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Blood Levels of Reduced and Oxidized Glutathione in Malignant and Non-malignant Human Colorectal Lesions

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Abstract—*Glutathione blood levels were determined in colorectal cancer patients* (n = 10), *patients with adenomatous colorectal polyps* (n = 8), *and healthy subjects (control group*; n = 10). *Mean GSH level* (μg/ml) *was significantly higher in cancer patients* [515.4 ± 76.1 (*S.D.*)] *than in those with polyps* [407.7 ± 90.5 (*S.D.*), $P < 0.05$] *and the control group* [360.9 ± 67.9 (*S.D.*), $P < 0.001$]. *Statistically significant lower GSSG blood levels were observed in cancer patients when compared to the other groups. The highest mean blood GSH/GSSG ratio (log transformed) was observed in cancer patients* [2.17 ± 0.108 (*S.D.*)] *and the lowest in healthy subjects* [1.88 ± 0.032 (*S.D.*)]. *All between-group differences in the GSH/GSSG ratio were statistically significant.*

These findings suggest that glutathione blood levels as well as GSH/GSSG ratio may have applicability as a guide for following the activity of colorectal diseases.

INTRODUCTION

GLUTATHIONE exists in high concentrations in mammalian cells [1]. It may be present within cells in its reduced form (GSH, γ-glutamyl-cysteinyl-glycine), as a glutathione disulphide (GSSH), and as a disulphide complexed with protein as well as non-protein sulphydryls. In normal cells the majority of glutathione exists as GSH, which is known to play an important role in protecting cells from free radicals, reactive oxygen compounds [2], and other cytotoxic agents as well [3, 4]. Glutathione offers protection against radical damage or lipid peroxidation either through a direct scavenging of free radicals [5] or acting as a cofactor for the enzyme glutathione peroxidase [6]. The protection offered by the cell appears to be directed toward maintaining a high GSH/GSSG ratio [7].

A possible role played by GSH in the process of carcinogenesis and in cancer therapy has been investigated by measuring GSH tissue levels in preneoplastic animal tissues as well as in neoplastic animal and human tissues. The studies conducted so far have reported conflicting results, indicating both increased and decreased levels of GSH [1, 4, 8–13].

The purpose of the present study was to evaluate whether there are differences in glutathione blood levels determined in healthy subjects, patients with single or discrete colorectal adenomatous polyps, which are well-known precancerous conditions, and colorectal cancer patients.

MATERIALS AND METHODS

The study subjects were identified among individuals who underwent a physical examination at the Gastrointestinal Unit of the National Cancer Institute of Genoa, Italy. Their health status was evaluated by the following serum parameters: haematocrit, haemoglobin, ferritin, total iron, transferrin, ceruloplasmin, total protein, albumin, β-globulin and lipid profile. Patients weighing 25% less than their usual body weight or receiving any type of therapy at the time of the examination were excluded from the study.

These inclusion criteria permitted identification of the following groups: 10 colorectal cancer patients, 55–74 years old, eight males and two females, eight polyp patients, 40–79 years old, four males and four females, and 10 healthy individuals 26–71 years old, five males and five females. Every lesion was histologically confirmed.

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Blood samples and assays

Fasting patients' blood samples (10 ml) were collected between 8 and 9 a.m. in plastic tubes containing 20 μl heparin. Whole blood samples were immediately analysed for the 'total' glutathione and for GSSG according to Tietze [14].

Statistical analysis

The normal distribution of GSH, GSSG and the GSH/GSSG ratio was verified and the log transformation of the GSH/GSSG ratio was used in the statistical comparison. Student's t test for unequal variances was performed to test differences between groups using the BMDP Statistical Software, procedure 4F [15]. Between-group differences were considered statistically significant at a P value below 0.05.

RESULTS

Figure 1 reports whole blood GSH and GSSG levels and the ratio GSH/GSSG (log transformed) by group of individuals. The mean GSH blood level was significantly higher among colorectal cancer patients [515.4 ± 76.1 (S.D.) μg/ml] than among both polyp patients [407.7 ± 90.5 (SD.) μg/ml, $P < 0.05$] and healthy subjects [360.9 ± 67.9 (S.D.) μg/ml, $P < 0.001$]. Although polyp patients showed a higher GSH blood level than healthy subjects, this difference was not statistically significant.

GSSG blood levels were found to be significantly lower in cancer patients [3.4 ± 0.6 (S.D.) μg/ml] than in subjects with adenomatous colorectal lesions [4.6 ± 1.1 (S.D.) μg/ml, $P < 0.05$] and controls [4.7 ± 0.7 (S.D.) μg/ml, $P < 0.001$]. The GSH/GSSG ratio (log transformed) was significantly increased in cancer patients [2.17 ± 0.108 (S.D.)] than both in polyp patients [1.95 ± 0.045, $P < 0.001$] and healthy subjects [1.88 ± 0.032, $P < 0.001$]. The difference in GSH/GSSG ratio observed in polyp patients when compared to healthy subjects was statistically significant ($P < 0.05$).

DISCUSSION

The principal purpose of our preliminary work was the blood evaluation of GSH and GSSG in non-malignant and malignant colorectal lesions to overcome the problems connected with human biopsies.

Mean GSH concentrations and the GSH/GSSG ratio in the blood of colorectal cancer patients were significantly higher than those detected either in normal subjects or in patients with adenomatous colorectal lesions. Although the reason for the increased blood GSH and GSH/GSSG ratios observed in patients suffering from colorectal lesions is unclear, the significant loss of GSSG in the blood of patients with colorectal carcinoma suggests an altered activity of glutathione-correlated redox enzymes [16] and other enzymes [9, 17] which are known to be involved in interorgan translocation and metabolism of glutathione [18].

The high GSH/GSSG blood ratio observed in the polyp patients does not seem to be attributable to a loss in GSSG as in the case of colorectal cancer patients. It could rather reflect an initial response to a pathological condition directed toward maintaining a high concentration of GSH relative to GSSG [7]. In fact, our findings indicate positive and negative trends in GSH and GSSG blood levels respectively, from the normal to the malignant condition.

To our knowledge this is the first time that the levels of GSH, GSSG and the ratio of GSH/GSSG have been determined in the blood of patients with colorectal diseases. These findings suggest the need for further studies to evaluate a possible applicability of GSH blood levels and the GSH/GSSG ratio as a tool in the study of the activity of human colorectal lesions.

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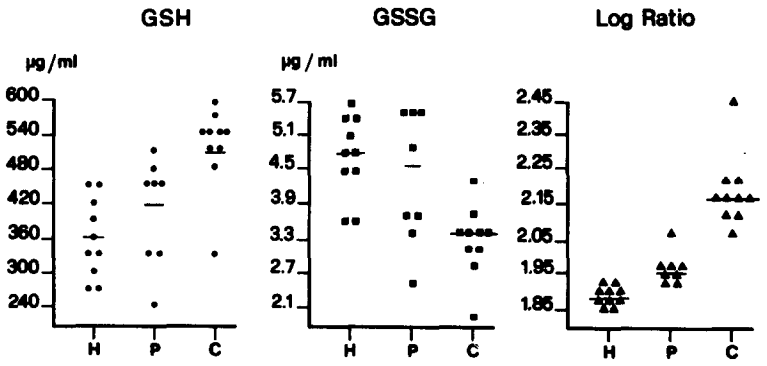

Fig. 1. GSH, GSSG blood levels and GSH/GSSH ratio (log transformed) in healthy subjects (H), adenomatous polyp (P), and colorectal cancer (C) patients; horizontal bars indicate mean values.

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