The ability of the red blood cell to synthesise glutathione in type 2 diabetes mellitus, and the implications for disease management

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Both the pathogenesis and complications of type 2 diabetes mellitus (NIDDM) have been associated with oxidative stress. Abdominal obesity and associated inflammation prior to the development of NIDDM is an oxidative stress that causes insulin resistance and deterioration of the β-cells of the pancreas. Hyperglycemia produces oxidative stress by promoting non-enzymatic glycation, glucose autoxidation (glycoxidation), and the formation of advanced glycation end products (AGE) and reactive oxygen species (ROS). Cells have antioxidant systems to deal with ROS, but high oxidative stress implies an inability of these systems to cope with the oxidative load.

The tripeptide glutathione (GSH) (γ-glutamyl cysteinyl glycine) is a ubiquitous intracellular antioxidant and is considered to be the largest mobile antioxidant pool and detoxifier. A decrease in GSH concentration in the red blood cells (RBCs) of diabetes subjects is widely reported. However, several authors report unchanged or elevated GSH concentrations in diabetes.

In this study, RBCs taken from 20 NIDDM subjects (58.3 ± 2.5 yr) with a mean HbA_{1c} of 8.34 ± 0.2%, and 20 healthy controls (46.6 ± 3.3 yr) with a mean HbA_{1c} of 5.7 ± 0.1% were GSH-depleted using 1-chloro-2,4-dinitrobenzene, and then incubated in a solution containing substrates for GSH synthesis (alanine, α-ketoglutarate, glycine and N-acetyl cysteine), and sampled for total free GSH using a DTNB/enzymatic recycling procedure . The NIDDM subjects had the same total free GSH concentration (1.89 ± 0.1 *vs.* 1.91 ± 0.1 mmol(L RBC)$^{-1}$), and the same rate of GSH synthesis (1.14 ± 0.1 *vs.* 1.06 ± 0.1 μmol(L RBC)$^{-1}$(min)$^{-1}$) as controls ($p > 0.05$), indicating that the GSH synthesizing enzymes were normal. NIDDM, but not controls, showed an increase in total GSH concentration ($p = 0.0001$ for slope, ANCOVA for TFG, $F_{(1,38)} = 7.5624$, $p = 0.0093$) and a trend toward increasing rates of GSH synthesis ($p = 0.09$) with increasing age, not related to the amount of glycation, as the HbA_{1c} was not well-correlated with age. Healthy controls had a positive correlation between the rate of GSH synthesis and total GSH concentration ($p = 0.0005$, $r = 0.71$). NIDDM subjects did not ($p = 0.731$, $r = 0.05$), indicating larger oxidative loads.

To our knowledge, our results provide the first evidence that intact RBCs from NIDDM subjects, given adequate substrate, are able to synthesise GSH at normal rates compared to healthy, age-matched controls.