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Effect of Exercise on Oxidative Stress in Individuals with Glucose-6-phosphate Dehydrogenase Deficiency

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Abstract. *The effect of exercise on oxidative stress in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals was investigated. Materials and Methods: Nine G6PD-deficient males and nine males with normal G6PD activity were selected and requested to run at ~75% their maximum heart rate for 45 min. Blood samples were collected prior to and immediately after exercise. Several hematological parameters, reduced glutathione (GSH), oxidized glutathione (GSSG), lipid hydroperoxides, thiobarbituric acid reactive substances (TBARS), protein carbonyls, catalase and total antioxidant capacity (TAC) were measured in the blood before and after each exercise bout. Results: GSH was significantly (more than two-fold) higher in the control group compared to the G6PD-deficient group at baseline, whereas GSSG, GSH/GSSG and lipid hydroperoxides were not different between the two groups. Exercise did not affect the levels of any oxidative stress marker. There was no evidence of Heinz body formation neither at rest nor after exercise in either group. Exercise of moderate intensity and duration did not result in an increase of blood oxidative-stress biomarkers in G6PD-deficient males nor in matched controls. It appears that G6PD-deficient individuals may exercise without experiencing a rise in oxidative stress at an exercise intensity ~75% of their maximum heart rate.*

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The vast majority of glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals are asymptomatic. However, those suffering a certain type of G6PD-deficiency are at risk of severe acute hemolytic anaemia under the effect of oxidative agents, following the ingestion of certain drugs, and especially after eating fava beans (1). G6PD catalyzes the first reaction of the pentose phosphate pathway involving the conversion of glucose into pentose sugars, while providing reducing power in the form of NADPH. The NADPH produced is crucial for the protection of cells, particularly erythrocytes, from oxidative stress. Erythrocytes, and other cells to a lesser extent, of individuals who are G6PD-deficient cannot generate sufficient NADPH to regenerate the reduced form of glutathione (GSH) from the oxidised form (GSSG), which theoretically impairs their ability to dispose lipid peroxides and H_2O_2. These compounds can cause oxidation of sulfhydryl groups in proteins and peroxidation of lipids in the membrane of a cell. In erythrocytes, peroxidation of lipids can cause lysis of the membrane, *i.e.*, hemolysis; if some of the sulfhydryl groups of hemoglobin become oxidized, the protein precipitates inside the erythrocyte, forming Heinz bodies (2).

It is now well established that heavy exercise can accelerate the generation of reactive oxygen species (ROS) frequently exceeding the capacity of antioxidant defences and resulting in oxidative stress, which can induce adverse effects on health (3). Erythrocytes are susceptible to oxidative damage because of the high polyunsaturated fatty acid content in their membranes and the high concentrations of oxygen and hemoglobin (4). During exercise, where the production of ROS increases, erythrocytes are at an increased risk of oxidative damage.

Erythrocytes, as well as the whole body, contain an antioxidant defence system that includes enzymatic and non-enzymatic antioxidants (from which, GSH is of great importance), in order to combat the formation of ROS.

Several reports in the literature have shown that G6PD-deficient individuals exhibit increased oxidative stress in several tissues. One possible reason that deficient individuals exhibit predisposition for generation of oxidative stress is the decreased levels of antioxidants in these individuals. For example, it has been reported that G6PD-deficient individuals have lower levels of vitamin E, vitamin C, carotenoids and glutathione (1).

The purpose of the present study was to examine the effects of a single bout of exercise on blood oxidative stress markers in G6PD-deficient individuals in comparison to matched controls.

Materials and Methods

Subjects. Nine males with established G6PD deficiency and nine males with normal G6PD activity (matched with the G6PD-deficient subjects for age, height, weight, %body fat and maximal oxygen consumption; VO_{2max}) participated in the present study. Subjects were non-smokers and were not receiving anti-inflammatory medication or nutritional supplements. Subjects were amateur runners and had been training approximately three times per week for about 1 h per session with moderate intensity for at least one year. A written informed consent to participate in the study was provided by all participants after they had been informed of all risks, discomforts and benefits involved in the study. The procedures were in accordance with the Helsinki declaration of 1975, and approval for this study was received from the Institutional Review Board of the University of Thessally, Greece.

Anthropometric measurements. Subjects reported to the laboratory twice. During their first visit, each participant reported to the laboratory in the morning after an overnight fast. After sitting for 5 min, a blood sample was drawn from a forearm vein to determine G6PD activity. Body mass was measured to the nearest 0.5 kg (Beam Balance 710, Seca, UK) with subjects lightly dressed and barefooted. Standing height was measured to the nearest 0.5 cm (Stadiometer 208, Seca, UK). Body fat percentage was calculated from seven skinfold measures (average of two measurements of each site) using a Harpenden calliper (John Bull, UK), according to published guidelines (5). The anthropometric characteristics of the subjects are shown in Table I.

Measurement of submaximal oxygen consumption. In order to establish that subjects of the control and G6PD-deficient group were of a similar level of fitness, VO_{2max} was extrapolated from a submaximal oxygen consumption test (6), using a progressive run test to achieve 85% of age-predicted maximum heart rate on a GXC200 treadmill (Powerjog, UK). Age-predicted maximum heart rate (HR_{max}) was calculated using the following equation: HR_{max} = 220 – age (5). A submaximal test was chosen because it was not known whether a maximal test would lead to any side-effects (such as hemolysis) in G6PD-deficient individuals. The predicted VO_{2max} of the subjects is shown in Table I.

Table I. *Characteristics of control and G6PD-deficient individuals (mean±SEM).*

	Control	G6PD
Age (years)	29.0±2.0	29.1±3.1
Height (cm)	175.2±3.3	175.0±2.5
Weight (kg)	73.8±9.3	75.9±5.4
Body fat (%)	18.4±1.6	17.6±2.7
VO_{2max} (ml/kg/min)	49.6±2.0	48.7±1.7

Exercise protocol. At least one week after the submaximal oxygen consumption test, the subjects performed an acute bout of submaximal exercise. Subjects abstained from alcohol and caffeine consumption for at least 24 h before the test. Participants reported to the laboratory at 09:00 and a resting blood sample was drawn by the aforementioned procedure.

The subjects then exercised for 45 min on the treadmill at an intensity corresponding to 70-75% of their HR_{max}, which represents an exercise intensity frequently recommended to improve health and aerobic fitness (5). Exercise heart rate was monitored by telemetry (Polar Tester S610, Polar Electro Oy, Finland) to ascertain the predetermined exercise intensity. Speed adjustments during exercise were made to ensure that the subjects were exercising within the 70-75% of predicted HR_{max}. Exercise was performed at a temperature of 21±2˚C and 45±4% relative humidity. In order to prevent discomfort and plasma volume changes, subjects had access to water *ad libitum*. Within two minutes from the completion of exercise, a post-exercise blood sample was drawn.

Blood handling. Blood was collected into a test tube containing EDTA to prevent clotting and immediately was placed on ice. A portion of this sample was used for the determination of hematocrit, hemoglobin, G6PD activity, Heinz bodies and GSH.

For GSSG determination, 100 μl of whole blood was mixed gently with 10 μl 1-methyl-2-vinyl-pyridinium trifluoromethane sulfonate. The remainder of the blood was centrifuged at 1,500 xg at 4˚C for 5 min. The plasma produced was promptly removed for the determination of lipid hydroperoxides. Hematocrit, hemoglobin, G6PD activity and Heinz bodies were determined on the day of blood collection. Blood samples for GSH, GSSG and lipid hydroperoxides were stored in multiple aliquots at –80˚C and thawed only once before analysis.

Assays. Post-exercise changes in plasma volume were computed based on hematocrit and hemoglobin, as previously described (7). The hematological parameters were measured in a Sysmex K-1000 autoanalyzer (TOA Electronics, Japan). G6PD activity was determined with commercially available kit from Sigma (USA).

For Heinz body determination, 0.5 ml of whole blood was mixed with 10 ml sodium nitrite (Merck, USA) and the solution was placed in a water-bath at 37˚C for 30 min. Thereafter, an equal volume of the solution and methyl violet (Amresco, USA) was laid on a glass slide and examined for Heinz bodies under a light microscope at x100 magnification.

Blood GSH and GSSG concentrations were determined spectrophotometrically using the GSH/GSSG-412 kit from

Table II. *Analysis of daily energy intake of control and G6PD-deficient individuals (mean±SEM).*

	Control	G6PD
Energy (MJ)	11.73±0.89	10.79±0.85
Carbohydrate (% energy)	47.6±5.3	45.2±5.2
Fat (% energy)	37.9±4.2	39.4±4.2
Protein (% energy)	14.5±1.1	15.4±0.7
Vitamin A (RE, mg)#	0.98±0.17	1.14±0.18
Vitamin C (mg)	141.0±40	171.0±49
Vitamin E (mg)	8.4±1.4	7.4±1.8
Selenium (mg)	0.12±0.02	0.14±0.01

#RE, retinol equivalents.

Table III. *Hematological variables in control and G6PD-deficient individuals pre- and post-exercise (mean±SEM).*

	Control		G6PD	
	pre	post	pre	post
Hct (%)	45.81±1.07	46.00±1.14	43.31±0.96*	43.44±1.20
Hb (g/dl)	14.93±0.27	15.06±0.31	14.81±0.28	14.86±0.40
RBC (10^{12}/l)	4.96±0.11	4.99±0.11	4.63±0.12	4.65±0.16

Hct, hematocrit; Hb, hemoglobin; RBC, red blood cell count.
*Significantly different from the respective value in the control group.

OxisResearch (USA), which is based on the method of Tietze (8). Lipid hydroperoxides were measured spectrophotometrically using the LPO-586 kit (OxisResearch), which is based on the method of Mattson *et al.* (9). All samples were determined in duplicate. All samples of the same assay were analyzed in a single run. The intra-assay coefficient of variation for each assay was: G6PD 2.9%; GSH 5.3%; GSSG 8.2%; and lipid hydroperoxides 4.0%. All spectrophotometric determinations were performed in a Spectronic 401 spectrophotometer (Milton Roy, USA).

Dietary analysis. In order to establish that participants of both groups had similar levels of macronutrient and antioxidant intake, they were asked to record their diet for three days before the exercise protocol. Each subject was provided with a written set of guidelines for monitoring dietary consumption and a record sheet for recording food intake. Diet records were analyzed using the computerized nutritional analysis system Science Fit Diet 200A (Sciencefit, Greece).

Statistical analysis. Data are presented as means±SEM. The distribution of all dependent variables was examined using the Kolmogorov-Smirnov test and was found not to differ significantly from normal. Significant differences between rest and exercise were detected by two-way (state x time) MANOVA with repeated measures on both factors. If a significant main effect was obtained, pairwise comparisons were performed through simple main effect analysis. Differences in physical characteristics, G6PD activity and diet between the two groups were examined using unpaired Student's *t*-test. The level of statistical significance was set at $\alpha=0.05$. The software package SPSS, version 12.0, was used for all analyses (SPSS Inc., USA).

Results

There were no significant differences in any of the physical characteristics or fitness level between the two groups. Additionally, no significant differences in daily energy, macronutrient or antioxidant intake were found between the two groups (Table II). The control subjects ran at an intensity corresponding to 74.6±0.7% of their HR_{max}, while the G6PD-deficient subjects at 73.3±1.2%. Post-exercise plasma volume relative to pre-exercise was 0.99±0.04 in control group and 0.99±0.05 in G6PD-deficient group (both not significant). When post-exercise GSH, GSSG, GSH/GSSG and lipid hydroperoxide values were corrected for plasma volume changes, the results of the statistical comparisons were not different from those performed on the original values, therefore the original values are presented.

G6PD activity was significantly higher (by 22-fold) in control compared to G6PD-deficient individuals (8.80±0.57 U/g Hb *vs.* 0.41±0.17 U/g Hb). Hematocrit was significantly lower in G6PD-deficient group at rest, whereas all other hematological variables were not different between the control and G6PD-deficient individuals, or between pre- and post-exercise values in both groups (Table III).

In order to examine if exercise brought about the oxidation of hemoglobin, erythrocytes were examined microscopically for the presence of Heinz bodies, which are various forms of denatured hemoglobin (2). However, Heinz body formation was not seen in either group, either pre- or post-exercise. Exercise did not alter the levels of any index of oxidative stress used in the present study (Figure 1). However, GSH was significantly lower (by 2.3-fold) in the G6PD-deficient group compared to the control group, both pre- and post-exercise.

Discussion

To our knowledge, this is the first attempt to investigate the effect of exercise on the redox status of individuals with G6PD deficiency. Our hypothesis was that exercise would result in greater oxidative stress in the G6PD-deficient group. However, our results revealed that the selected oxidative stress markers remained unaffected after exercise in participants regardless of whether they had G6PD deficiency or not. Therefore, G6PD-deficient individuals can exercise at a moderate intensity for up to 45 min without any side-effects, at least regarding their blood redox status.

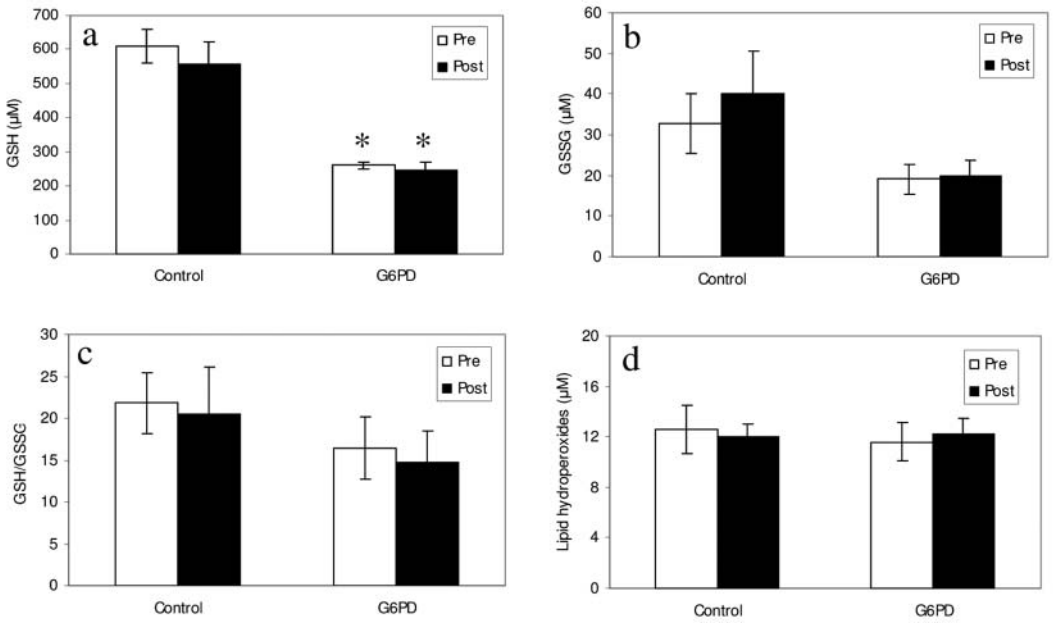

Figure 1. *The effect of exercise on (a) GSH, (b) GSSG, (c) their ratio and (d) lipid hydroperoxide concentration in control and G6PD-deficient individuals (mean±SEM). *Significantly different from the respective value in the control group. Abbreviations: GSH, reduced glutathione; GSSG, oxidized glutathione; G6PD, glucose-6-phosphate dehydrogenase.*

There is plenty of evidence which suggests that exercise can induce oxidative stress (3). The present study employed four widely used indices of oxidative stress: GSH, GSSG and GSH/GSSG as markers of glutathione redox status, and lipid hydroperoxides as a marker of lipid peroxidation. There may be several reasons why the exercise protocol selected did not provoke alterations in these indices. One reason may be the moderate exercise intensity used in the present study (10) (on average, at 74% of HR_{max}), which is estimated to correspond to 65% of VO_{2max} (11). Another reason, may be the duration of the exercise session (45 min), which can also be considered as moderate. Finally, the subjects that took part had a high aerobic capacity, which places them over the 80th percentile in the classification for maximal aerobic power (5). In support of this view, several human studies, using an exercise bout with generally similar characteristics to ours, have reported no alterations in blood GSH, GSSG, their ratio (12-16) or lipid hydroperoxides (17-20). Additionally, it is known that trained humans generally demonstrate a greater tolerance of exercise-induced disturbances of blood glutathione and lipid peroxidation (21, 22). Therefore, given the fitness level of our subjects and the moderate intensity and duration of the exercise session selected, it appears that the exercise stimulus might not have been adequate to elicit an increase in oxidative stress in these individuals.

Despite this limitation, it should be stressed that this was the first attempt to examine the effects of exercise on G6PD-deficient individuals and given that previous studies have reported that high intensity exercise may cause myoglobinuria in deficient individuals (23, 24), it was decided to use an exercise session with somewhat "safe" characteristics. In any case, it appears that running for 45 min at 75% of HR_{max} can be performed safely, at least as indicated by the oxidative stress biomarkers used in the present study, by those with G6PD deficiency.

Regarding the resting levels of glutathione, we found that GSH was more than two-fold higher in subjects with normal G6PD activity compared to deficient individuals. Similar findings have been reported by the majority of the relevant studies (25-28), eventhough Bilmen *et al.* (29) did not find such differences.

On the other hand, lipid peroxidation was not significantly different in G6PD-deficient individuals based on the plasma lipid hydroperoxides measured. The situation in the literature is not clear, since some studies have reported no differences (29) in TBARS (another index of lipid peroxidation) between G6PD-deficient and normal subjects and some have reported increased levels (30). Since we found less than half of the GSH and no differences in lipid peroxidation in G6PD-deficient individuals, it is probable that these individuals have developed alternative protective mechanisms.

To the best of our knowledge, the only studies relevant to the effect of exercise on G6PD-deficient subjects are three case reports (23, 24, 31). Ninfali *et al.* (24) reported that one G6PD-deficient individual was hospitalized for myalgia and myoglobinuria after intense exercise, while Bresolin *et al.* (23) reported that an athlete with G6PD deficiency developed myoglobinuria after intense exercise. However, these clinical symptoms may have appeared not because of the G6PD deficiency itself, but as a result of the preceding severe exercise bout. It is worth mentioning that the clinical symptoms referred to in the aforementioned reports can also be found in normal individuals after intense, particularly muscle-damaging, exercise (32, 33). It is therefore probable that the symptoms reported in these studies were due to the preceding exercise bout and not the G6PD deficiency itself. The third case report (31) showed that 30 min of treadmill exercise at 70-75% of VO_{2max} did not affect the levels of several oxidative stress indices in one individual with G6PD deficiency. However, the G6PD-deficient individual in this study was well-trained (his VO_{2max} was 57.1 ml/kg/min) and it is probable that this hindered the appearance of oxidative stress.

Conclusion

It was found that exercise of moderate intensity and duration did not result in an increase in blood oxidative-stress biomarkers in G6PD-deficient males nor in matched controls, despite the much lower levels of resting blood GSH of the former. It appears that G6PD-deficient individuals may exercise without experiencing a rise in oxidative stress or hemoglobin oxidation at an exercise intensity that corresponds to 74% of their HR_{max}, which represents an exercise intensity frequently recommended to improve health and aerobic fitness (5).

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