

# A Case Report of a 53-Year-Old Female with Rheumatoid Arthritis and Osteoporosis: Focus on Lab Testing and CAM Therapies

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## Abstract

A 53-year-old female presented with rheumatoid arthritis and osteoporosis. Additional conditions and symptoms included Raynaud syndrome, fatigue, irritable bowel syndrome-associated constipation (IBS-C), gastroesophageal reflux (GERD), menopausal symptoms, chronic urinary tract and upper respiratory infections, and weight gain. She was taking Arthrotec 75<sup>®</sup> (a combination of diclofenac and misoprostol – for pain and inflammation), Fosamax Plus D<sup>®</sup> (alendronate with vitamin D3 – recently prescribed because of low bone density), and Catapres<sup>®</sup> (clonidine – for menopausal symptoms). Against the advice of her rheumatologist, she had recently discontinued taking Plaquenil<sup>®</sup> (hydroxychloroquine), methotrexate, and prednisone, due to significant side effects. Lab tests to identify underlying imbalances and to direct treatment were ordered. Treatment included dietary, nutritional, hormonal, and mind/body support. After one year of therapy, the patient experienced improvement with all of her presenting conditions and symptoms, which enabled her to discontinue several medications. She became versed in identifying and avoiding the environmental triggers of her disease, including foods (dairy, wheat, eggs, and soy), molds, and emotional stress. Antinuclear antibodies were normalized. She experienced a 7.5-percent improvement in left trochanteric bone density – comparable to bisphosphonate therapy. Mild improvements were also noted in the spine and bilateral femoral neck.

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## Patient Medical History and Initial Visit Findings

NV was 53 years old when she presented with a four-year diagnosis of inflammatory arthritis (IA), which had been made by her rheumatologist. She complained of nearly constant swelling, stiffness, and pain, with occasional numbness and tingling in her hands, wrists, and elbows. At the visit, she reported her pain using a visual analog scale (VAS)

as 8/10 (0 = no pain; 10 = greatest pain) and stated that the morning pain was frequently unbearable, rating it as 9/10-10/10. The pain did not respond well to medication and lasted most of the morning. She had been using diclofenac 75 mg and misoprostol 200 mcg, twice a day for pain for about one year, with minimal relief. Because of the swelling in her fingers, she had been unable to wear her wedding ring for approximately one year. Although she thought she noted a worsening of IA symptoms when she ate dairy products, she continued to consume them.

NV recalled the onset of her arthritic symptoms, about 6.5 years earlier, coincided with the development of mold, which had been found after flooding in her basement. NV did not know what type of mold it was. She and her husband moved from the home two months after the start of her symptoms, and she experienced a full remission immediately after the move. She did not receive medical attention for her complaints at that time. Two years later, after the loss of a close aunt, NV experienced a return of all her arthritic symptoms. She was referred to a rheumatologist who, according to NV, diagnosed her with inflammatory arthritis and prescribed hydroxychloroquine, methotrexate, and prednisone. She did not recall the dosages of the medications. While they did help her arthritis, she was unable to tolerate the side effects of the medications (reflux, photosensitivity, and alopecia). She discontinued the medications against the advice of her rheumatologist and refused new medications. NV was also taking Arthrotec 75<sup>®</sup> (combination of the non-steroidal anti-inflammatory drug [NSAID] diclofenac with the synthetic prostaglandin misoprostol added to prevent NSAID-induced gastric ulcers), alendronate with D3 (Fosamax Plus D<sup>®</sup> – prescribed

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because of low bone density), and clonidine (Catapres® – for menopausal symptoms).

NV reported that laboratory results within the past six months showed a pronounced elevation of antinuclear antibodies (ANA) and erythrocyte sedimentation rate (ESR); rheumatoid factor (RF) was negative. She reported that her ANA had been consistently positive since she was first tested by the rheumatologist, about four and a half years earlier.

NV also reported severe fatigue and rated it at 9/10, (1 = no fatigue, 10 = severe fatigue), with the afternoons being the most difficult time of day. She awoke feeling tired and unrefreshed, a situation that she attributed to IA and insomnia secondary to hot flashes. Although NV took clonidine (0.2 mg qhs) for menopausal hot flashes at night, it was only mildly helpful.

Patient-reported medical history included chronic urinary tract infections (UTIs), Raynaud syndrome in both hands and occasionally in the feet upon exposure to cold temperatures, a recent diagnosis of osteoporosis, irritable bowel syndrome with severe constipation (IBS-C; 1-2 bowel movements per week), and gastroesophageal reflux disease (GERD). She had gained 30 pounds over the past four years. She had undergone a radical hysterectomy (uterus, ovaries, fallopian tubes, and cervix) due to severe uterine fibroids when she was 32 years old, at which time the hot flashes and

insomnia developed. NV had taken multiple antibiotics over the years for UTIs and upper respiratory tract infections.

NV’s past family and social history included stressors from caring for ailing parents. Her father, age 86, had type 2 diabetes and had experienced two myocardial infarctions. Her mother had died at age 85. Prior to her death, she had undergone three hip replacements to treat severe osteoporosis. She had had a complete thyroidectomy, but was unable to recall the medical reasons why this procedure was done.

NV had retired from nursing after 20 years. Her primary form of exercise involved training dogs. She was the primary caregiver of her father, who was living in her home. While they were very close, she found the caregiving highly stressful. She had a strong marriage and a number of good, supportive friends.

NV’s diet and nutritional history also included multiple stressors. She skipped breakfast, drank black tea daily, and frequently had double cheeseburgers from a fast food restaurant for lunch. Dinner was frequently eaten out, and most recently had included Mexican chicken with rice, chips, and salsa. NV craved salty and sweet foods and drank diet soda daily.

At first visit, NV was 5’6” tall and weighed 170 lbs. Her body mass index was 27.4. There was marked swelling, warmth, and reported tenderness

**Table 1. Results of ANA, hs-CRP, RF, and Thyroid Testing**

Test	Initial	6-month Follow-up	1-year Follow-up	Reference Range
Antinuclear Antibodies (ANA)	1:2860 (H)	1:2560 (H)	<1:40	<1:40
hs-CRP	5 (H)	5.6 (H)	N/A	< 1 mg/dL
Rheumatoid Factor	N/A	24 (H)	< 14	<14 IU/mL
Thyroid Stimulating Hormone	1.48	3.45	0.85	0.40-5.50 IU/mL
Free T3	2.5	2.1	2.7	2.0-4.4 pg/mL

H denotes value considered to be high for the indicated test. N/A indicates test not done.

in her metacarpal phalangeal joints and her proximal interphalangeal joints bilaterally with passive and active range of motion. There was limited digital flexion bilaterally. Her capillary refill rate was normal, with no evidence of digital cyanosis or ulceration. Her wrists and elbows were warm, with mild edema and tenderness to palpation; active and passive range of motion were within normal limits, but painful with passive and active range of motion. Her neck was supple, with no masses. Her thyroid was of normal size, smooth without masses, and not tender. Her heart demonstrated a regular rate and rhythm, with no murmurs or rubs noted; her lungs were clear to auscultation bilaterally. Blood pressure was 112/72 mm HG.

### Laboratory Tests and Findings

The list below summarizes the lab tests ordered for this patient and the clinical rationale for selecting these tests.

Complete blood count (CBC), comprehensive metabolic panel (CMP) with lipids, and thyroid panel (Table 1): Obtained to rule-out infection, anemia, and thyroid disease, and to check kidney and liver function.

Antinuclear antibodies (Table 1): ANAs are frequently elevated in inflammatory arthritis and indicate level of disease activity. They are useful for tracking treatment efficacy.

High-sensitivity C-reactive protein (hs-CRP) (Table 1): hsCRP is a standard acute phase reactant protein used to monitor general inflammation.

Rheumatoid factor: RF is an autoantibody, most relevant to rheumatoid arthritis.

Deoxypyridinoline (DPD) (Table 2): A marker of bone resorption tracked by a urine test to help monitor treatment efficacy for osteoporosis. Variability in serial testing is reduced by using the same lab and by testing at the same time of day.

Vitamin D (Table 2): Low levels are associated with increased inflammation and with increased incidence of numerous diseases.<sup>1</sup>

Food-specific IgG4 antibodies (Table 3): Food reactions have been associated with inflammatory arthritis.<sup>2,3</sup> Multiple IgG4 reactions suggest intestinal hyperpermeability, also a factor in inflammatory arthritis. Removing offending foods may reduce pain and inflammation.

Multiprofile panel (amino acids) and essential elements (Table 4), essential fatty acids (Table 5), organic acids (Table 6), and oxidative stress markers: Obtained to detect nutrient deficiencies or imbalances that might be contributing to inflammation (only significant findings are discussed below).

Stool test (assessment of GI inflammation, microbiota, and pancreatic exocrine function) (Table 7): GI imbalances have been identified as involved in the pathogenesis of rheumatoid arthritis.<sup>4</sup>

Initial and subsequent findings on all lab tests are noted in the tables below. (Note: Complete blood count, comprehensive metabolic profile [also known as a complete blood chemistry panel], and lipid testing were within normal lab reference ranges and are not presented in Table 1.)

Bone densitometry obtained by DEXA scan (DXA) within the previous two weeks prior to the initial visit demonstrated left trochanter osteoporosis,

**Table 2. Results of Bone DPD, DXA, and Vitamin D Testing**

Test	Initial	6-month Follow-up	1-year Follow-up	Reference Range
Deoxypyridinoline (DPD)	4.9	7.7 (H)	5.7	≤ 7.4 nm/millimole creatinine
DXA T score (left trochanter)	-2.7	N/A	-2.5	+1 to -1 normal; -1 to -2.5 osteopenia; < -2.5 osteoporosis
25-Hydroxyvitamin D	27	N/A	N/A	10-64 ng/mL

H denotes value considered to be high for the indicated test. N/A indicates test not done.

with a T-score of -2.7 (a score below -2.5 is indicative of osteoporosis by World Health Organization [WHO] standards) (Table 2). As a result, she had been started on alendronate.

### Initial Diagnosis

Although NV stated she had previously been diagnosed by her rheumatologist as having inflammatory arthritis, her clinical presentation strongly suggested rheumatoid arthritis (RA) as defined by 2010 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) collaborative initiative classification criteria.<sup>5</sup> These findings include involvement of greater than 10 joints (including at least one small joint), abnormal CRP, and greater than six weeks symptom duration.

NV's presentation also fit the older American Rheumatism Association diagnosis of RA, including morning stiffness lasting at least one hour, arthritis of three or more joint areas, hand joint involvement, and symmetrical distribution.

Anti-cyclic citrullinated peptide antibody (anti-CCP), a relatively new blood test used to help confirm a diagnosis of rheumatoid arthritis, was not conducted because, at the time patient first presented (2006), anti-CCP was not widely available. In 2010, anti-CCP testing was made a substantial part of the 2010 ACR-EULAR classification criteria for RA.<sup>5</sup>

Other potential issues revealed during initial testing or self-reported by the patient during intake included: osteoporosis (verified by DXA scan), Raynaud syndrome (patient self-reported), fatigue (patient self-reported), IBS-C (patient self-reported), GERD (patient self-reported), menopausal symptoms (patient self-reported), chronic UTIs (patient self-reported), several food sensitivities (verified with food-specific IgG4 antibodies) (Table 3), inflammation (verified with

hs-CRP), oxidative stress (verified with testing for oxidative stress markers), and dysbiosis (verified with stool testing).

### Intervention

The initial focus was on reducing gastrointestinal and systemic inflammation and treating nutrient deficiencies identified via laboratory tests (Tables 4-6), and clinical assessment specific to the patient. This was achieved by prescribing a gastrointestinal anti-inflammatory medicinal food (which included antioxidants, vitamins and minerals, hypoallergenic rice protein, glutamine, anti-inflammatory botanicals and active constituents), dietary supplements, and intravenous (IV) nutrients. Omega-3 fatty acids (EPA and DHA) were given to correct insufficiencies identified on plasma fatty acid testing. Vitamin D was supplemented to increase vitamin D levels to a more desirable range. A proteolytic enzyme compound was given to help reduce the inflammatory proteins associated with RA and because evidence suggests proteolytic enzymes can reduce inflammatory mediators in rheumatic diseases.<sup>6</sup> CoQ10 and L-carnitine were supplemented to correct insufficiencies detected in lab testing. An anti-inflammatory oligoantigenic diet based on food-specific IgG4 antibody findings (Table 3) was prescribed. This diet also emphasized increasing monounsaturated fatty acid intake. Because stool testing (Table 7) identified dysbiosis, a botanical antimicrobial formula was given to reduce the number of opportunistic bacteria. A digestive enzyme formula was used to improve digestion of food and assimilation of nutrients. Selected nutrients – minerals, amino acids, B vitamins, vitamin C, and glutathione – were delivered intravenously (IV) to achieve rapid repletion. Nutrient IVs are suggested to be effective at improving fatigue, which was a chief complaint of the patient.<sup>7</sup>

Protocol for supplementation is listed below; all supplementation was oral unless otherwise indicated.

- ◆ Anti-inflammatory medicinal food, 2 scoops every morning
- ◆ EPA/DHA concentrate 3,000 mg, 1 tsp/day
- ◆ Vitamin D 2,000 IU, 1 drop/day
- ◆ Proteolytic enzymes, 3-6 tablets three times daily between meals as needed for pain (includes pancreatin, bromelain, papain, trypsin, chymotrypsin, lipase, rutin)
- ◆ CoQ10 100 mg, 1 tab/day
- ◆ L-Carnitine 500 mg, 2 tabs/day

**Table 3. Results of Initial Food-Specific IgG Antibody Testing**

Reaction	Food
Severe	Eggs, Casein, Milk, Rye
Moderate	Wheat, Malt
Mild	Yeast, Chocolate, Broccoli

- ◆ Antimicrobial botanicals, 3 capsules twice daily (includes wormwood, oleuropein, berberine, grapefruit seed extract, thyme, uva ursi extract, black walnut hull extract, oregano extract)
- ◆ Plant-based digestive enzymes, 2 tabs with meals
- ◆ IV-nutrients therapy once weekly for two months (copper, magnesium, zinc, calcium, selenium, manganese, chromium, essential amino acids, B complex, glutathione, vitamin C)
- ◆ Diet: eliminate all moderate to severe food sensitivities identified by food-specific IgG antibody testing; follow anti-inflammatory diet; add green tea, nuts, seeds (raw, organic), olive oil, canola oil, fresh fatty fish (including wild-caught salmon and sardines); eat organic foods when possible; avoid processed foods. (Table 3)

**Follow-up Visits**  
**Two-Month Follow-Up**

After initiating the protocol, NV noted an improvement in energy and pain within a week. Her fatigue, which had been a 9/10, was now a 2/10 (1 = no fatigue, 10 = severe fatigue). The pain level in her hands and elbows based on VAS, previously reported at 8/10, was now at 4/10. As a result, she no longer required Arthrotec 75® for pain and inflammation. The swelling of hands and elbows also diminished enough that she could again wear her wedding ring. She reported increased episodes of Raynaud syndrome, however, with the onset of winter weather.

NV reported the dietary changes were difficult, but that she noticed the benefit of staying off the antigenic foods identified in the food-specific IgG4 antibody testing (Table 3); when she did avoid the offending foods, her energy, pain, and weight all improved. She reported temporary pain and swelling in her hands after eating take-out Chinese food, although the symptoms abated after one day.

NV noted a significant reduction in hot flashes with a corresponding improvement in sleep. Because of improvement in hot flashes, she had stopped taking clonidine. Her constipation had improved and she was having a normal bowel movement daily.

Three weeks prior to this visit, NV had started to experience temporomandibular pain, which she believed had been a result of the alendronate. As a result, she had decided to stop taking this osteoporosis medication. The jaw pain resolved with cessation of the medication. Because NV had

**Table 4. Results of Amino Acid and Essential Elements Testing**

Test	Patient Value	Lab Reference Range
<i>Amino Acid</i>		
Methionine	12 (LN)	14-30 (µmol/L)
Histidine	43 (LN)	41-82 (µmol/L)
Threonine	70 (LN)	63-181 (µmol/L)
Arginine	40 (LN)	37-114 (µmol/L)
Glutamine	387 (LN)	338-630 (µmol/L)
Tyrosine	34 (LN)	29-80 (µmol/L)
Tryptophan	35	30-67 (µmol/L)
<i>Essential Elements</i>		
Potassium	2,800 (LN)	2,426-4,472 (ppm packed cells)
Magnesium	38 (LN)	36-70 (ppm packed cells)
Zinc	8.8 (LN)	7.5-16.3 (ppm packed cells)
Copper	600 (LN)	535-962 (ppm packed cells)
Chromium	4.0 (LN)	3.6-10.1 (ppm packed cells)
Manganese	45 (LN)	44-69 (ppm packed cells)
Selenium	0.15 (LN)	0.14-0.47 (ppm packed cells)

LN denotes value considered to be in the low-normal range for the indicated test.

discontinued alendronate, calcitonin (200 IU, 1 spray intranasally daily, alternating nostrils) was added, and she was asked to start gentle weight-bearing exercises as interventions for osteoporosis.

Although reflux was generally improved, NV had felt that the GI anti-inflammatory medicinal food was causing her significant reflux, so she had stopped taking it. Because she felt it was causing reflux and had discontinued it, the inflammatory medicinal food was dropped from her treatment plan.

The original plan for nutrient IV therapy had been completed by this visit, so it was discontinued. Except for the changes noted, NV was advised to continue with the original supplementation and diet protocol.

Significant physical exam findings at this visit included reduced swelling in her hands and elbows, with reduced pain by VAS (now 4/10 instead of 8/10 at the first visit) during active and passive range of motion. The temporomandibular joints were non-tender to palpation, muscles were 5/5, range of motion of all joints was within normal limits, and there was full activity with no complaints. Systolic blood pressure had dropped from 112 mm Hg at initial visit to 102 mmHg; diastolic

blood pressure remained the same (72 mmHg). Weight had decreased from 170 lbs at initial visit to 156 lbs (a 14-pound weight loss); as a result, BMI had decreased to 25.2 from 27.4.

A urinary bone collagen peptide (DPD) follow-up test was also ordered (to be completed prior to the next visit) (Table 2) to get a baseline for bone resorption activity with the cessation of the alendronate.

### Five-Month Follow-Up

Because of several factors, one of which was grief, NV had been inconsistent with supplements and dietary changes between her two-month and five-month follow-up visits. During this three-month interval, her hands and elbows had become painful and swollen and, as a result, she was once again unable to wear her wedding ring. NV also experienced a new symptom of joint pain in her left shoulder, which improved with motion. She did not recollect overusing or injuring the area. Her constipation had returned and her sleep, especially her ability to fall asleep, had been poor. Because of the pain and difficulty falling asleep, NV had been taking Excedrin PM®. Her energy level was once again very low.

One month prior to this visit, NV's father died suddenly from a massive myocardial infarction. As previously mentioned, he had been living in her home and she was his primary caregiver. She was in very deep grief at the time of this office visit. Patient felt that the loss of her father had contributed to the flare-up in her RA symptoms. Soon after his death, NV had developed a severe UTI followed by pneumonia and was treated with antibiotics for both by her primary care physician.

Significant physical exam findings: Ears, eyes, nose and throat (EENT) and lung exams were unremarkable. Hands and elbows were swollen, tender to palpation, and slightly warm. Digital flexion was limited and painful. Left shoulder active range of motion was intact, but painful; although there was no swelling or warmth, the area was tender to palpation. She reported

**Table 5. Results of Plasma Fatty Acid Testing**

Fatty Acid	Patient Value	Lab Reference Range (µM)
<i>Polyunsaturated Omega-3 Fatty Acids</i>		
Alpha Linolenic	2 (L)	13-80
Eicosapentaenoic	7 (LN)	5-210
Docosapentaenoic	13 (LN)	11-50
Docosahexaenoic	25 (L)	31-213
Arachidonic	448	158-521
AA/EPA	64 (H)	1-57
<i>Monounsaturated Fatty Acids</i>		
Myristoleic	<0.8 (L)	0.8-9.7
Palmitoleic	40	30-256
Vaccenic	37 (L)	40-122
Oleic	541 (LN)	466-1,470
11-Eicosenoic	4.7	3.7-18.1
Nervonic	<1.1	<=2.4

L denotes value considered to be lower than the normal reference range for the indicated test. LN denotes value considered to be in the low-normal range for the indicated test. H denotes value considered to be high for the indicated test.

the pain in her fingers was once again 8/10 on the VAS.

DPD had increased significantly since the first visit and was now elevated (Table 2), demonstrating increased bone turnover. This finding was not surprising, because NV was taking alendronate when the first DPD test had been conducted and had discontinued this osteoporosis medication after developing jaw pain prior to the two-month follow-up visit when DPD had been reassessed. Although NV had been encouraged to participate in weight-bearing activity at the two-month visit, she had not followed through on this recommendation.

Since NV had been inconsistent with the nutritional and dietary interventions, rather than make significant changes in the protocol, she was once again prescribed the previously described supplements and reminded to avoid the antigenic foods identified on food-specific IgG antibody testing. Because results of DPD testing revealed an increase in bone turnover, and because NV had not initiated weight-bearing exercises on her own, she was once again encouraged to engage in this type of exercise (to be prescribed by an athletic trainer). In addition to the calcitonin spray, a general bone health nutrient supplement was introduced for the osteoporosis. Other new additions to the protocol included melatonin as needed at bedtime for insomnia, and homeopathic *Ignatia amara* as needed for grief and emotionally-mediated symptoms associated with menopause.<sup>8</sup> Because NV's emotional response appeared to have an immediate and marked impact on her physical condition, it was suggested that she consult a specialist in mind/body medicine. The added recommendations are listed below.

- ◆ Bone health formula, 4 caps twice daily (calcium, magnesium, vitamin D, vitamin K2, strontium, boron, silicon, phosphorus, essential trace minerals, B vitamins, and vitamin C)
- ◆ Melatonin 3 mg before bed, as needed for insomnia

**Table 6. Results of Urinary Organic Acid Testing**

Organic Acid	Initial	6-month Follow-up	Lab Reference Range
Quinolate	5.0 (HN)	2.8	<= 5.8*
5-Hydroxyindoleacetate	2.1	2.8	1.6 - 9.8*
8-Hydroxy-2-deoxyguanosine	6.3 (HN)	10.3 (H)	<= 7.6**
Sulfate	941 (LN)	1,230	690 - 2,988*
Pyruvate	6.2 (HN)	6.2 (HN)	<= 6.4*
alpha-Ketoglutarate	23.0 (HN)	N/A	<= 35.0*
Succinate	15.1 (HN)	15.1 (HN)	<= 20.9*
Fumarate	1.52 (H)	1.32 (HN)	<= 1.35*
Adipate	12.0 (H)	N/A	<= 8.3*
Malate	N/A	2.1 (HN)	<= 3.1*
Hydroxymethylglutarate	N/A	5.7 (H)	<= 5.1*

L denotes value considered to be lower than the normal reference range for the indicated test. LN denotes value considered to be in the low-normal range for the indicated test. H denotes value considered to be high for the indicated test. N/A indicates test not done. HN denotes value considered to be in the high-normal range for the indicated test. \*Units in µg/mg creatinine. \*\*Units in ng/mg creatinine

- ◆ Homeopathic remedy *Ignatia amara* 30c, 3 pellets under tongue away from food, as needed
- ◆ Counselor referral for mind/body therapy

Laboratory tests ordered for completion prior to next visit were: ANA, hs-CRP, RF, CBC, CMP with fasting lipids and insulin, thyroid stimulating hormone (TSH), food-specific IgG4 antibodies, and organic acids.

### Phone Call Follow-up

NV experienced some limited relief within the first few days of following the new treatment plan; however, after 10 days (five months and 10 days after beginning treatment) she reported severe exacerbation of her arthritic symptoms. She suspected the probable cause was the addition of the bone formula, which she had noticed contained

Table 7. Results of Stool Testing

Test	Out of Normal Findings
Opportunist Aerobic Bacteria	Bacillus sp. were rare; Enterococcus sp. were abundant
Yeast	+1 Candida sp.
Secretory IgA	130 (L) (reference range is 400-800 mg% dry weight)
Chymotrypsin	3 (L) (reference range is 4-9 U/10g)

L denotes value considered to be lower than the normal reference range for the indicated test.

sodium caseinate (as a preservative) – one of the compounds identified as causing a severe reaction in the food-specific IgG antibody testing. A supplement elimination and reintroduction trial confirmed her suspicion: the supplement was discontinued and her symptoms abated within a day; when the supplement was reintroduced, symptoms again flared. As a result, this bone formula was discontinued and she was started on a casein-free bone formula, which she subsequently tolerated. She also noticed soy sauce caused a similar exacerbation of arthritic symptoms. She was encouraged to continue to avoid foods and supplements that contain any of these offending compounds and congratulated for becoming versed in identifying these triggers. The results of this experience confirmed to her how important it was to avoid the milk protein casein (which was a significant trigger for her) and confirmed that even very small exposures to the compounds she reacted to could be problematic.

### Six-Month Follow-up

At her six-month follow-up visit, NV reported a general improvement in her arthritic and Raynaud symptoms, although fatigue and constipation continued. She noted that stress and dietary transgressions caused painful flare-ups, particularly in her hands and elbow and reported that when she took the prescribed homeopathic remedy, *Ignatia amara*, she experienced hours-long relief from the arthritic pain. She also reported that the melatonin helped with sleep.

NV continued to grieve the loss of her father. She stated that she was interested in the previously recommended referral to a mind/body therapist,

but had not yet pursued it.

The laboratory results ordered after the last visit reflected a decline in NV's health and an increase in disease activity. ANA and hs-CRP remained elevated (Table 1); RF was modestly high (positive) for the first time (Table 1), TSH was above the optimal range of 2.5 (Table 1).<sup>9</sup> Free T3 (fT3) remained low normal. These findings reflect a flare-up of RA activity. The overall number of food sensitivities had decreased: IgG4 antibodies to eggs, casein, and cow's milk continued to be severe.

Urinary organic acid findings had been retested prior to this visit. There had been a significant increase in 8-hydroxy-2-deoxyguanosine (8-OHdG), which indicated aggressive oxidative stress and was consistent with her increased disease activity.

Quinolate had gone from high normal to normal, and 5-hydroxyindoleacetate remained within the normal range, suggesting a reduction in inflammation and greater availability of tryptophan for serotonin production. Sulfate, which had previously been low normal, and adipate, which had been high normal, were within the normal range. Citric acid cycle intermediates – fumarate, malate, and succinate – remained elevated, suggesting a continued need for CoQ10 (Table 6). Pertinent negative laboratory results included CBC and CMP with lipids and insulin, which were within normal limits.

The previously prescribed supplements and dietary protocol were continued and importance of adherence was emphasized to NV because of the considerable flare-up and out-of-range laboratory findings. Because of the flare-up and worsened 8-OHdG, IV-nutrient therapy was reintroduced to enhance antioxidant and nutrient status. Probiotics, fiber, and magnesium were initiated for constipation and to improve GI function. Low-dose Armour® thyroid was introduced for the sub-optimal TSH and because clinical symptoms were consistent with sub-clinical hypothyroidism. Doses and schedules for these changes are listed below:

- ◆ IV-nutrient therapy once a week for two months (copper, magnesium, zinc, calcium, selenium, manganese, chromium, essential amino acids, B complex, glutathione, vitamin C)
- ◆ Probiotic blend – 100 billion CFUs, ¼ tsp daily
- ◆ Blue Herron GI botanical, probiotic, and fiber support, 1 scoop daily with water
- ◆ Magnesium citrate powder (600 mg elemental magnesium), 1 tsp daily



- ◆ Armour thyroid 30 mg, 1 tab/day taken away from food and other supplements
- ◆ Diet review: Continue all prior recommendations; handout and web resources on hidden sources of food antigens given to patient

Laboratory tests ordered (to be completed in 4-6 months) included DXA scan, X-ray series ordered for wrists and hands, ANA, RF, CBC, CMP with lipids and fasting insulin, thyroid panel, and DPD.

### One-Year Follow-up Visit

At her one-year follow-up visit, NV's symptoms were much improved and she had lost 30 lbs. There had been improvement in multiple lab measures. ANA and RF were undetectable, suggesting that her arthritis was in remission. hs-CRP was < 1 mg/dL (it had been 5.6 mg dL when last tested), which is consistent with reduced inflammation. TSH, and free triiodothyronine (fT3) levels were all within normal ranges (Table 1), indicating a positive response to thyroid hormone replacement therapy.

DPD levels had returned to within normal limits and there had been a 7.5-percent improvement in bone density (left trochanter T score -2.7 to -2.5, with milder improvement shown in all but one measurement) assessed by DXA (Table 2). The initial DPD testing was begun just after the initiation of alendronate, while the five-month follow-up was after cessation of alendronate. Final DPD levels were assessed after seven months of an integrative intervention program of calcitonin, bone support nutrients, general nutrients, and dietary changes. Despite encouragement to begin weight-bearing exercise, NV reported she had not yet followed through on this recommendation. The improvement from baseline in bone mineral density (BMD) as assessed by DXA (7.5 percent) is comparable to what might be expected after a 3-4 year course of alendronate therapy.<sup>10,11</sup>

At this visit NV spoke repeatedly about her gratitude for "having her life back." All of her symptoms were resolved or improved. Her fatigue rating was 1/10, demonstrating a normal energy level. Her arthritic pain was 1-2/10 on VAS, joint swelling was decreased, and she was able to wear her wedding ring most of the time. She had no reflux and had a complete bowel movement at least once per day. Insomnia and hot flashes were resolved. She was pleased to have lost 30 pounds since her initial visit (weight reduced from 170 to 140 lbs), which she attributed to eating the metabolically correct foods rather than calorie restriction.

She had visited a therapist who specialized in mind/body medicine, and connected two severe arthritic flare-ups to the loss of a relative (a close aunt) and then her father. She had not previously realized the extent of the impact of these events on her medical condition.

During this year NV had become aware of her disease triggers, including foods (eggs, dairy, gluten, and soy), emotions (particularly grief and stress), and physical demands (including overwork). Because NV recognized many of her arthritis triggers, she felt in control of, rather than a victim of, her RA.

At the end of this visit, NV was advised to continue her treatment plan with no changes.

### Discussion

One-in-five adult Americans (46 million) have been diagnosed with some form of arthritis.<sup>12</sup> The most common is osteoarthritis, followed by RA and systemic lupus erythematosus (SLE). The death rate from arthritis and other rheumatic conditions (AORC) rose almost 70 percent between 1979 and 1998, with significant contribution from autoimmune arthropathies, including RA and SLE. The total cost attributed to AORC was \$128 billion in 2003, up almost 48 percent since 1997.<sup>12</sup> RA, in particular, can be a debilitating condition associated with potentially devastating progression and a high personal and societal cost. The female-to-male ratio of RA is 3:1, and associated co-morbidities include cardiovascular disease, cancer, infection, and osteoporosis. Although the conventional medications have improved the quality of life in some RA patients, they are associated with a high risk of complications that include infection, cancer, liver and renal toxicity, and bone marrow suppression. Indeed, while the morbidity of RA may be lowered by the new class of biological medications, mortality may be higher.<sup>13,14</sup>

The pathophysiology of RA has been suggested to involve an initiation phase of nonspecific inflammation caused by a variety of stimuli, followed first by an amplification phase caused by T-helper 1 (Th1) cell activation, and then by a chronic inflammatory stage with active tissue injury.<sup>13,15</sup> Recent research suggests RA shares a trio of key pathogenic mechanisms with celiac disease and other autoimmune conditions. The trio includes a genetic predisposition, exposure to environmental antigen(s), and increased intestinal permeability (IP). IP is caused in part by the protein zonulin, production of which can be induced by gluten.<sup>4</sup> RA candidate genes include

HLA DRB1, PTPN22, CTLA4, and PADI4.<sup>16</sup> Microbes implicated in RA include *Proteus mirabilis*, Chlamydia,<sup>17,18</sup> and parvovirus.<sup>19</sup>

In this case, NV's family medical history and her own complaints (RA, IBS, Raynaud syndrome, UTI, GERD, osteoporosis) all share a strong inflammatory or microbial component. Her mother reportedly had thyroid disease, which is most commonly autoimmune, although the clinical specifics were unknown. Her mother also had had three hip replacements, suggesting degenerative joint disease, while her father had heart disease. RA patients have increased risk of both cardiovascular disease and osteoporosis,<sup>20</sup> inflammatory-mediated osteoclastic activity in RA induces osteoporosis,<sup>21</sup> and autoimmune thyroiditis and Raynaud syndrome have been associated with RA, and may all involve eicosanoid dysregulation.<sup>22-26</sup>

NV experienced a number of environmental exposures that likely contributed to RA pathogenesis. Most prominent was the patient-reported mold exposure and high emotional stress, both potential RA triggers.<sup>27,28</sup> As mentioned above, her chronic UTIs may have been caused by *Proteus mirabilis*, a microbe implicated in RA. Other possible triggers include foods, smoking,<sup>29</sup> toxins,<sup>30</sup> obesity,<sup>31</sup> and infection.<sup>32</sup> Long-standing gastrointestinal inflammation is often antecedent to RA. NV had a history of chronic antibiotic use, which is associated with altered intestinal flora<sup>33</sup> and thought to be an etiological factor in inflammatory arthritis.<sup>34</sup> Food sensitivities, of which NV had many, are associated with IBS<sup>35</sup> and intestinal hyperpermeability. Both have been proposed as factors contributing to the pathogenesis of RA.<sup>4,36,37</sup>

Laboratory evaluation in this case was broad, reflecting the molecular complexity of the conditions and the web of metabolic interactions. In addition to standard autoimmune biomarkers, investigation was made into gastrointestinal function, microbiota imbalances, food-specific IgG4 antibodies, organic and fatty acids, and micronutrient status.

The initial battery of testing (Table 1) demonstrated that ANA levels were elevated, which was to be expected given her reported history of long-standing ANA elevation and discontinuation of hydroxychloroquine, methotrexate, and prednisone, against the advice of her rheumatologist. ANA levels suggest she was in an active disease phase at this initial visit. Elevated ANAs indicate that damage was occurring in the joint space, an indication reflected clinically in the pain and swelling of her hands and elbows. Initial testing

also revealed a suboptimal vitamin D level (Table 2), insufficiency of which is associated with inflammatory arthropathies;<sup>38,39</sup> she was started on vitamin D supplements to correct this insufficiency. It has been suggested that vitamin D levels in complex disease be maintained at 55-70 ng/mL.<sup>39</sup> The level of DPD, a biomarker demonstrating bone resorption, is correlated with increased bone turnover in RA.<sup>40,41</sup> In this case, however, it appeared that NV's treatment with alendronate was sufficient to inhibit excess turnover, since her DPD level was within normal limits on initial testing. TSH and fT3 levels were within normal limits at the first visit. Because of the known association of thyroid disorders and RA, regular assessment of thyroid function was indicated.<sup>22,42</sup> As discussed, NV had a number of food-specific IgG4 antibodies (Table 3), which have been identified in RA and which suggest intestinal hyperpermeability.<sup>4,36,37</sup> Given the association with celiac disease,<sup>4,24</sup> a celiac panel would have been a reasonable assessment to consider in this patient, particularly given the severe IgG4 reaction to wheat. Because NV already knew she had a reaction to wheat, but claimed that she could tolerate other gluten containing grains, testing for celiac disease was not conducted.

NV's amino acid panel (Table 4) demonstrated a number of low values that may have had a negative impact on important metabolic activities. Methionine, the only essential sulfur-containing amino acid, was well below normal limits. In one animal study, methionine deficiency limited the production of sulfur-containing compounds including glutathione and sulfate, particularly during high detoxification demand.<sup>43</sup> The impact of low methionine in NV was suggested by the low urinary sulfate and the increased oxidative stress marker, 8-OHdG (Table 6). Taken together, these imbalances suggested insufficient glutathione, possibly due to increased utilization. Glutathione also requires glycine and glutamate, which may be derived from threonine and glutamine, which were also low. Glutamine is a potent anti-inflammatory amino acid that modulates systemic and gastrointestinal cytokines and increases production of glutathione.<sup>44</sup> Tyrosine, in the first quintile, is the precursor to thyroid hormones and catecholamines. Given the importance of these hormones in energy production, tyrosine insufficiency may have been contributing to NV's fatigue. Tryptophan level was also in the first quintile, whereas the tryptophan derivative quinolinate was elevated. Chronic elevation of quinolinate – an interferon-gamma

(INF- $\gamma$ ) -induced CNS inflammatory mediator with significant neurotoxic potential<sup>45</sup> – has been associated with tryptophan and serotonin depletion.<sup>46</sup>

NV's red blood cell essential element levels were uniformly low normal (Table 4). Toxic exposure, malabsorption, maldigestion, or insufficient intake may be causal factors.<sup>47</sup> Inadequate essential element status can have far-reaching effects, compromising optimal physiological function system-wide. Specific to NV, an inverse association between erythrocyte (and plasma) magnesium levels and superoxide dismutase has been found in inflammatory arthritis, increasing oxidative stress.<sup>48</sup>

The pathogenesis of RA is closely associated with the pro-inflammatory eicosanoids derived from arachidonic acid (AA), including prostaglandins, thromboxanes, and leukotrienes.<sup>49,50</sup> High-dose fish oil containing adequate amounts of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has been shown to inhibit AA-derived eicosanoids, thereby diminishing inflammation.<sup>48</sup> AA-derived inflammatory mediators are also implicated in NV's other complaints, including osteoporosis, Raynaud syndrome, and IBS.<sup>23,24,51-53</sup> NV's AA was high relative to the omega-3 fatty acids, particularly EPA (Table 5); the elevated AA/EPA ratio reflects the imbalance between the pro- and anti-inflammatory fatty acids.

Monounsaturated fatty acids (MUFA) were low to low normal (Table 5). Benefits of MUFA intake include improved membrane fluidity, reduced cardiovascular risk and decreased inflammation. The Mediterranean diet, which is rich in MUFAs, was shown to reduce pain, early morning stiffness, and systolic blood pressure in a small pilot study of women with RA.<sup>54</sup> Intake of oleic acid, the main constituent in olive oil, is inversely correlated with the level of CRP.<sup>55</sup>

As mentioned above, quinolinate was elevated in NV (Table 6). Quinolinate is a neuroinflammatory compound, produced in response to the Th1-derived cytokine INF- $\gamma$ , which, in turn, is stimulated by tumor necrosis factor-alpha (TNF- $\alpha$ ). Both of these cytokines are elevated in the synovium of RA patients and participate in the pathogenesis of the disease.<sup>56</sup> Chronic elevation of quinolinate, which antagonizes glutamatergic NMDA receptors in the central nervous system, is considered to be a source of oxidative stress.<sup>45,57</sup> Chronic elevation of quinolinate is also associated with depression, because excessive tryptophan catabolism leads to reduced serotonin availability.<sup>58</sup> This scenario is

suggested in the case of NV, because, in addition to the quinolinate elevation, the serotonin metabolite 5-hydroxyindoleacetate (Table 6) and plasma tryptophan (Table 4) were low. Given the level of inflammatory activity, it is not surprising that the oxidative stress marker, 8-OHdG, was elevated. In RA patients, 8-OHdG has been shown to be correlated with the inflammatory marker CRP.<sup>59</sup> Increased glutathione utilization secondary to oxidative stress may result in depleted sulfate and methionine, as shown in Tables 4 and 6.

Adipate may be produced when there is a compromise in mitochondrial  $\beta$ -oxidation of fatty acids (Table 6). Its elevation may therefore indicate a need for carnitine, which shuttles fatty acids into the mitochondria in the form of carnitine acyl-transferase for the production of metabolic energy. At her initial visit, NV reported a 30-pound weight gain and fatigue, both of which may have been partly due to compromised fatty acid metabolism. Organic acid assessment also revealed an accumulation of citric acid cycle (CAC) intermediates, providing functional evidence for a CoQ10 deficiency. Accumulation of the CAC intermediates, adipate and 8-OHdG, suggests subclinical mitochondriopathy, which is implicated as an underlying factor in most complex, chronic diseases and, in the case of NV, was a possible contributor to her fatigue.

Gastrointestinal bacterial overgrowth was evidenced by the presence of opportunistic organisms in the stool test (Table 7). Low stool secretory IgA suggests either a genetic deficiency or protracted GI inflammation. GI inflammation was also reflected in the numerous food sensitivities (Table 2). Chymotrypsin insufficiency suggests poor pancreatic output, leading to compromised macronutrient digestion.<sup>60</sup> Maldigestion may have contributed to insufficiency in amino acids and essential elements (Table 4).

## Conclusion

In this case, the patient presented with inflammatory arthritis of almost seven years' duration. She described the pain in her hands, wrists, and elbows as frequently unbearable, rating it 8/10 to 10/10 on a VAS. Despite the debilitating pain, she had discontinued three prescribed medications – hydroxychloroquine, methotrexate, and prednisone – against medical advice, because she experienced intolerable side effects, including reflux, alopecia, and severe photosensitivity. Her other complaints included osteoporosis, Raynaud syndrome, fatigue, IBS-C, GERD, menopausal

symptoms, chronic urinary tract and upper respiratory infections, and weight gain.

An initial comprehensive laboratory evaluation identified IgG4 food-specific antibodies, essential fatty acid and amino acid imbalances, nutrient and essential element deficiencies, and dysbiosis, in addition to elevated ANA and hs-CRP.

Clinical history identified the onset of RA as being associated with flooding of her home that may have caused mold exposure. Significant RA flare-ups were associated with the loss of a loved one. Treatment based on laboratory findings included reducing inflammation, eliminating food sensitivities, and restoring nutrient status and GI balance. Emotional support provided by a mind-body therapist was also a significant aspect of treatment. By a combination of lab testing and symptomatic flare-ups, the patient became versed in identifying and minimizing her RA triggers, which included foods, food preservatives, and emotional stress.

After one year of therapy, the patient experienced significant resolution of all subjective symptoms and was able to discontinue her medications. ANA and RF levels had normalized, indicating clinical remission of arthritis. She also experienced improvement in bone density, 30 pounds of weight loss, and improvements in sleep and menopausal symptoms.

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