OBSERVATIONS

Catalase Deficiency and Type 2 Diabetes

Recent data suggest that at low concentrations hydrogen peroxide acts as a cellular messenger in insulin signaling, whereas at high concentrations it is toxic, particularly in pancreatic cells, which are catalase poor. Erythrocyte catalase is the main regulator of hydrogen peroxide metabolism; any inherited or acquired deficiencies in erythrocyte catalase may cause increased hydrogen peroxide concentrations with both toxic and physiological effects.

Examination of 23,150 Hungarian subjects detected 2 acatalasemic homozygotes and 63 hypocatalasemic heterozygotes. The two acatalasemic subjects and five of the hypocatalasemic subjects had type 2 diabetes, and one hypocatalasemic subject had type 1 diabetes. The 11% frequency of type 2 diabetes among the 65 catalase-deficient subjects was significantly different ($P < 0.005$) from the 0% frequency among their normocatalasemic relatives and the 1.75% frequency among 60,000 Hungarian residents reported by Góth and Eaton (1).

The onset of diabetes for catalase-deficient patients appeared more than 10 years earlier than for the normocatalasemic subjects (43.1 ± 10.9 vs. 56.3 ± 11.2 years of age, $P < 0.001$). Four of the five hypocatalasemic subjects with diabetes had C-peptide concentrations below the reference range (2). Four different catalase gene mutations (Hungarian types A, B, C, and D) were detected among these five patients (3). Therefore, early development of type 2 diabetes associated with catalase deficiency is not due to a specific mutation but is more likely due to overall catalase deficiency and, consequently, increased hydrogen peroxide.

Diabetes-related effects of catalase deficiency were further evaluated in 36 nondiabetic subjects. Normocatalasemic subjects ($n = 18$; 44.7 ± 17.9 years of age) were compared with age-matched relatives who were catalase deficient ($n = 18$; 45.1 ± 17.9 years of age). Increased A1C (5.49 ± 0.53 vs. 4.88 ± 0.45%) and glucose (5.42 ± 0.80 vs. 4.83 ± 0.46 mmol/l) concentrations were detected in the catalase-deficient relatives ($P < 0.01$). The high average glucose concentration (5.42 mmol/l) of the hypocatalasemic subjects may indicate that they have a higher (3.05×) risk of type 2 diabetes than their (4.83 mmol/l, 1.81×) normocatalasemic relatives (4).

Blood catalase activity in the type 2 diabetic subjects was decreased ($P < 0.001$) compared with that in the nondiabetic control subjects (71.2 ± 14.6 mU/l, $n = 100$; vs. 104.7 ± 18.5 mU/l, $n = 80$) (5). Specifically, blood catalase decreased with age in type 2 diabetic subjects ($-0.329 \times \text{age} + 107.6$, $r = -0.2487$, $P < 0.001$) when compared with the control group ($-0.047 \times \text{age} + 115.5$, $r = -0.015$).

In type 2 diabetic subjects who had blood catalase <50% of normal, the Hungarian acatalasemic C and D genotypes were not found (5); the frequency of type A and B acatalasemic mutations was 1.1% (5 among 441 diabetic subjects) compared with the 0% frequency of type A and B mutations in those without diabetes (0 among 240) (3). These data may suggest that downregulation of catalase synthesis, rather than specific catalase gene mutations, may be responsible for decreased blood catalase activity in the type 2 diabetic subjects.

In conclusion, life-long increased hydrogen peroxide concentrations, due to catalase gene mutations, may be a risk factor for type 2 diabetes. This risk may be due to peroxide damage of normally catalase-poor pancreatic β-cells. In type 2 diabetic subjects without known catalase gene mutations, blood catalase seems to be downregulated. One possible explanation for this phenomenon may be that increased levels of hydrogen peroxide in muscle cells due to decreased blood catalase may favor insulin signaling via inactivation of the oxidation-sensitive tyrosine phosphatases that could not dephosphorylate insulin receptors.

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