ABSTRACT. Objectives. To investigate whether constitutional laxity of the connective tissues is more frequently present in adolescents with chronic fatigue syndrome (CFS) than in healthy controls. Increased joint hypermobility in patients with CFS has been previously described, as has lower blood pressure in fatigued individuals, which raises the question of whether constitutional laxity is a possible biological predisposing factor for CFS.

Design. Cross-sectional study.

Participants. Thirty-two adolescents with CFS (according to the criteria of the Centers for Disease Control and Prevention) referred to a tertiary hospital and 167 healthy controls.

Methods. The 32 adolescents with CFS were examined extensively regarding collagen-related parameters: joint mobility, blood pressure, arterial stiffness and arterial wall thickness, skin extensibility, and degradation products of collagen metabolism. Possible confounding factors (age, gender, height, weight, physical activity, muscle strength, diet, alcohol consumption, and cigarette smoking) were also measured. The results were compared with findings in 167 healthy adolescents who underwent the same examinations.

Results. Joint mobility, Beighton score, and collagen biochemistry, all indicators of connective tissue abnormality, were equal for both groups. Systolic blood pressure, however, was remarkably lower in patients with CFS (117.3 vs. 129.7 mm Hg; adjusted difference: −13.5 mm Hg; 95% confidence interval [CI]: −19.1, −7.0). Skin extensibility was higher in adolescents with CFS (mean z score: 0.5 vs. 0.1 SD; adjusted difference: 0.3 SD; 95% CI: 0.1, 0.5). Arterial stiffness, expressed as common carotid distension, was lower in adolescents with CFS (mean z score: −0.1 vs. −0.5; adjusted difference: −0.4; 95% CI: −0.7, −0.1). All analyses were adjusted for age, gender, body mass index, and physical activity. Additionally, arterial stiffness was adjusted for lumen diameter and pulse pressure.

Conclusions. These findings do not consistently point in the same direction of an abnormality in connective tissue. Patients with CFS did have lower blood pressure and more extensible skin but lacked the most important parameter indicating constitutional laxity, ie, joint hypermobility. Moreover, the collagen metabolism measured by crosslinks and hydroxyproline in urine, mainly reflecting bone resorption, was not different. The unexpected finding of stiffer arteries in patients with CFS warrants additional investigation. Pediatrics 2005; 115: e415–e422. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1515; chronic fatigue syndrome, connective tissue disease, cardiovascular factors, autonomic nervous system.

ABBREVIATIONS. CFS, chronic fatigue syndrome; EDS, Ehlers-Danlos syndrome; HP, hydroxyllysylpyridinoline; LP, lysylpyridinoline; CDC, Centers for Disease Control and Prevention; CIMT, carotid intimal-medial thickness; Hyp, hydroxyproline; CIS-20, Checklist Individual Strength-20; CI, confidence interval.

Chronic fatigue syndrome (CFS) is a frequently disabling illness of unknown etiology and variable prognosis. Scientific interest in the pathogenesis of this illness parallels the apparent increase in incidence.1,2 However, despite all scientific efforts, a plausible cause for CFS has not been established yet. Until now, there is insufficient support for either a purely somatic or psychic chain of causation. CFS is viewed as a multifactorial illness, and a distinction is made between constitutional, initiating, and perpetuating factors on both the biological and psychosocial levels.3

The prognosis for adolescents with CFS seems to be better than for adults, although as many as 44% of adolescents remain ill with significant symptoms, as observed in an 8-year follow-up study.4

This study focuses on a constitutional biological factor, which may partly explain the symptoms of fatigue and pain. The main question is whether constitutional laxity of the connective tissues is present more frequently in adolescents with CFS than in healthy controls. One of the reasons to perform this study was the previous finding of increased joint hypermobility in adolescents with CFS.5 Moreover, a former study in adolescents established the coexistence of CFS and Ehlers-Danlos syndrome (EDS) in a substantial part of the study population.6 Fatigue is not a diagnostic criterion in EDS and not often emphasized in the medical literature, likely because of the highly unspecific nature of the symptom fatigue.7 Also, in the more frequently diagnosed benign joint-hypermobility syndrome in childhood, fatigue is 1 of the clinical symptoms.8–10

From the Departments of *Pediatrics and §Pediatric Physical Therapy and Pediatric Exercise Physiology, Wilhelmina Children’s Hospital, and §Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands.

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Reprint requests to (E.M.v.P.) Department of Pediatric, Wilhelmina Children’s Hospital, University Medical Center Utrecht, KEO4.133.1, PO Box 85090, 3508 AB Utrecht, Netherlands. E-mail: e.vandeputte@wkz.azu.nl

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Additional motivation for the hypothesis that constitutional laxity may play a role in CFS comes from the finding that just like in EDS, the clinical symptoms in benign joint-hypermobility syndrome are not restricted to the musculoskeletal system. Other organs are possibly involved, such as blood vessels (with lower systolic and diastolic blood pressure), skin (with higher skin extensibility), and bone (with a lower quantitative ultrasound measurement). In addition, the patients with symptomatic generalized joint hypermobility have significantly lower excretion of urinary hydroxylysylpyridinoline (HP) crosslinks and lysylpyridinoline (LP) crosslinks.

A relation between stiffness of joints and skin and blood pressure is not restricted to patients with a known collagen abnormality. Also, in healthy children we recently described a relation between stiffness of joints and laxity of skin and blood pressure. Stiffness of joints seems to reflect other systemic changes in connective tissue, and this putative multiple-organ involvement, together with the clinical finding of fatigue in collagen disorders, led to the main research question: Is constitutional laxity of the connective tissues a possible biological factor in CFS?

**METHODS**

**Population**

A group of 32 patients with CFS ranging in age from 12 to 18 years were included. These patients were referred to a specific CFS clinic of the University Medical Center Utrecht between January 2001 and May 2002. All patients were white and fulfilled the Centers for Disease Control and Prevention (CDC) criteria for CFS at the time of inclusion. Supplementary to the CDC exclusion criteria, patients with an established diagnosis of a connective tissue disorder (with lower systolic and diastolic blood pressure), skin (with higher skin extensibility), and bone (with a lower quantitative ultrasound measurement). In addition, the patients with symptomatic generalized joint hypermobility have significantly lower excretion of urinary hydroxylysylpyridinoline (HP) crosslinks and lysylpyridinoline (LP) crosslinks.

As an index of skin extensibility, a vacuum-suction device was used for each subject as a measure for current wall thickness of the common carotid artery. The average of the intimal-medial thickness of 4 predefined angles was used for each subject as a measure for current wall thickness of the common carotid artery.

**Measurements**

A team of 4 examiners (physiotherapists) and the principal investigator (E.M.v.d.P.) conducted all measurements. The 4 physiotherapists were unaware of the study hypothesis. The same examiner conducted each specific measurement for all participants. No examiner was informed of the results of measurements taken by other examiners. All measurement procedures described below were similarly and in the same sequence applied to the patients and healthy controls (Table 1 summarizes the measurements in the applied sequence). Every 20 minutes the next participant started.

Body height and weight were measured, without shoes and heavy clothing, to the nearest 1 cm and 100 g, respectively. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of body height in meters. Systolic and diastolic blood pressure and pulse rate were measured with participants in an upright sitting position at the right brachial artery with an automated device (Dynapad 1846 SX, Kritikon Inc, Tampa, FL) at the start and end of the examinations, each after a rest period of 5 minutes.

As an indicator of arterial stiffness, the distal part of the right common carotid artery was assessed by using B-mode carotid ultrasonography with a 7.5-MHz linear array transducer (Sonosite 180 Plus; Sonosite Ltd, Biggleswade, United Kingdom). The difference between systolic and diastolic lumen diameter was determined from an M-mode image and averaged over 3 cardiac cycles to provide an estimate of distension (ie, change in lumen diameter during the cardiac cycle/stroke change in diameter) (Fig 1). Other parameters of arterial stiffness were calculated as described recently by our group.

The arterial wall thickness was assessed on a longitudinal 2-dimensional ultrasound image of the carotid artery by measuring intimal-medial thickness (CIMT) over a 10-mm segment of the distal common carotid artery. The average of the intimal-medial thickness of 4 predefined angles was used for each subject as a measure for current wall thickness of the common carotid artery. The actual measurements were performed offline. The sonographer and the reader were unaware of other participants’ measurement data. As a measure of stiffness of capsules and ligaments, the range of joint motion of 9 joints was assessed bilaterally to the nearest 5° with a standard 2-legged 360° goniometer, using the “anatomic-landmark” method. Shoulder (antelexion), elbow (flexion and extension), wrist (palmar and dorsal flexion), metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of the second ray (flexion, extension), hip (flexion and extension), knee (flexion and extension), and ankle (plantar and dorsal extension) were examined. Children were asked to actively stretch or bend the joint maximally without interference by the investigator and without help of the ipsilateral muscles by use of contralateral limbs. Range of joint motion of all the participants was measured by the same physical therapist. The intrarater reliability, assessed in 25 joints of 8 subjects, was high (intraclass correlation: 0.97; $P < 0.01$). The mean difference between 2 measurements was 2.4 degrees (SD: 4.6). Based on 9 measurements, the Beighton score was calculated as an indicator of the possible presence of generalized joint hypermobility (normal if <4; range: 0–9). As an index of skin extensibility, a vacuum-suction device was placed bilaterally at the ventral part of the forearm and at the medial part of the upper leg. Skin displacement as a result of a negative pressure of 10 kPa on the skin was indicated in millimeters. The reliability of this instrument has been shown to be high. Muscle strength was measured as a possible confounder, because it might partly explain maximal joint motion. The strength of the proximal and distal muscles in lower and upper extremities was measured with a hand-held myometer in Newtons. Measurements were performed sequentially 3 times, and the highest value was used for analysis. Shoulder abductors, grip strength, hip flexors, and dorsal extensors of the foot were measured bilaterally. Quantitative ultrasound measurement of bone was performed in the right os calcis with a Sahara ultrasound device (Hologic QDR 4500; Hologic Inc, Waltham, MA) measuring broadband ultrasound attenuation (dB/MHz) and speed of sound (m/second) as indicators of bone quantity and stiffness, respectively.

Acoustic phantoms provided by the manufacturer were scanned daily without deviation over the duration of the study.

Degradation products of collagen (hydroxyproline [Hyp], crosslinks) were measured in overnight urine specimens. HP is the major collagen crosslink in articular cartilage, and another crosslink is LP, which is a bone-specific degradation marker, as is Hyp. Hyp and crosslink analysis was conducted as described previously. Especially the amount of crosslink products correlates with joint mobility, with a lower amount of crosslinks in joint hypermobility and a higher amount of crosslinks in joint hypomobility.
Pain is a nonspecific feature of CFS and of joint hypermobility. An algometer was used to measure pain threshold at 4 sites: 2 bony sites (right femur lateral condyle and right elbow lateral condyle) and 2 muscle sites (musculus deltoideus right upper arm and musculus vastus medialis right leg). With the algometer, an increasing pressure is applied to the reference points, and the subject is asked to react verbally when the level of pressure is perceived as pain; this level is subsequently designated as the pain threshold (scores: 0–11). Algometry has an excellent test-retest reliability.24

The total examination time for each participant was 60 minutes. After the physical examinations, the subjects had to complete questionnaires regarding fatigue (Checklist Individual Strength-20 [CIS-20]), physical activity (cycling, leisure sport, and gym), school attendance, and lifestyle behavior (sleep, smoking, drinking, diet). The CIS-20 asks about fatigue in the 2 weeks preceding the assessment. There are 4 respective subscales (fatigue with 8 items, concentration with 5 items, motivation with 4 items, and physical activity with 3 items), and each item is scored on a 7-point Likert scale. A high score indicates a high level of subjective fatigue and concentration problems and a low level of motivation and physical activity. The questionnaire has good reliability and discriminative validity.25 The average time to complete these questionnaires was 20 minutes.

The medical ethics committee of the University Medical Center Utrecht approved this study. Written informed consent was obtained from the adolescents and their parents.

Data Analysis

Of all relevant variables, group-specific means and SDs or proportions were calculated for descriptive purposes. Joint motion, skin extensibility, and muscle force were determined at various locations. Because the absolute levels and the distributions differed considerably between locations, we calculated individual normal scores, the so-called $z$ scores ($z$ score = $x_{\text{index}} - x_{\text{mean}}$/SD or the number of SDs below or above the mean) for values at each location instead of simply averaging all measurement results. Subsequently, mean individual $z$ scores were calculated by averaging $z$ scores of all measured locations. These mean $z$ scores, indicating individuals' ranks in the distribution of joint mobility, skin extensibility, or muscle strength, were used for additional analysis.

The data were analyzed with linear regression using a group indicator (patient = 1, control = 0) as an independent variable and the investigated parameter as a dependent (outcome) variable. Results are presented as linear-regression coefficients representing mean group differences for the investigated parameter with their corresponding 95% confidence intervals (95% CIs). The same models were used to adjust for possible confounding factors such as age, gender, BMI, and physical activity. For evaluations of arterial stiffness, we constructed several parameters of stiffness to enable comparison with other studies. All these stiffness parameters are constructed as ratios in different formulas as we have described.15 However, in studies looking into etiology, analyses using ratios are difficult to interpret, because an observed relationship may be caused by the relation with the nominator, the denominator, or both. Therefore, a better approach in etiologic studies may be to use either the nominator or the denominator and adjust for the other factor in a regression model. Thus, we present the distension value (change in lumen diameter during the cardiac cycle), which is adjusted for pulse pressure and diastolic lumen diameter and additionally adjusted for age, gender, BMI, and physical activity, as the most appropriate measurement for stiff arteries in this etiologic study. A lower distension value inversely relates to a stiffer vessel, as do the cross-sectional compliance coefficient and the distensibility coefficient. The Peterson’s modulus is closely related to the inverse of the distensibility coefficient. Young’s elastic modulus provides direct information about the elastic properties of the wall material independent of the vessel geometry.15 Statistical significance was considered to be reached when 95% CIs did not include the null value, corresponding with a $P$ value $<.05$.

RESULTS

A summary of relevant characteristics of the adolescents with CFS is provided in Table 2. The majority of patients were females. There was considerable school absence and a high use of medication, and many patients were on a diet. Additionally, Table 2 shows a substantial use of health care services since the start of the symptoms, including psychotherapy and alternative treatment. Table 3 describes general characteristics of the adolescents with CFS and the controls. Both groups were comparable except for gender, BMI, and physical activity. Physical activity, computed in hours of physical activity per week, was 5.7 hours less in patients with CFS. Because gender, age, BMI, and physical activity may affect the studied collagen-related measurements, we considered
them to be possible confounding factors. The patients with CFS showed a higher score on all the subscales of the CIS-20.

Table 4 shows the joint mobility in 5 bilateral joints in both groups and the mean (adjusted) difference in joint mobility between the adolescents with CFS and the healthy adolescents. There were no group differences in joint mobility in these 5 joints. The median Beighton score in the healthy adolescents was 2, similar to the median Beighton score in the CFS group. Comparison of the Beighton scores between the 2 groups in a linear-regression model (adjusted for age, gender, and BMI) showed no difference as well (regression coefficient: 0.35; 95% CI: −1.0, 0.3). Generalized joint hypermobility (Beighton score ≥ 4) was present in 29 of 167 (17%) healthy adolescents,
whereas in the CFS group, 3 of the 32 adolescents with CFS (9%) showed hypermobility.

Mean differences in indicators of organ stiffness between patients with CFS and controls are presented in Table 5. Joint mobility of all the 34 examined joints did not differ between patients and controls. A separate analysis of small and large joints did not change this result. The skin of patients with CFS was more extensible, and adjustment for age, gender, and BMI did not materially change this finding.

There was a significant difference in muscle strength between the adolescents with CFS and the healthy adolescents (mean difference in z score: −0.7; 95% CI: −1.0, −0.4), even when adjusted for age, gender, and BMI (mean difference in z score: −0.6; 95% CI: −0.9, −0.4).

There was a significant difference in systolic and diastolic blood pressure and pulse pressure between the groups at the start of the examination. Blood pressure levels were lower in patients with CFS (−13.5 adjusted difference in systolic blood pressure, −6.7 mm Hg adjusted difference in diastolic blood pressure), without any effect on the heart rate, which was similar for both groups at the start. At the end of the examination, the blood pressure was comparable for both groups, but the heart rate was faster for the CFS group (mean difference: 4.9; 95% CI: −0.1, 9.8). Arterial stiffness expressed as common carotid distension and adjusted for lumen diameter and pulse pressure showed that patients with CFS have a lower value of distension than controls, reflecting stiffer arteries. The analyses of the various arterial stiffness parameters point toward arterial stiffness in the patients with CFS compared with controls. Although some of the associations do not reach statistical significance, the consistency of the findings enhances the validity of the finding.

Arterial wall thickness, as determined by the common CIMT, was equal for both groups. The bone parameters showed that there was less stiffness of bones in patients with CFS. Adjusting for confounding factors, including physical inactivity, attenuated this difference.

There were no clear differences between the groups with regard to collagen biochemistry (Table 5).

The mean pain threshold differed considerably between patients with CFS and controls. After adjusting for age, gender, and BMI, this lower pain threshold for patients with CFS remained.

### DISCUSSION

The results of our study do not consistently point toward an abnormality in connective tissue and therefore do not support the hypothesis that connective tissue laxity is a risk factor for the development of CFS in adolescents. Patients with CFS did have lower blood pressure during rest, more extensible skin, and less muscle strength but lacked the most important parameter indicating constitutional laxity: joint hypermobility. Another argument against constitutional laxity is the finding of an increased arterial stiffness in the patients with CFS. Moreover, the collagen metabolism measured by crosslinks and Hyp in urine, mainly reflecting bone resorption, did not differ between the 2 groups.

Before additional discussion about these results, some aspects of our study design need to be addressed. The cross-sectional design of our study limits causal interpretations. Furthermore, we attempted to measure all conceivable confounders of relations between stiffness parameters and disease status. However, we cannot exclude the possibility that there is residual confounding or unknown confounders. We do believe that we have sufficiently tackled problems with information bias, because examiners were blinded for other patient characteristics during measurement protocols.

Our results are incongruent with former studies with respect to joint mobility in adolescents with CFS. Whereas former studies established joint hypermobility in adolescents with CFS, we found a remarkably similar joint motion in adolescents with CFS and controls and a congruent Beighton score. The question is whether the CFS population under study is a representative sample of the CFS adolescent population in the Netherlands, which is estimated to consist of 2000 cases (the prevalence rate in the 5-15-year age group according to CDC criteria is 0.2 in Great Britain). Exact prevalence rates for the adolescent age group in the Netherlands are lacking. The Wilhelmina Children’s Hospital is a tertiary referral center for CFS (50 new patients with fatigue each year) and for children with joint hypermobility. A child with joint hypermobility initially referred to the department of pediatric physiotherapy for hyper-

### TABLE 4. Results and Mean Differences in Joint Mobility Between Patients With CFS and Healthy Controls

<table>
<thead>
<tr>
<th>Joint Mobility</th>
<th>Patients With CFS, Mean (SD) (n = 32)</th>
<th>Controls, Mean (SD) (n = 167)</th>
<th>Difference (95% CI)</th>
<th>Adjusted Difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right wrist palmar flexion</td>
<td>76.9 (7.6)</td>
<td>75.2 (8.3)</td>
<td>1.7 (−1.4, 4.8)</td>
<td>0.8 (−2.4, 3.9)</td>
</tr>
<tr>
<td>Left wrist palmar flexion</td>
<td>77.9 (7.3)</td>
<td>76.0 (8.3)</td>
<td>1.9 (−1.2, 5.0)</td>
<td>1.2 (−1.9, 4.4)</td>
</tr>
<tr>
<td>Right second-finger metacarpal extension</td>
<td>22.8 (11.5)</td>
<td>23.5 (10.4)</td>
<td>−0.7 (−4.7, 3.3)</td>
<td>−2.2 (−6.4, 1.8)</td>
</tr>
<tr>
<td>Left second-finger metacarpal extension</td>
<td>26.6 (12.0)</td>
<td>26.2 (12.0)</td>
<td>0.4 (−4.2, 4.9)</td>
<td>−1.3 (−5.9, 3.3)</td>
</tr>
<tr>
<td>Right elbow extension</td>
<td>3.4 (5.1)</td>
<td>3.5 (5.6)</td>
<td>0 (−2.2, 2.0)</td>
<td>−0.7 (−2.8, 1.4)</td>
</tr>
<tr>
<td>Left elbow extension</td>
<td>4.4 (4.4)</td>
<td>4.2 (5.9)</td>
<td>0.2 (−2.0, 2.3)</td>
<td>−0.5 (−2.7, 1.7)</td>
</tr>
<tr>
<td>Right hip flexion</td>
<td>111.3 (8.1)</td>
<td>112.4 (6.9)</td>
<td>−1.1 (−3.8, 1.6)</td>
<td>−0.4 (−2.8, 2.1)</td>
</tr>
<tr>
<td>Left hip flexion</td>
<td>111.9 (8.1)</td>
<td>113.5 (6.7)</td>
<td>−1.6 (−4.2, 1.1)</td>
<td>−1.0 (−3.4, 1.4)</td>
</tr>
<tr>
<td>Right knee extension</td>
<td>2.8 (3.8)</td>
<td>2.5 (4.0)</td>
<td>0.3 (−1.2, 1.8)</td>
<td>−0.3 (−1.8, 1.3)</td>
</tr>
<tr>
<td>Left knee extension</td>
<td>2.8 (3.8)</td>
<td>2.4 (3.9)</td>
<td>0.4 (−1.0, 1.9)</td>
<td>−0.2 (−1.7, 1.3)</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, and BMI.
### TABLE 5. Results and Mean Differences in Indicators of Organ Stiffness Between Patients With CFS and Healthy Controls

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Patients With CFS, Mean (SD)</th>
<th>Controls, Mean (SD)</th>
<th>Difference (95% CI)</th>
<th>Adjusted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure start, mm Hg</td>
<td>117.3 (14.2)*</td>
<td>129.7 (14.2)*</td>
<td>-12.6 (−18.0, −7.2)*</td>
<td>-13.5 (−19.1, −7.0)†</td>
</tr>
<tr>
<td>Systolic blood pressure end, mm Hg</td>
<td>120.2 (12.8)</td>
<td>121.6 (13.5)</td>
<td>-1.4 (−6.5, 3.7)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure start, mm Hg</td>
<td>65.7 (7.2)*</td>
<td>70.5 (9.1)*</td>
<td>-4.8 (−8.2, −1.5)*</td>
<td>-6.7 (−10.5, −3.0)†</td>
</tr>
<tr>
<td>Diastolic blood pressure end, mm Hg</td>
<td>67.7 (6.6)</td>
<td>67.6 (7.6)</td>
<td>0.1 (−2.7, 2.9)</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure start, mm Hg</td>
<td>51.6 (10.3)*</td>
<td>59.5 (12.1)*</td>
<td>-7.8 (−12.4, −3.2)*</td>
<td>-6.8 (−11.8, −1.8)†</td>
</tr>
<tr>
<td>Pulse pressure end, mm Hg</td>
<td>52.5 (10.7)</td>
<td>54.0 (12.1)</td>
<td>-1.5 (−6.0, 3.0)</td>
<td></td>
</tr>
<tr>
<td>Heart rate start, beats/min</td>
<td>83.5 (14.8)</td>
<td>83.0 (17.6)</td>
<td>0.5 (−6.0, 7.1)</td>
<td></td>
</tr>
<tr>
<td>Heart rate end, beats/min</td>
<td>80.6 (12.2)</td>
<td>75.7 (13.1)</td>
<td>4.9 (−9.1, 9.8)</td>
<td></td>
</tr>
<tr>
<td>Carotid artery stiffness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic lumen diameter, m/10^3 (D)</td>
<td>5.37 (0.35)</td>
<td>5.48 (0.5)</td>
<td>-0.11 (−0.29, 0.08)</td>
<td>-0.12 (−0.31, 0.07)</td>
</tr>
<tr>
<td>Stroke change in diameter, m/10^3 (ΔD)</td>
<td>0.67 (0.22)*</td>
<td>0.82 (0.26)*</td>
<td>-0.15 (−0.24, −0.05)*</td>
<td>-0.11 (−0.22, −0.01)†</td>
</tr>
<tr>
<td>Cross-sectional compliance, mm²/kPa (compliance coefficient)</td>
<td>0.84 (0.30)*</td>
<td>1.03 (0.42)*</td>
<td>-0.19 (−0.35, −0.04)*</td>
<td>-0.18 (−0.36, −0.01)†</td>
</tr>
<tr>
<td>Distensibility coefficient, kPa⁻¹ × 10⁻³</td>
<td>37.8 (13.9)</td>
<td>43.6 (16.8)</td>
<td>-5.8 (−12.2, 0.5)</td>
<td>-6.1 (−13.4, 1.1)†</td>
</tr>
<tr>
<td>Peterson’s modulus, kPa × 10^k</td>
<td>0.06 (0.04)*</td>
<td>0.05 (0.03)*</td>
<td>0.01 (0.00, 0.02)*</td>
<td>0.01 (0.00, 0.02)*†</td>
</tr>
<tr>
<td>Young’s elastic modulus, kPa × 10⁻³</td>
<td>0.37 (0.25)*</td>
<td>0.31 (0.14)*</td>
<td>0.06 (0.00, 0.13)*</td>
<td>0.04 (−0.03, 0.12)</td>
</tr>
<tr>
<td>Common CIMT, mm</td>
<td>0.48 (0.007)</td>
<td>0.48 (0.003)</td>
<td>0 (−0.02, 0.01)</td>
<td></td>
</tr>
<tr>
<td>Joint mobility and skin extensibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean z score joint mobility (34 joints)</td>
<td>0.05 (0.43)</td>
<td>-0.01 (0.45)</td>
<td>0.06 (−0.11, 0.23)</td>
<td>0.02 (−0.17, 0.14)§</td>
</tr>
<tr>
<td>Mean z score skin extensibility (4 locations)</td>
<td>0.5 (0.73)*</td>
<td>-0.1 (0.77)*</td>
<td>0.06 (0.3, 0.9)*</td>
<td>0.3 (0.1, 0.6)§</td>
</tr>
<tr>
<td>Bone parameters and collagen biochemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broadband ultrasound attenuation, dB/MHz</td>
<td>68.3 (12.2)</td>
<td>68.9 (15.0)</td>
<td>0.6 (−6.3, 5.0)</td>
<td></td>
</tr>
<tr>
<td>Speed of sound, m/s</td>
<td>1547.8 (19.5)*</td>
<td>1559.6 (29.6)*</td>
<td>-11.8 (−22.7, −0.9)*</td>
<td>-5.6 (−17.3, 6.1)†</td>
</tr>
<tr>
<td>HP/LP</td>
<td>4.2 (0.5)*</td>
<td>3.9 (0.7)*</td>
<td>0.3 (0.1, 0.6)*</td>
<td>0.13 (−0.2, 0.4)†</td>
</tr>
<tr>
<td>HP/creatinine, μmol/mmol</td>
<td>130.4 (82.4)</td>
<td>138.1 (89.2)</td>
<td>-7.7 (−41.8, 26.4)</td>
<td></td>
</tr>
<tr>
<td>Hyp/creatinine, μmol/mmol</td>
<td>60.4 (40.4)</td>
<td>68.1 (43.4)</td>
<td>-7.8 (−24.4, 8.8)</td>
<td></td>
</tr>
<tr>
<td>LP/creatinine, μmol/mmol</td>
<td>31.5 (21.3)</td>
<td>36.5 (27.1)</td>
<td>-5.0 (−15.2, 5.1)</td>
<td></td>
</tr>
<tr>
<td>Mean pain threshold, score</td>
<td>7.5*</td>
<td>9.8*</td>
<td>-2.3 (−2.9, −1.7)*</td>
<td>-2.0 (−2.7, −1.5)§</td>
</tr>
</tbody>
</table>

* Statistically significant associations (95% CI does not include the null value, corresponding with $P < .05$).
† Adjusted for age, gender, BMI, and physical activity.
‡ Adjusted for age, gender, BMI, physical activity, and lumen diameter and pulse pressure.
§ Adjusted for age, gender, BMI, and muscle strength.

mobility, and with possible CFS, is subsequently referred to the CFS clinic, and vice versa. Thus, the coincidence of being a tertiary clinic for both conditions and the internal referring for both conditions makes it unlikely that we missed the patient with CFS with joint hypermobility. We excluded from our initial sample of potential CFS cases 2 patients with a known collagen disorder (EDS, hypermobility type).

Because we were interested in generalized joint hypermobility, we applied the Beighton score for the assessment of hypermobility and in addition goniometry for the continuous measurement of joint mobility of 26 different joint movements.

The differences in systolic and diastolic blood pressure, which were evident only at the start of the examinations, are intriguing. The low blood pressure did not correlate with illness severity (CIS-20 score) or duration (Pearson correlation coefficients: 0.1 [$P = .6$] and $-0.2$ [$P = .2$], respectively), which makes a causal relationship between CFS and blood pressure not very likely. An association between systolic blood pressure and fatigue was established in a population study consisting of adult men and women with a linear trend showing more tiredness with lower systolic blood pressure. In a subsequently published cross-sectional study in civil servants, this strong association between tiredness and systolic blood pressure was reestablished but seemed confounded by minor psychological dysfunction. In this study we are not informed about minor psychological disturbances, and thus it is possible that the association between fatigue and blood pressure could be explained by unknown psychological factors.

Our study was explicitly not designed to study autonomic nervous dysfunction, which would have required appropriate measurements for the detection of orthostatic intolerance (eg, tilt-table testing). However, the lower blood pressure in sitting position in patients with CFS may be explained by alterations in the autonomic nervous system. Opposite to the finding of this lower blood pressure is the unexpected finding that patients with CFS do seem to have stiffer arteries than controls, established with different parameters of arterial wall stiffness and adjusted for possible confounding factors (age, gender, BMI, and physical activity). Residual confounding for lifestyle (smoking, alcohol consumption, and diet) and age of menarche was considered and investigated by determining for each factor the effect on the distension value. None of these factors influenced the distension value, and thus these lifestyle factors were not incorporated into the regression model. An explanation for stiffer arteries in patients with CFS is not available yet. It has not been reported in the literature, nor has increased cardiovascular disease among patients with CFS. It is credible that a stiffer carotid artery is the result of an
increased BMI\textsuperscript{30,31} and the decreased physical activity, but we adjusted for these possible confounding factors, as we did for lifestyle factors. There might be residual confounding in psychological factors, for example, the stress for patients with CFS to live with a disabling, unexplained condition.

The difference in arterial stiffness is not explained by arterial wall thickness, which was remarkably similar for both groups. Additional research is necessary to give more insight into this intriguing finding.

The difference in bone stiffness disappeared when we adjusted additionally for inactivity. Bone-resorption parameters in an overnight urine sample were the same for both groups. We could have expected a less active process of formation and resorption of bone in the patients with CFS, because of the inactivity, but this was not reflected in the data, possibly because of the large variation in these measurements in both groups.

The pain perception differed considerably between patients and controls. Although this was to be expected, because pain is a frequent complaint of patients with CFS, this is the first study to confirm this difference. Little is known about nociception, processing, cortical perception, and reporting of pain.\textsuperscript{32} It is surprising that the patients with CFS not only complain of more pain sensation on different locations but are also hypersensitive to visual,\textsuperscript{33} acoustic,\textsuperscript{34} and sensory signals. The processes underlying this increased sensory symptom perception in patients with CFS are not understood yet.

CONCLUSIONS

The findings of lower blood pressure, more extensible skin, arterial stiffening, and lower pain threshold in patients with CFS seem to be genuine but do not consistently point at a generalized abnormality in connective tissue. A more likely explanation is that these findings are caused by different mechanisms, such as complex disturbance of the autonomic nervous system in combination with a possible change in sensory symptom perception. More research is necessary to assess the pathogenicity of these findings and the reversibility after successful treatment of the adolescent with CFS.

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Is Chronic Fatigue Syndrome a Connective Tissue Disorder? A Cross-Sectional Study in Adolescents


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