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Increased plasma pro-inflammatory cytokine concentrations after myocardial infarction and the presence of depression during next 6-months

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Summary

Introduction. The connection between myocardial infarction (MI) and depression has been studied for more than 20 years and it is clear now that the consequences of this comorbidity are serious and cannot be ignored. One of the mechanisms underlying this connection is the role of inflammatory reaction and autoimmune processes present in MI and depression.

Aim. The aim of this study was to investigate plasma concentrations of four pro-inflammatory cytokines (IL17a, IL6, TNFα and IL12p70) in patients with myocardial infarction and to analyse them according to presence of depression observed during first 6 months after myocardial infarction.

Method. In 44 patients with the first acute STEMI (ST segment elevation myocardial infarction) plasma levels of IL17a, IL6, TNFα and IL12p70 were measured on the 3rd and 5th day after the MI. Cytokine concentrations were analyzed according to the presence of depression during 6 months of observation.

Results. Two groups of patients distinguished according to presence of depression during 6 months of observation differed in their inflammatory reaction to MI. In the depression group all four cytokines on the 3rd day after the MI were elevated compared to control and on the 5th day two of them: IL17a and IL6 were still elevated. In the group without depression on the 3rd day only two of four investigated cytokines were elevated and on the 5th day only IL6 concentration remained higher.

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Conclusions. It can be assumed that more pronounced inflammatory response as an element of stress reaction after MI can predispose to depression. IL17a increase can play particularly important role in this process.

Key words: depression, myocardial infarction, pro-inflammatory cytokines

Introduction

According to National Institute of Mental Health 12-month prevalence of depression in adult population is 6.7% [1], lifetime prevalence reaches 16.5% [2]. Depressive symptoms as well as depressive episodes are significantly more common in patients after myocardial infarction [3, 4]. According to meta-analysis by Thombs, the prevalence of MD (major depression) in patients after MI is about 20%. This meta-analysis showed that depression observed in patients hospitalized due to AMI (Acute Myocardial Infarction) persisted in more than half of the patients during the first 1 to 12 months after discharge [5]. In one of the analyzed studies, authors found that 15.5% of patients with recent MI had major and 26.8% had minor depression. After 3 to 4 months 36% of the patients with major depression at baseline still had major depression and another 36% had minor depression [6]. In pathogenesis of depression after MI not only biological, but also psychological and environmental factors play an important role [7, 8]. Myocardial infarction triggers a biological and psychological stress reaction. It causes myocardial necrosis and severe pain, activates the sympathetic nervous system and increases HPA axis output and pro-inflammatory cytokines production [9], which may explain higher risk of the occurrence of depression after MI.

The presence of depression is associated with increased levels of CRP and pro-inflammatory cytokines [10, 11]. It is assumed that depression is the result of the alteration of central monoaminergic neurotransmission accompanied by dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis, but activation of immune system also plays an important role [12]. Not many studies concerning circulating cytokines concentrations in patients with depression after MI have been published so far [13–15].

Based on above mentioned theoretical founds it can be assumed that the risk of developing depression after MI is higher in patients with stronger inflammatory response expressed by higher pro-inflammatory cytokine concentrations during first days after MI.

Aim

The objective of this study was to compare values of chosen pro-inflammatory cytokine concentrations during first days after MI in groups of patients distinguished according to presence of depression during 6 months after MI. Obtained results were also related to healthy control.

Methods

Subjects

40 patients (including 6 women – 15%) admitted to the First Department of Cardiology of the Medical University of Gdansk with their first acute MI with ST elevation (STEMI) were included. The mean age was 53.4 ± 8.1 years. All of the patients had a cardiovascular intervention and received standard pharmacological treatment. The left ventricle ejection fraction (LVEF) was ≥ 40% and the average BMI was 27.3 kg/m^2 (SD 4.1). The exclusion criteria were endocrine diseases such as diabetes, hypo- or hyperthyroidism, severe renal or hepatic failure, hormone therapy, active addiction to psychoactive substances and the presence of psychiatric disorders other than depression: anxiety disorders, stress related and adjustment disorders.

All patients were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders [16] three times during six months period after MI: on the second day and 3 and 6 month after MI. On the second day of MI 4 patients developed major depressive episode, 18 patients developed depressive disorder not otherwise specified (all 18 patients fulfilled criteria of minor depression from Appendix B of DSM IV-TR) which together made 22 patients. After 3 months 4 patients still fulfilled the criteria for major depression, 16 had minor depression and additional 6 patients developed minor depression (Table 1). After 6 months depressive symptoms were observed in only 12 patients, remaining 28 did not present any. To sum up, we found that during 6 months after MI depressive disorder (major and minor depression) was present in 28 (70%) of patients including 4 patients (10%) with major depression. The intensity of depressive symptoms was estimated three times during 6 months of observation with Hamilton Depression Scale (HAMD) and Beck Depression Inventory (BDI) [17, 18] (Table 2).

Table 1. **Presence of depression (major and minor)**

		Test II (after 3 months)		
		Depression (-)	Depression (+)	Total
Test I (second day after MI)	Depression (-)	12	6	18
	Depression (+)	2	20	22
	Total	14	26	40

Table 2. **Intensity of depressive symptoms (HAMD and Beck I) in groups with depression in respective phases of the study**

Test/Presence of depression		N	HAMD-17 Median (IQR)	Beck I Median (IQR)
Test I (second day of MI)	Depression (+)	22	12 (8, 16)	14 (10, 20)
	Depression (-)	18	2 (1, 4)	3 (1, 6)
Test II (after 3 months)	Depression (+)	26	10 (8, 14)	12 (10, 14)
	Depression (-)	14	2 (0, 6)	3 (2, 8)

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Test III (after 6 months)	Depression (+)	12	8 (7, 10)	10 (8, 13)
	Depression (-)	28	3 (1, 6)	4 (2, 7)

Depending on the presence of depression in the first 6 months after MI the entire group was divided into two groups. Depression group included 28 patients (5 women – 17.9%), the group without depression – 12 (including 1 women – 8.3%). Patients diagnosed with major and minor depression were included in one group, because the number of major depression patients was too small to consider it separately in the analysis. Mean age in depression group was 53.3 ± 8.1 years and 53.5 ± 8.8 years in no depression group.

The control group consisted of 14 healthy volunteers with no history of health problems, including depression and cardiovascular disorders. Mean age in control group was 50.78 ± 9.48 years, about 59% of the people in the group were males.

The study was approved by the Independent Ethics Committee of the Medical University of Gdansk (approval number NKEBN/205/2006). For each participant written consent was obtained.

Study protocol

Blood samples of patients with myocardial infarction were collected on 3rd and 5th day after MI twice at an interval of 20 minutes between 8:00 to 10:00 in the morning. The blood samples of control group were taken once. The blood samples were immediately centrifuged. The plasma samples were stored at -80^0 C.

Measurement of cytokine concentration

The concentration of cytokines in the supernatants (plasma) was determined using the cytometric bead array (CBA) flex set according to the manufacturer's protocol (BD, Franklin Lakes, NJ, USA). In brief, 50 µl of each of the samples and serial dilutions of cytokine standards were incubated in multiplexed antibody conjugated beads for 1 h. Thereafter, the PE detection reagent was added, and samples were incubated for an additional 2 h, and analyzed within the range 0–2500 pg/ml in a LSRII flow cytometer (BD). The data were analyzed with the FCAP Array Software (BD). The theoretical detection limits for cytokines were: IL6 – 1.6 pg/ml, IL-12p70 – 0.6 pg/ml, IL-17a – 2.9 pg/ml, TNFα – 0.7 pg/ml.

Statistical analysis was performed with the use of StatsDirect v. 2.8,0. [19]

Results

The whole group of the patients with acute myocardial infarction had significantly higher plasma concentrations of IL17a, IL6, TNFα and IL12p70 on the 3rd day of MI compared to control (Mann-Whitney U test). This statistically significant increase was still present on the 5th day with the exception of TNFa. There was no

statistically significant difference in cytokines concentrations between the 3rd and 5th day (Wilcoxon test).

We did not find statistically significant differences (Mann-Whitney U test) in cytokines concentrations between two groups of patients after MI distinguished according to presence of depression neither on the 3rd nor on the 5th day after MI. No statistically significant differences were found (Wilcoxon test) in cytokines concentrations between the 3rd and 5th day after MI within every group. The values of cytokine concentrations did not differentiate (Mann-Whitney U test) one group from the other as far as the time of depression appearance: immediately after MI (n = 22) and later (n = 6).

Additional analysis revealed differences between depression group and controls. Patients with depression after MI had significantly higher concentrations of all four studied cytokines on the 3rd day after MI. In the group of patients without depression after MI significantly higher level was found only for two of them: IL17a and IL6. In depression group higher concentrations of IL17a and IL6 were still present on the 5th day after MI while in no-depression group only IL6 concentration was higher (Table 3).

Table 3. **Group characteristics and plasma concentration of cytokines (pg/ml) on the 3rd and 5th day after MI – comparison to controls**

			Controls (n = 14)	Patients after MI		
				Whole group (n = 40)	No depression (n = 12)	Depression (n = 28)
Age		Mean (sd)	50.8 (9.5)	53.4 (8.1)	53.5 (8.8)	53.3 (8.1)
		p**		0.32	0.46	0.38
BMI		Mean (sd)	25.7 (3.2)	27.3 (4.1)	28.2 (3.8)	26.8 (4.2)
		p**		0.19	0.08	0.39
Women		N (%)	6 (42)	6 (15)	1 (8)	5 (18)
		p***		0.03	0.04	0.08
IL17a	Day 3	Median (IQR)	0 (0, 0)	16.1 (0, 22.4)	20.2 (0, 23.8)	14.2 (0, 21.6)
		p*		0.003	0.003	0.02
	Day 5	Median (IQR)		13.4 (0, 21.6)	0 (0, 23.8)	13.4 (0, 23.1)
		p*		0.01	0.1	0.009
IL6	Day 3	Median (IQR)	0 (0, 16.2)	17.8 (16.4, 20.4)	16.7 (16.2, 18.0)	17.9 (16.7, 20.6)
		p*		0.0000	0.005	0.0000
	Day 5	Median (IQR)		13.4 (0, 21.6)	16.7 (0, 17.9)	17.2 (16.0, 18.0)
		p*		0.002	0.03	0.001
TNFa	Day 3	Median (IQR)	0 (0, 0)	0 (0, 7.9)	0 (0, 0)	0 (0, 7.9)
		p*		0.03	0.3	0.01
	Day 5	Median (IQR)		0 (0, 8.4)	0 (0, 11.3)	0 (0, 7.9)
		p*		0.06	0.1	0.09

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IL12p70	Day 3	Median (IQR)	0 (0, 0)	11.7 (0, 13.3)	0 (0, 12.1)	12.1 (0, 13.4)
		p*		0.03	0.4	0.01
	Day 5	Median (IQR)		11.6 (0, 13.3)	11.9 (0, 13.3)	11.4 (0, 13.4)
		p*		0.04	0.09	0.06

Compared to controls: *Mann-Whitney U test; ** Student's t-test; *** independent proportion test

We did not find statistically significant differences between group of patients with depression and without depression considering age (Student's t-test: $p = 0.94$), BMI (Student's t-test: $p = 0.33$) and gender distribution (independent proportion test: $p = 0.40$).

Both groups as well as the whole studied population after MI did not differ significantly from control group as far as age and BMI. The proportion of females in control group was significantly higher compared to the whole group after MI as well as to group of patients without depression (table 3).

Discussion

We found increased levels of pro-inflammatory cytokines IL-17a, IL-6, TNF α and IL-12p70 in the whole group of patients after MI compared to age-matched controls. Statistically significant difference was observed in case all four tested cytokines on the 3rd day and in case of three (with exclusion of TNFα) on the 5th day after MI. Our results are consistent with other studies, elevated IL-6 and TNFα concentrations in patients with acute MI were shown before [20–23]. Elevated IL-6 concentration was observed for many days. In patients with the non-ST elevation acute coronary syndrome, the elevated IL-12p70 predicted worse outcome during hospitalization [24]. Recently attention has been drawn to IL-17 and its role in atherosclerosis. There is evidence for increased level of IL-17a in the systemic plasma of patients with acute coronary syndrome [25]. Cheng et al. found a significant increase in peripheral Th17 lymphocytes number and Th17 related cytokines (IL17, IL6, IL23) in patients with ACS [26].

We did not observe significant differences in tested cytokines concentrations neither on the 3rd nor on the 5th day of MI in groups distinguished according to presence of depression. In 22 patients depressive disorder started immediately after MI, only in 6 of them depression started later. Comparison of these groups did not reveal any relation of the time of depression onset (immediately after MI or later) and cytokine concentrations.

We have observed some differences in the dynamics of cytokine concentrations in groups distinguished depending on the presence of depression in comparison with control. In the group of patients with depression diagnosed during 6 months after MI, concentrations of all four cytokines were higher on the 3rd day. On the 5th day two of them: IL17a and IL6 were still elevated. In the group of patients without depression, on the 3rd day, concentrations of two cytokines: IL17a and IL6 were significantly higher and on the 5th day only IL6 concentration remained higher compared to controls. These results could suggest slightly stronger and longer inflammatory response

in the group of patients developing depression after MI. No statistically significant differences between distinguished subgroups suggest definitely cautious interpretation.

The observation of longer IL17a concentration increase in depression group compared to controls seems to be interesting for future investigation. There are studies underlining the role of Th17 lymphocytes activation and IL17a concentration increase in pathogenesis of depression. [27]. Other studies suggest potential importance of IL17 and Th17 activation in atherosclerotic plaque destabilization process [26, 28]. Therefore the role of IL17a in post-MI depression pathogenesis could be an interesting area for future studies.

Depressive episodes (especially major depression according to American classification) are connected with immune system activation with the increase of pro-inflammatory cytokines, mainly IL6 [29–31]. In the presented study we did not find significant difference in this cytokine concentration according to presence of depression. Few factors could play a role here. One of them is long lasting post-MI increase of IL6 observed in other studies [22, 23] and the second is mild intensity of depressive symptoms in our study group.

No significant differences concerning age and BMI between all analyzed groups eliminated potential influence of these factors on values of cytokines concentrations. Higher proportion of women in control group compared to the group of all patients after MI does not change our interpretation of results. Most studies show no significant gender differences concerning tested cytokines concentrations [32], some of them suggest even higher values (e.g. IL6) in women [33, 34].

Comparing analyzed subgroups one should remember that in depression group only small number of patients fulfilled the diagnostic criteria for major depression (4 patients, 14%), in most cases minor depression was diagnosed (24 patients, 86%). Therefore the obtained results should be referred generally to minor depression. Intensity of depression measured with HAMD and BDI was mild or minimal in most cases which could result in lack of significant differences between subgroups. According to studies the level of cytokines probably depends on severity of depression symptoms [10, 29].

A limitation of this study is the small number of patients in each group, non-normal data distribution and fair number of "zero" results. All mentioned factors weakened statistical power of conducted tests. It should also be noted that our flow cytometry method combined with Flex Set technology (simultaneous analysis of many proteins) has technical limitations. They result from fixed limits of detection in studied samples. In case of cytokines like TNF-α, IL-12p70, IL-17a, which appear in very low concentrations in physiological state, their detection is more difficult and the values might get close to zero [35–37]. Irrespective of described limitation this method allowed us to conduct quantitative analysis of cytokine concentrations in most patients which suggest that tests were well performed and samples properly stored.

Conclusions

Plasma pro-inflammatory cytokine concentrations increase in patients after myocardial infarction as a result of immune system activation.

We did not find significant differences in concentrations of inflammatory process indicators in groups distinguished according to the presence of depression. Comparing study groups with controls, however, can suggest that immune activation in depression group lasts longer. This applies especially to IL17a. Considering all listed limitations of the study this suggestion should be considered with caution.

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