# Serum insulin-like growth factor-I (IGF-I) does not correlate positively with isometric strength, fatigue, and quality of life in post-polio syndrome

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**Abstract**

*Objectives and background*: To determine if serum insulin-like growth factor-I (IGF-I) levels are associated with strength, body mass index (BMI), fatigue, or quality of life in post-poliomyelitis syndrome (PPS). PPS is likely due to a distal disintegration of enlarged post-polio motor units as a result of terminal axonal sprouting. Age-related decline in growth hormone and IGF-I (which support terminal axonal sprouts) is proposed as a contributing factor. *Methods*: As part of the North American Post-Poliomyelitis Pyridostigmine Study (NAPPS), baseline data on maximum voluntary isometric contraction (MVIC), BMI, subjective fatigue (fatigue severity scale, Hare fatigue symptom scale), health-related quality of life (short form health survey-36; SF-36), and serum IGF-I levels were gathered on 112 PPS patients. Pearson correlation coefficients were calculated to evaluate the association between serum IGF-I and MVIC in 12 muscles, BMI, two fatigue scales, and SF-36 scale scores. *Results*: There is a significant inverse correlation of IGF-I levels with MVIC in left ankle dorsiflexors ($r=-0.30$, $P<0.01$), and left and right knee extensors ($r=-0.22$, $-0.25$, $P=<0.01$, 0.01), but no significant correlations in other muscles. When men and women were evaluated separately, inverse correlations of IGF-I levels with MVIC were found only in men. IGF-I correlated inversely with BMI ($r=-0.32$, $P=0006$) and age ($r=-0.32$, $P=0.0005$). IGF-I did not correlate with the fatigue or SF-36 scales. *Conclusions*: In this exploratory study, we found that contrary to our expectations, IGF-I did not correlate positively with strength. IGF-I correlated negatively with strength in several lower extremity muscles, BMI, and age. IGF-I is likely not an important factor in the pathogenesis of fatigue and in determining quality of life in PPS, but its role on strength should be studied further. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords:* Poliomyelitis; Insulin-like growth factor-I; Quality of life; Strength; Body mass index; Fatigue

## 1. Introduction

Post-poliomyelitis syndrome (PPS) is a common neurological disorder which encompasses a constellation of new symptoms, notably new progressive weakness, generalized fatigue, muscle fatiguability, and pain in those who have recovered from paralytic poliomyelitis [1,2]. Following acute paralytic polio, remaining motor neurons elaborate axonal sprouts which can reinnervate some or all of the denervated muscle fibers. Continuous motor neuron remodeling, or denervation and reinnervation of muscle fibers within these very enlarged motor units, likely occurs as an ongoing process following paralytic polio [3,4]. Progressive loss of motor neurons occurs [5,6] and is likely associated with a gradual enlargement of motor units to a maximum size. Even though the exact cause of this disorder is still unknown, it is thought to be due to a distal degeneration of these enlarged motor units [3,4,7]. It has been proposed that the normal reduction in growth hormone with ageing, which produces a decline in circulating insulin-like growth factor-I (IGF-I) levels, may contribute to the onset of PPS [8,9]. New weakness in PPS may be due to a slowly progressive, uncompensated denervation of individual muscle fibers within a motor unit. Muscle fatiguability and consequently general fatigue in PPS may be due to terminal axonal dysfunction (including neuromuscular junction defects) [10]. Because IGF-I has been shown to stimulate synthesis of protein and nucleic acids in muscle cells, regeneration of peripheral nerves, and axonal sprouting [11,12], it was proposed that its decline with ageing could help precipitate PPS [8,9]. In addition, growth hormone and IGF-I have been considered as possible treatments for PPS and other neurological disorders [13–17].

Even though IGF-I has been considered as a treatment for PPS, there has been a paucity of studies which have evaluated the possible association of IGF-I with clinical parameters and quality of life in PPS. One group of investigators reported that serum IGF-I levels were lower in polio survivors than in age-matched normal controls [8,9], while another group reported no reduction in serum IGF-I in patients with previous polio as compared to age and sex-matched controls [18]. In addition, conflicting results were reported when serum IGF-I was correlated with certain clinical variables. Rao and co-workers [9] found that IGF-I was correlated with age, gender, body mass index (BMI), dependency, pain, and activities of daily living, but not with subjective decline in functional status. Sunnergan and colleagues [18] found no correlation of IGF-I with severity of original polio affliction, recovery status, need for ambulatory aids, or the presence of new symptoms. These studies did not assess the association of IGF-I with muscle strength or quality of life. Because of these conflicting results and the need for further studies in this area, we designed a study to determine if serum IGF-I is associated with isometric strength in 12 muscle groups, BMI, fatigue, or health-related quality of life in PPS.

## 2. Methods

### *2.1. Patient population*

Patients included in the study were all 112 patients who were randomized into the North American Post-Poliomyelitis Pyridostigmine Study (NAPPS) from February, 1996 to April, 1997 [19], and for whom baseline data on IGF-I were available. The NAPPS study was a multicenter, randomized, double-blinded, placebo-controlled therapeutic trial of pyridostigmine in 126 patients with PPS. Inclusion criteria for the study included: (1) a history and physical examination consistent with past paralytic polio; (2) a history of at least 10 years of functional stability following polio, and (3) new symptoms of general fatigue and/or muscle fatigue, and new weakness of at least one years duration. Exclusion criteria were the presence of other neurological diseases, fibromyalgia [20], depression [21,22], and other medical conditions which could produce similar symptoms to PPS or could be contraindications to usage of pyridostigmine. The criteria for PPS used for the study were a modified version of those previously proposed [23,24]. The NAPPS study was approved by the appropriate ethics committee at each site, and informed consent was obtained from each patient.

### *2.2. Data collection and outcome measures*

Data for this study was collected as part of the NAPPS trial which consisted of a screening visit, two baseline assessments, and three treatment assessments (at 6 weeks, 10 weeks, and 6 months). Two baseline assessments were performed to improve the reliability of the isometric muscle strength evaluations. The first baseline assessment occurred within 6 weeks of the screening visit, and the second within 4 weeks of the first. All data for the first three visits of the NAPPS study were gathered prior to initiation of the medication. Serum for IGF-I was obtained at the screening visit. At the time of the first baseline visit the following outcome assessments were performed: two subjective fatigue scales, short form health survey-36 (SF-36; [25]), and isometric strength. Isometric strength was evaluated again at the second baseline visit. Data on patient height and weight were gathered at the six month treatment visit. Because PPS patients are usually more tired at the end of the day, patient appointments were scheduled at approximately the same time of day for each visit (within 1 h). As part of the medical history, the degree of weakness at the time of acute polio was estimated on a 0 to 6 scale by patient history; one point was given for reported weakness in each of four limbs, one point for respiratory dysfunction, and one point for speech or swallowing dysfunction. Site monitoring was performed at each site prior to study initiation to ensure consistency of data collection.

The outcomes utilized for this study were serum IGF-I, isometric muscle strength as assessed by a modified Tufts

quantitative neuromuscular examination [26], BMI, the SF-36 [25], the Hare fatigue symptom scale [27], and the fatigue severity scale [28]. BMI was calculated as weight in kilograms divided by height in meters squared.

Serum for IGF-I was collected from patients and stored frozen at all centers at −20°C or lower. At completion of the NAPPS trial, all samples were sent to the laboratory of Dr Michael Pollak, Jewish General Hospital, McGill University on dry ice by courrier. Once the samples arrived, they were immediately stored at −80°C. This laboratory performed ELISA for IGF-I using an IGF-I ELISA kit from Diagnostic Systems Laboratories, Inc. (Webster, Texas) according to the method provided by the manufacturer. Total serum IGF-I was measured, which included binding to IGF binding proteins and acid labile subunit (ALS). The laboratory has extensive experience in the performance of this assay [29]. Serum IGF-I was performed on 112 of the 126 patients randomized into the NAPPS trial. For the remaining 14 patients, serum IGF-I samples were never received by the coordinating center or serum tubes were poorly labeled and were deemed to be unusable.

Maximum voluntary isometric contraction (MVIC) was measured with an electronic strain gauge in 12 muscle groups or functions (bilateral shoulder extensors, elbow flexors, hand grip, hip flexors, knee extensors, and ankle dorsiflexors) in each patient to assess isometric strength [26,30]. To ensure that the performance of isometric strength assessments was consistent among all centers, each center was visited by an expert physical therapist who had developed the measure. Intra-rater reliability was evaluated at each center prior to study initiation, and the average percent difference for all muscle groups between assessments was ≤10% at all centers. MVIC was measured in kilograms force, and a mean value was calculated from the two baseline assessments for each muscle for each patient. The kilograms force mean value was transformed to a percent predicted normal value based on patient sex, age, height, and weight [31]. The association of IGF-I with muscle strength was evaluated in 12 individual muscles rather than by using a summary muscle strength score for each patient because of the large variability of muscle strength within an individual patient, and the lack of a validated summary strength measure in this patient population.

The SF-36 assesses quality of life in eight health concepts: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. A 0 to 100 score can be calculated for each of eight health concepts. A higher score indicates a better quality of life, and a change in score of at least 5 is believed to be clinically significant [25]. Two summary measures, the Physical Component Summary (PCS) scale and the Mental Component Summary (MCS) scale can also be calculated, with scores ranging from 0 to 100. For some of the scales, only a few possible scores can be calculated (e.g., the emotional role scale has possible scores of 0, 33, 67, and 100). The Hare fatigue symptom scale [27] is a self-administered scale with nine possible levels of fatigue. These levels increase in half unit increments from 0 (none) to 4.0 (unbearable). The Hare fatigue scale is reliable in PPS with a test–retest reliability of $r=0.80$ (Pearson correlation coefficient [32]). For the study, each patient was asked to rate his/her level of fatigue for 1 week, at 3.00 to 5.00 p.m. every day, for 1 week prior to the study visit using a diary. A mean value for the week was calculated and used in further data analyses.

The fatigue severity scale (FSS) is a self-administered questionnaire [28] developed to facilitate research in disabling fatigue in medical and neurological disorders. It likely assesses primarily general fatigue in PPS. The FSS is reliable in PPS with a test–retest reliability of $r=0.90$ to 0.96 (Pearson correlation coefficient [32]). A score of 1 to 7 is obtained for this measure with a higher score indicating more fatigue.

### *2.3. Statistical analysis*

Descriptive statistics were calculated for the outcome measures. Pearson correlation coefficients were calculated to evaluate the bivariate association between serum IGF-I and isometric strength in each of 12 muscles, BMI, the two fatigue scales, the eight SF-36 scale scores, the two SF-36 summary scales, and age. Correlation coefficients were also adjusted for patient sex and age using multivariate regression analysis. To evaluate the potential confounding effect of gender, age-adjusted correlation coefficients were calculated for IGF-I and muscle strength in men and women separately. A $P$-value of less than 0.05 was considered to be statistically significant. The sex and age-adjusted $P$-values of the correlation coefficients were adjusted for multiple comparisons using the method developed by Benjamini and Hochberg [33], which controls strongly for the false discovery rate, and is less conservative than traditional approaches. This adjustment for multiple comparisons was performed separately for the SF-36 and isometric strength results, and did not include the other variables. The data were analyzed using SAS (SAS Institute, Cary, North Carolina).

## 3. Results

Some characteristics of the study population are presented in Table 1. Mean serum IGF-I levels of 112 patients were 185.5±77.0 ng/ml. Mean age of subjects was 56.5±10.1 years, and 67/112 (60%) were female. Mean height was 167.1±11.3 cm ($n=112$) and mean weight was 77.6±16.7 kg ($n=112$). The mean BMI for men was 27.1±4.4 ($n=45$), and for women was 28.3±6.1 ($n=67$), indicating that our subjects were overweight. Mean age at time of acute polio was 8.8±8.4 years ($n=112$), and duration of new weakness (after recovery from acute polio)

Table 1
Correlation coefficients of IGF-I with clinical variables in 126 post-polio syndrome patients[a]

| Clinical variable | *N* | Mean±S.D. | Correlation coefficient | *P*-value | Adjusted *P*-value* |
|---|---|---|---|---|---|
| Age | 112 | 56.5±10.1 | −0.32 | 0.0005 | |
| Body mass index | 112 | 27.8±5.5 | −0.32 | 0.0007 | 0.0006 |
| SF-36 | | | | | |
| Physical functioning | 112 | 38.4±20.9 | 0.04 | 0.69 | 0.56 |
| Physical role | 112 | 36.6±36.1 | 0.13 | 0.15 | 0.20 |
| Bodily pain | 112 | 51.2±18.5 | 0.01 | 0.89 | 0.75 |
| General health | 112 | 62.9±20.3 | 0.08 | 0.40 | 0.11 |
| Vitality | 112 | 40.8±21.4 | 0.06 | 0.53 | 0.34 |
| Social functioning | 112 | 71.4±23.8 | 0.04 | 0.66 | 0.53 |
| Role emotional | 112 | 78.6±32.2 | 0.28 | 0.002 | 0.03 |
| Mental health | 112 | 74.8±15.1 | −0.04 | 0.66 | 0.94 |
| PCS | 112 | 32.3±8.4 | 0.05 | 0.57 | 0.81 |
| MCS | 112 | 53.2±9.3 | 0.11 | 0.26 | 0.17 |
| Hare fatigue scale | 111 | 1.8±0.6 | 0.01 | 0.94 | 0.52 |
| Fatigue severity scale | 112 | 5.4±1.2 | 0.05 | 0.58 | 0.46 |
| Maximum voluntary isometric contraction[#] | | | | | |
| Right shoulder extension | 110 | 86.9±29.5 | 0.07 | 0.44 | 0.20 |
| Left shoulder extension | 110 | 92.6±32.0 | 0.01 | 0.91 | 0.57 |
| Right elbow flexion | 110 | 86.8±28.4 | 0.00 | 0.99 | 0.38 |
| Left elbow flexion | 110 | 97.5±32.7 | −0.11 | 0.26 | 0.83 |
| Right hand grip | 108 | 93.4±28.5 | 0.18 | 0.06 | 0.07 |
| Left hand grip | 108 | 95.9±30.4 | 0.09 | 0.33 | 0.31 |
| Right hip flexion | 99 | 64.2±35.9 | −0.11 | 0.27 | 0.33 |
| Left hip flexion | 100 | 65.0±34.1 | −0.13 | 0.19 | 0.12 |
| Right knee extension | 108 | 51.0±43.1 | −0.25 | 0.01 | 0.01 |
| Left knee extension | 107 | 55.4±38.4 | −0.22 | 0.02 | <0.01 |
| Right ankle dorsiflexion | 104 | 49.0±38.4 | −0.19 | 0.06 | 0.26 |
| Left ankle dorsiflexion | 105 | 46.5±34.6 | −0.30 | <0.01 | <0.01 |

[a] **P*-value is adjusted for age and sex. [#]Maximum voluntary isometric contraction (MVIC) was measured in kilograms force in 12 muscle groups in each patient. Values utilized are percent predicted normal muscle strength values (for each muscle group) based on patient sex, age, height, and weight. Abbreviations: S.D., standard deviation; SF-36, short form health survey-36; IGF-I, insulin-like growth factor-I; *N*, number of patients; PCS, SF-36 Physical Component Summary Scale; MCS, SF-36 Mental Component Summary Scale.

was 6.9±5.7 years ($n$=112). Mean weakness at acute polio (assessed by a 0 to 6 subjective weakness measure) was 2.6±1.4 ($n$=109). Seventy-six of 111 (69%) of patients had other concurrent medical conditions. Duration of new muscle fatigue was 7.1±6.6 years ($n$=112), and duration of new general fatigue was 6.9±6.2 years ($n$=112). On the SF-36 quality of life measure, patients were below the mean by greater than one standard deviation for norms from the general U.S. population of similar age (55 to 64 years) for the physical functioning scale (38.4±20.9 for PPS patients compared to 76.3±26.3 for the general U.S. population [25]). PPS patients were almost one standard deviation below the US population norms of similar age for two scales [25]. These were the physical role scale (36.6±36.1 vs. 73.7±38.4), and the vitality scale (40.8±21.4 vs. 60.37±22.59). PPS patients were similar to general U.S. population norms for the remaining five SF-36 scales.

Mean MVIC values in the upper extremities of PPS patients were similar to control values normalized to age, sex, height, and weight. Mean MVIC of the six muscles tested in the upper extremities ranged from 86.8 to 97.5 of percent predicted normal strength, but there was a large variability (standard deviation ranging from 28.4 to 32.7). Mean MVIC of the six lower extremity muscles tested was markedly lower than predicted normal strength, ranging from 46.5 to 65.0 percent predicted normal strength, again with a large variability in strength (standard deviation ranging from 34.1 to 43.1 percent).

The association between serum IGF-I and MVIC in 12 muscle groups, BMI, subjective fatigue (FSS, Hare fatigue symptom scale), health-related quality of life (SF-36), and age was evaluated in the entire population of 112 PPS patients (Table 1 and Fig. 1). A significant inverse correlation of IGF-I with MVIC in several lower extremity muscles was observed: left ankle dorsiflexors ($r$=−0.30, $P$<0.01); left knee extensors ($r$=−0.22, $P$=0.02); and right knee extensors ($r$=−0.25, $P$=0.01). There was a similar trend in the right ankle dorsiflexors ($r$=−0.19, $P$=0.06). There were no other significant correlations of IGF-I with MVIC in the remaining muscles tested. IGF-I correlated significantly and negatively with BMI ($r$=−0.32, $P$=0.0007) and with patient age ($r$=−0.32, $P$=0.0005). IGF-I correlated significantly and positively with

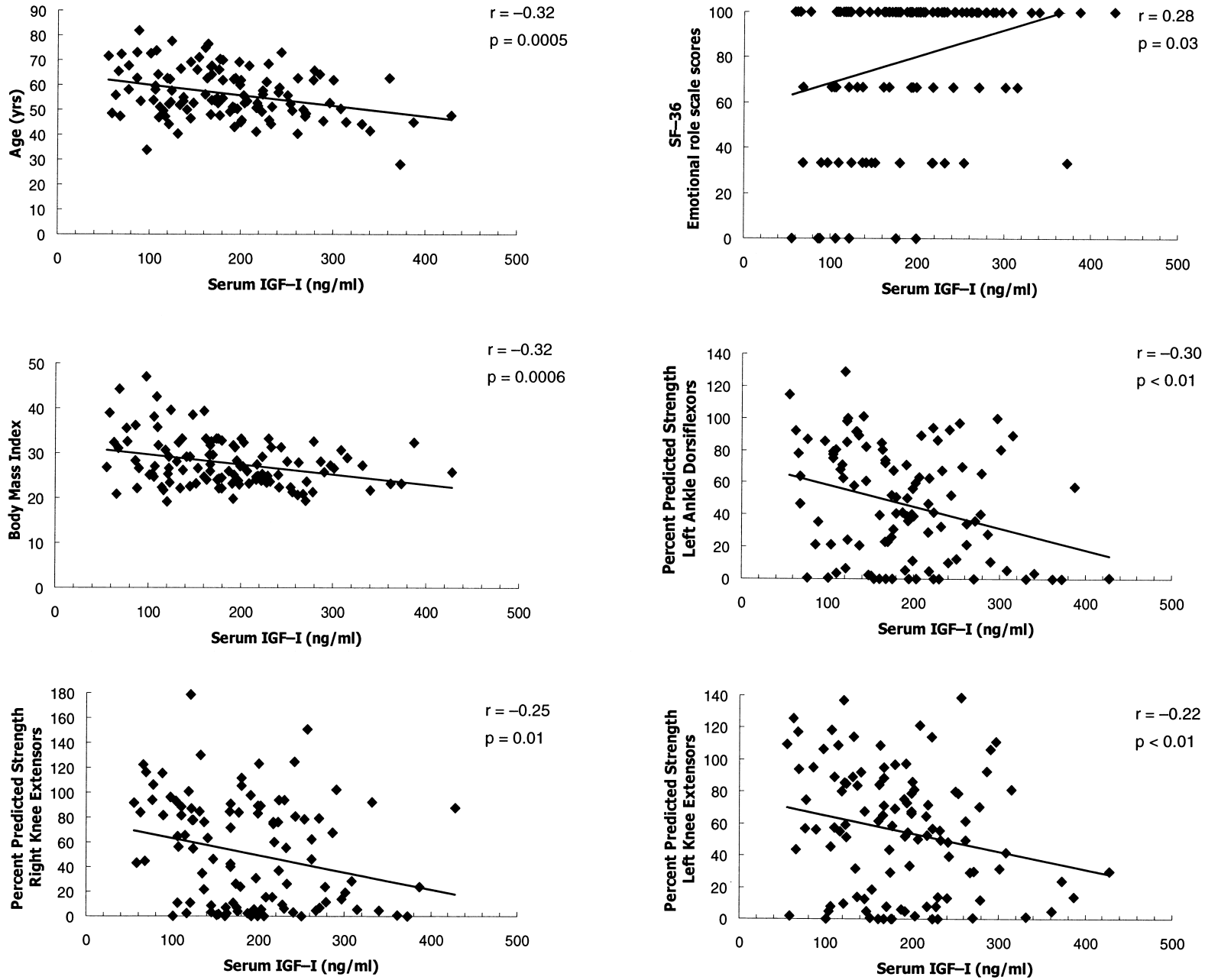


Fig. 1. Scatterplots of serum IGF-I values plotted against age, SF-36 emotional role scale scores, body mass index, and percent predicted maximum voluntary isometric contraction (MVIC) of left ankle dorsiflexors, right knee extensors, and left knee extensors. *P*-values for the plots of SF-36 emotional role, body mass index, and MVIC are adjusted for sex and age.

the emotional role scale of the SF-36 ($r=0.28$, $P=0.002$), but did not correlate significantly with the other seven SF-36 scales. IGF-I did not correlate with the Hare fatigue scale ($r=0.05$, $P=0.57$) or the fatigue severity scale ($r=0.05$, $P=0.57$).

To ensure that the above results could not be explained by a confounding effect of age and sex, adjusted $P$-values were calculated and similar results were observed. A significant inverse correlation was again observed between IGF-I and MVIC of the left ankle dorsiflexors ($r=-0.30$, $P<0.01$), left knee extensors ($r=-0.22$, $P<0.01$), and right knee extensors ($r=-0.25$, $P=0.01$). However, the association between IGF-I and right ankle dorsiflexors decreased ($r=-0.19$, $P=0.26$). A significant negative correlation between IGF-I and BMI was again observed ($r=-0.32$, $P=0.0006$). The positive correlation between IGF-I and the emotional role scale of the SF-36 remained ($r=0.28$, $P=0.03$) with this adjustment.

The age-adjusted correlation coefficients for IGF-I with MVIC were also calculated for men and women separately to examine the potential confounding of the IGF-I strength association by gender. When this was performed, inverse correlations of IGF-I with MVIC were observed in similar muscle groups in men, but not women. Correlation coefficients of IGF-I with left ankle dorsiflexors were $r=-0.51$ ($P<0.01$) in men and $r=-0.12$ ($P=0.24$) in women, with left knee extensors were $r=-0.43$ ($P<0.01$) in men and $r=-0.12$ ($P=0.22$) in women, and with right knee extensors were $r=-0.29$ ($P=0.07$) in men and $r=-0.17$ ($P=0.10$) in women. In addition, a significant positive correlation was observed with right hand grip ($r=0.32$, $P=0.02$) in men but not women ($r=0.06$, $P=0.67$). There were no significant correlations in the other muscle groups tested in men and women. Therefore, there were significant inverse correlations of IGF-I with MVIC in men in the left knee extensors and the left ankle dorsiflexors, and a positive correlation with right hand grip. There was a trend to an inverse correlation in the right knee extensors in men.

When a correction for multiple testing was applied to the results observed (for the age and sex adjusted analyses of SF-36 and MVIC in the 112 PPS patients), our findings of significant negative correlations of IGF-I with MVIC in the left ankle dorsiflexors and bilateral quadriceps were upheld. However, the finding of a significant positive correlation of IGF-I with SF-36 emotional role was not upheld.

## 4. Discussion

In this exploratory study, we evaluated the possible association of IGF-I with various clinical parameters in PPS. We found a significant inverse correlation of serum IGF-I with isometric strength in several lower extremity muscles, BMI, and age, and possibly a positive correlation of IGF-I with the emotional role scale of the SF-36, a health-related quality of life measure, in the entire population of patients. With further analysis, the inverse correlation with isometric strength was found to occur only in men and not women, and when adjustment for multiple comparisons was made the correlation of IGF-I with SF-36 emotional role was no longer significant. Serum IGF-I was not associated with subjective fatigue and the physical domains of health-related quality of life in PPS. Based on our results, serum IGF-I is likely not an important factor in the pathogenesis of fatigue and in determining quality of life in PPS, but its role on strength and BMI in PPS is likely not straightforward, and requires further investigation.

Even though IGF-I has been proposed as a treatment for several neuromuscular disorders (including PPS), and rhIGF-I has been evaluated in two large trials in ALS [16,17], this is the first study that evaluates the relationship of endogenous IGF-I with strength and quality of life in a neuromuscular disease. However, these associations have been previously studied in the elderly. Kiel and co-workers [34] evaluated the association of IGF-I with several parameters including isokinetic strength in several muscles, lean body mass as measured by dual X-ray absorptiometry, self-reported physical activity, and the SF-36 physical functioning scale in people over age 65 years. No significant association of IGF-I with these parameters was found in men and women separately, and after adjustment for age and weight.

The results of our study failed to show an expected positive correlation of IGF-I with muscle strength. We had expected that a positive correlation, if found, would occur in the larger and most used muscles, such as the quadriceps. Because IGF-I has known neurotrophic effects on the entire motor unit: the motor neuron, neuromuscular junction (NMJ), and skeletal muscle [35], a positive correlation of IGF-I with isometric strength had been expected. Instead, we found a negative correlation of serum IGF-I with isometric strength in several large lower extremity muscles in men, but not women with PPS. Our results indicate that the relationship of IGF-I with muscle strength in PPS and even other neuromuscular disorders are complex. It is possible that atrophic, weak muscles may exert a positive stimulus on the pituitary/hypothalamic axis in order to increase production of growth hormone and IGF-I to support the motor unit. Further support for this hypothesis is provided by our finding that the negative correlation of IGF-I with isometric strength occurred in the weaker lower extremity muscles and not the stronger upper extremity muscles (mean MVIC ranged from 86.8 to 97.5 of percent predicted normal in the upper extremity muscles, and 46.5 to 65.0 percent predicted normal in the lower extremity muscles). Because the inverse correlation of IGF-I with muscle strength was observed only in men, and not women, it is possible that IGF-I exerts its effect in concert with sexual hormones. Androgens together with IGF-I may have an anabolic role

on nerve and muscle, while estrogens may have a neuroprotective role. Estrogens have several known in vivo and in vitro neuroprotective effects [36–38], which may play a role in PPS.

Even though IGF-I has known trophic actions on the motor unit, it is important to note that most studies which have found these actions have been in vitro or in vivo animal studies. The effects of IGF-I administration have been evaluated in the healthy elderly, and in a few studies in patients with neuromuscular disease. Growth hormone can increase lean body mass in the elderly, but this increase probably represents a combination of fluid retention and increased nonmuscle protein [39]. Growth hormone has not been shown to improve muscle strength or function in healthy older persons [40]. In an open trial in five PPS patients, human growth hormone administration for 3 months produced little or no improvement in muscle strength [13]. A randomized, placebo-controlled trial of IGF-I in 22 PPS patients for 3 months showed no change in strength and fatiguability, but an improvement in recovery after exercise with IGF-I [15]. IGF-I has been evaluated as a treatment in two multicentered, randomized, placebo-controlled trials in amyotrophic lateral sclerosis (ALS) with conflicting results [16,17]. IGF-I has also been suggested as a possible treatment for myotonic dystrophy based on the positive results of a randomized, placebo-controlled trial in 16 patients [14]. Thus, even though pre-clinical studies indicate that IGF-I has trophic effects on the motor unit, clinical studies in the normal elderly and in individuals with neuromuscular disorders fail to definitively support these findings.

Interestingly, we found a significant negative correlation of IGF-I with BMI, an index for obesity, even after adjustment for age. This finding is in agreement with the results of Rao and colleagues [9] who reported a similar significant negative correlation in 124 polio survivors. These results in polio patients differ from those previously reported in adults without neuromuscular disease where IGF-I was not significantly correlated with BMI [41–43]. Therefore, IGF-I may have a direct protective role against the development of obesity in PPS. Alternatively, increased IGF-I may be an indirect measure of greater activity, which would be expected to reduce adiposity.

We found a positive correlation of IGF-I with the SF-36 emotional role scale, and no correlation with the remaining seven SF-36 scales. Because this finding was rejected with correction for multiple testing, it should be interpreted with caution. The role of corticotropin-hypothalamic releasing hormone (CRH), pituitary adrenocorticotrophic hormone (ACTH), and adrenocorticoids has been investigated extensively in depression, but there is a paucity of studies which have evaluated the possible effects of the growth hormone/IGF-I axis on emotional well-being and depression. In patients with severe depression, there is an increased activity in the hypothalamic–pituitary–adrenocorticoid system, with blunted glucocorticoid feedback inhibition [44]. One placebo-controlled study which involved the administration of IGF-I to 33 post-menopausal women found a reduction in depression and anxiety scores with IGF-I [45]. Thus, the growth hormone/IGF-I axis may be involved in emotional well-being through centrally mediated mechanisms in the neuroendocrine system.

We measured total circulating IGF-I levels due to the convenience and ease of measurement of this analyte in a clinical research study. However, it is likely that local IGF-I bioactivity at the tissue level is more important than serum IGF-I in determining clinical variables, and this could have accounted for some of our negative results. Locally produced IGFs are known to be important in the activity of several organ systems (e.g., bone, reproductive system), but the actions of these locally produced IGFs still need to be defined [46]. Tissue level IGF-I bioactivity is likely correlated with total IGF-I. The rationale for this is derived from the standard clinical indications for measuring IGF-I; acromegaly (excess IGF-I) and growth hormone deficiency (IGF-I deficiency). In these two extremes, tissue abnormalities are directly correlated with total IGF-I levels. Further support for this hypothesis comes from the recent identification of serum IGF-I as a predictor of prostate cancer [29]. It is therefore reasonable to assess total IGF-I as a surrogate for tissue level IGF-I bioactivity.

This exploratory study did not find a positive correlation of IGF-I with strength in PPS. We found a significant inverse correlation of IGF-I with isometric strength in several lower extremity muscles in men, a significant inverse correlation with BMI and age in all patients, but no correlation with fatigue and other SF-36 scales. These findings need to be further verified. If confirmed, they suggest a more complex relationship between muscle strength and serum IGF-I, perhaps involving stimulation of the growth hormone/IGF-I axis by weak, atrophic muscles.

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