

# Abstract

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## Deficient synthesis of glutathione underlies oxidative stress in aging and can be corrected by dietary cysteine and glycine supplementation.

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**BACKGROUND:** Aging is associated with oxidative stress, but underlying mechanisms remain poorly understood.

**OBJECTIVE:** We tested whether glutathione deficiency occurs because of diminished synthesis and contributes to oxidative stress in aging and whether stimulating glutathione synthesis with its precursors cysteine and glycine could alleviate oxidative stress.

**DESIGN:** Eight elderly and 8 younger subjects received stable-isotope infusions of [2H(2)]glycine, after which red blood cell (RBC) glutathione synthesis and concentrations, plasma oxidative stress, and markers of oxidant damage (eg, F(2)-isoprostanes) were measured. Elderly subjects were restudied after 2 wk of glutathione precursor supplementation.

**RESULTS:** Compared with younger control subjects, elderly subjects had markedly lower RBC concentrations of glycine ( $486.7 \pm 28.3$  compared with  $218.0 \pm 23.7$   $\mu\text{mol/L}$ ;  $P < 0.01$ ), cysteine ( $26.2 \pm 1.4$  compared with  $19.8 \pm 1.3$   $\mu\text{mol/L}$ ;  $P < 0.05$ ), and glutathione ( $2.08 \pm 0.12$  compared with  $1.12 \pm 0.18$   $\text{mmol/L RBCs}$ ;  $P < 0.05$ ); lower glutathione fractional ( $83.14 \pm 6.43\%$  compared with  $45.80 \pm 5.69\%/d$ ;  $P < 0.01$ ) and absolute ( $1.73 \pm 0.16$  compared with  $0.55 \pm 0.12$   $\text{mmol/L RBCs per day}$ ;  $P < 0.01$ ) synthesis rates; and higher plasma oxidative stress ( $304 \pm 16$  compared with  $346 \pm 20$  Carratelli units;  $P < 0.05$ ) and plasma F(2)-isoprostanes ( $97.7 \pm 8.3$  compared with  $136.3 \pm 11.3$   $\text{pg/mL}$ ;  $P < 0.05$ ). Precursor supplementation in elderly subjects led to a 94.6% higher glutathione concentration, a 78.8% higher fractional synthesis rate, a 230.9% higher absolute synthesis rate, and significantly lower plasma oxidative stress and F(2)-isoprostanes. No differences in these measures were observed between younger subjects and supplemented elderly subjects.

**CONCLUSIONS:** Glutathione deficiency in elderly humans occurs because of a marked reduction in synthesis. Dietary supplementation with the glutathione precursors cysteine and glycine fully restores glutathione synthesis and concentrations and lowers levels of oxidative stress and oxidant damages. These findings suggest a practical and effective approach to decreasing oxidative stress in aging.

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