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Associations between basic indicators of inflammation and metabolic disturbances*

Związek między podstawowymi parametrami stanu zapalnego i zaburzeniami metabolicznymi

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Abstract

Background: Inflammation is involved in initiation and progression of diabetic complications related to cell damage of tissues, especially endothelial cells, and deepening of metabolic disturbances. This study was conducted in order to assess potential associations between basic laboratory parameters of inflammation and common metabolic factors such as glycated hemoglobin and C-reactive protein.
Materials and methods: The studied group consisted of 95 patients with diabetes mellitus type 2 and 77 subjects without signs of disturbances in glucose metabolism, aged between 40 and 74 years. Fasting plasma glucose, glycated hemoglobin, complete blood count and high-sensitivity C-reactive protein concentration in blood were determined. Also blood pressure as well as weight and height measurements were taken to calculate BMI.
Results: Fasting plasma glucose and glycated hemoglobin concentrations, total leukocyte count and granulocytes were significantly higher in diabetics. Significant correlations between both glycated hemoglobin and BMI and C-reactive protein concentration were noted. However, after adjusting for age and gender, leucocyte count was independently related to BMI and glycated hemoglobin, while C-reactive protein concentration was dependent on gender and BMI.
Conclusion: Glycated hemoglobin as a marker of long-term glycemic control and BMI as an indicator of adipose tissue accumulation are significantly related to white blood cell count and C-reactive protein concentration, even when values of these parameters are in the normal range. This is consistent with the hypothesis that chronic activation of the immune system plays a role in the pathogenesis and progression of type 2 diabetes.

Key words: **Diabetes mellitus • body mass index • leukocytes • C-reactive protein**

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List of abbreviations: **AGE** – advanced glycation end products, **ARIC** – the Atherosclerosis Risk in Communities Study (ARIC), **BMI** – body mass index, **CI** – confidence interval, **CRP –** C-reactive protein, **FPG** – fasting plasma glucose, **GRAN** – granulocytes, **Hb** – hemoglobin, **HbA1c** – hemoglobin A1c, **HOMA-IR** – Homeostasis Model Assessment – Insulin Resistant Index, **hsCRP** – high-sensitivity C-reactive protein, **Ht** – hematocrit, **LYM** – lymphocyte count, **MON** – monocyte count, **PLT** – platelet count, **PTCA** – percutaneous transluminal coronary angioplasty, **RAGE** – receptor for advanced glycation end products, **RBC** – red blood cell count, **ROS** – reactive oxygen species, **T2D** – diabetes mellitus type 2, **UKPDS** – the United Kingdom Prospective Diabetes Study, **WBC** – white blood cell count.

Introduction

Inflammation is activated in response to a variety of pathological stimuli. It allows restoration of homeostasis. However, under pathological conditions development of a inflammatory process may cause various metabolic disturbances [38]. On the other hand, chronic metabolic disturbances can lead to immune imbalance and promote development of a chronic inflammatory state. Metabolic imbalance can induce starvation and immunosuppression on one hand and obesity and inflammatory diseases on the other hand [31,33]. Chronic low-grade inflammation often occurs in humans from highly industrialized societies and is associated with widespread unhealthy lifestyle [24]. Environmental factors, such as diet, physical activity, smoking and stress, are responsible for the phenomenon of subclinical inflammation and are involved in pathogenesis of such diseases as obesity, hypertension, atherosclerosis and diabetes [3,4,6,8].

Diabetes is a chronic metabolic disease, and the number of people suffering from it, especially type 2 diabetes (T2D), is constantly increasing up to the worldwide epidemic scale [1]. The inflammatory process plays a crucial role in the pathogenesis of T2D and precedes the onset of diabetes. Furthermore, subclinical inflammation contributes to further deepening of metabolic disturbances and finally development of vascular diabetic late complications [23,38], which are the major cause of morbidity and mortality in diabetic patients [22]. Hyperglycemia, the major feature of diabetes, results in disturbances in cellular metabolism due to cell hypoxia, increased production of reactive oxygen species (ROS) and nonenzymatic glycation of many macromolecules, leading to changes in their structure and function, and finally to formation of advanced glycation end products (AGE), which secondarily in different ways, e.g. via interaction with the specific receptor for AGE (RAGE), can further enhance metabolic disturbances and also increase ROS production [3,12,21]. Overproduction of free radicals and signaling proteins triggers changes leading to activation of the immune system and finally inflammation [2]. Moreover, excess of adipose tissue is also related to disturbances in carbohydrate metabolism. The body mass index (BMI) is not only used for assessment of weight categories but also provides a reliable indicator of body fatness for most people [20]. In obese people, with BMI above 30 kg/m^2, inflammation is considerably increased [8]. Numerous adipose cytokines interfere with insulin signaling in target cells, especially in cells with insulin-dependent glucose transport, leading to insulin resistance and in consequence development of diabetes [34]. The same adipocytokines, released from adipose tissue, also influence leukocyte count and interfere with their function [31].

The development of inflammation in the human organism can be assessed by different markers. The most popular in laboratory practice is estimation of leukocyte number, referred to as white blood cell (WBC) count. The number of leucocytes, especially the number of neutrophils, increases in response to inflammation because these cells represent a main part of the innate immune system. They are also a source of cytokines and free radicals released intercellularly and to the surrounding tissues, which in turn enhance the development of inflammation and metabolic disturbances. Long-term hyperglycemia, reflected by an enhanced level of glycated hemoglobin (HbA1c), also changes metabolism of neutrophils and causes their activation, increases their interactions with other cells and prolongs their circulation time in the blood stream [23]. Another commonly used indicator of inflammation is C-reactive protein (CRP), which is produced in the liver in response to acute and chronic inflammation related to infection or injury. CRP (determined as high-sensitivity CRP – hsCRP) has been also recognized as a good epidemiological predictor of the risk of cardiovascular diseases [16].

Various markers of inflammation have been investigated in different groups of patients with T2D, but frequently only modest correlations were observed between markers of inflammation and the degree of abnormalities in glucose level [5,7,18,35]. This may indicate the difficulty of characterizing a low-grade systemic inflammatory state on the basis of a single marker of inflammation. For this reason, the purpose of our study was to explore the association between two basic indicators of inflammation, WBC count and hsCRP concentration, and HbA1c as a marker of glycemic control in diabetics and BMI as

a marker of adipose tissue accumulation in middle-aged patients with and without diabetes.

Materials and Methods

This study was performed in the Department of Professional Training in Clinical Chemistry at the Medical University of Wroclaw. All patients included in this study were referred by a primary care physician and recruited among patients of the Teaching Medical Diagnostics Laboratory of Wroclaw Medical University and also among patients of the Regional Specialist Outpatient Clinic of Wroclaw. The total number of referred patients was 172 subjects in the one-year study period. All the participants were informed about the purpose of this study and written consent was obtained for each one. The study protocol was approved by the Ethics Committee of Wroclaw Medical University. At first, all participants completed the questionnaire including information on age, disease status, medication, physical activity, and smoking habits. Moreover, height and weight were measured under fasting conditions in subjects in light clothing and without shoes. Blood pressure was also measured under resting conditions. Patients with known acute infection, chronic inflammatory disease, renal and/or hepatic failure and any other systemic disease were not enrolled in this study. Smokers and chronic alcohol consumers were also excluded. Furthermore, the study was restricted to patients with WBC count and C-reactive protein concentration within a normal range: 4.0–10.0 G/L for WBC and 0.05-20.0 mg/L for hsCRP. Finally, 172 participants (63 male and 109 female) aged between 40 and 74 years were included in our study. Ninety-five of these (54 female and 41 male) had been diagnosed for type 2 diabetes mellitus, and in 77 participants (55 female and 22 male) no signs of disturbances in glucose metabolism were found. Diabetic patients had remained on unchanged hypoglycemic treatment for the last half year. Fifty of them received only oral agents, 14 were insulin-treated, and 31 received mixed therapy (both oral agents and insulin). Diabetic vascular late complications (micro- and macroangiopathy) were present in 28 of them. The more detailed characteristics of participants enrolled in this study are presented in Table 1.

In the morning (between 8:00 and 9:30 am) from each patient after 8-12 h overnight fasting vein blood samples were taken into a tube without any anticoagulant for serum preparation and to determine biochemical parameters and into three tubes containing EDTA for the determination of glycated hemoglobin, hematological parameters and glucose concentration. Serum CRP (hsCRP) concentration was determined using the ultrasensitive immunoturbidimetric assay DiaSys (Holzheim Germany). One EDTA tube was centrifuged immediately after blood sampling, plasma was transferred to a second tube and fasting plasma glucose (FPG) measurement was performed within two hours, using the GOD-POD method with reagents obtained from Thermo Scientific (Waltham, USA). The second tube was used to assess hemoglobin A1c by the immunoturbidimetric method with a reagent obtained from DiaSys (Holzheim Germany). Glucose, HbA1c and hsCRP assessments were performed using the automated analyzer Konelab 20i (Thermo Scientific, Waltham USA). The third tube was used for complete blood count determination using a 3-DIFF automated cell counter, Cell-Dyn 1700 (Abbott, Illinois USA), within 2 h after blood sampling.

Statistical analysis was performed using Statistica PL v.10. Distributions of variables were assessed by the Kolmogorov-Smirnov test. Because of skewed distribution of several parameters (see Table 1), their values were logarithmically transformed before statistical analysis to approximate normal distributions. Data are expressed as mean and standard deviation for continuous variable, as geometric mean for logarithmically transformed variables with 95% CI (confidence interval), and as median with interquartile interval for skewed variables. Student's t-test was used to evaluate differences between variables with normal distribution. For fasting glucose concentration and monocyte count, logarithmic transformation was not effective to obtain normal distribution of variables; therefore the nonparametric Mann-Whitney U-test was used. Pearson's correlation coefficient was calculated in order to assess the relationship between inflammatory markers (WBC and hsCRP), and other clinical parameters. Furthermore, multiple regression analyses were performed to assess independent relationships between inflammatory markers and other statistically significant associations after adjusting for appropriate covariates. A p-value less than 0.05 was accepted as statistically significant.

Results

The results of clinical and laboratory assays performed in blood samples of participants enrolled in the study are presented in Table I. When patients with documented diabetes mellitus type 2 and subjects without the disease were compared, significant differences not only in plasma glucose and HbA1c concentrations but also in total WBC count as well as granulocyte (GRAN) subpopulations were found. The levels of these parameters were enhanced by about 15%, 22%, 55% and 36% for WBC, GRAN, FPG and HbA1c, respectively, in diabetics. Differences in values of blood pressure and other hematological parameters were not statistically significant.

Results of correlation analyses between WBC count and hsCRP concentration (expressed as logarithm hsCRP) as basic indicators of inflammation and other analyzed parameters in studied subjects are shown in Table 2. Statistically significant correlations between WBC count and CRP concentrations and HbA1c and BMI were observed. The strongest correlations were noted between WBC count and HbA1c ($r = 0.39$, $p<0.001$) as well as WBC count and BMI ($r= 0.29$, $p=0.001$). Weaker, but still significant, relationships were also observed between hsCRP and BMI ($r=0.26$, $p=0.014$) and hsCRP and HbA1c ($r = 0.22$, $p=0.016$). Multiple regression analysis was used to examine whether the above relationships between inflammatory markers

Table 1. Clinical and biochemical characteristics of the participants (all, with and without diabetes) enrolled to the study

Parameter	All participants	Participants with type 2 diabetes	Participants without type 2 diabetes	p-value
Number of subjects (n)	172	95	77	-
Female/Male (n/n)[a]	109/63	54/41	55/22	0.48
Age (years)[b]	60 ± 12	62 ± 12	57 ± 12	0.002
Weight (kg)[b]	78.2 ± 14.6	78.9 ±	77.3 ± 14.4	NS
Hight (cm)[b]	165.8 ± 8.5	166.0 ± 8.1	165.2 ± 9.3	NS
Diabetes duration (years)[b]	-	9.5 ± 7.8	-	-
Body Mass Index (kg/m2)[b]	28.9 ± 4.8	29.5 ± 4.9	27.9 ± 4.6	NS
Systolic blood pressure (mmHg) [b]	135 ± 25	130 ± 25	140 ± 20	NS
Diasystolic blood pressure (mmHg) [b]	80 ± 10	80 ± 20	85 ± 15	NS
RBC (T/L)[b]	4.66 ± 0.48	4.67 ± 0.51	4.66 ± 0.43	NS
Hb (g/dL) [b]	13.6 ± 1.5	13.7 ± 1.7	13.5 ± 1.3	NS
Ht (%) [b]	41.2 ± 4.1	41.3 ± 4.7	41.11 ± 3.4	NS
PLT (G/L) [b]	237 ± 63	231 ± 76	243 ± 47	NS
WBC (G/L) [b]	6.64 ± 1.59	7.00 ±1.559	6.24 ± 1.52	0.002
GRAN(G/L) [b]	3.86 ± 1.2	4.14 ±1.2	3.53 ± 1.14	< 0.001
MON(G/L) [d]	0.40 (0.40-0.60)	0.50 (0.40-0.60)	0.40 (0.40-0.60)	NS
LYM(G/L) [b]	2.29 ± 0.59	2.33 ± 0.63	2.22 ± 0.54	NS
FPG (mmol/L)[d]	5.8 (5.0-7.4)	7.9 (6.7-12.0)	5.1 (4.7-5.5)	<0.001
HbA1c (%) [c]	6.44 (5.15-7.72)	7.28 (5.96-8.59)	5.55 (4.48-6.61)	<0.001
hsCRP (mg/L) [c]	3.11 (2.84-3.8)	2.02 (1.54-3.2)	1.59 (1.21-2.43)	NS

Data are presented as: [a] proportions (frequency) for categorical variables. $\chi 2$ test was applied; [b] mean ± SD for continues variables, t-Student test was applied; [c] geometrical mean for continues skewed variables (95% CI (Confidence Interval), t-Student test was applied; [d] median (interquartile range), U Mann-Whitney test was applied; p-value for variables compared between participants with and without diabetes.

and selected markers of metabolic disturbances remain significantly correlated after adjusting for covariates such as age and gender. We constructed two models: in Model 1, inflammation markers were adjusted for age, gender, BMI and HbA1c, whereas in Model 2 these parameters were adjusted for age, gender, BMI and presence of diabetes, instead of HbA1c level. Results of these analyses are shown in Table 3. The effect of age and gender was found to be irrelevant for WBC. White blood cell count was independently associated with HbA1c ($\beta = 0.35$, $p<0.001$) and BMI ($\beta = 0.19$, $p=0.022$) when the variables were adjusted for age and gender (Model 1). This model explains 24% ($R^2 = 0.24$) of observed changes of WBC count. However, in Model 2, occurrence of diabetes per se was not significantly related to the number of leukocytes ($\beta = 0.14$, $p>0.05$), but BMI remained still significantly correlated with WBC count ($\beta = 0.26$, $p<0.002$). This model explains 15% ($R^2 = 0.15$) of observed variability of WBC count. The same two models were used for analyzing hsCRP concentration. Whereas age was found to be irrelevant, gender turned out to be a significant factor influencing this parameter. In both models hsCRP concentration was also significantly correlated only with BMI (for Model 1 $\beta = 0.37$, $p<0.001$ and for Model 2 $\beta = 0.39$, $p<0.001$) and similar determination coefficient values were observed ($R^2 = 0.21$ and $R^2 = 0.20$, respectively).

Fig. 1 presents relationships between three factors, WBC, HbA1c and BMI, for which a significant correlation was observed in multiple regression analysis. The highest number of white blood cells was found in subjects with a high HbA1c level and high BMI. This may indicate that increased BMI and HbA1c are independently related to increased number of WBC.

Table 2. Results of correlation analysis between inflammatory markers and other examined parameters in all participants

Inflammatory markers	Variables	Correlation coefficient	p - value
WBC	ln HbA1c	0.39	< 0.001
	BMI	0.29	0.001
ln hsCRP	ln HbA1c	0.22	0.016
	BMI	0.26	0.014

Table 3. Results of multiple regression analysis of WBC count and hsCRP in all participants

Parmeters	WBC		hsCRP	
	β	p - value	β	p - value
Model 1	$R^2 = 0.24$		$R^2 = 0.21$	
Age	0.11	NS	-0.08	NS
Gender*	-0.02	NS	-0.30	**0.002**
BMI	0.19	**0.022**	0.37	**< 0.001**
HbA1c	0.35	**< 0.001**	0.12	NS
Model 2	$R^2 = 0.15$		$R^2 = 0.20$	
Age	0.08	NS	-0.045	NS
Gender*	-0.04	NS	-0.28	**0.005**
BMI	0.26	**0.002**	0,39	**<0.001**
Diabetes mellitus	0.14	NS	0.13	NS

In Model 1 parameters were adjusted for age, gender, BMI and HbA1c
In Model 2 parameters were adjusted for age, gender, BMI and prevalence of diabetes instead of HbA1c value;
In both models: * females as reference.

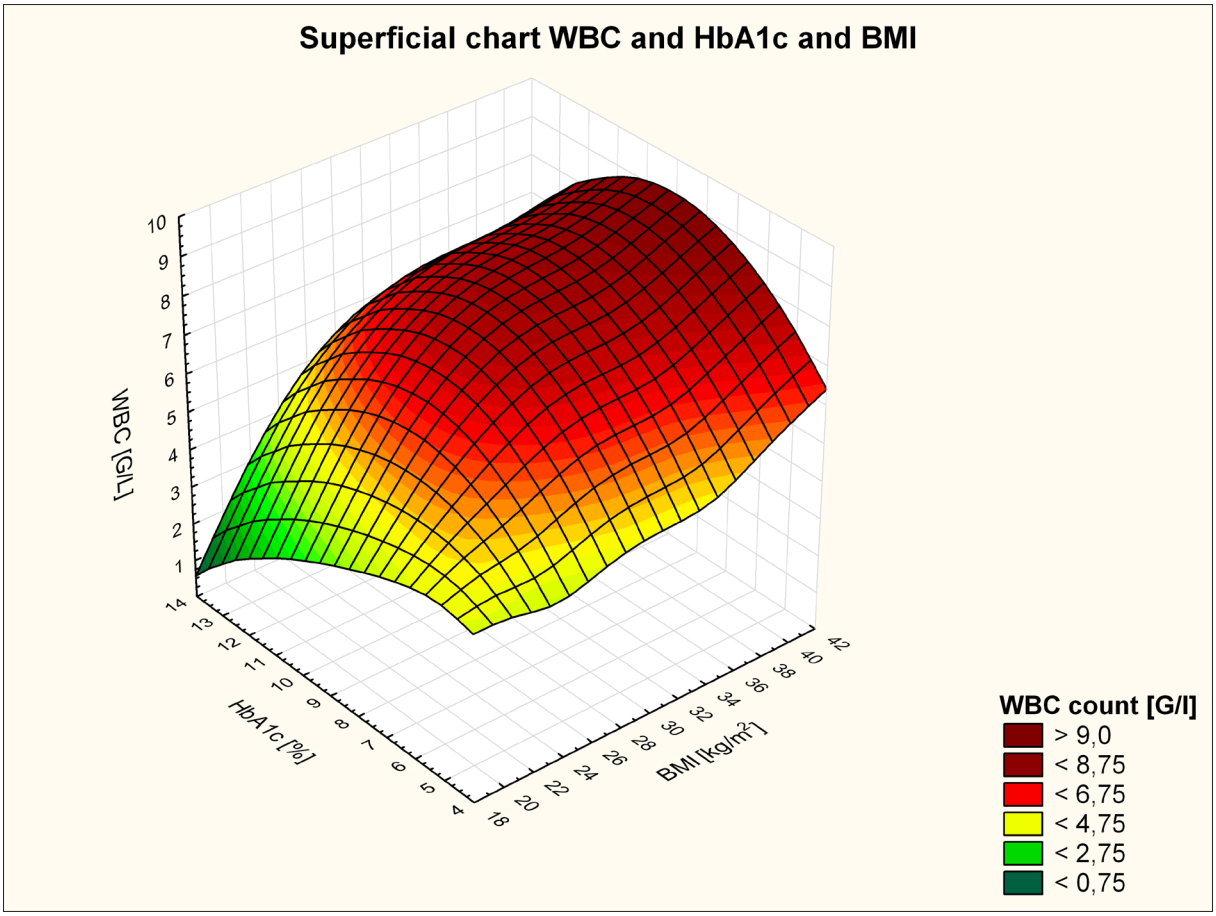

Fig. 1. Mutual relationship between WBC, HbA1c and BMI in all participants. (Different WBC count is reflected by appropriate colors); WBC – white blood cells count, HbA1c – hemoglobin A1c, BMI – Body Mass Index

In addition, the relationship between hsCRP, HbA1c and BMI is presented in Fig. 2. The concentration of hsCRP increases only with increasing BMI, but not when HbA1c level rises. In the whole range of examined HbA1c levels, both low and high hsCRP concentrations are observed.

Discussion

Chronic subclinical inflammation has been recognized to play a crucial role in both initiation and progression not only of type 2 diabetes but also cardiovascular diseases [13,14]. Metabolic disturbances related to diabetes and hyperlipidemia stimulate subclinical inflammation and production of many proinflammatory factors, which in turn possess the ability to worsen metabolic control. Therefore, it seems to be a vicious circle of disturbances [2]. In clinical practice, occurrence and intensity of inflammation may be assessed by determination of numerous biochemical parameters in the blood, such as CRP, interleukin-6, plasminogen activator inhibitor-1 and fibrinogen [9,37]. However, the most frequently used and cheap methods are estimation of white blood cell count and measurement of CRP concentration. In this study we examined the potential relation between hyperglycemia and BMI and WBC count and hsCRP concentration in middle-aged patients with and without diabetes, but without any acute inflammatory state as indicated by values of these parameters being in the normal range.

The Atherosclerosis Risk in Communities Study (ARIC) showed subclinical increase of some of these factors (IL-6, CRP, orosomucoid, sialic acid, fibrinogen concentration and white blood cell count) in smoking American people in middle age [7]. Numerous compounds occurring in tobacco smoke can damage cells and tissues, so smoking habit is a huge causative factor of inflammation [27]. For this reason, smokers were excluded from our investigations. In Pima Indians it was found that high WBC count predicted disturbances in insulin action and the development of type 2 diabetes [32]. Also a meta-analysis of cross-sectional and prospective studies of type 2 diabetic patients indicated a significant association between increased count of WBC and diabetes [13].

In our study, both WBC count and CRP concentration as markers of inflammation were higher in patients with diagnosed diabetes in comparison to those without diabetes. Total WBC count as well as granulocyte count was significantly different between these groups. We did not observe an increase in monocyte and lymphocyte count

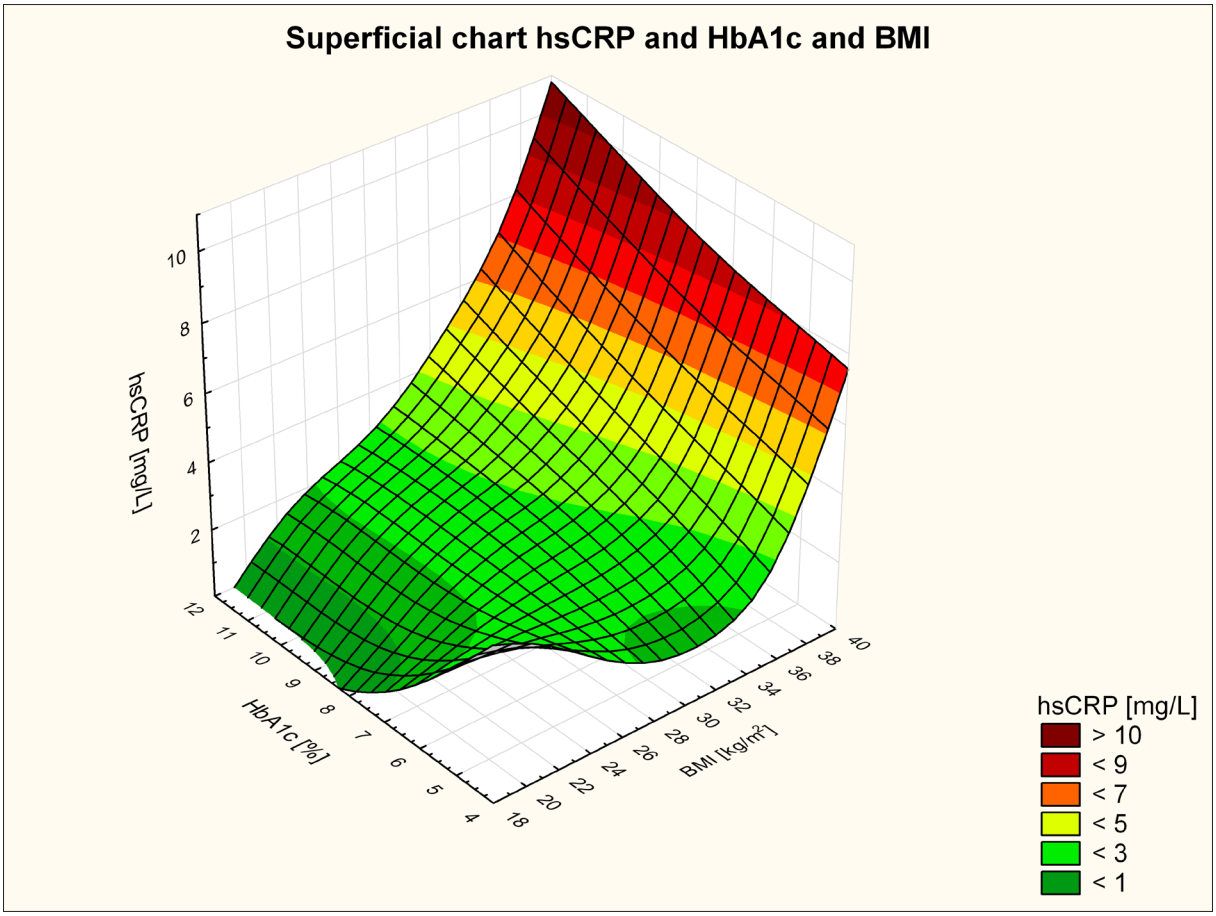

Fig. 2. Mutual relationship between hsCRP, HbA1c and BMI in all participants. (Different hsCRP concentration is reflected by appropriate colors); BMI – Body Mass Index, hsCRP – high sensitive C-reactive protein

in diabetics, but activation of these cells may occur without rising cell numbers [13]. The difference in hsCRP concentration was found to be not significant, although about 20% higher CRP levels were noted in diabetic participants. Our study was conducted in subjects with levels of inflammatory markers in the normal range; therefore, only occurrence of low-grade inflammation may be taken into account. The observed slight increase in the number of leukocytes is a result of an increased number of granulocytes. These cells take part in the immunological response to inflammation. Hyperglycemia affects leukocytes in different ways, e.g. by change of their metabolism, inhibition of their apoptosis and increasing cell mobilization from a marginal pool [23]. Moreover, AGE formed in hyperglycemic conditions, by interacting with RAGE receptors, located also on immunocompetent cells such as monocytes and macrophages, can stimulate them to increased secretion of proinflammatory cytokines [15].

C-reactive protein is currently recognized not only as an inflammatory marker but also as an epidemiological risk marker of cardiovascular diseases [25]. In our study, hsCRP concentration tended to be higher in the diabetes group, but the difference was not statistically significant, probably because of quite good glycemic control of our diabetic participants (Table 1). A rise in CRP concentration was observed in patients with documented disorders of carbohydrate metabolism and also in patients with a major risk factor of diabetes such as insulin resistance [5]. Also, investigations conducted in a Chinese population by Xu et al. [35] revealed a statistically significant increase of CRP concentration in subjects about 60 years old with impaired glucose tolerance and in diabetics as compared to subjects without any disturbance of carbohydrate metabolism. Additionally, CRP concentration and WBC count in this study were positively correlated with degree of insulin resistance, estimated by Homeostasis Model Assessment – Insulin Resistant Index (HOMA-IR).

Glycated hemoglobin is an established marker of long-term glycemic control, but data on its correlation with markers of inflammation are limited. In most publications, values of inflammatory markers are compared with a different state of carbohydrate disturbance reflected by glucose level [7,13,28,35], but only a few concern glycemic control measured by HbA1c [16,18]. A high level of HbA1c is associated with higher risk of micro- and macroangiopathy. A low-grade inflammatory state occurs in obesity,

because adipocytes are a source of many proinflammatory cytokines. Some of them have the ability to directly inhibit insulin action [30]. It should be underlined that a persistent inflammatory state contributes to appearance of insulin resistance. So, long-term duration of inflammation, in spite of the low degree, might have a strong influence on metabolic homeostasis of the organism. The high value of BMI is an important factor enhancing development of low-grade inflammation, insulin resistance, diabetes and vascular complications [19]. In this study, using linear regression analysis we found that HbA1c and BMI are significantly associated with the WBC count and hsCRP concentration. In the literature, a stronger association of hsCRP with postprandial glycemia than with fasting glucose was reported. Associations were also found between HbA1c and fibrinogen levels in patients with T2D [5]. Gustavsson et al. [16] also noted a significant association between HbA1c and WBC count, but that study was conducted in patients with stable coronary arterial disease undergoing percutaneous transluminal coronary angioplasty (PTCA).

Using multiple regression analysis, stratified by age and gender, we revealed that WBC count was independently associated with BMI and HbA1c, while hsCRP was associated with gender and BMI. This is clearly visible in Fig. 1 and 2. However, when diagnosed diabetes instead of HbA1c was included in the analysis (Model 2), only BMI remained significantly associated with examined inflammatory markers. We can conclude that an increase in WBC count is associated with the degree of glycemic control indicated by HbA1c level but not with diabetes per se and is closely associated with obesity described by BMI. The hsCRP concentration was related to BMI, but not to glycated hemoglobin levels. The effect of gender on the hsCRP concentration observed by us was also shown by Ford and colleagues [10] using data from the National Health and Nutrition Examination Survey 1999-2000. They found that women have a significantly higher hsCRP concentration compared to men.

Our findings underline the important role of adipose tissue in the activation and development of low-grade inflammation. Excess of adipose tissue, as a source of proinflammatory cytokines, may increase WBC count in blood. Furthermore, we can conclude that hyperglycemia does not have a direct influence on liver production of CRP. The proinflammatory state induced by hyperglycemia and obesity, and developing in vessels, directly influences metabolism of endothelial cells and development of microangiopathy [26,31]. The best way to reduce the level of low-grade inflammation is good glycemic control in diabetes patients and maintenance of proper body weight in all patients. The United Kingdom Prospective Study (UKPDS) in patients with type 2 diabetes clearly showed that intensive control of hyperglycemia can reduce the prevalence and progression of microvascular late diabetic complications (retinopathy, nephropathy and neuropathy) [29], especially because of metabolic memory [11].

In summary, long-term hyperglycemia and obesity are associated with enhanced levels of the inflammatory markers WBC and hsCRP in middle-aged subjects, independently of the presence or absence of diabetes, and enhanced adipose tissue content seems to have a greater influence than hyperglycemia on levels of these markers. Low-grade inflammation may lead to development of vascular complication in diabetics with poor glycemic control and healthy subjects with excess adipose tissue, so reduction and normalization of both these factors is important to maintain good life conditions in elderly patients.

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