CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will recognize the risk of osteoporosis in patients with anorexia nervosa

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Premenopausal osteoporosis, an overlooked consequence of anorexia nervosa

ABSTRACT

Many young women with anorexia nervosa develop premenopausal osteoporosis. In particular, female athletes have a much higher incidence of disordered eating than their peers and therefore are at a much higher risk of stress fractures and other traumatic bone pathology. This review summarizes factors affecting the development of premenopausal osteoporosis in these patients and identifies potential targets for intervention.

KEY POINTS

Women gain 40% to 60% of their bone mass during adolescence, a time coinciding with the peak incidence of anorexia nervosa, and they attain their peak bone mass by the time they are in their 20s.

The etiology of osteoporosis in anorexia nervosa is complex and multifaceted. Early detection and treatment are critical.

Osteoporosis in premenopausal patients is defined as low bone mineral density (a Z score below –2.0) in combination with risk factors such as chronic malnutrition, eating disorders, hypogonadism, glucocorticoid exposure, and previous fractures.

Restoring body weight is the key treatment. Vitamin D should be supplemented if low. Estrogen therapy has not been shown to be effective, and exercise may be counterproductive. Bisphosphonates and teriparatide should be used with caution, if at all.

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Among the devastating effects of anorexia nervosa, and one that is easily overlooked, is its impact on bone.

Probably more than half of young women with anorexia nervosa develop osteoporosis, and relatively quickly. Baker et al[1] obtained bone scans in a series of 56 young women, mean age 27 years, who had had an eating disorder for a mean of about 10 years, and found that the bone mineral density in the femur was below the critical fracture threshold in 42 (75%).

Osteoporosis is particularly common and worrisome in female athletes (and is becoming increasingly common in male athletes as well). Female athletes have a much higher incidence of disordered eating than their peers[2] and therefore are at a much higher risk of fractures.

This review summarizes the factors affecting the development of osteoporosis in these patients and discusses potential targets for intervention.

ANOREXIA AND BONE HEALTH: A COMPLEX RELATIONSHIP

Anorexia nervosa is characterized by an intense fear of gaining weight, a body weight less than 85% of expected, a distorted self-image, and, in women, missing three consecutive menstrual periods.[3] The lifetime prevalence in women is about 0.5%; it is much lower in men.[3] The prevalence of eating disorders in female athletes is much higher, estimated at 15% to 62%.[2]

The etiology of osteoporosis in patients with anorexia nervosa is complex and multifaceted. In these patients, bone resorption

is increased without a concomitant increase in bone formation, resulting in a net loss of bone.[4] Thus, markers of bone resorption such as N-teleopeptide and deoxypyridoline are elevated, but markers of bone formation such as osteocalcin are not.[4]

The loss of bone may be rapid and can occur relatively early in the disease. Some studies suggest that an illness duration longer than 12 months predicts significant loss of bone density.[5] Thus, early diagnosis and intervention are important to minimize bone loss.

Women gain from 40% to 60% of their bone mass during the pubertal growth spurt in ages 11 to 14, the time when anorexia nervosa is most prevalent.[6] Peak bone mass is attained by the third decade of life, but the rate of growth of bone mass is highest during adolescence and early adulthood.[7] Hence, it is important to optimize bone mass during this time, as small differences in bone density can have significant clinical implications later in life: a 5% increase in bone density significantly decreases fracture risk, whereas a 10% decrease in adult bone mineral density is associated with a two to three times higher risk of fracture (reviewed by Rome and Ammerman[6]).

What is the role of amenorrhea in the development of osteoporosis in premenopausal patients?

Given that two of the most characteristic manifestations of anorexia nervosa are low body weight and the absence of menses, these factors have been hypothesized to be potential causes of osteoporosis.

In general, young women who present with amenorrhea should be evaluated to determine if the amenorrhea is primary or secondary. Primary amenorrhea is the absence of menarche by age 16; secondary amenorrhea is the absence of menses for more than three cycles or more than 6 months in someone who previously had had menses. The most common causes of secondary amenorrhea are ovarian disease, hypothalamic or pituitary disease, and uterine disease. Anorexia nervosa causes hypothalamic dysfunction and is a cause of secondary amenorrhea. In clinical practice, it is also important to remember that pregnancy can occur even in the setting of amenorrhea.

Amenorrhea in patients with anorexia nervosa is related to hypothalamic suppression of the release of gonadotropin-releasing hormone, resulting in lower levels of follicle-stimulating hormone and luteinizing hormone and a resultant prepubertal low-estrogen state.

In a study of 73 women with anorexia nervosa and a mean age of 17.2 years,[8] 20 months of amenorrhea was the threshold above which the most severe osteopenia was seen, implying that the duration of amenorrhea affects bone health.

Which factors besides amenorrhea influence bone density in premenopausal women?

Undernutrition. Body weight has been suggested to have an independent effect on bone mineral density, and density has been found to increase following weight gain, even before the return of menses.[1] Once a regular menstrual cycle has been restored, significant increases in trabecular and cortical bone have been detected.[1]

Deficiency of insulin-like growth factor 1 (IGF-1). Anorexia nervosa is associated with decreased hepatic synthesis of IGF-I.[9] Low levels of IGF-I reduce the levels of osteocalcin, a marker of bone formation, and cause abnormalities in osteoblast function.[10] This deficiency is associated with the development of osteopenia in patients with anorexia nervosa.[11]

Loss of bone mineral density in anorexia may be rapid and may occur early in the disease

Low androgen levels are present in patients with anorexia nervosa, and levels appear to be further reduced by oral contraceptives.[12] It remains to be determined whether the further reduction in androgens in women with anorexia nervosa using oral contraceptives is harmful to skeletal health. Low testosterone levels in boys with anorexia nervosa have been associated with lower libido, fewer erections, and potentially lower bone density.[13]

Hypercortisolemia. Elevated levels of total and free serum cortisol and high 24-hour urinary free cortisol excretion have been noted in anorectic patients. Levels of cortisol are inversely related to levels of osteocalcin, and hypercortisolism has been shown to be associated with osteoporosis.[14,15] However, no study has yet shown causality in this population.

Osteoprotegerin has been recognized as an important regulator of bone resorption. Osteoprotegerin inhibits osteoclast differentiation and activation and stimulates osteoclast

TABLE 1

Potential factors influencing bone density in anorexia nervosa

Undernutrition
Seems to have an independent effect on bone mineral density

Exercise
Increases bone mineral density at weight-bearing sites but not necessarily at non-weight-bearing sites
Caution is advised before recommending exercise, as these patients may use it as a form of purging

Deficiency of insulin-like growth factor 1
Associated with the development of osteopenia

Low androgen levels
Correlate with bone resorption and formation markers in anorexia nervosa

Hypercortisolemia
Correlates inversely with osteocalcin levels and may decrease bone formation

Increased osteoprogerin
Higher levels seen in anorexia nervosa
May be released to preserve bone health

Reduced leptin
May have a role in adaptation to starvation
A relationship with bone formation has not yet been established

Ghrelin and obestatin
In vitro studies suggest that ghrelin promotes osteoblast proliferation and differentiation
In vivo studies in anorexia nervosa show only a weak association with bone mineral density
The ghrelin-obestatin ratio is decreased in anorexia nervosa
Further study is needed to determine the role of the ghrelin-obestatin ratio in osteoporosis risk

apoptosis, helping to preserve bone density.

Misra et al[16] showed that adolescent girls with anorexia nervosa have higher serum osteoprotegerin levels than controls and that osteoprotegerin levels correlate inversely with markers of nutritional status and lumbar bone density Z scores.[16] They and other investigators[17] postulate that osteoprotegerin may be released as a compensatory response to the bone loss seen in these patients in an attempt to preserve bone health.

Leptin is an adipocyte-derived hormone that acts on receptors in the hypothalamus, decreasing food intake and increasing energy expenditure. Low leptin levels are a key endocrinologic feature of anorexia nervosa.[18] Leptin helps to induce weight loss by stimulating neurons in the hypothalamus that express "weight-loss-inducing" neuropeptides such as pro-opiomelanocortin and inhibiting "weight-gain-inducing" peptides such as neuropeptide Y.[19]

Although leptin was first believed to be a hormone released to counteract obesity, recent studies[19,20] suggest that it is part of a major signaling system that controls adaptation to starvation. These studies have shown that the body senses its corporeal fat through leptin and inhibits ovulation when fat reserves are low.[19] In addition, luteinizing hormone and leptin levels have been shown to increase in parallel in patients with anorexia nervosa when weight is restored.[20] Thus, rising leptin levels correlate with the resumption of menses in women with anorexia nervosa and in turn have potential consequences for bone health.

Not enough ghrelin, too much obestatin? Ghrelin, a gastric hormone, acts as a natural antagonist to leptin, resulting in an increase in food intake and body weight.[19] Circulating ghrelin levels are higher in illness-induced anorexia as well as in anorexia nervosa, and they normalize with weight gain, perhaps as an adaptive mechanism to compensate for a negative energy balance.[21]

Several in vitro studies suggest that ghrelin directly promotes osteoblast proliferation and differentiation.[22] However, human studies of ghrelin's effects on bone are limited. In a study of healthy younger women, healthy boys, and anorexia nervosa patients, plasma ghrelin levels were only weakly associated with bone mineral density.[23]

The effects of obestatin, another gastric hormone, are still being investigated. Obestatin was initially shown to oppose the effects of ghrelin by decreasing appetite and weight gain. When given with ghrelin, obestatin appears to work with ghrelin at the hypothalamic level to modulate food intake and growth hormone secretion.[24]

Interestingly, obestatin and the ratio of ghrelin to obestatin are decreased in patients with anorexia nervosa, but the ratio is unchanged in thin women who have an equivalent body mass index but no eating disorder.[25] It has been hypothesized that the ghrelin-obestatin ratio may be the key to explaining

the eating restriction and reduced motivation to eat despite high ghrelin levels seen in anorexia nervosa.[26] Further studies are needed to determine the role of obestatin and the ghrelin-obestatin ratio in the bone health of women with anorexia nervosa.

While factors such as low body weight and amenorrhea have long been understood to play a role in the development of osteoporosis in women with anorexia nervosa, many complex hormonal factors contribute to bone deficits as well. Further study is needed to fully elucidate these hormonal factors and how they work together to cause osteoporosis. A list of the factors that potentially influence bone density and risk for osteoporosis in patients with anorexia nervosa is presented in **TABLE 1.**

HOW SHOULD WE DIAGNOSE OSTEOPOROSIS IN PREMENOPAUSAL PATIENTS?

Our approach to screening for and diagnosing osteoporosis is still largely based on measuring bone mineral density, although density by itself is not a perfect tool for predicting who will or will not experience a fracture, particularly in premenopausal women.[26,27] Most premenopausal women with low bone mineral density but no other risk factors for fracture such as previous fractures or glucocorticoid therapy are at very low short-term risk of fracture.[26]

For these reasons, in premenopausal women and adolescents, the International Society for Clinical Densitometry[28] advises against diagnosing osteoporosis on the basis of bone mineral density alone. Instead, it should be diagnosed in this population only if the bone mineral density is low (defined as a Z score below −2.0) *and* the patient has risk factors that suggest a higher short-term risk of bone mineral loss and fracture. Risk factors include chronic malnutrition, eating disorders, hypogonadism, glucocorticoid exposure, and previous fracture.[29]

A pitfall in interpreting low bone mineral density in premenopausal women younger than age 30 is the possibility that they may not yet have reached their peak bone mass. In addition, small stature and body size (and therefore bone size) also influence the results of dual-energy x-ray absorptiometry. This test may not be able to distinguish bone that is small but of normal density from bone that is of low density.[26]

Despite its limitations, until newer risk assessment tools are available for this patient population, measuring bone mineral density is still recommended in addition to assessing clinical risk factors to diagnose osteoporosis. Also, changes in bone mineral density over time can help to assess risk and guide treatment.

When should a patient with anorexia be screened for osteoporosis?

Because bone loss may begin early in the course of anorexia and progress rapidly (potentially inexorably), baseline screening is recommended for all patients who have had anorexia nervosa or amenorrhea for more than 6 to 12 months.[30] The National Osteoporosis Foundation recommends screening in women under age 65 who have a low body weight.[31] The American College of Sports Medicine recommends screening for osteoporosis in athletes with a history of hypoestrogenism or disordered eating for a cumulative total of 6 months or more, or with a history of stress fracture or fracture from minimal trauma.[32]

Knowledge of low bone mineral density and fracture risk can often guide treatment and prompt behavioral change. Given that most osteoporosis treatments do not lead to detectable changes in bone density until 18 months to 2 years, it is reasonable to repeat testing at this interval.[33]

Some girls with anorexia nervosa exercise compulsively, using it as a form of purging

NEW AND OLD TREATMENTS FOR LOW BONE DENSITY IN ANOREXIA NERVOSA

Weight restoration is the cornerstone

Restoration of body weight and nutritional rehabilitation remain the cornerstones of treatment. All patients with anorexia nervosa should be referred to a nutritionist to develop a meal plan that is adjusted for the amount of energy expended. The challenges lie in managing the complications of refeeding and the high relapse rate. The treatment goals in disordered eating are to optimize the overall nutritional status, normalize eating behavior, modify unhealthy thought processes that maintain the disorder, and treat possible emotional is-

sues that help create or maintain the disorder.

The younger the patient, the more the family's involvement is recommended. In addition to nutritional counseling, the care team should include a psychotherapist, a psychiatrist, and a primary care physician to assist with management and screening of medical complications.

Vitamin D for all

Low vitamin D levels have long been associated with low bone mineral density and risk of hip fracture.[34]

Vitamin D insufficiency is very common. More than 90% of blacks, Hispanics, and Asians and nearly 75% of whites have insufficient levels of vitamin D (25-hydroxyvitamin D_3 level < 30 ng/mL).[35] In a study of 307 healthy adolescents, vitamin D insufficiency (a 25-hydroxyvitamin D_3 level < 20 ng/mL) was found in 42% and vitamin D deficiency (a level < 15 ng/mL) in 24.1%.[36] In addition, this study confirmed an inverse correlation between body mass index and serum 25-hydroxyvitamin D_3 concentration.

Therefore, while vitamin D supplementation has not been consistently shown to improve bone loss in anorectic patients,[9] given the prevalence of vitamin D deficiency and insufficiency, supplementation is almost universally recommended.

IGF-1 deficiency has been linked to the development of osteopenia in anorexia nervosa

There is no consensus as to the amount of supplementation to recommend for women with anorexia nervosa. The American College of Sports Medicine recommends a total daily intake of 800 IU of vitamin D (ie, from diet and supplements). Therapy should be titrated to doses that result in normocalcemia and a serum 25-hydroxyvitamin D_3 concentration of at least 30 ng/mL.[37,38]

Does hormone treatment improve bone density?

In postmenopausal osteoporosis, estrogen therapy maintains or improves bone density and appears to reduce the rate of vertebral fractures.[39,40] Perhaps not so with premenopausal osteoporosis due to anorexia nervosa.

Why should this be? In postmenopausal women, estrogen therapy appears to work by impairing osteoclast-mediated bone resorption, but it has only limited effects on bone formation. In premenopausal anorexia, however, bone loss appears to be due to a unique uncoupling of osteoblastic and osteoclastic functions, resulting in both reduced bone formation and increased bone resorption, which estrogen therapy may not improve.[5]

Despite the documented association between anorexia nervosa and estrogen deficiency and the strong correlation between osteoporosis and the duration of amenorrhea, most studies have found no improvement in bone mass with hormonal therapy.[9] In particular, three randomized, placebo-controlled trials have been published to date, and not one showed a significant improvement in bone mineral density with estrogen therapy compared with placebo in patients with anorexia nervosa.[41–43]

Klibanski et al,[41] in the first of these trials, found no significant difference in spinal bone mineral density between treated patients and controls. However, estrogen-treated patients whose initial body weight was very low (< 70% of expected) had a significant increase in their bone mineral density, whereas those in the control group lost bone density.

Baker et al[44] suggest that hormone therapy might protect bone mass in athletes with amenorrhea, citing a study that found that women with a history of stress fractures were less likely to have used oral contraceptives previously than athletes without fractures.[45] However, no prospective randomized study to date has established that hormone therapy effectively preserves bone mass in athletes with amenorrhea.

Based on the data presented above, we have little evidence for using estrogen to treat or prevent premenopausal osteoporosis.

The American College of Sports Medicine[32] recommends consideration of estrogen therapy if there is evidence of a decline in bone mineral density in an athlete over the age of 16 with persistent functional hypothalamic amenorrhea despite adequate nutritional intake and weight. However, it acknowledges that restoring regular menstrual cycles with oral contraceptive pills will not normalize the metabolic factors that impair bone formation, health, and performance and is not likely to fully reverse low bone mineral density in this population.

What is the effect of exercise on bone health in these patients?

Several studies have examined the effect of weight-bearing exercise on bone density.

Young et al[46] compared normal teenagers, ballet dancers, and young women with anorexia nervosa and found that weight-bearing exercise protected against osteoporosis, but only at weight-bearing sites. Athletes in weight-bearing sports had a 5% to 15% higher bone mineral density in weight-bearing sites (ie, the femur) compared with nonathletes, but had lower bone mineral density in the spine.

Therefore, a Z score below –1.0 in an athlete, especially in a distal site, warrants further investigation and treatment.[32] In general, exercise does not necessarily protect against osteoporosis in this patient population, and it can sometimes mask underlying bone loss. In addition, keep in mind that many of these patients exercise compulsively, using it as a form of purging.

Insulin-like growth factor-1: More study needed

IGF-1 contributes to bone growth by stimulating osteoblasts, and patients with anorexia nervosa have been shown to have low levels of IGF-1.[9]

Grinspoon et al[10] randomized 60 patients with anorexia nervosa to receive IGF-1 alone, IGF-1 plus an oral contraceptive, an oral contraceptive alone, or placebo. All patients were given calcium and vitamin D and were followed for 9 months. Total bone mass increased significantly in those taking IGF-1 compared with those taking placebo. Those taking an IGF-1 and an oral contraceptive had a significant increase in spinal bone mineral density compared with those on placebo group. At other skeletal sites, however, IGF-1 plus an oral contraceptive and IGF-1 alone failed to produce significant increases in bone mineral density compared with placebo.

Further study is needed to determine the role of IGF-1 in treating low bone mineral density in anorexia nervosa.

Bisphosphonates: Not approved for this indication

In premenopausal women, bisphosphonates are approved by the US Food and Drug Administration (FDA) for use only in those taking glucocorticoids. Although bisphosphonates have been shown to significantly increase bone mineral density in young women with anorexia nervosa,[26] they should be used with caution in patients of childbearing age because they are teratogenic. Bisphosphonates have a long half-life and may continue to affect bone turnover for up to 2 years after they are discontinued.[47] In addition, they are not recommended in patients with a history of purging via vomiting, due to a risk of esophageal ulceration.

Parathyroid hormone therapy: Studies ongoing

The parathyroid hormone fragment teriparatide (Forteo) is widely used for treating postmenopausal osteoporosis.

Before teriparatide was approved, there was concern that it might increase the risk of osteosarcoma, as almost 45% of rats treated with this drug at the highest-tested dose level developed this aggressive form of bone cancer.[48] Balancing the proven benefits of teriparatide shown by clinical trials with the theoretic risk of teriparatide-induced osteosarcoma, the FDA mandated a "black-box" warning about this potential effect.

Studies of parathyroid hormone treatment in anorexia nervosa and other premenopausal patients are ongoing.[26]

Leptin: More study needed

Leptin is a potent stimulator of bone growth and has been shown to increase bone mineral density in vitro and in vivo.[19] However, concerns have been raised about giving supraphysiologic doses of leptin to patients with anorexia nervosa, as this may increase the risk of further weight loss and relapse.

More work is needed to determine the role of leptin for the treatment of osteoporosis in anorexia nervosa.

Ghrelin: Probably not effective as a single agent

Pharmacologic use of ghrelin increases food intake in healthy humans,[49] and it has been proposed as a treatment for weight restoration and bone health in anorexia nervosa. Preliminary studies have not shown it to increase

Screening of bone mineral density is recommended for all patients who have had anorexia nervosa or amenorrhea for more than 6 to 12 months

TABLE 2

Potential strategies for preventing osteoporosis in anorexia nervosa

Weight restoration
Restoration of weight is the cornerstone of treatment. The treatment team should include a nutritionist, a psychologist, a psychiatrist, and a medical provider.

Vitamin D
Given the prevalence of vitamin D insufficiency and deficiency, especially in the setting of low body mass index, vitamin D supplementation should be considered at a minimum of 800 IU/day. Titration is recommended to a serum 25-hydroxyvitamin D_3 level of at least 30 ng/mL.

Insulin-like growth factor 1
Initial studies show an increase in spinal bone mineral density with insulin-like growth factor 1 plus an oral contraceptive, but not at other skeletal sites. Further study is needed.

Bisphosphonates
They increase bone mineral density in anorexia nervosa but should be used with caution in females of childbearing age, as they are teratogenic. They are also not advisable in patients who purge via vomiting.

Parathyroid hormone therapy
Studies are ongoing. Concerns have been raised about the risk of osteosarcoma.

Leptin
In vitro studies have shown leptin to be a potent stimulator of bone growth. Further study is needed to determine improvement in bone mineral density in anorexia nervosa.

Ghrelin
Preliminary studies have not shown ghrelin treatment to improve appetite in anorexia nervosa patients. Further study is needed of its effect on bone mineral density.

Cannabinoids
Further study is needed to determine their effect on appetite stimulation and subsequent bone health in anorexia nervosa. Dependency is a concern.

appetite or weight gain,[50] but it did increase slow-wave sleep.

Based on these studies, it is unlikely that ghrelin will be effective as a single agent to stimulate appetite, but it may be helpful in conjunction with other therapies.

Cannabinoids: Little ongoing research

Cannabinoids have been proposed as a treatment for anorexia nervosa in the hope that they would induce weight gain and in turn prevent osteoporosis.

Interest in their use in anorexia nervosa stems from the discovery of two cannabinoid receptors (CB1 and CB2) located in the brain and peripheral organ systems. Anorexia nervosa has been associated with different alleles of the CB1 gene,[51] but the therapeutic implications of this are far from clear.

Cannabinoids appear to regulate eating behavior at several levels within the brain and periphery: the hypothalamus and hindbrain (integrative functions), the limbic system (for hedonic evaluation of foods), the intestinal system, and adipose tissue.[52] At each of these levels, the endocannabinoid system interacts with a number of better known peptides involved in appetite regulation, including leptin, ghrelin, and the melanocortins. In mouse studies, genetic leptin deficiency is associated with elevated hypothalamic endocannabinoid levels.

Appetite stimulation by cannabinoids has been studied for several decades, particularly in relation to cachexia and malnutrition associated with cancer. Very few trials have studied cannabinoids for anorexia nervosa.

In a 4-week crossover trial in 11 patients with anorexia nervosa,[53] tetrahydrocannabinol (THC) treatment resulted in an increase in sleep disturbances and interpersonal sensitivity, but it had no significant effect on weight gain compared with diazepam treatment.[53]

Another pilot study of nine outpatients with anorexia nervosa treated with THC showed a significant improvement in depression and perfectionism scores without any significant weight gain.[19]

Although this research was once promising, the risk was felt to outweigh the benefit, as cannabinoids may induce dependency in this patient group, who may already be at high risk of drug addiction, and very few have continued this line of investigation.

WHAT CAN WE DO FOR NOW?

- Weight restoration and nutritional rehabilitation remain the keys to treatment of low bone density to reduce the risk of osteoporosis in patients with anorexia nervosa. However, as many as one-third

of patients with anorexia nervosa relapse during their lifetime, and other treatments are needed to stabilize and prevent bone loss.

- Vitamin D deficiency is clearly associated with a risk of osteoporosis and fracture, and patients with vitamin D deficiency should be treated with supplementation.
- Standard therapies in postmenopausal patients (such as bisphosphonates and teriparatide) should be used with caution in premenopausal anorexia nervosa patients because of potential long-term health risks.
- Although treatment of amenorrhea and estrogen deficiency has been shown to at least stabilize bone density in postmenopausal patients, this does not appear to be the case in premenopausal girls and young women.
- As we learn more about hormonal factors in anorexia nervosa, we hope to identify interventions that will help restore weight and decrease the risk of osteoporosis. A summary of potential treatment strategies and targets for prevention of osteoporosis in anorexia nervosa is presented in **TABLE 2**.

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80 Years ago in the *Cleveland Clinic Bulletin*

At the Cleveland Clinic we do routine blood sugars in all new cases. The percentage of patients with unsuspected diabetes, discovered in this manner is considerable. You can imagine how chagrinned a physician feels when he has taken a careful history and has done a thorough physical examination and has sought the counsel of one or more specialists for whatever seemed indicated, and then a blood sugar report of 380 mg. per c.c. comes from the laboratory. This settles the problem of diagnosis, yet when the history is re-examined, there is not an inkling of a symptom or a complaint which would even suggest diabetes. …

By the prevention of obesity and infections, much can be done to prevent the development of diabetes. As compared with this, the treatment of diabetes plays but a secondary role, and is but a mere palliative measure. Prevention presents a challenge to accomplish something constructive. The symptomatic treatment of malaria did not solve the problem of malaria. The elimination of the mosquito was not treatment; but it did solve the problem of malaria!

John HJ. Some practical considerations in diabetes mellitus. Cleve Clin Bull 1931; 1(3):49-66.