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Patients with Fibromyalgia and Chronic Fatigue Syndrome show increased hsCRP compared to healthy controls

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ABSTRACT

Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM) are both chronic disorders that have a devastating effect on the lives of the affected patients and their families. Both conditions have overlapping clinical features that partly resemble those of inflammatory disorders. The etiology is still not understood, and it is suggested that the immune system might be a contributing factor. So far, the results are inconclusive. The purpose of this study was to compare the two conditions and investigate the level of the inflammatory marker high-sensitivity CRP (hsCRP) in CFS and FM patients compared to healthy controls.

Female participants aged 18–60 years were enrolled in this study. The group consisted of 49 CFS patients, 57 FM patients, and 54 healthy controls. hsCRP levels were significantly higher for both the CFS and the FM groups compared to healthy controls when adjusting for age, smoking, and BMI ($p < .001$). There was no difference between the two patient groups. The level of hsCRP was affected by BMI but not by age and smoking.

Patients with CFS and FM have higher concentrations of hsCRP compared to healthy controls. This remains significant even after adjusting for BMI. CFS and FM cannot be distinguished from each other on the basis of hsCRP in our study.

1. Introduction

The disorders Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM) are two distinct diagnostic groups; however, they show overlapping symptoms (Clauw, 2010). CFS is characterized by severe fatigue with distinct onset, lasting more than 6 months, not necessarily connected to ongoing exertion, not affected by rest, and causing reduced function. In addition, the occurrence of at least four of the following eight symptoms is observed: impairment in short-term memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, headaches of a new type, pattern, or severity, unrefreshing sleep, and post-exertional malaise lasting more than 24 h (Fukuda et al., 1994). Both CFS and FM diagnoses are based on specific inclusion criteria and exclusion of other diagnoses causing the same symptoms, although symptoms from both somatic and psychiatric origin seem to be present (Carruthers et al., 2011; Fukuda et al., 1994; Wolfe et al., 2016, 1990). These two conditions cause distress for the patients and potentially increase expenses for the health-care system. Thus, more knowledge is needed to alleviate the issues caused by CFS and FM.

Pain and fatigue are common traits in several inflammatory disorders. Inflammation directly activates pain systems (Sommer and Kress, 2004) and causes fatigue (Norheim et al., 2011; Sluka and Clauw, 2016). Another trait of several inflammatory disorders is "sickness behavior" referring to non-specific symptoms such as anorexia, depressive activity, loss of interest, and disappearance of body-care activities (Kent et al., 1992). Sickness behavior may be caused by immune mediators (e.g., IL-1; Kent et al., 1992). Thus, the immune system is an obvious candidate to investigate for its role in CFS and FM. So far, studies are inconclusive (Feinberg et al., 2017; Lyall et al., 2003; Raison et al., 2009; Sotzny et al., 2018; Wyller et al., 2017). We previously have shown a tendency to increased inflammation measured as increased TNF-α in CFS patients compared to controls (Groven et al., 2018).

Because the etiology for FM is as vague as that for CFS, we wanted to study similarities and differences between the two conditions. In the present study, the general and widely used immune marker hsCRP is explored in patients with CFS and FM and in healthy controls. hsCRP is a more accurate method of measuring levels of CRP.

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2. Method

2.1. Sample population

2.1.1. Patient groups

Female, non-pregnant patients aged 18–60 years admitted to the Multidisciplinary Pain Centre at St. Olav's University Hospital, Norway, for CFS and FM were eligible for the study. Patients with challenging clinical pictures regarding problems such as CFS and FM are referred to this centre by general practitioners in Mid-Norway.

Each participant went through a comprehensive clinical examination and was thoroughly evaluated by an expert team of medical doctors, physiotherapists, and psychologists. FM patients ($n = 58$) were diagnosed by using the 1990 ACR criteria (Wolfe et al., 1990). CFS patients ($n = 49$) were diagnosed according to the Fukuda criteria (Fukuda et al., 1994). Exclusion criteria were in accordance with diagnostic criteria including known inflammatory disease.

2.1.2. Healthy controls

A healthy group of 53 females aged 18–60 years was consecutively recruited by advertising through websites among the staff of the Norwegian University of Science and Technology and St. Olav's University Hospital. Their health was assessed by conducting a structured medical history and by using questionnaires included in this study measuring the symptoms of CFS and FM (see 2.4 Questionnaires and 2.5 Interview).

2.2. Procedure

The CFS patients were informed about the study by a letter sent by the hospital prior to or shortly after their evaluation or given during their evaluation at the centre. The FM patients were given an information letter by the staff during the examination and evaluation of their FM diagnosis. Both patient groups were then contacted by phone and asked for participation in this study by a member of staff, and an appointment was scheduled for those who accepted to join the study.

2.3. Study design and ethics

The assessment lasted approximately 30–40 min and included an interview, questionnaires, and blood sampling. Data were collected in the period from March 2015 to December 2016. The order of the assessments was random.

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 2014/711). Written informed consent was obtained from all participants.

2.4. Questionnaires

All participants filled out the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983), the FM 2011 and 2016 criteria (Wolfe et al., 2016; Wolfe and Hauser, 2011), the Chalder Fatigue Scale (Chalder et al., 1993), and the Brief Pain Inventory (BPI) (Cleeland, 1991; Klepstad et al., 2002).

2.5. Interview

For each participant, age, height, and weight were recorded. A structured clinical interview was conducted by the first author. History regarding infections, immune disorders, illness in general (somatic as well as psychiatric), comorbid disease, medication, menstrual cycle, use of contraceptives, status of menopause, duration of illness (if applicable), and level of physical activity during the previous two weeks was recorded.

2.6. Blood sampling

There were no restrictions given prior to blood sampling. The blood samples were collected in serum tubes (Vacuette® 5 ml Z Serum Sep Clot Activator) and analyzed for hsCRP at the hospital clinical lab by Siemens Advia Chemistry XPT and Roche Modular P according to the laboratory procedure. Blood samples were also screened for any signs of infection and inflammation (e.g., microbiological serology, white blood cell count, etc.). Signs of any abnormalities led to exclusion from the study.

2.7. Statistical analysis

We used the Statistical SoftWare Package (SPSS) Statistics, version 22. All variables were tested for normality and homogeneity by using the Kormaninov-Smirnov and Shapiro-Wilk tests and the Levene's test.

For comparison of age and BMI between groups, the Kruskall-Wallis test was applied. Mann-Whitney U was used for post-hoc analysis of pair-wise comparison. For the variable CRP, natural log transformed data (lnCRP) were used, and linear regression was applied. For these data, post-hoc pair-wise comparison was conducted by means of *Student's t-test*.

3. Results

The basic descriptives of key variables are summarized in Table 1. The total number of participants was 160, distributed among the three groups as follows: CFS ($n = 49$), FM ($n = 58$), and healthy controls ($n = 53$). The median hsCRP concentration was 0.94 mg/L for CFS, 1.30 mg/L for FM, and 0.60 mg/L for the control group. hsCRP was not normally distributed and hence was transferred into the natural log (lnCRP) for further analyses.

The Kruskall-Wallis test revealed statistically significant differences in age and BMI between the groups (Table 1). Pair-wise analyses for age and BMI are shown in Tables 2 and 3.

BMI made a considerable contribution to the model, accounting for 23.1% of the variance of lnCRP ($p < .001$, $F(1, 145) = 43.62$), whereas the group parameter accounted for 6.9% of the variance ($p = .001$, $F(2, 145) = 5.37$). Age had no effect on the outcome ($p = .200$, $F(1, 145) = 1.66$). There was no relationship between smoking status and hsCRP levels ($p = .925$, $\rho = -0.008$).

There was a strong positive correlation between hsCRP and BMI for the total sample population ($N = 150$, *Spearman's* $\rho = 0.439$, $p < .001$). We also observed a correlation between diagnostic group and hsCRP ($N = 153$, *Spearman's* $\rho = -0.190$, $p = .019$).

The difference in lnCRP was significantly higher in FM and CFS groups compared to the control group ($b = 0.591$, $p = .004$ and $b = 0.563$, $p = .009$, respectively). There was no difference between the two patient groups FM and CFS ($p = .902$; Table 2 and Fig. 1).

4. Discussion

CFS and FM groups showed significantly higher levels of hsCRP than the healthy-control group ($p = .009$ and $p = .004$, respectively) but could not be distinguished between each other ($p = .902$). hsCRP was correlated to BMI but not to age nor smoking. After adjustment for BMI, the increased hsCRP in both patient groups compared to healthy controls was still significant.

Although there are reports finding a lack of association between inflammation and CFS (Wyller et al., 2017), a substantial number of reports indicating an association are published (Patarca-Montero et al., 2001; Patarca, 2001; Raison et al., 2009; Russell et al., 2018). A recent review on CFS and autoimmunity does not mention CRP, although other immune markers are discussed (Sotzny et al., 2018). A recent report (Giloteaux et al., 2016) comparing patients with CFS and healthy controls found a slightly, but not significantly, higher level of hsCRP in

Table 1
Descriptives of C-reactive protein (CRP), age, and Body Mass Index (BMI).

	CFS				FM				Control				p^a
	n	Missing (*n*)	*M (SD)*	*Mdn*	*Range*	*n*	Missing (*n*)	*M (SD)*	*Mdn*	*Range*	*n*	Missing (*n*)	*M (SD)*	*Mdn*	*Range*	
Age	49	0	33.8 (11.3)	35	[18, 60]	58	0	42.0 (9.1)	42.5	[22, 60]	53	0	39.4 (10.4)	39	[23, 59]	< 0.001
BMI	47	2	24.0 (3.6)	23.1	[18.1, 34.6]	57	1	26.7 (5.6)	25.7	[16.3, 40.4]	53	0	24.7 (4.0)	23.8	[16.3, 41.7]	0.017
hsCRP[b]	47	2	2.34 (3.00)	0.94	[0.10, 13.74]	55	3	2.62 (2.74)	1.30	[0.18, 10.94]	51	2	1.13 (1.39)	0.60	[0.10, 7.11]	0.002
lnCRP[c]	47	2	0.117 (1.283)	−0.062	[−2.303, 2.620]	55	3	0.387 (1.152)	0.262	[−1.715, 2.392]	51	2	−0.413 (1.019)	−0.511	[−2.303, 1.962]	0.002

[a] Statistical difference (Kruskall-Wallis test).
[b] Raw scores of hsCRP in mg/L, unadjusted.
[c] Log transformed (natural log) of hsCRP.

Table 2
Pair-wise analysis of age between groups.

Comparison groups		U^a	*z*	*p*	p^b
CFS	Control	916.0	−2.56	0.010	0.029
FM	Control	1314.5	−1.32	0.189	0.545
CFS	FM	786.5	−3.97	< 0.001	< 0.001

[a] Mann-Whitney *U*.
[b] Adjusted by the Bonferroni correction for multiple tests.

Table 3
Pair-wise analysis of BMI between groups.

Comparison groups		U^a	*z*	*p*	p^b
CFS	Control	1095	−1.04	0.299	1
FM	Control	1182	−1.97	0.049	0.179
CFS	FM	928	−2.69	0.007	0.016

[a] Mann-Whitney *U*.
[b] Adjusted by the Bonferroni correction for multiple tests.

patients with CFS, whereas a previous study on CFS patients recruited from gastroenterology and rheumatology departments found significantly increased hsCRP levels among CFS patients compared to controls (Groeger et al., 2013). Both studies included both genders and a broader age span and did not adjust for BMI. Also, genetic studies in adolescents have indicated a link between immune activity and CFS (Nguyen et al., 2018). Raison et al. (2009) found that an increased hsCRP in patients with CFS was no longer significant after adjusting for age, sex, race, location of residence, BMI, depressive status, and immune-modulating medications. We had only one gender, none of the participants were taking immune-modulating medications, there was no comorbidity, and we did not find any effect of age in our groups. Regarding for race and location of residence, we did not record these data, but all our participants were recruited from rather homogenous areas in and around Trondheim, Middle Norway. The role and type of inflammation in CFS needs to be clarified to improve prevention and treatment of the condition. Our study is a contribution to this field because it explores the phenomenon between groups in which there are few differences apart from the presence of CFS (i.e., otherwise healthy, only one gender, socio-economically homogenous group, and narrow age span), and BMI is adjusted for.

A recent report measuring CRP in FM patients did not find any differences between patients and controls regarding hsCRP, although an effect was seen for leptin (Ataoglu et al., 2018). A large-population-based study found increased CRP among participants with self-reported diagnosis of FM and suggested that it was partially explained by BMI and comorbidity (Feinberg et al., 2017). Furthermore, a review of studies reporting the effect of non-pharmacological interventions in FM patients did not find a consistent effect on CRP. Still, baseline CRP levels were higher than the reference value in three of the included studies (Sanada et al., 2015). A subgroup of FM patients with inflammatory changes including altered CRP has also been suggested (Metyas et al., 2015). As shown by others (Xiao et al., 2013), we found that hsCRP was associated with BMI among all FM patients as well as healthy controls. However, after adjusting for BMI, there was still a significantly higher level of hsCRP among patients compared to controls. To our knowledge, this has not been consistently reported previously, and the phenomenon should be further explored.

In our study, both patient groups show significantly higher hsCRP than healthy controls. However, the patient groups do not deviate from each other. CFS and FM are defined as two distinct disorders although there is a high comorbidity, and there are several overlapping symptoms and findings between the two disorders (Clauw, 2010). Raison et al. (2009) found that people with CFS and a group with CFS-like illness could not be distinguished from each other on the basis of hsCRP

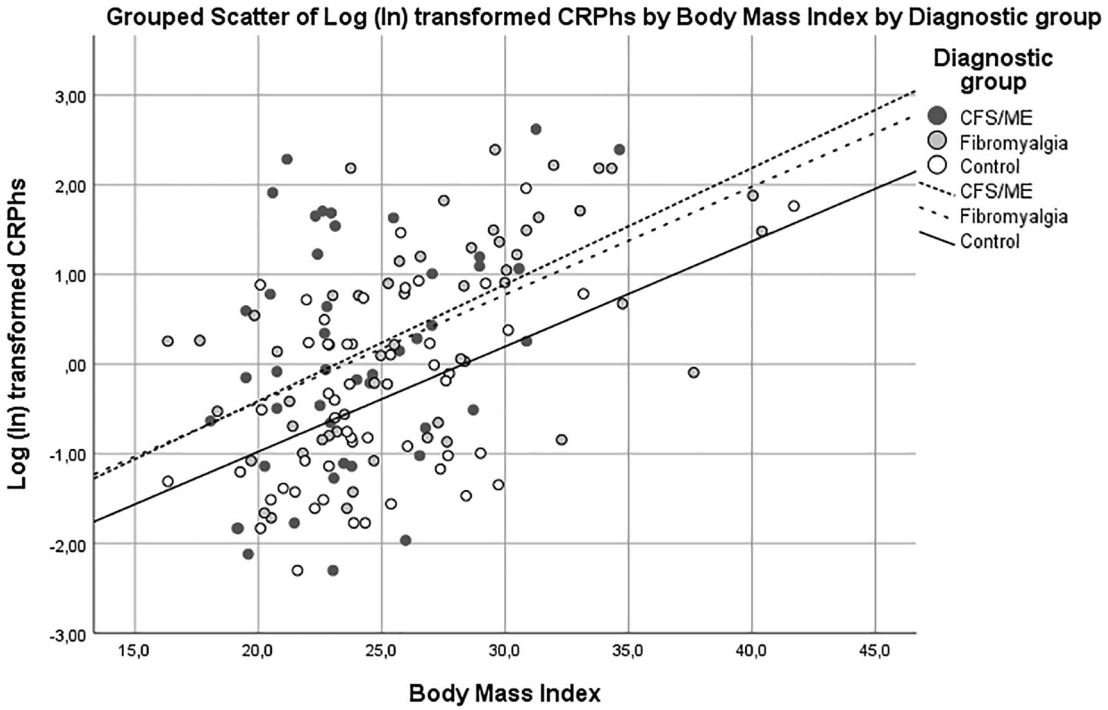

Fig. 1. *Linear regression for BMI and lnCRP.* Scatterplot showing the relationship between BMI and lnCRP for each of the diagnostic groups: CFS, ⟵ tight dashed line; FM, – – – lose dashed line; and control group, — solid line.

levels. It is important to keep in mind these biological similarities because there are deviating reports on the differences between CFS and FM regarding clinical symptoms such as personality (Ablin et al., 2016; Balbaloglu et al., 2018; Sirois and Molnar, 2014), cognition (Rasouli et al., 2019; Schmaling and Betterton, 2016), and balance (Rasouli et al., 2018).

BMI had a clear effect on hsCRP. This is in line with findings in several other studies and with the known effect of adipose tissue on the production of CRP (Lau et al., 2005). Our study confirms that studies on CRP as well as inflammation in general should be corrected for BMI.

We did not find an effect of age on CRP. This is in line with Xiao et al. (2013). This might be surprising because it is generally assumed that inflammation increases with age. However, our population overall may be too young to reveal this effect. CRP only seems to be increased with age in men but is manifested in women only after menopause (Poledne et al., 2009). Also, no effect of smoking was seen.

There might be differences in inflammatory markers between short- and long-term duration of CFS cases (Hornig et al., 2015). In a study of FM, weather sensitivity, and pain, duration also seemed to matter; it was concluded that FM patients with shorter duration of their illness were more sensitive to weather (Fors and Sexton, 2002). However, duration of illness did not affect the findings in the present material (data not shown).

4.1. Weaknesses and strengths

The study only gives information on a limited population, that is, female individuals aged 18–60 living in a homogenous area with well-developed social and health services. For other groups (males, children and adolescents, elderly, and somatically as well as psychiatrically very ill people), the mechanisms revealed may not be important for fatigue and pain. None of the patients were clinically depressed. In our study, we also recorded symptoms of anxiety and depression by using the HADS. Adjusting for these scores did not have any effect on hsCRP (data not shown).

Presumed low activity levels for the patients and high activity levels for the healthy controls could be a confounding factor influencing the results (Fedewa et al., 2017). CFS patients reported the lowest activity levels; FM patients' activity levels were higher; and the healthy control group reported the highest activity levels (data not shown). It is not surprising that patients with CFS report higher levels of inactivity because this is part of the characteristics of the disorder. Still, over half of the CFS patients were indeed active (data not shown), and we do not believe that this is a contributing factor to the higher inflammatory finding in our study. We also included BMI, thus controlling for the indirect link between low activity levels and BMI.

The study population is rather homogenous regarding age, gender, and socio-economical status and otherwise healthy and not on medications. This enables us to reveal differences independently of many confounding factors. Also, the study is well powered with a rather large clinical material. Patients were diagnosed according to the Fukuda and Canada criteria (Carruthers et al., 2011; Fukuda et al., 1994) at a specialized multidisciplinary unit in a university hospital, in addition to registering the new FM criteria (Wolfe et al., 2016; Wolfe and Hauser, 2011), making clinical diagnoses valid compared to what can be seen in larger population-based studies.

5. Conclusions

CFS and FM patients have higher concentrations of hsCRP compared to healthy controls. This remains significant after adjusting for age and BMI. CFS and FM cannot be distinguished between each other on the basis of hsCRP in our study.

Overall, our study gives an important contribution to the knowledge on CFS and FM. There seems to be a biological inflammatory activity in patients with CFS and FM that is not found in healthy controls of the same age and gender. The inflammatory changes, whether they are primary or secondary to other symptoms, may be perturbing symptoms. Inflammation is a well-known cause of fatigue (Norheim et al., 2011) and pain (Louati and Berenbaum, 2015; Sluka and Clauw, 2016) and may be a target for attack by medications (Zhang et al., 2016) as well as a marker for monitoring any treatment of these conditions. In accordance with the Centers for Disease Control and Prevention and the American Heart Association recommendations of hsCRP and risk-factor

assessment (Pearson et al., 2003), the hsCRP levels in our patient groups were mainly within the moderate-to-high-risk concentrations. As such, this has clinical relevance beyond defining the cause of CFS and FM.

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Conflict of interest

All the authors declare no conflict of interest.

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