Lipid peroxidation, total antioxidant status, and glycemic control in patients with type 2 diabetes mellitus

Peroksydacja lipidów, całkowity potencjał antyoksydacyjny i kontrola glikemii u pacjentów z cukrzycą typu 2

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Abstract. Oxidative stress promotes atherogenesis in diabetes. The aim of our study was to assess if there is increased lipid peroxidation and/or antioxidant depletion in diabetic patients and to establish whether these processes are interrelated and correlated with glycemic control. In 135 patients with type 2 diabetes and 64 non-diabetic controls we determined lipid peroxidation products in plasma (LPO), serum total antioxidants (TAS), glycated hemoglobin (HbA_{1c}) fructosamine, glucose, lipids (total cholesterol, triglycerides, and HDL cholesterol) and apolipoproteins A-I and B. LPO (sum of malondialdehyde and 4-hydroxynonenal) were significantly elevated in diabetics (1.34 ±0.51 *vs* 1.02 ±0.37 μmol/L; p <0.001). Serum total antioxidant status (TAS) remained unchanged in diabetes. Neither LPO nor TAS was correlated with glycated hemoglobin HbA1c, fructosamine, and fasting glucose. No correlation was observed between LPO and TAS. HDL-cholesterol and apolipoprotein A-I were decreased in diabetics. Our results showed increased lipid peroxidation in type 2 diabetes without measurable antioxidants depletion and without association with glycemic control. Furthermore, the results suggest that peroxidation and glycation may operate independently as atherosclerosis promoters in diabetes.
Key words: lipid peroxidation, glycation, antioxidants, diabetes

Streszczenie. Stres oksydacyjny sprzyja aterogenezie w cukrzycy. Celem badania było ustalenie, czy u pacjentów z cukrzycą typu 2 występuje nasilona peroksydacja lipidów osocza i/lub zmniejszenie stężenia antyoksydantów w surowicy oraz czy procesy te są wzajemnie powiązane i skorelowane z kontrolą glikemii. U 135 pacjentów z cukrzycą typu 2 i 64 osób bez cukrzycy oznaczono produkty peroksydacji lipidów w osoczu (LPO), całkowity potencjał antyoksydacyjny (TAS) w surowicy, odsetek hemoglobiny glikowanej (HbA_{1c}), stężenie fruktozaminy, glukozy, lipidy (cholesterolu całkowitego, triglicerydów i HDL-cholesterolu) oraz apolipoproteiny A-I i B. LPO (suma malondialdehydu i 4-hydroksynonenalu) były znacząco zwiększone u pacjentów z cukrzycą (1,34 ±0,51 *vs* 1,02 ±0,37 μmol/l; p <0,001). Całkowity potencjał antyoksydacyjny osocza (TAS) nie ulegał zmianie w cukrzycy. Ani LPO, ani TAS nie były skorelowane z odsetkiem HbA_{1c} (%) oraz stężeniami fruktozaminy i glukozy na czczo. Nie zaobserwowano korelacji między LPO i TAS. Stężenia cholesterolu HDL i apolipoproteiny A-I były zmniejszone u chorych na cukrzycę. Osoczowe stężenie produktów peroksydacji lipidów w cukrzycy typu 2 było zwiększone, ale bez wpływu kontroli glikemii i całkowitego potencjału antyoksydacyjnego, który był niezmieniony. Uzyskane wyniki wykazują zwiększenie peroksydacji lipidów w cukrzycy i sugerują, iż peroksydacja i glikacja mogą działać niezależnie jako czynniki sprzyjające rozwojowi miażdżycy w cukrzycy.
Słowa kluczowe: peroksydacja lipidów, glikacja, antyoksydanty, cukrzyca

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Introduction

Atherogenesis is distinctly accelerated in patients with type 2 diabetes [1-3]. This fact cannot be fully explained by quantitative lipid changes occurring in diabetes because frequently they are not strongly pronounced [4]. Therefore, it has been postulated that qualitative lipoprotein changes occur, namely glycation and peroxidation, which render lipoproteins more atherogenic [5,6]. Oxidized lipoproteins, especially oxidized LDL, are known to have a variety of biological actions promoting atherosclerosis [7]. They exert cytotoxic effect on endothelium and they are avidly taken up by macrophages [8] which triggers a complex cellular response, mediated by cytokines and growth regulatory factors, leading to plaque formation [9]. In diabetic patients production of lipid peroxides may be increased due to oxidative stress of diabetes [10]. The increased generation of reactive oxygen species seems to be connected with glycation of proteins and glucose autooxidation [11]. Thus the intensity of lipid peroxidation may be correlated with a degree of glycemic control.

Malonyldialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are aldehydic lipid peroxidation products. Their concentration in plasma is regarded as a measure of lipid peroxidation intensity [12,13]. Plasma levels of lipid peroxidation products in diabetic patients were reported to be elevated [14,15], or normal [16]. Some authors found MDA concentration in plasma to be associated with glycated hemoglobin [17], while others did not confirm any correlation between peroxidation and glycation [18,19]. Perhaps those discrepancies may be attributed to differences in plasma antioxidants levels in those study groups.

High levels of antioxidants may prevent lipids from peroxidation by scavenging free oxygen radicals. This process may in turn lead to depletion of antioxidants present in plasma. A number of antioxidant scavengers, including reduced glutathione and ascorbate [20] and α-tocopherol are reduced in plasma of diabetic patients [21].

The aim of our study was to assess if there is evidence of increased lipid peroxidation and/or antioxidant depletion in diabetic patients and to establish whether these processes, if they occur, are interrelated and, in addition, correlated with glycemic control.

Materials and methods

One hundred and thirty five patients with type 2 diabetes and 64 non-diabetic control subjects were studied. There were 80 males and 55 females in the diabetic group. The mean age of the diabetic patient group was 62.5 ±9.6 years (mean and standard deviation), range 39–83 years. Duration of diabetes was on average 9 years (1–39 years). Eighty eight patients were treated with oral hypoglycemic agents, 37 with insulin, 5 with the oral agent and insulin, and 5 with diet alone. There were 17 smokers in the diabetic group. The control group consisted of 64 apparently healthy subjects undergoing routine yearly medical check-up, without diabetes according to the World Health Organization criteria of 2 hours plasma glucose levels below 11.1 mmol/l. There were 26 females and 38 males in this group. The controls were also matched for body mass index; their age (59,9 ±8,0 years) was not significantly different from that of the patient group.

Blood samples were collected after an overnight fast by venipuncture into glass tubes containing K3EDTA and tubes without anticoagulant. Small volumes of the K3EDTA samples were used for glycated hemoglobin determination, and all the remaining samples were centrifuged at 2000 g for 15 minutes at temperature of 4–80°C to obtain plasma and serum.

Lipid peroxidation products (LPO) were determined in plasma by method described by Esterbauer and Cheeseman [22] using reagent set Bioxytech® LPO 586 from Oxis International, Inc., Portland, USA. We used the procedure which determines both malonylodialdehyde (MDA) and 4-hydroxynonenal (4-HNE). Serum antioxidants were determined using Total Antioxidant Status (TAS) reagent set manufactured by Randox, Ardmore, UK. In this assay ABTS® (2,2′-azino-di-/3-ethylbenzthiazoline sulphonate) is incubated with a peroxidase (metmyoglobin) and H2O2 to produce the radical cation ABTS® + which has relatively stable blue-green colour measured at 600 nm. Its production is suppressed by antioxidants in the added sample proportionally to their concentration. Total cholesterol, triglycerides, glucose were measured by standard enzymatic methods with Integra automatic analyzer (Roche Diagnostics, Basel, Switzerland). The same analyzer and Roche cassette reagents were used for assaying glycated hemoglobin (HbA_{1c} [immunoturbidimetric method]), fructosamine, HDL-cholesterol (direct method), apoA-I and apoB (immunoturbidimetry). LDL- cholesterol was calculated according to Friedewald formula [23].

Data are expressed as means and standard deviations. Mann-Whitney U test was used to assess differences between cases and control subjects. Spearman correlation coefficients were calculated for selected variables. Statistical analyses were performed with Statistica for Windows, Release 12 (StatSoft, Inc, Tulsa, OK, USA).

Table 1. Clinical and biochemical characteristics of patients with type 2 diabetes and controls
Tabela 1. Kliniczna i biochemiczna charakterystyka pacjentów z cukrzycą typu 2 i grupy kontrolnej

variables	controls (n =64) mean ±2SD	patients (n =135) mean ±2SD	statistical significance
age (years)	59.9 ±8.4	62.5 ±9.6	N.S.
BMI	26.9 ±2.9	27.6 ±4.0	N.S.
duration of diabetes (years)		9.0 (1–39)*	
HbA_{1c} (%)	5.37 ±0.24	7.64 ±.86	<0.001
fructosamine (μmol/L)	219 ±17	289 ±67	<0.001
fasting glucose (mmol/L)	4.96 ±0.51	8.00 ±3.46	<0.001
MDA +HNE (μmol/L)	1.02 ±0.37	1.34 ±0.51	<0.001
TAS (mmol/L)	1.58 ±0.10	1.60 ±0.15	N.S.
total cholesterol (mmol/L)	5.16 ±0.87	5.32 ±1.12	N.S.
triglycerides (mmol/L)	1.62 ±0.84	1.71 ±0.87	N.S.
LDL-cholesterol (mmol/L)	2.90 ±0.85	3.15 ±0.95	N.S.
HDL-cholesterol (mmol/L)	1.52 ±0.39	1.39 ±0.37	<0.05
ApoA-I (g/L)	1.53 ±0.25	1.44 ±0.27	<0.05
ApoB (g/L)	1.07 ±0.20	1.09 ±0.21	N.S.

* Mean and range
N.S. – not significant

Results

The clinical and biochemical characteristics of the study groups are presented in Table 1. The groups were matched for age, sex and BMI. The degree of glycemic control in diabetic patients is reflected by levels of HbA1c, fructosamine and fasting glucose; at least half of the diabetic patients were not satisfactorily controlled according to the criteria of International Diabetes Federation [24].

Lipid peroxidation products, measured as a sum of MDA and HNE, were distinctly and significantly elevated in diabetics. Total antioxidant status (TAS) remained unchanged. Neither lipid peroxidation products nor TAS was correlated with indices of glycemic control i.e. HbA_{1c}, fructosamine, and glucose. No correlation was observed between MDA + HNE and TAS. There were no statistically significant differences in lipid peroxidation products and TAS between men and women with diabetes (1.37 ±0.57 *vs* 1.30 ±0.42 μmol/L, and 1.59 ±0.16 *vs* 1.61 ±0.14 mmol/L respectively). TAS was positively correlated with the patients' age (Sperman r =0.254; p <0.01) whereas MDA + HNE did not show any association with the age. Neither lipid peroxidation products nor TAS were correlated with BMI, total cholesterol, LDL-cholesterol, triglycerides, HDL-cholesterol, apoB, and apoA-I in diabetic patients. There were no significant differences in lipid peroxidation products and TAS between diabetic smokers and diabetic non-smokers (1.26 ±0.47 *vs* 1.36 ±0.53 μmol/L, and 1,60 ±0.16 *vs* 1,59 ±0.15 mmol/L respectively).

Total cholesterol, LDL-cholesterol, triglycerides and apolipoprotein B concentrations did not differ significantly in comparison with the control group. HDL-cholesterol and apoA-I were reduced in the diabetic patient group. Among lipoprotein constituents triglycerides were correlated with the degree of glycemic control indices: fasting glucose, and HbA_{1c}; apoB and cholesterol were correlated significantly only with glucose (Table 2).

Discussion

The elevated level of lipid peroxidation products in plasma of diabetic patients indicate that increased lipid peroxidation is a biochemical abnormality of type 2 diabetes. Our finding is in agreement with most earlier reports [14,15,25-27]. However, some authors reported opposite results [16] perhaps due to different methods used to determine products of lipid peroxidation [12]. More recently, elevated MDA levels were also reported in patients with metabolic syndrome and increased triglyceride and glucose levels [28].

We did not find significant correlations between products of lipid peroxidation and levels of lipids and apolipoproteins B and A-I in serum. It seems that lipid peroxidation may depend more on intensity of reactive oxygen species generation than on availability of lipid

Table 2. Spearman correlation coefficients between biochemical variables in patients with type 2 diabetes
Tabela 2. Współczynniki korelacji Spearmana pomiędzy parametrami biochemicznymi u pacjentów z cukrzycą typu 2

variables	HbA_{1c}	fructosamine	fasting glucose
MDA +HNE	0.057	0.054	0.029
TAS	0.145	0.046	0.078
total cholesterol	0.097	0.103	0.184*
triglycerides	0.252**	0.016	0.325***
LDL-cholesterol	0,070	0,092	0,106
HDL-cholesterol	0.028	0.016	0.107
ApoA-I	0.064	0.019	0.003
ApoB	0.110	0.052	0.287***

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

"substrate" which is usually abundant. Our finding confirms that of Nourooz-Sadeh et al. [29] but not that of Nacitarhan et al. who reported higher MDA levels in diabetics with hyperlipidemia [30].

Peroxidation may occur in blood but it is assumed that most of it takes place in subendothelial space with active participation of macrophages and other cells of artery wall [7,31,32]. Normal total antioxidant status (TAS) found in serum of our diabetic patients suggests that blood may not be the most favorable milieu for intensive lipid peroxidation. Normal antioxidant activity of serum in diabetic patients was reported earlier by Ozdemirler et al. [33]. Abnormally low antioxidant status were found by other researchers in patients with type 2 diabetes [34,35]. These discrepancies may have been a result of putative differences in antioxidant content of diets in the studied populations. Lack of significant correlation between TAS and concentration of lipid peroxidation products in our patients suggests that plasma antioxidants may be sufficient to counterbalance free radicals activity remaining without measurable change.

Production of lipid peroxides is assumed to be favored by glycation [36]. However, we were not able to show any correlation between MDA and HNE and glycated hemoglobin, fructosamine and fasting glucose. One of the reasons behind that may be the fact that MDA and HNE are the end products of a very extensive oxidative lipoprotein modification [37] and perhaps production of less modified lipoproteins would be more dependent on glycation [32]. So contrary to the expectation, we did not show the dependence of lipid peroxides levels on glycemic control. Perhaps there is a low threshold above which further glycation of lipoproteins does not influence their oxidation. Such a threshold may result from permeability of endothelium. Perhaps more important factor is a size of modified lipoprotein than the mere fact of modification. Percentage of small LDL particles is increased in diabetes [38]. These particles are known to be more susceptible to oxidation [39] probably due to easier penetration into subendothelial space [40]. Lipid peroxidation is a complex and multifactorial process [41], while glycation is mainly dependent on hyperglycemia. Recently Harmon et al. have not showed statistically significant correlation between oxidised LDL (oxLDL) and HbA1c in Navajo Indian population with very high frequency of diabetes [42].

The only lipid change in our patients was a significant reduction in HDL cholesterol, which is a frequent phenomenon in diabetes. Low level of HDL cholesterol is sometimes ascribed to functional disturbance resulting from apoA-I glycation and consequent impairment of HDL-associated enzyme activities which leads to reverse cholesterol transport defect[43]. But the disturbance seems to be not only functional because the level of apo-AI is also reduced.

Our results showed poor association between levels of lipoprotein constituents and glycemic control in diabetic patients. Only triglicerides, apoB, and total cholesterol were correlated significantly with the degree of glycemic control (fasting glucose or HbA1c). Glycation of apoB in LDL was postulated to reduce its catabolism through classical LDL-receptor causing LDL retention and increasing probability of its oxidation in blood [44,45]. In diabetes percentage of glycated apoB is higher than in normoglycemia [46]. The retention of apoB may not necessarily occur because of alternative route of glycated LDL catabolism namely scavenger receptor pathway [47].

In summary, we have shown that type 2 diabetes mellitus is associated with increased lipid peroxidation products in plasma and, at the same time, normal total antioxidants in serum. Lipid peroxidation was not correlated with total antioxidant status and the degree of metabolic control. There is a possibility that lipoprotein peroxidation, glycation and the changes in their composition may operate more or less independently as atherosclerosis promoters.

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