REDUCED BLOOD GLUTATHION LEVELS IN PATIENTS WITH CHRONIC URTICARIA

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SUMMARY: Reduced glutathion (GSH) level of whole blood, an important parameter for evaluating the functional status of the cell membrane and of cellular metabolism was determined in 51 patients with chronic urticaria. One group of these patients revealed an increased level (65.0±6.2 mg %, 2p<0.001) of GSH compared to a series of normal controls (n=26) of which mean reduced glutathion level was 53.0±6.0 mg%. In the second group of patients, on the contrary, the GSH was significantly reduced (40.0±5.5 mg%, 2p <0.001).

Key Words: Reduced glutathion, zinc deficiency.

INTRODUCTION

Reduced glutathion (GSH) is a tripeptid containing glutamic acid, cystein and glycine which has an active sulphidryl (-SH) group. It is the nonspecific orginctive agent present in all living cells (19) and is therefore very important in oxidative processes (25). Activity of enzymes which is primarily dependant on the (-SH) group of the prosthetic surfaces are abundantly present in the living organism. An example is glyceraldehydes-3-P-dehydrogenase which is the key enzyme for carbohydrate metabolism. These enzymes are essential for life and are inactivated when oxidized or exposed to agents combining with their (-SH) groups. Regeneration of these enzymes is only possible by reduced glutathion.

Besides this function on enzymes, reduced glutathion has a protective role of the -SH groups of lipoproteins existing in the cellular membrane, as well as in hemoglobin (18, 21), the various proteins (10, 22, 25, 27) and in catalase (12). GSH also plays a very important part in detoxifying the drugs, anesthetic agents and toxins in the liver. It is believed that some of the liver toxins including C1 are excreted after combining with the (-SH) group of reduced glutathion (9).

Because allergic manifestations are to a large extent related to increased cellular permeability (3,4) we considered it possible that variations in glutathion might play a role in their pathogenesis. In fact we have in the past reported that serum zinc levels have a presently inadequately understood relation to allergic diseases (5-7). This fact is further supported by innumerable clinical observations as well as immunological studies (8, 15, 16, 26, 34). It is also known that zinc and selenium levels reveal a rather close parallelism (31). Selenium on the other hand is the activator of glutathion (32). This relationship suggests that glutathion may have a role in pathogenesis of allergic diseases. We therefore have planned a series of investigations to illuminate the role of zinc and selenium and several enzymes related to these trace elements in pathogenesis of allergic diseases. The present report is the first of the series.

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MATERIALS AND METHODS

Of 189 patients with urticaria referred to H.U. Medical and Surgical Research Center 51 were randomly chosen for this study. The control group consisted of 26 normal adults of comparable age who voluntarily came to blood bank of the hospital to donate blood. 0.2 ml of venous blood removed from the antecubital vein was used for measurement of GSH according to Beutler's method (1). All measurements were done in duplicate.

Detailed clinical and laboratory studies were carried out on the same patients and $ZnSO_4$ therapy was later initiated (5-7). $CuSO_4$ was also administered either in combination with $ZnSO_4$ (8) or alone when indicated. Results of blood taken before any therapeutic intervention was used for determination of GSH and formed the basis of this report.

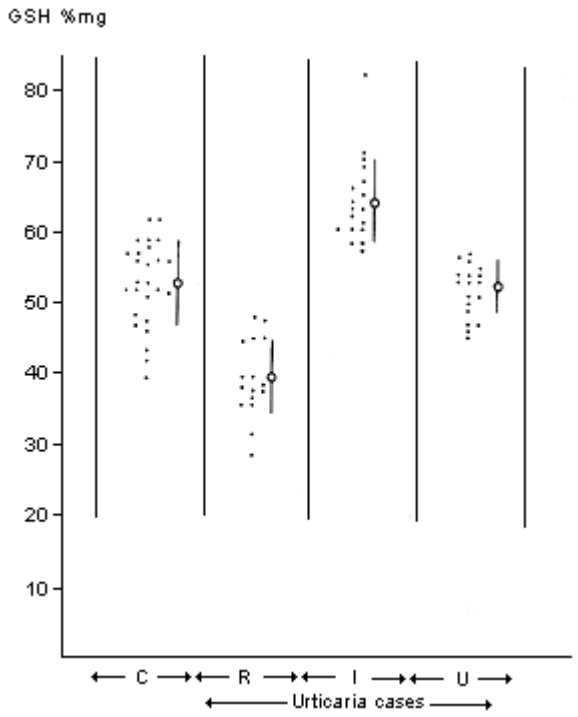

Figure 1: C: Control cases
R. I. U. : Three different subgroups in the urticaria cases
R: Cases with reduced GSH levels
I: Cases with increased GSH levels
U: Cases with unchanged GSH levels.

RESULTS

The mean of reduced-glutathion levels of 26 normal control cases was 53.0±6.0 mg% (Figure 1). The results of GSH of 51 cases with chronic urticaria averaged 52.7 ±11.3 mg% ($p > 0.05$). It was noticed however that the patients formed three groups so far as GSH results are concerned. It was markedly reduced in one group (40.0 ±5.5 mg%, $2p < 0.001$) while it was significantly increased the second (65.0±6.2 mg%, n=17, $2p < 0.001$) and remained unchanged in the third group (n=18, $p > 0.05$).

DISCUSSION

The nonprotein sulphydryl groups which are very important for the cellular metabolism and membrane function are of three components: reduced glutathion (GSH), cystein and ergothioneine. Cystein in the metabolic procursor of GSH and of protein. Its free form is almost non existent (33). Ergothioneine has recently been introduced as a co-enzyme. Its physiological function in mammals however is not clearly understood.

Reduced glutathion forms nearly 90% of nonprotein sulphydryl groups (NPSH) within the red cell. For this reason numerous investigators believe that reduced glutathion levels can be accepted to represent NPSH for practical purposes. The amount of oxydized glutathion on the other hand is very much less compared to GSH, it may even be practically neglected. Since reduced glutathion is rapidly oxidized, under in vitro conditions chemical procedure for its determination was performed without delay.

A rather close relationship has been demonstrated between GSH and pathogenesis of diabetes (13): It is interesting that by administration of GSH before alloxan in experimental animals which produces diabetes by damaging the B cell it is possible to prevent development of the disease (14). In primary gout glutathion reductase (GSSGR) enzyme is shown to increase while tophi are formed (2,23). GSSGR on the other hand needs flavin adenin di-nucleotid (FAD) as a co-factor in the process of reducing GSH. Change of riboflavin to its active form, the flavin mononucleotid (FMN) and flavin adenine dinucleotide (FAD) are regulated by thyroxin (20, 28, 29). Riboflavin deficiency should therefore be considered in cases where GSH was found below normal levels. The patients whose GSH is found below normal are presently under consideration of correlation between trace elements as the disease is being treated. It is also interesting to note here that reduced glutathion level and glutathion reductase enzyme activity has been found increased in light sensitive psoriasis and scleroderma (30). The blood GSH however has not been investigated in other dermatological cases. More importantly the relation between allergic

diseases and GSH, has escaped attention. We are therefore unable to compare our results since no similar study has been reported in the literature. It is possible that patients with other allergic manifestations may reveal variations in GSH level. This and influence of various pharmacological agents are presently under investigation in our laboratories as to their influence on GSH level.

It is already known that several dermatological diseases are related to derangements of carbohdyrate, purine, lipid, porphirine and Ca^{++} metabolism. Taking into consideration the fact that trace elements are responsible for activity of many enzyme (11) important for these metabolic events and that zinc and copper deficiency has been proven in several allergic diseases (5) it is easy to understand functional importance of the lowered level of glutathion in these patients. It should furthermore be remembered that trace metals and the enzymes related to them are numerous (10, 17, 24). Clinical conditions which may be as a result of their alterations in human body are at present subject to investigation however insufficiently realized.

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