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ORIGINAL PAPER

Is there an association between periprosthetic joint infection and low vitamin D levels?

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Abstract
Purpose Vitamin D is increasingly being recognized as an important mediator of immune function and may have a preventive role in the pathogenesis of periprosthetic joint infection. To the best of our knowledge, no other study has examined possible associations between periprosthetic joint infection and vitamin D deficiency. We investigated the rate of vitamin D deficiency in patients treated for periprosthetic joint infection and whether vitamin D deficiency is independent of other risk factors for vitamin D deficiency in patients with periprosthetic joint infection.
Methods Serum 25-hydroxyvitamin D (25OHD) levels of every patient scheduled to receive a total prosthesis either of the hip, knee, or shoulder in the orthopaedic department of the Johannes-Guttenberg-University Hospital in Mainz, Germany (109 patients), were measured after admission. Furthermore, serum 25OHD levels were measured for every patient presenting with periprosthetic joint infection (n=50) or aseptic loosening of the prosthesis (n=31) scheduled to undergo revision surgery. The prevalence of normal (>30 ng/ml), insufficient (20–30 ng/ml), and deficient (<20 ng/ml) 25OHD levels was determined.
Results All tested patient subgroups showed low vitamin D levels. Statistical analysis found no significant difference in vitamin D levels comparing patients with prosthesis and patients with aseptic prosthesis loosening (p=0.58). Significant differences in 25OHD levels were found comparing patients with periprosthetic joint infection and patients scheduled for primary arthroplasty (p<0.001). In addition, we found a significant difference (p<0,001) in 25OHD levels of patients with periprosthetic joint infection compared with patients with aseptic prosthesis loosening.
Conclusion We found a high frequency of vitamin D deficiency in patients being treated by primary arthroplasty and those with aseptic joint prosthetic loosening and periprosthetic joint infection. Vitamin D deficiency was severe in patients with periprosthetic joint infection.

Keywords Periprosthetic joint infection · Vitamin D deficiency · Arthroplasty · Infection

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Introduction

Vitamin D insufficiency and deficiency has been shown in populations all around the world. Several studies identified a widespread vitamin D deficiency in orthopaedic patients scheduled to undergo surgery [1–3]. Classic actions of vitamin D, such as promotion of calcium homeostasis and bone health are well known, and several studies suggest that it also regulates innate and adaptive immune function, including activation and differentiation of macrophages, dendritic cells and

lymphocytes [4]. Vitamin D's primary circulatory form, 25-hydroxyvitamin D (25OHD) induces its own conversion to the active form 1,25-dihydroxyvitamin D (calcitriol) and produces cathelicidin antimicrobial peptides in the presence of an antigen challenge [5]. Accordingly, low serum 25OHD levels have been linked to increased risk of respiratory tract infection, and a clinical trial demonstrated that vitamin D supplementation reduced the risk of influenza A infection [6–8]. Furthermore, vitamin D insufficiency may also be important in the pathogenesis of sepsis, the most fatal consequence of infection. In vitro and in vivo models of sepsis suggest that vitamin D treatment modulates proinflammatory cytokine production, deranged coagulation and activation of the vascular endothelium, as seen in sepsis syndromes [6, 9, 10].

In the field of orthopaedics, infections especially periprosthetic joint infections, are a devastating complication of total joint arthroplasty. Periprosthetic joint infection is the most common indication for revision of total knee arthroplasty and the third most common indication for revision total hip arthroplasty in the USA [11]. Periprosthetic joint infections have known modifiable and nonmodifiable risk factors [12]. Established modifiable risk factors include allogenic blood transfusion, excessive anticoagulation treatment, obesity, malnutrition, simultaneous bilateral surgery, alcoholism, use of surgical drain and long postoperative urinary catheterisation [12–16]. Interventions to prevent or correct these modifiable risk factors have the potential to lower the periprosthetic joint infection rate. We hypothesised a widespread vitamin D deficiency in patients treated for periprosthetic joint infection and that vitamin D deficiency is independent of other confounding risk factors for vitamin D deficiency in patients with periprosthetic infection.

Methods

Each institution approved the human protocol for this investigation, investigations were conducted in conformity with ethical principles of research and informed consent for participation in the study was obtained from each patient. Between 1 January 2011 and 31 December 2012, serum 25OHD levels of every patient scheduled to receive a total prosthesis either of the hip, knee or shoulder in the orthopaedic department of the Johannes-Gutenberg-University Hospital in Mainz, Germany (109 patients), were measured after admission. Furthermore, serum 25OHD levels were measured of every patient presenting with periprosthetic joint infection (n=50) or aseptic loosening of the prosthesis (n=31) and who were scheduled to undergo revision surgery (Table 1). Blood was generally taken on the day of admission. Inclusion criteria for patients presenting with periprosthetic joint infection or aseptic loosening were pain in the thigh or hip region, knee pain, shoulder pain, radiological symptoms of loosening (disintegration of prosthesis components with the bone, displaced components of the prosthesis) and elevated or normal levels of infection markers, such as C-reactive protein (CRP), white blood cell count (WBC) and erythrocyte sedimentation rate (ESR) (Table 2). Differentiation between periprosthetic infection and aseptic loosening was based upon the presence of intra-operative pus, sinus tract communication with the prosthesis or microbiological identification

Table 1 Patient characteristics

Characteristics	Primary arthroplasty	Periprosthetic infection	Aseptic loosening
No. of patients	109	50	31
Men	47 (43 %)	24 (48 %)	13 (40 %)
Women	62 (57 %)	26 (52 %)	18 (60 %)
Mean age (years)	65 (± 9.2)	68 (±16)	68.4 (± 8.6)
Alcoholism	7 (7 %)	2 (4 %)	2 (6 %)
Nicotine abuse	46 (42 %)	22 (44 %)	11 (34 %)
Obesity (BMI>30 kg/m2)	16 (14 %)	11 (22 %)	4 (12 %)
Carcinoma	5 (4 %)	3 (6 %)	2 (6 %)
Osteoporosis	12 (11 %)	4 (8 %)	3 (9 %)
Hypertension	45 (41 %)	25 (50 %)	16 (51 %)
Cardiovascular disease (chronic/congestive heart failure, myocardial infarction)	20 (19 %)	12 (24 %)	9 (27 %)
Thyroid abnormality (hypo-/hyperthyroidism)	31 (28 %)	21 (42 %)	9 (27 %)
Pulmonary disease (COPD, asthma)	8 (7 %)	2 (4 %)	3 (9 %)
Renal failure	9 (8 %)	5 (10 %)	3 (9 %)
Infectious diseases (HIV, hepatitis A, B, C virus, tuberculosis)	3 (3 %)	1 (2 %)	1 (3 %)
Vitamin D supplementation orally	15 (14 %)	3 (6 %)	7 (22 %)
Diabetes	17 (16 %)	7 (14 %)	1 (3 %)

BMI body mass index, *COPD* chronic obstructive pulmonary disease

Table 2 Clinical details of patients with periprosthetic joint infection

Patient no.	Age (years)/sex	Comorbidity	CRP	Joint	Age of the implant (in months)	Microbe
1	58/F	DM, HTN	28	Knee	36	*Staphlococcus aureus*
2	68/F	HTN	111	Knee	44	*S.aureus*
3	71/M	HTN	32	Hip	157	*S.warneri*
4	65/F	HTN	<5	Knee	168	*S.aureus*
5	67/M	HTN	47	Hip	6	*Klebsiella spp.*
6	74/F	HTN	51	Hip	123	*Corynebacterium spp.*
7	70/M	HTN, CRI	77	Hip	17	*S.aureus*
8	92/F		84	Knee	2	*S.aureus*
9	72/F	HTN	21	Knee	11	*S.capitis*
10	70/M	HTN	67	Shoulder	33	*Enterobacter cloacae*
11	71/M	–	24	Knee	201	*S.aureus*
12	78/M	HTN	<5	Hip	17	*S epidermidis*
13	63/F	HTN	34	Hip	25	*S.epidermidis*
14	69/M	DM, HTN	54	Knee	29	*E. cloacae*
15	76/M	–	18	Knee	47	*S.aureus*
16	68/M	HTN	48	Shoulder	8	*S.aureus*
17	64/M	–	27	Hip	16	*Klebsiella spp.*
18	68/F	–	<5	Hip	24	*S.epidermidis*
19	79/F	HTN	12	Hip	62	*S.gordini*
20	70/M	–	18	Knee	70	*S.aureus*
21	61/F	–	28	Knee	34	*S.aureus*
22	70/F	HTN	41	Hip	101	*Corynebacterium spp.*
23	68/M	HTN	37	Hip	4	*S.aureus*
24	78/F	–	44	Knee	3	*S.aureus*
25	59/F	–	28	Knee	76	*E. cloacae*
26	75/M	–	<5	Knee	16	*Corynebacterium spp.*
27	66/F	HTN	<5	Hip	24	*S.aureus*
28	82/F	HTN	24	Hip	47	*S.aureus*
29	69/M	–	89	Knee	55	*S.aureus*
30	64/M	–	134	Knee	52	*S.aureus*
31	57/F	–	89	Hip	3	*E. cloacae*
32	69/F	CRI	129	Hip	1	*E. cloacae*
33	73/F	HTN, CRI	<5	Hip	18	*S.aureus*
34	73/M	DM, HTN	67	Hip	205	*S.aureus*
35	61/F	DM, HTN	34	Hip	17	*S.aureus*
36	57/M	DM, HTN	<5	Knee	31	*S.aureus*
37	63/M	DM	<5	Knee	26	*Klebsiella spp.*
38	72/F	CRI	19	Shoulder	51	*S.epidermidis*
39	53/M	DM, HTN	39	Knee	8	*S epidermidis*
40	61/F	CRI	45	Hip	19	*S.epidermidis*
41	73/M	–	<5	Hip	21	*S.aureus*
42	55/M	DM, HTN	22	Knee	62	*S.capitis*
43	68/M	HTN	148	Knee	70	*E. cloacae*
44	67/F	–	223	Shoulder	34	*S.aureus*
45	69/F	–	96	Knee	132	*S.gordini*
46	68/M	–	<5	Hip	4	*S.aureus*
47	71/F	–	79	Hip	5	*S.aureus*
48	70/M	–	49	Knee	76	*Corynebacterium spp.*
49	69/F	HTN	203	Shoulder	26	*S.aureus*
50	63/F	–	67	Shoulder	18	*S.aureus*

CRP C-reactive protein, *DM* diabetes mellitus, *HTN* hypertension, *CRI* chronic renal insufficiency

of the infecting organism by two or more separate tissue or fluid samples. Aspiration of shoulder, hip or knee joints was performed, and fluid from aspirated joints was taken for culture. Furthermore, intraoperative samples were taken for microbiological identification.

Measurement of serum 250HD was standardised, the hospital laboratory used the ARCHITECT 25-OH Vitamin D assay (Fa Abbott Laboratories, Germany) and laboratory results were collected using a retrospective chart review. Patient demographic variables and background data were collected using a chart review of patient records (Table 1). As yet, there is no universally accepted classification of vitamin D levels. We defined sufficient vitamin D status as a serum 25OHD level >30 ng/ml [17]. All patients with valid 25OHD measurement were included in statistical analysis. Serum vitamin D levels were compared between cohorts using Student's *t* test for independent samples. All hypotheses were evaluated using two-tailed t tests with statistical significance set at $p \leq 0.05$.

After the initial analyses, an analysis of covariance (ANCOVA) and analyses of variance (ANOVA) were performed to evaluate possible effects of known risk factors of vitamin D deficiency within the tested groups. ANCOVA was used to control for the effect of age and ANOVA to analyse possible effects of age, gender, renal failure, obesity [defined as a body mass index (BMI) >30 kg/m^2], diabetes mellitus (DM), nicotine abuse, carcinoma, osteoporosis, hypertension (HTN), cardiovascular diseases, alcoholism, hyperthyroidism/hypothyreosis, pulmonary diseases, infectious disease and to check for possible interactions between the group variable and the above-mentioned categorical variables. Statistical analyses was performed with IBM SPSS Statistics software (Ver. 21; USA)

Results

We found that 64 % (n=70) of all patients who were to undergo primary arthroplasty (either hip, shoulder or knee) had inadequately low levels of vitamin D, with a mean of 19.46 ng/ml (± 9.49; range 2.8–48.7 ng/ml). A high percentage of patients scheduled to undergo a second surgery due to prosthesis loosening (n=16; 52 %) or periprosthetic joint infection (n =43; 86 %) had 25OHD values <20 ng/ml, with a mean level of 20.52 ng/ml (± 9.13; range 3.3–33,8 ng/ml) for aseptic prosthesis loosening and 13.29 ng/ml (± 6.54; range 4.9–31.5 ng/ml) for patients with periprosthetic joint infection). Statistical analysis found no significant difference between patients scheduled for primary arthroplasty and patients with aseptic prosthesis loosening (p=0.58). However, significant differences in 25OHD levels were found between patients with periprosthetic joint infection and patients scheduled for primary arthroplasty (p<0.001). Moreover, in comparison of patients with periprosthetic joint infection and patients with aseptic prosthesis loosening, a significant difference (p<0.001) was found (Table 2).

Following the univariate analyses, ANCOVA was performed to evaluate the effect of age on vitamin D levels in the tested groups. ANOVA was performed to check for main effects and interactions for gender, renal failure, obesity and DM on vitamin D levels in the three subgroups. After adjustment for the covariate age, mean differences between groups were similar (grade of freedom F=0.04; p=0.84); after adjustment for possible confounders, we found no significant main effect of the tested variables. Vitamin D levels were not dependent on gender (p=0.4), renal failure (p=0.94), obesity (p=0.42) or DM (p=0.26) and other tested possible confounders (Table 3), and stayed significantly lower in patients with periprosthetic infection after adjustment. Furthermore, we found no statistical interaction between gender (p=0.25), renal failure (p=0.82), obesity (p=0.62), HTN (p=0.51), pulmonary disease (p=0.81), cardiovascular disease (p=0.32) and patient subgroups. Due to the small sample size, interaction between DM, infectious disease and vitamin D levels was not evaluated.

Discussion

To the best of our knowledge, this study is the first to report a possible association between extremely low vitamin D levels and periprosthetic joint infection. Vitamin D status was evaluated in view of its immune-regulatory role in periprosthetic joint infection. We observed a high prevalence of vitamin-D-deficient states among patients receiving either operation for primary joint arthroplasty, periprosthetic joint infection or

Table 3 Analysis of variance (ANOVA) of potential confounders for vitamin D deficiency

	Grade of freedom	Significance (*P*)
Alcoholism	5.82	0.08
Nicotine abuse	4.43	0.95
Obesity (BMI>30 kg/m2)	3.63	0.42
Carcinoma	5.21	0.52
Osteoporosis	6.73	0.39
Hypertension	3.21	0.07
Cardiovascular disease	2.84	0.31
Thyroid abnormality	3.44	0.24
Pulmonary disease	5.32	0.73
Renal failure	4.31	0.94
Infectious diseases	6.72	0.33
Vitamin D supplementation	6.01	0.82
Diabetes	9.45	0.26

BMI body mass index

aseptic prosthesis loosening. A widespread prevalence of vitamin D deficiency has been shown in orthopaedic patients [1, 2, 18]. In former studies, we showed a high prevalence of vitamin D insufficiency and deficiency in German orthopaedic patients in the region around Mainz (50° northern latitude). No correlation between age or sex and vitamin D level was found [1, 3]. Our results are consistent with studies showing a high rate of vitamin D deficiency and insufficiency in our orthopaedic patient subgroups. Given the well-known effects of vitamin D on bone health and calcium homeostasis, an adequate level of vitamin D may improve postoperative settings. Screening for and treating hypovitaminosis D may therefore be of value to the treating orthopaedic surgeon. Notably, patients treated for periprosthetic joint infection in this study had comparatively higher prevalence of vitamin D deficiency and significant lower vitamin D levels than the other tested patient groups.

Previous studies have linked vitamin D with several other immunological alterations that are associated with increased susceptibility to infection [19]. Active vitamin D_3 stimulates phagocytosis and killing of bacteria by macrophages [20]. It suppresses T-cell proliferation and attenuates the production of T-helper type 1 cytokines while promoting the production of T-helper type 2 cytokines [19, 21]. T-helper type 2 cells primarily play a role in response to extracellular pathogens, such as most bacteria and parasites that cause periprosthetic joint infection. Gram-positive bacteria, mainly *Staphylococcus aureus* and *S. epidermidis*, predominate in cases of joint prosthesis contamination, but infections are also caused by Gram-positive bacilli and fungi [22]. In vitro studies proved vitamin D_3 has inhibitory activity on strains of *S. aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae* and *Escherichia coli*, as well as other bacteria. In the presence of vitamin D_3, such organisms were killed or demonstrated marked growth inhibition [23, 24]. Gram-positive bacteria, invasive pneumococcal disease, meningococcal disease and group A streptococcal disease are more common when vitamin D levels are low, raising the possibility that pharmacological doses of vitamin D may be an effective adjuvant therapy [23, 25]. Furthermore, vitamin D modulates the immunological response to intracellular pathogens by inducing cathelicidin antimicrobial peptide gene expression [26].

Consistent with our results, Tiwari et al. showed a high prevalence of vitamin D deficiency in patients with diabetic foot infection: 125 patients with diabetic foot infection were compared with diabetic patients without infection, and vitamin D levels were significantly lower in patients with an infection; vitamin D deficiency was prevalent and severe in patients with diabetic foot infection. The authors raised the issue of recognizsng severe vitamin D deficiency as a possible risk factor for diabetic foot infection [19].

The most fatal consequence of infection is sepsis. In a pilot study to evaluate the association between vitamin D status and sepsis severity, vitamin D insufficiency was consistently associated with severe sepsis. The authors suggested that vitamin D supplementation, particularly in higher-risk populations, holds the potential to lower the risk of incident infection and associated morbidity, such as sepsis. In addition to prevention, vitamin D has the potential to modulate inflammatory and coagulation-induced sepsis syndromes [6].

As with any single-centre analysis, ours has inherent weaknesses. The majority of tested patients in this study were light skinned. Given the predisposition of individuals with darker skin tones towards lower 25OHD levels, hypovitaminosis D among darker-skinned orthopaedic patients may be underrepresented in this study. Furthermore, the geographical localization of Mainz (50° northern latitude) limits our results to regions around this latitude (e.g. Paris 48°51′ N, Vancouver (49°15′ N), Calgary (51°3′ N), Kiev (50°27′) or those above 50° latitude. This was not a randomised prospective study, but it does have a control group. The reported associations do not prove a causal relationship. Clinical trials are needed before vitamin D supplementation can be recommended as an option to prevent periprosthetic joint infection.

In conclusion, we found a high frequency vitamin D deficiency in patients being treated by primary arthroplasty, those with aseptic joint prosthetic loosening and those with periprosthetic joint infection. Vitamin D deficiency was significantly severe in patients with periprosthetic joint infection. Vitamin D supplementation is safe and simple and may be a possible way to lower the risk of periprosthetic joint infection, but further randomized controlled trials on pre- and postoperative impact of vitamin D supplementation may be needed to confirm this hypothesis.

Conflict of interests None.

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