Cytokines, diabetes mellitus and psychopathology: a challenging combination

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Abstract

OBJECTIVES: The aim of this study was to investigate the association of IL-6, IL-12, and TNF-α with trait and state psychological factors in type 2 diabetic patients.

DESIGN: Patients were divided in two groups. Group A consisted of 86 controlled diabetic patients (HbA1c<7) and the Group B consisted of 45 uncontrolled diabetic patients (HbA1c≥7).

SETTINGS: During the initial phase of the study (T_0), blood samples were taken for measuring IL-6, IL-12 and TNF-α serum levels as well as a battery of psychometric instruments. One year later (T_1), the uncontrolled diabetic patients were re-evaluated with the use of the same psychometric instruments and with the identical blood analysis.

RESULTS: The average values of TNF-α were significantly different among controlled (7.73±5.51) and uncontrolled patients (9.29±4.52) at a significance level of 5% (p=0.009). Controlled diabetic patients show a statistically significant relationship between IL-6 and neuroticism (r_p=0.303, p=0.010), and between IL-12 and psychotism, (r_{sp}=0.382, p=0.001). Controlled diabetic patients show a statistically significant relationship between IL-12 and the act out hostility (r_{sp}=–0.307, p=0.009). The scores of the psychometric tests differ significantly between the first and second evaluation. Acting out hostility and the direction of hostility increased when HbA1c values fell below the threshold of 7, while the total hostility index, as well as all other scales, dropped when patients controlled their metabolic profile.

CONCLUSIONS: The present results provide evidence that IL-6, IL-12 and TNF-α are closely related to the course and treatment of type 2 diabetes.

ORIGINAL ARTICLE

INTRODUCTION

Interleukin-6 (IL-6) is a cytokine that plays an important role in function of the immune system but also in various psychopathological conditions, such stress and depression (Kiegolt-Glaser *et al.* 2005; O'Brien *et al.* 2004). In diabetes mellitus, there is some evidence linking IL-6 with the effect of physical exercise in delaying the appearance of glucose disturbances through the involvement of muscle activity in cytokine production (Shephard 2002). The acute inflammatory reaction that leads to cytokine production is often implicated in the pathogenesis of type II diabetes. IL-6 promotes the development of diabetes and several drugs with anti-inflammatory properties, such as aspirin and theiazolenidiones, increase the likelihood of the disease (Temelkova-Kurktschiev *et al.* 2002). Additionally in newly diagnosed patients with type II diabetes, in acute inflammatory response, inflammation markers such as C-reactive protein (CRP) and IL-6 are elevated (Pickup 2004). IL-6 is known to have an inhibitory effect on the functioning of pancreatic beta-cells that can lead to the destruction of pancreatic islets and, by extension, to diabetes (Libby *et al.* 2002).

Several studies have shown that the majority of patients with borderline personality disorder have experienced traumatic events in early life such as child abuse, neglect or early loss of parents. Research has shown that women with comorbid depression, obesity, and borderline personality disorder show increased concentrations of TNF-α and IL-6, while there is a significant correlation between insulin resistance and the levels of IL-6 (Kahl *et al.* 2005; Bendtzen *et al.* 1989).

Interleukin-12 (IL-12) is naturally produced by dendritic cells, macrophages and B-lymphoblasts (Nc-37) in response to an antigenic stimulus. IL-12 has been found elevated in patients at an early stage of diabetes. Furthermore, IL-12 is higher in patients with type 2 diabetes who are treated with sulfonylureas (Wegner *et al.* 2008). Adipose tissue is responsible for the excessive production of pro-inflammatory cytokines, and in particular interleukin-12, and this is the reason for the increased incidence of chronic inflammation in these patients (Rachman *et al.* 1997).

Crespo-Facoro and colleagues studied the effects of classic and atypical antipsychotics on the production of IL-12 in patients with schizophrenia. The results showed that, in comparison with healthy controls, patients with a first psychotic episode had a strong immunological reaction, with increased production of IL-12. The levels of IL-12 increased significantly after 6 weeks of treatment (Crespo-Facorro *et al.* 2008).

Concerning depression, the levels of interleukin-12 have been found to be elevated in comparative studies with healthy individuals. These findings in major depression indicate a possible activation of the immune system. Depressed patients show an increased production of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-gamma in mononuclear cells, and structural changes in the receptors of IL-2 and IL-6 (Singh *et al.* 2001; Kim *et al.* 2002). Moreover, further research has also reported that in depression there is an intense phagocytosis caused by neutrophils and monocytes (Maes 1995; Connor *et al.* 2000; Muller & Ackenheil 1998). The levels of cytokines are also affected even after the abuse of alcohol (Kim *et al.* 2003).

Tumor Necrosis Factor-alpha (TNF-α) is a chemical molecule has been the focus of intense scientific research interest in recent years. Recent studies show that plasma concentrations of TNF-α increase in insulin resistance conditions such as obesity and type 2 diabetes, raising questions about the mechanisms that lead to an inflammatory reaction in these two situations. Two mechanisms are probably involved. First, glucose and the overall diet can lead to oxidative stress and inflammatory responses. Second, insulin itself has an anti-inflammatory activity, both *in vitro* and *in vivo* (Dandona *et al.* 2004; Satoh *et al.* 2003; Creange *et al.* 1997).

Mikova and colleagues (2001) studied the levels of TNF-α in major depression before and after administration of antidepressant treatment with SSRI. The results showed that TNF-α levels decreased after antidepressant treatment, suggesting the possible involvement of the immune system in the pathophysiology of major depression (Mikova *et al.* 2001).

Schmitt and colleagues (2005) studied the changes in cytokine levels in patients with chronic schizophrenia and the results showed that age reduces the increased activity of TNF-α, while, in relation to sex, women with schizophrenia had higher levels of TNF-α compared with men suffering from schizophrenia (Scmitt *et al.* 2005).

Finally, Hounie and colleagues (2008) found a significant association between the 38 G/A polymorphism of TNF-α and obsessive-compulsive disorder in 111 patients with OCD (Hounie *et al.* 2008).

Considering the above, the aim of the present study is to explore the relationship between IL-6, IL-12, TNF-α and type 2 diabetes mellitus with psychological factors.

MATERIAL AND METHODS

The present study was conducted at Attikon University Hospital and the sample was randomly selected from the Diabetes Centre of the 2nd Department Internal Medicine-Propaedeutic, Research Institute. All the patients were suffering from type 2 diabetes mellitus. From the study were excluded patients with malignant diseases, endocrinological syndromes, known severe peripheral arteriopathy, coronary disease, kidney failure, patients with amputations, existent psychopathology and those that they were under treatment with antidepressants, tranquilizers, antipsychotic and anticonvulsant medication. The study was approved by the ethics committee of the Attikon University Hospital and all the participants were informed about the purposes of the study

and gave their written consent. The sample consisted of 131 diabetic patients, 76 males and 55 females. The demographic characteristics of the sample can be found in Table 1.

Patients were divided in two groups according to the level of diabetes control as indicated by Glycosylated Haemoglobin (HbA1c): Group A consisted of 86 controlled diabetic patients (HbA1c<7) and the Group B consisted of 45 uncontrolled diabetic patients (HbA1c ≥7). The group A, consisted of 36 female and 50 male participants, while the group B, of 20 female and 25 male participants respectively. During the initial phase of the study (T_0), During the initial phase of the study (T_0), blood samples were taken for measuring IL-6, IL-12 serum levels as well as a battery of psychometric tools was completed. One year later (T_1), the uncontrolled diabetic patients were re-evaluated with the use of the same psychometric instruments and with the identical blood analysis.

During the intermediate year, an intensive effort to improve their metabolic profile was performed with more frequent appointments at the Diabetes Center adjusting their medication and diet. From the initial sample of 45 uncontrolled diabetic patients, 4 died from natural causes, while 10 withdraw from the study for other personal and family reasons such as relocation. Finally, 31 uncontrolled diabetic patients were re-assessed. The re-evaluated sample consisted of 17 male and 14 female participants. Ten of these 31 uncontrolled patients had already managed to improve their metabolic profile (HbA1c<7) in the preceding year between Phase 1 (T_0) and Phase 2 (T_1) of the study.

During the initial evaluation, all the participants were assessed with the following psychometric questionnaires:

A. Psychometric Personality scale of extraversion, neuroticism, psychotism (Eysenck Personality Questionnaire, EPQ) (Eysenk & Eysenk 1975). The Eysenck personality questionnaire consists of 84 entries evaluated by the patient with a yes or no. The purpose of this questionnaire is to explore four dimensions of personality: psychotism (P), neuroticism (N) extraversion (E) and lying (L). A weighted Greek version is available (Dimitriou 1986).
B. Psychometric Hostility and Direction of Hostility Questionnaire (HDHQ) (Foulds 1960). The psychometric scale of hostility and direction of hostility consists of 51 entries, is self-completed. It consists of four subscales: (a) intropunitiveness (b) extrapunitiviveness (c) direction of hostility, and (d) general hostility. The assessment instrument consists of five subscales: (a) the act out hostility, (b) criticism of others (c) delusional or paranoid hostility, (d) self-criticism and (e) delusional guilt. The first three subscales are summed to form an extrapunitive score and the other two are summed to yield an intropunitive score.
C. Brief symptom Inventory (SCL-90) (Derogatis & Melisaratos 1983). The SCL-90 questionnaire is self-completed and measures 9 psychopathology parameters (as many as its subscales), which are: 1) somatisation, 2) depression, 3) anxiety, 4) phobic anxiety, 5) obsessive compulsive, 6) paranoid ideation, 7) psychoticism, 8) hostility, 9) interpersonal sensitivity. The questionnaire includes 90 questions in total. All entries are rated from 0 to 4, giving a total score of 360. The scale is used to extrapolate 3 aggregate indexes: a) the general severity index, b) the positive symptoms distress index c) the positive symptoms total. A weighted Greek version is available (Donias *et al.* 1991).
D. The Maudsley O-C Inventory Questionnaire (MOCI) (Hodgson1977): Obsessive-compulsive symptoms are measured using the Maudsley Obsessional Compulsive Inventory (MOCI). In our investigation, the focus was on the types of obsessive-compulsive symptomatology and not on obsessional personality traits. It appears that people who suffer from observable obsessive-compulsive rituals complain about 4 main types of problems which are labelled checking, cleaning, slowness and doubting. These labels refer to types of problems and not to types of people and that a person may suffer from more than one type (Rachman 1974).
E. The Zung Self Rating Depression Scale (ZDRS) (Zung 1965). Fountoulakis *et al.* (2001) introduced the Greek translation of the Zung scale, where they proposed five factors to explain the severity of depression (Fountoulakis *et al.* 2001). The first factor reflects anxiety-depression, the second is the thought content factor, the third describes gastroenterological problems, the fourth represents irritability and the fifth factor summarizes information about social functioning.

Tab. 1. Demographic characteristics of the sample.

	Total (n=131)		Controlled (n=86)		Uncontrolled (n=45)	
Age	64.0	(±9.95)	64.2	(±10.94)	63.6	(±7.84)
Education						
elementary	106	(80.9%)	71	(82.6%)	35	(77.8%)
Secondary	8	(6.1%)	5	(5.8%)	3	(6.7%)
Highest	17	(13.0%)	10	(11.6%)	7	(15.6%)
Occupation						
Housekeeping	49	(37.4%)	30	(34.9%)	19	(42.2%)
Pensioner	40	(30.5%)	26	(30.2%)	14	(31.1%)
Civil servant	10	(7.6%)	8	(9.3%)	2	(4.4%)
Self employed	32	(24.4%)	22	(25.6%)	10	(22.2%)
Duration	11.9	(±8.73)	11.5	(±8.96)	12.6	(±8.31)

(parenthesis display the standard deviations)

Statistical analysis

Continuous variables are presented as mean values with standard deviations, whereas, frequencies and percentages are given for the categorical variables. Association between the metabolic profile and each of the continuous variables is explored through the Students' t-test under the assumption of normally distributed variables and equality of variances. The hypothesis tests that compare the scores of the psychometric scales between the first and second evaluation are based on paired t-test when assuming normally distributed variables. In the case of small sample size or asymmetric distributions, the corresponding nonparametric tests are performed, such as Mann-Whitney test for t-test and Wilcoxon test for paired t-test. Linear relationships between continuous variables are measured through the Pearson correlation coefficients for normally distributed variables or the Spearman correlation coefficients otherwise. Associations between categorical variables are examined using χ^2 test. Multiple logistic regression analysis is performed to examine the association between the metabolic profile, IL-6, IL-12, TNF-α and Zung scale, MOCI scale, EPQ scale HDHQ scale and SCL-90 scale. The statistical test presented here are two-tailed and compared with the statistical level of 5%. All characteristics are presented as mean±SD for continuous variables, or percentages (%) for categorical variable.

RESULTS

First Evaluation: T_0

The comparison of the biochemical parameters with the metabolic profile of patients suggests that all parameters have higher values in uncontrolled, compared to controlled, patients. The average values of TNF-α were significantly different among controlled (7.73±5.51) and uncontrolled patients (9.29±4.52) at a significance level of 5% (p=0.009). The remaining differences between the mean values did not appear to differ significantly (Table 2).

We tested the relationship of the biochemical parameters with the subscales of the personality questionnaire EPQ. In specific, we examined whether these relationships differ as to their metabolic profile. The results are presented in Table 3.

Controlled diabetic patients showed a statistically significant relationship between IL-6 and neuroticism (r_p=0.303, p=0.010), and between IL-12 and psychotism, (r_{sp}=0.382, p=0.001). These relationships are statistically significant at 5% significance level with positive signs of the respective correlation coefficients. Therefore, controlled diabetics with higher IL-6 values are expected to have higher scores on the subscale of neuroticism. There was a similar relationship between IL-12 and psychotism.

The analysis then examined the existence of relationships between the biochemical parameters and the overall hostility scale and its subscales (HDHQ) (Table 4).

Controlled diabetic patients showed a statistically significant relationship between IL-12 and the act out hostility subscale (r_{sp}=–0.307, p=0.009). The signs of the relationships were negative, indicating a negative relationship between these biochemical parameters and the hostility subscale. The controlled patients with higher IL-12 values scored lower on the act out hostility subscale. We also see a statistically significant relationship between IL-6 and direction of hostility (r_p=0.275, p=0.019). There was no statistically significant relationships for uncontrolled patients.

Examining the relationship of IL-6, IL-12 and TNF-α with SCL-90 we noted a statistically significant correlation with anxiety (r_{sp}=0.257, p=0.029), depression (r_p=0.497, p<0.001), obsessive compulsive behaviour (r_p=0.372, p=0.001) and the general index (r_p=0.389, p=0.001). IL-6 correlated positively with the above scales, i.e. higher values correspond to higher scores. There were no statistically significant relationships between uncontrolled patients.

Examining the relationship of IL-6, IL-12 and TNF-α and MOCI scale there was evidence for a statistically significant relationship between IL-12 and the subscale of the doubting (r_{sp}=0.357, p=0.028) for uncontrolled diabetic patients.

There were no statistically significant relationships between the biochemical parameters and the subscales of the MOCI for controlled patients.

Evaluating the relationship between IL-6, IL-12 and TNF-α with the Zung scale in controlled diabetic patients, we noted a statistically significant correlation between IL-6 and the Zung depression scale

Tab. 2. IL-6, IL-12, TNF-α in controlled and uncontrolled diabetic patients.

	Controlled diabetic patients (T_0)			Uncontrolled diabetic patients (T_0)			*p*-value
	(Mean ± SD)	Median	Width	(Mean ± SD)	Median	Width	
IL-6	1.78±1.44	1.42	5.71	2.15±1.42	2.28	5.02	0.091[β]
IL-12	0.55±0.62	0.21	2.76	0.71±0.77	0.43	2.73	0.232[β]
Tnf-α	7.73±5.51	6.14	37.78	9.29±4.52	9.16	22.52	**0.009**[β]

[α] t-test
[β] Mann-Whitney

(r_p=0.339, p=0.004), IL-6 and the stress and depressed affect subscale (r_p=0.241, p=0.042), as well as of IL-6 with the social functioning subscale (r_p=0. 378, p=0. 001). Finally, it was noted that IL-12 correlates significantly with the stress and depressed affect subscale (r_p=–0.240, p=0.044). All relationships, apart from that of IL-12 and the stress and depressed affect subscale, have a positive sign, indicating a positive relationship between the variables; therefore, the higher the values of these biochemical parameters, the greater the scores in the respective psychometric tests will be (Table 5). There were no statistically significant relationships in uncontrolled patients.

The relationship of the biochemical parameters with the Zung scale was explored further by converting the 20 questions of the scale into binary variables, so that when the patient's response was *rarely*, this corresponded to 0, while all other answers were grouped in the same category, assuming the value 1. The purpose of this categorization was to examine the existence of a relationship between patients' responses and their metabolic profile, while it was also interesting to explore whether the mean values of the biochemical parameters vary depending on the patients' response.

Table 6 presents the relationships of the biochemical parameters with the questions of the Zung scale, which appear statistically significant at a 5% or lower significance level. We observe that controlled diabetic patients who have rarely depressed affect have lower IL-6 values than those who have depressed affect some times or more often (1.28±1.11 versus 2.04±1.54, p=0.029). There is a similar relationship between the values of IL-6 and crying spells (1.33±1.21 versus 2.01±1.48, p=0.026), and fatigue (1.38±1.12 versus 2.11±1.61, p=0.047). This is not the case as regards the relationship of the values of IL-6 and decreased libido in controlled patients, where these values increase for those who rarely have decreased libido (2.31±1.63 versus 1.39±1.17, p=0.007).

The values of IL-12 were greater in patients who have rarely psychomotor agitation problems (0.74±0.63 versus 0.41±0.58, p=0.009). Furthermore, we observed that controlled patients with rare tachycardia have greater IL-12 values than those who have tachycardia more often (0.63±0.67 versus 0.37±0.45, p=0.034). The more often the patients present constipation, the lower their IL-12 values (0.61±0.59 versus 0.44±0.67, p=0.001).

Moreover, we observed that there was a statistically significant relationship between TNF-α and decreased libido; namely, patients with rarely decreased libido have higher TNF-α values (9.90±7.33 versus 6.36±3.36, p=0.017).

Furthermore, we observed that in uncontrolled diabetics there was a statistically significant relationship between weight loss and TNF-α; namely, patients who rarely showed weight loss had higher TNF-α values (10.24±3.84 versus 7.56 5.23, p=0.012).

Tab. 3. IL-6, IL-12, and EPQ subscales.

EPQ	IL-6 N=72	IL-12 N=72
Controlled diabetic patients (N=86)		
Psychotism	r_{sp}=0.295; p=0.006	r_{sp}=0.382; p=0.001
Neuroticism	r_p=0.303; p=0.010	
Uncontrolled diabetic patients (N=46)		
Psychotism		
Extraversion	r_p=–0.349; p=0.019	

Tab. 4. IL-6, IL-12 and HDHQ subscales.

HDHQ	IL-6 N=72	IL-12 N=72
Controlled diabetic patients		
Act out hostility		r_{sp}=–0.307; p=0.009
Direction of hostility	r_p=0.275; p=0.019	

Tab. 5. IL-6, IL-12 and Zung subscales.

	IL-6	IL-12
Controlled diabetic patients		
Zung	r_p=0.339; p=0.004	
Anxious and depressed affect	r_p=0.241; p=0.042	r_{sp}=–0.240; p=0.044
Social Functioning	r_{sp}=0.378; p=0.001	

Second Evaluation – T_1

During the second evaluation we examined one year later all the uncontrolled patients of the first evaluation. The sample this time consisted of 31 diabetic patients of whom 10 had managed to become controlled (5 males and 5 females), while 21 remained uncontrolled (11 males 10 females). We used a paired test to conclude whether, on average, the levels of the biochemical parameters and psychometric tests differed in the 10 individuals found to have achieved control at the second evaluation.

We note that the values of IL-6, IL-12 and TNF-α increased when patients reduced their levels of HbA1c below 7. However, the changes of these biochemical parameters during the first and second assessment do not appear to be statistically significant, except the change in IL-12 (0.51±0.23 vs 0.870.46, p=0.042), as shown in Table 7.

Similarly, we explored whether the scores of the psychometric tests differ significantly between the first and second evaluation. We observe in Table 8 that the scores of psychotism, neuroticism and lying declined when uncontrolled patients achieved control, while the extroversion score increased.

Tab. 6. IL-6, IL-12, TNF-α in correlation with the Zung items and metabolic profile in controlled diabetic patients.

		Interleukin-6				
		N	Mean value ± SD	Median	Width	*p*-value β
Depressed affect	A little of the time	25	1.28±1.11	0.99	4.57	0.029
	Some of the time or good part of the time	47	2.04±1.54	1.91	5.71	
Crying spells	A little of the time	29	1.33±1.21	0.90	4.57	0.026
	Some of the time or good part of the time	42	2.01±1.48	1.87	5.71	
Decreased libido	A little of the time	30	2.31±1.63	2.19	5.71	0.007
	Some of the time or good part of the time	42	1.39±1.17	1.14	4.76	
Fatigue	A little of the time	33	1.38±1.12	1.15	4.57	0.047
	Some of the time or good part of the time	39	2.11±1.61	2.09	5.71	
		Interleukin-12				
		N	Mean value ± SD	Median	Width	*p*-value β
Psychomotor agitation	A little of the time	31	0.74±0.63	0.66	2.68	0.009
	Some of the time or good part of the time	41	0.41±0.58	0.12	2.76	
Tachycardia	A little of the time	51	0.63±0.67	0.34	2.76	0.034
	Some of the time or good part of the time	20	0.37±0.45	0.12	1.34	
Constipation	A little of the time	47	0.61±0.59	0.37	2.68	0.001
	Some of the time or good part of the	25	0.44±0.67	0.12	2.76	
		Tumor necrosis factor-α				
		N	Mean value ± SD	Median	Width	*p*-value β
Decreased libido	A little of the time	33	9.90±7.33	7.31	37.16	0.017
	Some of the time or good part of the time	52	6.36±3.36	5.83	17.24	

β Mann-Whitney

Tab. 7. Mean values of IL-6, IL-12, TNF-α among the first and second evaluation.

	Uncontrolled diabetic patients T_0				Controlled diabetic patients T_1				*p*-value
	N	Mean value ± SD	Median	Width	N	Mean value ± SD	Median	Width	
IL-6	10	1.77±1.26	1.80	3.50	9	2.08±1.72	1.56	3.95	0.404α
IL-12	8	0.51±0.23	0.57	0.68	9	0.87±0.46	0.72	0.85	**0.042**α
TNF-α	10	9.16±3.19	8.81	11.81	10	10.26±2.98	10.47	4.44	0.159α

α Paired t-test
β Wilcoxon signed rank test

Acting out hostility and the direction of hostility increased when HbA1c values fell below the threshold of 7, while the total hostility index, as well as all other scales, dropped when patients controlled their metabolic profile. The reduction of the total index of hostility, of criticism of others, and of extroversion appeared statistically significant (p=0.032, p=0.011 and p=0.038).

In addition, we examined whether the mean values of the subscales of SCL-90 changed significantly when patients regulated their metabolic profile (Table 9). The scale of somatization did not change between the first and second evaluation, while the scale of anger-hostility increased. The remaining scales were reduced when HbA1c values fell below 7. However, those that marked

Tab. 8. Mean values of EPQ and HDHQ subscales in the first and second evaluation.

	Uncontrolled T_0				Controlled T_1				*p*-value
	N	Mean value ± SD	Median	Width	N	Mean value ± SD	Median	Width	
EPQ									
Psychotism	10	1.20±0.63	1.00	2	10	1.00±0.00	1.00	0	0.317[β]
Neurotism	10	14.40±2.59	15.00	7	10	12.20±2.57	12.00	9	0.077[α]
Extraversion	10	14.10±4.07	15.00	12	10	15.60±2.46	16.00	7	0.254[α]
Lying	10	13.90±3.35	14.00	9	10	13.40±2.50	13.50	8	0.440[α]
HDHQ									
Hostility-total	10	17.00±7.59	15.50	25	10	10.60±3.75	11.50	11	**0.019**[β]
Act out hostility	10	0.90±0.32	1.00	1	10	1.00±0.00	1.00	0	0.317[α]
Criticism of others	10	6.10±2.92	5.50	10	10	1.00±0.00	1.00	0	**<0.0001**[α]
Paranoid hostility	10	3.00±2.98	2.00	8	10	2.70±1.06	3.00	4	0.782[α]
Self critisism	10	4.50±1.78	4.50	5	10	3.80±2.20	4.00	6	0.242[β]
Delusional guilt	10	2.50±1.78	2.00	5	10	2.10±1.37	1.50	4	0.343[α]
Introversion	10	14.00±6.32	12.00	18	10	11.80±6.43	12.00	18	0.170[α]
Extroversion	10	10.00±5.33	9.50	17	10	4.70±1.06	5.00	4	**0.015**[α]
Direction	10	4.00±5.50	4.50	16	10	7.10±6.10	6.00	17	0.141[α]

[α] Paired T-test
[β] Wilcoxon signed rank test

Tab. 9. Mean values of scl-90 subscales in the first and second evaluation.

	Uncontrolled T_0				Controlled T_1				*p*-value
	N	Mean value ± SD	Median	Width	N	Mean value ± SD	Median	Width	
SCL-90									
Somatization	10	0.53±0.35	0.42	1.17	10	0.53±0.39	0.5	1.5	0.797[β]
Obsessive compulsive	10	1.19±0.72	1.2	2.4	10	1.02±0.57	1.05	1.6	0.622[α]
Interpersonal sensitivity	10	1.21±0.8	1.06	2.89	10	0.53±0.36	0.56	1.11	**0.028**[β]
Depression	10	1.34±1.04	0.92	2.85	10	0.62±0.43	0.58	1.54	0.184[β]
Anxiety	10	0.72±0.59	0.55	1.9	10	0.43±0.28	0.3	0.8	0.260[β]
Hostility	10	0.65±0.62	0.5	2.17	10	0.78±0.85	0.42	2.5	0.623[β]
Phobic anxiety	10	0.37±0.52	0.29	1.57	10	0.2±0.19	0.14	0.57	0.343[β]
Paranoid ideation	10	1.17±0.93	0.83	2.67	10	0.77±0.57	0.75	1.67	0.398[β]
Psychotism	10	0.51±0.58	0.4	2	10	0.15±0.18	0.1	0.5	**0.024**[β]
General severity index	10	0.87±0.6	0.66	2.04	10	0.55±0.29	0.48	1.04	0.333[β]

[α] Paired t-test
[β] Wilcoxon signed rank test

a statistically significantly decrease were the subscales of interpersonal sensitivity and psychotism (p=0.028 and p=0.024).

Finally, we examined whether the mean values of the MOCI and Zung subscales changed significantly when patients regulated their metabolic profile (Table 10). The Zung scale did not change between the first and second evaluation. The subscales Thought content and Irritability increased between the first and second evaluation, while the rest declined. In the MOCI scale, the subscales of slowness and uncertainty did not change between the first and second evaluation. The control scale dropped, while the subscale of doubt increased between the first and second evaluation.

However, the differences in the mean values of the Zung and Maudsley scales and their subscales during the first and second evaluation did not appear to be statistically significant, as shown in Table 10.

Tab. 10. Mean values of ZUNG and MOCI subscales in the first and second evaluation.

	Uncontrolled T_0				Controlled T_1				*p*-value
	N	Mean value ± SD	Median	Width	N	Mean value ± SD	Median	Width	
ZUNG	10	34.50±5.30	34.00	16	10	34.50±6.82	33.50	23	1.000[α]
Anxious and depressed affect	10	9.10±1.20	9.00	4	10	8.80±1.75	9.00	5	0.718[α]
Thought content	10	10.50±3.75	10.00	12	10	12.50±3.66	12.00	11	0.130[α]
Gastrenterological problems	10	5.80±1.99	6.00	6	10	4.70±1.25	4.00	4	0.075[α]
Irritability	10	4.50±1.43	4.00	4	10	5.40±1.51	5.50	5	0.095[α]
Social Functioning	10	7.70±2.11	8.00	6	10	7.10±1.60	7.00	5	0.329[α]
MOCI	10	13.30±4.45	14.00	15	10	13.30±4.14	14.00	13	1.000[α]
Checking	10	4.00±2.21	4.50	6	10	3.60±1.58	4.00	5	0.657[α]
Cleaning	10	3.10±1.91	2.50	6	10	3.50±1.43	3.50	5	0.662[α]
Slowness	10	1.90±1.37	2.00	4	10	1.90±1.10	1.50	3	0.931[β]
Doubting	10	4.30±1.25	4.00	4	10	4.30±1.25	4.00	3	0.903[β]

[α] Paired t-test
[β] Wilcoxon signed rank test

DISCUSSION

The examination of the relationship between IL-6 and psychometric instruments revealed that controlled diabetic patients with high values of interleukin-6 (IL-6) show high neuroticism values in the EPQ personality questionnaire.

Neuroticism refers to the general emotional instability of individuals, their emotional hyper-reactivity and their tendency to develop neurotic symptoms under stress. People with high neuroticism values are anxious, easily upset, sullen and often sad. They complain of insomnia and psychosomatic disorders and show strong emotional reactions, which interfere with their normal adjustment. In a study of 6 148 individuals in the general population, Sutin and colleagues (Sutin *et al.* 2010) showed that high levels of neuroticism were associated with high levels of IL-6. Studies focusing on the relationship between personality and diabetes demonstrated that extraversion has been both negatively (Lane *et al.* 2000) and positively correlated with glycaemic control in patients with diabetes. Nevertheless, Hepburn and colleagues (Herburn *et al.* 1994) found no correlation between extroversion and HbA1c. Furthermore, the correlation between neuroticism and HbA1c has also been questioned (Gordon *et al.* 1993). Instead, the data on personality relate to the way in which the patient perceives health and illness (Costa & McCrae 1987). For example, people with high neuroticism levels experience greater psychological stress, while in diabetes, neuroticism has been associated with more psychosomatic symptoms and greater worries and concern about hypoglycaemia (Hepburn *et al.* 1994). These findings reinforce the view that personality can enhance the patients' self-perception regarding their physical symptoms. Neuroticism has been found to affect the self-care of patients by influencing their individual convictions. Taylor and colleagues (Taylor *et al.* 2003) found that their convictions about the threat of diabetes to their health links neuroticism and self-care, and neuroticism was correlated with the individual's satisfaction with quality pf life but also with anxiety about the future consequences and complications of diabetes.

A significant positive relationship between IL-6 and the direction of aggression subscale of the HDHQ in controlled diabetic patients. In a study of 90 patients with depressive symptoms, Suarez and colleagues (Suarez 2003) found a significantly positive correlation between aggression in men and levels of IL-6. Aggression in men was associated with an increased likelihood of cardiovascular complications and increased levels of IL-6 and aggression were associated with daily stressors. Stoney and colleagues (Stoney & Engebretson 2000) believe that aggression represents an emotional reaction to stressful events and is associated with the increase of the sympathetic tone, which contributes to the increase of polystyrene. An increased sympathetic tone has been observed in obesity and hyperinsulinaemia.

In controlled diabetic patients, IL-6 was found to have a positive correlation with the subscale of depression, anxiety and obsessive compulsive behaviour, as well as with the general symptom index on the SCL-90 scale. In a study of patients with hepatitis C, Dieperink and colleagues (Dieperink *et al.* 2000) observed that IL-6 correlated positively with the depression subscale of the SCL-90. In a study of patients with post-traumatic stress disorder, Song and colleagues (Song *et al.*

2007) showed a positive correlation between IL-6 levels and the depression and phobic anxiety subscale of the SCL-90 scale.

In controlled diabetic patients, IL-6 correlates positively with the subscales of depression, anxiety and depressive effect and also with the social activity subscale of the Zung scale. In a study of 44 patients on dialysis, Sonikian and colleagues (Sonikian *et al.* 2010) found that the score of the Zung scale was higher in these patients compared with the controls. Moreover, IL-6 was correlated positively with the Zung scale. There are several possible mechanisms correlating cytokines with depression. Cytokines such as IL-2, INF-gamma or the TNF-α factor activate the enzyme indoleamine 2.3-dioxygenase, which acts on tryptophan, causing its reduction and therefore leads to a reduction of serotonin levels, associated with causing depressive symptoms. On the other hand, cytokines – and especially IL-6 – are associated with an over activity of the HPA axis, through the disruption of the negative feedback regulation of corticosteroids (Shephard 2002).

In another study studying 35 patients with heart failure, Parissis and colleagues (Parissis *et al.* 2004) found that depressed patients with high scores on the Zung scale showed high levels of IL-6, as well as a positive correlation between the anxiety and depression subscales and IL-6 was reported. Modern literature indicates that depression is accompanied by the activation of the immune system and that cytokines and the subsequent activation of the immune system are associated with mortiferous behaviour in experimental models. The study of correlations between the immune system, somatization and depression showed that stressful factors can cause an increase in CD3 and CD4, while studies on mental fatigue showed an induction of the increase of IL-6 (Rief *et al.* 2001; Wegner *et al.* 2008).

When checking the relationship between IL-2 and psychometric tools, we found that, in controlled diabetic patients, high IL-2 values are associated with high psychotism scores on the EPQ scale. The correlation of psychotism with a pre-psychotic phase probably associates our findings with those of other studies, whose results showed that, compared with healthy controls, patients in a first psychotic episode showed a strong immunological reaction with increased production of IL-12 (Crespo-Facorro *et al.* 2008).

Psychotism as described by Eysenck corresponds to the personality characteristics of a person who is aggressive, stubborn, egocentric, unloved, manipulative, purposeful and dogmatic (Eysenck & Eysenck 1975).

Furthermore, in uncontrolled patients, IL-12 presents a positive correlation with the MOCI subscale of doubt. Only one study, by Gabbay and colleagues (Gabbay *et al.* 2009), correlates IL-12 with OCD in patients with Gille de la Tourette syndrome in which IL-12 levels were elevated compared with a control group consisting of healthy individuals and a patient group with only OCD. In controlled diabetic patients, IL-12 is negatively correlated with the anxiety and depressive effect subscale of the Zung scale.

In depression, the levels of interleukin-12 were elevated in comparative studies with healthy individuals. These findings in major depression indicate a possible activation of the immune system. Existing literature suggests that depressed patients show an increased production of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-gamma in mononuclear cells, and structural changes in the receptors of IL-2 and IL-6 (Kim *et al.* 2008). In addition, in depression we often note intense phagocytosis by neutrophils and monocytes (Connor *et al.* 1998).

In the second assessment, comparing the biochemical parameters those who managed to control their metabolic profile able to regulate their metabolic profile in relation to the first assessment, we note that IL-12 (0.51±0.23 VS 0.87±0.46) decreased significantly. In existing literature, studies have focused on the role of hyperglycaemia in causing atherosclerosis lesions, which are associated with inflammatory activity and increased levels of IL-12. Therefore, uncontrolled diabetic patients are associated with higher levels of IL-12 (Crespo-Facorro *et al.* 2008).

During the first assessment, the mean values of the tumour necrosis factor-alpha (TNF-α) represent the only significant difference between controlled and uncontrolled diabetic patients, being greater in uncontrolled diabetic patients. The elevated levels of TNF-α observed in type 2 diabetes are associated with hyperglycaemia and poor control, which triggers the production of macrophages, thus causing oxidative stress. Hyperglycaemia causes protein glycolysis and can trigger cytokine production with simultaneous activation of the immune system. In a study of 35 diabetic patients (17 with type 1 diabetes and 18 with type 2 diabetes), Freitas and colleagues (Freitas-Foss *et al.* 2008) found that uncontrolled diabetics – especially those with type 1 diabetes – had higher TNF-α values. In type 2 diabetics, endogenous insulin may be normal or even increased due to insulin resistance, and thus the TNF-α factor is less elevated in most uncontrolled patients with type 1 diabetes.

Furthermore, we observed that uncontrolled diabetic patients showed a statistically significant relationship between weight loss and TNF-α. Specifically, patients who rarely show weight loss have higher TNF-α values.

The correlation of biochemical parameters with psychometric variables in the clinical setting could provide the clinician diabetologist great help in evaluating potential psychopathological conditions that are undermined and revealed through the endocrinological-immunological profile of the diabetic patient.

In conclusion, taken together, the present results provide evidence that IL-6, IL-12 and tnfa are closely related to the course and treatment of type 2 diabetes. Although the specific implications of the research on

clinical practice remain uncertain, it is likely that additional work in this area will further demystify and validate essential mechanisms involved in the pathogenesis of type 2 diabetes. Such an approach also promises to help treatment selection by providing an enhanced vocabulary for discussing concepts central to the treatment of diabetes.

LIMITATIONS

1. The small number of participants during the second evaluation, which was 45 uncontrolled diabetic patients at baseline assessment, while finally we evaluated 31 uncontrolled diabetic patients of whom 10 were able to achieve control.
2. This is a sectional study in a specific period and a prospective study would be desirable. It probably makes sense for the research strategies to be perspective rather than sectional, by inclusion of the relevant genetic variables. A prospective study of promises to also determine additional relevant parameters (cost, quality of life, pain). In recent years, the understanding of the pathogenetic contribution of psychosocial factors in diabetic morbidity / mortality has increased substantially. On the contrary, the development of effective therapeutic interventions to change pathological lifestyles/behaviours and to reduce their impact remains a life challenge. The compliance of the patient with the therapeutic regimen is a fundamental problem. The issues raised for investigation are: Apart from depression, which other psychosocial variables have causative significance?
   If other variables are involved, is there a one-way interaction or should we expect "synergies"?
   What is the importance of the chronicity of stressful conditions?
3. It concerns a subset of the spectrum of psychopathology-personality.
4. It assumes the co-evaluation of intra-phenotypic and genotypic variables.

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Declaration of Interest

The authors report no declarations of interest.

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