, and Frank Breunig declare that they have no conflict of interest.

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