

## COMMENT AND RESPONSE

### Change in Bone Mineral Density Is an Indicator of Treatment-Related Antifracture Effect

**TO THE EDITOR:** We disagree with Leslie and colleagues that their "data support the use of serial [bone mineral density (BMD)] monitoring in routine clinical practice" (1) and suggest that much of the observed association may be explained by the inclusion of fractures that occurred before the follow-up BMD testing and regression to the mean (RTM). In line with the journal's policies, we suggest that the study protocol and data set be made available to facilitate replication and reanalysis.

The authors counted any incident fracture after baseline as the outcome of interest, including those that occurred before the follow-up BMD testing. Women who qualified for treatment because of prior or incident fracture would be at higher risk than those without fracture who qualified for treatment because of low BMD. This is especially so for women with incident fracture who would be counted as outcome-positive even before their follow-up measurement. Fracture-related bed rest, disability, and inactivity leading to accelerated bone loss may explain much of the observed association between change in BMD and fracture risk (that is, reverse causation). These (high-risk) women would also be less likely to show apparent increases in BMD than those who had sufficiently low BMD at baseline to qualify for treatment, some of whom would show RTM.

Regression to the mean occurs when a chance low measurement (due to random variations in measurement) is followed by a higher measurement closer to the true underlying BMD (2). Although the authors allow for some measurement variation by using the least significant change, this does not negate the effects of RTM for more extreme chance measurements (3). If the initial BMD measurement is falsely low, then follow-up measurements will reflect the true (higher) value; clinicians may mistakenly attribute the observed increase in BMD and lower risk for fracture to treatment and not measurement variability. The issue is compounded by overadjustment for baseline risk: A falsely low initial BMD will result in a falsely high estimate of baseline risk.

Without a randomized comparison with a placebo group, it is difficult to know whether women with an observed decrease in BMD are still truly benefitting from treatment (4, 5). Evidence that detection of bone loss in women receiving established treatment leads to benefit is lacking, but it may cause harm if beneficial treatment is stopped or replaced with less effective treatment. False suspicion of nonadherence damages the physician-patient relationship, conceivably causing adherent persons to become nonadherent, or results in unnecessary testing for secondary causes of osteoporosis or unnecessary further BMD monitoring.

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**IN RESPONSE:** Dr. Bell and colleagues question whether inclusion of fractures that occurred before the second (follow-up) BMD test might affect results through reverse causation. As noted in our article, the proportional hazards assumption was confirmed, indicating stable effects during follow-up. Indeed, there is progressive divergence in cumulative fracture incidence (Figure 1) that extends beyond the second BMD test (average interval between tests, 4.5 years). The data in Table 3 further show that 10-year cumulative incidence for any fracture is twice the 5-year cumulative incidence regardless of whether it is based on the BMD change category (ratios, 1.98 to 2.05) or compared with stable BMD (ratios, 1.88 to 2.05).

The question of RTM is of great importance in BMD monitoring, particularly with short-term (for example, 1-year) testing, as we and others have previously noted (1, 2). We are confident that RTM is not responsible for our findings for several reasons. The hallmark of RTM is a negative correlation between change in the first versus the second interval (2).

Although we evaluated only 1 testing interval, the correlation in change in BMD between the lumbar spine and hip measurements was positive ( $r = 0.48$  for the lumbar spine vs. the femoral neck measurement, and  $r = 0.54$  for the lumbar spine vs. the total hip measurement), contrary to what would be predicted if there were a large effect of RTM. Furthermore, as noted by Dr. Bell and colleagues, small fluctuations in BMD due to measurement error would be largely eliminated by using a 95% least significant change to classify change as currently recommended (3, 4). Moreover, RTM should be more evident with short-term testing intervals and less evident with long-term ones. We found no effect of the BMD testing interval on our results, and results were similar even with testing intervals greater than 5 years.

Finally, our results were similar when we repeated our analyses using baseline fracture probability computed without BMD. For example, compared with stable total hip BMD, a detectable decrease was still associated with an increase in the absolute 10-year cumulative incidence of any fracture (4.5% [95% CI, 1.9% to 7.1%]) and hip fracture (2.3% [CI, 0.8% to 3.8%]), whereas risk was lower for a detectable increase (−2.2% [CI, −4.2% to −0.3%]). Similar results were seen for the femoral neck and lumbar spine, and statistical significance was maintained even when analysis was performed without any adjustment for baseline fracture risk whatsoever (to address concerns about overadjustment).

The final question relates to reproducibility in research, principles that we strongly support. Manitoba Health no longer permits data to go outside of the province—all analyses must be performed locally, and our data-sharing agreement with the government of Manitoba precludes us from posting or sharing any individual-level data (even those that are de-identified). However, the research data set was prepared by persons with the Manitoba Center for Health Policy and the government of Manitoba, who were completely independent from the research team. We remain happy to provide the SAS code used for producing the directly adjusted risk estimates and variable definitions used for the analysis.

We stand by our original findings and conclusions that, for the first time to our knowledge, provide an evidence base for the judicious use and interpretation of repeated BMD testing in routine clinical practice to assess benefits of antiosteoporosis treatment.

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## OBSERVATIONS

### IgG4-Related Disease in Monozygotic Twins: A Case Report

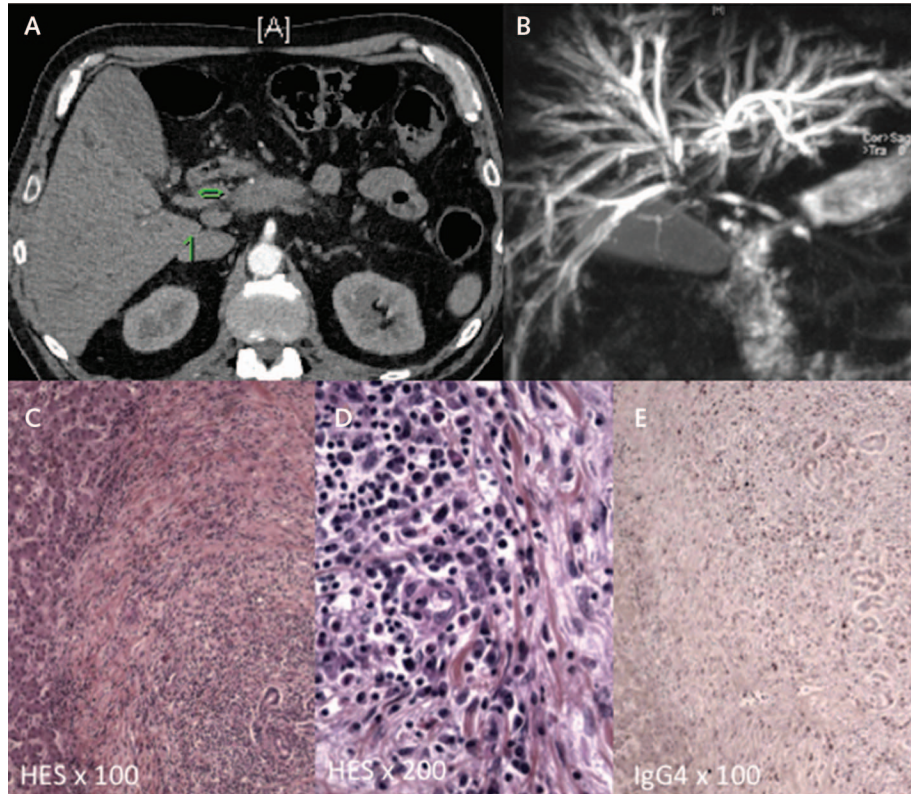
**Background:** IgG4-related disease is a recently recognized chronic inflammatory disorder (1, 2). It is characterized by infiltration of almost any tissue with CD4<sup>+</sup> T-lymphocytes and many IgG4-positive plasma cells (>10 per high-powered field, with an IgG4-IgG plasmacyte ratio >40%). Infiltration may be organized into masses. Fibrosis is a leading characteristic and often includes obliterative phlebitis and elevated serum IgG4 levels. IgG4-related disease occurs more frequently in men older than 50 years. The pathogenesis is unknown. Genetic studies in Japanese patients with disease of the pancreas or salivary and lachrymal glands have shown some association with haplotypes, genes, or gene polymorphisms (3). However, to our knowledge, familial aggregation has not been reported.

**Objective:** To report IgG4-related disease in monozygotic twins.

**Case Report:** The first patient was a 62-year-old white man who presented with abdominal pain. Computed tomography, magnetic resonance imaging, and echoendoscopy showed enlargement of the pancreas. Results of pancreatic needle biopsy revealed lymphoplasmacytic infiltrates and fibrosis and elevated serum IgG4 levels (2.50 g/L [normal levels, <1.35 g/L]). The patient also had sclerosing cholangitis and, despite normal renal function, abnormally low densities on computed tomography. This finding raised suspicion of bilateral kidney involvement.

The patient did not respond to prednisolone, 40 mg/d for 4 weeks. However, he did experience complete remission (resolution of clinical symptoms and of the pancreatic and renal abnormalities on computed tomography and magnetic resonance imaging and normalization of serum IgG4 levels) during 2 years of rituximab therapy (375 mg/m<sup>2</sup> of body surface area every week for 4 weeks and then every 3 months for 2 years). He has remained in complete remission during the 1 year since rituximab therapy was stopped.

**Figure.** Results of imaging and laboratory studies of the mass in the second patient.



**A.** Computed tomographic scan showing a mass at the bile duct convergence with intrahepatic bile duct dilatation. **B.** Magnetic resonance image of the bile duct showing diffuse bile duct dilatation with hilar bile duct obstruction. **C.** Hematoxylin-eosin stain of the mass showing many lymphoplasmacytic infiltrates associated with storiform fibrosis (magnification,  $\times 100$ ). **D.** Hematoxylin-eosin stain showing dense lymphoplasmacytic infiltrates with sparse eosinophils (magnification,  $\times 200$ ). **E.** Anti-IgG4 MAb staining showing many IgG4 plasmacytes (magnification,  $\times 100$ ).

The second patient is the twin brother of the first patient who developed abdominal pain, jaundice, and weight loss at age 63 years. We consider these patients to be monozygotic twins, because birth records describe a single placenta and there is a physical resemblance. Computed tomography and magnetic resonance imaging showed a mass in the hepatic hilum with intrahepatic bile duct dilatation (Figure, A and B). The mass was surgically removed and consisted of polyclonal lymphoplasmacytic infiltrates, periductal fibrosis, and obliterative phlebitis (Figure, C and D). Immunohistochemical studies showed 100 IgG4<sup>+</sup> plasmacytes per high-powered field with an IgG4-IgG ratio of 80% (Figure, E).

The patient was treated with prednisolone, 0.6 mg/kg, and rituximab, 375 mg/m<sup>2</sup>, every week for 4 weeks and then every 3 months for 2 years. When measured during treatment, serum IgG4 levels were elevated (3.85 g/L) but the CD19<sup>+</sup>-C38<sup>+</sup>-CD27<sup>+</sup> plasmablast cell count was low (0.5% of CD19<sup>+</sup> cells or 0.00095  $\times 10^9$  cells/L. HLA testing revealed HLA class I A\*02:32 B\*27:51 and class II DRB1\*01:03 and DQB1\*02:05. This patient has been in complete remission on rituximab therapy alone since 18 months after the diagnosis.

**Discussion:** These patients have many characteristics of IgG4-related disease, namely, male sex; age older than 50 years; disease in the pancreas and biliary ducts and probably in the kidneys; typical findings on imaging studies; elevated

serum IgG4 levels; and histologic findings that were compatible in the first patient and typical in the second patient (1, 2, 4).

The patients have not lived close to each other since age 20 years and have had different professional activities. Their 85-year-old father has normal serum IgG4 levels and no history suggestive of IgG4-related disease. Their mother is deceased, but her health records were not suggestive of this condition. The first patient has twin sons aged 41 years and a daughter aged 24 years, both of whom are in good health and have normal serum IgG4 levels.

These observations suggest that 1 of the parents had a de novo mutation with autosomal-dominant transmission or that both parents were heterozygotes for a gene with autosomal-recessive transmission (5).

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## Hypervitaminosis D Associated With Tanning Bed Use: A Case Report

**Background:** The amount of ultraviolet B (UV-B) radiation absorbed by the skin determines serum 25-hydroxyvitamin D

(25-[OH]D) concentrations. Conventional teaching holds that UV-B radiation from sunlight or tanning beds cannot induce vitamin D toxicity (1).

**Objective:** To support recent information that contradicts this conventional teaching (2).

**Case Report:** A 48-year-old postmenopausal woman developed a spontaneous pubic and bilateral sacrum fracture in December 2012. Nine months earlier, she had undergone surgical fusion of the second lumbar vertebra to the sacrum for degenerative scoliosis with secondary neurogenic claudication. Blood tests found increased levels of total alkaline phosphatase and 25-(OH)D with normal levels of calcium (calciuria was not evaluated) (Table). A radionuclide bone scan showed intense tracer uptake in the pelvis, skull, and multiple ribs. Computed tomography confirmed pagetic bone at these sites and revealed a dorsal vertebral fracture. Dual-energy x-ray absorptiometry T-scores, which describe the number of SDs from the mean value of peak bone density measured in women aged 20 to 29 years, were  $-1.1$  at the hip and  $-1.7$  at the radius. A single zoledronic acid infusion in September 2013 normalized alkaline phosphatase levels.

When the patient was referred to our clinic in May 2014, we determined that she had normal levels of calcium in the blood and urine and markedly increased values for 25-(OH)D (measured using the DiaSorin radioimmunoassay). Retesting in July 2014 confirmed elevated 25-(OH)D levels and increased values for 1,25-dihydroxyvitamin D<sub>3</sub> (measured using liquid chromatography tandem mass spectrometry [3]). She lived in Belgium, had not traveled outside the country in recent years, and had never taken vitamin D or calcium supplements.

Clinical examination revealed a white woman with a tan complexion. She reported using a tanning bed 4 to 5 times weekly and sitting in natural sunlight as much as possible to alleviate chronic musculoskeletal pain. Extensive querying of external hospital, pharmacy, and general practitioner records did not reveal any exposure to vitamin D-containing supplements. The vitamin D-binding protein concentration measured by radial immunodiffusion with a polyclonal antibody (4) was normal. Liquid chromatography-tandem mass spectrometry did not detect 1,25-dihydroxyvitamin D<sub>2</sub>, which excluded unintentional overdose from food products supplemented with vitamin D<sub>2</sub>, and the chromatogram had a normal peak for 24,25-dihydroxyvitamin D, which excluded 24-hydroxylase deficiency (data not shown).

In July 2014, we advised the patient to decrease use of the tanning bed. She decreased it to approximately once

**Table.** Serum Levels

Variable	Normal Range	December 2012	May 2014	July 2014	August 2015	February 2016
Alkaline phosphatase levels, $\mu\text{kat/L}$	0.6-1.8	2.1*	1.0	ND	0.7	-
25-hydroxyvitamin D levels, $\text{nmol/L}$	50-150	332	344	484	297	146
1,25-dihydroxyvitamin D levels, $\text{pmol/L}$	47-187	ND	ND	372	155	ND
Calcium levels, $\text{mmol/L}$	2.13-2.55	2.29	ND	2.43	2.13	ND
Phosphorus levels, $\text{mmol/L}$	0.74-1.52	ND	1.47	1.39	1.32	ND
Intact parathyroid hormone levels, $\text{ng/L}$	15.0-65.0	ND	56.3	34.6	42.5	ND
Vitamin D-binding protein levels, $\text{mg/L}$	275-391	ND	ND	ND	365	ND

ND = not done.

\* Before zoledronic acid infusion.

weekly, and 25(OH)-D and 1,25-dihydroxyvitamin D concentrations returned to normal during the next several months (Table).

**Discussion:** We believe that this patient's hypervitaminosis D was the result of tanning bed use, because we excluded other possible causes and hypervitaminosis D resolved when she decreased frequency of use. The dogma that UV-B radiation cannot induce vitamin D toxicity is based on the following 2 arguments: UV-B rays break down previtamin D in the skin during prolonged acute exposure and increase skin pigmentation, and vitamin D toxicity is absent in equatorial populations with plentiful skin exposure to natural sunlight (1). However, because sunlamps can increase 25(OH)-D levels and few mechanisms prevent its accumulation (1, 5), we believe that frequent tanning bed use in white persons (2) can lead to hypervitaminosis D and that tanning bed use should be added to the differential diagnosis of this condition.

This patient's fractures probably resulted from surgery on pagetic bone. Because factors that increase bone turnover can exacerbate Paget disease, we suggest that the hypervitaminosis D may have increased turnover in this patient's pagetic bone and thus contributed to the fractures.

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