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Fatigue symptoms relate to systemic inflammation in patients with type 2 diabetes

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ABSTRACT

Fatigue is frequent in patients with diabetes and this symptom appears to be more prominent in type 2 rather than type 1 diabetic subjects. Chronic inflammation represents one characteristic of type 2 diabetes that may contribute to fatigue symptoms. This possibility was assessed in a sample of 20 type 2 diabetic patients relatively to a group of 20 type 1 diabetic subjects. Specific dimensions of fatigue, including general fatigue, physical fatigue, reduced activity, mental fatigue and reduced motivation, were assessed using the Multidimensional-Fatigue-Inventory (MFI). Biological assays comprised the measurement of serum inflammatory markers [high-sensitive C-reactive-protein (hsCRP), high-sensitive interleukin-6 (hsIL-6), high-sensitive tumor-necrosis-factor-α (hsTNF-α) and neopterin]. Clinical parameters including indexes of adiposity were collected. In comparison to type 1 diabetic subjects, patients with type 2 diabetes exhibited higher fatigue scores, notably in the dimensions of general fatigue, physical fatigue and reduced activity, together with greater levels of inflammatory markers that correlated with indexes of adiposity. Regression analyses controlling for diabetes duration, insulin treatment status, glycemic control and fasting status, indicated that levels of inflammatory markers, in particular hsIL-6, hsCRP and neopterin, were associated with MFI fatigue dimensions in type 2 diabetic patients. Mediation analyses revealed that adiposity did not significantly account for the relationship of inflammatory markers with fatigue scores albeit coefficient regressions decreased somewhat when this variable was controlled for in regression models. These findings indicate that systemic low-grade inflammation relates to fatigue symptoms in patients with type 2 diabetes and suggest the involvement of inflammatory processes in the pathophysiology of diabetes-related fatigue.

1. Introduction

Fatigue represents a common complaint of patients with diabetes as it can be reported in up to 60% of patients (Drivsholm et al., 2005; Fritschi and Quinn, 2010). This symptom not only impacts the patient's quality of life and compliance to treatment, but it is also associated with an increased risk of disease complications (Fritschi and Quinn, 2010). In a recent comparative study assessing fatigue symptoms in patients with type 1 and type 2 diabetes, we found that fatigue was particularly prominent in patients with type 2 diabetes and concerned primarily physical aspects rather than mental components. In patients with type 1 diabetes, fatigue scores were comparable to scores measured in healthy volunteers (Lasselin et al., 2012).

The pathophysiological mechanisms leading to the development of fatigue symptoms in patients with type 2 diabetes remain largely unknown. While many biological and psychological factors may contribute, several lines of evidence point to the possibility that inflammatory factors are also involved. In support of this notion, recent data indicate that blockade of the inflammatory cytokine interleukin (IL)-1β with the monoclonal anti-IL1β antibody, XOMA052, partly improves motor fatigue in patients with type 2 diabetes (Cavelti-Weder et al., 2011). The ability of pro-inflammatory cytokines (e.g., IL-6, IL-1β, tumor necrosis factor (TNF)-α) to act on the brain and to induce behavioral symptoms, including fatigue, is well documented in both experimental and clinical studies (Capuron and Miller, 2011; Dantzer et al., 2008; Kelley et al., 2003; Majer et al., 2008). At the clinical level, the involvement of inflammation in the development of fatigue symptoms has been shown in patients with chronic medical conditions, including cancers, multiple sclerosis and chronic fatigue syndrome (Bower et al., 2002; Flachenecker et al., 2004; Fletcher et al., 2009; Heesen et al., 2006; Orre et al., 2009; Raison et al., 2009). Moreover, studies conducted in our group have shown that inflammation plays a

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major role in the development of fatigue symptoms in medically ill patients treated with cytokines, notably interferon-α (Capuron et al., 2002, 2007). Similar results were found in the elderly subject (Capuron et al., 2011a). All of these conditions share in common the chronic activation of immune/inflammatory processes. Similar to these conditions, diabetes is characterized by a chronic, low-grade, inflammatory state. While this activation of inflammatory processes has been described in both type 1 and type 2 phenotypes (Basu et al., 2005; Devaraj et al., 2006; Pickup et al., 2000; Su et al., 2011), increased levels of circulating inflammatory markers were found to be significantly more prominent in type 2 diabetes (Alexandraki et al., 2008; Pham et al., 2011). Whereas increased inflammatory markers, notably C-Reactive Protein (CRP), were found to relate to long disease duration and diabetes complications in type 1 diabetes (Devaraj et al., 2007; Treszl et al., 2004), systemic inflammation in type 2 diabetes is believed to originate, at least partially, from the adipose tissue (Mraz et al., 2011; Pedersen et al., 2003; Sam et al., 2009). Adiposity is a distinguishing characteristic of type 2 diabetes that may easily promote the development of chronic inflammation, as adipocytes and infiltrated macrophages in the adipose tissue have the ability to secrete pro-inflammatory factors (Trayhurn and Wood, 2004; Wellen and Hotamisligil, 2003). Interestingly, systemic inflammation was found in many studies to be associated with an increased risk of developing type 2 diabetes, suggesting that inflammatory processes may also contribute to the pathophysiology of the disease (Duncan et al., 2003; Festa et al., 2002; Hu et al., 2004; Schmidt et al., 1999; Spranger et al., 2003). Given the well documented role of inflammation in the development of fatigue in chronic or immune-based conditions (Bower, 2007; Capuron and Miller, 2011; Miller et al., 2008), it appears highly possible that systemic inflammation also contributes to fatigue symptoms in patients afflicted with diabetes, notably of type 2 phenotype.

The objective of this study was to assess the inflammatory status of patients with type 2 diabetes comparatively to a group of type 1 diabetic subjects and to evaluate the involvement of systemic low-grade inflammation in fatigue symptoms in the same population.

2. Patients and methods

2.1. Participants

This study included 20 patients with type 2 diabetes and 20 patients with type 1 diabetes recruited from the service of diabetology at the Haut-Lévêque Hospital in Bordeaux, France. Type 2 diabetic patients had a personal history of overweight, 10 of them were treated with insulin and the remainder 10 patients were either treated with oral antidiabetic medications ($N = 6$) or untreated ($N = 4$). All type 1 diabetic patients were treated with insulin, they had no personal history of overweight and they had shown significant weight loss at the onset of the disease. Clinical variables including the medical history of patients, duration of diabetes, glycated hemoglobin (HbA1C) levels (as indexes of diabetes control), treatment status, body mass index (BMI) and waist circumference (as indexes of adiposity) were collected in all participants. Patients with current major depressive disorder, as assessed by a structured clinical diagnostic interview with the Mini-International-Neuropsychiatric-Interview (MINI) (Sheehan et al., 1998), patients treated with antidepressants or neuroleptics, and patients suffering from chronic inflammatory medical conditions were excluded.

The study was approved by the local Committee for the Protection of Persons (CPP Bordeaux). All participants were adults and written informed consent was obtained from each of them after reading a complete description of the study.

2.2. Biological measurements

Blood samples were obtained for the measurement of serum concentrations of the inflammatory markers, high sensitivity (hs)CRP, hsIL-6 and hsTNF-α, as well as neopterin as marker of macrophage activation. Samples were centrifuged (10 min, 1000*g*, 4 °C) after clotting and sera were stored at −80 °C until the assays. Biological markers were assayed by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's specifications (hsIL-6 and hsTNF-α: R&D Systems, Minneapolis, Minnesota; hsCRP: CYT298, Millipore, Billerica, Massachusetts; neopterin: IBL International, Hamburg, Germany). Intra- and inter-assay variability were respectively ±7.4% and ±7.8% for hsIL-6, ±5.3% and ±8.4% for hsTNF-α, ±4.6% and ±6.0% for hsCRP, 3.6–6.8% and 7.6–10.3% for neopterin. Sensitivities were 0.039 pg/mL for hsIL-6, 0.106 pg/mL for hsTNF-α, 0.20 ng/mL for hsCRP and 0.7 nmol/L for neopterin.

2.3. Assessment of fatigue

Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI), a 20-item self-report questionnaire measuring five dimensions of fatigue corresponding respectively to general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation (Smets et al., 1995). Each dimension contains four items, scored from 1 to 5 with higher scores corresponding to greater levels of fatigue.

2.4. Data analyses and statistics

Raw values for the biological markers, hsIL-6, hsCRP and hsTNF-α, were log-transformed because of non-normality. Characteristics of participants were compared across diabetes phenotype (type 1 *versus* type 2 diabetes) using two-sample *t*-tests for continuous variables and Chi-square tests for categorical variables. MFI fatigue scores were compared across groups using analysis of covariance (ANCOVA) controlling for insulin treatment status, diabetes duration and HbA1C levels. Due to logistic and/or medical constraints inherent to clinical setting and to the situation of diabetes, the collection of blood samples in fasting conditions was possible only in 30% of study participants. In order to control for this variation across subjects, analyses performed on biological markers were therefore systemically adjusted for fasting status in addition to insulin treatment status, diabetes duration and HbA1C levels. Three participants exhibited extreme (outlier) values (>3 SD above the mean) for at least one inflammatory marker and thus were excluded from analyses performed on biological data. Factor (principal component) analysis with varimax rotations was performed on biological markers to assess their interconnections and to eventually extract one composite inflammatory component. The relationship of adiposity (i.e., BMI and waist circumference) with inflammatory markers was estimated using Bravais–Pearson correlations performed in the whole population under study and separately in each diabetes phenotype. Multivariate regression analyses entering biological markers as predictors in separate models were performed to assess the relationship of levels of inflammatory markers with fatigue symptom dimensions in each diabetes phenotype. Models were adjusted for diabetes duration, HbA1C levels, insulin treatment and fasting status. Contribution of adiposity to the relationship between systemic inflammation and fatigue symptoms was assessed using the method recommended by Baron and Kenny (1986). According to this method, mediation takes place when (1) the initial variable is significantly associated with the outcome; (2) the initial variable is significantly correlated with the mediator; (3) the mediator has a significant effect on the outcome, when controlling for the initial variable; and

(4) the relationship between the initial variable and the outcome is reduced or no longer significant, when controlling for the mediator. The significance of the mediation (indirect effect) was tested using both conservative (Sobel) and non-parametric tests (bootstrapping resampling method as described by Preacher and Hayes, 2008). Statistical analyses were performed with SPSS Statistics version 19. All probabilities were two-sided with the degree of significance set at $p < 0.05$.

3. Results

3.1. Characteristics of participants

As shown in Table 1, there was no significant difference between type 1 *versus* type 2 diabetic patients in terms of age and gender. Duration of diabetes (time since diagnosis) was longer in type 1 diabetic patients compared to type 2 diabetic subjects. Moreover, HbA1C levels were lower (indicative of a better control of diabetes) in type 1 diabetic patients. Finally, adiposity markers (i.e., BMI, waist circumference) were higher in type 2 diabetic patients compared to type 1 diabetic subjects.

3.2. Inflammatory markers

Overall, levels of circulating inflammatory markers were higher in type 2 diabetic patients compared to type 1 diabetic subjects (Fig. 1). More specifically, patients with type 2 diabetes exhibited significantly higher concentrations of hsCRP, hsTNF-α and neopterin (respectively, $F(1,31) = 9.8$, $p < .01$; $F(1,31) = 5.1$, $p < .05$ and $F(1,31) = 4.4$, $p < .05$). Similarly, concentrations of hsIL-6 were higher in type 2 diabetic patients compared to type 1 diabetic subjects, but at a statistical trend level only ($F(1,31) = 3.6$, $p = .07$). Factor analysis performed on inflammatory markers in the whole population under study revealed that these markers were interconnected and composed altogether one *composite inflammatory* dimension explaining 49% of the variance.

As expected, BMI and waist circumference correlated significantly with the composite measure of inflammation and with levels of individual inflammatory markers in the whole population under study, with increased adiposity indexes being related to higher levels of inflammation (Table 2 and Fig. 2). Further correlational analyses performed separately in each of the two diabetic populations revealed that these correlations were primarily significant in type 2 diabetic patients (Table 2).

Given the association of BMI and waist circumference with inflammatory markers in type 2 diabetic patients, complementary analyses using multivariate regression models were performed to assess the contribution of these variables to the relationship of type 2 diabetes with systemic inflammation (Table 3). Consistent with results presented in Fig. 1, type 2 diabetes was significantly associated with levels of inflammatory markers. This association did not remain significant when controlling for BMI or waist circumference, suggesting that adiposity was one major determinant of systemic inflammation in type 2 diabetes.

Table 1
Characteristics of study participants.

	Type 1 diabetes	Type 2 diabetes
Sample size (*N*)	20	20
Age, mean (SD)	51.8 (14.1)	50.3 (13.5)
Women, *n* (%)	5 (25)	3 (15)
Time since diabetes diagnosis, years (SD)	17.8 (13.9)	9 (6.7)*
HbA1C, % (SD)	7.5 (1.8)	9.7 (2.4)**
BMI, kg/m^2 (SD)	25.8 (4.2)	31.4 (5.2)***
Waist circumference, cm (SD)[a]	91.8 (12.0)	108.6 (13.3)***

Analyses were performed using two-sample *t*-tests for continuous variables and chi-square tests for categorical variables.
Abbreviations: BMI: body mass index; HbA1C: glycated hemoglobin.
* $p < .05$ *versus* type 1 diabetic patients.
** $p < .01$ *versus* type 1 diabetic patients.
*** $p < .001$ *versus* type 1 diabetic patients.
[a] Waist circumference value was missing in three type 2 diabetic patients.

3.3. Fatigue symptoms and association with adiposity

Compared to type 1 diabetic patients, patients with type 2 diabetes exhibited higher MFI total scores ($F(1,35) = 8.8$, $p < .01$), particularly in the dimensions of general fatigue, physical fatigue and reduced activity ($F(1,35) = 12.7$, $p < .01$, $F(1,35) = 12.2$, $p < .01$ and $F(1,35) = 7.6$, $p < .01$, respectively) (Table 4), consistent with previous findings (Lasselin et al., 2012). Scores of mental fatigue and reduced motivation were comparable across the two diabetic populations ($F(1,35) = 2.2$, $p = .15$ and $F(1,35) = .55$, $p = .46$, respectively).

No significant relationship was found between fatigue symptoms and BMI or waist circumference in patients with type 1 diabetes. In type 2 diabetic patients, however, BMI was associated with the specific dimensions of mental fatigue and decreased motivation ($\beta = .770$, $p < .05$ and $\beta = .768$, $p < .05$, respectively). No significant association was found with the dimensions of general fatigue, physical fatigue and reduced activity. Similarly, no significant relationship was found between waist circumference and fatigue symptoms in type 2 diabetic patients, except with the dimension of mental fatigue at a marginal statistical level only ($\beta = .715$, $p = .05$). Mediation analyses revealed that systemic inflammation (hsIL6, hsCRP and composite inflammation in particular) significantly accounted for the associations of BMI with scores of mental fatigue and reduced motivation, as these associations did not remain significant when controlling for inflammatory markers (e.g., $\beta = .382$, $p = .33$ for mental fatigue and $\beta = .290$, $p = .45$ for reduced motivation, with control of composite inflammation). The largest mediating effect was obtained with hsIL6 (Sobel: $Z = 1.85$, $p = .06$ for mental fatigue and $Z = 2.21$, $p < .05$ for reduced motivation). Similar results were obtained with the non-parametric bootstrapping resampling method (result not shown).

3.4. Relationship between inflammation and fatigue symptom dimensions

Separate multivariate regression analyses controlling for diabetes duration, insulin treatment, HbA1C levels and fasting status were conducted to assess the relationship of inflammatory markers with fatigue scores. While no significant relationship was found in patients with type 1 diabetes, analyses revealed significant associations between inflammatory markers and fatigue symptom dimensions in patients with type 2 diabetes. In those patients, the composite measure of inflammation and the specific inflammatory markers of hsIL-6 and hsCRP were associated with MFI total fatigue scores, notably with the dimensions of mental fatigue and reduced motivation, with higher levels of inflammation predicting greater fatigue scores. HsCRP and hsIL-6 were also positively associated with the dimension of reduced activity, but at a statistical trend level only. A significant association was also found between neopterin and scores of general fatigue in type 2 diabetic patients, with higher neopterin levels predicting more intense general fatigue in these patients (Table 5).

Given the significant associations found between adiposity (BMI in particular) with both inflammation and fatigue symptoms, mediation analyses were conducted to test the indirect effect of adiposity on the relationship of inflammatory markers with fatigue scores in type 2 diabetic patients. Although some of the regression coefficients decreased somewhat when controlling for BMI in

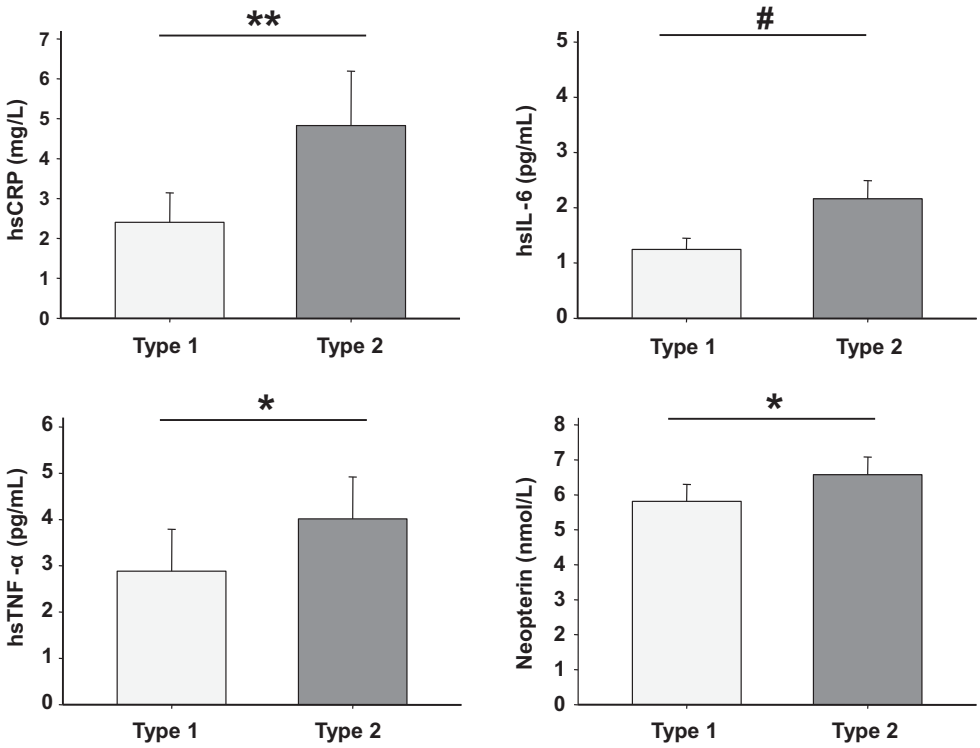

Fig. 1. Concentrations of biological markers in patients with type 1 diabetes (□) *versus* type 2 diabetes (■). *Abbreviations*: hsCRP: high-sensitive C-reactive protein; hsTNF-α: high-sensitive tumor-necrosis-factor-α; hsIL-6: high-sensitive interleukin-6. Data are shown as mean (+SEM). Raw values for the biological markers, hsIL-6, hsCRP and hsTNF-α were log-transformed for statistical analyses, but shown in the figure as geometric means (from raw values) for information and readability purposes. $^{**}p < .01$; $^{*}p < .05$; $^{\#}p = .07$.

Table 2
Relationship of adiposity (e.g., body mass index and waist circumference) with inflammatory markers.

	All participants		Type 1 diabetes		Type 2 diabetes	
	BMI	Waist circumference	BMI	Waist circumference	BMI	Waist circumference
hsCRP	.494**	.480**	.067	.115	.747***	.712**
hsIL-6	.445**	.470**	.163	.242	.528*	.446#
hsTNF-α	.421**	.424**	.369	.292	.232	.312
Neopterin	.205	.331*	.073	.194	.193	.334
Composite inflammation	.569***	.611***	.257	.323	.656**	.688**

Bravais–Pearson correlations (*R*).
Abbreviations: BMI: body mass index; hsCRP: high sensitive C-reactive protein; hsIL-6: high sensitive interleukin-6; hsTNF-α: high sensitive tumor necrosis factor-α. The factor *composite inflammation* corresponds to the first factor extracted from the principal component analysis performed on biological markers. This factor was saturated by each biological marker (e.g., hsCPR, hsIL-6, hsTNF-α and neopterin) and explained 49% of the variance.
* $p < .05$.
** $p < .01$.
*** $p < .001$.
# $p = .08$.

multiple regression models (Table 5), mediation analyses revealed that, overall, this variable did not significantly mediate the relationship of systemic inflammation with fatigue symptoms in type 2 diabetic patients (Sobel; all $p > .05$), supporting the independent and direct effect of inflammatory markers on fatigue scores. Similar results were obtained with respect to waist circumference and when using non-parametric bootstrapping resampling method (results not shown).

4. Discussion

Results from the present study indicate a higher prevalence of fatigue symptoms together with increased signs of systemic inflammation in patients with type 2 diabetes relatively to type 1 diabetic subjects. Consistent with our previous data (Lasselin et al., 2012), fatigue symptoms in type 2 diabetic patients manifested primarily in the dimensions of general fatigue, physical fatigue and reduced activity. Interestingly, significant associations were found between fatigue symptom dimensions and circulating levels of inflammatory markers in type 2 diabetic patients, suggesting the involvement of inflammatory processes in the development of type 2 diabetes-related fatigue. To our knowledge, this is the first time that such an association is shown in a diabetic population.

In line with previous reports (Alexandraki et al., 2008; Pham et al., 2011), low grade inflammation was found to be more prominent in type 2 diabetic patients compared to type 1 diabetic

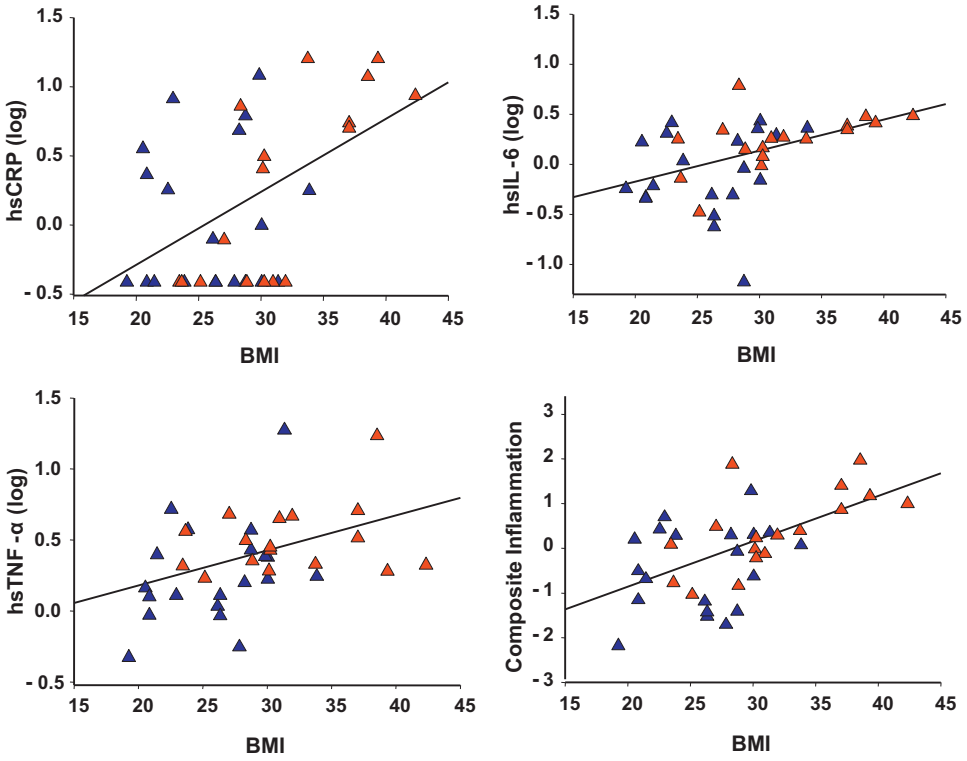

Fig. 2. Relationships between adiposity and inflammatory markers in patients with type 1 diabetes (▲) *versus* type 2 diabetes (▲). *Abbreviations*: hsCRP: high-sensitive C-reactive protein; hsTNF-α: high-sensitive tumor-necrosis-factor-α; hsIL-6: high-sensitive interleukin-6. The displayed correlations were obtained in the whole population under study. Values for hsCRP, hsIL-6 and hsTNF-α were log-transformed for statistical analyses.

Table 3
Influence of adiposity on the relationship between type 2 diabetes and inflammatory markers.

Predictors	Inflammatory markers														
	hsCRP			hsIL6			hsTNF-α			Neopterin			Composite inflammation		
	β	*F*	*p*	*β*	*F*	*p*	*β*	*F*	*p*	*β*	*F*	*p*	*β*	*F*	*p*
Initial model															
Type 2 diabetes	.561	9.8	<.01	.381	3.6	.07	.427	5.0	<.05	.368	4.4	<.05	.616	10.8	<.01
BMI	.495	12.3	<.01	.470	9.8	<.01	.458	10.0	<.01	.276	3.7	.06	.612	19.6	<.001
Waist circumference	.474	10.5	<.01	.463	9.7	<.01	.439	8.8	<.01	.342	5.9	<.05	.614	19.8	<.001
Model controlling for BMI															
Type 2 diabetes	.282	1.5	.23	.001	.01	.99	.099	.2	.68	.255	1.2	.29	.211	.9	.36
Model controlling for waist circumference															
Type 2 diabetes	.304	1.6	.21	−.020	.01	.94	.115	.2	.64	.150	.4	.53	.184	.6	.43
Separate effect of covariates															
– Diabetes duration	−.085	.2	.62	−.255	2.4	.13	.131	.6	.44	.294	3.0	.08	−.018	.01	.92
– HbA1C levels	−.185	1.2	.27	.150	.8	.38	−.030	.03	.86	−.394	6.4	<.05	−.128	.6	.45
– Insulin treatment	.318	3.9	.06	−.250	2.3	.14	−.243	2.2	.15	−.057	.1	.74	−.079	.2	.64
– Fasting status	.243	2.2	.15	−.238	2.1	.16	−.077	.2	.65	.061	.1	.72	−.017	.01	.92

Multivariate regression analyses. All models were adjusted for diabetes duration, HbA1C levels, insulin treatment and fasting status (covariates). HsCRP, hsIL-6 and hsTNF-α were log-transformed due to non-normality. Separate effects of covariates on the outcomes of interest are given for information. *Abbreviations*: hsCRP: high sensitive C-reactive protein; hsIL-6: high sensitive interleukin-6; hsTNF-α: high sensitive tumor necrosis factor-α. BMI: body mass index; HbA1C: glycated hemoglobin. The factor *composite inflammation* corresponds to the first factor extracted from the principal component analysis performed on biological markers. This factor was saturated by each biological marker (e.g., hsCPR, hsIL-6, hsTNF-α and neopterin) and explained 49% of the variance.

subjects. In patients with type 2 diabetes, systemic inflammation was characterized relatively to type 1 diabetic subjects by increased circulating concentrations of hsCRP, hsIL-6 and hsTNF-α together with increased levels of neopterin, indicative of macrophage activation. These biological variations were interconnected suggesting the activation of common inflammatory pathways. The finding that neopterin was higher in type 2 diabetic patients comparatively to type 1 diabetic subjects is in accordance with recent data showing greater concentrations of this markers in a larger group of type 2 diabetic patients in comparison to healthy subjects (Baris et al., 2009). Interestingly, systemic inflammation in patients with type 2 diabetes correlated with adiposity markers

Table 4
Fatigue symptoms in type 1 *versus* type 2 diabetes.

	Type 1 diabetes	Type 2 diabetes
MFI total score, mean (SD)	43.8 (13.7)	52.6 (11.3)**
Fatigue symptom dimensions		
General fatigue, mean (SD)	9.7 (3.6)	12.4 (2.9)**
Physical fatigue, mean (SD)	9.2 (2.9)	12.0 (3.0)**
Reduced activity, mean (SD)	8.5 (3.4)	11.0 (2.8)**
Mental fatigue, mean (SD)	8.4 (3.2)	8.7 (3.0)
Reduced motivation, mean (SD)	8.1 (3.4)	8.6 (2.7)

ANCOVA controlling for insulin treatment status, diabetes duration and HbA1C levels.
Fatigue symptom dimensions were assessed using the Multidimensional Fatigue Inventory (MFI).
** $p < .01$ *versus* type 1 diabetic patients.

(e.g., BMI and waist circumference), with increased adiposity associating with higher inflammation. Moreover, the relationship of type 2 diabetes with systemic inflammation was significantly reduced when controlling for adiposity markers (i.e., BMI or waist circumference) suggesting that adiposity was a major determinant of type-2 diabetes related inflammation. This result supports the notion that low-grade systemic inflammation in type 2 diabetes originates, at least partially, from the adipose tissue and is consistent with previous reports documenting associations between circulating levels of inflammatory markers and abdominal fat mass in cohorts of type 2 diabetic subjects and in the elderly afflicted with type 2 diabetes (Pedersen et al., 2003; Sam et al., 2009).

The finding that systemic low-grade inflammation was associated with fatigue symptom dimensions in patients with type 2 diabetes is particularly original, and suggests the involvement of inflammatory processes in the pathophysiology of diabetes-related fatigue. This result is in accordance with the well documented role of inflammation in the development of behavioral alterations, including fatigue (Capuron and Miller, 2011; Dantzer et al., 2008; Kelley et al., 2003; Majer et al., 2008). The association of inflammatory markers with fatigue symptoms was found in multivariate regression models controlling for diabetes duration, insulin treatment status and HbA1C levels, attesting of the strength of the relationship and indicating that it did not rely on confounding factors nor it was explained by variations in diabetes length, treatment options and/or glycemic control. Moreover, mediation analyses revealed that adiposity did not significantly account for the relationship of inflammatory markers with fatigue scores in type 2 diabetic patients, albeit this variable correlated with both inflammation and specific fatigue dimensions in those patients and while coefficient regressions decreased somewhat when adiposity was controlled for in regression models. This finding highlights the possibility that the few associations that were measured between BMI and fatigue scores in type 2 diabetic patients were due to the interrelationship of adiposity with inflammatory markers. Moreover, this result suggests that, while related to adiposity, systemic inflammation has a specific and independent/direct effect (unmediated by adiposity characteristics) on fatigue symptoms in type 2 diabetes. Among the biological markers that were assessed in this study, hsIL-6 and hsCRP were those showing the strongest connections with fatigue scores, notably with the dimensions of mental fatigue, reduced motivation and reduced activity, in type 2 diabetic patients. This finding is consistent with previous reports (some of them emanating from our group) indicating the involvement of IL-6 and/or CRP in fatigue symptoms and neurobehavioral alterations in patients afflicted with chronic conditions (e.g., metabolic disorders, chronic fatigue syndrome, cancers) (Bower et al., 2011; Capuron et al., 2008, 2011b; Collado-Hidalgo et al., 2006; Fletcher et al., 2009; Orre et al., 2009, 2011) and in healthy models of chronic low grade inflammation such as normal aging (Capuron et al., 2011a; Valentine et al., 2011). Similar associations have been reported in healthy individuals (Cho et al., 2009; Rief et al., 2010; Thomas et al., 2011). Interestingly, higher neopterin concentrations were also found to relate to increased scores of general fatigue in the type 2 diabetic population from the present study. Surprisingly, albeit type 2 diabetic patients exhibited high scores of physical fatigue, no significant relationship was found between physical fatigue and levels of inflammatory markers. This result may be explained by the relatively small samples of diabetic subjects recruited in the present study. This limitation may have lead to reductions in statistical power, notably in linear regression models that controlled for multiple covariates with potential confounding effect. This limitation warrants further investigations on larger diabetic populations to comfort findings from the present study.

The mechanisms by which systemic inflammation may participate in the physiopathology of fatigue symptoms in patients with type 2 diabetes remain to be elucidated. Such mechanisms may include specific interactions between metabolic and inflammatory processes leading to subsequent alterations in brain chemistry (e.g., neurotransmitter and endocrine systems) and neurocircuitry involving notably the basal ganglia and fronto-thalamic loops (Capuron and Miller, 2011; Majer et al., 2008; Rocca et al., 2007). In addition, enzymatic variations responsible for alterations in the metabolism of neurotransmitters may be involved as inflammatory factors have potent effects of the activity of the enzymes, indoleamine-2,3-dioxygenase (IDO) and GTP cyclohydrolase-1 (GTP-CH1), involved in the biosynthesis of noradrenalin, dopamine and serotonin. Further clinical and experimental studies are needed to specifically address this question.

One question remains regarding the possibilities to prevent and/or treat diabetes-related fatigue – and subsequently improve patients' quality of life – using interventions to reduce inflammation. The association measured in the present study between adiposity and inflammatory markers supports the idea that reduced inflammation may be achieved by weight loss strategies, as shown in previous reports (Viardot et al., 2010). Nutritional strategies may be also envisaged to modulate inflammation and its central/behavioral effects in patients with type 2 diabetes. Omega-3 polyunsaturated fatty acids ($n-3$ PUFA) may represent good candidates for such a strategy, as these nutrients have been shown to exert potent anti-inflammatory effects (Calder, 2006). Relevant to diabetes, $n-3$ PUFA supplements were found to downregulate inflammation-related genes in the adipose tissue of women with type 2 diabetes (Kabir et al., 2007). In addition, these nutrients have been shown to reduce or prevent insulin resistance in experimental and clinical studies, although results in clinical settings are less consistent than in animal studies (Poudyal et al., 2011 review; Storlien et al., 1987). Finally, exercise training may represent another alternative since this strategy was found to reduce inflammatory markers in overweight individuals with type 2 diabetes (Kadoglou et al., 2007).

In conclusion, the present findings indicate that systemic low-grade inflammation is associated with fatigue symptom dimensions in patients with type 2 diabetes and suggest the involvement of inflammatory processes in the pathophysiology of diabetes-related fatigue.

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Table 5
Relationship of inflammatory markers with fatigue symptoms in patients with type 2 diabetes.

Fatigue symptoms	Predictors	Model 1			Model 2 (adjusting for BMI)			Mediation Sobel			Separate effects of covariates		
	Inflammatory markers	β	F	p	β	F	p	Z	p		β	F	p
Total fatigue	hsCRP	.755	5.4	<.05	.553	2.0	.18	.88	.38	Diabetes duration	.242	.9	.35
	hsIL6	.650	11.6	<.01	.677	5.3	<.05	−.12	.90	HbA1C levels	.025	.01	.92
	hsTNF−α	.059	.04	.84	−.217	.6	.46			Insulin treatment	.322	1.7	.21
	Neopterin	.451	2.3	.16	.305	1.1	.32			Fasting status	.293	1.4	.25
	Composite inflammation	.610	6.7	<.05	.499	2.2	.17	.47	.64				
General fatigue	hsCRP	.222	.6	.45	.177	.2	.63			Diabetes duration	.496	4.9	<.05
	hsIL6	.256	1.9	.19	.362	1.6	.23			HbA1C levels	−.091	.1	.73
	hsTNF−α	.042	.04	.85	−.024	.01	.92			Insulin treatment	.503	5.1	<.05
	Neopterin	.471	6.0	<.05	.473	4.9	<.05	−.03	.98	Fasting status	.520	5.6	<.05
	Composite inflammation	.304	2.3	.16	.405	2.0	.19						
Reduced activity	hsCRP	.698	3.5	.09	.748	2.6	.13	−.20	.84	Diabetes duration	.085	.1	.75
	hsIL6	.483	3.6	.08	.711	3.5	.09	−.79	.43	HbA1C levels	.151	.3	.56
	hsTNF−α	−.150	.2	.63	−.329	.9	.35			Insulin treatment	.108	.2	.68
	Neopterin	.052	.02	.88	−.034	.01	.93			Fasting status	.059	.05	.82
	Composite inflammation	.360	1.4	.26	.378	.7	.41						
Mental fatigue	hsCRP	.903	8.8	<.05	.623	3.3	.09	1.23	.22	Diabetes duration	.009	.01	.97
	hsIL6	.707	14.9	<.01	.600	4.6	.05	.52	.61	HbA1C levels	−.075	.1	.78
	hsTNF−α	.155	.3	.60	−.172	.4	.53			Insulin treatment	.375	2.4	.14
	Neopterin	.408	1.7	.22	.204	.5	.48			Fasting status	.295	1.4	.25
	Composite inflammation	.689	9.2	<.05	.468	2.2	.17	.97	.33				
Reduced motivation	hsCRP	.930	9.1	<.05	.663	3.6	.09	1.17	.24	Diabetes duration	−.077	.1	.77
	hsIL6	.765	20.2	.001	.728	7.7	<.05	.19	.85	HbA1C levels	.252	1.0	.33
	hsTNF−α	.225	.6	.45	−.081	.09	.78			Insulin treatment	.074	.1	.78
	Neopterin	.427	1.8	.20	.225	.6	.46			Fasting status	−.029	.01	.91
	Composite inflammation	.745	11.5	<.01	.577	3.5	.09	.76	.45				

Separate multivariate regression analyses before (model 1) and after adjustment for BMI (model 2). All models were adjusted for diabetes duration, HbA1C levels, insulin treatment and fasting status (covariates). Inflammatory markers were entered in separate models. HsCRP and hsIL-6 were log-transformed due to non-normality. The mediating effect of BMI on the relationship between inflammatory markers and fatigue symptoms was tested according to method described in Baron and Kenny (1986). The Sobel test was used to test the significance of the mediation. Separate effects of covariates on the outcomes of interest are given for information.
Abbreviations: MFI: Multidimensional Fatigue Inventory; hsCRP: high sensitive C-reactive protein; hsIL-6: high sensitive interleukin-6; hsTNF-α: high sensitive tumor necrosis factor-α; HbA1C: glycated hemoglobin. The factor *composite inflammation* corresponds to the first factor extracted from the principal component analysis performed on biological markers. This factor was saturated by each biological marker (e.g., hsCPR, hsIL-6, hsTNF-α and neopterin) and explained 49% of the variance.

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