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MARKERS OF LOW-GRADE INFLAMMATION IN PATIENTS WITH ACUTE CORONARY SYNDROME AND 2 TYPE DIABETES MELLITUS

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Cardiovascular diseases cause approximately one-third of all deaths in the world, of which 7.5 million deaths are estimated to be due to ischemic heart disease (IHD). Acute coronary syndromes (ACS) and sudden death cause most IHD-related deaths, which represent 1.8 million deaths per year. Established, that patients with diabetes mellitus (DM) are more likely to experience of ACS and heart failure and are at greater risk for dying after an acute cardiac event, than patients without diabetes.

***The purpose of this study** is evaluation of leukocyte and its populations count, leukocytes indices and plasma level of high sensitive C-reactive protein (hsCPR) in patients hospitalized due to ACS with or without of 2 type DM.*

***Material and Methods.** We observed of 124 patients with ACS which were randomized into two groups: 1st group – 93 patients with ACS and DM; 2nd group – 31 patients with ACS without 2 type DM. 30 apparently healthy persons were included into control group. We studied of leukocytes count and their subpopulations in blood; calculated of their subpopulation indices: neutrophils to lymphocytes ratio (NLR), neutrophils to monocytes ratio (NMR), neutrophils to lymphocytes+monocytes ratio (N/LMR), lymphocytes to monocytes ratio (NMR) at admission. The plasma levels of hs-CRP were detected by ELISA method.*

***Results of study.** The significant increase of white blood cells count and neutrophils count in patients with ACS at admission was detected in our study, especially in cases with DM. On the contrary, the counts of lymphocytes were decreased in patients with ACS and ACS with 2 type DM, versus data in control group. In patient with ACS the increased parameter of NMR was observed ($p<0.001$). Similarly, the following indices were higher, compared with control group parameters: NLR – for 3.32 times (in patients with ACS and DM) and for 2.43 times (in patients with ACS and without DM) ($p<0.001$); N/LMR – for 2.98 times (in patients with ACS and DM) and for 2.14 times (in patients with ACS and without DM) ($p<0.001$). On the contrary, LMR was decreased in both groups of patients with ACS – for 1.4 times*

and 1.36 times, respectively (p<0.05). The increased plasma levels of hs-CRP were detected in patients with ACS, more significant – in case of 2 type DM (fig. 1): for 2.1 times and for 2.59 times, respectively (p<0.001).

Conclusion. *ACS is characterized of raised white blood cells and neutrophils count and low lymphocyte count, especially in cases of association with 2 type Diabetes Mellitus. Low-grade inflammation in patients with ACS and DM caused of increased levels of hs-CRP and some leukocyte ratios: NMR, N/LMR, NLR.*

Key words: *diabetes, acute coronary syndrome, inflammation, leukocyte indices, C-reactive protein.*

Introduction. Diabetes mellitus (DM) has been recognized by the World Health Organization (WHO) as one of the four major non-communicable diseases that should attract urgent attention from all key shareholders; seen as the third highest risk factor for worldwide premature mortality due to hyperglycaemia [1]. The last epidemiological data from the International Diabetes Federation (IDF) suggests that about 415 million people live with DM in the world with a prevalence rate of 8.8% (of this, 75% live in low and middle income countries). It is estimated that by 2040, about 642 million people will be diabetic with type 2 DM as the major type of diabetes [2].

Cardiovascular diseases cause approximately one-third of all deaths in the world, of which 7.5 million deaths are estimated to be due to ischemic heart disease (IHD). Acute coronary syndromes (ACS) and sudden death cause most IHD-related deaths, which represent 1.8 million deaths per year [3].

Established, that patients with DM are more likely to experience of ACS and heart failure and are at greater risk for dying after an acute cardiac event, than patients without diabetes. Recent meta-analysis of 9 case-control and 10 cohort studies with data for 10 856 279 individuals and at least 106 703 fatal and nonfatal ACS events showed that in patients with DM compared with those without this disease, women had a significantly greater risk of ACS. The pooled maximum-adjusted RR of ACS associated with DM was 2.46 (95% CI, 1.92-3.17) in women and 1.68 (95% CI, 1.39-2.04) in men [4]. Furthermore, among patients with ACS, those with DM are at particularly high risk of recurrent cardiovascular events and premature death. The registry data from real-life clinical practice (a total of 10 registries provided data in a systematic manner on ACS patients with DM (total *n* =28 899), and without DM (total n= 97 505)) showed pooled risk ratios comparing cohorts with DM vs. no DM were in-hospital significantly higher in DM for all-cause death (1.66; 95% CI 1.42–1.94), for cardiovascular death (2.33; 1.78-3.03), and for major bleeding (1.35; 1.21–1.52) [5].

Table 1. White blood cells and their subpopulation count in patients with ACS

Parameters	**Control group, n=30**	**Patients with ACS, n=124**	
		ACS+DM, n=93	**ACS, n=31**
Leukocytes, x 10^9 perliter	5.41 [5.16; 5.74]	10.95 [9.35; 11.89] p_1-p_2<0.001	8.73 [6.87; 10.44] p_1-p_3<0.01 p_2-p_3<0.05
Neutrophils, x 10^9 perliter	3.61 [3.34; 3.96]	9.42 [7.42; 9.88] p_1-p_2<0.001	7.14 [5.28; 8.56] p_1-p_3<0.001 p_2-p_3<0.05
Lymphocytes, x 10^9 perliter	1.47 [1.31; 1.59]	1.17 [1.03; 1.35] p_1-p_2<0.01	1.21 [1.11; 1.35] p_1-p_3<0.05 p_2-p_3>0.05
Monocytes, x 10^9 perliter	0.34 [0.29; 0.37]	0.38 [0.29; 0.51] p_1-p_2>0.05	0.37 [0.27; 0.48] p_1-p_3>0.05 p_2-p_3>0.05

Many studies have shown that low-grade inflammation is associated with the risk of developing type 2 DM. Although the mechanism through which chronic inflammation stimulate the development of type 2 DM is not well understood, however, it has been observed that adipose tissue can synthesize main pro-inflammatory cytokines and chemokines, and that inflammatory biomarkers are linked with body fat mass, suggesting that activated innate immunity and inflammation are important biological factors in the pathogenesis of DM and in the complications of type 2 DM [1].

Similarly, the chronic low-grade inflammation plays a key role in the initiation and development of the atherosclerotic plaque, which subsequently leads to the plaque's instability with a thrombus formation [6]. In recent years, a strong interest has been drawn to different inflammatory markers (such as leukocyte count and indices, cytokines and chemokines levels in blood etc) given that they may provide independent information on pathophysiology, risk stratification, and optimal management. Furthermore, many studies have pointed at their effective prognostic value in all-cause mortality, major cardiovascular events, stent thrombosis, arrhythmias, and myocardial perfusion disorders in terms of ACS.

The purpose of this study is evaluation of leukocyte and its populations count, leukocytes indices and plasma level of high sensitive C-reactive protein (hsCPR) in patients hospitalized due to ACS with or without of 2 type DM.

Material and Methods. In this observational cohort trial, we observed of 124 patients with ACS in period from 1 January 2020 to 30 July 2020, which were hospitalized at Ivano-Frankivsk Regional Cardiology Center, Ivano-Frankivsk Central City Hospital and Kyiv National Institute of Cardiovascular Surgery (Ukraine). The diagnosis of ACS was verified by laboratory and instrumental methods according to European Society of Cardiology guidelines (2017, 2020) [7, 8]. The diagnosis of DM was verified by laboratory and instrumental methods according to American Diabetes Association guidelines (2020) [9]. All patients were randomized into two groups: 1st group - 93 patients with ACS and DM; 2nd group – 31 patients with ACS without 2 type DM. 30 apparently healthy persons were included into control group.

Table 2. White blood cells indices in patients with ACS and DM

Parameters	**Control group, n=30**	**Patients with ACS, n=124**	
		ACS+DM, n=93	**ACS, n=31**
NMR	10.68±0.53	23.74±2.14 p_1-p_2<0.001	19.21±1.93 p_1-p_3<0.001 p_2-p_3>0.05
LMR	4.31±0.18	3.08±0.13 p_1-p_2<0.05	3.18±0.14 p_1-p_3<0.05 p_2-p_3>0.05
NLR	2.43±0.09	8.07±0.13 p_1-p_2<0.001	5.91±0.12 p_1-p_3<0.001 p_2-p_3<0.05
N/LMR	2.04±0.05	6.07±0.12 p_1-p_2<0.001	4.37±0.11 p_1-p_3<0.001 p_2-p_3<0.05

We studied of leukocytes count and their subpopulations in blood; calculated of their subpopulation indices: neutrophils to lymphocytes ratio (NLR), neutrophils to monocytes ratio (NMR), neutrophils to lymphocytes+monocytes ratio (N/LMR), lymphocytes to monocytes ratio (NMR) at admission. The plasma levels of hs-CRP were detected by ELISA method.

The study was performed in accordance with the Good Clinical Practice Guideline and Helsinki Declaration. The written informed consent was obtained from all patients and this study was approved by the local ethics committee. Categorical variables are presented as percentages, whereas continuous variables are presented as mean (M) and standard error of mean (m) if normally distributed, or as median and interquartile range (Me [IQR]), if not. Categorical variables were compared by the χ^2 test and continuous va-

riables by the t test or the Mann–Whitney U test. The p value of <0.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with Statistica system software, version 12.0.

Results of study. The mean age of all observed patients with ACS was (67.3±10.4) years; 63 (50.8%) were males and 61 (49.2%) females among them. ACS without persistent ST segment elevation was diagnosed in 24 (19.4%) cases; instead ACS with persistent ST segment elevation – in 100 (80.6%) cases.

The significant increase of white blood cells count and neutrophils count in patients with ACS at admission was detected in our study, especially in cases with DM (table 1). On the contrary, the counts of lymphocytes were decreased in patients with ACS and ACS with 2 type DM, versus data in control group.

In patient with ACS the increased parameter of NMR was observed (table 2): 19.21±1.93 – without DM; 23.74±2.14 – with DM (versus, 10.68±0.53 – in control group; p<0.001). Similarly, the following indices were higher, compared with control group parameters: NLR – for 3.32 times (in patients with ACS and DM) and for 2.43 times (in patients with ACS and without DM) (p<0.001); N/LMR – for 2.98 times (in patients with ACS and DM) and for 2.14 times (in patients with ACS and without DM) (p<0.001). On the contrary, LMR was decreased in both groups of patients with ACS – for 1.4 times and 1.36 times, respectively (p<0.05).

The increased plasma levels of hs-CRP were detected in patients with ACS, more significant – in case of 2 type DM (fig. 1): for 2.1 times and for 2.59 times, respectively (p<0.001).

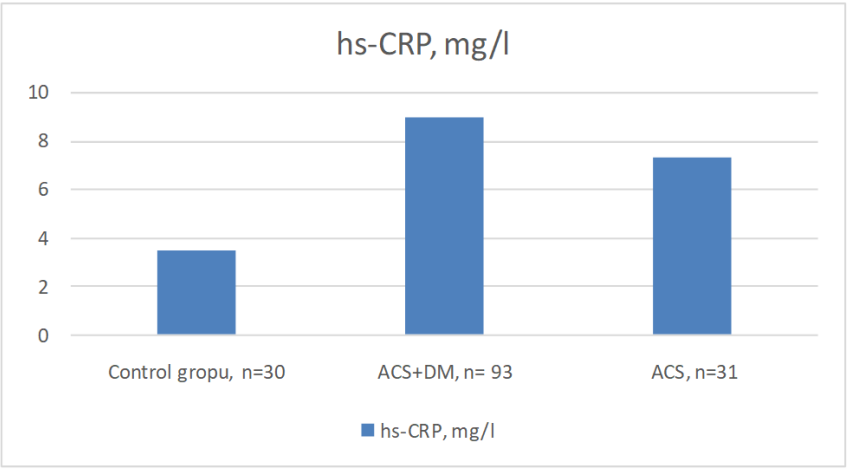

Fig.1. The plasma levels of hs-CRP in patients with ACS (differences with control group ** - p<0.001; with ACS patients' group # - p<0.05)

Discussion. The earlier studies demonstrated an association between WBC and MACE in patients with ACS. In the multicenter, prospective, observational PARIS study (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients Registry) was established, that after adjustment for baseline and procedural characteristics, WBC remained independently associated with MACE (hazard ratio [HR] per 10^3 cells/μL increase, 1.05 [95% confidence intervals (CI), 1.02–1.09]; *P*=0.001), cardiac death (HR, 1.10 [95% CI, 1.05–1.17]; *P*<0.001), and clinically indicated target revascularization (HR, 1.04 [95% CI, 1.00–1.09]; *P*=0.03) but not stent thrombosis (HR, 1.07 [95% CI, 0.99–1.16]; *P*=0.10) or spontaneous myocardial infarction (HR, 1.03 [95% CI, 0.97–1.09]; *P*=0.29) [10].Different trials have showed that elevated neutrophil counts in patient with ACS is associate with worse outcome [11]. For our opinion, the increased counts of white blood cells and neutrophils in patients with concomitant 2 type DM could be indicator of high level of chronic low-grade inflammation in this cohort and predictor of worse outcome.

The results of our study showed of decline of lymphocytes counts in patients with ACS with or without concomitant DM. Several trials showed that low lymphocyte count in patients with ACS is associated with poor outcomes; conversely, high lymphocyte count reflect a strong immune response and better prognosis [12].

Last meta-analysis of 8 studies with 9406 patients indicated that elevated pretreatment NLR was a poor prognostic marker for patients with recent ACS in predicting medium to long-term mortality/MACEs (OR 1.26, 95%CI 1.13–1.41). This analysis showed that higher pretreatment NLR value was associated with higher in-hospital mortality in ACS patients (OR 6.39, 95%CI 1.49–27.38, $p < 0.001$); and NLR value of 5.0 maybe a cut-off value for ACS risk [13].

The LMR is a combination of two independent markers of inflammation, and is a novel systemic inflammatory marker. Recently studies showed the association of LMR with no-reflow phenomenon and in-hospital adverse outcomes in patients who underwent a primary percutaneous coronary intervention for ST-elevation MI; and with the severity of coronary atherosclerosis [14].

The high levels of hs-CRP in blood in patients with ACS is an independent marker of poor prognosis. The recent meta-analysis of 13 trials enrolling 30,289 patients with ACS showed that elevated blood concentration of CRP may be independently associated with higher risk of MACE, cardiovascular and all-cause mortality in these patients [15].

Conclusion. ACS is characterized of raised white blood cells and neutrophils count and low lymphocyte count, especially in cases of association with 2 type Diabetes Mellitus. Low-grade inflammation in patients with ACS

and DM caused of increased levels of hs-CRP and some leukocyte ratios: NMR, N/LMR, NLR.

Perspectives of future research is evaluate of different pharmacological strategies influence for low-grade inflammation course in patients with ACS and 2 type DM.

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МАРКЕРИ ЗАПАЛЕННЯ НИЗЬКОЇ ІНТЕНСИВНОСТІ В ХВОРИХ НА ГОСТРИЙ КОРОНАРНИЙ СИНДРОМ ТА ЦУКРОВИЙ ДІАБЕТ ДРУГОГО ТИПУ

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Серцево-судинні захворювання обумовлюють близько третини смертей у світі, причому, 7,5 млн. смертельних випадків виникають унаслідок ішемічної хвороби серця (ІХС). Гострі коронарні синдроми (ГКС) та раптова серцева смерть є найбільш частою причиною ІХС-залежних смертей; складають 1,8 млн летальних випадків щорічно. Встановлено, що хворі на цукровий діабет 2 типу (ЦД) часто хворіють на ГКС та серцеву недостатність, а також мають вищий ризик гострих серцево-судинних подій.

***Метою дослідження** була оцінка вмісту в крові лейкоцитів та їх субпопуляцій; лейкоцитарних індексів та концентрації високочутливого С-реактивного протеїну (СРП).*

Матеріали та методи. *Було обстежено 124 пацієнти із ГКС, рандомізованих у дві групи: перша група – 94 хворі на ГКС та супутній ЦД; друга група – 31 хворих на ГКС без ЦД. 30 практично здорових осіб склали контрольну групу. Вивчали показник лейкограми, обчислювали лейкоцитарні індекси: індекс співвідношення нейтрофілів до лімфоцитів (ІНЛ), індекс співвідношення нейтрофілів до моноцитів (ІНМ), індекс співвідношення лімфоцитів до моноцитів (ІЛМ) та індекс співвідношення нейтрофілів до лімфоцитів та моноцитів (ІН/МЛ). Плазові рівні СРП визначали методом ІФА.*

Результати дослідження. *Вірогідне підвищення кількості лейкоцитів та нейтрофілів виявлене у хворих на ГКС, більш виразніше – за умови супутнього ЦД 2 типу. На противагу, кількість лімфоцитів у таких пацієнтів була вірогідно нижчою, ніж у групі контролю. У хворих на ГКС із чи без ЦД відмічене підвищення ІНМ (p<0.001). Подібно, порівняно з практично здоровими особами, наступні співвідношення були вищими при ГКС: ІНЛ – у 3,32 рази (в хворих на ГКС та ЦД) та в 2,43 раза (у хворих на ГКС без ЦД) (p<0,001); ІН/ЛМ – у 2,98 рази (при поєднанні ГКС та ЦД) та в 2,14 рази (у хворих на ГКС без супутнього ЦД) (p<0,001). На противагу, ІЛМ був нижчим у обох групах обстежених хворих на ГКС: у 1,4 рази та 1,36 рази, відповідно (p<0,05). Підвищені плазмові рівні СРП були визначені в хворих на ГКС, більш вірогідно – за у мови супутнього ЦД 2 типу (p<0,001).*

Висновки. *ГКС характеризується підвищеним вмістом у крові лейкоцитів та нейтрофілів, а також – зниженням кількості лімфоцитів, особливо при супутньому ЦД. Низько-інтенсивне запалення в хворих на ГКС та ЦД 2 типу характеризується зростанням рівнів СРП у крові та окремих лейкоцитарних індексів: ІНМ, ІН/ЛМ, ІНЛ.*

Ключові слова: *цукровий діабет, гострий коронарний синдром, запалення, лейкоцитарні індекси, С-реактивний протеїн.*