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Female fibromyalgia patients: Lower resting metabolic rates than matched healthy controls

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Summary

Background: Many features of fibromyalgia and hypothyroidism are virtually the same, and thyroid hormone treatment trials have reduced or eliminated fibromyalgia symptoms. These findings led the authors to test the hypothesis that fibromyalgia patients are hypometabolic compared to matched controls.

Material/Methods: Resting metabolic rate (RMR) was measured by indirect calorimetry and body composition by bioelectrical impedance for 15 fibromyalgia patients and 15 healthy matched controls. Measured resting metabolic rate (mRMR) was compared to percentages of predicted RMR (pRMR) by fat-free weight (FFW) (Sterling-Passmore: SP) and by sex, age, height, and weight (Harris-Benedict: HB).

Results: Patients had a lower mRMR (4,306.31±1077.66 kJ vs 5,411.59±695.95 kJ, p=0.0028) and lower percentages of pRMRs (SP: –28.42±15.82% vs -6.83±12.55%, p<0.0001. HB: –29.20±17.43% vs -9.13±9.51%, p=0.0008). Whereas FFW, age, weight, and body mass index (BMI) best accounted for variability in controls' RMRs, age and fat weight (FW) did for patients. In the patient group, TSH level accounted for 28% of the variance in pain distribution, and free T_3 (FT_3) accounted for 30% of the variance in pressure-pain threshold.

Conclusions: Patients had lower mRMR and percentages of pRMRs. The lower RMRs were not due to calorie restriction or low FFW. Patients' normal FFW argues against low physical activity as the mechanism. TSH, FT_4, and FT_3 levels did not correlate with RMRs in either group. This does not rule out inadequate thyroid hormone regulation because studies show these laboratory values do not reliably predict RMR.

key words: **resting metabolic rate • fibromyalgia • body composition • TSH • free T_4 • free T_3**

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Background

Fibromyalgia (FM) is the most common disorder of chronic widespread pain and abnormal tenderness. There is currently no consensus on the underlying mechanism of FM. However, a line of evidence collectively indicates that inadequate thyroid hormone regulation, due to hypothyroidism (HO) or the peripheral type of cellular resistance to thyroid hormone (PRTH), is the main mechanism. (1) The symptoms and signs of FM are virtually identical to those of HO and PRTH [1–17]. (2) Studies have shown elevated thyroid autoantibodies among FM patients [18,19] and an increased incidence of primary and central HO [20–26]. Compared to a 1–5% incidence of primary HO in the general population [27,28], the reported incidence among FM patients is 10–24% [20,29–32]. The incidence of central HO in the general population has been estimated to be 0.00021%, while among 92 FM patients it was 43.5% [21]. All of the objectively verified abnormalities in FM and HO are plausibly explained by inadequate thyroid hormone regulation (ITHR) of transcription, alternative splicing, or mistranslation at the cellular level [1]. (3) Most objectively verified abnormalities of FM resemble those of HO or PRTH [1,33–35]. (4) Only in open [36–40] and blinded [41–45] clinical trials using thyroid hormone have FM patients recovered from their symptoms. Significant improvement of patients treated with thyroid hormone persisted 1–5 years in a follow-up study [46].

If ITHR is the mechanism of FM, patients should have the abnormally low resting metabolic rates (RMRs) characteristic of HO [47,48] and PRTH [49]. The purpose of this study was to compare the RMRs of FM patients to those of matched healthy controls, and through regression analysis, test for the RMR-regulating factors that best account for the variability in subjects' RMR values.

Material and Methods

The patient group consisted of 15 females who met the American College of Rheumatology (ACR) criteria for FM. FM status was quantified by percentage of the body in chronic pain, presence of tender points (pressure-pain threshold determined by algometry), scores on the Fibromyalgia Impact Questionnaire (a validated instrument for assessing functional ability [50]), visual analog scales of 13 associated FM symptoms, and Zung's Self-Rating Depression Scale. Patients were carefully interviewed to ensure that they were not restricting calorie intake and had not participated in regular fitness training in the last six months (running, swimming, cycling, weight training, aerobics, tennis), but were regularly engaged in work and routine life-maintenance activities (for example, shopping, yard work, local travel). Twenty-one applicants were excluded from the FM group because they had anemia, diabetes, cardiovascular disease, used medications that may alter RMR (β-adrenoceptor antagonists, metformin hydrochloride, thyroid hormone, oral contraceptives, or norepinephrine reuptake inhibitors), or engaged in regular fitness training.

The control group consisted of 15 females who failed to meet the ACR criteria for FM and who were free from any illness or injury that could influence RMR. "Healthy" status was determined by routine physical examination by a physician, blood tests, and psychological and health history questionnaires. Controls were matched to patients by sex, age, height, weight, absence of calorie restriction, and general physical activity level. Twelve applicants were excluded from the control group because they engaged in regular fitness training, were on an unusual diet, or used medications that can alter RMR.

Both premenopausal and postmenopausal subjects were included to allow testing of the null hypothesis that menstrual status is unrelated to either measured RMR (mRMR) or predicted RMRs (pRMRs). All subjects were nonsmokers and nonpregnant. Laboratory biochemical tests were performed, including a comprehensive metabolic profile, lipid profile, AM cortisol, TSH, free T_3, and free T_4. No subjects were excluded because their thyroid test results met current criteria for hyperthyroidism or HO. The reason is that although several studies have failed to find a correlation between mean thyroid function test values and RMR, one purpose of this study was to test for correlations between these measures and RMR values among FM patients.

The study design was approved by the Ethics Committee of the Fibromyalgia Research Foundation. Each subject signed an informed consent after reading, and receiving an oral description of, the study protocol. Subjects were not paid but were given copies of their test results.

Subjects were given written and oral instructions on how to prepare for laboratory biochemical testing and measurement of RMR and body composition. Accordingly, they fasted overnight for ≥12 hours before appearing at the medical laboratory (Boulder Community Reference Laboratory) to undergo a blood draw. The following day, after another ≥12-hour fast, they traveled to the metabolic testing facility. After arising from sleep, they used house and automobile heating and clothing to remain comfortably warm, and avoided physical and psychological stresses.

Upon arriving at the metabolic testing facility at 0900, each subject voided and disrobed to her underwear. Weight was measured on a balance beam scale (Healthometer, Continental Scale Corp, Bridgeview, IL). Height was measured using an attached stadiometer. Only the subject and tester were present. The temperature of the semidarkened, quiet room was adjusted so that it was comfortably warm for each subject. The subject then relaxed supine on a comfortable table under a warm cover for ≥30 minutes; she was visually monitored to make sure she was lying still but awake. Pulse and blood pressure were taken unobtrusively after RMR was measured.

Basal metabolic rates (BMRs) and RMRs usually increase during the luteal phase of the menstrual cycle and are lowest during menstruation [51,52]. For this reason, indirect calorimetry was performed during the follicular phase for all premenopausal women.

All RMR measurements were taken by the same technician using the MedGem®, a hand-held indirect calorimeter (Healthetech, Golden, Colorado). The device measures VO_2 and calculates RMR using a modified Weir equation with a constant respiratory quotient value of 0.85 ($RMR=6.931\times VO_2$) [53]. The MedGem® has been found to measure VO_2 and calculate RMR as accurately and reliably as reference systems

Table 1. Anthropometric data (mean ±SD).

	Patients	Controls	p*
Age	46±8.82	46±11.83	0.972
Height	166.99±5.63 cm	168.70±7.11 cm	0.470
	(65.74±2.22 in)	(66.42±2.80 in)	
Weight	74.30±10.69 kg	70.47±15.48 kg	0.437
	(163.79±23.56 lb)	(155.36±34.12 lb)	
BMI	26.61±3.38 kg/m^2	24.65±4.51 kg/m^2	0.175
FFW	47.44±6.18 kg	46.24±7.41 kg	0.633
	(104.59±13.63 lb)	(101.94±16.33 lb)	
% Body fat	35.89±4.61	33.42±6.04	0.218
FW	26.85±6.14 kg	24.23±9.17 kg	0.365
	(59.20±13.53 lb)	(53.42±20.21 lb)	
BBT	36.08±0.35°C	36.41±0.33°C	0.013
	(96.95±0.63° F)	(97.54±0.59°F)	

* Difference significant (independent t-tests) at p<0.05 level.

Table 2. Measured RMR and predicted RMRs (mean ±SD).

	Patients	Controls	p*
mRMR	4,306.31±1077.66 kJ	5,411.59±695.95 kJ	0.0028
	(1,029.23±257.57 kcal)	(1,293.40±166.34 kcal)	
pRMR by SP**	6,039.14±787.00 kJ	5,885.93±942.97 kJ	0.633
	(1,443.39±172.06 kcal)	(1,406.77±225.38 kcal)	
pRMR by HB***	6,110.07±542.86 kJ	5,972.81±637.93 kJ	0.531
	(1,460.34±129.75 kcal)	(1,427.54±152.47 kcal)	

* Difference significant (independent t-tests) at p<0.05 level;
** SP: Sterling-Passmore equation, uses FFW;
*** HB: Harris-Benedict equation, uses sex, age, height, weight.

Table 3. Measured RMR as percentages of predicted RMRs (mean ±SD).

Equation	Patients	Controls	p*
% of pRMR (SP**)	–28.42±15.82	–6.83±12.55	0.0001
% of pRMR (HB***)	–29.20±17.43	–9.13±9.51	0.0008

* Difference significant (independent t-tests) at p<0.05 level;
** SP: Sterling-Passmore equation, uses FFW;
*** HB: Harris-Benedict equation, uses sex, age, height, weight.

[54–57]. A recent study showed that the energy cost of subjects holding the MedGem is 255±84 kJ/day, but when adjusted for this increase, mRMR by the MedGem did not significantly differ from mRMR by the Sensormedics 2900 indirect calorimeter [54]. To avoid the increase in RMR from holding the instrument, each subject's arm and hand were carefully supported with cloth padding so that muscle contraction was not necessary. mRMR was then converted to percentages of RMR predicted by the subject's fat-free weight (FFW) (Sterling-Passmore equation: SP) and sex, age, height, and weight (Harris-Benedict equation: HB).

In preparation for body composition measurement, each subject avoided alcohol for 24 hours and drank at least two glasses of water on the morning of the test. After indirect calorimetry was performed, body composition was measured by tetrapolar bioelectrical impedance (Biodynamics Model 310, Seattle, WA).

Statistical analysis

Data are expressed as means ±standard deviations (SD), and t-tests for independent samples were used to look for differences between anthropometric variables and mRMRs, pRMRs, and percentages of pRMRs. Point-biserial correlation coefficient was used to test for correlations between continuous and dichotomous variables. Stepwise multiple regression analysis was used to determine which factors known to regulate RMR significantly accounted for the variability of mRMR and percentages of pRMRs. Level of significance was set at p≤0.05. Statistical analyses were performed with the SPSS for Windows (SPSS, Inc, Chicago, IL).

Results

Patients and controls did not significantly differ on anthropometric measures with the exception of basal body temperature (BBT) (see Table 1). Patients' mean BBT was significantly lower than that of controls. The groups also significantly differed on mRMR (Table 2) and on pRMR by FFW (SP equation) and by sex, age, height, and weight (HB equation) (Table 3). Patients and controls significantly differed on FM measurement scores (see Table 4).

Table 5 summarizes results of the R^2 analyses for both groups, showing the predictive power of independent variables on the variability within the groups of mRMR and mRMR as percentages of pRMRs. For controls, the best predictor of mRMR was FFW, accounting for 34% of the variance of mRMR (r=0.585029, p=0.0220). The predictive power of age was slightly less, accounting for 27% of the variance (r=–0.527223, p=0.0118). Weight was the only predictive variable for mRMR as a percentage of pRMR by FFW, accounting for 54% of the variance (r=–0.7322, p=0.0019). For mRMR as a percentage of pRMR by sex, age, height, and weight, fat weight (FW) was most predictive, accounting for 28% of the variance (r=–0.5280, p=0.0431). FW and body mass index (BMI) accounted for 58% of the variance.

In contrast, none of the independent variables tested predicted the variance of mRMR of patients. For mRMR as percentage of pRMR by FFW, age was the best predictor, accounting for 38% of the variance (r=0.6128, p=0.0151). For mRMR as percentage of pRMR by sex, age, height, and weight, age was the best predictor, accounting for 29% of the variance (r=0.539070, p=0.0381); and age and FW together accounted for 50% of the variance (r=–0.4569, p=0.0464).

TSH, FT_3, and FT_4 levels did not significantly differ between groups. Within groups, the levels did not significantly correlate with mRMR or mRMRs as percentages of

Table 4. FM measures (mean ±SD).

	Patients	Controls	p*
Pain distribution**	44.86±22.58%	3.73±3.97%	<0.0001
Tender points***	1.73±0.64 kg	2.40±0.73 kg	0.012
FibroQuest#	6.58±1.46	2.84±1.05	<0.0001
FIQ##	48.82±15.01	5.85±4.71	<0.0001
Zung's category###	2.47±1.19	1.13±0.35	0.001

* Difference significant (independent t-tests) at p<0.05 level;
** Percentage of 36 body divisions containing pain; and satisfying the ACR criteria of axial and bilateral pain, and pain above and below the waist, all of at least three months duration;
*** Kg pressure required to induce perception of tenderness at 16 predictable tender point sites;
# Mean intensity of 13 most common FM symptoms by visual analog scales. Severity: 1–10 point scale with 10 being the most severe;
Fibromyalgia Impact Questionnaire: standardized instrument for assessing functional status of FM patients. Range: 0–80; the higher the score, the lower the functional ability of the patient;
Zung's Self-Rating Depression Scale: 1=none, 2=mild, 3=moderate, 4=severe.

Table 5. Independent variables* as predictors of measured RMR, and measured RMR expressed as percentages of predicted RMRs.

Controls	Number of variables	R^2
mRMR	FFW (kg)	0.3423
	FFW, age	0.6202
mRMR as percentage of pRMR (SP**)	Weight (kg)	0.5361
mRMR as percentage of pRMR (HB***)	FW (kg)	0.2788
	FW, BMI	0.5768
Patients	**Number of variables**	**R^2**
mRMR	None	
mRMR as percentage of pRMR (SP**)	Age	0.3755
	Age, FW (kg)	0.5898
mRMR as percentage of pRMR (HB***)	Age	0.2906
	Age, FW (kg)	0.4972

* Independent variables: sex, age, height, weight, FFW, FW, BMI, TSH, FT_3, and FT_4;
** SP – Sterling-Passmore equation, uses FFW;
*** HB – Harris-Benedict equation, uses sex, age, height, weight.

pRMRs. However, R^2 analyses revealed that patients' TSH level accounted for 29% of the variability in pain distribution (r=0.5334, p=0.0406), and the FT_3 level accounted for 30% of the variability in pressure-pain threshold (r=–0.5499, p=0.0337).

The mRMR and mRMR as percentages of pRMRs did not differ when patients were grouped as pre- or postmenopausal. However, when controls were grouped as pre- or postmenopausal, the mRMR of premenopausal controls was significantly higher than that of postmenopausal controls (5754.20±718.90 vs 5111.80±552.83, p=0.0365). Also, when expressed as percentage of pRMR by HB, mRMR of postmenopausal controls was significantly lower than that of premenopausal controls (–12.95±10.11 vs –4.77±7.08, p=0.04838). When patients and controls were grouped as non-depressed and depressed based on the Zung's Self-Rating Depression Scale scores, no RMR values significantly differed.

Discussion

This study is the first to document that female FM patients have low RMRs compared to matched healthy controls. However, in this study RMR values did not correlate with any measure of FM status.

Careful selection of subjects, strict preparation of subjects for measurements, and R^2 analyses were used to determine the metabolism-regulating factor(s) that most likely account for differences in the RMR values of patients and controls. These steps make it unlikely that differences in sex, age, height, weight, calorie restriction, menstrual status, loss of FFW from relative physical inactivity, physical or emotional arousal, or ambient temperature were responsible for differences in RMR values.

FFW is the best single predictor of RMR [51,58–64], accounting for approximately 82% of the variance in RMR [65]. In this study, FFW was the best predictor of controls' mRMR. FFW did not predict the mRMR of patients even though the FFW of patients did not differ from that of controls. In addition, patients' creatinine levels were within the reference range and the mean did not significantly differ from that of controls, indicating that patients' muscle mass was not reduced [66]. These findings show that reduced FFW due to relatively low physical activity was not responsible for patients' low RMR values, and contradict the hypothesis that FM patients' symptoms are due to physical deconditioning [67]. The findings also suggest that growth hormone, insulin-like growth factor-1 [68,69], or testosterone deficiencies [70,71] were not responsible for patients' low RMR values, as these deficiencies should have been reflected in reduced FFW. Since we did not measure levels of these hormones, however, we cannot exclude the possibility of deficiencies.

Patients' mRMR was –28.42% of their pRMR based on FFW, and –29.20% of that predicted from sex, age, height, and weight. Age and FW were the best predictors of the low RMRs. Younger patients' RMRs were lower than those of older patients, and patients with higher FW had lower RMRs. For controls, too, higher body fat was associated with lower mRMR as a percentage of pRMR by sex, age, height, and weight. Other studies, however, have shown that among sedentary individuals, age is inversely associated with RMR [72,73], and higher FW is positively associated with RMR

[74]. In this study, then, for patients, the associations of age and FW to RMR values as percentages of pRMRs are opposite to those expected. That both patients and controls were sedentary probably accounts at least in part for their higher than expected FW. Gilliat-Wimberly et al, for example, found that compared to habitually exercising women, sedentary women had lower RMRs and higher FW [75].

The FW of patients in this study may be a result of their lower RMRs. A low RMR is a major risk factor for obesity [65]. Long-term follow-up has shown that subjects with lower RMRs gained significantly more body fat than those with higher RMRs [65,76–78]. For example, when subjects were followed for 10–12 years, lower baseline RMR strongly correlated with increased FW (r=-0.50; p<0.001) [78].

The unexpected findings raise the possibility that ITHR was the mechanism of patients' lower RMR values. In this study, TSH, FT_3, and FT_4 levels do not correlate with patients' RMR values. This is not, however, unexpected, especially in view of the small number of patients and controls taking part in the study. In a study of 108 obese patients with untreated subclinical HO and 131 matched obese controls, the TSH only weakly correlated with RMR/FFW (r=–0.200, p=0.007) for HO patients [79]. For controls, the TSH did not correlate with RMR/FFW (r=0.026, p=0.796). FT_4 did not correlate with RMR for either group. In a study of 9 HO patients in which 27 comparisons were made of TSH and RMR values, the TSH did not correlate with RMR (r=–0.3437, p=0.079) until TSH values were log transformed (r=–0.4654, p=0.014) [80]. In a study of 103 euthyroid subjects, the FT_4 inversely correlated with BMR (r=–0.51, p<0.001), but the FT_3 and BMR did not correlate [81]. In another study, no correlation was found between the FT_4 index and BMR of untreated hyperthyroid and hypothyroid patients [82]. However, correlations were found between the FT_3 index and BMR for hyperthyroid (r=0.63, p<0.01) and hypothyroid (r=0.61, p<0.01) patients. Hence, the lack of correlation between TSH, FT_3, and FT_4 levels and RMR values in this study does not rule out ITHR as a mechanism of patients' low RMRs.

In this study, TSH level positively correlated with patients' pain distribution, and the FT_3 level inversely correlated with pressure-pain threshold. In view of previous studies showing a high incidence of primary HO in FM, the positive correlation between TSH level and pain distribution raises the possibility that pain distribution in FM is associated with primary HO.

A mechanism for the inverse relationship between FT_3 and pressure-pain threshold is not clear. Elevated serum T_3 due to selective anti-T_3 antibodies that prolonged the serum time span of T_3 has been reported [83]. By extension from hypothetical mechanisms proposed by other researchers, however, patients' FT_3 levels may have been high due to decreased plasma membrane transport of T_3 [84], resulting in low intracellular concentrations of T_3 [81].

A low T_3 concentration in nociceptive afferent neurons disinhibits substance P synthesis and secretion, increasing substance P and its augmentation of nociceptive signals [85,86]. Thyroid hormone inhibits the synthesis and secretion of substance P in many CNS cells [87–91]. It does so by repressing transcription of the preprotachykinin-A gene. Preprotachykinin-A is the precursor of substance P and its cognate substance P receptor [90,92]. Thyroidectomized rats had a 100% increase in dorsal horn substance P [89,93]. Thyroid hormone administration lowered the level to baseline [93], and excess thyroid hormone exposure lowered substance P below baseline [88]. The cerebrospinal fluid level of substance P in FM patients has been reported to be 90–300% higher than normal [94–97]. Because of this, reduced substance P was conjectured to be responsible for the decrease in FM patients' pain distribution and pressure-pain threshold in T_3 phases of three blinded trials. Conversely, increased substance P was conjectured to be responsible for the increase in pain distribution and pressure-pain threshold during placebo phases [41–43].

Whether or not patients' pressure-pain threshold in this study was low because of a low T3 concentration in their nociceptive neurons (despite a high serum FT3) with consequent high substance P levels cannot be determined from this study. If other researchers also find this inverse relationship (FT3 level to pressure-pain threshold) in FM patients, studies should be conducted to determine the responsible mechanism and its possible relationship to lower pressure-pain threshold.

This study appears to be the first to document significantly lower BBT in FM patients compared to matched controls. The lower BBT is consistent with HO [98,99].

There were at least three limitations to this study. The TSH, FT_4, and FT_3 assays assess function of the pituitary-thyroid axis. Reference range levels, however, fail to rule out two types of ITHR: central HO and PRTH. Both disorders can lower patients' RMRs [49,100]. Previous studies by our group found that 44% of FM patients had test results consistent with central HO, which is 250,000 times the incidence in the general population [20,21]. The laboratory test most useful for identifying patients' with central HO is the dynamic TRH-stimulation test. Because the test is no longer available, patients in this study were not tested for possible central HO.

An evaluation of available evidence suggests that 34.5% of FM patients have PRTH [101]. Clinical criteria for determining PRTH are the relief of hypothyroid-like symptoms in response to supraphysiologic dosages of T_3 with a high free T_3 level and absence of thyrotoxicosis [1]. Whether any patients had PRTH cannot be determined because treatment was not part of this study.

The first 4 patients and 2 controls completed diet and physical activity logs, but this requirement was abandoned for two reasons. First, too many applicants declined to take part in the study if required to keep logs. Second, patients and controls who did the logs substantially underreported their calorie intake. This is consistent with reports by other researchers for obese, lean, and athletic subjects [102–109]. Underreporting has been shown to range from 20–30% [103,108] and 40% [104–106]. For subjects in this study who filled out the logs, calorie intake was 32% below calorie expenditure due to underreporting. For this reason, applicants were carefully interviewed instead to ensure they were not restricting calories and that they were not completely sedentary or engaged in regular fitness training. Because this

method did not provide an accurate account of subjects' calorie intake or energy expenditure, future studies should employ a computer-based diet assessment and a computerized device such as an accelerometer to document energy expenditure through activity.

CONCLUSIONS

FM patients had significantly lower RMRs than matched healthy controls. The lower RMRs did not appear to be a result of calorie restriction, lower physical activity level, loss of FFW, measurement during the menstrual period, or use of drugs such as β-blockers. TSH positively correlated with pain distribution and FT_3 inversely correlated with pressure-pain threshold. TSH, FT_3, or FT_4 did not correlate with RMR values. For two reasons, however, ITHR cannot be ruled out as the mechanism of FM patients' lower RMRs: (1) TSH, FT_3, and FT_4 levels have not been shown to reliably correlate with RMR values, and (2) these tests evaluate only pituitary-thyroid axis function and cannot rule out central HO and PRTH.

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