Chapter 5

Oxidative Stress in Type 1 Diabetes Mellitus: Ethnic Aspects

Lyubov I. Kolesnikova, Marina A. Darenskaya, Lyudmila A. Grebenkina, Svetlana V. Gnusina and Sergey I. Kolesnikov

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Abstract

Numerous researches show that data on an ethnic origin can give additional information for the personified approach in treatment of different diseases. The aim of this study was to evaluate the level of some lipid peroxidation components and antioxidant defense system in Mongoloid and Caucasian patients with Type 1 diabetes mellitus. Conjugated dienes, ketodienes and conjugated trienes, thiobarbituric acid reactants, total antioxidant activity, α-tocopherol, retinol, superoxide dismutase activity, reduced and oxidized glutathione, and oxidative stress coefficient levels were evaluated in 65 patients with type 1 diabetes (38 Mongoloids and 27 Caucasians) and in 82 healthy people (42 Mongoloids and 40 Caucasians). Spectrophotometric and fluorometric methods were used. The intensity of LPO in Mongoloid patients was lower than in Caucasians: the level of primary and intermediate products was by lower 1.53 and 1.83 times, while total antioxidant activity was elevated by 1.44 times, and decreased α-tocopherol level by 1.32 times, which was also supported by oxidative stress coefficient (1.35 in Mongoloids and 2.32 in Caucasians). Activity of the POL-AOD system in Mongoloids is low, which is probably due to the increase of antioxidant defense system work. These results are consistent with clinical characteristics of type 1 diabetes mellitus with infrequent development of complications in Mongoloids living in Eastern Siberia.

Keywords: type 1 diabetes mellitus, oxidative stress, antioxidant defense, ethnos

1. Introduction

Type 1 diabetes mellitus (T1DM) is common in the world and is considered as one of the severe human diseases. This disease is the cause of heart disease, blindness, stroke, kidney

failure, foot ulcers, and so on. A number of studies have shown that complications rate of T1DM depends on different factors including geographic residence and human ethnicity [1–4]. The dominance of T1DM is there in the countries of Scandinavia—Finland and Sweden (63 cases per 100,000 population) [5], while the lowest prevalence is observed in the East and South-East Asia where representatives of the Mongoloid race live [6]. In Russian Federation, there are more than 250,000 patients with T1DM [7]. Some studies revealed that low morbidity of T1DM among the aboriginal people in Arctic and Siberian regions resulted from the presence of the protective allele's genes for this disorder [6]. The prevalence of this form of diabetes among indigenous people in the Buryatia Republic is 24.18 per 100,000, which is below the average level in Russia (224.5 per 100,000) [8, 9].

Oxidative stress is an imbalance between increase reactive oxygen species and an antioxidant ability to detoxify the reactive components. Oxidative stress is thought to be involved in the development of different diseases [10–12].

Many experimental [13] and clinical studies [14] suggest that free-radical processes are activated during different stages and in different types of diabetes mellitus, even in its subclinical forms [15, 16]. In patients with diabetes mellitus, oxidative stress (OS) caused by elevated production of reactive species of oxygen and decrease of antioxidant defense system (AOD) level, leads to activation of lipid peroxidation (LPO) and oxidative lipoprotein modification with increasing atherogenicity [17]. Hyperglycemia can induce damage of β-cells functions with development of OS and decrease of thioredoxine level [18]. Marra et al. suggest that T1DM patients with a short duration of disease and good metabolic control show an early imbalance in their antioxidant capacity and augmented levels of lipid hydroperoxides and conjugated dienes (CDs) [19]. Diabetic women show, independently from other factors, a decreased antioxidant capacity and an increased rate of lipoperoxidation compared with diabetic men [19].

At the same time, the link between certain metabolic characteristics in patients with T1DM and their race remains poorly studied. The **aim** of this study was to evaluate the level of some LPO components and AOD system in Mongoloid and Caucasian patients with T1DM.

2. An evaluation of the level of some lipid peroxidation components and antioxidant defense system in mongoloid and Caucasian patients with type 1 diabetes mellitus

Biochemical parameters in 147 persons (healthy and with T1DM) both Mongoloids (ethnic group is Buryats) and Caucasians (ethnic group is Russians) living in the modern city Ulan-Ude (East-Siberia) were assessed. The diagnosis of T1DM was confirmed in all patients based on clinical and laboratory investigations, severe comorbidities and severe diabetic complications were excluded. Main group's characteristics are presented in **Table 1**. There were no

statistically significant differences in sex, age, duration of disease, Hb $A_{1C,}$ body mass index (BMI), arterial pressure in T1DM groups. There were no statistically significant differences in diets and physical activity between the patients of both ethnic groups with T1DM.

Blood samples were taken after 12 h of fasting during night, then were centrifuged for 5 min at 4°C, and erythrocytes were washed three times with NaCI 0.9% (wt/vol). Aliquots of EDTA plasma and washed erythrocytes were used immediately or kept frozen at −40°C but not more than 1 month. Blood plasma and hemolysate were used as the materials for analysis. The blood was taken from the cubital vein in accordance with accepted requirements. The intensity of LPO was evaluated by the level of diene conjugates (DC), ketodienes (KD), and conjugated trienes (CT). The concentration of DCs detected on absorbance of plasma heptanes extracts at 232 nm (μmol/liter), KD and CT at 278 nm (arb. units) [20]. Thiobarbituric acid reactants (TBARs) levels were identified by fluorometry methods and were considered in μmol/liter [21]. An evaluation of AOD activity was carried out on total radical-trapping antioxidant parameter (TRAP), which was measured by specific methods on 2,2′-azinobis-(3-ethylbensothazoline-6-sulphonate) radical action formation (absorbance at 734 nm) in conditions of exogenous H_2O_2 presence [22].

Also contents of other components of AOD system were determined: α-tocopherol and retinol [23], superoxide dismutase (SOD) [24], and reduced and oxidized glutathione (GSH and the GSSG) [25]. Measurements were carried out on the Shimadzu RF-1501 and Shimadzu RF-1650 spectrofluorometer. For more informative description of the LPO–AOD, coefficient of oxidative stress (COS) was calculated as the ratio of LPO–AOD system values in T1DM patient to the mean control group values. At COS > 1, oxidative stress was stated [26]. In our study,

Clinical	**Mongoloids**		**Caucasians**	
Data	**T1DM**	**Control group**	**T1DM**	**Control group**
n	38	42	27	40
Sex (M / F)	15/23	22/20	15/12	20/20
Age (years)	34.4 ± 11.7	31.4 ± 8.0	32.7 ± 11.9	27.8 ± 7.7
Duration of disease (years)	12.1 ± 3.5	–	12.9 ± 4.0	–
Hb A_{1C} (%)	9.29 ± 3.06	–	8.74 ± 2.24	–
Body mass index (kg/m^2)	23.7 ± 2.1	20.3 ± 1.3	24.6 ± 3.1	21.4 ± 3.4
Total cholesterol (mmol/l)	4.65 ± 1.2	4.28 ± 1.29	5.66 ± 1.22	4.24 ± 1.25
Triglycerides level (mmol/l)	1.01 ± 0.58	0.67 ± 0.21	1.53 ± 0.66	0.54 ± 0.19
Systolic pressure (mm Hg)	115 ± 11	116 ± 12	117 ± 10	113 ± 11
Diastolic pressure (mm Hg)	73 ± 12	71 ± 12	74 ± 9	76 ± 12

Table 1. General characteristics of patients with T1DM and control subjects.

all patients and control groups signed informed consent according to the World Medical Association Declaration of Helsinki (1964, 2000). For statistic analysis of the data, Statistica 6.1 software (StatSoft Inc.) was used. To determine normal distribution of the quantitative data, graphic visual method and Kolmogorov-Smirnov Test with Lilliefors and Shapiro-Wilk corrections were used. The variances equality was verified by Fisher's Test. Descriptive statistics was applied for quantitative data description: mean ± error of the mean. The differences between parameters of groups by parametric Student's Test for independent samples and non-parametric Mann–Whitney Test were analyzed. The critical significance level was considered 5% ($p < 0.05$).

3. Results

The oxidative stress is considered an imbalance in the redox-state with isolated or combined variations in the pro- or antioxidant components concentration. Our study has shown higher concentration of DC (by 1.35 times; $p < 0.01$) in Mongoloid patients as well as higher levels of DC (by 2.4 times; $p < 0.001$) and KD and CT (by 2.71 times; $p < 0.05$) in Caucasian patients in comparison to the corresponding control groups (**Table 2**).

No statistically significant differences between investigated groups in the TBA-reactive products level of lipid peroxidation processes were identified. In conditions of increased generation of LPO products are observed changes permeability of cell membranes for a lot of ions, nonelectrolytes, and macromolecules [27]. This processes in loss of barrier function of cell membranes that is the pathogenesis of different diseases, including development of vascular disorders in T1DM due to lipid peroxidation activation during prolonged hyperglycemia [9, 28]. The observed increase in LPO activity cannot provide sufficient information about the redox-status in patients with T1DM, because it indicates one aspect of the study, LPO excluding of AOD activity. The study of the AOD integral parameter level, TRAP in patients with T1DM, an increase (by 1.54 times; $p < 0.001$) in this indicator in Mongoloid patients in comparison with the control group was shown (**Table 3**).

In Caucasian patients with T1DM, statistically significant differences from the control group included reduced GSH values (by 1.16 times; $p < 0.05$) and increased GSSG level (1.26-times,

Parameters	Mongoloids		Caucasians	
	Control group	T1DM	Control group	T1DM
Diene conjugates, μmol/liter	0.57 ± 0.03	0.77 ± 0.04*	0.51 ± 0.07	1.2 ± 0.11*,+
Ketodienes and conjugated trienes, arb. units	0.31 ± 0.05	0.35 ± 0.04	0.24 ± 0.06	0.65 ± 0.13*,+
TBA-reactive products, μmol/liter	1.57 ± 0.10	1.81 ± 0.11	1.93 ± 0.10	2.05 ± 0.12

Here and in **Table 3**: $p < 0.05$ in comparison with *corresponding control, +Caucasian T1DM patients.

Table 2. Level of LPO products in DM1 mongoloid and Caucasian patients (M ± m).

Parameters	Mongoloids		Caucasians	
	Control group	T1DM	Control group	T1DM
TRAP, arb. Units	14.35 ± 0.72	22.17 ± 1.08*	17.68 ± 1.36	15.42 ± 0.96+
α-tocopherol, μmol/liter	6.85 ± 0.38	6.23 ± 0.32	6.72 ± 0.3	8.21 ± 0.78*,+
retinol, μmol/liter	2.7 ± 0.18	2.29 ± 0.15	2.38 ± 0.13	2.33 ± 0.17
SOD, arb. Units	1.41 ± 0.04	1.26 ± 0.03	1.43 ± 0.44	1.57 ± 0.24
GSH, mmol/liter	2.79 ± 0.16	2.79 ± 0.11	2.90 ± 0.14	2.51 ± 0.13*
GSSG, mmol/liter	2.03 ± 0.15	2.15 ± 0.09	1.72 ± 0.09	2.16 ± 0.10*

Table 3. AOD values in T1DM in mongoloid and Caucasian patients (M ± m).

$p < 0.001$) (**Table 2**). Also in this group in comparison with control, statistically significant differences in activity of SOD, α-tocopherol, and retinol levels were not noted. Initiation of processes of lipid peroxidation at primary and intermediate stages in the absence of natural AOD activity enhancement can lead to function impairment of different components of hemostasis and increased aggregation of blood cell, which will increase blood viscosity, induce thickening of the vascular wall basal membrane, slower blood flow in small and medium vessels, deterioration of microcirculation [24]. The given changes in parameters of lipid peroxidation can attest about the presence of risk factors for microangiopathy development in Caucasian patients with T1DM. Comparison of LPO values in Caucasian and Mongoloid patients showed decreased DC (by 1.56 times; $p < 0.001$), KD and CT (by 1.86 times; $p < 0.05$) values, increased TRAP (by 1.44 times; $p < 0.001$), and decreased α-tocopherol levels (1.22-times, $p < 0.01$) in Mongoloid patients with T1DM in compare with the same values in Caucasian patients with T1DM (**Tables 1** and **2**). Coefficient of oxidative stress (COS) in Mongoloid patients was 1.35, in Caucasian patients was 2.32 ($p < 0.05$). It is believed that COS value>1 indicates activation of oxidative stress. The higher is COS, the more insensitive are processes lipid peroxidation processes and less effective is the antioxidant defense system in the examined patients with different diseases. So, our results indicate increased LPO processes in groups of patients with diabetes mellitus and intensity of LPO processes depends on ethnicity [29]. Noted changes in LPO-AOD system in Mongoloid patients with T1DM were less insensitive than in Caucasian patients, that allows to make a recommendation on highly individualized approaches to the complex therapy.

4. Conclusions

We suppose that ethnic factor plays one of the most important roles in the course of various diseases, including T1DM. It is quite possible that the low incidence in T1DM in Mongoloids is based on less LPO-AOD metabolic imbalance. Further studies of ethnically associated metabolic features can give more opportunities for developing specific approaches for diagnostics, prophylactic and treatment of T1DM in patients of different ethnic groups.

Conflict of interest

There is no conflict of interest.

Author details

Lyubov I. Kolesnikova[1], Marina A. Darenskaya[1]*, Lyudmila A. Grebenkina[1], Svetlana V. Gnusina[1] and Sergey I. Kolesnikov[1,2]

*Address all correspondence to: marina_darenskaya@inbox.ru

1 Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation

2 Lomonosov Moscow State University, Moscow, Russian Federation

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