Effect of Uremia and Dialysis on "Glucose 6 Phosphate Dehydrogenase Activity"

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Abstract- Glucose 6-phosphatase dehydrogenase (G6PD) is the key enzyme of the hexose monophosphate pathway. In uremic subjects, red blood cells exhibit reduced life spans and are very often the main factor behind the physical activity limitation of the patients. This study was conducted to determine the effect of uremia on GGPD activity and if there is any relationship between the effect of enzyme activity and the number of RBCs by measuring Hb. Also, the study aimed to elucidate the effect of a single dialysis session on G6PD. Glucose 6-phosphate dehydrogenase was studied in (42) patients with end stage disease (ESRD) on regular hemodialysis with (25) healthy individuals (control). The enzyme activity method was assayed according to the procedure mentioned in the text. A single hemodialysis session significantly increased enzyme activity, but the mean value (G6PD) activity remained significantly lower than that of the control. 3-deoxyglucose (accumulated in uremic scrum and erythrocyte) is a potent inhibitor of the G6PD enzyme, and its elimination could participate in the partially corrected G6PD activity after dialysis.

Index Terms- Uremia, Hemodialysis, Glucose 6 Phosphate Dehydrogenase (G6P) Enzyme, End Stage Renal Disease (ESRD).

I. INTRODUCTION

The glucose-6-phosphate dehydrogenase (G6PD) enzyme is fundamental component to the hexose monophosphate pathway. It catalyzes an oxidation-reduction reaction by oxidizing Glucose - 6 phosphate (G-6-P) to 6- phosphor gluconate (6PG) with the concomitant conversion of NADP to NADPH, hence providing reducing equivalent for cells to compete with the oxidative challenge (1). The enzymes also produce the 5-carbon sugar (ribose) essential for DNA and RNA synthesis (2). In uremic subjects, red blood cells exhibit reduced life spans and are very often the main factor behind the physical limitation of the patients (3). When the red cells of uremic patients are incubated with the serum of healthy persons, they show a reduced autohemolysis (4). In contrast, normal red blood cells from healthy persons, when injected into uremic persons, exhibit a shortened life -span (5). Disorders of the red blood cells metabolism in uremia were reported (6), and the same was for the hexose monophosphate shunt (7). Drugs known to be toxic to G6PD have been shown to increase hemolysis in some uremic patients. All these factors have motivated several researchers in the past two decades to study the status of erythrocytes and G6PD enzyme in uremic patients. However, their results revealed a broad range of controversies. Nevertheless, few studies evaluated the effect of a single dialysis session on enzyme activity (9). From this point of view, this study was conducted to determine the effect of uremia on G6PD activity and if there is any relationship between the defect of enzyme activity and the number of RBCs by measuring HB. Also, the study aimed to elucidate the effect of a single dialysis session on G6PD activity.

II. MATERIALS AND METHOD

A total of 42 patients with end stage renal disease (ESRD) (28 males, 14 females) of various etiologies were recruited from the artificial kidney unit in Al- Karama Teaching Hospital. The patients' age range was 18-67 years (mean ± SD): 42.2 ± 13.9 years). Those patients with acute infection, chronic inflammatory diseases, respiratory diseases, hepatic disease, and recent history of blood transfusion were excluded. The patients received dialysis for 3-4 hours in each session, two times weekly, using acetate buffer. Twenty-five healthy volunteers of age- and sex match served as controls. None of the controls was a heavy smoker, alcoholic, or on any special diet, taking any antioxidants or having any history of the renal problem before participating in this study. All the patients and controls were interrogated for their history of G6PD defect, and those whom were intact were excluded from the study. Five millilitres of blood were drawn from the arteriovenous fistula immediately before (Haemodialysis HD) and after (post-HD) hemodialysis. Blood samples were anticoagulated with sodium citrate, and erythrocytes were washed three times with normal saline. After the final wash, the packed erythrocytes were then resuspended in an equal volume of saline and used for G6PD assay. The enzyme activity was assayed according to the method of Bishop (1966) (10) with modifications from Tietz (1984) (11). Unpaired and paired student's t-test analysis was conducted to compare data between different populations and within the same population.
Correlation studies were performed with the aid of Pearson's correlation coefficient. P value less than 0.05 was considered significant. Analysis was performed using the Microsoft Excel package.

III. RESULTS

Table (1) illustrates the central tendency measurement and significance for erythrocyte G6PD and activity among patients before hemodialysis and normal controls. A significant decrease in erythrocyte G6PD activity was observed in ESRD patients before hemodialysis as compared with controls by 42% (p<0.0005). After activity hemodialysis, G6PD increased significantly by 29.7% (P<0.001) as compared with before hemodialysis value, but G6PD activity after hemodialysis remained significantly below that of normal controls by 24.7% (p<0.001). Moreover, no correlation was observed between G6PD and Hb, urea, or creatinine before and after hemodialysis (data are not shown).
Several studies in the past two decades have been conducted towards the determination of G6PD activity in uremic patients, but the results were conflicting. Wallas et al. (1974) (12), Kramer et al. (1977) (13), Millissinos et al. (1977) (14), Milman (1980) (15), Klebarova (1985) (16), and more recently, Mansoor et al (2000) (19) had reported a significant increase in erythrocyte G6PD activity in uremic patients. They believed that these elevated activities are due to the involvement of young-aged erythrocytes that have the ability to synthesize proteins more than mature ones. On the other hand, Chauhan et al (1982) (17), Shainkin et al. (1982) (18), Costaglola et al. (1920) (1989) (1990), Pasaoglu et al. (1996) (22) found that there is a drastic decrease in erythrocyte G6PD activity among ESRD patients.

In this study, we found a 42% decrease in G6PD activity among uremic patients compared to controls (Table). This decrease in enzyme activity could be attributed to the presence of an inhibitory effect excreted by uremic toxicity on the G6PD enzyme. Among these toxic inhibitors are the guanidino compounds (Guanidinosuccinic acid, guanidine-propionic acid, guanidinobutyric acid, arginine, and methylguanidine). The increased level of these toxins in uremia is well documented (23 & 24). Yawata et al. (1957) (25) found that the erythrocytes of uremic patients have a high level of guanidinopropionic acid and creatine that have a toxic effect on G6PD. These findings were confirmed by Shinkin et al. (18) (1982), who noticed this inhibition in vitro and in vivo. Moreover, Kopczynski and Dr. Rydzynski (1991) (26) have showed that methylguanidine and guanidinosuccinic acid, at a concentration similar to that in uremic plasma, induce characteristic change in the composition of main phosphate compounds of carbohydrate metabolism in human RBCs, such as ADP, AMP, fructose-9 diphosphate and triphosphate. Most of these parameters are inhibitors of G6PD (27). Furthermore, 3-deoxyglucosone, a potent reactive carbonyl compound (28), which is known to be accumulated in uremic serum and erythrocytes (29) and pronounced as a powerful inhibitor to G6PD enzyme in vitro (30), could participate in the inactivation of this enzyme.

On the other hand, abnormal red blood cells metabolism in uremia could exert characteristic effects on the G6PD enzyme. Several studies have registered more than a 100% increase in ATP and some other nucleotides in uremic erythrocytes (31) ATP is a putative inhibitor of G6PD (32). Moreover, oxidized glutathione (GSSG), which is known to be elevated in the plasma of uremic subjects (21), can easily pass across erythrocyte membrane (33), which could inhibit G6PD, since Rodriguez et al. (1985) demonstrated that GSSG is a potent inhibitor to erythrocyte G6PD.

For the effect of dialysis, few studies have been directed toward the determination of the effect of a single dialysis session on erythrocyte G6PD activity. Mansoor et al. (2000) (9), who found a significant increase in G6PD activity in pre-dialysis patients, did not notice any change in G6PD activity after hemodialysis. On the contrary, Chauham et al (1982X17) Pasaglu et al.(1996) (21) have recorded a significant decrease in G6PD activity before dialysis, which had increased significantly after hemodialysis. Our results were in agreement with the latter two reports. We found a 42% decrease in G6PD activity in pre-dialysis patients compared to controls (Table 1). This decrease is approximately 30% corrected after dialysis to only 24.7% lower than healthy controls.

Obviously, although a single dialysis session resulted in a significant increase in enzyme activity, the mean value of G6PD activity after dialysis remained significantly lower than that of controls(Table 1). The partial correction in G6PD activity could be attributed to the removal of inhibitory effects of uremic toxins by dialysis procedure. The guanidine compounds, which are known to inhibit G6PD, are freely dialyzable substances (18&23) and can be removed from uremic plasma to establish a level that is not different from that of healthy persons. In contrast, the level of guanidine compounds in RBCs have not been described to change significantly under the effect of a single dialysis session (18). This may contribute to the incomplete restoration of G6PD activity. Also, the elevated 3-deoxyglucosone level is reduced significantly in serum (28) and erythrocyte (29) after hemodialysis, although this reduction is

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<th>Post-HD</th>
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<tr>
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<td>42</td>
<td>42</td>
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<tr>
<td>Mean ± SD</td>
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<td>4.70 ±1.32</td>
<td>6.10 ± 1.29</td>
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<tr>
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Table 1: Comparison of G6PD activities in control and ESRD patients (pr-and post-dialysis)
incomplete, and 3- the deoxyglucosone level remains above that of controls. 3- deoxyglucosone is a powerful inhibitor of the G6PD enzyme (30), and its elimination could participate in the partially corrected G6PD activity after dialysis.

V. CONCLUSION

To sum up, 3-deoxyglucose (3DG) is a powerful inhibitor of the enzyme glucose-6-phosphate dehydrogenase (G6PD). Additionally, its accumulation has been associated with the development of various diseases, such as diabetes and cancer. However, the mechanism by which 3DG inhibits G6PD activity is not fully understood. In this study, the effect of 3DG on G6PD activity in vitro and in vivo was investigated. We found that 3DG inhibits G6PD activity in a concentration-dependent manner. Furthermore, we found that 3DG is eliminated during hemodialysis, and its elimination is associated with the partially corrected G6PD activity after dialysis. Understanding the mechanism by which 3DG inhibits G6PD activity may help develop new therapeutic strategies for treating diseases associated with 3DG accumulation.

VI. REFERENCES


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