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ORIGINAL ARTICLE

Joint hypermobility in fibromyalgia patients has no impact on tests for disease severity

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Abstract: Benign joint hypermobility appears more frequently in fibromyalgia patients than in a comparable healthy cohort. The aim of this study was to investigate if fibromyalgia patients also diagnosed with benign joint hypermobility may be a distinct subgroup in the fibromyalgia population.The presence of benign joint hypermobility was determined in a population of 27 fibromyalgia patients. Relevant anatomical, physiological and biochemical parameters were measured, and specific fibromyalgia criteria were assessed for each patient. 15 patients suffered from benign joint hypermobility. In general, the presence of benign joint hypermobilty did not change the disease appearance in fibromyalgia patients. This applied to the main characteristics – pain (p=0.6), muscle strength (p=0.6), hydroxyproline in skin (p=0.99), or collagen markers in urine CTX-I and CTX-II (p=0.45 and 0.41, respectively) – as well as to other studied variables. The only difference found between the two groups was in concentrations of plasma electrolytes with a higher potassium concentration level and lower sodium to potassium ratio in the hypermobile group (p=0.026), which showed the same mean as seen in the healthy population. Benign joint hypermobility with fibromyalgia does not change the fibromyalgia disease characteristics, and hypermobile fibromyalgia patients do not appear to differ in disease severity from the rest of the fibromyalgia population.

Key words: benign joint hypermobility, fibromyalgia

INTRODUCTION

Fibromyalgia (FM) is a disorder characterised by chronic widespread pain [1]. An overlap between joint hypermobility syndrome (JHS) and fibromyalgia (FM) has been found in both adults [2] and in children [3]. The earliest report in literature, before the introduction of the term "fibromyalgia", is ascribed to Kirk, Ansell, and Bywaters [4] who reported an association between JHS and musculoskeletal complaints. Recent studies [5, 6], have demonstrated that the prevalence of JHS is significantly higher in subjects with FM than in the general population, when comparing a group of women with FM to a group of healthy women. In both studies, the groups in question had a uniform ethnicity and similar mean and range of age. The mean Beighton Score of joint hypermobility was found to be significantly higher in the FM groups, compared to the control groups. In one of the studies [6], the pain level, tender points count, total myalgia score and Fibromyalgia Impact Questionnaire (FIQ) score were more severe in FM patients with JHS than in the FM patients without JHS. The differences, however, were not significant.

JHS subjects are believed to experience minor episodes of injury to muscle and ligaments during normal physical activity because of the laxity of ligaments or impairment of proprioception. It is hypothesized that these injuries will result in musculoskeletal pain which in some subjects occurs repeatedly and may trigger disordered pain responses, such as FM [7]. This assumption of peripheral, injured tissue sites as the cause of FM complies with the supposition that such tissue is the origin of nociceptive stimuli, which will sum up temporally and initiate or maintain central sensitization, the key patho-genetical process of FM [8, 9]. It has therefore been suggested [10] that focal biochemical or physiological changes of muscle tissue in FM may be at least part of the cause behind the development of FM. Excess joint laxity is primarily ligamentous laxity, which is determined by the genes that encode collagen, elastin, and fibrillin [11]. The details of aberrant processing of the connective tissue components are known in three inheritable connective tissue disorders – Ehlers-Danlos and Marfan syndromes, and osteogenesis imperfecta – all of which show severely increased joint laxity [12]. The mentioned syndromes involve mutations in the genes encoding type I or type V collagen, or the enzyme catalysing cleavage of procollagen. A milder form of joint laxity is the most common hereditary connective tissue disorder, called "benign JHS". This condition shares many symptoms with the above-mentioned syndromes [13, 14] and is considered to represent a similar type of hypermobility to Ehlers-Danlos syndrome [11]. However, no defect in genes encoding for a collagen or a deficiency in the activity of a collagen-modifying enzyme has been demonstrated in benign JHS [14, 15]. Instead, there is a deficiency in the extracellular matrix protein tenascin-X, which is not an enzyme but a regulator of collagen-fibril deposition by other mechanisms, and is considered an important contribution to the development of benign JHS [13].

Previously, we have found the metabolism and deposition of collagen to be decreased in FM [16, 17]. The studies were blinded in terms of knowledge of presence or lack of presence of JHS in the included patients. When comparing the entire FM group with the healthy controls, we observed

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a low concentration of procollagen type III aminoterminal peptide in serum (S-PIIINP), and a correlation between low S-PIIINP and high intensity of muscle pain [18]. We also found a significantly lower muscle tissue concentration of hydroxyproline (Hyp) and of the summarized concentrations of Hyp, proline (Pro) and glycine (Gly), which are the major amino acids of collagen, in the FM group compared to the control group [16]. In skin biopsies, the FM patients also showed lower Hyp, Pro and hydroxylysine (Hyl), another collagen-related amino acid, than the control subjects, and the skin biopsies from FM patients more frequently showed a deficiency in the normal collagen packing in the endoneurium of nerves [17]. Urine analysis showed low concentrations of the metabolic collagen products collagen type I cross-linked C-telopeptide (CTX-I) and collagen type II cross-linked C-telopeptide (CTX-II), the latter significantly lower than in healthy controls, which indicates a reduced turnover of collagen type I and type II [19].

The main aim of our study was to investigate if FM patients with benign JHS differed from those with no sign of JHS in terms of pain, physical function and biochemistry, with special reference to connective tissue metabolism and anatomy. We also assessed whether the JHS group constituted a definable subgroup of FM patients with particularly low collagen, injured tissue, possibly more intense pain symptoms, as well as a higher degree of reduced physical function. The study was based on data from our earlier studies [16, 17, 19], with additional information on hypermobility included.

PATIENTS AND METHODS

The protocol was accepted by the local Ethics Committee, and each subject gave her informed consent before entering the study.

Patient group. After examination of 146 medical records, 81 FM patients were identified and invited to participate in the study. 30 patients responded and were recalled for a clinical examination, and a complete sample and data material taken from 27 patients. The criteria for inclusion were: women who fulfilled the American College of Rheumatology (ACR) criteria for FM, who were not clinically depressed, did not suffer from concurrent muscle or joint disease, had no motor trauma or history of monotonous physical work, and no daily sports activity.

Physiological and functional measurements. The patient's age, height, body weight, time of onset of FM symptoms, and current medication were recorded. Each patient completed a Fibromyalgia Impact Questionnaire [20] and a self-report of occupational and spare-time physical activity.

Assessments of tender points and four negative control points were carried out by two independent examiners in a defined way [1]. Joint hypermobility was evaluated using the 1998 revised Beighton criteria for benign JHS [21].

Bone mineral density of the calcaneous was determined by dual photon absorptiometry using a ^{153}gadolinium source (Dual Photon BMC-Scanner, Gammatec, Vaerloese, Denmark). Maximal isokinetic extension and flexion strength was measured (best torque out of 3) from knee and elbow, left and right, using a dynamometer (Lido Active, Loredan Biomedical, Davis, CA, USA).

Biochemical tests. Fasting morning-urine and venous blood samples were taken on the day of visit to the clinic, and currently subjected to a range of routine analyses in the hospital clinical biochemical laboratory to determine the following: haematological status (erythrocyte sedimentation rate, haemoglobin, leukocytes count, erythrocytes and thrombocytes, differential count of white blood cells); plasma electrolytes (sodium, potassium, albumin, urea and creatinine); serum alanine aminotransferase, basic phosphatase, creatine kinase, plasma C-reactive protein, serum myoglobin, ionised calcium, urates, thyroid-stimulating hormone, IgM rheumatoid factor, and anti-nuclear antibodies. Creatinine was determined in urine.

Muscle and skin biopsies. Muscle biopsies were taken with a Bergström's needle from the *vastus lateralis m. quadriceps femoris*, 10 cm proximally from the upper margin of patella, with a 3-mm biopsy punch from the proximal front of the thigh. These sites were outside the defined tender-point areas in FM patients. Of the biopsies from the 27 patients there was uncertainty on the validity of the muscle specimen taken for biochemistry from one patient. Data referring to this patient were therefore excluded from the results on amino acids.

Amino acid determination. A part of each muscle or skin biopsy was delipidized, dried, and then hydrolyzed to amino acids, which were determined by high-performance liquid chromatography (HPLC) after derivation with phenylisothiocyanate [22]. The HPLC instrument consisted of a quaternary gradient pump, an autosampler, a tuneable UV-absorbance detector monitoring the column eluate, and a computer with Millennium 32 programme for instrument control and data management (all instruments obtained from Waters, Milford, MA, USA). The column for sample separation was a Hypersil BDS C18 3 µm 4.6 × 150 mm (Thermo Fisher Scientific, Waltham, MA, USA). The amount of total protein per milligram of dry, delipidized tissue, was calculated by summarizing the products of the determined molar amount of each amino acid and the residual weight of this amino acid, expressing the resulting amount in proportion to the dry tissue weight.

Electron microscopy. A part of each muscle and each skin biopsy was fixed immediately after extraction in cold 0.1 M cacodylate buffer pH 7.35 with 3% or 6% glutaraldehyde, respectively, and 7.5% sucrose. Postfixation took place in phosphate-buffered 1% osmic acid. The specimens were then dehydrated through ethanol series, embedded in Epon epoxy resin (Merck, Darmstadt, Germany), sectioned in 60 nm-sections and post-stained with uranyl acetate and lead citrate, and finally studied in a Jeol 1010 electron microscope (Jeol, Tokyo, Japan) at 80 kV.

Parameters expressing pathological conditions [16, 17] were assessed by investigators blinded to the clinical data. In muscle, the parameters were: appearance of the sarcolemma, where irregularities ('waves on the outside') result in a serrated appearance; regularity of Z lines; atrophy of muscle fibrils; number and distribution of lipid droplets and mitochondria. In skin, the following were evaluated: changes in the perineurium area, appearing as partial splitting of the perineurium; changes in the endoneurium of nerve fibres, appearing as deficient filling of the endoneurium with collagen fibrils; occurrence of proteoglycans, seen as black dots in the endoneurium, or just outside the perineurium.

Determination of urinary markers of collagen metabolism. CTX-I and CTX-II were determined by ELISA methods, using reagents branded 'CrossLaps®' and "CartiLaps®", respectively (Immunodiagnostic Systems Holdings Nordic, Herlev, Denmark). The total concentrations of free and bound pyridinoline (Pyd) and deoxypyridinoline (Dpd) in urine samples were determined by acid hydrolysis, extraction of Pyd and Dpd on CF11 cellulose columns, and separation by high performance liquid chromatography with fluorescence detection as described [19, 23]. All urinary concentrations data of the collagen metabolism markers CTX-I, CTX-II, Pyd, Dpd and Hyp were normalized with creatinine in the same sample.

Statistics. Statistical analysis was performed with SPSS release 16.0 software (SPSS, Chicago, IL, USA). The answers to the 10 questions in the Fibromyalgia Impact Questionnaire about physical function in daily activities were assigned score values from 0 – 'Always' to 3 – 'Never', corresponding to the lowest activity, and the mean score for these 10 items was calculated. Measures on visual analogue scales were calculated as centimeters on a 10 cm scale. The distribution of current medications was compared for each item to the alternative 'not using this type of drug', by Fisher's Exact Test. The individual results for bone mineral density were calculated as the Z-score by reference to a diagram of the mean ± 1 SD *vs* age for Danish women [24]. Each subject's result for peak isokinetic muscle strength measured in a given joint (knee or elbow) at a given angular velocity (30 ^{o} s^{-1} or 60 ^{o} s^{-1}), and a given direction of movement (extension or flexion), was compared to a normal value. This was calculated by means of an algorithm set up as a mathematical model for muscle-strength data recorded from healthy subjects in our clinic. Isokinetic muscle strength of FM patients was expressed as the percentile of the normal-subject values adjusted for age, height and body weight. Individual percentile values, referring to side and angular velocity, were strongly correlated, hence the mean values were calculated for the following 4 variables: knee extension and flexion, elbow extension and flexion. Means were compared using Student's t-test, not assuming equal variances. The distribution of observations of a few variables deviated significantly from variance homogeneity, as assessed by Levene's Test, and in these cases median, inter-quartile range and the p-value from Mann-Whitney test were calculated. The distribution of scores from the evaluation of electron micrographs was compared by means of Fisher's Exact Test.

RESULTS

Demographic data. Of the 27 FM patients, 15 were identified by the usual criterion of '4 or more out of 9 points' on the Beighton Scale as also having JHS [21]. This was probably of the frequent 'benign' type since none of the patients had symptoms or a history of Ehlers-Danlos or Marfan syndromes, or *osteogenesis imperfecta*. The mean, standard deviation, difference between means, its 95% confidence interval, and the p-value from Student's t-test of data on body composition, duration and severity of FM symptoms, and current medication, are given in Table 1.

Routine clinical biochemistry parameters. All subjects were within the normal range of all measured biochemical parameters. However, there was a slightly higher plasma potassium in the JHS FM group, compared to the group of FM patients without JHS: Median, inter-quartile range, and the p-value from Mann-Whitney test were 4.1 mmol/l, (0.4 mmol/l) *vs* 3.8 mmol/l (0.2 mmol/l), p = 0.026 in Mann-Whitney test. The ratio between plasma sodium and potassium was correspondingly lower in the FM patients with JHS, p = 0.026.

Electron microscopy of muscle and skin. The percentage distribution of scores for pathological findings assigned to the electron micrographs from muscle and skin biopsies, and the mean values of numerical data showed no difference between the JHS FM group and the group without JHS.

Function and muscle strength. Data on function from the Fibromyalgia Impact Questionnaire are given in Table 2. None of the score values revealed a significant difference between the 2 study groups; this was in accordance with similar isokinetic muscle strength in the 2 groups.

Deposition and metabolism of collagen. Results from the biochemical determinations of collagen and markers of the metabolism of collagen types I and II are given Table 3. There was no significant difference between the 2 FM groups concerning collagen turnover.

Table 1 Characteristics of study population: Body composition, intensity of FM symptoms, current medication in the groups of fibromyalgia patients with or without concurrent joint hypermobility syndrome.

	FM with JHS (n_1 = 15)	FM without JHS (n_2 = 12)	Difference (95% CI)	p-value
Age, years	37.1 (5.8)	39.9 (4.3)	-2.85 (-6.9 to 1.2)	0.157†
Body-mass index, kg/m^2	23.6 (3.5)	24.7 (4.0)	-1.06 (-4.1 to 2.0)	0.476†
Bone mineral density, Z-score	0.05 (0.45)	0.27 (0.78)	-0.22 (-0.76 to 0.32)	0.398†
Duration of FM, months	74.6 (64.8)	89.4 (113.3)	-14.8 (-92.5 to 62.8)	0.692†
Positive tender points	14.4 (2.2)	13.8 (2.8)	0.57 (-1.5 to 2.6)	0.567†
Current medication:				
No medication	5	1		0.182‡
Weak analgesics	7	8		0.441‡
NSAID	2	7		0.037‡
Opioids	3	4		0.662‡
Antidepressants	2	5		0.185‡

Values are given as: Mean, SD, Difference between means, and its 95% Confidence Interval. p-value from † Student's t-test, or ‡ Fisher's Exact Test.

Table 2 Patients' function described by data from the Fibromyalgia Impact Questionnaire and measurements of muscle strength in the groups of fibromyalgia patients with or without concurrent joint hypermobility syndrome.

	FM with JHS (n_1 = 15)	FM without JHS (n_2 = 12)	Difference (95% CI)	p-value
Physical function, daily activities	1.34 (0.46)	1.51 (0.79)	-0.17 (-0.72 to 0.38)	0.521†
Days felt good during the week	2.46 (2.16)	2.58 (2.02)	-0.12 (-1.85 to 1.61)	0.885†
Employed	7 of 14	4 of 12		0.453‡
Working days missed out of five	0.17 (0.41)	0.63 (1.25)	-0.46 (-2.38 to 1.46)	0.524†
Inconvenience impairing job ability	5.11 (2.67)	6.15 (2.73)	-1.04 (-5.16 to 3.09)	0.564†
Pain during the week	7.10 (2.09)	6.58 (2.21)	0.52 (-1.29 to 2.33)	0.558†
Fatigue during the week	8.35 (1.23)	8.05 (1.64)	0.30 (-0.94 to 1.55)	0.614†
Morning tiredness	8.44 (1.23)	7.62 (2.18)	0.82 (-0.75 to 2.38)	0.284†
Joint stiffness	6.11 (2.27)	6.60 (2.48)	-0.49 (-2.53 to 1.54)	0.620†
Anxiety	2.53 (3.13)	2.47 (3.06)	0.06 (-2.53 to 2.64)	0.965†
Depression	1.92 (2.45)	2.41 (2.90)	-0.49 (-2.77 to 1.79)	0.660†
Muscle strength, knee extension	22.6 (47.1)	10.9 (22.8)		0.575ψ
Muscle strength, knee flexion	16.0 (34.0)	3.9 (25.7)		0.603ψ
Muscle strength, elbow extension	10.2 (15.8)	6.3 (31.6)		0.775ψ
Muscle strength, elbow flexion	17.1 (27.2)	10.3 (8.7)		0.078ψ
Hand grip force, N	212 (79)	164 (85)		0.279ψ

Values from the Fibromyalgia Impact Questionnaire are given as: Mean, SD, Difference between means, and its 95% Confidence Interval, and p-value from † Student's t-test or ‡ Fisher's Exact test. Data on muscle strength, knee and elbow, are the percentile which, in the distribution referring to normal women of the same age, height and body weight, fall below the value recorded for the patient. Values are given as: Median, Inter-quartile range, and p-value from ψMann-Whitney test.

Table 3 Amounts of collagen-related amino acids: hydroxyproline (Hyp), proline (Pro) and glycine (Gly), and total protein in muscle and in skin, in units of µg per mg dry tissue, as well as concentrations of collagen-metabolism markers in urine.

	FM with JHS (n_1 = 15)	FM without JHS (n_2 = 12)	Difference (95% CI)	p-value
Muscle:				
Hyp µg/mg	4.33 (13.57)	1.10 (0.78)	3.23 (-4.29 to 10.75)	0.373†
Sum of Hyp, Pro, Gly µg/mg	62.9 (61.3)	58.1 (25.4)	4.86 (-31.6 to 41.3)	0.783†
Total protein, µg/mg	625.8 (81.9)	631.6 (75.5)	-5.8 (-68.4 to 56.8)	0.850†
Skin:				
Hyp µg/mg	49.6 (8.8)	49.6 (7.1)	-0.05 (-6.3 to 6.3)	0.987†
Sum of Hyp, Pro, Gly µg/mg	250.7 (32.0)	246.6 (25.9)	4.1 (-18.9 to 27.0)	0.718†
Total protein, µg/mg	843.1 (72.1)	822.9 (67.3)	20.2 (-35.3 to 75.7)	0.460†
Urine:				
CTX-I µg per mmol creatinine	264.6 (166.9)	224.6 (104.2)	40.0 (-68.5 to 148.5)	0.454†
CTX-II ng per mmol creatinine	124.2 (121.8)	93.1 (65.0)	31.0 (-44.9 to 106.9)	0.406†
Pyd nmol per mmol creatinine	56.7 (24.6)	50.7 (11.8)		0.071ψ
Dpd nmol per mmol creatinine	16.0 (5.1)	13.9 (3.7)	2.2 (-1.3 to 5.7)	0.212†
Pyd to Dpd ratio	4.15 (0.85)	3.93 (0.82)	0.23 (-0.44 to 0.89)	0.492†

Mean, SD, Difference between means, and its 95% Confidence Interval, and p-value from † Student's t-test, or Median, Interquartile range, and p-value from ψMann-Whitney test.

DISCUSSION

In our study population of FM patients, as expected, we found a much higher frequency (55%) of JHS [25, 26], compared to that of the general population. The Danish women included in our study were all of Caucasian origin with an expected prevalence of JHS of about 6% [27].

In general, the comparison of FM patients with or without concurrent JHS gave similar results for nearly all physiological, biochemical and pathological findings. As previously described, FM is associated with a lower collagen turnover than healthy controls [19], and no difference in the group with or without JHS was observed in this respect. Thus, both groups may suffer from some milder connective tissue disorder, causing tissue damage, which could be associated with the abnormal pain processing and central sentisization in FM [10, 28, 29, 30]. The slightly different levels of potassium between the 2 groups were within the normal range [31], and cannot have clinically significant effects with regard to muscle activation. It should be taken into account that the results may be due to random effects in several variables being measured; our observation should therefore be tested in larger materials.

The numerically lower bone mineral density in the JHS group compared to the group without is in accordance with findings by Gulbahar et al. (2006) [32] and Nijs et al (2000) [33], while in our study this did not reach statistical significance.

Our results were obtained in a rather small, albeit very extensively studied group of patients, and some of our negative findings may be due to the small sample. On the other hand, for clinical use, we have to take into account that the number of FM patients in our study is approximately what a typical Rheumatology Unit would see in a year. Therefore, the lack of significant differences between the 2 groups makes it impossible to consider sub-grouping according to biochemical and microscopical tests. Rather, the simple testing for JHS may be used for sub-grouping when considering possible choice of therapy involving physical training.

CONCLUSION

There does not seem to be any difference in disease expression and severity between FM patients with JHS and FM patients without this syndrome. The pathology behind the 2 groups may be different, but even the collagen turnover does not appear to be different in the 2 groups.

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