Other arthritic topics of interest

A. HLA B27 spondyloarthropathies - linked by the gene expression and pattern of spinal involvement
   1. Ankylosing spondylitis
      a. cause of severe low back pain and stiffness in young men > women (late teens to early twenties)
      b. familial
      c. strongly associated with inflammatory eye disease (anterior uveitis), inflammatory bowel disease (ulcerative colitis, Crohn's disease)
   2. reactive arthritis (formerly Reiter's disease)
      a. frequently arises in association with gastrointestinal or genitourinary infections
      b. arthritis mainly affecting feet, ankles and knees
      c. inflammation at ligament attachments insertions (enthesitis)
      d. skin rash, painful urination, eye inflammation (acute anterior uveitis)
   3. arthritis of inflammatory bowel disease (enteropathic arthropathy)
      a. Ulcerative colitis, Crohn's disease
      b. Peripheral arthritis, mainly of the lower extremities; can cause profound knee swelling
      c. Sacroiliitis
      d. Arthritis can be responsive to definitive management of the bowel disease
   4. Psoriatic arthritis: occurs in ~ 1/3 of patients with the skin rash
B. Lyme disease: a bacteria born disease (Borrelia burgdorferi) transmitted through the bite of a tick (ixodes)
   1. Three phases of illness
      a. Early localized: Skin rash at the site of the tick bite within days to weeks (" bull's eye " rash – erythema migrans)
      b. Early disseminated – weeks to months following initial infection; bacteria migrate to form new skin lesions, joint pains and muscle stiffness, heart (diagnosed electrocardiographically), central and peripheral nervous systems (Bell's palsy)
      c. Late disease : more severe expression of Early Disseminated
   2. Diagnosis - finding of antibodies to the bacterium (IgM early, IgG after six weeks
C. Rheumatic fever – post streptococcal " reactive " arthritis
   1. Joint pain
   2. Skin rash
   3. Cardiac (carditis)
   4. (nodules)
   5. (chorea): involuntary movements
D. Osteoporosis : a condition of decreased bone density resulting from loss of cancellous (trabecular)bone due to imbalance of bone remodeling rendering bones prone to fracture
   1. WHO definition – T score greater than two standard deviations below the mean (of a control population of thirty year olds on standard DEXA scanning)
   2. Osteopenia : DEXA reading of less than 2 S.D. below the mean
   3. Bones affected
      a. Spine : lower thoracic > lumbar
      b. Hip : femoral neck : high mortality of up to 20% within a year of fracture

c. Wrists: radius

4. Treatment:
   a. Vitamin D and calcium – RDA
      1. Will not reverse osteoporosis
      2. Important in maintaining calcium homeostasis , preventing activation of parathyroid hormone in response to low calcium detected by kidneys
   b. Blockers of osteoclast function – results in increased bone mass by reducing resporption
      1. Bisphosphonates
      2. Denosunab – by injection
      3. Reloxifene : SERM
   c. anabolic stimulation of osteoblasts to make new bone – teriparatide (by injection)

A bite from this tick, found locally, can cause lifelong allergy to red meat

BY KEVIN AMBROSE

Our recent warm weather has reawakened ticks, and one type in particular is becoming more common in the D.C. area: the lone star tick. One bite from this tick, which is easily identified by the white spot on its back if it's a female, can cause a lifelong adverse reaction to eating red meat.

The lone star tick originated in the southern states but has spread north and west to cover much of the eastern half of the country. With a warming climate, more ticks survive the winter months, and their range is expanding.

Unlike the black-legged (deer) tick, the lone star tick doesn't transmit Lyme disease, but it can produce a severe food allergy in people known as alpha-gal syndrome, which is an allergy to red meat.

When lone star ticks feed on mammals, such as mice, rabbits or deer, they ingest alpha-gal sugars. Later, if the ticks bite and feed on humans, they inject the alpha-gal sugars with their saliva into their human host.

Because people don't have alpha-gal in their bodies, the human immune system recognizes alpha-gal from a tick bite as a foreign substance and mounts a response, including the development of antibodies. Often, the bite site becomes swollen and itchy.

But red meat, which contains alpha-gal sugars, can further trigger reactions. If red meat is eaten by people bitten by the lone star tick, the immune system recognizes the alpha-gal from the meat as a foreign substance. As a result, the body mounts a response, often much more severe than the initial response to the tick bite.

The alpha-gal allergy to red meat can lead to a rash, hives, itching, swelling, shortness of breath, headaches, abdominal pain, diarrhea and vomiting. With severe cases, a person may suffer anaphylaxis, a potentially fatal allergic reaction.

Initially, alpha-gal syndrome was hard to diagnose because the allergic reaction occurs many hours after meat is ingested. In addition, the allergy to red meat lasts a lifetime and can become worse over time.

Living with alpha-gal syndrome

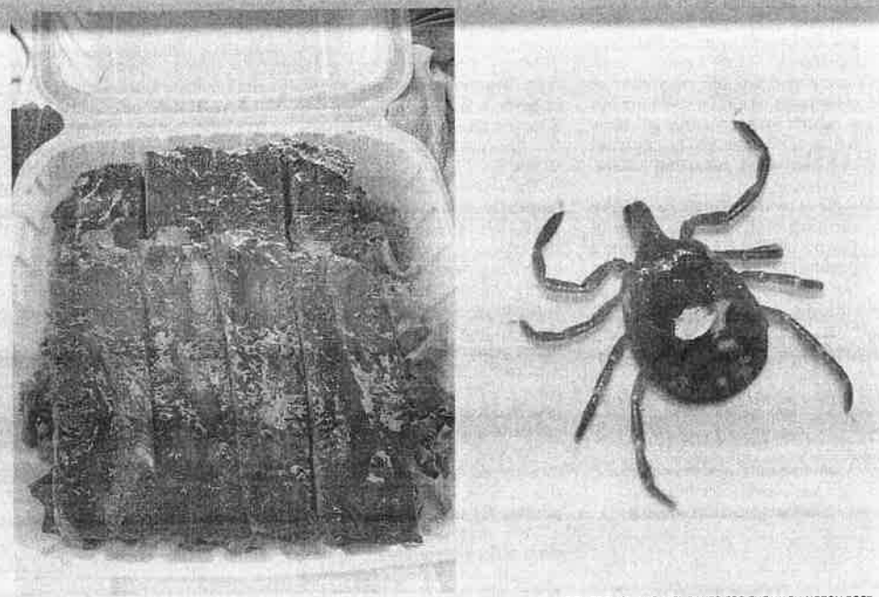
Keith Tremel from Edgewater, Md., is a competitive barbecue cook who can't eat or taste his smoked beef and pork dishes. He needs to wear rubber gloves when handling red meat, or he'll break out in a rash. He contracted alpha-gal syndrome after a lone star tick bite five years ago and is highly allergic to most of the meat he cooks.

Tremel remembers the tick bite: "I was bitten on the thigh by a tick while I was sleeping. It woke me up. I pulled the tick off and immediately saw the white dot. I had recently read an article about alpha-gal and lone star ticks, so I instantly recognized it. I wouldn't say the bite was painful, but it did wake me up."

Soon after the tick bite, Tremel ate a hamburger and broke out in a rash over most of his body. A week later, another hamburger caused the same rash. Later, a third hamburger led to a similar outcome, and Tremel went to see a doctor, fearing alpha-gal syndrome.

Tremel's doctor had never heard of alpha-gal and looked it up on his laptop while Tremel waited. The diagnosis was indeed alpha-gal syndrome. "It was not comforting when I realized I knew more about alpha-gal than a medical professional," he said in an email.

"Before my diagnosis, I loved bacon cheeseburgers. My wife and two kids both like bacon, and my son enjoys steak, so cooking that for them can be a little bit of torture. As for barbecue competitions and catering, I'm used to it now, but in the beginning, it was frustrating."



KEITH TREMEL; MICHAEL RAUPP FOR THE WASHINGTON POST

Eating pork ribs, left, and other red meat can produce a severe allergic reaction in people with alpha-gal syndrome caused by the bite of the lone star tick, right. The tick can be found in the D.C. region.

Tremel and his teammates compete in the Kansas City Barbeque Society, cooking chicken, ribs, pork and brisket at each contest. Chicken, he said, is the only meat he can sample. For the rest of the dishes, he relies on his "teammates' taste buds to make any last-minute changes to our turn-ins, like does it need more spice, less spice, is it salty, too sweet, etc.?"

Since Tremel's alpha-gal diagnosis, his favorite foods have changed to chicken tacos and pizza. "So far, dairy has not affected me, so cheese is still okay."

William Gimpel, a retired entomologist from the Maryland Department of Agriculture, was bitten a while ago by a tick in the Northern Neck of Virginia. But he wasn't officially diagnosed with alpha-gal syndrome until six years ago.

> *"I developed hives, fainted, my blood pressure dropped, and I told my wife on the way to the ER that I could not see."*
>
> **William Gimpel,** a retired entomologist diagnosed with alpha-gal syndrome

Gimpel's allergic reaction to red meat was severe. He said in an email: "I developed hives, fainted, my blood pressure dropped, and I told my wife on the way to the ER that I could not see. That has been my most serious reaction."

Initially, Gimpel was told he was allergic to beef. So, he dined on pork, lamb and venison for several years. Then he had an allergic reaction to pork, and three months later he reacted poorly to lamb. Finally, he found an allergist who correctly diagnosed his condition as alpha-gal syndrome.

Gimpel remains optimistic despite his allergy. He wrote, "The best news is I eat all of the non-red meats, including chicken, turkey, fish, crabs, and other shellfish!"

The increase in ticks can be attributed to warmer temperatures across the seasons. Michael Raupp, entomology professor emeritus at the University of Maryland, said warmer temperatures in the winter allow more ticks to survive the usually harsh season. Mild weather in the fall, winter and spring also allows them to actively seek hosts for longer periods, which increases their chances of survival. In addition, Raupp said, a boost in animals on which the ticks feed, such as white-tailed deer, also helps increase the tick population.

In addition to alpha-gal, the lone star ticks transmit diseases, including Southern Tick Associated Rash Illness (STARI), which produces a rash, fever, fatigue and pain in muscles and joints, and ehrlichiosis, which produces flu-like symptoms, including headache, joint and muscle aches, fever and fatigue.

The female lone star tick has a white spot on its back, but the male does not, making it harder to identify. However, the lone star tick has a different shape from the dog tick and is much larger than the deer tick (see photo above).

If you do contract alpha-gal syndrome, though, genetically modified meat may be an option. Recently, pigs have been genetically modified to remove alpha-gal sugars so their organs can be transplanted in humans with a lower chance of rejection. The leftover meat can be used as food for people with alpha-gal syndrome.

One company, Revivicor, has been mailing packages of its alpha-gal-free pork to people with the syndrome. The meat appears not to produce an allergic reaction.

In December 2020, the Food and Drug Administration approved the genomic alteration of pigs for human food and cosmetics, so there may be a future for selling alpha-gal-free meat to people with the syndrome.

Perhaps one day, Tremel can barbecue pork ribs for competition and do his own taste test. And then eat the leftovers.

MEDICAL MYSTERIES

Intractable pain was 'tipping point' for her

She had a bad back for 30 years. A recurring clue in her medical records sparked an overdue diagnosis.

BY SANDRA G. BOODMAN

As a 16-year-old high school volleyball star, Charlene Gervais particularly dreaded what long bus rides did to her lower back. Away games in northern Minnesota meant more than an hour rumbling along rural roads, trips that left her stiff and sore. The pain in her spine and hips receded once she began playing, only to fire up when she headed home. And it flared at other times, usually without an obvious trigger. ¶ For three decades Gervais, now a 54-year old Chicago brand strategy consultant, assumed that periodic and often unpredictable back pain was her genetic fate. Her father had suffered from the same problem. ¶ The doctors and trainers Gervais consulted over the years offered various diagnoses including a herniated disk, bone spurs and dysfunction of the sacroiliac joints at the base of the spine. But none of the remedies they recommended diminished her pain or stiffness for long. ¶ To cope, Gervais devised workarounds. She became adept at picking up objects — pens, towels, clothing — with her toes to avoid bending forward at the waist, a movement that could cause her back to lock, leaving her in intense pain and unable to straighten up. ¶ It wasn't until Gervais reached what she called "a tipping point" — the culmination of nine months of intractable pain — that she decided she needed to change course. She printed out years of medical records and read through them, struck by a word that cropped up repeatedly.

SEE MYSTERY ON E4

ILLUSTRATION BY CAMERON COTTRILL FOR THE WASHINGTON POST

A fresh approach helped diagnose her aching back

MYSTERY FROM E1

That discovery quickly led to a new approach to the problem that had bedeviled Gervais since adolescence. Its speed and success caused her to wonder whether greater engagement on her part might have short-circuited years of distress.

"I delegate a lot," she said, adding that she also has a long-standing aversion to "googling medical things."

"I find experts and trust them to do their work," Gervais added. She believes that method has worked for her professionally, but had drawbacks when it came to her medical care.

Misaligned spine?

As a teenager, Gervais saw a chiropractor for back pain. "My parents were big fans" as was her family doctor of the treatment that involves spinal manipulations aimed at lessening pain.

Gervais said the chiropractor told her she was suffering from spinal misalignment. Sometimes her back hurt so much she missed volleyball practice. Mostly she tried to downplay the problem for fear of being pulled from games.

"There never seemed to be much of a pattern," Gervais recalled. She noticed that her condition tended to be worse when she woke up in the morning and improved if she moved around. Sometimes months would go by without any pain.

As an adult Gervais continued to see chiropractors and personal trainers whom she believed could recommend exercises to strengthen her body and treatments to manage her pain. She worked out faithfully at a gym and remembers periodically overdoing it in class.

"I'm competitive and would repeatedly hurt myself rather than scale back," she recalled.

An avid traveler who has visited 100 countries, Gervais said she remained determined not to let her bad back slow her down. About 15 years ago she earned a pilot's license, although climbing in and out of a small plane could be tough.

By her early 40s, after years of focusing on things other than her health, Gervais said it was becoming clear that her strategy of benign neglect was faltering. "For me, the method was just push on: I hadn't spent a lot of time helping myself."

CHARLENE GERVAIS

Charlene Gervais spent years unsuccessfully trying to treat the recurring stiffness in her hips and back with chiropractic manipulation and exercise. Despite unpredictable pain, she traveled widely and earned a pilot's license, but sometimes she had trouble climbing in and out of a small plane.

Once she had to be carried up five flights of stairs to her office after her back locked. Sneezing was particularly fraught unless she was in a fetal position on the floor; otherwise it felt like "a grenade shooting up my spine." To get to standing from a seated position, Gervais said, she sometimes rolled off the sofa and crawled around her house before attempting to stand. At times turning over in bed was an impossibility.

Medications were largely ineffective. Anti-inflammatory drugs had stopped working, and opioids made her itchy and irritable.

Gervais's longtime internist was sympathetic.

"She sent me to a lot of specialists — but none that could help me," Gervais said. She saw an orthopedist and several physical therapists along with an occasional chiropractor. Gervais tried gait training to improve her walk and acupuncture to relieve the pain. And she continued to work out regularly with a personal trainer, including one who was so aggressive that Gervais wept from the pain.

"I believed it was a muscle knot and that it would help," she said. "I do trust people when they say they're experts. And I give people the benefit of the doubt. I'm very loyal."

"Why is it that nobody put it together?"

Charlene Gervais

But one expert whose recommendation she rebuffed was an orthopedic surgeon who recommended fusing her sacroiliac joints.

"It seemed like he was saying, 'Yeah, maybe this will help,' " Gervais recalled. She also eschewed recommendations for cortisone injections, fearing possible side effects.

Common as a cold

While reading through her medical records, Gervais, then 46, said that one thing stood out: repeated references to her joints. An online search for "doctors who fix joints" yielded websites about rheumatologists, internists or pediatricians who specialize in the treatment of joints, muscles, bones and the immune system. Gervais had never seen a rheumatologist and asked her internist for a referral to Arthur M. Mandelin, an associate professor of medicine at Northwestern University's Feinberg School of Medicine.

Her initial appointment in June 2012 was "the most thorough work-up I've ever had," Gervais said.

Gervais remembers answering yes to a series of questions Mandelin posed: Do you have trouble standing after sitting for a long period? Are your symptoms alleviated after a walk? "It was the first time the right questions were being asked," she said.

Based on her history and a physical exam, Mandelin told Gervais he suspected she had ankylosing spondylitis (AS), a form of chronic inflammatory spinal arthritis that causes stiffness and back pain. AS, which can affect other parts of the body, results from inflammation between the vertebrae and in the sacroiliac joints. The cause of the disease, which typically develops in late adolescence or early adulthood, is unknown but is believed to result from both environmental and genetic factors.

The severity of AS varies; some people develop a markedly stooped posture or "bamboo spine" in which the bones of the spine do not move because they have fused.

The disease has long been thought to primarily affect men, but recent research has suggested that it may have been overlooked in women, Mandelin noted. Treatment involves medications, exercise and sometimes surgery.

Delayed diagnosis of AS, Mandelin said, is the rule, although the 30 years it took Gervais is on the longer side.

"Back pain is the common cold of musculoskeletal disease," Mandelin said. There are many causes and sorting them out can be tricky, he said, adding that he had the benefit of Gervais's long history as he tried to determine what might be wrong. "Most causes of chronic back pain don't have great testing."

Doctors may not have considered AS in Gervais's case because they were unaware of it.

"There's a maxim from my training: 'Your eyes will not see what your mind does not know,' " he observed.

Some people with AS delay seeking help because over-the-counter anti-inflammatory drugs are effective initially, then stop working because they are inadequate to treat the level of pain.

"The thing that caught my attention," Mandelin said, "is that her back pain has these inflammatory features . . . she had trouble first thing in the morning and improved after she moved." The opposite would be true if her pain was the result of an injury: rest would lessen the pain.

"And there was no inciting event," such as an injury, he noted.

Early diagnosis and treatment are important, Mandelin said. "Intervening early and aggressively has the best chance to control the disease" and reduce damage to the spine and other parts of the body.

To help confirm the diagnosis, Mandelin ordered blood tests, including one for HLA-B27, a protein found on the surface of white blood cells that increases the risk of developing AS but is not a screening test.

Gervais, whose test was negative, said she was elated to receive a provisional diagnosis and even happier shortly after starting a potent anti-inflammatory drug called indomethacin.

"It was literally life changing," she said. Within days "I could bend forward like a normal person."

Her "exuberant" response to the drug was the clincher for Mandelin. "That was impressive," he said. "In rheumatology, we have very, very few blood tests that are gold standard reliable."

But Gervais was unable to tolerate the drug, which left her dizzy and confused. "I'd find myself just staring at my desk in a total fog," she recalled. Piloting a plane was out of the question.

She began receiving biweekly injections of Humira instead. The drug suppresses the immune system and is used to treat other forms of arthritis and Crohn's disease, which sometimes accompanies AS.

"We were looking for medication that would keep things on a low simmer," Mandelin said. The drug has worked well for Gervais, who has not experienced side effects. Her condition has remained stable for the past decade, said Mandelin, who sees her every six months.

Gervais said she now moves without difficulty. She walks five miles a day and works out three times a week without pain.

"I'm good — really good," she said. A brief flare several months ago triggered by gardening left her wondering how she managed all those years.

"What stands out is the incredible frustration of not getting a valid diagnosis," she said. "Why is it that nobody put it together?"

Submit your solved medical mystery to *sandra.boodman@washpost.com*. No unsolved cases, please. Read previous mysteries at *wapo.st/medicalmysteries*.

New laws in a post-*Roe* America declaring that life begins at conception may have additional ramifications. In vitro fertilization (IVF) did not exist before *Roe*. Since its development in 1978, use of IVF has grown, and 2% of all U.S. births now result from assisted reproductive technology, most commonly IVF.[8] IVF procedures usually result in numerous oocytes ovulated per cycle, and fertilization frequently creates numerous embryos. Because modern IVF practice favors single-embryo transfers whenever possible, to reduce risks of multiple gestation and attendant complications, unused embryos are generally frozen for potential future transfer. Nationwide, there are tens of thousands of human embryos cryopreserved in IVF laboratories. While "adoption" programs exist to allow persons to donate their unused embryos to others who would like to implant them, many people are uncomfortable with this option, and unused embryos are often destroyed. If these embryos are declared human lives by the stroke of a governor's pen, their destruction may be outlawed. What will be the fate of abandoned embryos, of the people who "abandon" them, and more broadly of IVF centers in these jurisdictions?

For nearly 50 years, Americans have lived under the protection of *Roe v. Wade*, free to determine their own reproductive destinies. At a time when dozens of other countries around the world are codifying protections for reproductive decision making for their citizens, we are turning the clock backward to take these rights away from our citizens. As has been pointed out by others,[9-11] the most privileged members of U.S. society will always be able to work around restrictive laws and find abortion care in jurisdictions that permit it. Currently proposed changes in our laws will be most burdensome and unfair to the low-income persons and persons of color who are least able to overcome the impediments placed in their paths. These changes will inevitably exacerbate our already vast disparities in wealth and health.

By abolishing longstanding legal protections, the U.S. Supreme Court's reversal of *Roe v. Wade* serves American families poorly, putting their health, safety, finances, and futures at risk. In view of these predictable consequences, the editors of the *New England Journal of Medicine* strongly condemn the U.S. Supreme Court's decision.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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VITAL Findings — A Decisive Verdict on Vitamin D Supplementation

Steven R. Cummings, M.D., and Clifford Rosen, M.D.

An estimated one third or more of U.S. adults 60 years of age or older take vitamin D supplements, not including those who take multivitamins or other compounds containing vitamin D.[1] Yet controversy continues about its overall benefits. In this issue of the *Journal*, LeBoff and

EDITORIALS

Lawmakers v. The Scientific Realities of Human Reproduction

The Editors

The recently announced U.S. Supreme Court decision in *Dobbs v. Jackson Women's Health Organization* represents a stunning reversal of precedent that inserts government into the personal lives and health care of Americans. Yet it was not unexpected. In the long, painful prelude to the decision, many states have severely limited access to reproductive health care. The fig-leaf justification behind these restrictions was that induced abortion was a dangerous procedure that required tighter regulation to protect the health of persons seeking that care. Facts belie this disingenuous rhetoric.[1,2] The latest available U.S. data from the Centers for Disease Control and Prevention and the National Center for Health Statistics are that maternal mortality due to legal induced abortion is 0.41 per 100,000 procedures, as compared with the overall maternal mortality rate of 23.8 per 100,000 live births.[3,4]

Experience around the world has demonstrated that restricting access to legal abortion care does not substantially reduce the number of procedures, but it dramatically reduces the number of *safe* procedures, resulting in increased morbidity and mortality. Millions of persons in states lacking protections for abortion care are also likely to be denied access to medication-induced abortions. It may be difficult for many Americans in 2022 to fully appreciate how complicated, stressful, and expensive, if even attainable, their most private and intimate decisions will become, now that *Roe* has been struck down. A recent *New York Times* article recounted the experiences of women, now in their 60s and 70s, who sought abortions before *Roe*.[5] They described humiliating circumstances, unsafe procedures literally performed in back alleys, and the deep shame and stigma they endured. Common complications of illegal procedures included injury to the reproductive tract requiring surgical repair, induction of infections resulting in infertility, systemic infections, organ failure, and death.[6] We now seem destined to relearn those lessons at the expense of human lives.

Without federal protection, recent state laws curtailing or eliminating the right to abortion care will deny Americans' reproductive autonomy and create an Orwellian dystopia. Examples are the Oklahoma law enacted on May 25, 2022, that declares life to begin at fertilization and the Texas bill that went into effect on September 1, 2021, which empowers third parties to bring civil suits and collect damages against persons who perform, aid, or abet abortions. Defendants in such suits will bear their legal costs, while plaintiffs are indemnified against countersuits for bringing groundless actions. Use of postcoital contraception, either hormonal contraception or placement of an intrauterine device, could be equated with abortion and prosecuted; some jurisdictions (e.g., Mississippi) are already considering such actions. A single act of coitus not timed with respect to the menstrual cycle has a 3% probability of causing conception.[7] After conception, approximately 14 days elapse before chorionic gonadotropin reaches detectable levels in maternal blood. Approximately 30% of recognized pregnancies result in miscarriages. Thus, in some jurisdictions, people could be prosecuted for aborting a pregnancy by using postcoital contraception, despite a 98% probability that their actions did not cause an abortion, but there is no way to prove or disprove that they were pregnant.

colleagues[2] report findings from an ancillary study of the Vitamin D and Omega-3 Trial (VITAL),[3] which extend the results of that trial; taken together, VITAL and this ancillary study show that vitamin supplements do not have important health benefits in the general population of older adults, even in those with low 25-hydroxyvitamin D levels.

VITAL grew from the landmark 2011 Institute of Medicine (IOM) report that established recommended dietary allowances for vitamin D of 600 to 800 IU per day to meet the bone health needs of 97.5% of the general population.[4] The IOM report also recommended that large clinical trials of vitamin D be undertaken to determine the role of supplementation for the prevention or treatment of common diseases. VITAL has been the largest, most prolific, and most definitive trial to date. In a two-by-two factorial design, VITAL randomly assigned 25,871 U.S. men 50 years of age or older and women 55 years of age or older to one of four groups: vitamin D_3 (cholecalciferol, 2000 IU per day) plus n–3 fatty acids (1 g per day), vitamin D_3 plus placebo, n–3 fatty acids plus placebo, or double placebo.[3] Notably, 20% of the participants were Black, although only a small proportion of the participants were Hispanic. Baseline blood samples were obtained from nearly 17,000 participants. Annual questionnaires collected information about numerous health outcomes. Results of analyses from VITAL published in peer-reviewed journals have shown that vitamin D supplementation did not prevent cancer or cardiovascular disease, prevent falls, improve cognitive function, reduce atrial fibrillation, change body composition, reduce migraine frequency, improve stroke outcomes, decrease age-related macular degeneration, or reduce knee pain.[5-8]

In the ancillary study published in this issue of the *Journal*, LeBoff and colleagues report that, contrary to expectations, vitamin D_3 did not reduce the risk of fractures over a median follow-up of 5.3 years, even in the 20% of the participants taking supplemental calcium at a dose of up to 1200 mg per day. 25-Hydroxyvitamin D is essential for the absorption of calcium in the gut and is produced by nonenzymatic skin conversion of previtamin D with activation of the prohormone by liver and renal hydroxylation. Virtually every tissue in the body has vitamin D receptors, a finding that has engendered considerable interest in the potential benefits of vitamin D for multiple health conditions.

The skeleton is one of the most prominent targets of vitamin D actions through the vitamin D receptors, directly by stimulating bone remodeling and indirectly through induction by parathyroid hormone. More than a century ago, nutritional rickets, a devastating and disfiguring skeletal disease in infants and children, was noted to be cured by artificial ultraviolet light, irradiation of food, or supplementation with phytosterol. Hence, it was logical to presume that a deficiency of vitamin D could lead to osteoporosis. Observational studies showed that low vitamin D levels were associated with osteoporosis and other health conditions, but these were at least partially confounded by covariation with its vitamin D–binding protein. Critically, randomized, placebo-controlled trials remain the reference standard of evidence. Recently, a trial of vitamin D that used high-resolution computed tomography showed that bone mineral density and structure did not differ significantly between participants who received vitamin D and those who received placebo.[9] The long-anticipated results of VITAL now clearly demonstrate that daily supplementation with 2000 IU of vitamin D_3 does not reduce the risk of total, hip, or nonvertebral fractures. Subgroup analyses showed a similar lack of effect on fracture risk according to sex, age, race or ethnic group, body-mass index, and other characteristics.

More than 10 million serum 25-hydroxyvitamin D tests are performed annually in the United States. Results from these tests often include the classification of vitamin D "insufficiency" (<30 ng per milliliter) and "deficiency" (<20 ng per milliliter), prompting vitamin D supplementation. In this ancillary study and other VITAL studies, no subgroups defined according to baseline 25-hydroxyvitamin D level, even below 20 ng per milliliter, benefited from supplements.[2,3,7] Thus, there is no justification for measuring 25-hydroxyvitamin D in the general population or treating to a target serum level. A 25-hydroxyvitamin D level might be a useful diagnostic test for some patients with conditions that may be due to or that may cause severe deficiency. For example, persons living in residential settings with little or no sunlight exposure or malabsorption or those receiving treatments for osteoporosis that might cause

hypocalcemia may benefit from vitamin D supplementation; the need for measuring serum 25-hydroxyvitamin D levels in these groups remains uncertain. Otherwise, the use of the terms vitamin D "insufficiency" and "deficiency" should now be reconsidered.

What are the implications of VITAL? The fact that vitamin D had no effect on fractures should put to rest any notion of an important benefit of vitamin D alone to prevent fractures in the larger population. Adding those findings to previous reports from VITAL and other trials showing the lack of an effect for preventing numerous conditions suggests that providers should stop screening for 25-hydroxyvitamin D levels or recommending vitamin D supplements, and people should stop taking vitamin D supplements to prevent major diseases or extend life.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the University of California, San Francisco, San Francisco (S.R.C.); and Maine Medical Center Research Institute, Scarborough (C.R.).

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A Better Treatment for Advanced-Stage Hodgkin's Lymphoma?

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Treatment for patients with Hodgkin's lymphoma is one of the success stories of modern medicine. A once uniformly fatal disorder is now curable, even in an advanced stage, in the great majority of patients. In fact, particularly in limited-stage Hodgkin's lymphoma, much of the therapeutic focus is on maintaining the high probability of cure while reducing the incidence of toxic effects. How little therapy can we give without losing efficacy?

For patients with advanced-stage, high-risk disease, debates regarding the best currently available approach have centered on the "old standard" ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen,[1] the very intensive escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen,[2] and risk-adapted approaches that use interim positron-emission tomographic (PET) scans (usually after two cycles of therapy) as the basis of either intensifying or deescalating therapy.[3] The clearance of a positive PET scan after the second cycle of therapy (PET2-negative status) is thought to carry an excellent prognosis and can serve to limit the extent of treatment; often, patients with PET2-negative status can stop therapy after two additional cycles of treatment. The introduction of the anti-CD30 antibody–drug conjugate brentuximab vedotin and its high response rate as a salvage treatment, including durable responses in some patients,[4] offers a new approach. The hope has been that brentuximab vedotin, when substituted for bleomycin in the ABVD regimen, would lead to better survival when used as primary therapy, without the serious toxic effects that are associated with escalated BEACOPP.

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Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults

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ABSTRACT

BACKGROUND

Vitamin D supplements are widely recommended for bone health in the general population, but data on whether they prevent fractures have been inconsistent.

METHODS

In an ancillary study of the Vitamin D and Omega-3 Trial (VITAL), we tested whether supplemental vitamin D_3 would result in a lower risk of fractures than placebo. VITAL was a two-by-two factorial, randomized, controlled trial that investigated whether supplemental vitamin D_3 (2000 IU per day), n–3 fatty acids (1 g per day), or both would prevent cancer and cardiovascular disease in men 50 years of age or older and women 55 years of age or older in the United States. Participants were not recruited on the basis of vitamin D deficiency, low bone mass, or osteoporosis. Incident fractures were reported by participants on annual questionnaires and adjudicated by centralized medical-record review. The primary end points were incident total, nonvertebral, and hip fractures. Proportional-hazards models were used to estimate the treatment effect in intention-to-treat analyses.

RESULTS

Among 25,871 participants (50.6% women [13,085 of 25,871] and 20.2% Black [5106 of 25,304]), we confirmed 1991 incident fractures in 1551 participants over a median follow-up of 5.3 years. Supplemental vitamin D_3, as compared with placebo, did not have a significant effect on total fractures (which occurred in 769 of 12,927 participants in the vitamin D group and in 782 of 12,944 participants in the placebo group; hazard ratio, 0.98; 95% confidence interval [CI], 0.89 to 1.08; P=0.70), nonvertebral fractures (hazard ratio, 0.97; 95% CI, 0.87 to 1.07; P=0.50), or hip fractures (hazard ratio, 1.01; 95% CI, 0.70 to 1.47; P=0.96). There was no modification of the treatment effect according to baseline characteristics, including age, sex, race or ethnic group, body-mass index, or serum 25-hydroxyvitamin D levels. There were no substantial between-group differences in adverse events as assessed in the parent trial.

CONCLUSIONS

Vitamin D_3 supplementation did not result in a significantly lower risk of fractures than placebo among generally healthy midlife and older adults who were not selected for vitamin D deficiency, low bone mass, or osteoporosis. (Funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases; VITAL ClinicalTrials.gov number, NCT01704859.)

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Fractures are major public health problems, especially among older adults. An estimated 53.6 million Americans have osteoporosis, low bone mass, or both,[1] and in the United States, 2 million osteoporotic fractures occur annually, a number projected to exceed 3 million fractures per year by 2040, with related costs of more than $95 billion per year.[2-4] Vitamin D supplements are widely recommended to the general population as a means to promote bone health. Between 1999 and 2012, use of vitamin D supplements increased from 5.1% to 19% among U.S. adults.[5] However, data on whether these supplements prevent fractures are conflicting.[6-10]

Vitamin D may support skeletal health and improve bone mineralization by increasing intestinal calcium absorption, reducing secondary hyperparathyroidism, and decreasing bone turnover.[11] Furthermore, in bone, vitamin D receptors and extrarenal activation of 1,25-dihydroxyvitamin D have been identified and linked to the formation of osteoblast progenitors, which suggests a role in bone formation.[12,13]

In 2011, the Institute of Medicine (IOM) established recommended dietary allowances for vitamin D of 600 to 800 IU per day, corresponding to a total 25-hydroxyvitamin D level of at least 20 ng per milliliter, in order to meet the bone health needs for 97.5% of the population.[8] Other societies or foundations recommend vitamin D intakes of at least 800 to 2000 IU per day for adults 50 years of age or older to attain 25-hydroxyvitamin D levels of at least 30 ng per milliliter.[8,14]

Results from randomized, controlled trials investigating the effects of supplemental vitamin D on fracture outcomes have been inconsistent, with trials finding evidence for benefit, no effect, or harm.[4,15-17] Differences to explain the divergent results across these trials include the use of bolus dosing,[17,18] coadministration of vitamin D with calcium,[19,20] and small sample sizes.[15] No large randomized, controlled trials have tested the effects of daily supplemental vitamin D alone (without coadministered calcium) in preventing fractures in the U.S. population.

Systematic reviews and meta-analyses of randomized, controlled trials have raised questions about whether supplemental vitamin D has beneficial effects for primary prevention of fractures.[21,22] In 2021, the U.S. Preventive Services Task Force found no effect of supplemental vitamin D on fracture incidence among community-dwelling adults with low 25-hydroxyvitamin D levels.[10] The IOM identified an increased risk of fractures at both low and high 25-hydroxyvitamin D levels and emphasized the need for more research from large randomized, controlled trials.[8] To address these knowledge gaps, we investigated whether supplemental vitamin D_3 would result in a lower risk of incident fractures than placebo among generally healthy U.S. adults in an ancillary study of the large Vitamin D and Omega-3 Trial (VITAL).[23]

METHODS

TRIAL DESIGN AND OVERSIGHT

VITAL was a randomized, controlled trial that investigated the effects of supplemental vitamin D_3 (cholecalciferol, 2000 IU per day), n–3 fatty acids (Omacor [Pronova BioPharma and BASF], 1 g per day), or both on the primary prevention of cancer and cardiovascular disease in a two-by-two factorial design. The rationale for this vitamin D_3 dose was that it would achieve a mean 25-hydroxyvitamin D level of approximately 40 ng per milliliter in the vitamin D group and a favorable balance of safety and efficacy.[23]

The trial protocol has been described previously[23,24] and is available with the full text of this article at NEJM.org. Among the exclusion criteria was a history of cancer, cardiovascular disease, or hypercalcemia (Fig. 1). Participants were not recruited on the basis of vitamin D deficiency, low bone mineral density, or fracture history. After a 3-month placebo run-in phase, participants who took at least two thirds of the trial pills underwent randomization. Participants agreed to limit any nontrial supplements of vitamin D to 800 IU per day and of calcium to 1200 mg per day.[8,23]

In this ancillary study, we examined the effects of supplemental vitamin D_3 as compared with placebo on incident fractures in 25,871 U.S. men (age, ≥50 years) and women (age, ≥55 years), including 5106 Black participants, who were enrolled from all 50 states and followed for a median of 5.3 years. During the run-in phase, participants completed detailed questionnaires to assess baseline demographic characteristics, medical history, medication use, and supple-

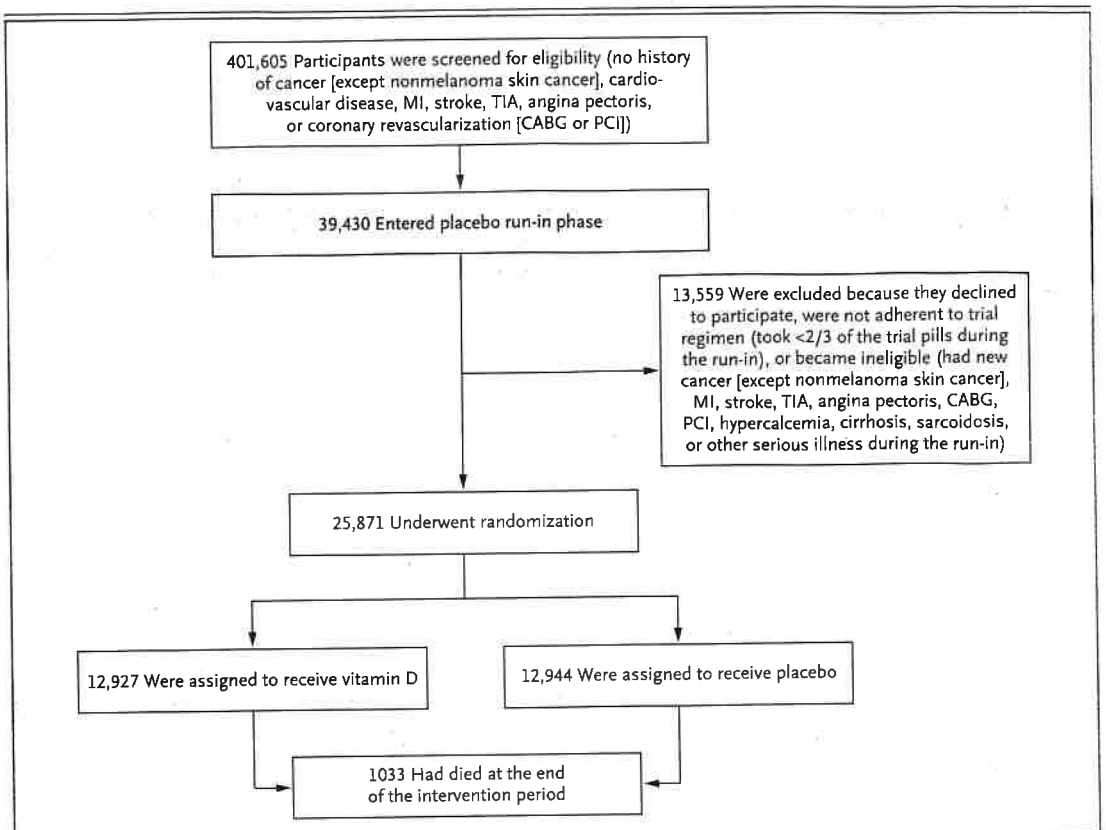


Figure 1. Screening, Randomization, and Follow-up of the Participants.
CABG denotes coronary-artery bypass grafting, MI myocardial infarction, PCI percutaneous coronary intervention, and TIA transient ischemic attack.

ment use (e.g., calcium, vitamin D, and fish oil). Annual questionnaires assessed adherence to trial regimens, side effects, use of nontrial supplements (e.g., calcium and vitamin D) and medications, the development of major illnesses, osteoporosis or related risk factors,[19,25] physical activity, falls, and fractures.[24]

Baseline and follow-up blood samples were provided by 16,956 and approximately 6,000 participants, respectively. Quest Diagnostics measured total 25-hydroxyvitamin D levels using liquid chromatography–tandem mass spectrometry; assays were calibrated to Centers for Disease Control and Prevention (CDC) standards.[23] This protocol was approved by the Mass General Brigham institutional review board, and participants gave written informed consent.

TRIAL END POINTS

The primary end points were first incident total, nonvertebral, and hip fractures. Fractures were initially reported by the participants on annual questionnaires. Participants who reported a fracture were sent an authorization form to obtain their medical records and a fracture questionnaire, in which they recorded date, fracture location, any association with cancer or prosthesis (e.g., joint replacement), and circumstances of the fracture. Requests for medical records were then sent to health care professionals or medical facilities that provided fracture care, including radiologic reports, orthopedic notes, other hospital records, and operative or procedure reports. For participants who reported hip or femur fractures, radiologic images were also requested. All incident fractures were centrally adjudicated by investigators and study staff who were unaware of the trial-group assignments. Fractures were coded according to anatomical location and level of trauma. We included fractures regardless of the level of trauma for all end-point analyses, because even high-trauma

fractures are associated with an increased risk of subsequent fractures.[26,27]

Secondary end points were incident total, nonvertebral, and hip fractures, with the exclusion of toe, finger, skull, periprosthetic, and pathologic fractures. We identified 42 periprosthetic and 29 pathologic fractures (e.g., tumors and Paget's disease). For hip or femur fractures, a musculoskeletal radiologist (the fifth author) reviewed radiographs and determined whether fractures were periprosthetic or atypical femur fractures using criteria from an American Society for Bone and Mineral Research task force.[28] Three female participants had a total of 4 atypical femur fractures; two were taking alendronate and had pathologic fractures. In exploratory analyses, we examined major osteoporotic fractures (defined as hip, wrist, humerus, or clinical spine fractures), pelvic fractures, and wrist fractures.

STATISTICAL ANALYSIS

The primary aim was to assess the main effects of vitamin D supplementation as compared with placebo on first incident total, nonvertebral, and hip fractures in intention-to-treat analyses; secondary end points excluded toe, finger, skull, periprosthetic, and pathologic fractures. To ensure balance, we compared baseline characteristics according to randomized trial-group assignment. We used t-tests and analysis of variance to compare continuous variables across randomized groups and used chi-square tests to compare proportions. We used Cox proportional-hazards models to allow for variable follow-up lengths and estimated the cause-specific hazard ratio for fracture incidence for each intervention using indicators for treatment exposure, controlling for n–3 fatty acid randomization group, age, sex, and race or ethnic group. In a post hoc analysis, we applied the Andersen–Gill model allowing for multiple events per person with different time between events. We also assessed for effects of adherence by censoring data from participants who were taking fewer than two thirds of the assigned trial pills and for latency by excluding the first 1 and 2 years of follow-up.

We examined modification of the treatment effect in prespecified subgroups, defined by sex, race or ethnic group, body-mass index (BMI; the weight in kilograms divided by the square of the height in meters), baseline use of calcium or vitamin D supplements, baseline serum total 25-hydroxyvitamin D levels (above or below the median and according to quartiles), and trial group. In addition, we explored whether treatment effect varied according to history of fragility fractures or baseline use of osteoporosis medications. The primary aims were to examine the effects of vitamin D and n–3 fatty acids in this two-by-two factorial trial. Here, we present the main effects of vitamin D as compared with placebo, because there was no interaction between vitamin D and n–3 fatty acids in the analysis of fracture outcomes. There was no control for multiple hypothesis testing, and no adjustment was made to the P values or confidence intervals. Thus, results regarding secondary and exploratory end points, as well as those regarding subgroups, should be interpreted with caution.

This study was designed by the first author in conjunction with the last author. The first four authors had full access to trial data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The manuscript was written by the first author with contributions from all the authors.

RESULTS

TRIAL PARTICIPANTS

Participants were randomly assigned to one of four groups: vitamin D plus n–3 fatty acids, vitamin D plus placebo, n–3 fatty acids plus placebo, or double placebo. Baseline characteristics (Table 1, and Table S2 in the Supplementary Appendix, available at NEJM.org) were balanced between the trial groups. The mean (±SD) age of the participants was 67.1±7.1 years, 50.6% (13,085 of 25,871) were women, and 20.2% (5106 of 25,304) were Black. The mean BMI was 28.1±5.7. Only 4.8% of the participants (1240 of 25,690) were taking osteoporosis medications at baseline, yet 10.3% (2578 of 25,023) had a history of fragility fracture. At baseline, a total of 42.6% (11,030 of 25,871) took nontrial vitamin D supplements limited to 800 IU per day, and 20.0% (5166 of 25,871) took calcium supplements limited to 1200 mg per day. Table S1 shows the representativeness of VITAL participants to the general U.S. population.

The mean baseline 25-hydroxyvitamin D level (16,757 participants) was 30.7±10.0 ng per mil-

Table 1. Characteristics of the Participants at Baseline, According to Randomized Assignment to Vitamin D or Placebo.*

Characteristic	Total (N=25,871)	Vitamin D Group (N=12,927)	Placebo Group (N=12,944)
Female sex — no. (%)	13,085 (50.6)	6,547 (50.6)	6,538 (50.5)
Age — yr	67.1±7.1	67.1±7.0	67.1±7.1
Race or ethnic group — no./total no. (%)†			
Non-Hispanic White	18,046/25,304 (71.3)	9,013/12,647 (71.3)	9,033/12,657 (71.4)
Black	5,106/25,304 (20.2)	2,553/12,647 (20.2)	2,553/12,657 (20.2)
Non-Black Hispanic	1,013/25,304 (4.0)	516/12,647 (4.1)	497/12,657 (3.9)
Asian or Pacific Islander	388/25,304 (1.5)	188/12,647 (1.5)	200/12,657 (1.6)
American Indian or Alaskan Native	228/25,304 (0.9)	118/12,647 (0.9)	110/12,657 (0.9)
Other or unknown	523/25,304 (2.1)	259/12,647 (2.0)	264/12,657 (2.1)
Body-mass index‡	28.1±5.7	28.1±5.7	28.1±5.8
Diabetes — no./total no. (%)	3,537/25,824 (13.7)	1,804/12,900 (14.0)	1,733/12,924 (13.4)
Parental history of hip fracture — no./total no. (%)	3,704/23,979 (15.4)	1,809/11,970 (15.1)	1,895/12,009 (15.8)
Rheumatoid arthritis — no./total no. (%)	1,118/25,512 (4.4)	556/12,749 (4.4)	562/12,763 (4.4)
History of fragility fracture — no./total no. (%)	2,578/25,023 (10.3)	1,287/12,513 (10.3)	1,291/12,510 (10.3)
Unintentional fall in the past year — no./total no. (%)	6,921/25,715 (26.9)	3,521/12,848 (27.4)	3,400/12,867 (26.4)
Current use of osteoporosis medication — no./total no. (%)§	1,240/25,690 (4.8)	609/12,835 (4.7)	631/12,855 (4.9)
Current smoker — no./total no. (%)	1,835/25,488 (7.2)	921/12,732 (7.2)	914/12,756 (7.2)
Current use of supplemental vitamin D — no. (%)¶	11,030 (42.6)	5,497 (42.5)	5,533 (42.7)
Current use of glucocorticoids — no./total no. (%)	461/25,427 (1.8)	239/12,705 (1.9)	222/12,722 (1.7)
Servings of milk per day	0.71±0.91	0.71±0.89	0.72±0.92
Baseline 25-hydroxyvitamin D level — ng/ml‖	30.7±10.0	30.7±10.0	30.7±10.0
Baseline calcium level — mg/dl**	9.00±1.61	9.00±1.61	9.00±1.61

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participants.
‡ A total of 30.1% of the participants had a normal body-mass index (18.5 to <25), 40.1% were overweight (25 to <30), and 28.9% were obese (≥30).
§ Osteoporosis medications included alendronate (Fosamax), raloxifene (Evista), risedronate (Actonel), zoledronate (Reclast), denosumab (Prolia), teriparatide injection (Forteo), salmon calcitonin (Miacalcin or Fortical), and other osteoporosis medications not listed above.
¶ The mean 25-hydroxyvitamin D level at baseline was 34.9 ng per milliliter for participants taking vitamin D supplements (total, <800 IU per day) and 27.4 ng per milliliter for participants not taking vitamin D supplements.
‖ Data were available for 16,757 participants.
** Data were available for 15,884 participants.

liliter. At baseline, 401 (2.4%) had 25-hydroxyvitamin D levels of less than 12 ng per milliliter and 2161 (12.9%) had levels of less than 20 ng per milliliter. Among participants who provided 2-year blood samples, mean 25-hydroxyvitamin D levels increased from 29.2 ng per milliliter to 41.2 ng per milliliter in the vitamin D group (P<0.001, 1347 participants) and decreased slightly from 30.0 ng per milliliter to 29.4 ng per milliliter in the placebo group (P=0.01, 1308 participants). Mean parathyroid hormone levels decreased in the vitamin D group from 40.8 ng per milliliter to 37.2 ng per milliliter (P<0.001, 1396 participants), with no changes in the placebo group. There were no 2-year changes in calcium levels in either group. Adherence to trial pills was 87.3% at 2 years and 85.4% at 5 years.

FRACTURE INCIDENCE

A total of 87.0% of the participants who reported a fracture consented to medical-record review, and documentation was obtained for 91.3% of these participants. We adjudicated 2133 total fractures and confirmed 1991 fractures (93.3%)

Table 2. Hazard Ratios for the Primary, Secondary, and Exploratory End Points, According to Randomized Assignment to Vitamin D or Placebo, in Intention-to-Treat Analyses.*

End Point	Vitamin D Group (N=12,927)	Placebo Group (N=12,944)	Hazard Ratio (95% CI)
	no. of participants with event		
Primary end points: confirmed incident fractures			
Total	769	782	0.98 (0.89–1.08)
Nonvertebral	721	744	0.97 (0.87–1.07)
Hip	57	56	1.01 (0.70–1.47)
Secondary end points: confirmed incident fractures excluding toe, finger, skull, periprosthetic, and pathologic fractures			
Total	678	685	0.99 (0.89–1.10)
Nonvertebral	630	649	0.97 (0.87–1.08)
Hip	54	52	1.03 (0.70–1.52)
Exploratory end points: confirmed incident fractures excluding periprosthetic and pathologic fractures			
Major osteoporotic fractures: hip, wrist, humerus, or clinical spine fractures	276	278	0.99 (0.83–1.17)
Pelvic	32	29	1.08 (0.64–1.80)
Wrist	118	132	0.89 (0.69–1.15)

* Analyses were performed with the use of Cox proportional-hazards models that were adjusted for age, sex, race or ethnic group, and n–3 fatty acid randomization group. Confidence intervals were not adjusted for multiple comparisons, and inferences drawn from them may not be reproducible.

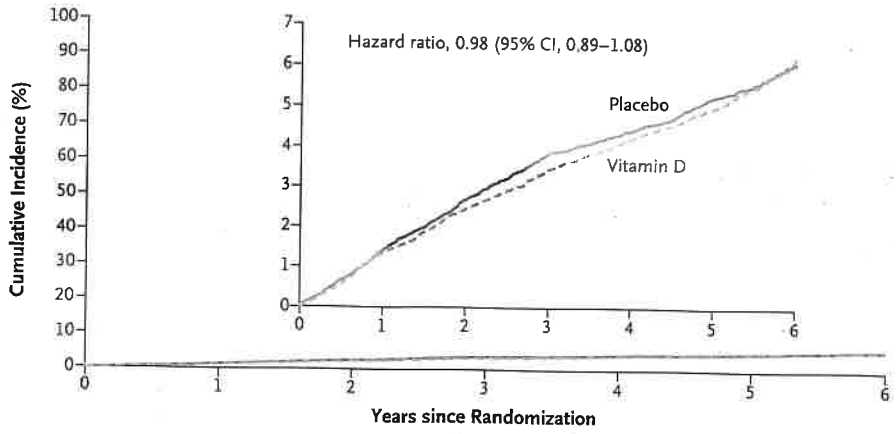
in 1551 participants during the intervention period, with a median follow-up of 5.3 years. Supplemental vitamin D_3, as compared with placebo, did not have a significant effect on first incident total fractures (which occurred in 769 of 12,927 participants in the vitamin D group and in 782 of 12,944 participants in the placebo group; hazard ratio, 0.98; 95% confidence interval [CI], 0.89 to 1.08; P=0.70), nonvertebral fractures (in 721 participants in the vitamin D group and in 744 in the placebo group; hazard ratio, 0.97; 95% CI, 0.87 to 1.07; P=0.50), or hip fractures (in 57 participants in the vitamin D group and in 56 in the placebo group; hazard ratio, 1.01; 95% CI, 0.70 to 1.47; P=0.96), with adjustment for age, sex, race or ethnic group, and n–3 fatty acid randomization group (Table 2 and Fig. 2).

There was no effect modification according to baseline age, sex, race or ethnic group, BMI, or personal use of supplemental calcium or vitamin D (Tables 3, S3, and S4). Baseline 25-hydroxyvitamin D levels, when stratified above or below the median (31 ng per milliliter) or in quartiles (≤24.0, 24.1 to 30.0, 30.1 to 36.9, or ≥37.0 ng per milliliter), as prespecified, did not modify the effects of supplemental vitamin D_3 as compared with placebo on incident total, nonvertebral, or hip fractures. In exploratory analyses, there was no significant effect modification on fracture incidence between the vitamin D and placebo groups according to baseline clinically relevant 25-hydroxyvitamin D thresholds (<12, <20, <30, or ≥50 ng per milliliter), serum calcium levels (15,884 participants), or parathyroid hormone levels (16,803 participants). There were no significant differences in fracture incidence among participants using osteoporosis medications or among those with a history of fragility

Figure 2 (facing page). Cumulative Incident Fractures in the Vitamin D and Placebo Groups.

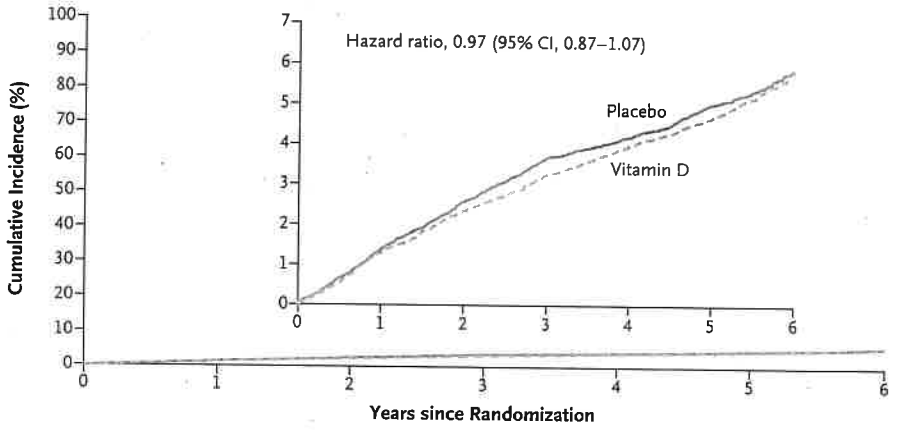
The median follow-up was 5.3 years. Analyses were conducted with the use of Cox regression models that were controlled for age, sex, race or ethnic group, and n–3 fatty acid randomization group (intention-to-treat analyses). The insets show the same data on an enlarged y axis.

A Total Fractures



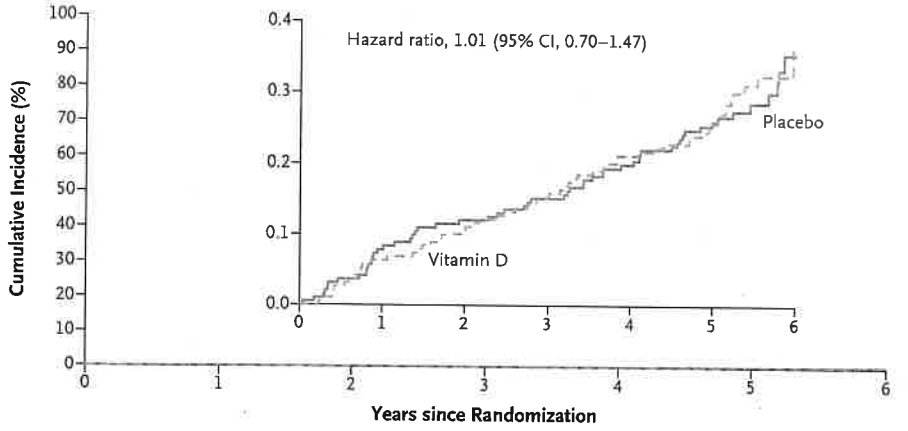
No. at Risk							
Placebo	12,927	12,737	12,578	12,438	12,218	9830	793
Vitamin D	12,944	12,742	12,561	12,399	12,188	9785	782

B Nonvertebral Fractures



No. at Risk							
Placebo	12,927	12,743	12,595	12,468	12,256	9867	800
Vitamin D	12,944	12,749	12,579	12,425	12,225	9820	784

C Hip Fractures



No. at Risk							
Placebo	12,927	12,915	12,907	12,898	12,776	10,383	847
Vitamin D	12,944	12,929	12,921	12,915	12,773	10,378	843

Table 3. Hazard Ratios for Total Fractures with Vitamin D as Compared with Placebo, According to Subgroup.*

Subgroup	No. of Participants	Vitamin D Group (N=12,927)	Placebo Group (N=12,944)	Hazard Ratio (95% CI)
		no. of participants with event		
Age				
<Median of 66.7 yr	12,859	282	285	0.99 (0.84–1.18)
≥Median of 66.7 yr	13,012	487	497	0.97 (0.86–1.10)
Sex				
Male	12,786	265	250	1.07 (0.90–1.28)
Female	13,085	504	532	0.94 (0.83–1.06)
Race or ethnic group				
Non-Hispanic White	18,046	655	658	0.99 (0.89–1.11)
Black	5,106	53	59	0.89 (0.62–1.30)
Other	2,152	46	51	0.90 (0.61–1.35)
BMI category				
<25	7,849	300	327	0.93 (0.79–1.09)
25 to <30	10,127	254	271	0.93 (0.78–1.11)
≥30	7,294	198	165	1.17 (0.95–1.44)
BMI				
<Median of 27.1	12,589	435	456	0.95 (0.83–1.09)
≥Median of 27.1	12,681	317	307	1.03 (0.88–1.20)
Osteoporosis medication†				
Yes	1,240	62	79	0.74 (0.53–1.03)
No	24,450	704	697	1.01 (0.91–1.12)
History of fragility fractures†				
Yes	2,578	146	161	0.87 (0.69–1.09)
No	22,445	598	595	1.01 (0.90–1.14)
Baseline use of supplemental vitamin D				
Yes	11,030	393	399	0.97 (0.84–1.12)
No	14,841	376	383	0.99 (0.86–1.14)
Supplemental calcium				
≤1200 mg/day	5,166	228	232	0.92 (0.77–1.11)
None	20,705	541	550	1.00 (0.89–1.13)
Baseline 25-hydroxyvitamin D level, according to median				
<Median of 31 ng/ml	8,430	239	241	1.02 (0.85–1.22)
≥Median of 31 ng/ml	8,327	329	344	0.93 (0.80–1.08)
Baseline 25-hydroxyvitamin D level in quartiles				
Quartile 1: ≤24.0 ng/ml	4,270	115	112	1.04 (0.80–1.36)
Quartile 2: 24.1–30.0 ng/ml	4,104	122	128	0.98 (0.77–1.26)
Quartile 3: 30.1–36.9 ng/ml	4,097	151	154	0.98 (0.78–1.23)
Quartile 4: ≥37.0 ng/ml	4,286	180	191	0.89 (0.73–1.10)
Baseline 25-hydroxyvitamin D level, according to threshold of 12 ng/ml†				

Table 3. (Continued.)

Subgroup	No. of Participants	Vitamin D Group (N=12,927)	Placebo Group (N=12,944)	Hazard Ratio (95% CI)
		no. of participants with event		
<12 ng/ml	401	7	8	1.03 (0.36–2.95)
≥12 ng/ml	16,356	561	577	0.97 (0.86–1.09)
Randomization in the n–3 fatty acids portion of the trial				
Placebo group	12,938	374	392	0.95 (0.82–1.09)
Active-agent group	12,933	395	390	1.02 (0.88–1.17)

* Analyses were conducted with the use of Cox proportional-hazards models that were adjusted for age, sex, race or ethnic group, and n–3 fatty acid randomization group (intention-to-treat analyses). Confidence intervals were not adjusted for multiple comparisons, and inferences drawn from them may not be reproducible.

† These subgroups were not prespecified, but a subgroup defined by a baseline 25-hydroxyvitamin D level of less than 10 ng per milliliter (201 participants) was prespecified.

fracture. In sensitivity analyses, results did not change among participants adherent to trial pills, and no latency effect was found. Supplemental vitamin D_3 also did not result in a lower risk of recurrent fractures than placebo.

Findings for vitamin D as compared with placebo were similar with respect to secondary end points, excluding toe, finger, skull, periprosthetic, and pathologic fractures: total fractures (hazard ratio, 0.99; 95% CI, 0.89 to 1.10), nonvertebral fractures (hazard ratio, 0.97; 95% CI, 0.87 to 1.08), and hip fractures (hazard ratio, 1.03; 95% CI, 0.70 to 1.52) (Tables 2 and S5). Findings were also similar for exploratory end points: major osteoporotic fractures (hazard ratio, 0.99; 95% CI, 0.83 to 1.17), pelvic fractures (hazard ratio, 1.08; 95% CI, 0.64 to 1.80), and wrist fractures (hazard ratio, 0.89; 95% CI, 0.69 to 1.15), excluding periprosthetic and pathologic fractures (Tables 2 and S6).

ADVERSE EVENTS

There were no substantial differences in the incidence of hypercalcemia and kidney stones between the vitamin D and placebo groups as assessed by the VITAL data and safety monitoring board.[23]

DISCUSSION

In this large randomized, controlled trial, supplemental vitamin D_3 (2000 IU per day) without coadministered calcium did not result in a lower risk of fractures than placebo (with adjustment for age, sex, race or ethnic group, and n–3 fatty acid randomization group) among U.S. adults who were not selected on the basis of vitamin D deficiency, low bone mass, or osteoporosis. Findings were similar for secondary end points, which excluded toe, finger, skull, periprosthetic, and pathologic fractures. We also found no effect of supplemental vitamin D_3 as compared with placebo on major osteoporotic fractures and other exploratory end points, including pelvic and wrist fractures. No latency effect was found. Data are presented as supplemental vitamin D_3 as compared with placebo because there was no interaction between vitamin D and n–3 fatty acids in the analysis of fracture outcomes.

It has been suggested that the effects of supplemental vitamin D_3 might be limited to those with low 25-hydroxyvitamin D levels. Higher prevalences of vitamin D deficiency have been reported among Black adults (from reduced cutaneous vitamin D synthesis and other mechanisms),[29] persons with obesity[30] (from vitamin D sequestration and increased volume in fat), postmenopausal women, older men, and older persons with hip fractures.[31-33] However, our results did not suggest any differences in the effects of supplemental vitamin D_3 on fracture outcomes according to race or ethnic group, BMI, or age. Although most participants in our cohort may have already reached the 25-hydroxyvitamin D level needed for bone health (mean baseline 25-hydroxyvitamin D level, 30.7±10.0 ng per milliliter), VITAL was large enough to stratify participants according to baseline 25-hydroxyvitamin D levels. We found no significant differences in fracture incidence between trial groups accord-

ing to various 25-hydroxyvitamin D thresholds. In post hoc analyses, we found no benefit for supplementation in the relatively small number of participants with baseline 25-hydroxyvitamin D levels of less than 12 ng per milliliter (401 participants). Similarly, a study conducted in the Netherlands showed that supplemental vitamin D (400 IU per day) had no effect on hip or peripheral fractures in elderly adults with very low vitamin D levels.[34] In post hoc analyses, we also found no substantial between-group differences in fracture incidence among participants who were at high fracture risk (i.e., those taking osteoporosis medications [1240 participants] or with a history of fragility fractures [2578 participants]). Other randomized, controlled trials[19,20] and meta-analyses[35] have shown that vitamin D and calcium coadministration reduce fracture risk modestly. However, in post hoc analyses, we found no substantial differences in the 20.0% of the participants who took supplemental calcium.

Previous randomized, controlled trials from around the world that investigated the effects of supplemental vitamin D on fracture outcomes have shown conflicting results. In a British trial, supplemental vitamin D_3 (100,000 IU every 4 months) as compared with placebo for 5 years resulted in a marginal reduction in the relative risk of first hip, wrist, forearm, or spine fracture in men and women.[18] A trial in Australia, however, showed that very high oral doses of vitamin D (500,000 IU per year) resulted in an increased fracture risk among older women, who were found to have reached a 25-hydroxyvitamin D level of 48 ng per milliliter 1 month after bolus dosing.[16] However, we did not find any evidence of increased fracture risk among participants with baseline 25-hydroxyvitamin D levels of 50 ng or more per milliliter in exploratory analyses. The Vitamin D Assessment Study involving 5110 older men and women in New Zealand investigated supplemental vitamin D (100,000 IU per month) as compared with placebo and showed no effect on incident nonvertebral fractures over a period of 3.3 years.[17] Bolus dosing, however, has been shown to result in nonphysiologic variability in blood 25-hydroxyvitamin D levels.[36] The DO-HEALTH trial examining the effect of supplemental vitamin D (2000 IU per day) on nonvertebral fractures in 2157 older European adults also had null findings of vitamin D supplementation on fracture risk.[15]

In VITAL, we previously found that vitamin D supplementation did not affect incident fall risk or changes in bone mineral density or structure.[37,38] We did find that in participants with baseline free 25-hydroxyvitamin D levels below the median, supplemental vitamin D_3 had a slight benefit on spine and total hip bone mineral density.[38] Ongoing studies in VITAL are assessing whether baseline measured free 25-hydroxyvitamin D levels or genetic variation in vitamin D absorption, metabolism, or receptor function may identify a subgroup of patients who may benefit from vitamin D supplementation with respect to fracture outcomes.

Strengths of this study include the large, diverse sample size and high adherence. Incident fractures were adjudicated and confirmed. Levels of 25-hydroxyvitamin D were measured and calibrated according to standards set by the CDC. This study also has limitations. We evaluated only one vitamin D dose, and the trial was not designed to test the effects of vitamin D supplementation in those who are vitamin D deficient. Only a small percentage of participants (2.4%) had vitamin D levels of less than 12 ng per milliliter. It would not have been feasible or ethical to study the effects of vitamin D as compared with placebo on incident fractures in a population preselected for vitamin D deficiency. No adjustment was made for multiplicity for secondary, exploratory, or parent trial end points. In addition, results may not be generalizable to adults with osteoporosis or osteomalacia or older institutionalized persons.

In this randomized, controlled trial, supplemental vitamin D_3 did not result in a lower risk of incident total, nonvertebral, or hip fractures than placebo among generally healthy midlife and older adults who were not selected for vitamin D deficiency, low bone mass, or osteoporosis.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.