Metabolic and Endocrine Abnormalities in Patients With Nonunions

Mark R. Brinker, MD, Daniel P. O'Connor, PhD,† Yomna T. Monla, MD,‡ and Thomas P. Earthman, MD§*

Objectives: To determine whether patients with unexplained nonunions, patients with a history of multiple low-energy fractures with at least one progressing to a nonunion, and patients with a nonunion of a nondisplaced pubic rami or sacral ala fracture would have an underlying metabolic or endocrine abnormality that had not been previously diagnosed.

Design: Case series.

Setting: Tertiary referral center.

Patients and Intervention: From a larger series of 683 consecutive patients with nonunion seen by us between January 1998 and December 2005, 37 patients were referred to 1 of 2 clinically practicing endocrinologists to undergo an evaluation for metabolic and endocrine abnormalities. The screening criteria were: 1) an unexplained nonunion that occurred despite adequate reduction and stabilization (and debridement in initially infected cases) without obvious technical error and without any other obvious etiology; 2) a history of multiple low-energy fractures with at least one progressing to a nonunion; or 3) a nonunion of a nondisplaced pubic rami or sacral ala fracture.

Results: In all, 31 of the 37 patients (83.8%, 95% CI: 71.3% to 93.8%) who met our screening criteria had one or more new diagnoses of metabolic or endocrine abnormalities. The most common newly diagnosed abnormality was vitamin D deficiency (25 of 37 patients; 68%). Other newly diagnosed abnormalities included calcium imbalances, central hypogonadism, thyroid disorders, and parathyroid hormone disorders. All newly diagnosed abnormalities were treated medically. Eight patients who underwent no operative intervention following the diagnosis and treatment of a new metabolic or endocrine abnormality achieved bony union in an average of 7.6 months (range, 3 to 12 months) following their first visit to the endocrinologist.

Conclusions: Although our study does not prove a causal link between metabolic and endocrine abnormalities and either the development or healing of nonunions, 84% of the patients who met our screening criteria were found to have metabolic or endocrine abnormalities, and eight of our patients achieved bony union following medical treatment alone. All patients with nonunion who meet our screening criteria should be referred to an endocrinologist for evaluation because they are likely to have undiagnosed metabolic or endocrine abnormalities that may be interfering with bone healing.

Key Words: fractures, ununited, bone, hormone, calcium, vitamin D, hypogonadism

(*J Orthop Trauma* 2007;21:557–570)

Approximately 5% to 10% of all patients will have some problems obtaining final union of their fractures.[1,2] The most advanced form of difficulty is a fracture nonunion, where the normal biologic healing process ceases to the extent that solid bony union will not occur without further treatment.

In some cases, the etiology of a nonunion is clear, such as the patient with inadequate stabilization or a large gap between bony fragments. In other cases, however, a patient may present with a well-stabilized fracture that fails to unite in a seemingly healthy patient with good local biology at the site of injury.

Fracture nonunion is a multifactorial phenomenon. Predisposing mechanical, anatomical, and biological factors for nonunion include instability, inadequate vascularity, and poor bone-to-bone contact. A variety of other contributing factors, such as cigarette smoking and malnutrition, have also been described.[3] Abnormalities of vitamin D, calcium, and parathyroid hormone in particular may adversely affect fracture healing due to their importance in bone metabolism.[4–8] To the best of our knowledge, no prior large consecutive series has actually documented a relationship between metabolic and endocrine abnormalities and fracture nonunion.

In January 1998, we began to refer a subset of our patients with fracture nonunion who met certain screening criteria for a thorough endocrinology workup. The purpose of this study was to determine the effectiveness of our screening criteria for identifying metabolic and endocrine abnormalities in patients who present with a fracture nonunion. Our hypothesis was that a high proportion of patients who met our screening criteria would have an underlying metabolic or endocrine abnormality that had not been previously diagnosed.

PATIENTS AND METHODS

Subjects

The study group was identified from a larger group of 683 consecutive patients with nonunion seen at our center by the first author between January 1998 and December 2005.

Accepted for publication July 6, 2007.

From the *The Center for Problem Fractures and Limb Restoration, Fondren Orthopedic Group, Texas Orthopedic Hospital; †Joe W. King Orthopedic Institute; ‡The Endocrine Center; and §Gallagher & Earthman, Houston, TX.

Reprints: Mark R. Brinker, MD, Fondren Orthopedic Group, 7401 S. Main Street, Houston, TX 77030 (e-mail: mbrinker@houston.rr.com).

Copyright © 2007 by Lippincott Williams & Wilkins

The diagnosis of nonunion was confirmed in all cases by the presence of one or more of the following: 1) gross motion at the injury site on physical examination; 2) obvious motion at the injury site under fluoroscopic stress views; 3) bridging bone on 0 of 4 cortices of the anteroposterior and lateral radiographs, as described by Heckman et al[9]; 4) a computed tomography (CT) scan showing no purposeful cross-sectional area of healing.

Of these 683 patients with nonunions, we referred 37 patients to 1 of 2 clinically practicing endocrinologists to undergo evaluation for metabolic and endocrine abnormalities (Table 1). These endocrinologists were involved in the planning and execution of this study. The study protocol was approved by the facility's institutional review board.

The specific criteria for referral to an endocrinologist are outlined in Figure 1 and included any one of the following: 1) an unexplained nonunion that occurred despite adequate reduction and stabilization (and debridement in initially infected cases) without obvious technical error[10–13] and without any other obvious etiology (26 patients); 2) a history of multiple low-energy fractures with at least one progressing to a nonunion (8 patients); or 3) a nonunion of a nondisplaced pubic rami or sacral ala fracture (3 patients). The determination as to whether each patient met the criteria for referral was evaluated by the orthopaedic surgeon during the initial history and physical examination. None of the other 646 patients with nonunions met the criteria and were therefore not referred to an endocrinologist.

The study group consisted of 27 women with an average age at presentation of 52.2 years and 10 men with an average age at presentation of 45.7 years (Table 2). The average time between the initial fracture and presentation to our center was 22.1 months (range, 3 months to 104 months). The patients had undergone an average of 2.4 (range, 0 to 9) surgeries prior to referral to our center. The 37 patients had a total of 46 noncontiguous nonunion sites in 36 bones and 4 joints. The 46 nonunion sites were: femur (16), tibia (13), humerus (4), ankle (4), pubic rami (4), sacral ala (3), radius (1), ulna (1) (Table 2).

The distribution of nonunion types[3] at the 46 sites were: oligotrophic (23), atrophic (12), infected (7), and hypertrophic (4). Nonunion type was determined by the treating orthopaedic surgeon based on plain radiographs and computed tomography.[3] Oligotrophic nonunions were identified as those with an apparently adequate blood supply but little or no callus formation.[3] Atrophic nonunions were identified as those with an apparently inadequate blood supply and no callus formation.[3] Infected nonunions were identified as those with infection of bone or soft tissues or both at the nonunion site.[3] Hypertrophic nonunions were identified as those with abundant callus but a clear radiolucent line at the fracture site.[3] At the time of referral to the endocrinologist, none of the seven patients with seven sites that had been previously classified as an infected nonunion had any clinical signs or symptoms of active infection or any laboratory or radiographic studies that were diagnostic of ongoing infection.

Evaluation and Treatment

Evaluation for metabolic and endocrine abnormalities in the study group included blood and urine tests to identify hormonal, protein, mineral, and vitamin imbalances (Table 1). All of the tests were ordered, evaluated, and interpreted by one of the two clinically practicing endocrinologists who were involved in this study.

The consulting endocrinologist provided medical treatment of metabolic and endocrine abnormalities (Table 2). The treating orthopaedic surgeon provided treatment for the nonunion site; 27 of the patients underwent one or more surgical procedures, and 10 patients were treated nonoperatively.

Data Analysis

We computed the proportion and 95% confidence interval (95% CI) of patients with newly diagnosed metabolic or endocrine abnormalities as a result of this study. Analysis of variance was used to evaluate whether patient age differed between patients with metabolic and endocrine abnormalities and patients without these abnormalities. Chi-square tests were used to evaluate whether gender or nonunion type was related to the prevalence of metabolic and endocrine abnormalities. A P value of 0.05 or less was considered to be statistically significant.

RESULTS

In all, 31 of 37 patients (83.8%) who met our screening criteria and therefore underwent evaluation by an endocrinologist had one or more new diagnoses related to metabolic or endocrine abnormalities (Table 2). Six of the 37 patients who met our screening criteria had no new metabolic or endocrine abnormality. The 95% confidence interval for having a metabolic or endocrine abnormality for patients with nonunion who met our screening criteria was 71.3% to 93.8%. Of the 31 patients, 24 had more than one metabolic or endocrine abnormality (Table 2).

With the numbers available, average age at presentation was not significantly different between patients with (49.9 years, SD = 15.1 years) and without (53.8 years, SD = 10.3 years) metabolic or endocrine abnormalities ($P = 0.531$). With the numbers available, the prevalence of metabolic and endocrine abnormalities in the men (100.0%) and women (77.8%) in our study was not significantly different ($P = 0.162$). With the numbers available, the prevalence of metabolic and endocrine abnormalities did not differ significantly by nonunion type: 17 of 23 oligotrophic sites (73.9%), 10 of 12 atrophic sites (83.3%), 7 of 7 infected sites (100%), 4 of 4 hypertrophic sites (100%; $P = 0.373$).

The most common newly diagnosed abnormality was vitamin D deficiency in 25 of the 37 patients (68%, 95% CI = 53% to 82%). Twenty-one of the 37 patients (57%) had vitamin D 25(OH) deficiency; three of the these patients also had vitamin D $1,25(OH)_2$ deficiency. Four patients had deficiency of only vitamin D $1,25(OH)_2$.

Six of the 25 patients with a vitamin D deficiency were diagnosed with mild vitamin D deficiency, defined as vitamin D 25(OH) levels between 20 ng/mL and 30 ng/mL or vitamin D $1,25(OH)_2$ levels between 15 pg/mL and 25 pg/mL. Nineteen of the 25 patients were diagnosed with frank vitamin D deficiency, defined as vitamin D 25(OH) below 20 ng/mL or vitamin D $1,25(OH)_2$ levels below 15 pg/mL.

© 2007 Lippincott Williams & Wilkins

TABLE 1. Metabolic and Endocrine Related Laboratory Tests With Normal Values and Interpretation of Abnormal Values in Adults

Laboratory Test	Normal Range	Abnormal Values	Interpretation
Hormones			
Adrenocorticotropic hormone (ACTH) Cortisol	9–52 pg/mL 2–25 μg/dL	Low ACTH Low cortisol	Exogenous Cushing syndrome (secondary to corticosteroid use) Central or secondary adrenal insufficiency
		High ACTH High cortisol	Endogenous Cushing syndrome/pituitary tumor Peripheral paraneoplasia/ectopic production of ACTH
Cortisol (24-hour urine)	<45 μg/day	Low 24-hour urine cortisol	Adrenal insufficiency
		High 24-hour urine cortisol	Cushing disease
Dehydroepiandrosterone sulfate (DHEA-S)	35–430 μg/dL	Low DHEA-S	Hypogonadism Adrenal insufficiency
		High DHEA-S	Polycystic ovary syndrome, congenital adrenal hyperplasia Hyperprolactinemia
Growth hormone (GH)	0.06–5.00 ng/mL	Low GH Low IGF-1	Isolated growth hormone deficiency Panhypopituitarism
Insulin-like growth factor 1 (IGF-1)	116–225 ng/mL (for adults greater than 20 years of age)	High GH High IGF-1	Acromegaly Pituitary tumor and hyperprolactinemia
Intact parathyroid hormone (iPTH)	7–80 pg/mL	High iPTH	Pseudohypoparathyroidism Osteopetrosis Primary: parathyroid adenoma/hyperplasia Secondary: vitamin D deficiency, vitamin D resistance Tertiary: renal transplant following chronic renal failure Renal osteodystrophy
		Low iPTH	Hypoparathyroidism
Follicle stimulating hormone (FSH) Luteinizing hormone (LH)	Men: 1.5–14 mIU/mL Women: 1.9–20 mIU/mL Men: 1.0–9.0 mIU/mL Women: 1.0–62 mIU/mL	Low FSH Low LH Low estrogen/testosterone	Central hypogonadism (hypopituitarism) Sheehan syndrome (postpartum hypopituitarism)
Total estrogen Estradiol (E2) Testosterone Free testosterone	35–297 pg/mL 12–199 pg/mL; postmenopause 14–61 pg/mL Men: 241–827 ng/dL Women: 14–76 ng/dL Men: 9–30 pg/mL Women: <10 pg/mL	High FSH High LH Low estrogen/testosterone	Primary hypogonadism
Prolactin	2–27 ng/mL	High (hyperprolactinemia)	Hypothyroidism Adrenal insufficiency Cirrhosis Polycystic ovary syndrome Pituitary adenoma Chronic renal insufficiency or failure Empty sella syndrome Medications: estrogens, verapamil, dopamine receptor agonists, dopamine depleting drugs, tricyclic antidepressants, monoamine hypertensives, opiates, others

(*continued on next page*)

© 2007 Lippincott Williams & Wilkins

TABLE 1. (*continued*) Metabolic and Endocrine Related Laboratory Tests With Normal Values and Interpretation of Abnormal Values in Adults

Laboratory Test	Normal Range	Abnormal Values	Interpretation
Thyroid function test	Thyroid stimulating hormone (TSH) = 0.3–5.1 mIU/mL Free T4 = 0.73–1.95 ng/dL Free T3 = 2.3–4.2 pg/mL	High TSH Low free T4 Low free T3	Hypothyroidism
		Low TSH High free T4 High free T3	Hyperthyroidism
		Low TSH Low free T4 Low free T3	Central hypothyroidism Drug effects
Serum protein electrophoresis and immunofixation electrophoresis	Varies	Varies; used to rule out multiple myeloma	
Vitamins and minerals			
Calcium	8.5–10.5 mg/dL	High calcium (hypercalcemia)	Adrenal insufficiency Hyperparathyroidism Milk alkali syndrome Aluminum toxicity Vitamin A toxicity Vitamin D toxicity Tamoxifen Multiple myeloma Bony metastases Hypophosphatasia Familial hypocalciuric hypercalcemia Paget's disease Hyperthyroidism Pheochromocytoma Granulomatous disease Multiple endocrine neoplasia type I
		Low calcium (hypocalcemia)	Hypoparathyroidism Pseudohypoparathyroidism Osteopetrosis Vitamin D deficiency or resistance Rickets Renal osteodystrophy
Calcium (24-hour urine)	100–250 mg/day	Low 24-hour urine calcium	Calcium deficiency Chronic renal failure Vitamin D dependent rickets (types I and II) Hypoparathyroidism Pseudohypoparathyroidism Vitamin D deficiency Familial hypocalciuric hypercalcemia
		High 24-hour urine calcium	Hyperparathyroidism Bony metastases Hyperthyroidism Vitamin D intoxication Distal renal tubular acidosis Fanconi syndrome Immobilization Malignancy
Magnesium	1.3–2.3 mg/dL	Low magnesium	Hypocalcemia (low iPTH and increased resistance to PTH) Gastrointestinal malabsorption
		High magnesium	Magnesium hydroxide toxicity (antacid abuse) Leads to decreased phosphorus and osteomalacia

(*continued on next page*)

© 2007 Lippincott Williams & Wilkins

TABLE 1. (*continued*) Metabolic and Endocrine Related Laboratory Tests With Normal Values and Interpretation of Abnormal Values in Adults

Laboratory Test	Normal Range	Abnormal Values	Interpretation
Phosphorus (phosphate, PO_4)	2.2–4.5 mg/dL	Low PO_4 (hypophosphatemia)	Hypophosphatemic rickets Tumor-induced osteomalacia Primary hyperparathyroidism Vitamin D deficiency Phosphorus deficiency Osteopetrosis
		High PO_4 (hyperphosphatemia)	Chronic renal failure Pseudohypoparathyroidism Hypoparathyroidism Hypophosphatasia Vitamin D intoxication Bony metastases
Alkaline phosphatase	30–132 U/L	Low alkaline phosphatase	Hypophosphatasia
		High alkaline phosphatase	Chronic renal failure Vitamin D deficiency Calcium deficiency Paget's disease Phosphate deficiency Vitamin D dependent rickets (types I and II) Hypophosphatemic rickets Tumor-induced osteomalacia
		Normal to high alkaline phosphatase	Hyperparathyroidism Bony metastases Vitamin D intoxication
25-hydroxyvitamin D [vitamin D 25(OH)]	20–57 ng/mL	Low 25-hydroxyvitamin D	Vitamin D deficiency Liver disease Gastrointestinal malabsorption Pancreatic insufficiency Anticonvulsant medications
		High 25-hydroxyvitamin D	Vitamin D toxicity Sarcoidosis Rickets type I and type II
1,25-dihydroxyvitamin D [vitamin D $1,25(OH)_2$]	15–75 pg/mL	Low 1,25-dihydroxyvitamin D	Chronic renal failure (secondary hyperparathyroidism) Hypoparathyroidism Pseudohypoparathyroidism Bony metastases Vitamin D deficiency Tumor-induced osteomalacia Vitamin D dependent rickets type I Phosphorus deficiency Calcium deficiency
		High 1,25-dihydroxyvitamin D	Primary hyperparathyroidism Granulomatous disease Sarcoidosis/tuberculosis Vitamin D dependent rickets type II Lymphoma Calcium deficiency

All laboratory tests are serum levels unless otherwise indicated. Cells that contain two or more laboratory tests indicate that these tests are interpreted in concert.

Abnormal 24-hour urine calcium was the second most common finding, newly identified in 13 of 37 patients (35%, 95% CI = 23% to 53%); 10 of these 13 patients also had vitamin D deficiency. Abnormally low 24-hour urine calcium was found in 7 of the 37 patients. Abnormally high 24-hour urine calcium was found in 6 other patients.

Nine of the 37 patients (24%, 95% CI = 14% to 41%) had newly identified abnormalities related to the thyroid gland. Three patients had elevated thyroid stimulating hormone; one of these three also had decreased free T_3 (triiodothyronine). Three patients had decreased thyroid stimulating hormone; one of these patients also had decreased T_3

© 2007 Lippincott Williams & Wilkins

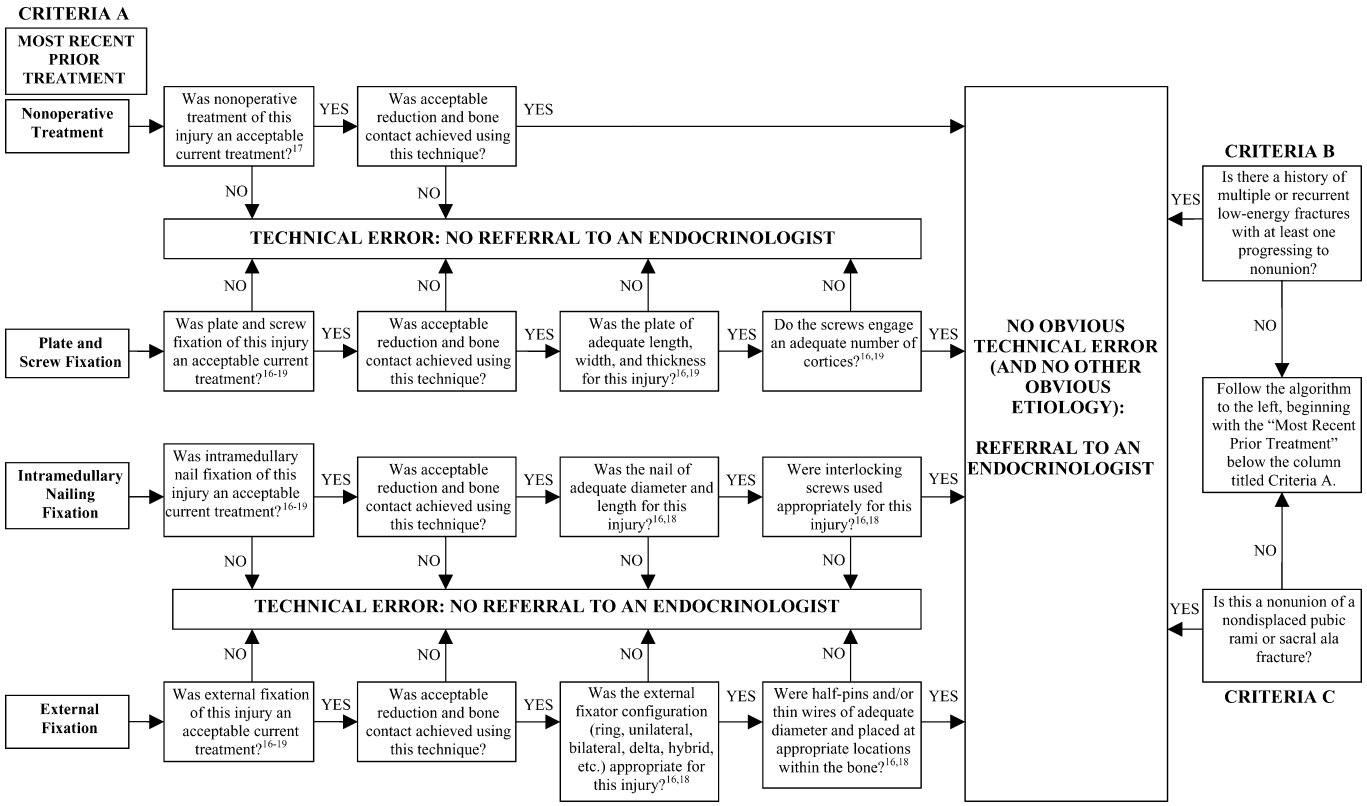

FIGURE 1. Algorithm illustrating the application of our screening criteria.

and another one of these patients also had decreased T_3 and elevated T_4 (thyroxine). In the remaining 3 of the 9 patients, 2 had decreased T_3 and 1 had elevated T_3. Five of the 9 patients were newly diagnosed with hypothyroidism, and 2 were newly diagnosed with autoimmune thyroiditis from overtreatment of hypothyroidism (iatrogenic hyperthyroidism).

Eight of the 37 patients (22%, 95% CI = 12% to 38%) had newly identified abnormalities of one or more hormones related to the reproductive system. Five of the 37 patients (4 men and 1 woman) had newly diagnosed central hypogonadism.

Abnormally high alkaline phosphatase was newly identified in 6 of the 37 patients (16%, 95% CI = 8% to 32%). One of these 6 patients and 1 additional patient had newly identified high serum phosphate levels.

Other newly identified abnormalities were less common. Four of the 37 patients (11%, 95% CI = 5% to 26%) had elevated parathyroid hormone levels. Two of the 37 patients had hyperprolactemia (5%, 95% CI = 2% to 18%). One of the 37 patients had increased growth hormone (3%, 95% CI = 1% to 14%).

Thirty of the 31 patients with newly identified metabolic or endocrine abnormalities after referral to us achieved bony union in an average of 9.6 months (range, 2 to 23 months) after the endocrinology evaluation and medical treatment. One patient (patient 20) with a subtrochanteric nonunion who was newly diagnosed with vitamin D deficiency and iatrogenic hyperthyroidism underwent total hip arthroplasty because there was inadequate bone stock for revision open reduction internal fixation. Ultimately, 27 of the 31 patients with newly identified metabolic or endocrine abnormalities underwent operative treatment by us (Table 3). Eight patients who underwent no surgical intervention following the diagnosis and treatment of a new metabolic or endocrine abnormality achieved bony union in an average of 7.6 months (range, 3 to 12 months) following their first visit to the endocrinologist. Four of these 8 patients received no surgery from us; the other four patients received surgery from us before being referred for their endocrinology examination.

Five of the 6 patients with no newly identified metabolic or endocrine abnormalities achieved bony union, 4 following operative intervention and 1 following nonoperative treatment. The sixth patient underwent a total hip arthroplasty to treat a femoral neck nonunion of 12 months duration.

DISCUSSION

Our sample data indicates that nearly 85% of patients with nonunion who met our screening criteria had previously undiagnosed metabolic or endocrine abnormalities. This finding did not vary by patient age, gender, or nonunion type. Our results suggest that metabolic or endocrine abnormalities play a role in the development or persistence of nonunion in some patients. We recommend that a patient who has a nonunion and meets our criteria be referred for a complete metabolic and endocrine evaluation. While our study does not prove a causal link between metabolic and endocrine abnormalities and either

© 2007 Lippincott Williams & Wilkins

TABLE 2. Reason for Endocrinology Referral, and Newly Diagnosed Metabolic and Endocrine Abnormalities

Patient	Age at Presentation (Years)	Sex	Months From Initial Fracture to Presentation	Nonunion Location (Type)	Reason for Referral to an Endocrinologist	Metabolic and Endocrine Abnormalities [Value] (Normal Range)
1	51	Female	7	Distal tibia (oligotrophic)	B	High 24-hour urine calcium [300 mg] (100–250 mg) Low-normal 1,25-dihydroxyvitamin D [17 pg/mL] (15–75 pg/mL)
2	70	Female	3	1) Left sacral ala (oligotrophic) 2) Right sacral ala (oligotrophic)	C	None
3	24	Male	9	Femoral shaft (oligotrophic)	A	Low 25-hydroxyvitamin D [18 ng/mL] (20–57 ng/mL)
4	59	Male	6	Failed ankle fusion (atrophic)	A	High alkaline phosphatase [211 U/L] (30–132 U/L) Low 24-hour urine calcium [30 mg] (100–250 mg) High 25-hydroxyvitamin D [65 ng/mL] (20–57 ng/mL)
5	69	Female	59	Distal femur (atrophic)	A	High intact parathyroid hormone [85 pg/mL] (7–80 pg/mL) Low 24-hour urine calcium [60 mg] (100–250 mg)
6	84	Female	5	Distal femur (oligotrophic)	A	High intact parathyroid hormone [84 pg/mL] (7–80 pg/mL) High 24-hour urine calcium [260 mg] (100–250 mg) Low-normal 1,25-hydroxyvitamin D [16 pg/mL] (15–75 pg/mL)
7	70	Female	6	Distal femur proximal to below knee amputation (oligotrophic)	A	None
8	46	Male	3	Distal femur (atrophic)	B	Low dehydroepiandrosterone sulfate [63 μL/dL] (35–430 μL/dL) Low free testosterone [6.6 pg/mL] 9–30 pg/mL High 24-hour urine calcium [382 mg] (100–250 mg)
9	47	Male	18	Distal tibia and fibula (infected) Proximal humerus (atrophic)	B	Low dehydroepiandrosterone sulfate [64 μL/dL] (35–430 μL/dL) Low testosterone [97 ng/dL] (241–827 ng/dL) High free T3 [4.5 pg/mL] (2.3–4.2 pg/mL) High phosphate [5.4 mg/dL] (2.2–4.5 mg/dL)
10	29	Female	11	Tibial shaft (infected)	A	Low dehydroepiandrosterone sulfate [32 μL/dL] (35–430 μL/dL) High prolaction [30.9 ng/mL] (2–27 ng/mL) High thyroid stimulating hormone [5.4 mIU/mL] (0.3–5.1 mIU/mL) High 24-hour urine calcium [288 mg] (100–250 mg) Low 25-hydroxyvitamin D [8 ng/mL] (20–57 ng/mL)
11	39	Female	20	Distal femur (oligotrophic)	A	Low thyroid stimulating hormone [0.1 mIU/mL) (0.3–5.1 mIU/mL) Low 25-hydroxyvitamin D [6 ng/mL] (20–57 ng/mL) Low 1,25-dihydroxyvitamin D [11 pg/mL] (15–75 pg/mL)
12	71	Female	6	Proximal humerus (oligotrophic)	A	Low free T3 [2.2 pg/mL] (2.3–4.2 pg/mL) Low dehydroepiandrosterone sulfate [30 μL/dL] (35–430 μL/dL) Low 24-hour urine calcium [90 mg] (100–250 mg) Low 25-hydroxyvitamin D [15 ng/mL] (20–57 ng/mL)

(*continued on next page*)

© 2007 Lippincott Williams & Wilkins

TABLE 2. (*continued*) Reason for Endocrinology Referral, and Newly Diagnosed Metabolic and Endocrine Abnormalities

Patient	Age at Presentation (Years)	Sex	Months From Initial Fracture to Presentation	Nonunion Location (Type)	Reason for Referral to an Endocrinologist	Metabolic and Endocrine Abnormalities [Value] (Normal Range)
13	62	Male	54	Subtrochanteric femur (oligotrophic)	A	Low dehydroeipandrosterone sulfate [67 μL/dL] (35–430 μL/dL) Low free testosterone [6.1 pg/mL] (9–30 pg/mL) Low 25-hydroxyvitamin D [9 ng/mL] (20–57 ng/mL)
14	72	Female	4	Tibial shaft (oligotrophic)	A	Low follicle stimulating hormone [1.5 mIU/mL] (1.9–20 mIU/mL) Low luteinizing hormone [0.1 mIU/mL] (1.0–62 mIU/mL)
15	36	Female	12	Femoral neck (atrophic)	A	None
16	54	Male	6	Distal femur (oligotrophic)	B	Low 24 hour urine calcium [80 mg] (100–250 mg) Low-normal 25-hydroxyvitamin D [22 ng/mL] (20–57 ng/mL) Low-normal 1,25-dihydroxyvitamin D [18 pg/mL] (15–75 pg/mL)
17	36	Male	18	Distal tibia (atrophic)	A	High growth hormone [6.92 ng/mL] (0.06–5.00 ng/mL) High prolactin [33 ng/mL] (2–27 ng/mL) Low luteinizing hormone [0.1 mIU/mL] (1.0–9.0 mIU/mL) Low testosterone [240 ng/dL] (241–827 ng/dL) High alkaline phosphatase [213 U/L] (30–132 IU/L) Low 25-hydroxyvitamin D [5 ng/mL] (20–57 ng/mL) Low 1,25-dihydroxyvitamin D [14 pg/mL] (15–75 pg/mL)
18	48	Female	59	Failed ankle fusion (oligotrophic)	A	Low thyroid stimulating hormone [0.1 mIU/mL] (0.3–5.1 mIU/mL) High free T4 [2.05 ng/dL] (0.73–1.95 ng/dL) Low free T3 [2.2 pg/mL] (2.3–4.2 pg/mL) High alkaline phosphatase [186 U/L] (30–132 U/L) Low 24 hour urine calcium [21 mg] (100–250 mg) Low 25-hydroxyvitamin D [11 ng/mL] (20–57 ng/mL) Low 1,25-dihydroxyvitamin D [14 pg/mL] (15–75 pg/mL)
19	51	Female	6	Humeral shaft (infected)	A	Low 24 hour urine calcium [90 mg] (100–250 mg) Low 25-hydroxyvitamin D [19 ng/mL] (20–57 ng/mL)
20	67	Female	62	Subtrochanteric femur (infected)	A	Low thyroid stimulating hormone [0.2 mIU/mL] (0.3–5.1 mIU/mL) High free T3 [5.2 pg/mL] (2.3–4.2 pg/mL) Low-normal 25-hydroxyvitamin D [23 ng/mL] (20–57 ng/mL)
21	51	Female	29	1) Proximal tibia (infected) 2) Distal tibia (oligotrophic)	A	Low-normal 25-hydroxyvitamin D [21 ng/mL] (20–57 ng/mL)
22	62	Male	8	Failed ankle fusion (infected)	A	Low-normal 1,25-dihydroxyvitamin D [18 pg/mL] (15–75 pg/mL)
23	46	Female	60	Failed ankle fusion (oligotrophic)	A	High thyroid stimulating hormone [5.9 mIU/mL] (0.3–5.1 mIU/mL) Low 25-hydroxyvitamin D [13 ng/mL] (20–57 ng/mL)

(*continued on next page*)

© 2007 Lippincott Williams & Wilkins

TABLE 2. (*continued*) Reason for Endocrinology Referral, and Newly Diagnosed Metabolic and Endocrine Abnormalities

Patient	Age at Presentation (Years)	Sex	Months From Initial Fracture to Presentation	Nonunion Location (Type)	Reason for Referral to an Endocrinologist	Metabolic and Endocrine Abnormalities [Value] (Normal Range)
24	43	Female	15	Proximal tibia (oligotrophic)	B	Low free T3 [1.8 pg/mL] (2.3–4.2 pg/mL) High phosphate [4.6 mg/dL] (2.2–4.5 mg/dL) High alkaline phosphatase [251 U/L] (30–132 U/L) Low-normal 1,25-dihydroxyvitamin D [16 pg/mL] (15–75 pg/mL)
25	58	Female	24	Tibial shaft (atrophic)	A	Low 25-hydroxyvitamin D [9 ng/mL] (20–57 ng/mL) High alkaline phosphatase [143 U/L] (30–132 U/L)
26	30	Male	4	Proximal tibia (oligotrophic)	A	Low 25-hydroxyvitamin D [5 ng/mL] (20–57 ng/mL)
27	26	Female	12	Sacral ala (oligotrophic)	C	Low 25-hydroxyvitamin D [17 ng/mL] (20–57 ng/mL)
28	29	Female	25	Ulnar shaft (atrophic)	A	Low 24 hour urine calcium [5.5 mg] (100–250 mg) Low 25-hydroxyvitamin D [18 ng/mL] (20–57 ng/mL)
29	45	Female	59	Tibial shaft (atrophic)	A	Low 25-hydroxyvitamin D [13 ng/mL] (20–57 ng/mL)
30	52	Female	6	1) Distal femur (oligotrophic) 2) Radial shaft (oligotrophic)	B	None
31	37	Male	24	Humeral shaft (oligotrophic)	A	High intact parathyroid hormone [83 pg/mL] (7–80 pg/mL) Low 25-hydroxyvitamin D [14 ng/mL] (20–57 ng/mL)
32	47	Female	3	1) Tibial shaft (infected) 2) Femoral shaft (oligotrophic)	B	High alkaline phosphatase [153 IU/L] (30–132 IU/L) Low 25-hydroxyvitamin D [19 ng/mL] (20–57 ng/mL)
33	57	Female	21	1) Left superior pubic rami (hypertrophic) 2) Right superior pubic rami (hypertrophic) 3) Left inferior pubic rami (hypertrophic) 4) Right inferior pubic rami (hypertrophic)	C	High intact parathyroid hormone [151 pg/mL] (7–80 pg/mL) High 24 hour urine calcium [286 mg] (100–250 mg) Low 25-hydroxyvitamin D [18 ng/mL] (20–57 ng/mL)
34	55	Female	4	1) Femoral shaft (atrophic) 2) Femoral neck (atrophic)	B	High follicle stimulating hormone [58 mIU/mL] (1.9–20 mIU/mL) High 24 hour urine calcium [265 mg] (100–250 mg) Low 25-hydroxyvitamin D [19 ng/mL] (20–57 ng/mL)
35	53	Female	35	Subtrochanteric femur (oligotrophic)	A	None
36	52	Female	10	Distal tibia (oligotrophic)	A	High thyroid stimulating hormone [7.9 mIU/mL] (0.3–5.1 mIU/mL)
37	43	Female	104	Distal femur (atrophic)	A	None

Criteria for referral as outlined in Figure 1: A, an unexplained nonunion that occurred despite adequate reduction and stabilization (and debridement in initially infected cases) without obvious technical error[16–19] and without any other obvious etiology; B, a history of multiple low-energy fractures with at least one progressing to a nonunion; C, a nonunion of a nondisplaced pubic rami or sacral fracture.

the development or healing of nonunions, most of the patients who met our criteria were found to have metabolic or endocrine abnormalities. Furthermore, eight of our patients achieved bony union following medical treatment alone after the identification of a new metabolic or endocrine abnormality.

The response to fracture involves many metabolic and endocrine factors, including biochemical interactions of growth factors, bone morphogenetic proteins, vitamins, minerals, and hormones. Impairment of any of these factors could potentially affect fracture healing. Many endocrine and metabolic disorders that affect these factors have been shown to be associated with alterations in bony metabolism.[4–6,14–19]

Several authors have described adverse effects on bone healing and bone structure among patients with various

© 2007 Lippincott Williams & Wilkins

TABLE 3. Metabolic and Endocrine Diagnosis, and Medical and Orthopaedic Treatment

Patient	New Metabolic and Endocrine Diagnosis	Medical Treatment for New Metabolic and Endocrine Disorders	Orthopaedic Treatment for Nonunion
1	Mild vitamin D deficiency	Discontinue Boniva Actonel 35 mg weekly Calcium 500 mg with vitamin D 800 IU 3 times/day	Ilizarov external fixation
2	None	None	Pain management
3	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day Sit in sunlight for 30 minutes per day	Exchange nailing
4	Poor dietary calcium intake	Actonel 35 mg per week Calcium 500 mg 3 times/day	Open reduction internal fixation
5	Poor dietary calcium and vitamin D intake	Discontinue Evibra Actenol 35 mg/week Calcium 500 mg with vitamin D 800 IU 3 times/day Increase dairy products	Slow compression over a nail with external fixation
6	Mild vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day Actonel 35 mg/week Rocaltrol 0.25 mg every other day	None
7	None	None	Open reduction internal fixation with autograft
8	Central hypogonadism due to partial empty sella (small pituitary gland)	Testosterone replacement therapy Calcium 500 mg with vitamin D 800 IU 3 times/day Actonel 35 mg/wk	Casting/bracing
9	Central hypogonadism due to partial empty sella (small pituitary gland)	Calcium 500 mg with vitamin D 800 IU 3 times/day Testosterone replacement therapy	Tibia: Ilizarov bone transport, ankle arthrodesis Humerus: Open reduction internal fixation with autograft
10	Vitamin D deficiency Hypothyroidism and secondary hyperprolactemia	Fosamax weekly Calcium 500 mg with vitamin D 800 IU 3 times/day Synthyroid to normalize prolactin levels	First: Ilizarov bone transport Second: Intramedullary nailing Third: Nail dynamization Electromagnetic stimulation
11	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day Fosamax Sit in sunlight for 30 minutes per day	Open reduction internal fixation with autograft and OP-1
12	Vitamin D deficiency Hypothyroidism, poorly controlled	Actonel 35 mg/wk Increase Synthyroid dose Calcium 500 mg with vitamin D 800 IU 3 times/day, changed to calcium 1500 mg/day after vitamin D levels normalized	Electromagnetic stimulation
13	Partial central hypogonadism Vitamin D deficiency	Fosamax Calcium 500 mg with vitamin D 800 IU 3 times/day Prescribed low-dose testosterone gel, but never started due to benign prostate hypertrophy (PSA normal)	Open reduction internal fixation with autograft
14	Central hypogonadism	Continue postmenopausal hormone therapy	Bracing
15	None	None	Total hip arthroplasty
16	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day Niacalcin nasal spray Multivitamin supplement	Bracing
17	Central hypogonadism Pituitary microadenoma Mild hyperprolactemia (secondary to chronic renal insufficiency) Vitamin D deficiency	Testosterone replacement therapy Calcium 500 mg with vitamin D 800 IU 3 times/day Actenol 35 mg/wk	Bracing
18	Vitamin D deficiency Overtreated hypothyroidism (iatrogenic hyperthyroidism)	Change Synthyroid to 0.2 mg/day Rocaltrol 0.25 mg bid Calcium 500 mg with vitamin D 800 IU 3 times/day	First: Ilizarov external fixation Second: intramedullary nailing Third: open reduction internal fixation
19	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day Actonel 35 mg/wk	First: Ilizarov bone transport Second: open reduction internal fixation with autograft
20	Mild vitamin D deficiency Overtreated hypothyroidism (iatrogenic hyperthyroidism)	Decrease Synthyroid to 150 μg/day Calcium 500 mg with vitamin D 800 IU 3 times/day	Total hip arthroplasty
21	Mild vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day Actonel 35 mg/wk	Proximal tibia: slow compression over a nail with external fixation Distal tibia: Ilizarov external fixation
22	Mild vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day Sit in sunlight for 30 minutes per day	Ilizarov bone transport

(*continued on next page*)

© 2007 Lippincott Williams & Wilkins

TABLE 3. (*continued*) Metabolic and Endocrine Diagnosis, and Medical and Orthopaedic Treatment

Patient	New Metabolic and Endocrine Diagnosis	Medical Treatment for New Metabolic and Endocrine Disorders	Orthopaedic Treatment for Nonunion
23	Vitamin D deficiency Subclinical hypothyroidism	Synthyroid 0.05 mg per day Calcium 500 mg with vitamin D 800 IU 3 times/day Actonel 35 mg/wk	Ilizarov external fixation
24	Hypothyroidism Mild vitamin D deficiency	Calcium 1500 mg/day Synthyroid 0.05 mg per day Actonel 35 mg/wk	Ilizarov external fixation
25	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day Actonel 35 mg/wk	Intramedullary nailing
26	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day	Ilizarov external fixation
27	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day	None
28	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day Fosamax	Open reduction internal fixation Vascularized free fibula transfer
29	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day	First: Ilizarov bone transport Second: open reduction internal fixation with autograft Electromagnetic stimulation
30	None	None	Femur: First: slow compression over a nail using external fixation Femur: Second: open reduction internal fixation with autograft Radius: open reduction internal fixation with autograft
31	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times per day	Open reduction internal fixation with autograft
32	Vitamin D deficiency	Calcium 500 mg per day Vitamin D 400 IU 3 times per day	Tibia: First: Ilizarov bone transport Second: open reduction internal fixation with autograft Tibia: Electromagnetic stimulation Femur: First: exchange nailing Femur: Second: slow compression over a nail using external fixation
33	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day	None
34	Vitamin D deficiency	Calcium 500 mg with vitamin D 800 IU 3 times/day	Femoral shaft: exchange nailing Femoral neck: total hip arthroplasty (after femoral shaft united)
35	None	None	Open reduction internal fixation with autograft
36	Hypothyroidism	Synthyroid 0.05 mg per day	Ilizarov bone transport
37	None	None	Casting/bracing

endocrine and metabolic abnormalities. Diamond and coauthors reported that the prevalence of vitamin D deficiency ($<$20 ng/mL) and hypogonadism (serum free testosterone $<$11 pg/mL) among 41 men over 60 years of age who had sustained osteoporotic hip fractures was higher than the prevalence of these abnormalities among age-matched controls.[20] Lancourt and Hochberg reported four patients for whom hyperparathyroidism was identified as a causative factor for fracture nonunion.[21] Misol and colleagues reported a case in which a patient with low growth hormone levels had delayed healing (20 weeks without callus formation) of a femoral shaft fracture and hypothesized that the hormonal deficiency may have had a role in the delay of bony union.[22] In a case-control study of 107 patients, Rosén and colleagues reported that patients with growth hormone deficiency have a three times greater risk of fracture, suggesting that growth hormone contributes to bone strength.[23] Several other factors affect the endocrine system and various metabolic pathways related to bone formation, such as diabetes mellitus,[15–17] malnutrition,[18,19] cigarette smoking,[28–34] alcohol abuse,[35,36] and certain medications (eg, nonsteroidal anti-inflammatory drugs).[37–41]

Vitamin D deficiency may account for the concomitant findings of elevated alkaline phosphatase, elevated parathyroid hormone, and decreased calcium observed in some of our patients.[5,6] All of these factors have been shown to be associated with impaired fracture healing.[14] Long-term exposure to chronically elevated parathyroid hormone levels increases bone resorption, as observed in secondary hyperparathyroidism in chronic renal disease.[4] Intestinal calcium absorption is less effective with vitamin D deficiency, thus depriving the fracture site of the calcium necessary for mineralization. Any of these correlates of vitamin D deficiency can adversely affect fracture healing and conceivably contribute to the development of nonunion.

An elevated alkaline phosphatase level, an indicator of bone formation, is a normal reaction within 3 to 6 weeks of

© 2007 Lippincott Williams & Wilkins

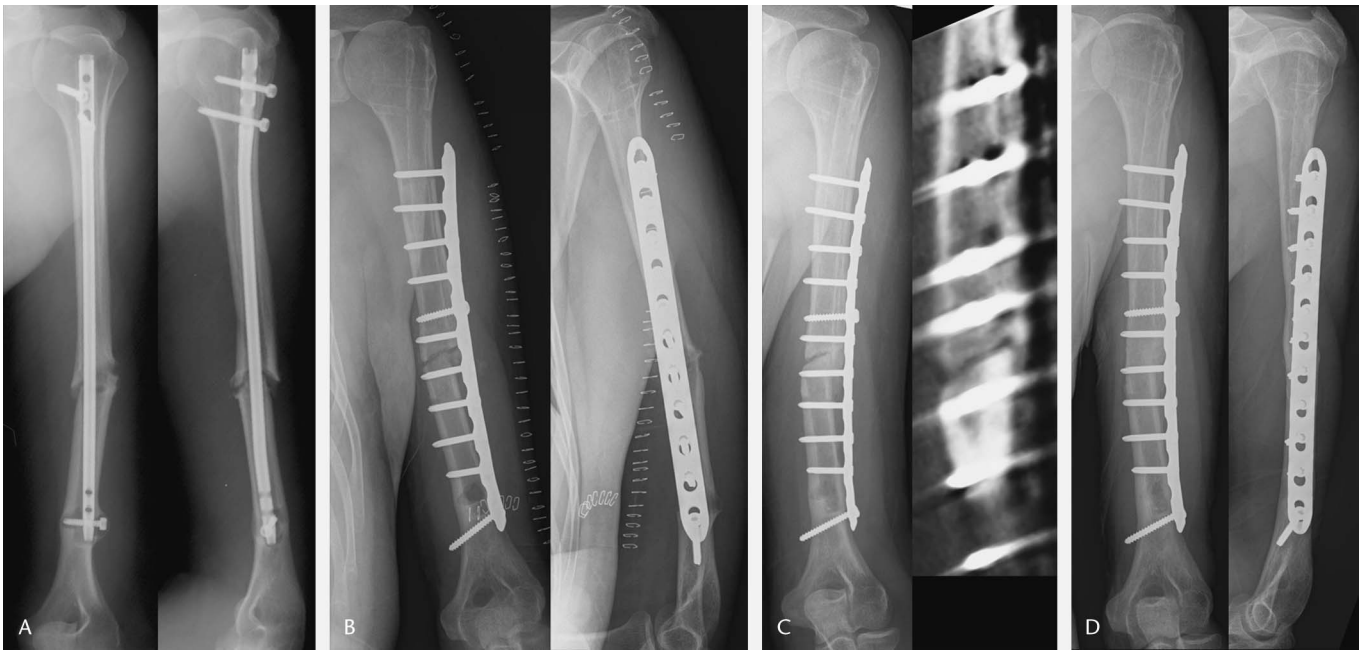

FIGURE 2. A, Anteroposterior and lateral radiograph of a 37-year-old man (patient 31), who was referred 24 months following intramedullary nail fixation of a humeral shaft fracture. The patient had no significant past medical history and the workup for infection, including aspiration of the nonunion site and blood work, was negative. The patient was taken to the operating room and underwent nail removal, trimming of the nonunion site, autogenous posterior iliac crest bone grafting, and plate stabilization with compression applied across the nonunion site. B, Anteroposterior and lateral radiographs 2 weeks following nonunion treatment as described above. C, Anteroposterior radiograph and CT scan 6 months later shows a persistent nonunion with no cross-sectional area of healing. At this point the patient continued to complain of pain and was referred for endocrinology evaluation. The evaluation revealed vitamin D deficiency [the patient had high intact parathyroid hormone (83 pg/mL) and low 25-hydroxyvitamin D (14 ng/mL)]. The patient was started on calcium 500 mg with vitamin D 800 IU three times per day to treat his vitamin D deficiency. D, Anteroposterior and lateral radiographs 5 months following initiation of medical treatment show solid bony union; no further operative intervention was performed. The patient has returned to full painless function at preinjury levels.

fracture.[24–27] In our patients with nonunion, the presence of elevated alkaline phosphatase well beyond six weeks may represent a failing attempt to heal the fracture site. The failure to heal despite apparent active bone formation in these cases may be attributable to vitamin D deficiency causing inadequate calcium availability or increased bone resorption due to chronically elevated parathyroid hormone levels or both.

Based on the results of our investigation, we make several recommendations. First, all patients with nonunion who meet our screening criteria as outlined in Figure 1 should be referred to an endocrinologist for evaluation. According to our data, patients with a nonunion who meet our criteria are likely to have undiagnosed metabolic or endocrine abnormalities. The goal of the evaluation is to identify any metabolic or endocrine abnormalities and to have the endocrinologist institute medical treatment. Treatment of the metabolic or endocrine abnormalities may facilitate the biological component of bone healing during orthopaedic treatment of the nonunion.

Second, we encourage further investigation to determine whether all patients with nonunion should receive an endocrinology evaluation. The biological factors that contribute to development of a nonunion are currently not completely understood. Patients with clinically undetected metabolic or endocrine abnormalities may be at greater risk for persistent nonunion, just as patients with certain metabolic disorders are known to be at greater risk for fracture.[23,42–44]

Third, it may be possible to develop simple clinical screening criteria for patients with fractures to identify those who are at risk for developing nonunion due to an undiagnosed metabolic or endocrine abnormality. If metabolic or endocrine abnormalities are shown to be a causative factor in the development of nonunion, identifying patients with such abnormalities and providing the appropriate medical treatment early in the fracture healing process may decrease the incidence of fracture nonunion. For example, given the high prevalence of inadequate vitamin D levels in the general population,[45] it is likely that many patients who sustain a fracture may also have a vitamin D deficiency that can contribute to the formation of nonunion. Development of such screening criteria would require prospective studies of large series or samples of patients with a fracture who all receive an endocrinology evaluation.

It was beyond the intent and scope of this study to show that metabolic and endocrine abnormalities caused nonunion in our patients. While we believe our data is compelling, with a prevalence of 84% of newly diagnosed metabolic and endocrine abnormalities in patients with nonunion who met our screening criteria, our study design did not allow us to

© 2007 Lippincott Williams & Wilkins

prove a causal link. It was also beyond the intent and scope of our investigation to demonstrate the effectiveness of medical treatment on healing the nonunion in our patients, although in eight cases (such as patient 31, Fig. 2) orthopaedic treatment had failed and the medical intervention alone led to solid bony union.

In conclusion, our screening criteria can be used to identify patients with a nonunion who are likely to have undiagnosed metabolic or endocrine abnormalities that may be interfering with the bone healing process. All patients with nonunion who meet our screening criteria should be referred to an endocrinologist for evaluation. Future studies are needed to confirm the causal association of metabolic and endocrine abnormalities with the development of nonunion and to develop appropriate clinical screening criteria to identify patients with fractures who are at high risk for nonunion due to these abnormalities.

ACKNOWLEDGMENT

The authors would like to gratefully acknowledge T. Bradley Edwards, MD, Howard R. Epps, MD, Vasilios Mathews, MD, and Gregory W. Stocks, MD, for editorial assistance with the manuscript.

REFERENCES

1. Einhorn TA. Enhancement of fracture healing. *Instr Course Lect*. 1996; 45:401–416.
2. Praemer A, Furner S, Rice DP, eds. *Musculoskeletal Conditions in the United States*. Park Ridge, IL: American Academy of Orthopaedic Surgeons; 1992.
3. Brinker MR. Nonunions: Evaluation and Treatment. In: *Skeletal Trauma: Basic Science, Management, and Reconstruction*. Browner BD, Levine AM, Jupiter JB, et al, eds. Philadelphia: W.B. Saunders; 2003:507–604.
4. de Francisco AL. Medical therapy of secondary hyperparathyroidism in chronic kidney disease: old and new drugs. *Expert Opin Pharmacother*. 2006;7:2215–2224.
5. Jesudason D, Need AG, Horowitz M, et al. Relationship between serum 25-hydroxyvitamin D and bone resorption markers in vitamin D insufficiency. *Bone*. 2002;31:626–630.
6. Need AG. Bone resorption markers in vitamin D insufficiency. *Clin Chim Acta*. 2006;368:48–52.
7. Simpson AH, Mills L, Noble B. The role of growth factors and related agents in accelerating fracture healing. *J Bone Joint Surg Br*. 2006;88: 701–705.
8. Skripitz R, Aspenberg P. Parathyroid hormone–a drug for orthopedic surgery? *Acta Orthop Scand*. 2004;75:654–662.
9. Heckman JD, Ryaby JP, McCabe J, et al. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. *J Bone Joint Surg Am*. 1994;76:26–34.
10. Browner BD, Levine AM, Jupiter JB, et al, eds. *Skeletal Trauma: Basic Science, Management, and Reconstruction*. Philadelphia: W.B. Saunders; 2003.
11. Bucholz RW, Heckman JD, Court-Brown CM, et al, eds. *Rockwood and Green's Fractures in Adults*. Philadelphia: Lippincott Williams & Wilkins; 2001.
12. Rüedi TP, Murphy WM, eds. *AO Principles of Fracture Managment*. New York: Thieme Medical Publishers; 2001.
13. Wagner M, Frigg R, eds. *AO Manual of Fracture Management: Internal Fixators*. New York: Thieme Medical Publishers; 2006.
14. Komnenou A, Karayannopoulou M, Polizopoulou ZS, et al. Correlation of serum alkaline phosphatase activity with the healing process of long bone fractures in dogs. *Vet Clin Pathol*. 2005;34:35–38.
15. Kayal RA, Tsatsas D, Bauer MA, et al. Diminished bone formation during diabetic fracture healing is related to the premature resorption of cartilage associated with increased osteoclast activity. *J Bone Miner Res*. 2007;22: 560–568.
16. Follak N, Kloting I, Merk H. Influence of diabetic metabolic state on fracture healing in spontaneously diabetic rats. *Diabetes Metab Res Rev*. 2005;21:288–296.
17. Follak N, Kloting L, Wolf E, et al. Delayed remodeling in the early period of fracture healing in spontaneously diabetic BB/OK rats depending on the diabetic metabolic state. *Histol Histopathol*. 2004;19:473–486.
18. Hughes MS, Kazmier P, Burd TA, et al. Enhanced fracture and soft-tissue healing by means of anabolic dietary supplementation. *J Bone Joint Surg Am*. 2006;88:2386–2394.
19. Day SM, DeHeer DH. Reversal of the detrimental effects of chronic protein malnutrition on long bone fracture healing. *J Orthop Trauma*. 2001;15:47–53.
20. Diamond T, Smerdely P, Kormas N, et al. Hip fracture in elderly men: the importance of subclinical vitamin D deficiency and hypogonadism. *Med J Aust*. 1998;169:138–141.
21. Lancourt JE, Hochberg F. Delayed fracture healing in primary hyperparathyroidism. *Clin Orthop Relat Res*. 1977;124:214–218.
22. Misol S, Samaan N, Ponseti IV. Growth hormone in delayed fracture union. *Clin Orthop Relat Res*. 1971;74:206–208.
23. Rosén T, Wilhelmsen L, Landin-Wilhelmsen K, et al. Increased fracture frequency in adult patients with hypopituitarism and GH deficiency. *Eur J Endocrinol*. 1997;137:240–245.
24. Obrant KJ, Ivaska KK, Gerdhem P, et al. Biochemical markers of bone turnover are influenced by recently sustained fracture. *Bone*. 2005;36: 786–792.
25. Ivaska KK, Gerdhem P, Akesson K, et al. The effect of fracture on bone turnover markers: a longitudinal study comparing marker levels before and after injury in 113 elderly women. *J Bone Miner Res*. 2007;22: 1155–1164.
26. Nakagawa H, Kamimura M, Takahara K, et al. Changes in total alkaline phosphatase level after hip fracture: comparison between femoral neck and trochanter fractures. *J Orthop Sci*. 2006;11:135–139.
27. Akesson K, Kakonen SM, Josefsson PO, et al. Fracture-induced changes in bone turnover: a potential confounder in the use of biochemical markers in osteoporosis. *J Bone Miner Metab*. 2005;23:30–35.
28. El-Zawawy HB, Gill CS, Wright RW, et al. Smoking delays chondrogenesis in a mouse model of closed tibial fracture healing. *J Orthop Res*. 2006;24:2150–2158.
29. Skott M, Andreassen TT, Ulrich-Vinther M, et al. Tobacco extract but not nicotine impairs the mechanical strength of fracture healing in rats. *J Orthop Res*. 2006;24:1472–1479.
30. Little CP, Burston BJ, Hopkinson-Woolley J, et al. Failure of surgery for scaphoid non-union is associated with smoking. *J Hand Surg [Br]*. 2006; 31:252–255.
31. Castillo RC, Bosse MJ, MacKenzie EJ, et al. Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures. *J Orthop Trauma*. 2005;19:151–157.
32. Gullihorn L, Karpman R, Lippiello L. Differential effects of nicotine and smoke condensate on bone cell metabolic activity. *J Orthop Trauma*. 2005;19:17–22.
33. Hak DJ, Lee SS, Goulet JA. Success of exchange reamed intramedullary nailing for femoral shaft nonunion or delayed union. *J Orthop Trauma*. 2000;14:178–182.
34. Adams CI, Keating JF, Court-Brown CM. Cigarette smoking and open tibial fractures. *Injury*. 2001;32:61–65.
35. Chakkalakal DA. Alcohol-induced bone loss and deficient bone repair. *Alcohol Clin Exp Res*. 2005;29:2077–2090.
36. Chakkalakal DA, Novak JR, Fritz ED, et al. Inhibition of bone repair in a rat model for chronic and excessive alcohol consumption. *Alcohol*. 2005;36:201–214.
37. Leonelli SM, Goldberg BA, Safanda J, et al. Effects of a cyclooxygenase-2 inhibitor (rofecoxib) on bone healing. *Am J Orthop*. 2006;35:79–84.
38. Bergenstock M, Min W, Simon AM, et al. A comparison between the effects of acetaminophen and celecoxib on bone fracture healing in rats. *J Orthop Trauma*. 2005;19:717–723.
39. Gerstenfeld LC, Einhorn TA. Developmental aspects of fracture healing and the use of pharmacological agents to alter healing. *J Musculoskelet Neuronal Interact*. 2003;3:297–303.
40. Koester MC, Spindler KP. Pharmacologic agents in fracture healing. *Clin Sports Med*. 2006;25:63–73.

© 2007 Lippincott Williams & Wilkins

41. Giannoudis PV, MacDonald DA, Matthews SJ, et al. Nonunion of the femoral diaphysis. The influence of reaming and non-steroidal anti-inflammatory drugs. *J Bone Joint Surg Br*. 2000;82:655–658.
42. Stanley HL, Schmitt BP, Poses RM, et al. Does hypogonadism contribute to the occurrence of a minimal trauma hip fracture in elderly men? *J Am Geriatr Soc*. 1991;39:766–771.
43. WHO Study Group on assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group (Technical Report Series, No. 843). Geneva: World Health Organization; 1994:5–6.
44. Wüster C, Abs R, Bengtsson BA, et al. The influence of growth hormone deficiency, growth hormone replacement therapy, and other aspects of hypopituitarism on fracture rate and bone mineral density. *J Bone Miner Res*. 2001;16:398–405.
45. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc*. 2006;81:353–373.

© 2007 Lippincott Williams & Wilkins