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# Lower Resting Metabolic Rate and Basal Body Temperature of Fibromyalgia Patients Compared to Matched Healthy Controls

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**ABSTRACT**. ***Introduction.*** All symptoms and most objectively verified abnormalities of fibromyalgia are common among patients with hypothyroidism or partial peripheral thyroid hormone resistance. In treatment trials, thyroid hormone therapy has reduced or eliminated fibromyalgia symptoms, and a long-term follow-up study showed that improvement with thyroid hormone therapy lasted 1-to-5 years. In a previous study by the authors, solicited female fibromyalgia patients had significantly lower resting metabolic rates and basal body temperatures than matched healthy controls. In this study, the resting metabolic rates and body temperatures of fibromyalgia patients previously evaluated at a specialty metabolic clinic were compared with healthy controls to whom they were matched.

***Methods***. Fifteen female fibromyalgia patients and 15 healthy females served as study subjects. Patients were clinical cases selected to match controls by sex, age, weight, and activity level. Resting metabolic rate (RMR) was measured by indirect calorimetry (MedGem®), basal body temperature with digital thermometers, and body composition by bioelectrical impedance. The mean measured resting metabolic rate (mRMR) was compared to percentages of the mean predicted RMR (pRMR) by two methods: fat-free weight (Sterling-Passmore equation: SP) and sex, age, height, and weight (Harris-Benedict and Mifflin-St. Joer equations: HB and MSt.J). Measurements were taken during the follicular phase of subjects' menstrual cycles.

***Results***. Patients had a lower mean mRMR (939.70 ± 216.04 kcal/d vs 1293.40 ± 166.34 kcal/d, $p = 0.00001$) and lower mRMRs as percentages of pRMRs (SP: -26.91 ± 13.36% vs -6.826 ± 12.55%, $p < 0.0001$. HB: -32.45 ± 13.48% vs -9.13 ± 9.51%, $p = 0.0001$; MSt.J: -27.96 ± 14.53% vs -5.089 ± 11.30%, $p = 0.0002$). Age and fat-free weight accounted for 62% of variability in controls'mRMRs. Fat-free weight, water as a percentage of body weight, and fibromyalgia symptom intensity accounted for 83% of the variability of patients' mRMRs. Patients' mean basal body temperature was significantly lower than that of controls (96.38 ± 0.98° F vs 97.54 ± 0.59° F, $p = 0.001$). Patients' serum free $T_3$ level was significantly lower than that of controls (3.18 ± 0.559 vs 3.75 ± 0.717 pg/mL, $p = 0.023$).

***Conclusions.*** The patient group had a lower mean mRMR and lower mRMR as percentages of pRMRs. Patients also had a significantly lower mean basal body temperature. Neither calorie restriction nor low fat-free weight accounted for patients' lower RMRs. As in the previous study, fibromyalgia patients' normal fat-free weight argues against low physical activity with poor physical fitness as the mechanism of their low RMRs. Free $T_4$, free $T_3$, and TSH levels did not correlate with fibromyalgia measures or RMRs in either patient or control group. The lack of correlation does not rule out inadequate thyroid hormone regulation as the mechanism of the low RMRs because studies have not shown that these laboratory values reliably predict RMR values.

**KEY WORDS.** Resting metabolic rate, fibromyalgia, basal body temperature, body composition, TSH, free $T_4$, free $T_3$.

## *INTRODUCTION*

"Fibromyalgia syndrome" is the diagnosis that clinicians most often give patients who have chronic widespread pain and abnormal tenderness. Most fibromyalgia researchers state that the etiology of the disorder is unknown. In doing so, they fail to account for a line of evidence that indicates that the main mechanism of fibromyalgia is inadequate thyroid hormone regulation. For some fibromyalgia patients, the inadequate regulation is due to hypothyroidism; for others, it is due to partial peripheral cellular resistance to thyroid hormone.

### Evidence

The evidence that inadequate thyroid hormone regulation is the main mechanism of fibromyalgia falls into four categories: (1) symptoms, (2) studies of thyroid status, (3) objectively verified abnormalities, and (4) clinical trials with thyroid hormone therapy.

***Symptoms***. The symptoms of fibromyalgia are identical to symptoms of hypothyroidism and peripheral resistance to thyroid hormone.[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17]

***Studies of Thyroid Status***. A significant percentage of fibromyalgia patients have elevated thyroid autoantibodies[18][19] and an increased incidence of thyroid function test results consistent with primary and central hypothyroidism.[20][21][22][23][24][25][26] While the incidence of primary hypothyroidism in the general population is 1%-to-5%,[27][28] among fibromyalgia patients, the reported incidence is 10%-to-24%.[20][23][24][29][32] While the estimated incidence of central hypothyroidism in the general population is 0.00021%, among 92 fibromyalgia patients it was 43.5%.[21]

***Objectively Verified Abnormalities***. All other hypotheses of the etiology of fibromyalgia plausibly account for only a few objectively verified abnormalities among fibromyalgia patients. In contrast, at least 38 such abnormalities of fibromyalgia patients are credibly explained by inadequate thyroid hormone regulation of transcription, alternative splicing, or translation at the cellular level (see Table 1). All of these abnormalities have been reported to occur in either hypothyroidism, thyroid hormone resistance, or both.[1]

***Clinical Trials with Thyroid Hormone Therapy***. The only studies in which patients have recovered from their fibromyalgia status have been open[172][173][174][175][176] and blinded[177][178][179][180][181] clinical trials in which the patients were treated with thyroid hormone therapies other than $T_4$-replacement. A long-term follow-up study showed that compared to matched controls, fibromyalgia patients treated with thyroid hormone significantly improved; their improvement persisted through 1-to-5 years, depending on the time of follow-up since they began treatment.[182]

If inadequate thyroid hormone regulation is the mechanism of the symptoms and objective abnormalities of fibromyalgia, patients should have abnormally low resting metabolic rates (RMRs), as do patients with hypothyroidism[183][184] and/or peripheral thyroid hormone resistance.[57] In a previous study,[238] Lowe, Yellin, and Honeyman found that 15 female fibromyalgia patients had a significantly lower mean RMR than 15 matched healthy controls. Based on sex, age, height, and weight, the patients' mean RMR was 28.42% (± 15.82%) below normal. Based on the patients' fat-free weight, their mean RMR was 29.20% (± 17.43%) below normal. Patients' mean basal body temperature was significantly lower than that of controls (96.95 ± 0.63°F vs 97.54 ± 0.59°F, $p = 0.013$).

In the previous study,[238] patients were solicited from the general public for participation. In the present study, patients were selected from a large pool of cases at a clinic specializing in the diagnosis and treatment of hypometabolism. They were selected to match the healthy controls from the previous study.

The purpose of the present study was to compare the RMRs of our clinical fibromyalgia patients to those of matched healthy controls. Another purpose was to use regression analysis to test for the RMR-regulating factors that best account for the variability in study subjects' RMR values.

## *METHODS*

The patients in the study were 15 females who met the American College of Rheumatology (ACR) criteria for fibromyalgia. Their fibromyalgia status was quantified by five measures: (1) the percentage of 36 body divisions in chronic pain, (2) presence of tender points (pressure-pain threshold determined by algometry), (3) scores on the Fibromyalgia Impact Questionnaire (a validated instrument for assessing functional ability[185]), (4) visual analog scales of 13 associated fibromyalgia symptoms, and (5) Zung's Self-Rating Depression Scale.

Researchers reviewed patients' records for three purposes: (1) to make sure that patients were not restricting calorie intake, (2) had not engaged in regular fitness training in the last six months (running, swimming, cycling, weight training, aerobics, or tennis), (3) but were regularly participating in work and routine life-maintenance activities (for example, shopping, house or yard work, local travel). No patient was included who had any disorder that could affect metabolic rate; the main disorders that excluded patients from the study were anemia, diabetes, and cardiovascular disease. Patients were also excluded if they used medications that could alter metabolism, such as β-adrenoceptor antagonists, metformin hydrochloride, thyroid hormone, oral contraceptives, or norepinephrine reuptake inhibitors.

The control group consisted of 15 females. Each failed to meet the ACR criteria for fibromyalgia and did not have an illness or injury that could influence resting metabolic rate. The subjects were classified as healthy based on a physical examination by a physician, blood tests, and psychological and health history questionnaires. Patients were matched to controls by sex, age, weight, absence of calorie restriction, and general physical activity level. Twelve applicants were excluded from the control group. They were excluded because they engaged in regular fitness training, were on a diet that could alter metabolism, or used a medication that could affect the metabolic rate.

Both premenopausal and postmenopausal subjects were included in the study. (Matching of patients to controls took menstrual status into consideration through the age criterion.) The purpose for this inclusion was to allow testing of the null hypothesis that menstrual status is unrelated to either measured RMR (mRMR) or predicted RMRs (pRMRs). No subjects smoked cigarettes or were pregnant. Laboratory biochemical tests performed inclu-

ded a comprehensive metabolic profile, lipid profile, AM cortisol, TSH, free $T_3$, and free $T_4$. Subjects were included regardless of their thyroid test results (whether consistent with euthyroidism, hyperthyroidism, or hypothyroidism). This was done so that statistical tests could be performed to determine whether these measures correlated with RMR values.

The Ethics Committee of the Fibromyalgia Research Foundation approved the study design. Each subject signed an informed consent after reading, and receiving an oral description of, the protocol. No subjects were paid for participating in the study; they all received copies of their test results.

Subjects were given oral and written instructions on how to prepare for laboratory biochemical testing and measurement of their RMR and body composition. They fasted overnight for ≥12 hours before blood draws at the medical laboratory (Boulder Community Reference Laboratory). After rising from sleep, they used house and automobile heating and extra clothing to remain comfortably warm. Having fasted for ≥12 hours, they drank no more than two 8 oz. glasses of water after awaking. They also carefully avoided physical and psychological stresses.

After the blood draw and upon arriving at the metabolic testing facility (the Center for Metabolic Health, LLC, in Boulder, Colorado) at 9 AM, each subject voided and disrobed to her underwear. A researcher then measured her weight on a balance beam scale (Healthometer, Continental Scale Corp., Bridgeview, IL) and measured her height with an attached stadiometer. Only the subject and tester were present. The temperature of the semidarkened, quiet room was such that it was comfortably warm for each subject. The subject relaxed supine on a comfortable table under a warm cover for ≥30 minutes. The tester visually monitored her to make sure she was lying still and was awake. Pulse and blood pressure were taken after RMR was measured.

Basal metabolic rates (BMRs) and RMRs are usually

**Table 1.** Same objectively verified abnormalities in fibromyalgia (FM) as compared to hypothyroidism (HO) or peripheral resistance to thyroid hormone (PRTH).

| ABNORMALITIES | FM | HO or PRTH |
|---|---|---|
| ***Histological*** | | |
| ↑ Hyaluronic acid | 34,35* | 36* |
| ↑ Ground substance proteoglycans | 11,12,37-39 | 40-43 |
| ↓ Collagen | 44,45 | 46,47 |
| ↓ Pyridinoline | 48,49 | 50,51 |
| ↓ Procollagen III | 52-54 | 36,55,56 |
| ↓ Hydroxyproline | 44,45,48,49 | 47,50,57,58 |
| ↑ Mast cells | 37,38,59 | 46,60-64 |
| ***CSF*** | | |
| ↑ Substance P | 65-68 | 69-72 |
| ↓ Dopamine (homovanillic acid) | 73 | 74,75 |
| ↓ Tissue norepinephrine | 73 | 76-78 |
| ↓ Urinary 5-hydroxyindole acetic acid | 79 | 80 |
| ↓ Brain 5-hydroxytryptophan | 73,81 | 82 |
| ↑ Nerve growth factor | 83 | 84,85 |
| ***Molecular*** | | |
| ↑ α-Adrenoceptors | 86,87 | 88-95 |
| ***Mitochondria*** | | |
| Ragged red fibers | 96,97 | 98,99 |
| ↓ Cytochrome-c-oxidase | 100 | 98,99 |
| ***Physiological*** | | |
| Exercise intolerance | 101-104 | 105-108 |
| ↓ Muscle relaxation time | 109 | 110 |
| Blunted cortisol response to ACTH | 111,112 | 113 |
| Orthostatic hypotension | 114,115 | 116 |
| Joint hypermobility | 117,118 | 119 |
| ↓ Brain blood flow | 120-122 | 123 |
| ↓ Peripheral blood flow | 124-126 | 127 |
| Blunted sympathetic and end-organ response to stress | 101,115,128-131 | 132-135 |
| Excess urination | 136,137 | 138,139 |
| ↓ Delta-wave and nonrestorative sleep | 140,141 | 138,142-144 |
| ***High-energy phosphates*** | | |
| ↓ ATP | 145 | 146-149 |
| ↑ Phosphodiesters | 150-152 | 153 |
| ↑ Inorganic phosphate (Pi) | 151 | 153,154 |
| ↓ Phosphocreatine (PCr) | 145 | 146 |
| ↓ PCr/Pi ratio | 145 | 154,155 |
| ***Carbohydrate metabolism*** | | |
| ↑ Pyruvate | 156-158 | 105,156,159 |
| ↓ LDH | 150,156 | 150,156 |
| ↓ Intracellular pH | 150 | 153,154 |
| ↓ Skeletal muscle glucose use | 160 | 161-163 |
| ***Endocrine*** | | |
| ↓ HPA axis function | 131,164 | 165,166 |
| ↓ GH and IGF-1 | 167-169 | 170,171 |
| ↑ Hypothyroidism | 20-26 | n/a |

*All numbers are references at the end of this paper.

**Table 2.** Anthropometric data (mean ± SD).

| | Patients | Controls | *p** |
|---|---|---|---|
| Age | 47.73 ± 11.78 yrs | 45.67 ± 11.83 yrs | 0.635 |
| Height | 64.05 ± 2.85 in (162.68 ± 7.23 cm) | 66.42 ± 2.80 in (168.70 ± 7.11 cm) | 0.029 |
| Weight | 151.75 ± 39.78 lb (68.84 ± 18.04 kg) | 155.36 ± 34.12 lb (70.47 ± 15.48 kg) | 0.792 |
| BMI | 25.88 ± 5.90 kg/m$^2$ | 24.65 ± 4.51 kg/m$^2$ | 0.527 |
| FFW | 93.42 ± 16.26 lb (42.38 ± 7.38 kg) | 101.94 ± 16.33 lb (46.24 ± 7.41 kg) | 0.164 |
| % Body fat | 36.93 ± 6.59 | 33.42 ± 6.04 | 0.140 |
| FW | 57.85 ± 24.84 lb (26.24 ± 11.27 kg) | 53.42 ± 20.21 lb (24.23 ± 9.17 kg) | 0.596 |
| BBT | 96.38 ± 0.98° F (35.76 ± 0.54° C) | 97.54 ± 0.59° F (36.41 ± 0.33° C) | 0.001 |

*Difference significant (independent t-tests) at $p < .05$ level.

lowest during menstruation and are elevated during the luteal phase of the menstrual cycle.[186][187] For this reason, premenopausal patients underwent indirect calorimetry during the follicular phase of their menstrual cycle.

One or the other of two testers, using a hand-held indirect calorimeter (the MedGem®, Healthetech, Golden, Colorado), measured the RMRs of all subjects. The device measures $VO_2$ and calculates RMR using a modified Weir equation. In the equation, a constant respiratory quotient value of 0.85 (RMR = 6.931 x $VO_2$)[188] is used. Researchers have reported that the MedGem® measured $VO_2$ and calculated RMR as accurately and reliably as reference calorimeters.[189][190][191][192]

One research group reported that the energy cost of subjects holding the MedGem® is 255 ± 84 kJ/day. When adjusted for this increase, however, mRMR by the MedGem® did not significantly differ from mRMR by the Sensormedics® 2900 indirect calorimeter.[189] To avoid the increase in RMR from holding the instrument, each subject's arm and hand were supported with cloth padding so that muscle contraction was not necessary. After measuring the RMR, the measurement was converted to percentages of RMR predicted by the subject's fat-free weight (Sterling-Passmore equation) and sex, age, height, and weight (Harris-Benedict and Mifflin-St. Joer equations).

In preparing for their body composition to be measured, subjects avoided alcohol for 24 hours and drank up to two glasses of water on the morning of the test. After the tester measured a subject's RMR, he or she then measured the subject's body composition by 4-electrode bioelectrical impedance (Biodynamics® Model 310, Seattle, WA).

### Statistical Analysis

Data are expressed as means ± standard deviations (SD). We used t-tests to determine differences between anthropometric variables and between mean mRMR, pRMRs, and percentages of pRMRs. Correlations between continuous and dichotomous variables were determined by means of the point-biserial correlation coefficient. Stepwise multiple regression analysis ($R^2$) was used to determine which factors known to regulate RMR significantly accounted for the variability of mRMR and percentages of pRMRs. The level of significance was set at $p \leq 0.05$. SPSS for Windows (SPSS, Inc., Chicago, IL), VassarStats: Website for Statistical Computation, and Microsoft® Excel 2002 were used for statistical analyses.

## *RESULTS*

### Anthropometrics and RMR

With the exception of height and basal body temperature, patients and controls did not significantly differ on anthropometric measures (see Table 2). Patients' mean basal body temperature was significantly lower than that of controls (96.38 ± 0.98° F vs 97.54 ±0.59° F, $p = 0.001$). As Table 3 shows, the groups' mRMRs also significantly differed (939.70 ± 216.04 kcal/d vs 1293.40 ± 166.34 kcal/d, $p = 0.00001$), but their pRMRs by fat-free weight (SP equation) and by sex, age, height, and weight (HB and MStJ equations) did not differ.

### RMR and Regression

We used regression analysis to determine which if any factors known to regulate RMR best accounted for the variability in RMR and basal body temperature values. Table 4 summarizes results of the $R^2$ analyses for both groups. It shows how closely the variability of independent measures mirrored the variability of mRMR and mRMR as percentages of pRMRs.

***Controls.*** The variance of fat-free weight most closely resembled the variance of mRMR and accounted for 34% of the variability in mRMR. (The Pearson correlation coefficient showed that fat-free weight positively correlated with mRMR: $r = 0.5850$, $p = 0.022$.) Age and fat-free weight together accounted for 62% of the variability in

mRMR. (Pearson showed that age negatively correlated with mRMR: $r = -0.5209$, $p = 0.046$.)

Also for controls, the variance of weight best fit the variance of mRMR as a percentage of pRMR by fat-free weight (Sterling-Passmore equation). Weight, then, accounted for 49% of that variability. (By the Pearson correlation coefficient, the correlation of the two variables was significantly negative: $r = -0.6999$, $p = 0.004$.)

The variance of controls' fat weight most closely resembled that of mRMR as a percentage of pRMR by sex, age, height, and weight (Mifflin-St. Joer equation), accounting for 33% of the variability. BMI and fat weight accounted for 64% of the variance, and BMI, fat weight, and pain distribution accounted for 75%.

And finally, the variability of fibromyalgia symptom intensity (FibroQuest score) most closely fit that of mRMR as a percentage of pRMR by sex, age, height, and weight (Harris-Benedict equation), and accounted for 32% of the variance. This mRMR value also positively correlated with symptom intensity ($r = 0.5640$, $p = 0.029$).

***Patients.*** As for controls, the variance of patients' fat-free weight best fit the variance of mRMR, accounting for 53% of the variability. Together, the variance of patients' fat-free weight and water as a percentage of body weight accounted for 69%. And when we combined the variance of fat-free weight, water as a percentage of body weight, and fibromyalgia symptom intensity, these three independent variables accounted for 83% of the variations in mRMR.

The Pearson correlation coefficient showed that patients' fat-free weight positively correlated with mRMR ($r = 0.7210$, $p = 0.002$). However, the test showed no significant correlation between mRMR and either water as a percentage of body weight (-0.2060, $p = 0.461$) or fibromyalgia symptom intensity (-0.4183, $p = 0.121$).

No independent measure's variability fit that of mRMR as a percentage of pRMR by fat-free weight (SP) or by sex, age, height, and weight (either HB or MStJ). Also, we found no significant correlations between these RMR values and any independent variable tested.

**Basal Body Temperature**

In stepwise regression analysis, no independent measure accounted for the variability of controls' basal body temperature. For patients, water as a percentage of fat-free weight was the only independent measure that accounted for the variability of basal body temperature. This measure strongly negatively correlated with the temperature ($r = -0.6178$, $p = 0.0141$) and accounted for 38% of the variability of the temperature.

**Thyroid Function Tests**

TSH and free $T_4$ levels did not significantly differ between groups. However, patients had a significantly lower mean free $T_3$ level than did controls (3.18 ± 0.559 pg/mL vs 3.75 ± 0.717 pg/mL, $p = 0.023$). In neither group did TSH, free $T_4$, or free $T_3$ levels significantly correlate with mRMR or mRMRs as percentages of pRMRs. Also, in neither group did the laboratory test levels significantly correlate with any fibromyalgia measure.

**Menopausal Status**

Postmenopausal controls had a significantly lower mean mRMR (1221.75 kcal/d vs 1375.29 kcal/d, $p = 0.0365$) and percentage of pRMR by the Harris-Benedict equation using sex, age, height, and weight (-12.95% vs -4.77%, $p = 0.0484$). The percentage of pRMR by the Sterling-Passmore equation using fat-free weight was almost significantly lower for postmenopausal controls (-11.33% vs -1.67%, $p = 0.0714$). The basal body temperature of postmenopausal controls was significantly higher than that of premenopausal controls (97.81° F vs 97.23° F, $p = 0.0558$), as were their $T_4$ levels (1.389 ng/dL vs 1.036 ng/dL, $p = 0.039$). The basal pulse rate of postmenopausal controls was almost significantly higher (72.08 bpm vs 67.12 bpm, $p = 0.0574$). And, the mean fibromyalgia symptom intensity of postmenopausal controls was sig-

**Table 3.** Measured RMR and predicted RMRs (mean ± SD).

| | Patients | Controls | *p** |
|---|---|---|---|
| mRMR | 939.70 ± 216.04 kcal/d (3931.71 ± 903.93 kJ/d) | 1293.40 ± 166.34 kcal/d (5411.59 ± 695.95 kJ/d) | 0.00001 |
| pRMR by SP** | 1289.20 ± 224.42 kcal/d (5394.00 ± 938.98 kJ/d) | 1406.77 ± 225.38 kcal/d (5885.93 ± 942.97 kJ/d) | 0.16329 |
| pRMR by HB*** | 1391.41 ± 166.54 kcal/d (5821.66 ± 696.81 kJ/d) | 1427.54 ± 152.47 kcal/d (5972.81 ± 637.92 kJ/d) | 0.54049 |
| pRMR by MStJ**** | 1308.88 ± 190.71 kcal/d (5476.36 ± 797.91 kJ/d) | 1372.71 ± 181.00 kcal/d (5743.40 ± 757.30 kJ/d) | 0.35518 |

*Difference significant (independent t-tests) at $p < .05$ level.
**SP: Sterling-Passmore equation, uses FFW.
***HB: Harris-Benedict equation, uses sex, age, height, weight.
****MStJ: Mifflin-St. Joer equation, uses sex, age, height, weight.

nificantly lower than that of premenopausal controls (2.29 vs 3.47, $p = 0.023$).

Compared to premenopausal patients, postmenopausal patients had a lower mean basal body temperature (95.92° F vs 97.07° F, $p = 0.0092$) and basal pulse rate (61.10 bpm vs 69.47 bpm, $p = 0.0385$). Postmenopausal patients also had a significantly higher free $T_3$ level (3.46 pg/mL vs 2.76 pg/mL, $p = 0.0111$). TSH and free $T_4$ levels did not significantly differ between post- and premenopausal patients, and no RMR values significantly differed between the two patient groups.

**Depression Status**

When grouped as nondepressed or depressed, controls did not differ in RMR values, fibromyalgia scores, or thyroid function test results. However, when patients were grouped according to depression level, those with moderate-to-severe depression had a significantly wider pain distribution (34.63% vs 21.21%, $p = 0.0254$) than did patients with no depression-to-mild depression.

## *DISCUSSION*

Female fibromyalgia patients in this study had significantly lower RMR values and basal body temperatures than did matched healthy controls. These results are consistent with those from our previous study[238] of the RMRs and basal body temperatures of fibromyalgia patients.

**RMR Values**

Patients and controls did not significantly differ in pRMRs calculated by fat-free weight or by sex, age, height, and weight (see Table 3). However, patients' mRMR was significantly lower than that of controls (939.70 ± 216.04 kcal/d vs 1293.40 ± 166.34 kcal/d, $p = 0.00001$). Patients' mean mRMR was 26.91% below their pRMR calculated from fat-free weight (see Graph 1 for a data point-line display of the differences; also see Table 5). Using sex, age, height, and weight, their mRMR was 32.45% below their pRMR (Harris-Benedict equation; Graph 2 and Table 5), and 27.96% below pRMR (Mifflin-St. Joer equation; Table 5). Compared to the control group, then, the patient group was severely hypometabolic.

***Controls.*** For controls, mRMR significantly positively correlated with fat-free weight and significantly negatively correlated with age. These results are consistent with other reports for healthy controls.[186][193][194][195]196][197][198][199] Weight significantly negatively correlated with mRMR as a percentage of pRMR by fat-free weight ($r = -0.6999$, $p = 0.004$); that is, heavier controls had lower mRMRs. Despite this, mRMR did not significantly differ from mRMR as a percentage of pRMR by fat-free weight.

Also for controls, fat weight, BMI, and pain distribution accounted for 75% of the variance of mRMR expressed as a percentage of pRMR by sex, age, height, and weight (Mifflin-St. Joer equation; see Table 4). BMI did not significantly correlate with this RMR value, though fat weight did inversely ( $r = -0.5714$, $p = 0.026$). In other words, the higher the fat weight, the lower the mRMR. This is not consistent with what researchers generally report. For example, Ravussin et al. found that the mean RMR increases stepwise from nonobese controls, to moderately obese subjects, on to severely obese subjects.[195,p.566] They stated that the higher RMRs in heavier subjects resulted from their higher oxygen consumption in daylight hours, and that 8% of the higher RMR of obese subjects resulted from factors such as the increased energy cost of moving their heavier weight about. Goran reported that the effect of fatness on energy expenditure is negligible other than a small effect on RMR. He noted that patients with more fat are less likely to be physically active, but when they are active, the energy cost of moving about is higher than people with less fat.[33,p.355] From these reports, one would expect the opposite from our test results: that our controls with higher fat weight would have had higher RMR values rather than lower.

Of particular interest is the finding that the lower the controls' mRMRs as a percentage of pRMR (Mifflin-St. Joer equation) were, the higher was the percentage of their bodies in pain. Widespread pain is common among patients who are hypometabolic from hypothyroidism, peripheral thyroid hormone resistance, or a sedentary lifestyle.[1] It is possible that our controls were mildly hypometabolic due to their sedentary lifestyle (a matching criterion for inclusion in the study), and because of this, had some degree of chronic pain. Nonetheless, the controls' pain distribution was significantly lower than that of patients (3.73 ± 3.97% vs 26.07 ± 12.66%, $p = 0.00003$).

The controls' sedentary lifestyle may also account for the positive correlation ($r = 0.5640$, $p = 0.029$) between fibromyalgia symptom intensity and mRMR as a percentage of pRMR using sex, age, height, and weight (Harris-Benedict equation). Controls' symptom intensity, however, was significantly lower than that of patients (2.84 ± 1.048 vs 6.65 ± 1.335, $p = 0.00000001$).

***Patients.*** The variance of fat-free weight best fit the variance of mRMR, accounting for 53% of the variability (Table 4). Of all the independent variables measured in patients, only fat-free weight significantly correlated with mRMR and the relationship was strong ($r = 0.7210$, $p = 0.002$). Despite these two findings, the overall evidence does not indicate that patients' mRMR was a function of their fat-free weight.

One might presume that the close fit of the variability of fat-free weight, and the strong positive correlation, with mRMR indicate that patients' low mRMRs were due to

low fat-free weight. From that, one might also presume that the low fat-free weight was due to lost skeletal muscle mass from low physical activity. However, as is clear from Graph 1, these presumptions are not correct. The top trend line in the graph represents the pRMR calculated directly from patients' fat-free weight using the Sterling-Passmore equation. The bottom trend line represents the patients' mRMRs. The Sterling-Passmore equation—using patients' actual fat-free weight—predicted that patients' mRMR would be 26.91% higher than it actually was.

In addition, as Table 2 shows, the fat-free weight of controls and patients did not significantly differ. As Table 3 shows, however, the patients' mean mRMR was significantly lower than that of controls (939.70 ± 216.04 kcal/d vs 1293.40 ± 166.34 kcal/d, $p$=0.00001).

Moreover, patients' mean creatinine level was within the reference range (value: 0.83; range: 0.5-1.2 mg/dL). Controls' creatinine level was slightly higher (87 mg/dL), but the groups' levels did not significantly differ. In that creatinine is considered to reflect muscle mass,[201] patients' mean creatinine level, like their fat-free weight, indicates that they did not have low muscle mass. As in our first study of the RMRs of fibromyalgia patients,[238] fat-free weight and creatinine values argue against low physical activity as a mechanism of patients' low RMRs. The values also contradict the hypothesis that physical deconditioning is the etiology of fibromyalgia patients' symptoms.[202]

On the other hand, the sedentary lifestyles of the two groups may be associated to a small degree with widespread pain and fibromyalgia symptoms in both groups. We hasten to add, though, that since many fibromyalgia patients only become sedentary after their symptoms become severe, their sedentary lifestyle is most likely a result, rather than a cause, of their fibromyalgia.

**Table 4.** Independent variables* as predictors of measured RMR, and measured RMR expressed as percentages of predicted RMRs.

| Controls | Number of variables | $R^2$ |
|---|---|---|
| mRMR | Fat-free weight | 0.3423 |
| | Age, fat-free weight | 0.6202 |
| mRMR as percentage of pRMR (SP**) | Weight | 0.4898 |
| mRMR as percentage of pRMR (HB***) | Fibromyalgia symptom intensity^ | 0.3181 |
| mRMR as percentage of pRMR (MStJ****) | Fat weight | 0.3265 |
| | BMI, fat weight | 0.6351 |
| | BMI, fat weight, pain distribution | 0.7503 |
| **Patients** | **Number of variables** | $R^2$ |
| mRMR | Fat-free weight | 0.5278 |
| | Fat-free weight, water as % body weight | 0.6902 |
| | Fat-free weight, water as % body weight, fibromyalgia symptom intensity^ | 0.8286 |
| mRMR as percentage of pRMR (SP**) | None | |
| mRMR as percentage of pRMR (HB***) | None | |
| mRMR as percentage of pRMR (MStJ****) | None | |

*Independent variables: age, height, weight, FFW, FW, BMI, % body fat, total body water, water as % of body weight, water as % of fat-free weight, TSH, $FT_3$, $FT_4$, basal body temperature, basal pulse rate, ^FibroQuest score, Fibromyalgia Impact Questionnaire score, mean tender point in kg/cm$^2$, and pain distribution.
**SP: Sterling-Passmore equation, uses FFW.
***HB: Harris-Benedict equation, uses sex, age, height, weight.
****MStJ: Mifflin-St. Joer equation, uses sex, age, height, weight.

In that patients' fat-free mass was not abnormally low, it may seem a paradox that regression analysis showed a tight fit between the variability of fat-free weight and patients' mean mRMR. The apparent paradox may come from a term that some researchers, ourselves among them,[238] have used to describe the close-fitting variances of independent and dependent variables. When the variance of a particular independent variable "fits" the variance of the dependent variable more closely than the variances of other independent variables, researchers often

write that the particular independent variable "best predicted" the dependent variable. This is appropriate when, among healthy controls, we state that fat-free weight best predicts mRMR. In general, fat-free weight is the strongest determinant of mRMR,[186][193][194][195][196][197][198][199] and accounts for some 82% of the variance in mRMR.[200] To some, however, this terminology always implies a causative relationship between the two variables—the independent variable causing the dependent variable.

However, even when two variables with tightly-fitting variances are causatively related in general, their variances may tightly fit only coincidentally. We emphasize, then, that for patients in our study, the significant fit of the variances of fat-free weight and mRMR, and their strong positive correlation, do not show that patients' low mRMRs were caused by low fat-free weight. We can consider the significant fit, in this case, to be coincidental because enough other evidence contradicts a causative relationship.

Of nineteen tested independent variables that might influence patients' RMR values, none significantly fit the variances of mRMR as percentages of pRMRs (using the Sterling-Passmore, Harris-Benedict, and Mifflin-St. Joer equations, see Table 4). Furthermore, as we have indicated elsewhere,[238] the thyroid laboratory values we tested (TSH, free $T_3$, and free $T_4$) are dubious as predictors of RMR. Hence, the lack of significant correlation and the lack of significant fit between these values and RMR values do not rule out inadequate thyroid hormone regulation as the underlying mechanism of patients' low RMRs.

### Basal Body Temperature

The significantly lower mean basal body temperature of patients compared to controls (96.38 ± 0.98° F vs 97.54 ± 0.59° F, $p = 0.001$) is consistent with hypothyroidism.[225][226] From the beginning of thyroid hormone therapy, temperature has been important to many clinicians in the diagnosis and treatment of hypothyroid patients.[1,p.842] For example, in 1891, physician George Murray reported the first hypothyroid patient treated with thyroid extract in the United Kingdom.[242] Before treatment, her temperature varied between 95.6° F and 97.2° F. After Murray began injecting her with sheep thyroid extract, her temperature rose to 98.2° F.[243] Murray titrated each of his patient's thyroid extract dosage according to changes in pulse rate and temperature.

Today, many alternative/complementary physicians consider a low basal body temperature an objective indication of hypothyroidism when the patient has symptoms characteristic of the disorder.[31][218][244][245][246][247][248][249] Barnes defined the reference range for basal body temperature as 97.8° F-to-98.2° F.[244,p.46] Using this range, both our patients' and controls' mean temperatures were abnormally low (96.38 ± 0.98° F and 97.54 ± 0.59° F). Nonetheless, the patients' mean temperature was significantly lower than that of controls. The patients' low temperatures and low RMR values indicate that their oxidative metabolism and heat-generating enzyme systems were inadequately regulated by thyroid hormone.

### Differences Between Premenopausal and Postmenopausal Groups

We found several differences between premenopausal and postmenopausal groups among both controls and patients.

***Controls.*** Seven controls were premenopausal; eight were postmenopausal. An unexpected finding is that the mean fibromyalgia symptom intensity of premenopausal controls was significantly higher than that of postmenopausal controls (3.47 vs 2.29, $p = 0.023$). However, the mean symptom intensity (scale ranges from 0-10) of all controls combined was significantly lower than that of patients (2.84 vs 6.65, $p < 0.000000001$).

The premenopausal controls had a significantly lower mean basal body temperature (97.138° F vs 97.810° F, $p = 0.0361$). This raises the possibility of suboptimal RMRs, although no RMR values were significantly different between the two groups of controls.

As we stated above, fibromyalgia symptoms such as widespread pain are common among those who are hypometabolic from hypothyroidism, peripheral thyroid hormone resistance, or a sedentary lifestyle. In view of this, it is possible that our control subjects were mildly hypometabolic due to their sedentary lifestyle. Because of this, they may have had mild symptoms of hypo-

**Table 5.** Measured RMR as percentages of predicted RMRs (mean ± SD).

| Equation | Patients | Controls | *p** |
|---|---|---|---|
| % of pRMR (SP**) | -26.91 ± 13.36 | -6.83 ± 12.55 | 0.0001 |
| % of pRMR (HB***) | -32.45 ± 13.48 | -9.13 ± 9.51 | 0.0001 |
| % of pRMR (MStJ****) | -27.96 ± 14.53 | -5.09 ± 11.30 | 0.0002 |

*Difference significant (independent t-tests) at $p < .05$ level.
**SP: Sterling-Passmore equation, uses FFW.
***HB: Harris-Benedict equation, uses sex, age, height, weight.
****MStJ: Mifflin-St. Joer equation, uses sex, age, height, weight.

metabolism that for purposes of classification we consider symptoms of fibromyalgia.

It is within the realm of possibility, though, that the premenopausal controls had suboptimal metabolism due to lower free $T_4$ levels. The premenopausal controls' mean level of 1.036 ng/dL was slightly above the cutoff point (0.99 ng/dL) between the first and second quartiles of the reference range of 0.59 ng/dL-to-2.19 ng/dL. By contrast, the $T_4$ level of postmenopausal controls, 1.389 ng/dL, was at the midpoint of the upper end of the reference range. Point biserial correlation coefficient showed that premenopausal controls' levels were significantly lower than those of postmenopausal controls (1.036 ng/dL vs 1.389 ng/dL, $p = 0.039$). Such hair-splitting distinctions with thyroid function tests, however, are dubious in view of the rapid significant changes in levels throughout the day.[241]

***Patients.*** Six patients were premenopausal; nine were postmenopausal. Postmenopausal patients had significantly lower basal pulse rates than premenopausal patients (61.1 bpm vs 69.47 bpm, $p = 0.039$). They also had significantly lower basal body temperatures (95.919° F vs 97.072° F, $p = 0.0093$). However, postmenopausal patients had significantly higher free $T_3$ levels than did premenopausal patients (3.46 pg/mL vs 2.76 pg/mL, $p = 0.0112$). As we have previously suggested,[238,p.CR286] a higher serum free $T_3$ level in patients with lower temperatures and pulse rates may indicate lower intracellular $T_3$ levels. Lower intracellular levels may result in lower metabolism with consequent lower heart rates and temperatures.

TSH and free $T_4$ levels did not significantly differ between pre- and postmenopausal patients. No RMR values significantly differed between the two patient groups.

**Differences Related to Severity of Depression**

***Controls.*** When grouped as depressed or nondepressed, controls did not differ in RMR values, thyroid function test results, or fibromyalgia scores.

***Patients.*** According to Zung's Self-Rating Depression Scale, all patients had some degree of depression. Seven patients had mild depression; eight had moderate-to-severe depression. There were no differences between the two depression groups' temperatures, pulse rates, thyroid laboratory test results, Fibromyalgia Impact Questionnaire scores, or fibromyalgia symptom intensity (other than severity of depression).

However, patients with moderate-to-severe depression had a lower mean tender point pressure/pain threshold than mildly depressed patients (1.7513 kg/cm$^2$ vs 2.5457 kg/cm$^2$, $p = 0.0179$). The moderate-to-severe depression group also had a significantly wider pain distribution (32.05% vs 19.25%, $p = 0.046$).

There are at least three possible explanations for the association of worse depression with greater tenderness and wider pain distribution: (1) patients with more widely distributed pain may have been more depressed because of more suffering; (2) the slumped posture often chronically assumed by depressed patients may have induced pain at multiple biomechanical stress vectors associated with the slumping, as has been reported in fibromyalgia patients;[237] and (3) as the authors believe to be most likely, both a wider pain distribution and depression may have been concomitant effects of inadequate thyroid hormone regulation.[1]

Increased pain perception is predictable from inadequate thyroid hormone regulation. As we explained in detail in the report of our previous RMR study,[328,p.CR286] thyroid hormone normally inhibits excess synthesis and secretion of substance P, a compound that augments pain perception.[69][70][72][222][223] It does so by regulating transcription of the gene that codes for preprotachykinin-A, the precursor of substance P and its receptor.[222][224] When rats were made hypothyroid, the substance P concentration in their dorsal horn nociceptive neurons increased as much as 100%.[71][72] Administering thyroid hormone lowered the concentration to normal.[70][71] Researchers have reported that the substance P level in fibromyalgia patients' cerebrospinal fluid is 90%-to-300% higher than normal.[65][68] As we formerly conjectured, the reduction of fibromyalgia patients' pain and tenderness in $T_3$ phases of our three double-blind trials, and the return of pain and tenderness in placebo phases, may have resulted respectively from decreases and increases of the patients' substance P levels.[177][178][179]

Of course, in addition to depression and pain, inadequate thyroid hormone regulation also credibly accounts for the two most important findings in this study: patients' lower metabolic rates and lower body temperatures.

**Thyroid Function Tests**

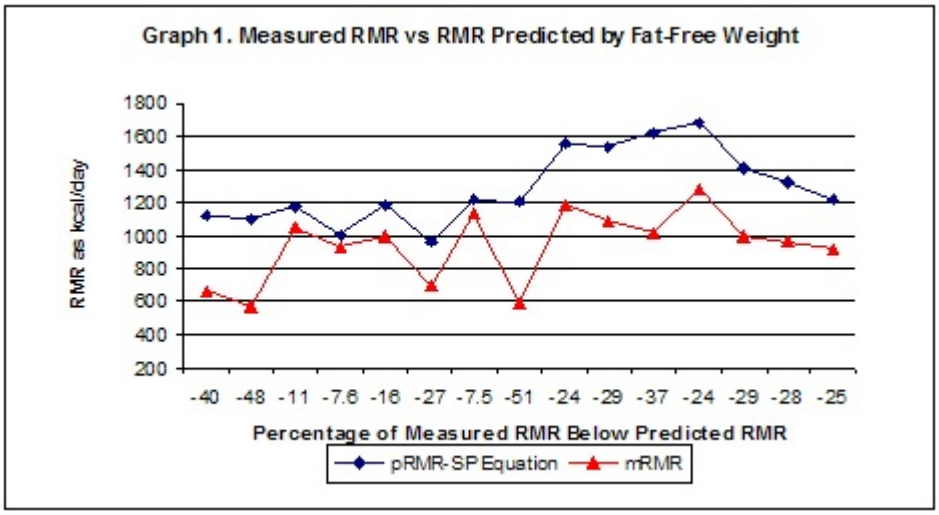
In our previous study,[238] patients' TSH level positively correlated with their pain distribution. This raised the possibility that pain distribution in fibromyalgia is associated with primary hypothyroidism. This putative association is consistent with previous studies showing a high incidence of primary hypothyroidism among fibromyalgia patients.[20][21][24][29][219] In the present study, however, neither TSH, free $T_3$, nor free $T_4$ levels correlated with any measure of fibromyalgia.

In the previous study,[238] the mean free $T_3$ level of 4 pg/mL was within the reference range (2.77 pg/mL-to-5.27 pg/mL), and the mean free $T_3$ levels of patients and controls did not significantly differ. However, the mean free $T_3$ level inversely correlated with pressure-pain threshold ($r = -0.5499$, $p = 0.0337$).

In this study, patients' mean free $T_3$ level, 3 pg/mL,

was in the lower quartile of the reference range (2.77 pg/mL-to-5.27 pg/mL) and was significantly lower than that of controls. Controls' free $T_3$ level of 4 pg/mL was in the middle of the range (midpoint: 4.02 pg/mL). The differences in free $T_3$ levels of patients and controls in the two studies are probably of no importance in that the levels of free $T_3$, just as those of TSH and free $T_4$, significantly vary every 15 minutes.[241]

As we documented in our previous report of low RMRs among women with fibromyalgia,[238] studies have not shown that thyroid function test results reliably correlate with RMR values.[214][215][216][217] Because of this, the lack of correlation between the results of thyroid function tests (TSH, free $T_3$, and free $T_4$) and RMR values in this study does not rule out inadequate thyroid hormone regulation as the mechanism of our patients' low RMR values.




## Limitations

The limitations of this study are the same as in the first.[238] We are aware of at least three.

***Hormone Deficiencies.*** A deficiency of growth hormone, insulin-like growth factor-1,[203][204] or testosterone[205][206] can lower RMR values by lowering fat-free weight. We did not measure levels of these hormones so we cannot exclude the possibility of one or more deficiencies. But the fat-free weight and creatinine levels of our patients suggest that such deficiencies are unlikely causes of their low RMR values.

***Calorie Intake and Expenditure.*** In our previous study, patients and controls objected to keeping diet and physical activity logs. For this reason, in the present study, we did not require subjects to keep the logs.

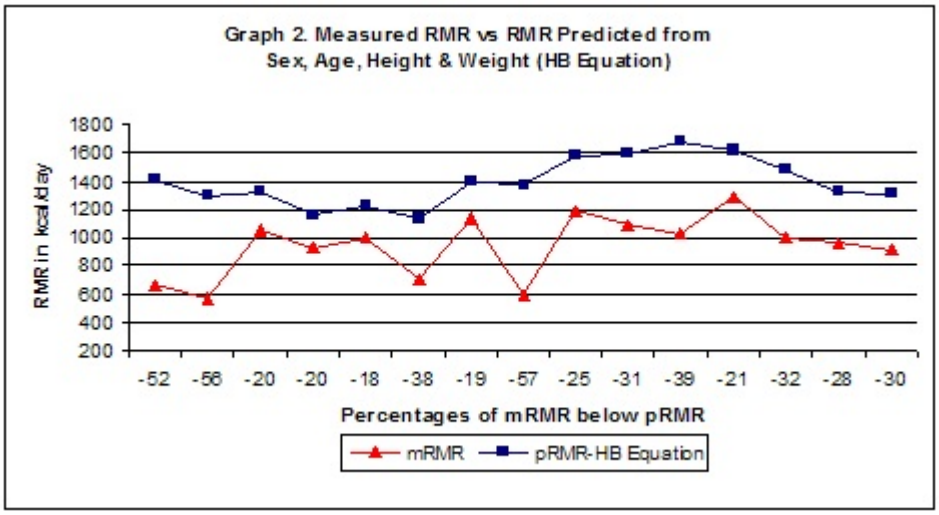
In trying to keep diet logs early in our first study,[238] several subjects substantially underreported their calorie intake. The logs showed that calorie intake was 32% below calorie expenditure due to underreporting. Such underreporting is common in studies in which subjects keep logs;[229][230][231][232][233][234][235][236] underreporting has ranged from 20%-to-30%[230][235] and 40%.[231][232][233]

Because subjects did not keep diet and activity logs in the present study, we examined the daily food consumption that patients reported on their medical history and health status form (FibroQuest Long Form). We ensured that they were not restricting calorie intake and that they were neither completely sedentary nor engaged in regular fitness training. The same information was acquired from healthy controls through careful questioning.

Examining reports from the patients' FibroQuest Long Forms and questioning controls did not allow an actual measurement of subjects' calorie intake or energy expenditure. This shortcoming should be corrected in future studies by the use of both a computer-based diet assessment program and a computerized device, such as an accelerometer, to calculate energy expenditure through measured activity level.

***Source of Possible Inadequate Thyroid Hormone Regulation.*** The TSH, free $T_4$, and free $T_3$ tests assess only the function of the pituitary-thyroid axis. When the test results are within their reference ranges, they do not rule out two types of inadequate thyroid hormone regulation that can lower RMR: central hypothyroidism and partial peripheral resistance to thyroid hormone.[57][227] In previous studies, our research group found that 44% of fibromyalgia patients had test results consistent with central hypothyroidism.[20][21] Because the dynamic TRH-stimulation test that can identify patients with central hypothyroidism is no longer available in the United States, the patients in this study were not tested for possible central hypothyroidism.

Evidence indicates that approximately 35% of fibromyalgia patients have peripheral thyroid hormone resistance.[228] Four clinical criteria are necessary to determine that a patient has peripheral resistance: the patient (1) is euthyroid (according to thyroid function test results including the TRH stimulation test, if possible) before beginning the use of $T_3$; (2) recovers from hypothyroid-like fibromyalgia symptoms and signs with supraphysiologic dosages of $T_3$; (3) has an extremely high serum free $T_3$ level once reaching his or her effective dose of $T_3$; and (4) has no evidence of tissue thyrotoxicosis, according to the results of serial ECGs, serum and urine biochemical tests, and bone densitometry.[1][30] Because patients in this study




have not been shown to reliably correlate with RMR values, and (2) these laboratory tests evaluate only pituitary-thyroid axis function and cannot identify central hypothyroidism or partial peripheral resistance to thyroid hormone.

In summary, none of the variables we tested appeared to have a causative relationship to our patients' low RMR values and low basal body temperatures. The low measures, however, are characteristic of inadequate thyroid hormone regulation. In view of this and our inability to eliminate inadequate thyroid hormone regulation as a causative factor, it remains the most likely mechanism of our patients' low metabolism and low basal temperatures.

did not undergo treatment, we do not know if any of them would have met these criteria.

## *CONCLUSIONS*

Our data indicate that among controls, lower RMRs were associated with a small degree of two fibromyalgia features: symptom intensity and pain distribution. These features were mild and were significantly lower than among fibromyalgia patients. A possible mechanism of these features is the controls' sedentary lifestyle, which was a criterion for inclusion in this study. If so, this lends credibility to an ancient observation by writers such as Maimonides, Galen, and Sidenham:[1,p.59] a sedentary lifestyle causes some people to develop chronic aches and pains with fatigue. These are symptoms that today we might diagnosis as fibromyalgia. However, low physical fitness is highly unlikely to account for our fibromyalgia patients' more severe symptoms and extreme hypometabolism. This is unlikely because controls and patients were matched according to physical activity level.

As in our first study of the RMRs and basal body temperatures of fibromyalgia patients,[238] patients in this study had a significantly lower mean RMR and basal body temperature than did matched healthy controls. The lower RMRs did not appear to be a result of calorie restriction, lower physical activity level, loss of fat-free weight, menstrual phase, or metabolism-lowering drugs such as β-blockers.

Patients mean free $T_3$ level was within the reference range but was significantly lower than that of controls. TSH and free $T_4$ levels did not differ between the groups. In neither group did TSH, free $T_3$, or free $T_4$ levels correlate with any RMR value or any measure of fibromyalgia status. For two reasons, however, inadequate thyroid hormone regulation cannot be ruled out as the mechanism of patients' lower RMRs: (1) TSH, free $T_3$, and free $T_4$ levels

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