I COMPLICATIONS & SIDE EFFECTS

A. Shifting from survival to health maintenance

For the first 15 years of the AIDS pandemic, doctors were busy trying to help people with HIV/AIDS (PHAs) recover from complications brought about by infections.

After 1996, highly active antiretroviral therapy (HAART) became increasingly available in high-income countries and deaths from infections became less common. As people lived longer, strange side effects began to appear in many HAART users, including changes in body shape as well as elevated levels of fatty substances and sugar in the blood. These changes are collectively called the lipodystrophy syndrome.

When this syndrome first appeared, particularly the changes in body shape, many PHAs and doctors suspected that it was the fault of the newest group of HIV medications on the market—protease inhibitors. After many years of study it is now clear that different aspects of the lipodystrophy syndrome may have different causes. For instance, lipoatrophy—the loss of the fatty layer just under the skin—has been linked to the use of d4T (stavudine, Zerit) and, to a lesser extent, AZT (zidovudine, Retrovir). More recently there have been concerns that efavirenz (Sustiva, Stocrin) may also have similar effects.

Other issues that are seen in some HAART users—such as cardiovascular disease and diabetes—may have more complex origins, arising...
from an interaction of several potential factors, including the following:

- long-term HIV infection and its effect on many organs
- co-infections and their effects on organs
- changes to the immune system
- aging
- drug side effects

Because there are so many possible factors to sort, it may take years before the origin of some of these complications becomes clear.

In this issue of TreatmentUpdate, an often-overlooked part of the body comes under scrutiny—bones. New information about the long-term health of the bones of HAART users and risk factors for thinning bones is presented.

B. At risk for bone breaking

In the past seven years, several studies in North America and Western Europe have reported that some PHAs have less-than-normal levels of bone density. In HIV negative people, having thin bones increases the risk that they will break during accidents or falls. So, maintaining or increasing bone density is going to become more important for PHAs, particularly as they age.

Inside bones

Even though bones are hard, they are alive and constantly in the process of “remodeling”—tearing down parts and rebuilding them. Indeed, on average, the entire skeleton is replaced every decade. Bones are made up of cells and collagen and are connected in a framework that gives them strength and allows them to support the body’s weight. The minerals calcium, phosphorus and perhaps magnesium all play a role in maintaining and strengthening bones. When these minerals are removed from bone faster than they can be replaced, osteopenia, or a moderate degree of bone thinning, occurs. If this process continues over years, bones can become very thin and porous—the onset of osteoporosis. Sometimes bones can become soft, a condition called osteomalacia, as happens when vitamin D becomes deficient or when there is not enough calcium available.

Thick or thin?

To find out about the density of bones, low-dose X-ray scans called DEXA (dual-energy X-ray absorptiometry) are performed of the limbs and hips. The scan is interpreted by a computer program that compares it to reference values and makes adjustments for age, gender and ethnicity before providing a result. Bone density can be expressed as a T-score. The World Health Organization (WHO) has defined osteopenia as a T-score between -1 and -2.5 and osteoporosis as a T score beyond -2.5.

Things that make bones thin

There are many factors that can have an impact on bone health. Some of these can be changed while others cannot. Here are some of the risk factors for bone thinning:

- not enough physical activity
- not enough calcium in the diet
- low levels of vitamin D₃
- less-than-normal levels of testosterone
- smoking tobacco
- regular use of opiates
- alcohol abuse
- menopause
- lower-than-normal body weight
- older age
- ethnicity
- family history of osteoporosis

All of these can be risk factors for osteoporosis in PHAs. But some experts suspect that there may be additional risk factors that PHAs can have, including the following:

- duration of HIV infection
- lower-than-ideal body weight
- a history of unintentional weight loss
- use of corticosteroids

HIV infection damages the intestine, which reduces the body’s ability to absorb nutrients such as calcium. This virus can also damage the kidneys, which produce vitamin D₃, the active form of vitamin D. Issues related to osteoporosis, calcium and vitamin D₃ are covered elsewhere in this issue of TreatmentUpdate.

Treatment options

Screening for osteoporosis is an important first step on the road to better bone health. If a moderate degree of osteopenia is detected and there are risk factors for bone thinning, doctors may consider several therapies.
In HIV negative people, a group of drugs called bisphosphonates is usually very effective at increasing bone density in men and women. Examples of these drugs include the following:

- alendronate (Fosamax)
- risedronate (Actonel)
- zoledronic acid (zoledronate, Zometa)

These drugs work by limiting the breakdown of bone and the release of calcium from bones. Results from small studies of these drugs in HIV positive people have been mixed. However, two recent studies—one in the United States called ACTG 5163 using the drug alendronate and the other from New Zealand using zoledronic acid—are much more promising.

Other medications that can improve bone density, such as parathyroid hormone and calcitonin, are very expensive and have not been tested in controlled clinical trials with HIV positive people.

Fracture risk
While most studies in the past seven years have found an increased prevalence of bone thinning in PHAs, reports of fractures have been uncommon. However, a recent study of about 600 men who have HIV or are at high risk for HIV infection has arrived at a different conclusion. In that study, researchers found that men with HIV infection had 21 reports of fractures compared to 12 reports of fractures among HIV negative men. Although this difference was not statistically significant, it underscores that fractures do occur among PHAs, despite findings from previous studies.

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C. HAART and bones—mixed messages
Studies have found that some PHAs have greater-than-expected rates of moderate (osteopenia) or severely reduced (osteoporosis) bone density. These studies were generally of a cross-sectional design; that is, they were based on data captured at one particular instant in time. With this type of study design, it is hard to draw conclusions about the cause of reduced bone density. In some of these studies, PHAs were taking HAART, which further complicates drawing conclusions about the cause of thinning bones as this is yet another factor to analyse. So, although in some cross-sectional studies researchers may have found an association between HAART and reduced bone density, by their nature such studies are not able to accurately assess the link between cause and effect.

Perhaps a more useful approach is one that can monitor changes in participants over time—a longitudinal study. Researchers in Auckland, New Zealand, recently completed their analysis of data from a study that monitored the bone density of both HIV negative and HIV positive men. The HIV positive men were taking HAART. Findings from this study suggest that accelerated bone thinning does not occur in some HAART-treated men.

Study details
Researchers reported results on 49 men—23 with HIV infection and 26 who were HIV negative. As the focus of this report will generally be on the HIV positive men, here is their average profile at the start of the study:

- age – 47 years
- weight – 76 kg
- body mass index (weight divided by square of height) – 24
- percent body fat – 19%
- current tobacco use – 43%
- level of vitamin D3 in the blood – 73 nmol/l
- current CD4+ count – 490 cells
- lowest-ever CD4+ count – 138 cells
- current viral load – 200 copies
- highest-ever viral load – 50,000 copies

Over the two years of this clinical trial, the men visited the study site on a regular basis to have blood drawn for analysis and to have other assessments, such as bone density scans, performed.

The HIV positive men were generally similar to the HIV negative men in age and other factors such as those listed above. An exception was tobacco smoking: HIV positive men were about 10 times more likely to smoke.

None of the study volunteers had significant liver, kidney or thyroid dysfunction.
Results
Of the 23 PHAs who used HAART, 17 had their viral load remain below the 50-copy mark. In the remaining six men, viral load suppression was intermittent due to HIV resistance or difficulty adhering to medications. CD4+ counts generally stayed above the 200-cell mark except in two of the six men whose viral load was not regularly suppressed.

Changes in bones
Among PHAs, bone density in the spine increased by 2.6% and by 0.1% in the hip.

Among the HIV negative people, bone density in the spine increased by 1.5% and decreased by 0.1% in the hip.

Body composition
The proportion of body fat in PHAs decreased by 2 kg over the course of the study. In the HIV negative men, body fat increased by 2 kg.

Overall
In this New Zealand study, there was no evidence that HAART accelerated bone loss in HIV positive men. Indeed, bone density increased among HAART users when compared to HIV negative men. This increase in bone density is striking because the HIV positive men were more likely to have two important risk factors for osteoporosis:

- lower body weight
- greater use of tobacco

Changes in bone density were not linked to CD4+ count, viral load or substances in the blood suggestive of bone rebuilding.

Potential drawbacks
The research team notes that its study was relatively small and that the men enrolled had “normal to above average” bone density at the start of the study. The results from the New Zealand study may therefore not apply to men with much thinner bones. And there are at least several other drawbacks with this study:

- It was not randomized to reduce the possibility of bias.
- There was a relatively small number of participants. This raises a number of possibilities, including that the men in the study may not necessarily be representative of the average HIV positive man in New Zealand (or in other high-income countries).

- Participants may have been more concerned about their health in general and bone health in particular than men who were not recruited. Indeed, the men in the study may have had an above-average ability to care for themselves. A clue about this possibility comes from the relatively high levels of vitamin D₃ that were detected in their blood. This relatively high level of vitamin D₃ (73 nmol/l) is not normally achieved from food sources alone in the average person. Moreover, some estimates suggest that a dose of vitamin D₃ ranging between 800 and 1,700 international units (IU) per day may be necessary to achieve such a level in the blood.
- It may be argued that another possible reason the men in this group had such high levels of vitamin D₃—which can be made when one is exposed to sunlight—is that they were all employed in careers that provided them with a great deal of exposure to sunlight (such as farmers or lifeguards). In people who work outdoors, even higher levels of vitamin D₃ have been found. However, most of the participants were of European ancestry and surveys from New Zealand (and Canada) have found less-than-optimal levels of vitamin D₃ in the blood of volunteers. Plus, a recent study from a sunny region—the Hawaiian Islands—has found less-than-optimal levels of vitamin D₃ in a large proportion of HIV negative adults.
- Another, perhaps more remote, possibility is that study participants may have been using the lipid-lowering medication atorvastatin (Lipitor). One study in HIV negative elderly people suggests that the use of this drug can modestly increase vitamin D levels in the blood.

Bones and the immune system
Whatever the reasons, the results from the small New Zealand study clash with preliminary results from a larger study in the United States. In an analysis of 157 PHAs who initiated therapy with either nelfinavir (Viracept) or efavirenz (Sustiva), American researchers found that use of HAART appeared to be associated with a small but continuing decrease in bone density (about 1% per year over two years). Unfortunately, precise details from this study, called ACTG A5005s, are not publicly available at this time. The researchers speculate that the decrease in bone density does not appear to be directly caused by HAART. However, they think it may be due to changes in the immune system brought about by the use of HAART.
Overall, these results emphasize the importance of minimizing risk factors for osteoporosis and the need for more research on prevention and treatment of this condition in PHAs.

REFERENCES:

D. Are methadone users at risk for osteoporosis?

Because HIV can be spread through sharing substance-using equipment, many injection drug users (IDUs) are infected with HIV. Some IDUs manage their addiction with the use of methadone.

Opioids—including codeine, heroin and morphine—can impair the functioning of cells that repair bones. These drugs can also impair the formation of new bones. Opioids can also reduce the level of hormones such as testosterone, estrogen and DHEA. Less-than-normal levels of these hormones may cause unexpected tiredness, depression and bone loss.

Researchers in Boston conducted a study with 92 volunteers who were using methadone as part of an addiction recovery program. They found that 83% of participants had thin bones. Indeed, 35% had osteoporosis and none of them had previously received this diagnosis. Many study participants had several risk factors for developing thinning bones.

Study details

The research team recruited volunteers from a methadone treatment program. The average profile of participants was as follows:

- 64% female, 36% male
- age – 42 years
- 40% were obese
- 91% currently smoked tobacco
- most had been using heroin for 14 years
- 28% were HIV positive

Bone density was assessed with DEXA scans.

Results

Generally, men had a more serious degree of bone loss than women. This is not normally the case among HIV negative people, where women are more likely to have thinner bones than men. The proportion of participants who had thinning bones was as follows:

**Osteopenia** (moderately thin bones)

- men – 36%
- women – 54%

**Osteoporosis** (very thin bones)

- men – 61%
- women – 20%

Risk factors

In this group of volunteers, researchers assessed possible risk factors for low bone density and found the following:

- being male
- a lower-than-ideal body weight
- years of heavy alcohol use

The results from this study suggest that some methadone users may be at increased risk for fractures. People with addictions are often at high risk for accidents and injuries, so preventing fractures and bone loss should become a concern for their care providers.

The reasons for the unexpectedly high rates of osteoporosis in men in this study are not clear.

Design issues

The type of study conducted by the Boston researchers is called a cross-sectional study; it is a snapshot in time. It cannot definitively link the concepts of cause and effect.
Moreover, the study team regrettably did not take into account other factors that could have affected participants’ risk for bone loss, such as family history of osteoporosis or their level of physical activity.

Despite these limitations, the study’s findings underscore the need for getting recovering substance users into comprehensive medical care. Additional studies on bone density should be performed in other regions to confirm the Boston researchers’ findings. If they are confirmed, then scans for bone density should be part of that care as should support for osteoporosis prevention and recovery.

REFERENCE:

E. Zoledronic acid for thicker bones
Several therapies are used to prevent and treat osteoporosis. The most commonly used group of drugs are bisphosphonates, such as the following:

• risedronate (Actonel)
• alendronate (Fosamax)

Most studies with PHAs have used alendronate. A newer drug related to these medications is zoledronic acid (zoledronate, Zometa). An advantage of this medication is that it only needs to be taken once a year. Researchers in New Zealand recently completed a two-year clinical trial of this drug along with supplemental vitamin D3 in PHAs who had thinning bones. They obtained favourable results.

Study details
In 2003, researchers screened 220 HIV positive men before recruiting 43 who were randomly assigned to receive a mega-dose of 50,000 IU of vitamin D3 once a month along with 400 mg of calcium daily and one of the following interventions:

• zoledronic acid, 4 mg via infusion once a year
• placebo

All participants had some degree of bone thinning detected with DEXA scans prior to receiving either drug or placebo.

The average profile of participants at the start of the study was as follows:

• age – 49 years
• weight – 74 kg
• body mass index (weight divided by square of height) – 24
• 60% were former smokers and 25% were currently smoking
• participants received about 900 mg of calcium from their diet every day
• the level of vitamin D3 in their blood was below what most experts consider optimal – 64 nmol/l
• current CD4+ count – 540 cells
• viral load – less than 60 copies

Results
Participants who received zoledronic acid had significantly improved bone density compared to placebo. Here are the results with different bones/joints:

Spine
• zoledronic acid: +9%
• placebo: +3%

Hip
• zoledronic acid: +4%
• placebo: -1%

Overall body
• zoledronic acid: +2%
• placebo: -1%

Over two years, changes in the proportion of participants with osteopenia at the spine or hip were as follows:

• zoledronic acid: a decrease from 52% to 28%
• placebo: an insignificant decrease from 55% to 53%

There was no apparent relationship between CD4+ counts, viral load and recovery from osteopenia.

Checking on turnover
A marker of bone “turnover”—a term that describes the tearing down and building up of bone—is the presence of a small molecule called NTx (N-telopeptide of type 1 collagen) in the urine. Levels of NTx decreased by 61% during the first three months of zoledronic acid therapy and...
remained stable for the rest of the study. Among users of placebo, NTx remained high.

Fractures
One person who received placebo developed a fracture nearly two years into the study. No one on zoledronic acid broke any bones.

Side effects
Zoledronic was “generally well tolerated,” according to the study team. However, two volunteers who received the drug developed a reaction to it, consisting of a flu-like syndrome. They had to leave the study. No other side effects were reported.

This is the first report of a reversal of bone thinning in PHAs who used zoledronic acid. Its effects appear to be similar to alendronate.

REFERENCE:

F. Benefits of bone drugs appear to outweigh risks
A group of drugs called bisphosphonates are commonly used in the treatment of the following conditions:

- thinning bones—osteopenia or osteoporosis
- bone cancer
- bone-cancer related complications such as fractures or excessive calcium in the blood

These drugs have been available for several decades in high-income countries but only in 2003 did reports of a disturbing side effect appear—decaying jawbones or osteonecrosis of the jaw (ONJ).

Most published reports of ONJ have occurred in people who have received bisphosphonates because they also had cancer. This point is important to note because doses of these drugs used in people with cancer are about 12 times greater than the doses used to treat osteoporosis in people without cancer.

ONJ appears to occur after several years of therapy with bisphosphonates. In many cases, it appears to be triggered after dental trauma. This could take the form of dental surgery, including tooth extractions or irritation from poorly fitted dentures.

Researchers are still trying to understand why ONJ occurs. One theory is as follows: Bisphosphonates accumulate in bone. Removal of teeth or other dental surgery can release large concentrations of these drugs to the surrounding mucosal tissue of the mouth. These tissues are sensitive to bisphosphonates and are weakened when exposed to these medications. Indeed, lab research suggests that bisphosphonates can damage the tissues of the mouth. So, after dental surgery in people taking these medications, the damaged mucosal tissue is slow to heal. This allows bacteria in saliva direct access to the jawbone, which then can become infected, inflamed and die.

This theory seems reasonable and may explain why bone death and destruction associated with the use of bisphosphonates has not been reported in other parts of the skeleton such as the hips, ribs and spine. Based on this theory, the other parts of the body that may be sensitive to soft tissue damage associated with bisphosphonates include the nasal sinuses and inner ear. So far, one case of osteonecrosis of the inner ear canal has been reported in a person who used bisphosphonates. However, this man had been battling bone cancer for many years and had received chemotherapy for several years.

Putting it in perspective
ONJ appears to occur most commonly in people with bone cancer who use bisphosphonates. This group of people has a much higher than average exposure to bisphosphonates.

No cases of ONJ have been reported in 60,000 people who have participated in randomized clinical trials of bisphosphonates for at least two years.

No cases of ONJ have been reported in HIV positive people who have been using bisphosphonates.

Some HIV positive people appear to be at increased risk for thinning bones and may be prescribed bisphosphonates.

The benefits of using bisphosphonates to prevent fractures appear to outweigh the risks of ONJ development in HIV negative people. The risk of developing ONJ may be as high as 1 in 60,000 people, or perhaps lower, depending on the region where the calculation was done.
In high-income countries, it may be useful for everyone to get a dental exam at least once a year to assess oral health and detect any problems so that they can be treated before they become serious.

REFERENCES:

G. Muscle mass important for maintaining bone density in women

Studies have found that women with HIV infection are at high risk for developing thinner-than-normal bones. The precise cause for this in HIV positive women is not yet clear, but there may be a variety of factors at work, including the following:

- age
- smoking tobacco
- lower-than-ideal body weight
- reduced levels of the hormones estrogen and testosterone

To try to find out more about the effects of weight, body composition and testosterone levels on bone density, researchers at Harvard University conducted a study. Their findings suggest that a number of factors can affect bone density in HIV positive women.

Study details
Researchers enrolled 152 HIV positive women and 100 HIV negative women who were similar in age and race. They divided the women into three groups as follows:

- HIV positive women with low body weight; body mass index (BMI) of 19
- HIV positive women with normal weight; BMI of 26
- HIV negative women whose weight was somewhat greater than normal; BMI of 27

Researchers use BMI to help them decide if a person’s weight is within an acceptable range. BMI is calculated by dividing a person’s weight (in kg) by the square of their height (in m).

In our report we will focus on the HIV positive women. Here is their average profile:

- age – 40 years
- most were taking anti-HIV therapy
- about 55% currently smoked tobacco

Bone density was assessed by means of DEXA scan and fat and muscle content of the body were assessed using CAT scans. Researchers also assessed levels of the hormone testosterone.

Results
Levels of testosterone were lower among HIV positive women than among HIV negative women. Testosterone deficiency was found in the following proportion of women in each group:

- HIV positive women with low body weight: 27%
- HIV positive women with normal body weight: 19%
- HIV negative women: 12%

Levels of other hormones, such as estrogen and FSH (follicle-stimulating hormone), were not different among the three groups of women.

Bone mineral density
The general trend within the study, whether for the hip or spine, was that bone density was lowest in thin HIV positive women and highest among HIV negative women.
The proportion of women in each group with moderately thin bones (osteopenia) was as follows:

- HIV positive women with low body weight: 50%
- HIV positive women with normal body weight: 30%
- HIV negative women: 20%

The proportion of women in each group with more serious bone loss (osteoporosis) was as follows:

- HIV positive women with low body weight: 12%
- HIV positive women with normal body weight: 6%
- HIV negative women: 3%

Points to consider
Key findings from this study are as follows:

- Bone density at the spine and hip is reduced in HIV positive women with lower-than-normal weight.
- This bone loss seems to be greater than previously reported in other studies.
- Bone thinning also occurs in HIV positive women with normal body weight, but this loss of bone density is much less than in underweight people.
- Testosterone deficiency was very common among women with osteopenia and osteoporosis.

Having less-than-normal levels of testosterone may make it more difficult for the body to build up and maintain muscle mass. Muscles are joined to bone, and exercising muscles stimulates bones and helps strengthen them.

Other findings from this study:

- The women enrolled were relatively young—40 years old—yet nearly 40% of the HIV positive women had menstrual irregularities such as skipped periods. This problem was only present in 18% of the HIV negative women. Other studies in HIV negative women suggest that menstrual dysfunction is linked to an increased risk of bone loss.
- White women had a greater increased risk for thin bones than Black women.

Based on the results of this study (as well as others), the scientists suggest that more research needs to be done to find out if some HIV positive women with menstrual dysfunction and lower-than-ideal body weight can benefit from supplements of low doses of estrogen.

Additionally, they also note the possibility that some HIV positive women with menstrual dysfunction and thin bones may benefit from supplements of low-dose testosterone.

REFERENCE:

H. Calcium and vitamin D

At least two nutrients are important for the maintenance of bone health—calcium and vitamin D.

The body needs calcium every day and if its needs are not met then calcium is removed from bones. HIV infection damages the intestine and is associated with wasting, suggesting that not enough nutrients are absorbed. One such nutrient may be calcium. Perhaps it is not surprising that some studies have found that some PHAs can have a greater-than-expected degree of bone loss.

Vitamin D is a nutrient that helps the intestines absorb calcium. Vitamin D may also have other, poorly understood effects on the immune and nervous systems. There are several forms of compounds that are called vitamin D. The two usually used in human nutrition are:

- vitamin D<sub>2</sub>—ergocalciferol
- vitamin D<sub>3</sub>—cholecalciferol

However, only vitamin D<sub>3</sub> is the active form of this nutrient.

Although this vitamin can be made when a person is exposed to sunlight, a number of studies have found that some people living in sunny locations such as the Hawaiian Islands have less-than-optimal levels of this nutrient. Studies from Calgary and Toronto, places that experience shorter periods of sunlight in the winter, suggest that consuming 200 IU/day of vitamin D<sub>3</sub> was not able to prevent a deficiency of this vitamin.

A study in New Zealand with three different ethnoracial groups—European, Maori and Asian people—found that the level of vitamin D deficiency increased as skin pigmentation increased.
Food

Vitamin D is found naturally in oily saltwater fish. To determine the amount of this nutrient available, researchers at Boston University analysed the flesh of several fish species. In 100 grams of fish, here’s what they found:

- wild salmon – about 1,000 IU of vitamin \(D_3\)
- farmed salmon – about 240 IU
- blue fish – 280 IU
- cod fish – 104 IU
- grey sole – 56 IU
- Ahi-tuna – 404 IU
- farmed trout – 388 IU
- mackerel – 24 IU

Baking the salmon resulted in no change to the vitamin \(D_3\) content. However, frying the salmon in oil resulted in a loss of 50% of the vitamin D.

Overall, this research suggests that the vitamin \(D_3\) content of some foods may not be as great as anticipated.

For more information on nutrition and bone health, check out “Good to the bone” in the Fall/Winter 2001 issue of The Positive Side (www.positiveside.ca).

Research on vitamin D

Scientists who study human nutrition and osteoporosis and who are also experts in the field of vitamin D research recommend that a minimum of 700 to 800 IU of vitamin \(D_3\) per day is needed by adults. The goal of this level of supplementation, they suggest, should be to raise levels of vitamin \(D_3\) in the blood to at least 75 nmol/l.

The safe upper limit of vitamin D intake is not yet clear and physicians caring for patients with osteoporosis may need to guide their vitamin \(D_3\) intake by monitoring blood levels of this nutrient. Concentrations of vitamin \(D_3\) ranging between 135 to 163 nmol/l have been found in lifeguards and farmers—people who get a great deal of sun exposure. Signs/symptoms of vitamin \(D_3\) toxicity occur when levels of this vitamin exceed 200 nmol/l in the blood.

To give some idea of the range of possible tolerable levels of vitamin \(D_3\), researchers have found that White people exposed to sunlight for 15 to 20 minutes produced 10,000 IU of vitamin \(D_3\). Greater exposure to sunlight did not result in higher levels of vitamin \(D_3\). This suggests the possibility that the body can tolerate somewhat higher levels of vitamin \(D_3\) than the 400 IU that is often included in daily multivitamins.

Overall, research on relatively high doses of vitamin \(D_3\) and its impact—not just on bones but other parts of the body as well—is just beginning. Decades ago, some nutritionists thought that a daily dose of 400 IU of this nutrient was sufficient. However, the trend in the past decade has been to use higher doses in studies of osteoporosis. As scientists find out more about vitamin \(D_3\), this trend is likely to continue.

REFERENCES:


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