

Vitamin D Deficiency and Reduced Hodgkin Lymphoma Survival

Nancy A. Melville

June 18, 2018

STOCKHOLM — Vitamin D deficiency is strongly associated with lower rates of progression-free survival (PFS) and overall survival (OS) in patients with Hodgkin lymphoma, independently of key factors that include tumor mass, patients' clinical condition, and the type of treatment received, according to new research.

The finding was presented here at the European Hematology Association (EHA) 2018 Congress.

"Vitamin D deficiency at baseline [in patients with Hodgkin lymphoma] is a clinically modifiable risk factor for progression-free survival and overall survival across multiple studies with long-term follow-up," said lead author Sven Borchmann, MD, of the German Hodgkin Study Group (GHSG) and the University Hospital of Cologne, in Germany.

In the study, Borchmann and his colleagues evaluated data from the GHSG HD7, HD8, and HD9 clinical trials. Disease status ranged from favorable to advanced. An enriched analysis was compiled using data on the patients' pretreatment serum samples and their documented progression or relapse.

The final analysis included 351 patients; 233 were relapse-free, and 118 experienced relapsed.

Among all patients, 175 were determined to be vitamin D deficient, 83 were determined to have insufficient levels of vitamin D, and 93 had sufficient levels. Determinations were based on guidelines from the Food and Nutrition Board of the Institute of Medicine. These guidelines define serum levels of less than 30 nmol/L as deficient, those of 30 to 50 nmol/L as insufficient, and levels of 50 nmol/L or higher as sufficient.

Patients who experienced progression or relapse were found to have significantly lower median baseline vitamin D levels than those who were relapse free (21.4 vs 35.5 nmol/L). They were also more likely to be deficient in vitamin D (68% vs 41%; $P < .0001$). Effects were similar across all treatment arms.

The final weighted analysis was designed to correct for the fact that the cohort was enriched; adjustments were made for various factors, including the season of diagnosis, age, and sex. The analysis showed vitamin D deficiency to be strongly associated with lower PFS (hazard ratio [HR], 2.13; 95% confidence interval [CI], 1.84 - 2.48; $P < .0001$) over a median observation time of 156 months.

In terms of OS, vitamin D–deficient patients also had a significantly higher risk for death (HR, 1.82; 95% CI, 1.53 - 2.15; $P < .0001$), after adjustments, over a median observation time of 192 months in the weighted analysis.

Hodgkin lymphoma was the cause of death of 24 patients (38%) who were vitamin D deficient, compared to only four patients (22%) whose level of vitamin D was insufficient, and three patients (18%) who had sufficient levels of vitamin D.

In addition, total deaths of all causes were higher in patients who were vitamin D deficient ($n = 63$; 36%) compared to those whose levels were insufficient ($n = 18$; 22%) or sufficient ($n = 17$; 18%).

"It appears the differences in overall survival rates are mainly due to significantly more Hodgkin lymphoma–associated deaths among those who were vitamin D deficient," Borchmann said.

No correlations were seen between vitamin D levels and other factors, including age, sex, clinical stage, large mediastinal mass, extranodal involvement, having three or more nodal areas affected, elevations in erythrocyte sedimentation rate, B-symptoms, or Karnofsky index score.

Vitamin D deficiency is a known predictor of poor prognoses in many other cancers; however, there have been no data on pretreatment vitamin D levels in patients with Hodgkin lymphoma, nor have there been data on whether vitamin D levels correlate with patient characteristics and outcomes, Borchmann noted.

That being said, the increased risk that was demonstrated was a bit of a surprise, he told *Medscape Medical News*.

"If you look at the hazard ratios we got — 2.13 for PFS and 1.82 for OS in the weighted models, respectively — these are quite high compared to other studies in solid cancers," Borchmann said, "especially considering the fact that the order of magnitude of the effect is similar to the improvements that are usually deemed practice changing when it comes to evaluating a new intervention."

"This is obviously not directly comparable, but any intervention, such as a new drug or treatment modality that would show this difference in a prospective trial in Hodgkin lymphoma, would likely be quickly picked up by practitioners, given safety and a reasonable cost-benefit ratio."

Although the mechanisms behind the association are not known, Borchmann suggested that an effect on immunosuppression may be at play.

"These days, there is a lot of talk about immunotherapy in cancer, which has also been shown to be highly successful in Hodgkin lymphoma, and we do know that vitamin D plays a role in maintaining various aspects of immune function," Borchmann explained.

"Our study showed quite a strong effect, and given that Hodgkin lymphoma is so intertwined with its microenvironment, consisting of many different immune cell subtypes, this might point to a specific role vitamin D deficiency has in maintaining a supportive microenvironment for Hodgkin lymphoma to survive," he added.

Underscoring that the theories are entirely speculative, Borchmann added that "it would make a lot of sense to follow up on the research we presented with both prospective intervention studies and laboratory experiments that look at effects of active forms of vitamin D on cell proliferation of Hodgkin lymphoma and how it interacts with various immune effector cells."

He added that although Hodgkin lymphoma has in the past been a challenge to model in cell culture experiments or in animals, "part of our efforts in Cologne are to develop new models that will allow us to further investigate mechanisms of immunomodulation in Hodgkin lymphoma."

Seasonality Findings Add to Speculation of Vitamin D Role

Another finding from the new study was expected: patients' vitamin D levels were shown to highly correlate with the season of diagnosis.

Table. Correlation of Vitamin D Level and Season of Diagnosis

Season of Diagnosis	Median Vit D Blood Level (nmolL)	Rate of Vit D Deficiency
Spring	27.7	55%
Summer	42.9	34%
Autumn	30.8	48%
Winter	22.0	55%

In a [study](#) published in 2017, Borchmann and his colleagues found a seasonal pattern with respect to both incidence and mortality in Hodgkin lymphoma that was associated with latitude. In that analysis of more than 41,000 Hodgkin lymphoma cases, the incidence of diagnoses was 15.4% higher in March compared to September; the pattern was more pronounced in higher latitudes.

The authors speculated that seasonal differences in vitamin D levels, resulting from increased ultraviolet radiation in warmer seasons, at least partly explained the differences.

"Strikingly, the seasonal incidence pattern observed in Hodgkin lymphoma cases almost exactly resembles the seasonal pattern of vitamin D levels in humans," they said.

"Findings Are Compelling"

Approached for comment on the new research, Stefano Luminari, MD, assistant professor of oncology at the University of Modena and Reggio Emilia, in Modena, Italy, said he agreed that the findings are compelling.

"It's not new that vitamin D levels would somehow be connected with the prognosis of these patients. We already know from other solid tumors but also non-Hodgkin lymphomas that low vitamin D levels are prognostic for shorter progression-free and sometimes overall survival," said Luminari, who comoderated the session.

"But this is the first time that in a very large study, vitamin D levels were shown to also be prognostic for Hodgkin lymphoma. It was really surprising to see such a large effect on progression-free and overall survival," he told *Medscape Medical News*.

He said the study raises two key questions: why is there the association, and what can be done?

"This is a modifiable risk factor, and it's very safe and easy to replace, so the question is, can we revert the prognostic features by supplementing these patients with vitamin D therapy?" he said.

Other trials are investigating the association of vitamin D supplementation in hematologic cancers, including follicular lymphoma. A [prospective study](#) on vitamin D supplementation in diffuse large B-cell lymphoma was recently published, and those results, as well as others, should help shed light on the issue, Luminari said.

"This [correlation] is interesting and independent of all other known prognostic factors," Luminari commented. "We don't know why these patients have poorer outcomes, but it's something that's clearly relevant and hopefully is modifiable to help improve the outcomes our patients."

Dr Borchmann and Dr Luminari have disclosed no relevant financial relationships.

European Hematology Association (EHA) 2018 Congress. Abstract S111, presented June 16, 2018.

For more news, join us on [Facebook](#) and [Twitter](#)

Medscape Medical News © 2018

Cite this article: Vitamin D Deficiency and Reduced Hodgkin Lymphoma Survival - *Medscape* - Jun 18, 2018.