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Effect of C111T polymorphism in exon 9 of the catalase gene on blood catalase activity in different types of diabetes mellitus

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Abstract

Hydrogen peroxide plays a major role in the pathomechanism of diabetes mellitus and its main regulator is enzyme catalase.

The blood catalase and the C111T polymorphism in exon 9 was examined in type 1, type 2 and gestational diabetes mellitus.

Compared to the control group (104.7 ± 18.5 MU/l) significantly decreased ($p < 0.001$) blood catalase activities were detected in type 2 (71.2 ± 14.6 MU/l), gestational (68.5 ± 12.2 MU/l) diabetes mellitus and without change in type 1 (102.5 ± 26.9 MU/l). The blood catalase decreased ($p = 0.043$) with age for type 2 diabetics and did not change ($p > 0.063$) for type 1, gestational diabetic patients and controls. Blood catalase showed a weak association with hemoglobin A1c for type 1 diabetic patients ($r = 0.181$, increasing).

The mutant T allele was increased in type 1 and gestational diabetes mellitus, and CT + TT genotypes showed decreased blood catalase activity for type 1 and increased activities for type 2 diabetic patients.

The C111T polymorphism may implicate a very weak effect on blood catalase activity in different types of diabetes mellitus.

Keywords: *Diabetes mellitus: type 1, type 2, gestational, blood catalase, C111T polymorphism in exon 9, mutation determination*

Introduction

Increasing evidence in both experimental and clinical studies suggest that oxidative stress plays a major role in the pathogenesis and in the long term complications of diabetes mellitus. Free radicals are formed in diabetes by glucose oxidation, non-enzymatic glycation of proteins, and the subsequent oxidative degradation of glycated proteins [1]. Increased flux of glucose may cause generation of excess of reactive oxygen species. These species and the impaired antioxidant status are involved in the oxidative stress associated with diabetes mellitus. The pancreatic beta-cells are sensitive to oxidative stress due to their very low activities of the main antioxidant enzymes which are superoxide dismutase, glutathione peroxidase and catalase. The high glucose flux may change the expression of these enzymes that protect against oxidant damage and may accentuate the oxidative injury [2]. Superoxide dismutase converts the superoxide anion into less toxic hydrogen peroxide but its high concentration also causes damage of cells, proteins and DNA. This effect is more serious when the very aggressive hydroxyl radicals are formed from hydrogen peroxide in the Fenton reaction. On the other hand, the low concentration of reactive oxygen species, including hydrogen peroxide which is generated in response to insulin stimulation, may

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serve as a second messenger in the insulin action cascade [3]. It can mimic insulin action by oxidation of the cystein rich part of protein-tyrosine kinases and phosphatases such as insulin receptor and insulin substrates [4].

The enzyme catalase is the main regulator of the hydrogen peroxide metabolism, especially in the erythrocytes [5,6]. Due to the small, chargeless, and diffusible hydrogen peroxide molecule the high concentration of erythrocyte catalase can control the hydrogen peroxide formed inside and outside the erythrocytes [7]. High concentration of hydrogen peroxide is decomposed by catalase in a very effective and fast reaction [8] but due to the special Ser 198 and Arg 144 gating mechanism, catalase reveals a very weak affinity to the physiological concentration of hydrogen peroxide [8,9].

We have reported on the high incidence (11.7 vs. 1.7%) of diabetes mellitus in inherited catalase deficiency [10], and decreased blood catalase activities in different types (1, 2 and gestational) of diabetes mellitus [11,12]. The chronic exposure to relatively high levels of hydrogen peroxide have also been associated with functional beta-cell impairment and the chronic complications of diabetes [3,13,14]. The experiments with cell lines showed that the over-expression of catalase protected the insulin producing pancreatic beta cells against hydrogen peroxide toxicity [15].

There are only few papers on the association of diabetes and catalase mutations [16]. Chystakov et al. [17] found a weak association of C1167T polymorphism in the flanking region of the catalase gene and diabetes mellitus.

The C111T polymorphism of exon 9 (rs769217) was first detected in Japan [18]. It is a by-product which was detected during the molecular analysis of human acatalasemia. In 2002, Casp et al. [19] found a possible genetic association of this polymorphism and vitiligo susceptibility. Gavalas et al. [20] in a recent paper also detected this association. They supposed that the different gene expression of the wild-type and mutant alleles may be responsible for the lower catalase activity.

The different expression of the wild and mutant alleles have been discussed widely but the catalase activities of these catalase alleles have not been reported to support this phenomena [21].

The decreased blood catalase activity together with the increased production of hydrogen peroxide in diabetes mellitus [22] leads to the increase of hydrogen peroxide concentration which may lead to toxic effects. The low catalase activity is likely to result from allelic variants in the catalase gene which may cause different expression or different regulation. There are no data concerning the effect of C111T single nucleotide polymorphism on the catalase activity in diabetes mellitus.

The aim of this study was to measure the blood catalase activities, to examine its relation to the diabetic therapeutic marker of haemoglobin A1c. We examined C111T polymorphism in exon 9, and its possible effect on blood catalase activity in different types (1, 2 and gestational) of diabetes mellitus.

Materials and methods

Thirty-three pregnant women with gestational diabetes but without family history of diabetes mellitus were included in this study, who underwent treatment at the Department of Obstetrics and Gynecology of Medical Health Science Center. All received insulin therapy and blood samples were taken in the second trimester for women between the ages of 23 and 41 (mean $\pm$ SD = 30.8 $\pm$ 4.6 years).

One hundred and six patients with type 1 (insulin dependent) diabetes mellitus were from the Diabetes Clinics of Internal Medicine Department of Medical and Health Science Center. They were treated with insulin and their therapy was followed by measurement of blood hemoglobin A1c. This group had 46 males (43.4%, 43.3 $\pm$ 21.8 years) and 60 females (56.6%, 48.7 $\pm$ 20.5 years).

One hundred patients with type 2 (non-insulin dependent) diabetes mellitus were treated at the same department. This group included 33 males (33%, 56.6 $\pm$ 17.1 years) and 67 females (67%, 58.9 $\pm$ 15.9 years).

The control subjects were 60 hospital employees of the Medical Health Science Center of Debrecen University from the Eastern region of Hungary. Subjects were excluded if they had medical history of diabetes or if they were pregnant. This group included 19 males (31.7%, 37.0 $\pm$ 910.3 years) and 41 females (68.3%, 38.2 $\pm$ 9.9 years).

The patients and controls were randomly selected during a period from 2003 to 2005.

Blood samples were stored at -20°C for 2 days for blood catalase determination and not more than 7 days for extraction of genomic DNA.

Blood catalase activity was measured by a spectrophotometric assay with the reference range of 113.3 $\pm$ 16.5 MU/l ($n = 1756$). The within run and day to day precision (coefficient of variation) of blood catalase determination is 3.1 and 5.1% [23,24].

Blood hemoglobin A1c (HbA1c) was measured with a HPLC system (Diamat, Bio-Rad, Hercules, CA, USA) with a reference range of 4.2–6.1%.

Genomic DNA was extracted from leukocytes using a QIAmp Blood Kit from Qiagen (Hilden, Germany). PCR and primers (forward primer: tgttactgccctagtcagt, reverse primer: agagggcacgtggagcagat) were the same as described by Kishimoto et al. [25] and the region amplified included 139 nucleotides in exon 9, plus 56 nucleotides of intron 8 and 43 nucleotides of intron 9. Reagents (ReadyMix REDTaq with $MgCl_2$)

and primers were purchased from Sigma (Sigma-Aldrich, St Louis, Missouri, USA). Amplifications were performed in total volumes of 12.0 μl. The mixture of 5.0 μl H_2O, 1 μl of each primer (10 μmol/l), and 2.0 μl of genomic DNA (0.2 μg/μl) was incubated at 94°C for 5 min. After that 5.0 μl ReadyMix RED Taq (20 mmol/l Tris–HCl pH:8,3, 100 mmol/l KCl, 3 mmol/l $MgCl_2$, 0.002% gelatine, 0.4 mmol/l dNTP mix, 60 U TaqDNA) was added. Thirty amplification cycles (94, 55 and 72°C for 0.5, 0.5 and 1.0 min, respectively) were performed in a DNA thermal cycler (TC1, Perkin Elmer-Cetus, Norwalk, CT, USA).

For the single strand conformational polymorphism (SSCP) method 10 μl of PCR product was mixed with 4 μl of loading dyes (0.05% bromphenol blue and 0.05% cylene cyanol in glycerol) and loaded directly into the gel.

Electrophoresis was performed in 6% polyacrylamide (acrylamide for molecular biology from Sigma-Aldrich and 5x TAE puffer) gel (175 × 160 × 1.5 mm) at 170 V and room temperature for 3 h. DNA bands were visualized by silver staining.

For DNA sequence analyses, the PCR products were purified by agarose gel electrophoresis.

Sequencing reactions were carried out using Taq Dye-Deoxy Termination Cycle Sequencing Kits and DNA fragments were separated and detected by capillary electrophoresis (3100-Avant, Genetic Analyzer, ABI PRISM, Applied Biosystems, Foster City, CA, USA).

The Student *t*-test was used to evaluate the statistical significance of differences in blood catalase activities. We used the Microsoft Excel program to perform the multivariate analyses and trend test. For case/control association studies, the significance of observed differences in allelic or genotypic frequencies between the diabetic patients and controls was determined using standard $\chi 2$-test on 2 × 2 contingency tables. p values <0.05 (two tailed) were regarded as significant. Odds ratio (OR) with 95% confidence intervals (95% CI) were calculated using a 2 × 2 contingency table.

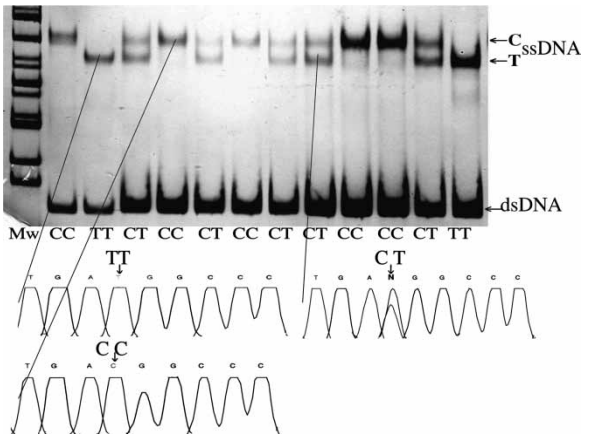

Figure 1. C111T polymorphism in exon 9 of the catalase gene (dsDNA, duble stranded DNA; ssDNA, single stranded DNA) and nucleotide sequence analysis of CC, CT and TT genotypes.

Results

The type 2 and gestational diabetes mellitus showed significant ($p < 0.001$) decrease in blood catalase activities. The blood catalase was higher for males than females in patients and in controls. This increase was significant ($p = 0.033$) only for type 2 diabetic males.

The blood catalase did not change ($p > 0.063$) with age for type 1, gestational diabetic patients and controls.

For type 2 diabetic patients the blood catalase decreased with age ($p = 0.043$) showing the highest values (78.9 ± 10.8 MU/l) between 20 and 40 years of age and the lowest ones (68.0 ± 14.4 MU/l) between 61 and 80 years (Table I).

The blood catalase increased with blood hemoglobin A1c (slope = 2.412 $r = 0.1819$) in type 1 diabetes and decreased in type 2 and gestational diabetes (slope = −0.309, $r = 0.036$ and slope = −1.537, $r = 0.067$) as shown in Figures 2–4.

The C111T polymorphism of exon 9 of catalase gene with PCR–SSCP and nucleotide sequencing analysis is shown in Figure 1.

Table I. Blood catalase activities (MU/l) in diabetes mellitus and in controls.

Groups	Type 1 Mean ± SD (*n*)	Type 2 Mean ± SD (*n*)	Gestational Mean ± SD (*n*)	Control Mean ± SD (*n*)
Sex				
Male	104.5 ± 25.8 (40)	77.7 ± 18.8 (33)*		109.6 ± 16.6 (19)
Female	101.1 ± 27.8 (60)	69.1 ± 11.9 (67)*	68.5 ± 12.2 (30)	102.5 ± 19.5 (41)
Age (year)				
20–40	94.0 ± 05.7 (17)	78.9 ± 10.6 (13)*	67.9 ± 12.1 (30)*	105.4 ± 19.1 (36)
41–60	110.3 ± 26.7 (36)	73.6 ± 15.3 (35)*	74.2 ± 13.5 (3)*	106.4 ± 20.4 (24)
61–80	100.9 ± 26.9 (32)	68.0 ± 14.4 (52)*		
Total	102.5 ± 26.9 (106)	71.2 ± 14.6 (100)*	68.5 ± 12.2 (33)*	104.7 ± 18.5 (60)

*$p < 0.001$ (t-probe when compared to the control).

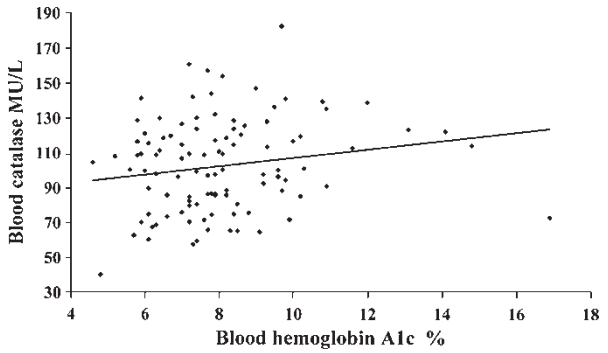

Figure 2. Blood hemoglobin A1c and blood catalase in type 1 diabetes mellitus ($y = 2.412x + 83.1$, $r = 0.182$, $n = 106$).

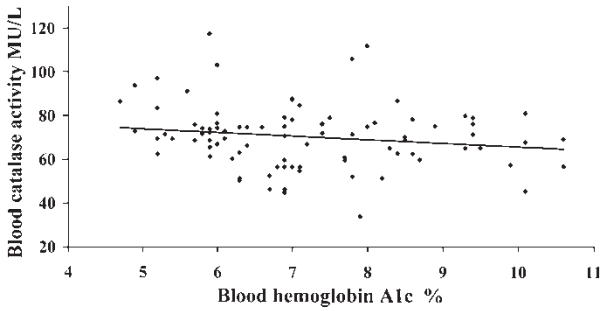

Figure 3. Blood hemoglobin A1c and blood catalase in type 2 diabetes mellitus ($y = -0.309x + 73.4$, $r = 0.036$, $n = 100$).

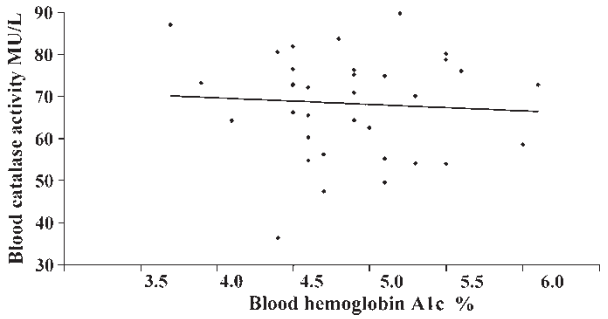

Figure 4. Blood hemoglobin A1c and blood catalase in gestational diabetes mellitus ($y = -1.537x + 75.9$, $r = 0.067$, $n = 33$).

The frequency of mutant T allele and OR were increased in type 1 and gestational diabetes when it was compared to that of the controls (Table II).

The mutant genotypes (CT + TT) yielded a significant ($p < 0.02$) decrease in blood catalase activity for type 1 and an increase for type 2 diabetic patients (Table III).

Discussion

Our previous report [11] showed significantly ($p < 0.001$) decreased blood catalase activity of 94.4 ± 19.2 MU/l in 137 diabetic patients. In this study, we analyzed the type 1 and 2 of diabetes mellitus separately. For comparison we used the values of a control group of 60 hospital employees whose blood catalase activity was lower (104.7 ± 18.5 MU/l, $p < 0.001$) than that of the reference subjects (113.3 ± 16.5 MU/l *n*: 1756). This difference may be attributed to the more serious criteria of exclusion which we used for the definition of a reference subject [23] and the higher ratio of females in the control group. Females have lower blood catalase than males.

The type 2 diabetic group revealed significantly ($p < 0.001$) decreased (67.9%) blood catalase activity. It decreased ($p = 0.043$) with age and males had higher ($p < 0.001$) catalase activities than females.

In gestational diabetes the decreased (68.5 ± 12.2 MU/l) blood catalase activity was similar to our previous report (74.0 ± 14.0 MU/l, *n*: 60) [12].

The decreased blood catalase activities in type 2 and gestational diabetic patients result in a lower antioxidant capacity against the hydrogen peroxide which is increased in diabetes mellitus [22].

The widely used blood haemoglobin A1c reflects the mean glucose concentration of the previous 6–8 weeks. The blood catalase reflects the mean of the catalase synthesis for the same period. The relationship between blood haemoglobin A1c and blood catalase showed an increase (slope of +2.412) with a weak correlation ($r = 0.182$) for type 1 diabetes mellitus. For type 2 and gestational diabetes mellitus this slope had adverse values (−0.309 and −1.537) with a poor correlation ($r = 0.036$ and 0.067).

To explain the decrease of blood catalase we could not find human examinations but some animal experiments are available in the literature. It was reported for rat mitochondrial catalase that high insulin diminishes rates of catalase synthesis [26]. Type 1 diabetes may be associated with higher as well as lower insulin concentrations due to difficulties in this therapy. The high concentration of insulin may decrease the formation of hemoglobin A1c and the synthesis of catalase which may yield low hemoglobin A1c concentration and low catalase activity. Furthermore, the low concentration of insulin favours the formation of hemoglobin A1c and increases catalase synthesis. These two antagonistic effects may cause the unchanged mean value (102.5 ± 26.9 MU/l, *n*: 106 vs. 104.7 ± 18.5 MU/l, *n*: 60) of blood catalase due to the wide range (4.3–17%) of hemoglobin A1c in insulin dependent diabetes mellitus.

In animal experiments the appropriate diabetes therapy normalized the activity and protein expression of antioxidant enzymes [27], decreased the formation of reactive oxygen species and prevented the development of insulin resistance [28].

Type 2 diabetic patients, due to their lower catalase, may reveal a decreased defense against the toxic effect of hydrogen peroxide.

Table II. Genotype, allele frequencies and OR, CI of TT + CT vs. CC genotypes in different types of diabetes mellitus and in controls.

Groups	Type 1 (*n*: 106)	Type 2 (*n*: 100)	Gestational (*n*: 33)	Control (*n*: 60)
Genotype frequency	*n* (%)	*n* (%)	*n* (%)	*n* (%)
CC	51 (48.1)	67 (67.0)	17 (51.5)	38 (63.3)
CT	49 (46.2)	26 (26.0)	14 (42.4)	21 (35.0)
TT	6 (5.7)	7 (7.0)	2 (6.1)	1 (1.7)
T allele frequency (%)	28.7⋆	20.0	27.2⋆	19.2
OR	1.736	0.702	1.625	
95% CI	0.937–3.42	0.357–1.37	0.613–4.08	

⋆ χ^2 probe, significant when compared to the control.

Table III. Blood catalase activities and genotypes in different types of diabetes mellitus and controls.

	Mean ± SD (*n*)			
Groups	Type 1	Type 2	Gestation	Control
CC	108.7 ± 27.6 (51)	67.5 ± 10.3 (67)	69.6 ± 10.6 (17)	98.9 ± 24.5 (38)
CT	94.5 ± 22.7 (49)	87.8 ± 10.5 (26)	66.4 ± 13.0 (14)	93.9 ± 25.5 (21)
TT	103.1 ± 18.5 (6)	71.3 ± 11.2 (7)	80.4 ± 21.9 (2)	103.2 (1)
Ratio of mutant (TT + CT) genotypes and wild (CC) genotypes				
Catalase	0.86⋆	1.24⋆	0.93	0.96

⋆ $p < 0.02$ (t-probe when compared to wild genotype).

In vitiligo Casp et al. [19] and Gavalas et al. [20] detected increased T allele frequencies and they supposed that the transcription from the T allele is slower than from the C allele.

In type 1 diabetes mellitus we also detected the increase of T allele frequency (28.7 vs. 19.2%). Furthermore, catalase activity of mutant genotypes decreased (0.86 vs. 0.96) and the mean value of blood catalase did not change (102.5 ± 26.9 vs. 104.7 ± 18.5 MU/l).

In type 2 diabetes mellitus the T allele frequency did not change (20.0 vs. 19.2%) but the activity of mutant genotypes increased (1.24 vs. 0.96) and the mean of blood catalase significantly decreased (71.2 ± 14.6 vs. 104.7 ± 18.5 MU/l).

In gestational diabetes the T allele frequency increased (27.2 vs. 19.7%), the activity of mutant genotypes did not change (0.93 vs. 0.96) but the mean catalase activity significantly decreased (68.5 ± 12.2 vs. 104.7 ± 18.5 MU/l).

From these controversial results we may conclude that C111T polymorphism may have a minor and adverse contribution to the regulation of catalase synthesis in different types of diabetes mellitus. Our genetic data supported by blood catalase determination may suggest a different mechanisms for catalase synthesis in diabetes mellitus compared to that of in vitiligo [19,20].

The allele frequencies were similar in Hungarian and USA control patients (C: 80.8% vs. 82.4) but they were different from the Japanese (C: 80.8 vs. 52.5%) patients [18,19] and UK patients (80.8 vs. 69.8%) [20].

In conclusion, the decreased blood catalase activity in non-insulin dependent and gestational diabetes means a lower capacity against hydrogen peroxide which is increased in these diseases. The C111T polymorphism seems to have a very weak effect on blood catalase activity in diabetes mellitus. The strong decrease in blood catalase in type 2 and gestational diabetes may be attributed to other new mutations or regulatory mechanisms which require further examinations.

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