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Effects of metabolic control and vascular complications on indices of oxidative stress in type 2 diabetic patients

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Abstract

The direct effect and the interaction of diabetic angiopathy and metabolic control on free radical and antioxidant activity indices was investigated in 48 patients with type 2 diabetes mellitus. Conjugated dienes (CD) and thiobarbituric acid-reacting substances (TBARS) levels were 34 and 178% of control values, respectively. An approximate two-fold decrease in plasma thiols (PSH) and erythrocyte lysate thiols (LSH) concentrations, parameters reflecting protein oxidative damage, was found. Impairment of blood antioxidant potential in diabetic patients was reflected by an 81% increase in superoxide dismutase (SOD) activity, a 30% decrease in catalase (CT), 20% decrease in glutathione peroxidase (GPx) and glutathione reductase (GR) activities as well as by lowered total antioxidant status (TAS). CD, TBARS and SOD values were positively correlated with plasma glucose concentration and glycated hemoglobin level. A negative correlation existed between levels of LSH, PSH, CT, GPx or TAS and both glucose and HbA_{1c}. Blood glucose control and vascular complications had strong independent effects on prooxidant–antioxidant status, apart from blood glucose and GR activity. In addition, glycemic control and diabetic vasculopathy interact in their influence on most of the free radical and antioxidant indices, except for CD, LSH levels and CT activity. Thus, we observed different mechanisms by which vascular complications and glucose control affect blood free radical indices and antioxidant status parameters in type 2 diabetic patients.

Keywords: Diabetes; Lipid and protein oxidative modification; Antioxidants

1. Introduction

Controversy exists around the factors involved in the pathogenesis of diabetic complications. Recent evidence clearly establishes hyperglycemia as the primary causal factor responsible for endothelium dysfunction and the development of diabetes complications [1–3]. Overactivity of the sorbitol pathway, activation of endothelial cyclooxygenase, increased protein kinase C activity and glycation of proteins and lipoproteins are all mechanisms by which hyperglycemia could lead to a sequence of biochemical events

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resulting in structural and functional vascular changes [1,2,4]. Increased reactive oxygen and nitrogen species (ROS/RNS) formation and disturbances in the antioxidant system potential have also been considered as factors participating in the initiation and/or evolution of the micro- and macrovascular complications of diabetes [5–7].

Reactive oxygen and nitrogen species, if not trapped by antioxidants, attack proteins, lipids, nucleic acids and carbohydrates by a series of reactions (oxidation, fragmentation, cross-linking) affecting cellular structure and function, including endothelial cells [8]. Damage to endothelium by ROS or their oxidation products (oxidized LDL) with simultaneous activation of blood platelets, monocytes and neutrophils, results in increased vascular permeability, decreased antithrombogenicity and reduced fibrinolytic activity [9,10]. These mechanisms favor the development of diabetic angiopathy. However, the contribution of oxidative damage to the development of vascular complications and the conclusive evidence for a causal link between them remains to be demonstrated.

Previous studies evaluating the prooxidant–antioxidant status in type 2 diabetes mellitus were based mainly on the determination of single indices either of free radical or antioxidant blood activity [11–13]. Although the relationship between blood levels of the oxidative reaction products and free radical scavengers was also described in these studies [11–14], our understanding remains poor. Furthermore, none of the studies describe the relationships between the free radical and antioxidant activities and glucose control in diabetic patients with and without complications. For this reason, the present study was designed to investigate direct and interactive effects of glucose control and diabetic vasculopathy on free radical and antioxidant activity levels.

2. Materials and methods

2.1. Subjects

Studies were carried out on 48 patients with type 2 diabetes mellitus (26 females and 22 males) aged from 37 to 58 years (mean 49 years), and with mean diabetes duration of 7.0 years. Patients were prescribed oral hypoglycemic agents (sulphonylureas,

Table 1
Clinical characteristics of control subjects and diabetic patients (mean ± S.D.)

	Control subjects	Diabetic patients			
		Good glucose control		Poor glucose control	
		Without vascular complications	With vascular complications	Without vascular complications	With vascular complications
Subjects (*n*)	25	12	12	12	12
Sex (female/male)	11/9	7/5	6/6	7/5	6/6
Age (years)	45.3 ± 5.2	50.1 ± 3.2	52.4 ± 1.7	51.1 ± 3.7	54.9 ± 3.2
Diabetes duration (years)	–	6.3 ± 0.4	6.9 ± 0.7	6.6 ± 0.8	7.2 ± 0.5
Systolic blood pressure (mmHg)	120 ± 6	129 ± 5	132 ± 7	137 ± 10	139 ± 12
Diastolic blood pressure (mmHg)	73 ±4	75 ± 6	77 ± 5	79 ± 6	82 ± 11
HbA_{1c} (%)	4.8 ± 0.4	6.6 ± 0.5[a]	6.7 ± 0.3[a]	8.2 ± 0.9[a,b,c]	9.2 ± 1.6[a,b,c,d]
Serum glucose (mmol/L)	4.4 ± 0.5	6.8 ± 1.4[a]	5.6 ± 1.0[a,b]	8.9 ± 2.1[a,b,c]	10.4 ± 1.7[a,b,c,d]
Serum cholesterol (mmol/L)	5.0 ± 0.8	4.8 ± 0.8	5.2 ± 1.0	5.9 ± 0.6[a,b,c]	5.8 ± 1.3[a]
Serum HDL-cholesterol (mmol/L)	1.1 ± 0.2	1.0 ± 0.1	0.9 ± 0.2[a]	1.1 ± 0.1[c]	1.0 ± 0.3
Serum triglycerides (mmol/L)	1.2 ± 0.4	1.3 ± 0.4	1.5 ± 0.5	2.1 ± 0.9[a,b]	1.8 ± 0.9[a]
Serum creatinine (μmol/L)	70.7 ± 17.7	79.6 ± 26.5	106.1 ± 35.4	70.7 ± 26.5	114.9 ± 26.5
Urine glucose (mmol/L)	–	–	–	46.15 ± 8.34	69.5 ± 17.8[d]
Albuminuria (mg/L)	3.7 ± 1.3	9.6 ± 2.1	28.6 ± 4.3[a,b]	13.7 ± 3.2[a,b]	33.8 ± 5.13[a,b,d]
Proteinuria (g/L)	–	–	0.45 ± 0.18	–	0.49 ± 0.13

[a] $p < 0.05$, compared vs. control group.
[b] $p < 0.05$, compared vs. good glucose control without vascular complication group.
[c] $p < 0.05$, compared vs. good glucose control with vascular complication group.
[d] $p < 0.05$, compared vs. poor glucose control without vascular complication group.