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Review Article

Blood Catalase Activities, Catalase Gene Polymorphisms and Acatalasemia Mutations in Hungarian Patients with Diabetes Mellitus

Abstract

Introduction: Catalase decomposes hydrogen peroxide into oxygen and water. Its low concentration could be involved in signaling while its high concentration is toxic.

Aim: This short review discusses the association of blood catalase and diabetes mellitus in Hungarian diabetic patients.

Results: Several cohort studies showed decreased blood catalase activity in type 2 diabetes and in gestational diabetes.

Among the catalase gene polymorphisms rs769217 showed a weak association with type 1 diabetes. Regarding rs1001179 polymorphism patients with TT genotype have a risk for lower life expectancy.

In acatalasemics the frequency of diabetes mellitus is higher ($P<0.001$) than in the Hungarian population. 11 of 12 known Hungarian acatalasemia mutations are found in diabetic patients. Acatalasemia may be associated with a higher risk for diabetes mellitus especially for its type 2 form.

Acatalasemia mutations could explain the decreased (<50%) blood catalase activities only in 17.4% of the cases.

Conclusions: Blood catalase activity is decreased in type 2 and gestional diabetes. Patients with inherited catalase deficiency and known acatalasemia mutation are at higher risk of diabetes mellitus.

The lifelong effect of oxidative damage on the oxidant sensitive, insulin producing pancreatic beta-cells could contribute to the manifestation of diabetes mellitus especially to type 2 form.

Acatalasemia mutations could explain the reason for the catalase decrease while for the other (82.6 %) cases it remains unsolved.

The decreased blood catalase activity in type 2 and gestational diabetes rather due to regulatory mechanisms than to the catalase gene mutations.

Introduction

Human enzyme catalase (EC 1.11.1.6, BCBI: 9060) decomposes hydrogen peroxide into oxygen and water. Low concentration of hydrogen peroxide plays an important role in signaling while its high concentration is toxic [1]. Decreased activity of catalase may lead to an increase of hydrogen peroxide concentration which may contribute to the manifestation of various age related diseases including diabetes mellitus [2]. Human tissues such as erythrocytes and liver have the highest concentrations of catalase, and more than 99 % of blood catalase derives from the erythrocytes. Therefore, blood catalase activity is expressed in M (mega: 10^6) units per liter of blood (MU/L). Reference range of blood catalase activity is 113±16.5 MU/L [3].

The human catalase gene (CAT, NCBI Gene ID: 847, NM_001752.3, NP1743.1) has 13 exons, 12 introns and 33,135 nucleotides [4].

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and either insufficiency of insulin secretion or diminished insulin sensitivity. Gestational diabetes occurs with variable severity in 3%-5% of all pregnancies. It is related to oxidative stress and impaired antioxidant defense [5]. Furthermore, Hur et al., conducted a web-based search for genes associated with reactive oxygen species and diabetes mellitus. This search showed that among the targets insulin was the first and catalase the second [6].

There are several reports on decreased blood catalase activities in diseases of Hungarian subjects [7-10]. The main reasons for the blood catalase decrease might be caused by gene polymorphisms and mutations as well as regulatory mechanisms [11,12].

In this mini review, we discuss the blood catalase activity in different types of diabetes mellitus. For explanation of decreased blood catalase activity in type 2 and gestational diabetes the effects of catalase gene polymorphisms on catalase activity was examined. Furthermore, the mutational search of the catalase gene exons in diabetics with highly decreased blood catalase activity is explained. Finally, the association of acatalasemia and type 2 diabetes is evaluated.

Discussion and Results

Blood catalase activities in diabetes mellitus

For Hungarain patients with type 1, type 2 and gestational diabetes four papers report on the results of the determination of blood catalase activities [7-9,13].

In a total of 137 randomly selected diabetic patients (type 1:45, type 2: 92) the mean blood catalase activity was 94.4±19.2 MU/L. It means a significant (P 0.001) decrease when compared to that of reference range (113.3±16.5 MU/L) [7].

The mean activity of blood catalase was decreased (P0.001) in pregnant patients without diabetes (89±18 MU/L, n: 169) when compared to the control group of females (109±13 MU/L, n: 235). For diabetic pregnants the blood catalase (74±14 MU/L, n: 60) was decreased (P0.001) when compared either to that of controls (89±18 MU/L) or to those of pregnant without diabetes (89±18 MU/L [8].

For another cohort (diabetes type 1: 10^6, type 2: 100, gestational: 33, control: 60) the blood catalase activity was decreased in two types (type 2: 71.2±14.6 MU/L, P0.001, gestational: 68.5±12.2 MU/L, P0.001) of diabetes mellitus, while it was unchanged (P0.05) in type 1 (102.5 MU/L) when compared to that of controls (104.7±18.5 MU/L). In the group of type 2 diabetic the blood catalase decreased with age (P: 0.043) showing the highest activities (78.9±10.8 MU/L) between 20 and 40 years of age and the lowest ones (68.0±14.4 MU/L) for elder patients between 61 and 80 years [9].

A further cohort with a more diabetic patients (type 1: 115, type 2: 225) and controls (n: 295) yielded similar results. Blood catalase of type 1 diabetics was not changed (101±24 MU/L, P0.05) while type 2 diabetics had significantly (P0.001) lower blood catalase compared either to type1 diabetics or to controls (104±15 MU/L) [13].

These studies clearly showed that blood catalase activity decreases in type 2 and gestational diabetes while it does not change in type 1 diabetes mellitus. For genetic explanation of this decrease the examination of catalase gene polymorphisms and mutations might give an answer.

rs769217 and rs11001179 catalase gene polymorphisms in Hungarian diabetic patients

To date 748 single nucleotide polymorphisms (SNPs) have been reported for the human catalase gene [14], including 89 SNPs (59 missense, 29 synonymous, and 1 nonsense) in the exons [15]. Among the several SNPs only two attracted studies in details on diabetes mellitus. These two polymorphisms are the C111T in exon 9 (+22348C→T, rs769217, Asp389Asp) and -262C→T (rs1001179) which is located 262 base pairs from the transcription start site.

rs769217 polymorphism

This polymorphism was described by Wen in 1990 [14]. The effect of this polymorphism on blood catalase activity in patients with diabetes mellitus was examined firstly in Hungarian patients [9,13].

For type 2 diabetes the blood catalase activity was decreased (P0.005) in every genotypes (TT: 91±24 MU/L, CT: 90±24 MU/L, TT: 95±15 MU/L) when compared either to those of controls or to type 1 diabetics without differences in genotypes (P0.05).

For type 1 diabetics the TT genotype frequencies were higher (P0.02) than in type 2 diabetics and controls. Furthermore, the C allele frequency was higher than that of T allele in both types of diabetes (type 1 C: 0.68, T: 0.32, type 2 C: 0.72, T: 0.28) and in controls (C: 0.72, T: 0.28). From these data may be concluded that the rs769217 polymorphism yielded a weak association with type 1 diabetes mellitus (OR: 1.25, 0.9CI: 0.90-1.75). Furthermore, this silent polymorphism yielded no association with type 2 diabetes mellitus. For several cases the recent evidence has indicated that silent (synonymous) mutations may affect splicing and/or mRNA stability causing slower transcription from the mutant allele than from the wild allele [17].

rs11001179 polymorphism

Forsberg et al. reported on the -262C→T polymorphism in the 5'-region of the catalase gene that might have impact on catalase protein expression. In 29 Swedish controls they found that the subjects with T alleles had higher (P0.03) catalase activities [18]. For explanation, they assumed that the variant promoter sequence region can bind different transcription factors, which could explain the differences in promoter activity.

Chistiakov et al., reported on susceptibility of this polymorphism to type 1 diabetes mellitus in Russian population [19], but this susceptibility was not affirmed in UK and US populations [20].

In Hungarian diabetics and controls [13], the examination of this polymorphism showed decreased blood catalase activity for CC (98±30 MU/L), CT (88±34 MU/L) and TT (84±23) genotypes of type 2 diabetics compared to those (CC:109±25 MU/L, CT: 102±16 MU/L, TT: 103±17 MU/L) of the controls. The three genotypes had similar (P0.6) blood catalase activities and it did not yielded difference (P0.2) between types 1 and type 2 diabetics. These results showed that this polymorphisms could not explain the decrease in blood catalase activity, as all genotypes yielded the same change.

Further analyses of this polymorphisms revealed interesting findings. For type 2 diabetics it was detected that the mean age of patients with CC genotype (62±10 years) was higher (P0.006) than those of with TT genotype (54±9 years) without change in age of disease onset or disease duration. Furthermore, in the sulphonylurea treated group the number of type 2 diabetics was lower (P0.001) in TT genotype when compared to those with CC genotype (OR: 6.18, 0.95CI:2.39-15.9) or to all type 2 diabetics (OR: 3.36 0.95CI: 1.61-7.03). For explanation, we could assume that the sulphonylurea treatment of diabetics with TT genotype may have been less effective and the clinicians may have opted for other treatment. Furthermore,

this group of diabetics had decreased HDL and increased levels of glucose, hemoglobin A1c, cholesterol and ApoB. These results may suggest that diabetics with TT genotype of rs11001179 polymorphism have a risk for lower life expectancy due to their decreased blood catalase and their pathological carbohydrate and lipid biomarkers.

Contrary to findings in Swedish controls [18], these results showed the lowest blood catalase activities to the TT genotype similarly (P06) to the other two genotypes. Furthermore, the higher risks of these patients with the TT genotype suggests that this polymorphism might have an effect on other regulatory mechanisms of diabetes mellitus.

Mutational screening of catalase gene exons in diabetic patients with less than half of blood catalase activity [21,22]

Examination of possible catalase gene mutations which could be responsible for the highly (less than half of normal) decreased blood catalase activity was performed in 380 diabetics (type 1: 115, type 2: 205, gestational: 60). Highly decreased blood catalase activity was detected in 23 patients (6.0 %). These patients had type 1 (6), type 2 (14), gestational (3) diabetes. Their blood catalase activities were less than 52 MU/L which means the 50% of mean (52 MU/L) of the controls (104±15 MU/L, n: 295).

The mutational screening of their exons yielded four acatalasemia mutations (for type 1: 0, type 2: 3, gestational: 1). These acatalasemia mutations were marked as the Hungarian subtypes: H1(c.379CT) for the gestational patients, and H2(c.390TC), H3(c.434AT), G1(c.106.107insC) for type 2 diabetics. For the controls no one yielded either blood catalase activity bellow 52 MU/L (50%), or acatalasemia mutation.

From these results in may be concluded that an association may exist between the acatalasemia mutations and type 2 diabetes (OR: 144.8, 0.95CI: 21.5-974.1), and gestational diabetes (OR:144,8, 0.95CI: 10.2-2059.6).

Furthermore, these acatalasemia mutations could explain only the decreased (50%) blood catalase activities in 21.4 % (3/14) of type 2 diabetics, and 33.3% (1/3) of gestational diabetics.

Inherited catalase deficiency (acatalasemia) and diabetes mellitus

Acatalasemia refers to inherited deficiency of the catalase enzyme. It was one of the first inherited enzyme deficiencies. It was detected in Japan by Takahara S. in 1946 and he reported on its nine cases in 1952 [23]. To date for acatalasemia there are reports on 118 homozygotes and 364 heterozygotes in 12 countries. The frequency of acatalasemia is 0.08/1000 in Japan, 0.04/1000 in Switzerland, and 0.05/1000 in Hungary. The 15 genetic mutations of acatalasemia is known for 17 homozygous state and for 65 heterozygous state. Of 15 acatalasemia mutations 12 was detected in Hungarian patients [2,21]. Oral gangrene (Takahara disease) was detected in about half of the early cases of acatalasemia in the late 1940s and early 1950s when oral hygiene was poor in Japan. Due to it, the hydrogen peroxide generated by phagocytic cells and oral bacteria could damage the soft tissue in the mouth. Later, when oral hygiene improved the prevalence of Takahara disease decreased and it ceased [24]. Acatalasemia was thought at first to be an asymptotic disorder but recent findings suggest that it may be a risk factor in various age related diseases [2].

The first paper on association of acatalasemia and diabetes mellitus appeared in 2000 [25].

In 57 Hungarian patients with known acatalasemia mutations 17 (23.8%) had diabetes mellitus (type 1: 1, type 2:16). These patients were from 13 families with 66 non diabetic, normocatalasemic family members. It means a significantly higher frequency of diabetes (P0.001) in inherited catalase deficiency than its estimated frequency (6,5%) in Hungary.

Table 1 shows that eleven of twelve Hungarian acatalasemia mutations that were found in patients with diabetes mellitus. In inherited catalase deficiency the type 2 (n:16) is more frequent (P0.001) than type 1(n:1) of diabetes mellitus. Among the diabetics there are more females (n: 13, 76.4%) than males (n: 4, 23.6%) and this is significantly higher (P: 0.0040, Odds ratio: 5.44, 0.95CI: 1.71-17.26, Risk ratio: 6.80, 0.95CI: 2.01-23.01) when compared to that of normocatalasemic family members (female: 80, male: 134) [22].

The onset of diabetes for catalase deficient patients (43.1±10.9 years) appeared more than 10 years earlier (P0.001) than for the normocatalasemic subjects (56.3±11.2 years) [26].

Table 1: Hungarian subtypes of acatalasemia mutations in diabetes mellitus.

Type	n	Homo zygote	Hetero zygote	Male	Female	Catalase %	Exon	Intron	Mutation	Protein
A	2	2			2	4, 6	2		c.138_139insGA	p.Val134X
A*	4		4	2 2 22,46,54,54 2 c.138_139insGA p.Val134X						
B	3		3	3 67,51,54 2 c.79_80insC p.Thr71X						
C	1		1	1 58 7 IVS7+5C>T						
D	1		1	1 45 9 c.1060G>A p.Arg354His						
F1	1		1	1 53 2 c.161T>A p.Asp54Glu						
F2	1		1	1 52 2 c.201G>C p.Glu68Asp						
G1	1		1	1 44 2 c.106_107insC p.Glu71X						
H1**	1		1	1 50 4 c.379C>T p.Arg127Tyr						
H2	1		1	1 43 4 c.390T>C p.Arg130Leu						
H3	2		2	1 1 48,43 4 c.431A>T p.Asp143Val						
All	17	2	15	4 14 4-6, 22-67 2,4,9 7						

Abbreviations: A* Type 1 n:1, Type 2 n:3, H1** gestational diabetes.

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Furthermore, examination of 36 non diabetic subjects, including 18 normocatalasemic subjects and their age-matched hypocatalasemic relatives, yielded increased (P0.001) hemoglobin A1c (5.49±0.53%) and glucose (5.42±0.80 mmol/l) for catalase deficient patients when compared to those of their normocatalasemic relatives (hemoglobinA1c:4.88±0.45%, glucose: 4.83±0.46 mmol/L). The higher (5.42±0.80 mmol/L) average glucose concentration of hypocatalasemic patients may indicate that they have a higher (3.05X) risk of type 2 diabetes than their normocatalasemic relatives (glucose: 4,83±0.46 mmol/L, risk:1.81X) [26,27].

These data suggest, that inherited catalase deficiency may contribute to the manifestation of type 2 diabetes mellitus.

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Conclusion

From these results, the following conclusions may be drown.

1. Blood catalase activity in diabetes mellitus.

Blood catalase activities were significantly decreased in type 2 and gestational diabetes without change in type 1 diabetes mellitus.

2. The genetic analyses for explanation of decreased blood catalase activity yielded the following results.

It seems that rs769217 (C111T in exon 9, +22348C→T, Asp389Asp) a silent mutation and rs1001179 (-262C→T) in the 5' region of catalase gene have no effect on blood catalase activity.

The significantly higher frequency of diabetes (23.8 %, P0.001, compared to the 6.5 % of Hungarians) was found in inherited catalase deficiency. It may mean that the increased hydrogen peroxide concentration due to the low catalase activity may contribute to the damage of the oxidation sensitive pancreatic beta--cells. Furthermore, not the type of mutation but the oxidative damage due to their lowering effect on blood catalase may play a role in diabetes mellitus as 11 of 12 Hungarian acatalasemic mutations were found in diabetics.

These data may suggest that the lifelong effect of oxidative damage on the oxidant sensitive, insulin producing pancreatic beta-cells could contribute to the manifestation of diabetes mellitus especially to type 2 form [2,23,25,26,28,29]. These suggestions are in agreement with those found in animal experiments. Their authors reported that the acatalasemic mice were found susceptible for diabetes hich was caused by the oxidative stress of alloxan [30,31].

3. For 23 diabetics with decreased (50%) blood catalase activities only four (17.4%) acatalasemia mutations could explain the reason for the catalase decrease while for the other (82.6 %) cases it remains unsolved.

On the basis of these results it may be thought that the decreased blood catalase activity in type 2 and gestational diabetes rather due to regulatory mechanisms than to the catalase gene mutations.

Recent findings have revealed such mechanisms. Glorieux C. et al., in their review reported that the core promoter of the catalase gene has binding sites for transcription factors like NF-Y, Sp1, FoxO3a, and PPARγ, Oct-1. These factors may play an essential role in the regulation of catalase expression [11]. Dawson NJ, and Storey KB. Found that wood frog catalase could be activated by phosphorylation of serine and thyrosine of the catalase protein. They are suggesting that researchers should explore the activation of catalase enzyme by phosphorylation in other catalases especially in human catalase enzyme [12]. Veal E et al., reported on the hydrogen peroxide signaling which could be enhanced in catalase deficiency [1].

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