A Combination of 6 Months of Treatment with Pyridostigmine and Triweekly Exercise Fails to Improve Insulin-Like Growth Factor-I Levels in Fibromyalgia, Despite Improvement in the Acute Growth Hormone Response to Exercise

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ABSTRACT. ***Objective.*** People with fibromyalgia (FM) often have low insulin-like growth factor-I (IGF-I) levels and a suboptimal growth hormone (GH) response to acute exercise. As previous work had demonstrated a normalization of the acute GH response to exercise with the use of pyridostigmine (PYD), we tested the hypothesis that 6 months of PYD therapy plus supervised exercise would increase IGF-I levels.

Methods. Subjects with primary FM were randomized into 4 groups: (1) PYD/exercise; (2) PYD/diet recall; (3) placebo/exercise; and (4) placebo/diet recall. The dosing of PYD was 60 mg tid for 6 months. Resting IGF-I levels were measured at baseline and after 6 months of treatment. In addition the acute GH response to exercise at VO_2 max was measured at baseline and after treatment.

Results. A total of 165 FM subjects (mean age 49.5 yrs, 5 male) were entered and 154 (93.3%) completed the study. Six months of therapy (PYD plus exercise or exercise alone) failed to improve the IGF-I levels. The use of PYD 1 hour prior to exercise improved the acute GH response (4.54 ng/dl) compared to placebo (1.74 ng/dl) ($p = 0.001$) at the end of the 6-month trial. The acute GH response to exercise at baseline did not correlate with IGF-I, age, depression, medications, estrogen status, or obesity.

Conclusion. A combination of triweekly supervised exercise plus the daily use of PYD for 6 months failed to increase IGF-I levels in patients with FM, despite the confirmation that PYD normalizes the acute GH response to strenuous aerobic exercise. (First Release April 1 2007; J Rheumatol 2007; 34:1103–11)

Key Indexing Terms:
FIBROMYALGIA EXERCISE PYRIDOSTIGMINE
GROWTH HORMONE INSULIN-LIKE GROWTH FACTOR-I

Fibromyalgia (FM) is a chronic disorder of widespread pain, disrupted sleep, and fatigue[1]. People with FM typically have low levels of physical fitness and often report symptom exacerbation after exercise[2-4]. Contemporary research has provided persuasive evidence that the pain component of FM is, in part, related to abnormal sensory processing within the central nervous system[5,6]. However, it is less clear why patients with FM have fatigue and postexertional aggravation of symptoms. We have previously surmised that in some cases these problems may result from an adult-onset growth hormone (GH) deficiency[7]. According to one study of 500 patients with FM, about one-third had low levels of insulin-like growth factor-I (IGF-I)[8]. IGF-I is the main effector molecule for the actions of GH, and low levels are suggestive of the GH deficiency state[9]. Recombinant GH therapy was found to normalize IGF-I and improve FM symptoms in women with low IGF-I levels[10]. We have reported that patients with FM have a subnormal GH response to an exercise stress test and that this can be normalized by prior administration of pyridostigmine (PYD)[11,12]. Our results as well as those of others[13,14] suggest that low levels of IGF-I in patients with FM are not due to pituitary disorders, but more likely result from disordered physiology of hypothalamic releasing factors. It is hypothesized that PYD, a potent cholinergic stimulus, effects this normalization of GH secretion by its inhibitory effect on the hypothalamic release of somatostatin (an antagonist of hypothalamic GHRH release).

The normalization of IGF-I levels with recombinant GH therapy is very expensive and requires daily injections. Thus a less costly strategy, using a combination of a physiological

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stressor (i.e., exercise) and an inexpensive and readily available oral medication (i.e., PYD) might prove to be an attractive alternative. The objectives of our study were 3-fold: (1) test the hypothesis that the daily use of PYD, either by itself or in combination with regular exercise, would improve IGF-I levels in patients with FM; (2) determine whether our original report, of impaired GH release in FM patients and its normalization by PYD, can be reproduced with a larger cohort[12]; and (3) explore the contribution of various factors that may alter IGF-I levels and influence the acute GH response to the stress of exercise.

MATERIALS AND METHODS

Study design. Our study was a single-site randomized, controlled, clinical trial of 6 months' duration. Subjects were randomized into 4 groups: (1) PYD/exercise; (2) PYD/diet recall; (3) placebo/exercise; and (4) placebo/diet recall. Age, sex, and body mass index (BMI) were block factors in the random assignment. The PYD arm was double-blinded. The exercise versus attention control (diet recall) could not be double-blinded. The university's Institutional Review Board and General Clinical Research Center (GCRC) approved the protocol, and all patients provided written informed consent. A detailed description of the multistep recruitment process has been published[15].

The target population was adults aged 18–65 years, both female and male, who fulfilled the American College of Rheumatology (ACR) FM classification criteria[1] and were medically capable of engaging in an exercise program. The exclusion criteria were: any other rheumatic disorder, current or past history of cardiovascular, pulmonary, neurological, endocrine, or renal disease that would preclude involvement in treadmill testing to VO_2 max or alter the GH/IGF-I axis; current use of PYD, high-dose beta-blockers, systemic steroids; currently exercising more than 30 min per week; score ≥ 29 on the Beck Depression Scale modified for FM; BMI > 45 kg/m^2; pregnant or nursing; planned elective surgery during the study period; and ongoing, unresolved disability litigation. The laboratory portion of the study was conducted at the GCRC. The exercise classes were conducted in a specially designed suspended wood floor aerobics studio located on the university campus.

Subject recruitment. Study subjects were randomly selected from the study team's clinical database of over 8000 patients with FM seen on referral at a university tertiary care center. Those patients who were interested in participating were randomly assigned to one of 4 groups (PYD + exercise, PYD + diet recall, placebo + exercise, placebo + diet recall) by the team's statistician, who had no contact with the subjects.

Demographic data such as age, weight, height, BMI, estrogen status (menopausal status and/or use of estrogen), current medications, duration of FM, and Beck Depression Inventory scores were obtained. Percentage body fat was estimated with 2 measurements: (1) 7 point skin-fold caliperimetry (chest, axilla, triceps, subscapula, abdomen, suprailiac, thigh) with a 2 prong spring-loaded Harpenden caliper per standardized anthropomorphic guidelines[16]; and (2) bioelectrical impedance using a standardized technique in supine subjects who had been fasting overnight and without water for 4 h prior to measurement[17]. VO_2 max was measured with treadmill and metabolic cart, as described[18].

Laboratory measurements. GH, IGF-I, and IGF-I binding protein 3 (IGF-IBP3) were measured by chemiluminescence assay analysis on automated Immulite platform (Diagnostic Procedures Corp., Los Angeles, CA, USA). GH assay sensitivity was 0.01 ng/ml; the mean intraassay coefficient of variation (CV) was 5.8%. IGF-I assay sensitivity was 20 ng/ml and the mean intraassay CV is 3.6% and mean interassay CV 6.6%. IGF-IBP3 assay sensitivity was 0.02 μg/ml, the mean intraassay CV was 4.2%, and mean interassay CV 8.6%.

Study procedures. Study subjects withheld all medications and fasted from midnight the previous night (water allowed until 6:00 AM). All tests were performed between 10:00 AM and noon to minimize circadian influences on GH release. Baseline blood samples for GH and IGF-I were obtained through an indwelling intravenous catheter that was inserted at least 30 min prior to the first blood draw. One hour later, GH was repeated. Subjects walked or jogged on a treadmill (SMC 2000) using a Balke protocol modified for FM[19]. Respiratory gas exchange was measured by a metabolic cart (SensorMedics Vmax 29). Continuous monitoring of the electrocardiogram (ECG) was performed using a SensorMedics Cardiosoft ECG system. Subjects exercised to the point of volitional exhaustion, which was defined when either of 2 goals were met: (1) respiratory quotient of > 1.1 for 30 consecutive s, indicative of anaerobic metabolism; or (2) self-reported exhaustion (SRE) ≥ 18, as reported on a 0–20 point perceived Borg effort scale. Immediately at the point of SRE or VO_2 max, blood was collected for GH (time 3). Study subjects then rested in a seated position and the final serum GH was measured exactly 1 hour after the previous blood draw.

Study subjects were then randomized to receive PYD (ICN Pharmaceuticals, Costa Mesa, CA, USA) or placebo, as well as exercise classes or diet recall (attention control). Patients titrated the study drug to full dose over the following 11 days. Titration protocol was 30 mg of PYD on Day 1, increasing by 30 mg each day until a dosage of 60 mg 3 times a day was achieved. The total daily dose (180 mg) was based on our previous acute dosing trial[12] and clinical experience[20]. The study subjects were instructed to take the study drug in the morning, 1 hour prior to exercise class (based on our pilot data)[12], and at bedtime to maximize GH release during stages 3 and 4 sleep when 70%–80% of GH is produced[21]. Weekly data logs were used to confirm the dose of training exercise, monitor for adverse events, and document drug side effects.

Treatment protocol for exercise classes. The exercise classes were supervised by the same instructor and were group-based (10–20 per group), 60 min in duration, 3 times per week, lasting for 6 months. The format included warmup and cardioaerobics training 30 min, strength training for 10 min, flexibility training for 5 min, balance training for 5 min, and relaxation for 10 min. The cardioaerobic exercise consisted of low impact, nonrepetitive floor aerobics with intensity goal of 40%–50% maximum heart rate or perceived exertion of 10–12 of 20. Talk-test and age-adjusted pulse rates were used for intensity feedback. Strength training included muscular awareness education, breathing, and alignment instruction, elastic bands and free weights used for resistance; titration was achieved by 3 plus variations of banding and weight strengths. All major muscle groups were worked throughout each week. Flexibility training included static and nonballistic stretching, taken only to the point of gentle tension, specific to all major muscle groups. Balance training was both static and dynamic and included standing poses on balance boards and foam pads. Progressive relaxation was achieved without muscle tensing and included guided imagery with breathing awareness. The intensity of exercises was purposefully lower than American Academy of Sports Medicine guidelines, due to recognition of baseline physical deconditioning in FM that predisposes patients to enhanced delayed muscle pain, symptom flare, and aggravation of FM tender point areas[3].

Treatment protocol for attention control. All study subjects randomized to the attention control groups received attention from a registered nurse weekly by telephone and a 2 hour personal monthly visit. The study subjects were told that they were providing dietary data that potentially could be used in future diet intervention studies in FM. They completed objective diet recall surveys and provided narrative diet history regarding type of foods [carbohydrate, fat, protein, micronutrients, vitamins, herbs, and chemicals (e.g., MSG, aspartame)] as it related to their overall FM symptoms[22,23]. The registered nurse was in close contact with the exercise instructor so that a similar supportive message would be conveyed to both groups.

Final visit. Subjects returned at the end of the 6-month study for a second treadmill test. The procedures were the same as the baseline with one key difference: half the subjects (those already taking PYD) were given one 60 mg tablet of PYD 1 hour before starting the treadmill, and the other half received placebo. In the event that a subject requested to withdraw from the study, the final laboratory visit was conducted within 2 weeks of withdrawal, if the subject agreed to the visit.

Statistical analysis. To test for differences at baseline, we used 2 (drug, placebo) × 2 (exercise, no-exercise) analyses of variance or chi-square tests depending on the character of the variable. We used 2 (drug, placebo) × 2 (exercise, no-exercise) analyses of covariance (ANCOVA) on outcomes at followup, controlling for baseline scores on the outcome under consideration, to evaluate the combined effects of drug and exercise. This approach offered us more statistical power than using a repeated-measures approach. This ANCOVA answers the question whether there are group differences at followup, after controlling for differences that existed at baseline. The null hypothesis was that PYD plus exercise would not improve IGF-I/IGF-IBP3 levels and would not enhance the acute GH response to exercise. The means that are reported are the part of the post-test scores that could not be predicted by the pre-test scores, or the residualized post-test scores. We refer to these means as the "adjusted means." The unadjusted means, referred to as "raw means," are also reported. Correlation analysis was used to determine what factors were related to serum markers at baseline. In order to correct for an inflation in Type I error due to multiple testing, we interpreted both ANCOVA and correlation results as significant only if $p < 0.01$.

Power analysis. As we had no previous data on the IGF-I response to longterm PYD use, we made the assumption that a sustained improvement in GH secretion would result in significantly increased IGF-I levels. The sample size was therefore calculated by a power analysis based on a previous study of 20 subjects with FM who reported normalization of GH secretion after the use of PYD[12]. In our study, GH was the primary outcome variable; resting levels were 0.57 ± 0.82 [mean ± standard deviation (SD)] and they increased to 4.70 (SD 3.80) with the use of PYD plus exercise. Assuming the same effect size for the placebo + no exercise group as compared to the PYD + no exercise group, a sample of 30 patients in each group was determined to provide statistical power > 0.95 with an alpha level of 0.05 for serum GH. We set the sample size to be recruited at 144 (36 per group) to allow for up to 18% noncompliance and loss to followup.

RESULTS

Consort flow chart. A flow chart for participants is depicted in Figure 1. Of the 165 study subjects who attended the baseline laboratory visit, 41 were assigned to the placebo/no training exercise group, 39 to the placebo/training exercise group, 42 to the PYD/no exercise group, and 43 to the PYD/exercise group. Eleven of these 165 subjects did not attend the 6-month followup visit (4 were "too busy," 3 developed medical problems unrelated to FM, 2 had PYD side effects of abdominal pain, 1 was in a serious motor vehicle accident, and 1 relocated). The analyses were done on completers and thus were not intention-to-treat.

Demographics. Demographic and clinical characteristics for each group are presented in Tables 1 and 2. No statistically significant differences were found among the 4 groups at baseline on age, sex, years with FM, estrogen status, medications (i.e., tricyclic antidepressants, selective serotonin reuptake inhibitors, tramadol, opioids, nonsteroidal antiinflammatory drugs, hypnotics), depression, number of tender points, BMI, percentage body fat, VO_2 max, time on treadmill, baseline GH at peak treadmill, IGF-I, and IGF-IBP3. The mean IGF-I (141 ng/ml) was low, compared to published age-adjusted norms in healthy adults[24].

Effect of treatment on IGF-I levels. Our major hypothesis, that daily PYD would enhance GH release during the exercise classes and as a result raise IGF-I levels, was not sustained

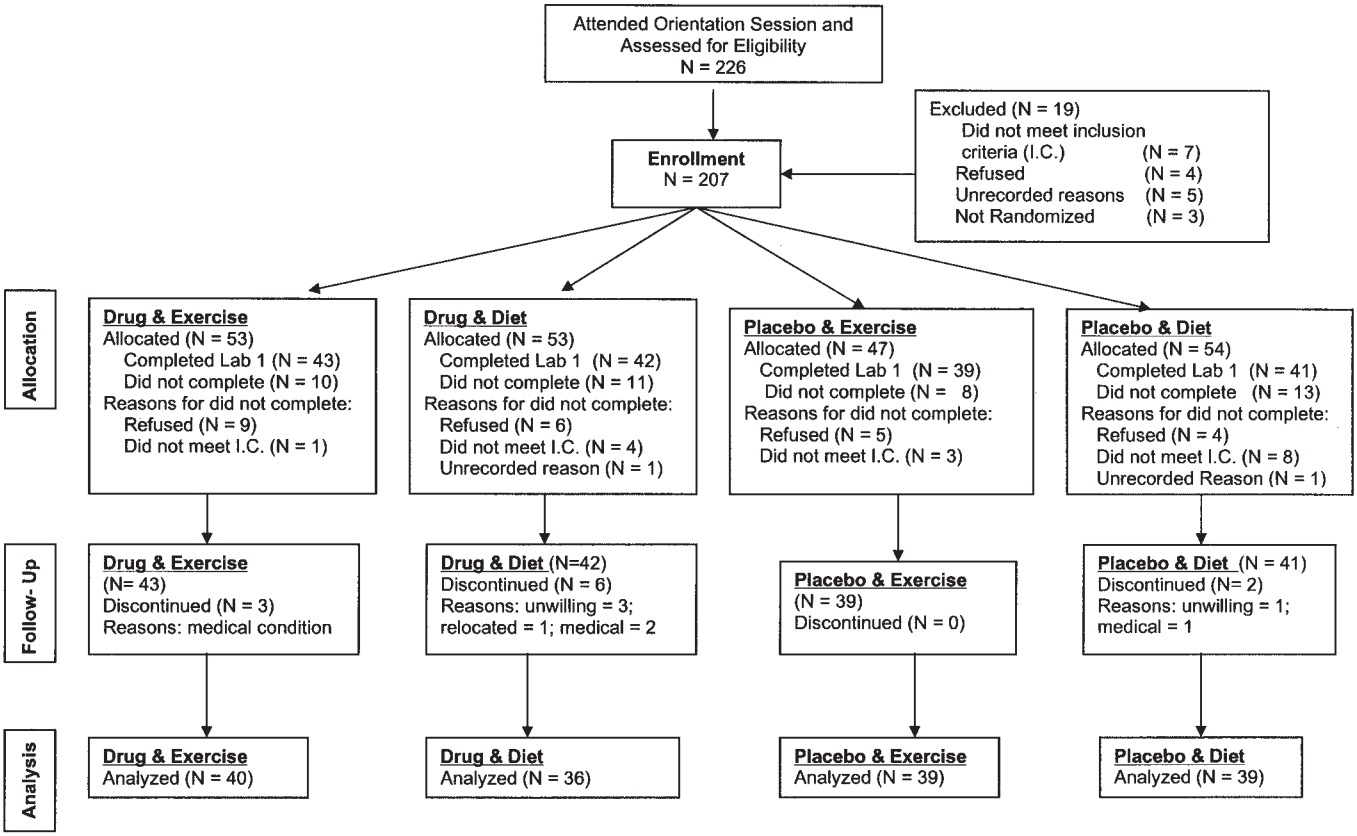

Figure 1. Participants' progress through the study. IC: inclusion criteria.

Table 1. Baseline demographics. One-way ANCOVA were used to test for statistical differences between the 4 groups on age and years with FM symptoms. No statistical tests were conducted on sex or ethnicity due to the small number of patients in some cells.

	Placebo/No Training Exercise		Placebo/Training Exercise		PYD/No Training Exercise		PYD/Training Exercise		
	%	N	%	N	%	N	%	N	p
Sex		41		39		42		43	
Female	100.0		94.9		92.9		100.0		
Male	0.0		5.1		7.1		0.0		
Ethnicity		41		39		40		41	
White	87.8		89.7		92.5		100.0		
Non-white	12.2		10.3		7.5		0.0		
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	
Age, yrs	49.78 (7.87)	41	49.62 (7.65)	39	49.31 (7.89)	42	49.12 (8.95)	42	0.984
Yrs with FM	14.91 (10.62)	41	16.91 (11.94)	38	14.81 (9.74)	39	14.97 (10.48)	39	0.704

Table 2. Baseline clinical characteristics.

	Placebo/ No Exercise		Placebo/ Exercise		PYD/ No Exercise		PYD/ Exercise		
	%	N	%	N	%	N	%	N	p
Pre-menopausal or post-menopausal with HRT	61.0	25	62.2	23	75.0	27	60.5	26	0.504
Taking TCA	39.0	16	34.2	13	47.4	18	51.2	21	0.409
SSRI/SNRI	37.5	15	34.2	13	41.7	15	42.5	17	0.869
Tramadol	14.6	6	23.7	9	21.1	8	14.6	6	0.645
Opioids	31.7	13	28.9	11	23.7	9	29.3	12	0.884
NSAID	46.3	19	42.1	16	47.4	18	43.9	18	0.967
Hypnotics	26.8	11	26.3	10	23.7	9	29.3	12	0.957
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	
Beck Depression	8.97 (6.51)	41	10.58 (6.81)	39	9.99 (5.90)	41	7.85 (6.27)	43	0.155
BMI kg/m^2	30.22 (6.54)	41	30.08 (6.30)	39	28.99 (6.01)	42	29.01 (6.12)	43	0.363
% body fat (7 site skinfold formula)	35.54 (6.89)	40	35.32 (8.60)	39	33.36 (8.54)	42	34.25 (8.03)	42	0.590
% body fat (bio-electrical impedance	33.33 (7.00)	41	33.26 (7.34)	39	31.33 (8.21)	42	32.26 (8.18)	41	0.604
Abdominal site for skinfold thickness	38.75 (12.75)	40	40.21 (15.45)	39	36.90 (14.34)	42	36.88 (14.13)	42	0.672
VO_2 max ml/kg	20.4 (4.52)	40	21.39 (4.91)	38	22.95 (4.74)	41	22.11 (5.13)	43	0.110
Total time on treadmill, s	526.5 (260.0)	42	590.0 (283.0)	38	715.0 (292.0)	42	638.8 (270.0)	42	0.018
GH at VO_2 max ml/kg without PYD	1.41 (2.94)	41	1.01 (1.26)	39	2.95 (5.31)	42	1.61 (3.09)	43	0.069
IGF-I at rest	140.46 (52.07)	41	126.73 (63.32)	39	148.44 (56.26)	42	151.5 (58.93)	43	0.222
IGF-I BP3 at rest	4.97 (1.3)	41	4.61 (1.21)	39	4.5 (1.11)	42	4.91 (1.06)	43	0.204

PYD: group of subjects who would be taking pyridostigmine throughout the study. The baseline exercising GH test was performed before the subjects started on PYD. TCA: tricyclic antidepressant; SSRI: selective serotonin reuptake inhibitor; SNRI: selective serotonin/norepinephrine reuptake inhibitor; NSAID: nonsteroidal anti-inflammatory drugs.

(Figure 2, Table 3). This hypothesis was analyzed with 2 × 2 ANCOVA on followup scores controlling for the baseline value of the variable of interest. The interaction of PYD plus exercise classes was not significant for IGF-I level ($F(1,147) = 5.26$, $p = 0.022$). The main effect of PYD, collapsing across the exercise class groups, was not significant ($F(1,147) = 0.02$, $p = 0.891$). The main effect of exercise classes, collapsing across the categories of PYD, was also not significant ($F(1,147) = 0.28$, $p = 0.600$. In sum, these results indicate that neither PYD nor exercise classes had a significant effect on IGF-I levels. Further, they indicate PYD did not enhance the effect of exercise classes on IGF-I levels. Table 3 displays the raw means and SD at baseline as well as the means from the ANCOVA.

Effect of treatment on IGF-IBP3 levels. The interaction of PYD plus exercise classes was not significant for IGF-IBP3

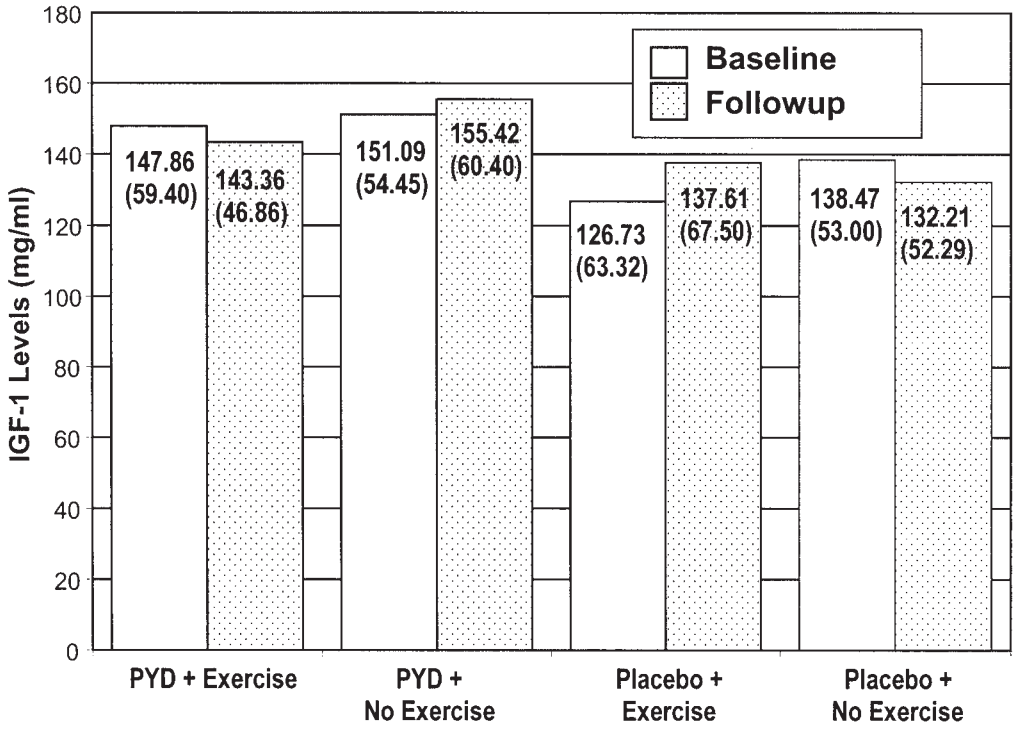

Figure 2. Baseline and followup raw mean data (standard deviations) taking IGF-I.

Table 3. Means (SD) for serum markers and exercise testing at baseline and followup.

	Raw Statistics				Adjusted Followup Statistics from ANCOVA[a]			
	Baseline		Followup					
	Exercise M (SD)	No Exercise M (SD)	Exercise M (SD)	No Exercise M (SD)	Exercise N	Exercise M (SD)	No Exercise N	No Exercise M (SD)
GH 30 min prior to treadmill								
PYD	1.62 (2.07)	2.60 (4.41)	1.48 (1.99)	1.44 (2.19)	40	1.53 (2.17)	36	1.17 (2.18)
Placebo	1.27 (1.73)	1.62 (5.00)	1.79 (3.53)	1.13 (1.62)	39	1.95 (2.17)	37	1.18 (2.17)
GH immediately prior to treadmill								
PYD	0.97 (2.30)	0.57 (1.22)	1.08 (1.61)	1.00 (1.43)	40	1.04 (1.64)	35	1.01 (1.63)
Placebo	0.73 (2.04)	0.48 (0.81)	1.27 (2.04)	0.91 (1.38)	38	1.26 (1.63)	37	0.93 (1.64)
GH at peak treadmill								
PYD	1.48 (3.07)	2.99 (5.37)	4.95 (7.85)	4.92 (7.79)	40	5.12 (5.12)	35	3.96 (5.21)
Placebo	1.01 (1.26)	1.49 (3.07)	1.77 (2.86)	1.00 (1.49)	38	2.34 (5.18)	38	1.16 (5.18)
GH at 1 h post treadmill								
PYD	0.37 (0.64)	0.39 (0.59)	1.25 (1.64)	1.85 (3.86)	40	1.25 (2.00)	34	1.04 (2.00)
Placebo	0.28 (0.45)	0.46 (1.03)	0.39 (0.45)	0.18 (0.18)	38	0.45 (2.01)	37	1.26 (2.00)
IGF-I								
PYD	147.86 (59.40)	151.09 (54.45)	143.36 (46.86)	155.42 (60.40)	40	137.70 (32.63)	36	147.13 (32.70)
Placebo	126.73 (63.32)	138.47 (53.00)	137.61 (67.50)	132.21 (52.29)	38	149.15 (31.81)	39	134.57 (32.60)
IGF-IBP3								
PYD	4.94 (1.06)	4.51 (1.11)	4.55 (0.84)	4.94 (1.06)	40	4.43 (0.88)	36	4.59 (0.88)
Placebo	4.61 (1.21)	4.84 (1.19)	4.55 (1.19)	4.44 (1.05)	39	4.62 (0.87)	38	4.38 (0.87)
VO_2 max ml/kg								
PYD	21.74 (4.65)	23.13 (4.84)	20.83 (4.22)	21.38 (4.42)	40	20.46 (3.15)	34	21.03 (3.18)
Placebo	21.39 (4.91)	20.68 (4.54)	20.83 (5.16)	19.07 (3.65)	38	19.74 (3.15)	37	20.81 (3.17)
Time on treadmill, s								
PYD	632.95 (265.92)	721.49 (282.23)	673.63 (239.40)	729.43 (326.11)	40	648.17 (193.65)	35	662.65 (196.79)
Placebo	581.49 (284.23)	548.95 (256.15)	630.13 (318.88)	514.89 (270.31)	39	570.61 (194.07)	38	660.01 (195.23)

[a] ANCOVA were conducted on followup scores adjusting for differences at baseline on a particular outcome. GH: growth hormone; PYD: pyridostigmine.

(F(1,147) = 1.95, p = 0.165). The main effect of PYD on IGF-IBP3, collapsing across the training exercise groups, was not significant (F(1,147) = 0.00, p = 0.966). The main effect of exercise classes on IGF-IBP3, collapsing across the categories of PYD, was not significant (F(1,147) = 0.06, p = 0.800). In sum, these results indicate that neither PYD nor exercise classes had a significant effect on IGF-IBP3. Further, they indicate PYD did not enhance the effect of exercise classes on IGF-IBP3 levels.

Effect of PYD on GH secretion at VO_2 max/SRE. The main effect of PYD on GH response at VO_2 max/SRE, collapsing across the exercise class groups, was significant (F(1,147) = 10.93, p = 0.001, Cohen's d = 0.54, 99% CI 0.12–0.97). The PYD groups (adjusted mean 4.54 ng/ml, SD 5.19) had a higher GH at followup than the placebo groups (adjusted mean 1.74 ng/ml, SD 5.17; Figure 3). The interaction of PYD plus exercise classes was not significant for GH response at VO_2 max/SRE (F(1,147) = 0.00, p = .988). In order to illustrate the pattern of change the raw means are shown in Figure 3. The main effects of the exercise classes, collapsing across the categories of PYD, was not significant (F(1,147) = 1.84, p = 0.177). In sum, these results indicate that PYD increases the acute GH response at VO_2 max. There is no evidence that training exercise improves the GH response at VO_2 max/SRE. Further, the results indicate that the exercise classes did not enhance the effect of PYD on GH response to VO_2 max/SRE.

Effect of treatment on VO_2 max and time on treadmill. In order to understand the lack of treatment effect on IGF-I levels, we determined whether the exercise classes improved aerobic conditioning. Using a 2 × 2 ANCOVA on followup scores, controlling for the baseline value of the variable of interest, neither PYD + exercise, nor PYD alone, nor exercise alone resulted in a significant improvement in VO_2 max or time on treadmill.

Variables that modify the acute GH response and IGF-I levels. To identify factors related to GH release at VO_2 max/SRE and IGF-I, we examined the correlations at baseline (without PYD). The VO_2 max (r = 0.25, p < 0.002) and time on treadmill (r = 0.31, p < 0.001) were positively correlated with GH release (Figure 4). On the other hand, age, sex, BMI, percentage body fat (7 site skin-fold formula and bioelectrical impedance), single abdominal site for skin-fold thickness, estrogen status, IGF-I, medications, and depression did not correlate with GH secretion at VO_2 max/SRE.

Baseline IGF-I was significantly correlated with age (r = –0.45, p < 0.001), measures of aerobic fitness (VO_2 max, r = 0.28, p < 0.001), time on treadmill (r = 0.34, p < 0.001), and measures of body composition (BMI, r = –0.34, p < 0.001); percentage body fat by 7 site skin-fold formula (r = –0.30, p < 0.001); percentage body fat by bioelectrical impedance (r = –0.40, p < 0.001); abdominal site for skin-fold caliperimetry (r = –0.26, p < 0.001). Baseline IGF-I was not associated with estrogen status, medications, depression, or duration of FM symptoms.

Adverse reactions. PYD has been used for over 30 years in the treatment of myasthenia gravis, and its adverse effects are well known. Two subjects dropped out due to unacceptable adverse effects (abdominal pain). The reported adverse effects in subjects taking PYD and placebo are given in Table 4. The commonest adverse effects reported with PYD were loose

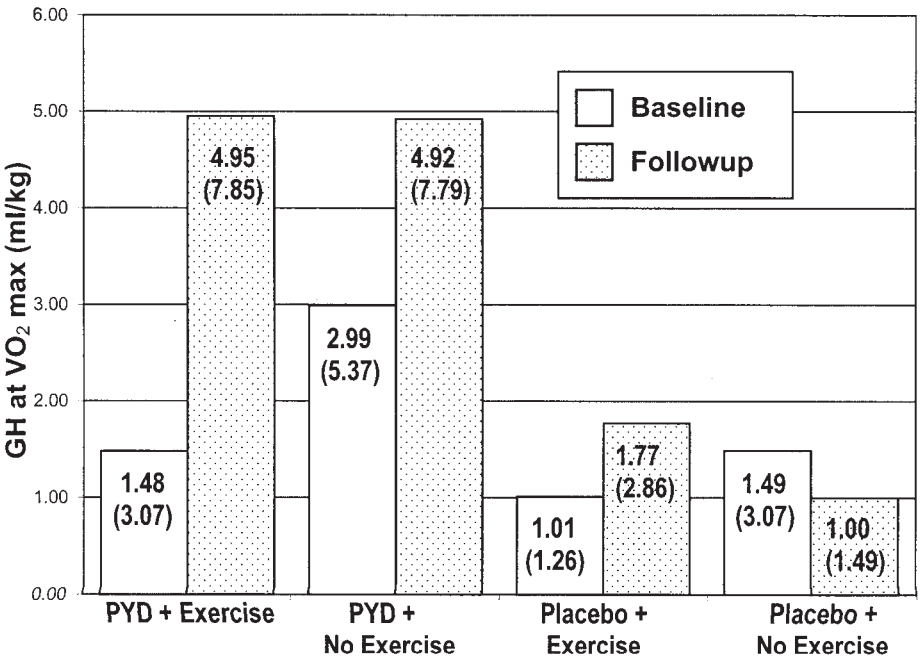

Figure 3. Baseline and followup raw mean data (SD) taking growth hormone at VO_2 max.

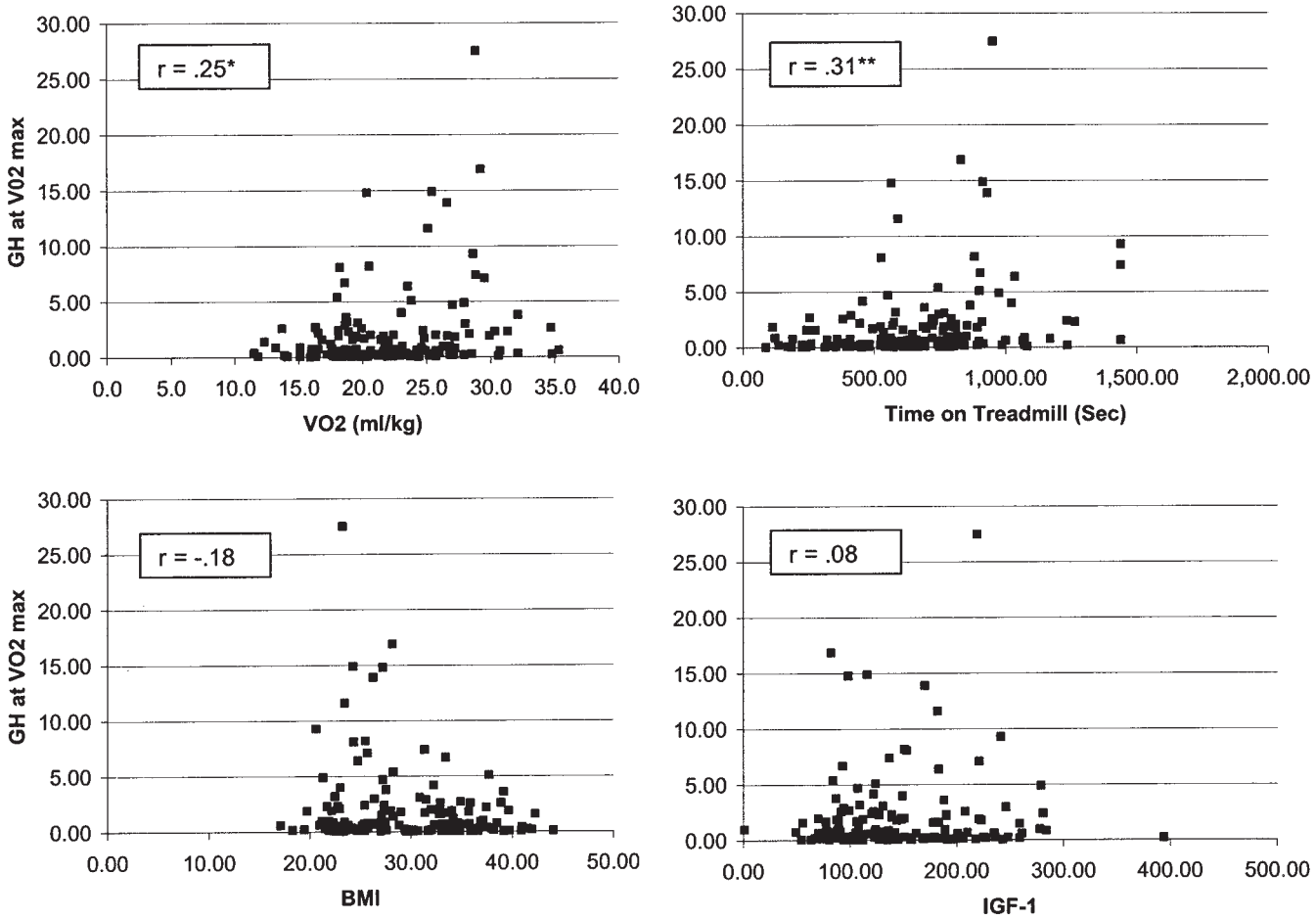

Figure 4. Pearson correlations of GH at peak treadmill with VO_2, time on treadmill, body mass index, and IGF-I. *p < 0.01, **p < 0.001.

Table 4. Percentage of participants who reported common side effects at least once during the first 6 months.

Side Effect	Placebo N	Placebo %	Pyridostigmine N	Pyridostigmine %	p
Abdominal pain	24	40.0	41	62.1	0.013
Nausea/vomiting	13	22.4	18	29.0	0.408
Headache	52	92.9	52	85.2	0.191
Hot flashes/flushing	9	15.0	17	26.2	0.125
Decreased pain/muscle pain/stiffness	21	33.9	33	50.8	0.054
Improved sleep/dreaming	11	19.3	17	27.9	0.274
Diarrhea/more frequent bowel movements	27	43.5	52	77.6	0.000
Increased muscle cramping/twitchy muscles	1	1.8	15	24.6	0.000
Fatigue	10	17.5	12	20.0	0.734
Improved cognition/improved memory	14	24.1	14	23.0	0.879
Increased energy/increased stamina/less winded/better exercise tolerance/more alert	24	40.0	31	50.0	0.267
Increased salivation/increased tearing/less dry eyes	15	26.3	19	30.6	0.601

stools, abdominal pain, and increased muscle cramping/twitching.

DISCUSSION

Several reports suggest that a subset of patients with FM are growth hormone-deficient, with low levels of IGF-I[25]. There are some similarities between the symptoms of adult GH deficiency and FM[7], and the daily use of GH injections for 9 months was reported to improve symptoms in GH-deficient patients with FM[10]. Due to the prohibitive cost of injectable

GH, this therapy is seldom used in contemporary management of patients with FM.

The primary aim of this 6-month trial of PYD plus exercise study was to determine whether a combination of exercise and a readily available low cost generic drug (i.e., PYD) would increase IGF-I levels in patients with FM. This aim was not achieved, as neither the PYD plus exercise, the PYD alone, nor the exercise alone improved IGF-I levels at the end of 6 months.

The second aim of our study was achieved, in that a low acute GH response to strenuous exercise[26] and its normalization by PYD was demonstrated in a larger cohort of subjects with FM. Thus, our work substantiates the findings of 2 previous studies[11,12]. However, 6 months of triweekly exercise classes did not provide any additional effect of PYD on the acute GH response to strenuous exercise.

Our third aim was to investigate factors influencing IGF-I levels and the acute GH response to strenuous exercise (i.e., VO_2 max/SRE). Our work confirms the results of one study[27] regarding the association of depressed IGF-I levels with adiposity. However, another study has cast some doubt on the notion that there is a direct linear relationship between IGF-I and BMI[28]. Obesity is comorbid in some patients with FM, and its relationship to the GH-IGF-I axis requires further analyses with particular attention to intraabdominal fat as measured more directly by computerized tomography or magnetic resonance imaging.

Our study failed to show any relationship between an exercise-induced GH response and adiposity, as measured by BMI and measurements of body fat (bioelectrical impedance and 7 point skin caliperimetry). This finding is in contrast to the study of McCall-Hosenfeld, *et al*[27], who reported that an impaired stress-induced GH response was negatively associated with BMI, and surmised that the defective GH response in FM was mainly a result of obesity. These results may differ from our findings, in that the McCall-Hosenfeld study used a different stress response (a hypoglycemic clamp) and their subjects were generally thinner than our subjects (BMI mean 25 ± 4 vs 29.8 ± 6.3 with only 21% vs 42% patients with FM having BMI > 30). To explore this issue further, we made a median split on BMI at 26.6, and again found no relationship between GH responses to acute exercise and obesity.

Our study has several limitations. It does not provide any information whether the enhanced GH release to the stress of strenuous exercise can be attributed to the acute dosing with PYD (60 mg 1 h prior to start of exercise) or the use of PYD over the 6-month study period, as the PYD groups took a dose immediately prior to the treadmill test and the placebo groups did not. It seems unlikely that PYD had any chronic effect, as IGF-I levels and the resting GH levels did not improve. Based on lack of change in IGF-I, one may presume that the GH effect of PYD and exercise was most likely reflecting an acute rather than a chronic change. An additional treadmill test after the first dose of PYD would be needed to differentiate the acute versus chronic effect of PYD on GH.

Analyzing completers as a whole, we observed no improvement in the VO_2 max at the end of the study, so it is reasonable to hypothesize that the lack of any chronic PYD effect may have been a result of an inadequate GHRH response to exercise. Although most of the subjects had a low IGF-I level for their age, subjects were not required to have a low level for entry into the study. It is possible that restricting enrollment to subjects with definite GH deficiency, as in a previous study[10], would have yielded different results. As low numbers of men and ethnic minorities were enrolled, it was not possible to make any statistically valid comparisons between these subgroups.

In summary, these data add to the increasing evidence that patients with FM have objective abnormalities in their acute GH stress response[25]. This acute stress response can be normalized by the administration of PYD (a cholinergic agent that reduces somatostatin levels at the level of the hypothalamus) 1 h prior to the exercise stressor. However, the combination of daily PYD and 6 months of supervised exercise classes failed to improve IGF-I levels. This apparently paradoxical result is in accord with reports that IGF-I levels increase in response to very "strenuous exercise"[29] but not "moderate exercise"[30,31]. We hypothesize that, even when inhibitory somatostatin tone is chronically reduced by the use of daily PYD, patients with FM are unable to exercise with enough intensity to chronically stimulate GHRH secretion, and thus improve IGF-I levels.

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