

Association Between Insulin-like Growth Factor Status and Physical Activity Levels in Rheumatoid Arthritis

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ABSTRACT. Objective. To determine if the altered insulin-like growth factor (IGF) status in rheumatoid arthritis (RA) is due to inflammation, altered body composition, or lack of exercise.

Methods. Subjects included 73 patients with RA, 54 patients with other rheumatic diseases, both inflammatory and noninflammatory, and 28 healthy, physically active controls. Serum levels of IGF-I, IGF-II, and IGF binding protein-3 (IGFBP-3) were measured by radioimmunoassay. Body composition was estimated by bioelectrical impedance analysis, and habitual exercise level approximated by questionnaire. Statistical analysis was performed by 2 and 3 way ANOVA and moderated hierarchical regression.

Results. Serum IGF-I ($p < 0.001$), IGFBP-3 ($p < 0.001$), and the BP-3:total IGF molar ratio ($p < 0.001$) were depressed in both patient groups relative to controls. In contrast, IGF-II levels were depressed only in patients with RA ($p < 0.01$). Differences in the IGF proteins between patients and controls could not be attributed to inflammation. Habitual exercise level, but not body composition, was shown to be a significant predictor for IGF-I, IGFBP-3, and BP-3:total IGF molar ratio ($p < 0.001$).

Conclusion. Our results indicate that the reduction in circulating IGF proteins observed in our patients is more related to their sedentary lifestyle than to the inflammatory process. This conclusion is in agreement with reports that show that highly active individuals typically exhibit higher levels of systemic IGF proteins than age matched sedentary controls. (J Rheumatol 2001;28:29–34)

Key Indexing Terms:

INSULIN-LIKE GROWTH FACTOR
RHEUMATOID ARTHRITIS

GROWTH HORMONE
EXERCISE

Muscle wasting, weakness, fatigue, problems with coordination and balance, and poor aerobic function are common in patients with rheumatoid arthritis (RA)¹⁻³ and play an important role in the disability that characterizes the disease. These decrements in physical function are the consequence of both the inflammatory nature of RA and the subsequent inactivity the condition encourages.

Inherent in RA, as in other chronic inflammatory diseases, is an imbalance between synthetic and degradative processes, with catabolism prevailing. Roubenoff, *et al*⁴ have shown that adults with well controlled RA have a 13% reduction in body

cell mass (BCM) relative to appropriately matched controls. This is due to increased whole-body protein breakdown and a 12% elevation in resting energy expenditure. Such losses in BCM are accompanied by a decrement in muscle bulk^{5,6} and, consequently, strength and endurance⁵. The principal stimulus for the catabolism in RA is thought to be the inflammatory cytokine network with hypermetabolism directly associated with mononuclear cell production of tumor necrosis factor α (TNF- α) and interleukin 1 β (IL-1 β)⁷. This cytokine driven loss of lean body mass in RA has been termed “rheumatoid cachexia”⁷ and is considered an important contributor to the morbidity and mortality of the disease^{2,7}.

Exacerbating this upregulated catabolism in RA is a possible downregulation of anabolic pathways. Insulin-like growth factor-I (IGF-I) mediates much of the anabolic action of growth hormone (GH) and thus is essential for somatic growth, metabolism, and other cellular proliferation and differentiation. Reduced serum levels of IGF-I and its principal carrier in the circulation, IGF binding protein-3 (IGFBP-3), are characteristic of conditions that feature reductions in lean body mass, increases in fat mass, and diminished strength^{8,9}, and have been described in a variety of rheumatic disorders such as juvenile chronic arthritis¹⁰⁻¹³, osteoarthritis¹⁴⁻¹⁶, and fibromyalgia¹⁷. However, there is relatively little information about IGF status in RA, and existing studies are limited by small samples and inappropriate control groups^{7,16,18,19}.

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IGF, which were initially observed as a consequence of their ability to stimulate the uptake of sulfate into cartilage^{20,21}, play a key role in the maintenance of the steady state metabolism of cartilage, with several studies having shown that both IGF-I and II stimulate the synthesis and decrease the degradation of proteoglycans in cultured cartilage explants^{22,23}.

Our group has shown that a disruption of the local IGF system in the knee joints of patients with RA, which attenuates IGF's anabolic action, contributes to the catabolism occurring within the joint¹⁶. Thus, impaired systemic IGF function in RA would be anticipated to markedly exacerbate the catabolism of the disease since IGF-I is a powerful anabolic mediator, has been shown to counteract catabolism in various conditions, and *in vitro* attenuates the catabolic effects of TNF- α and IL-1 β .

Whereas catabolic conditions typically present diminished serum IGF-I and IGFBP-3 levels, physical fitness is positively correlated with IGF function²⁴⁻²⁷. In healthy adults, exercise is accepted as an important modulator of IGF proteins²⁴⁻³¹ and the age related decline in IGF-I and IGFBP-3 appears, at least in part, to reflect reduced habitual physical activity with aging^{24-26,32}. Whether exercise has a similar role in maintaining IGF function in individuals with disease related catabolism, such as those with RA, is not yet known.

Thus we aimed to characterize the IGF status of patients with RA and to evaluate the relative importance that putative factors such as age, sex, habitual physical activity, body composition, and inflammation have on IGF function in RA.

MATERIALS AND METHODS

Patients and controls. Serum was obtained from 73 adults with RA, 54 adults with other rheumatic disorders both inflammatory (n = 12) and noninflammatory (n = 42), and 28 healthy, physically active, lean controls matched for age and sex. The patients with RA met the appropriate American College of Rheumatology (ACR) criteria for the disease³³. The non-RA inflammatory rheumatic patients comprised 9 with spondyloarthritis, 2 with polymyalgia rheumatica, and one patient with systemic sclerosis. The noninflammatory rheumatic patients included 19 with osteoarthritis, 8 with soft tissue rheumatism, 5 with fibromyalgia, 4 with chronic low back pain, and 6 with miscellaneous nonspecific complaints. Since determining the effects of physical activity level and body composition on IGF variables was a principal objective of this study, our control subjects were selected specifically to provide a contrast to the patient groups, whom we anticipated would be relatively sedentary and, as a consequence, relatively high in adiposity. Thus for our control group we chose individuals who characterized themselves as habitually active and gave evidence of this by satisfying the requirements for leanness (< 25% body fat for men, < 30% body fat for women). However, none of our controls were elite athletes. All subjects were Caucasian, and the demographic characteristics of the 3 groups are shown in Table 1.

Joint inflammation in patients with RA was assessed clinically as the number of swollen and the number of tender joints.

Body composition. Percentage body fat was measured by bioelectrical impedance absorption using a Bodystat 1500 (Bodystat Ltd., Isle of Man, UK).

Exercise. The habitual level of physical activity was estimated for all the subjects using a questionnaire³⁴ slightly modified for use in this study (Appendix), which quantifies physical activity undertaken during a normal week on an 8 point scale. Although not previously validated in patients with

rheumatic diseases, this scale was chosen because the range of activities described proved to be appropriate to this patient population in a pilot study (Maddison and Lemmey, unpublished observations).

Measurement of IGF-I, IGF-II, and IGFBP-3. Serum levels of IGF-I, IGF-II, and IGFBP-3 were determined by radioimmunoassay (RIA). All tracers were iodinated using the chloramine-T method. The measurement of IGF-I and IGF-II was as described³⁵. Endogenous binding proteins were first removed using an acid/acetone extraction procedure described by Bowsher, *et al*³⁶. The IGF-I used for the standard curve and tracer was obtained from Kabi Pharmacia (Stockholm, Sweden). The monoclonal antibody to IGF-I was obtained from Blood Products (Elstree, Hertfordshire, UK). The lower limit for the detection of IGF-I was 0.25 μ g/l. Excess IGF-II (Gropep, Adelaide, Australia) was added to the IGF-I assay to saturate any residual binding proteins remaining after the extraction. The IGF-II assay was standardized against the WHO international standard IGF-II preparation. The lower limit for detection was 0.6 μ g/l. Excess IGF-I was added to each sample to saturate any residual binding proteins not removed by the extraction procedure. The monoclonal antibody to IGF-II was a gift from Dr. Ann White (Manchester University, Manchester, UK).

The IGFBP-3 method was as described³⁷. Serum samples for the IGFBP-3 assay were diluted 1:100 before assaying. The antibody employed was an in-house polyclonal antibody raised against recombinant nonglycosylated IGFBP-3 and was used at a final dilution of 1:20,000. The glycosylated IGFBP-3 standard was a generous gift from Dr. C. Maack (Celltrix, Santa Clara, CA, USA).

C-reactive protein (CRP). Serum levels of CRP, determined by immunoturbidimetric assay, were used as a systemic measure of inflammation in the RA patients. This measure is a routine procedure in the Chemical Pathology Department of Ysbyty Gwynedd.

Statistical analysis. Results are given as the mean \pm standard deviation (SD). Statistical analysis was performed with SPSS software using analysis of variance and regression analyses as appropriate. The technique of moderated hierarchical regression analysis was used to assess the relative importance of selected variables on IGF and IGFBP results.

RESULTS

The patients with rheumatic diseases and the healthy controls were similar in age range and sex distribution. However, both the RA and the non-RA patient groups showed a low level of exercise (p < 0.001) and a high percentage body fat (p < 0.001) in comparison to the healthy normal group (Table 1).

The serum levels of IGF-I, IGF-II, and IGFBP-3 as well as the calculated molar ratio of IGFBP-3 to total IGF in the 3 groups of subjects are summarized in Table 2. Significantly lower levels of IGF-I, IGFBP-3, and BP-3:total IGF molar ratio were found in patients with rheumatic diseases than in the healthy controls (p < 0.001). In this respect RA patients were not different from the non-RA patients. Importantly, within the RA group there was no significant difference for these values between the patients with active and those with non-active disease. This was assessed clinically by the numbers of tender and swollen joints and by measuring serum CRP. Similarly, within the non-RA group no differences were detected between patients with inflammatory and noninflammatory conditions (data not shown). However, RA patients had significantly lower levels of IGF-II than the other groups (p < 0.01).

The influence of variables such as age, sex, degree of inflammatory disease (in the RA patients), body composition,

Table 1. Subject characteristics; mean value (\pm standard deviation).

Group	Female:Male	Age, yrs	Percentage Body Fat	Exercise Level
RA, n = 73	46:27	52.9 (12.9)	36.6 (12.8)	0.8 (0.7)
Non-RA, n = 54	37:17	52.2 (13.0)	37.0 (13.3)	0.7 (1.1)
Controls, n = 28	16:12	47.4 (10.0)	17.0* (7.6)	5.4* (1.7)

*p < 0.001, controls vs RA and non-RA.

Table 2. Serum levels of IGF-I, IGF-II, IGFBP-3, BP-3:total IGF molar ratio (mean value \pm standard deviation, SD) and CRP (mean value and range) in patients with rheumatic diseases and healthy controls (mean value \pm SD).

Group	IGF-I, ng/ml	IGFBP-3, ng/ml	IGF-II, ng/ml	BP-3:IGF Molar Ratio	CRP, mg/l
RA, n = 73	99.5 (32.5)	5150 (1588)	1074* (41)	0.857 (0.034)	23.68 (5–305)
Non-RA, n = 54	94.9 (28.7)	5792 (1574)	1362 (73)	0.803 (0.037)	NA
Controls, n = 28	163.0** (35.6)	7400** (1384)	1225 (88)	1.081** (0.062)	NA

*p < 0.01, RA versus non-RA and controls; **p < 0.001, controls versus RA and non-RA.

and habitual level of exercise on IGF and IGFBP-3 status was assessed using moderated hierarchical regression analysis. Results are summarized in Table 3. Sex had no effect on any of the values, while age had a small but expected negative influence on IGF-I, IGFBP-3, and BP-3:IGF molar ratio, but no effect on IGF-II. Of the independent variables assessed, the level of exercise was by far the most influential with regard to IGF-I and IGFBP-3 status, accounting for 24.7% and 11.9% of the variance reported for IGF-I and IGFBP-3 levels, respectively, with age failing to explain any additional variance for IGF-I (r^2 change = 0.013, p = 0.107), but significantly contributing to the prediction of IGFBP-3 (r^2 change = 0.023, p = 0.047). The magnitude of the influence of exercise on IGF-I levels was such that it explained exactly the same proportion of variance as IGFBP-3, although hierarchical regression also revealed that these effects were largely independent. On the

other hand, habitual exercise level had no effect on circulating IGF-II values.

These results applied to the total population of subjects (patient groups and controls). When the group with RA was analyzed independently the effect of exercise showed the same pattern, but evidence for a significant influence on growth factor levels was much weaker, failing to reach significance for IGF-I levels (r^2 change = 0.051, p = 0.056) and just reaching significance for BP-3:IGF molar ratio (r^2 change = 0.057, p = 0.044). Again, there was no effect on levels of circulating IGF-II (r^2 change = 0.006, p = 0.521).

Interestingly, in this study, the presence of inflammation as judged by the number of swollen or tender joints (data not shown) or the serum level of CRP did not influence the IGF or IGFBP results for patients with RA, thus supporting the lack of effect of inflammation revealed by the analysis of vari-

Table 3. Moderated hierarchical regression analysis of variables such as age, CRP, percentage body fat, and exercise that potentially influenced IGF status (r^2 change).

Variable	IGF-I	IGFBP-3	IGF-II	BP-3:IGF Molar Ratio
Age	0.050*	0.066*	0.011	0.068*
CRP [†]	0.034	0.001	0.001	0.0002
Percentage body fat	0.065*	0.017	0.007	0.022
Exercise	0.247**	0.119**	0.083	0.089**
IGF-I		0.247**	0.011	0.073*
IGFBP-3	0.247**		0.156**	

*p < 0.05; **p < 0.001.

[†]CRP was measured only in patients with RA.

ance on the patient subsets (i.e., active RA versus non-active RA; inflammatory rheumatic diseases versus noninflammatory rheumatic diseases).

DISCUSSION

Our observation of markedly reduced serum levels of IGF-I, IGFBP-3, and BP-3:total IGF molar ratio in patients with RA was not unexpected. The same phenomenon has been described in several studies of juvenile idiopathic arthritis¹⁰⁻¹³ and has been suggested by reports on adult patients with RA^{7,16,18,19}. In fact, the pattern of reduced serum IGF-I, IGFBP-3, and BP-3:IGF molar ratio is characteristic of catabolic conditions and thus would be anticipated in RA, a disease associated with a high prevalence of catabolism⁴. What was unexpected was that the same degree of reduction was observed in non-RA patients, including those with noninflammatory disorders.

We presume that a combination of factors is involved in this decrement of IGF function. In other studies where comparisons have been made between patients with specific inflammatory joint disorders and healthy controls, emphasis has been placed on the role of inflammation *per se*^{10,13,19,38}. These reports showed an inverse relationship between the ESR and the serum levels of IGF-I, IGF-II, and IGFBP-3. It is likely that inflammation influences GH function and it is hypothesized that proinflammatory cytokines can inhibit IGF-I and IGFBP-3 production. This is supported by animal models, for example the inhibition by IL-1 β and TNF- α of GH stimulated IGF-I synthesis by rat hepatocytes in primary culture³⁹. In this study we did not measure GH levels and consequently are unable to say whether the low levels of IGF-I and IGFBP-3 observed are due to reduced production of GH or acquired GH resistance.

In contrast to the studies cited, our data suggest that inflammation, assessed clinically and by measuring CRP, had no influence on IGF-I, IGF-II, and IGFBP-3 levels. Interestingly, Cimaz, *et al*¹³, while observing an inverse correlation between serum levels of IGF-I and ESR in children with juvenile idiopathic arthritis, also found no correlation with CRP.

It is well known that age and body composition influence circulating levels of IGF-I and IGFBP-3³². The significant decline in serum IGF-I and IGFBP-3 levels with age also observed in this study is generally thought to be related to the progressive decline in pulsatile secretion of GH that occurs especially after the 6th decade⁴⁰. However, of the variables we assessed, level of exercise was clearly the most influential with regard to circulating IGF-I and IGFBP-3 status, and diminishing activity levels with aging appeared to be responsible for the age related decline in IGF-I, and also for most of that of IGFBP-3. However, evidence of this effect of exercise was only strong when the total population of subjects and controls was analyzed. A similar pattern was seen in the RA population, but evidence for an exercise effect on growth factor

levels was weaker mainly because these patients were almost uniformly inactive (Table 1). Although percentage body fat and exercise level were strongly correlated ($r = -0.58$, $p < 0.01$), hierarchical regression analysis showed that percentage body fat had only a relatively small, albeit significant, effect on IGF-I levels and no effect on IGFBP-3. Notably, when percentage body fat was entered in the regression analysis after exercise level it failed to explain any additional variance for IGF-I (r^2 change = 0.001, $p = 0.619$).

The lack of an exercise effect on the serum level of IGF-II, which is independent of GH, suggests that the effect of exercise on the IGF system was exerted through GH. The reduction of IGF-II in RA is unexplained. While IGF-II has a well established role in embryonic and fetal development, its role in postnatal life is unclear, although it is by far the most abundant IGF present⁴¹. Interestingly, levels of IGF-II are reported as remarkably stable, not changing with altered hormonal or metabolic status or in a variety of pathological conditions⁴¹. The phenomenon observed in the RA patients in this report is therefore of interest.

The observation that the sedentary lifestyle of our rheumatic disease patients had a major effect on the circulating levels of IGF-I and IGFBP-3 is in agreement with other reports that show that highly active individuals typically exhibit higher circulating levels of IGF-I than age matched sedentary controls. Physical fitness and exercise are positively correlated with GH secretion⁴² and IGF-I production²⁴⁻³¹, and acute exercise is an acknowledged stimulus of both, with the intensity, duration, and type of exercise being important factors in the magnitude of the response^{27,28,31,42,43}. An important question is whether the anabolic stimulus of exercise reduces the catabolic processes in diseases such as RA.

Several groups have investigated the efficacy of exercise training programs in patients with RA, using either a resistance or an aerobic training protocol⁴⁴⁻⁵⁰. Improvements have been reported not only in muscle function but also in disease variables such as number of swollen joints and ESR, as well as reduced protein breakdown. To date, only Rall, *et al*⁵¹ have investigated the effect of exercise on GH and IGF-I levels. In that small study ($n = 8$), protein catabolism was positively correlated with levels of TNF- α , but negatively correlated with serum levels of GH. There was a trend, albeit not statistically significant, toward increased serum levels of GH and IGF-I after a 12 week exercise training program.

As reported, the BP-3:IGF molar ratio was lower in the patient groups relative to the physically active, healthy controls. Arithmetically this was because of a relative reduction in the GH dependent IGFBP-3. In the relative absence of IGFBP-3 there may be a proportional increase in other IGFBP (e.g., IGFBP-2 and -4), which are characteristically inhibitory to the expression of IGF-I action⁵². Thus, both of our groups of rheumatic disease patients appear to present with IGF characteristics classical for catabolic conditions: a reduction in IGF-I with a concurrent increase in the more inhibitory bind-

ing proteins, with both changes serving to undermine the anabolic role of IGF-I.

We conclude that a low habitual level of exercise is an important factor in the reduced serum levels of IGF-I and IGFBP-3 observed in both inflammatory and noninflammatory rheumatic disorders. However, this predominantly circumstantial evidence needs to be confirmed in an interventional study. Since downregulation of IGF action potentially exacerbates the cytokine driven catabolism that characterizes RA, we hypothesize that manipulation of IGF status by exercise might be an important intervention in RA and is worthy of further study.

Appendix. Physical Activity Scale³⁴

Score

Does not participate regularly in programmed recreation, sport, or heavy physical activity.

0 Avoids walking or exertion, e.g., always uses lift; drives wherever possible instead of walking.

1 Walks for pleasure, routinely uses stairs; occasionally exercises sufficiently to cause heavy breathing or perspiration.

Participates regularly in recreation or work requiring modest physical activity, such as golf, horseback riding, callisthenics, gymnastics, table tennis, bowling, weight lifting, heavy gardening.

2 10 to 60 minutes per week.

3 Over one hour per week.

Participates regularly in heavy physical exercise such as running or jogging, swimming, cycling, rowing, or engaging in vigorous aerobic activity such as tennis, squash, or football.

4 Runs less than one mile per week or spends less than 30 minutes per week in comparable physical activity.

5 Runs 1 to 5 miles per week or spends 30–60 minutes per week in comparable physical activity.

6 Runs 5–10 miles per week or spends 1–3 hours per week in comparable physical activity.

7 Runs over 10 miles per week or spends over 3 hours per week in comparable physical activity.

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