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Role of Glutaredoxin-1 and some Oxidative Stress Enzymes in Acute Lymphocytic Leukemia Patients

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ABSTRACT

The pathophysiological relationship of leukemia has been linked to Oxidant compounds, as an imbalance between oxidants and Antioxidants compounds leads to a state of oxidative stress (OS), and this leads to increased activation of different transcription factors in leukemia patients. Leukemia treatment and diagnosis are closely linked to OS, which is an important factor in the appearance and development of the disease. The goal of this study was to evaluate the level of Glutaredoxin-1 (Grx1), Methionine sulfoxide reductase A (MsrA), Catalase (Cat), Myeloperoxidase (MPO), Lipooxygenase (LOX), Xanthine oxidase (XO), Lactoperoxidase (LP) and Glutathione S-Transferase (GST) in leukemia patients and compared it with the control group, to determine of Grx1 level and some OS Enzymes, effect of age and increasing the period for the occurrence of the disease, as well as the effect of body mass index on patients.

This research included 90 samples, 64 ALL patients and 26 healthy people. Samples were collected from a dedicated pediatric leukemia teaching hospital from Dohuk and Mosul, Iraq from September to December 2023. Depending on this study, Grx1, CAT, XO and GST elevated greatly in ALL patients compared with the control group, but MsrA and MPO levels decreased statistically significantly. Age effect with increases showed that Grx1, CAT, MPO and XO increased significantly in groups of patients, but MsrA declined with increasing age. Grx1 and GST increased in patients with an increased duration of illness. MsrA level from 1 to 24 months has a non-significant difference between the three groups but in 25 to 36 months have increased between the three groups, and MPO level from 1 to 24 months has declined significantly. Finally, the effect of BMI on ALL patients, Grx1, CAT, MPO, XO and GST levels have increased statistically significantly with increased BMI, and MsrA levels have declined significantly in patients. It was noted from our study that the levels of Grx1 and MsrA have a prominent role in determining the extent to which patients are affected by ALL, which can have a role in treating and monitoring the development of the disease.

Keywords: Acute lymphocytic leukemia, glutaredoxin, methionine sulfoxide reductase, body mass index.

INTRODUCTION

White Blood Cells (WBCs), grow abnormally in the bone marrow of the human body and cause leukemia, a type of blood cancer. Both acute and chronic leukemia can be distinguished from one another; the former grows more quickly than the latter. Moreover, lymphocytic and myeloid subcategories exist for both kinds (Ratley *et al*., 2020). The reduction of thiol-disulfide exchange processes is catalyzed by ubiquitous redox enzymes called glutaredoxins (Grxs), which are members of the thioredoxin family this process is dependent on glutathione (GSH) (Saninjuk *et al*., 2023). Grxs are tiny, multipurpose redox proteins that exhibit glutathione-dependent oxidoreductase activity (Kumar *et al*., 2020). Protein S-glutathionylation, a common and reversible posttranslational alteration, is the process by which GSH is added to and removed from a cysteine thiol in proteins. Thiol oxidoreductases Grx1 catalyze these processes by S-glutathionylating and deglutathionylating target proteins. Protein folding, calcium handling, apoptosis, energy metabolism and sensing, and signaling are just a few of the physiological and environmental causes that are modulated by the GSH-modified proteins. In addition, protein S-glutathionylation functions as an overlaid signal that coordinates with other pathways to control cellular processes (Mailloux *et al*., 2020). As a result, the OS imbalance can activate and be associated with producing leukemia and prognosis (Dong *et al*., 2021).

Grx1 is the removal of glutathionylation, and it maintains a reducing environment inside a cell under any different conditions through the reversal of S-glutathionylation. It performs many functions as an antioxidant in preventing the accumulation of protein disulfides, which reduces protein-protein aggregation, and prevents the accumulation of protein disulfides and mixed thiols. And programmed cell death of lens epithelial cells (Li *et al*., 2023).

MsrA reduces the oxidation of methionine (Met-O) in biological compounds to methionine (Met), meaning it is an oxidation repair enzyme. Its essential role in cellular processes may be demonstrated by the expression, silencing, or destruction of MsrA or deletion of the gene that Msr A is encoded in many types (Veerapandian *et al*., 2023). Under physiological conditions oxidative stress occurs in the biological system; the common phenomenon is methionine oxidation and reduction. In a cell or organ, methionine sulfoxide (MetO) levels depend on the redox state. It may change its function or cause accumulation of toxic proteins due to molecular modification of proteins. Accordingly, the level of the redox molecules Meto and the associated MsrA system are regulated by the ubiquitous and evolutionarily conserved methionine (Moskovitz and Smith, 2021).

Lipoxygenases (LOX) in plant and animal cells, this enzyme is widely distributed (Shi *et al*., 2020). This enzyme produces hydroperoxides from the lipid peroxidation process of many types of fatty acids. This enzyme is widely distributed. LOX reactions can be desirable or undesirable. Most aromatic compounds are produced from the reactions of the lipoxygenase enzyme and can affect the properties of food, especially those stored for a long time (Al-Helaly *et al*., a2017; Lončarić *et al*., 2021). Catalase protects the cell from OS (Hameed and Al-Helaly, 2020; Guo *et al*., 2022), one of the body's natural protection mechanisms, which accelerates the decomposition of the formed hydrogen peroxide. Internal poisoning in the body is evaluated by catalase (Boriskin *et al*., 2019)

Therefore, the focus of our study was on estimating the level of Grx1 and others enzymatic (MsR, MPO, CAT, LOX, LP, GST, and XO) in this disease to determine the state of oxidative stress.

MATERIALS AND METHODS

This research included 90 samples, 64 ALL patients and 26 healthy people. Samples were collected from Ibn Al-Atheer Teaching Hospital, Al-Hadbaa Blood Hospital in Mosul and Al-Jin Specialized Center for Pediatric Hematology and Cancer in Dohuk from September to December 2023. A complete medical history is taken for all patients and healthy people, which is collected according to a questionnaire sheet that was prepared previously. The study was approved by the

Medical Research Ethics Committee. The approval number and date for the study is (37170 on 20/09/2023) in Mosul, as well as the approval of the Planning Department, Scientific Research Division. The approval number and date for the study is (12205 on 15/10/2023) in Dohuk.

Depending on the increasing age the all patients group was divided into three groups (1-5y), (6-10y) and (11-15y) while, to study the effects of duration of illness the samples were divided into three groups (1-12), (13-24) and (25-36) months, besides of, according to the values of body mass index (BMI = weight (Kg) / (Height)^2 (m^2)), divided into two groups (BMI 9-19 Kg/m^2 (1st stage) and BMI 20 Kg/m^2 and above(2nd stage)). The serum was isolated, frozen, and used in the estimation of parameters: Glutaredoxin1(Grx1) levels were assessed using an ELISA kit from China Biotest Technology Laboratory, Glutathione S-transferase (GST) catalyzes the association of compounds containing electrophilic groups such as 1-chloro-2,4-dinitropenzene (CDNB) (Habig *et al*.,1974). Lipooxygenase (LOX) activity was estimated by the method of researchers (Shastry and Rao, 1975) and Myeloperoxidase (MPO) activity was estimated by the method of researchers (Kumar *et al*., 2002). Then, methionine sulfoxide reductase A (MsrA) activity was estimated by the method used by the researchers (Wu *et al*., 2013), Xanthine oxidase (XO) activity was estimated by the method used by the researchers (Ackerman and Brill, 1974), Lactoperoxidase (LP) an enzyme oxidizes Pyrogallol according to a method (Tayefi-Nasrabadi *et al*., 2011), and finally, catalase (CAT) activity in blood serum was estimated based on the standard method. To determine enzyme activity (Boriskin *et al*., 2019), which is based on the oxidation of molybdenum-4-ammonium.

Statistical analysis:

The data analysis is performed using the statistical program SPSS 23 (SPSS Software, SPSS Inc., Chicago, Illinois, USA). The data is presented as means with standard diversion (SD). A considerable variation was regarded when P-value was ≤ 0.05 using a t-test, for multiple variable comparisons are analyzed by one-way analysis of variance (ANOVA test) (Faizi and Alvi, 2023).

RESULTS AND DISCUSSIONS

The groups selected in the following research can be described according to the following (Table 1), there is no significant difference in age and BMI between the patient group and the control group.

Table 1: Demographic characteristics of ALL patients and control subjects.

Biochemical parameters	Control group	ALL patients
	X±SD	X±SD
Age (Year)	8.39±0.51	7.74±0.51
BMI (Kg/m^2)	18.14±1.09	16.95±0.50

The parameters in ALL patients group compared with the control group as we noted in (Table 2), have a noteworthy elevation in the levels of Grx1, CAT, XO, and GST noticed in all patients compared with the control group. While a considerable reduction in levels of MsrA, MPO and LOX compared with the control group. Furthermore, LP gives non-considerable variations between the two groups.

Table 2: Concentration of Grx1 and other enzymes in participating individuals.

Biochemical parameters	Control group	ALL patients	Sig
	X±SD	X±SD	
Glutaredoxin-1(ng/mL)	347.77±31.83	445.51±45.91	0.031*
Methionine sulfoxide reductase A (U/L)	513.78±63.00	397.60±25.43	0.011*
Catalase (mKat/L)	101.17±13.25	122.28±12.61	0.041*
Myeloperoxidase (U/L)	156.20±12.63	136.05±10.18	0.045*
Lipoxygenase (U/L)	42.17±3.37	36.62±2.65	0.029*
Xanthine oxidase (U/L)	121.20±16.96	315.09±31.23	0.04*
Lactoperoxidase (U/mL)	41.93±3.24	37.10±2.37	0.95
Glutathione S-Transferase (U/L)	219.83±35.52	351.40±28.62	0.023*

*Significant at (P≤0.05).

The comparator of the mean values of Grx1 and other parameters in all patients compared with the control group as we noted in (Table 2), a considerable elevation in the levels of Grx1, CAT, XO, and GST were noticed in all patients compared with the control group. In the latest study, Grx1 and CAT show a significant increase in all patients, because one of the causes of leukemia is the formation of free radicals and an imbalance with the antioxidants in the body, which is why the levels of Grx1 and Cat increase, the present findings are in line with those of (Ademi, 2022), and also the antioxidant status of the cell is significant in stress conditions, when the production of free radicals is intensified. When cells are exposed to oxidative stress, they increase the expression and activity of antioxidant enzymes as a compensatory mechanism to better protect against ROS-induced damage (Hamdon and Al-Helaly, 2019; Hameed and Al-Helaly, b2021). Several studies indicate that moderate levels of toxic reactive radicals induce the expression of genes responsible for the synthesis of antioxidant enzymes and their activity, while very high levels reduce the same enzyme activity as a result of damage to the molecular machinery required for the induction of these enzymes (Al-Hamdani and Al-Helaly, 2023).

The variations in the mean values studied in age effect Grx1 and other enzymes in ALL patients; As we noted in (Table 3), a considerable decline in means of MsrA and LOX in the third group (11-15y) comparison with the first and second age groups (1-5y), (6-10y) severally and considerable rises in Grx1, CAT, MPO and XO in the third group (11-15y) comparison with the first and second age groups (1-5y), (6-10y) severally. The biomarkers of LP and GST showed a non-considerable variation between the three groups.

Table 3: Age effect on Grx1 and other enzymes in all patient groups.

Biochemical parameters	1-5y	6-10y	11-15y
	X±SD	X±SD	X±SD
Glutaredoxin-1(ng/mL)	451.00 ±111.83 **a**	610.07 ±97.30 **b**	673.81 ±90.60 **c**
Methionine sulfoxide reductase A (U/L)	452.65 ±41.21 **b**	367.80 ±48.81 **a**	363.03 ±41.48 **a**
Catalase (mKat/L)	97.50 ±19.85 **a**	111.04 ±16.46 **b**	169.37 ±26.17 **c**
Myeloperoxidase (U/L)	128.24 ±19.95 **a**	136.16 ±13.34 **b**	146.57 ±19.09 **b**
Lipoxygenase (U/L)	39.65 ±4.55 **b**	41.48 ±4.54 **b**	29.59 ±3.42 **a**
Xanthine oxidase (U/L)	285.07 ±33.26 **a**	306.41 ±34.35 **b**	359.40 ±49.90 **c**
Lactoperoxidase (U/mL)	38.48 ±4.12 **a**	33.13 ±3.41 **a**	39.81 ±4.87 **a**
Glutathione S-Transferase (U/L)	348.05 ±53.34 **a**	346.21 ±43.53 **a**	360.50 ±53.80 **a**

Different letters (a, b, c) horizontally indicate that the means are different significantly at $p \leq 0.05$, among the studied groups.

According to the duration of the disease, the patient samples were divided into three groups, which are between the first stage (1-12 months), second stage (13-24 months) and third stage (25-36 months) (Table 4).

The results showed a significant increase in Grx1, MsrA and GST, but a significant decrease in MPO with increased duration of the disease. The biomarkers of CAT, LOX, XO and LP showed a non-considerable variation between the three stages; as seen in (Table 4).

Table 4: The effect of the duration of illness on Grx1 and other enzymes in all patient groups.

Biochemical parameters	1-12 month	13-24 month	25-36 month
	X±SD	X±SD	X±SD
Glutaredoxin-1(ng/mL)	393.61±97.89 **a**	413.04±93.50 **b**	573.11±83.71 **c**
Methionine sulfoxide reductase A (U/L)	376.67 ±32.36 **a**	368.89±42.81 **a**	507.65±56.75 **b**
Catalase (mKat/L)	125.44 ±16.05 **a**	129.92±22.39 **a**	127.10±33.30 **a**
Myeloperoxidase (U/L)	152.45 ±13.66 **b**	110.38±23.79 **a**	117.24±18.24 **a**
Lipoxygenase (U/L)	37.43±3.66 **a**	32.10±4.45 **a**	38.15±6.04 **a**
Xanthine oxidase (U/L)	313.31±44.92 **a**	284.16±90.40 **a**	336.85±49.60 **a**
Lactoperoxidase (U/mL)	38.43 ±3.92 **a**	38.59±5.12 **a**	34.00±2.85 **a**
Glutathione S-Transferase (U/L)	340.65±36.07 **a**	390.52±55.06 **b**	435.58±70.77 **c**

Different letters (a, b, c) horizontally indicate that the means are different significantly at $p \leq 0.05$, among the studied groups.

According to the value of body mass index (BMI), which divided into two groups BMI of 9-19 Kg/m^2 (1st stage) and a BMI of 20 Kg/m^2 and above (2nd stage). As we noted in (Table 5) reported a considerable decline of serum in MsrA and LOX in 2nd stage of this case compared with 1st stage. While showed a considerable increase in BMI, GRX1, CAT, MPO, XO, LP and GST in 2nd stage compared with the 1st stage of this group.

Table 5: The effect of BMI on Grx1 and other antioxidant enzymes in ALL patient groups.

Biochemical parameters	BMI 9-19 Kg/m^2	BMI 20 Kg/m^2 and over	Sig
	X±SD	X±SD	
Glutaredoxin-1(ng/mL)	409.44±84.07	558.22±94.71	0.019*
Methionine sulfoxide reductase A (U/L)	418.51±27.38	331.10±29.00	0.013*
Catalase (mKat/L)	116.38±15.06	139.40±22.99	0.040*
Myeloperoxidase (U/L)	131.37±10.68	154.20±28.08	0.046*
Lipoxygenase (U/L)	39.38±2.96	24.55±3.89	0.057*
Xanthine oxidase (U/L)	288.42±36.53	379.09±37.73	0.033
Lactoperoxidase (U/mL)	34.28±2.05	44.46±2.32	0.05*
Glutathione S-Transferase (U/L)	317.70±27.00	477.76±39.69	0.022*

*Significant at (P≤0.05)**.**

Based on research by Moskovitz and Smith, (2021) MsrA level usually does not increase under conditions of oxidative stress, aging, inflammation, and oxidative stress-associated diseases and these are consistent with recent research.

The MsrA shows reduction in ALL patients group, because MsrA is an antioxidant repair enzyme that indirectly maintains the ROS levels within the cells by reducing the oxidized methionine in proteins (Boschi-Muller *et al*., 2005). MPO in the latest study, shows a marked reduction in all patients, because the MPO activity is regulated in the body, an overproduction of HOCl and other ROS may increase OS which can intensify inflammation leading to tissue damage (Al-Helaly *et al*., a2017; Rashid *et al*., 2022).

An important enzyme family is formed on iron due to which the level of LOx decreases. It catalyzes the hydro-oxidation of polyunsaturated fatty acid derivatives, which consist of cis-1,4-pentadiene (for example, arachidonic and linoleic acids) (Brash, 1999). Acute and chronic diseases in which their role has been proven, such as inflammation, cancer, asthma, allergies, and stroke (Feltenmark *et al*., 2008). Given their potential as therapeutic targets, there is a synthesis and great interest in discovering these elements. Potent and new LOx inhibitors (Alavi *et al*., 2018) by using the ischemic scavenging property, most oxidation inhibitors achieve their action.

Based on research (Czuczejko *et al*., 2019) and (Ambad *et al*., 2021) in general, there is an increase in GST activity in alcoholics, a decrease in total thiol status, and a decrease in the level of protein thiol, which negatively affects protein oxidation products. These indicate liver damage, the liver cell has been weakened, and liver function tests indicate abnormalities. In this GST study, there is an increase in the results. This indicates that whenever alcohol or medications increase in the body, liver enzymes increase liver cirrhosis appears, and the GST enzyme, among the liver enzymes, appears to increase, and what it does naturally is the removal and transport of toxins (Al-Helaly, 2022).

Level of the XO increasing because it is consistent with the research that the level of xanthine increases in the body of a cancer patient because it causes an increase in free radicals (Ruan *et al*., 2020), Based on scientific research (Boucheffa *et al*., 2022) and supported by other research (Busso and So, 2010; Haidari *et al*., 2008), Therefore, For the treatment of chronic inflammation, inhibition of XO is a potential target. The final metabolite in the human purine catabolic pathway from uric acid, If the body loses it and disposes of it, it can cause various diseases, Because XO is one of the free radical generators and plays an essential role in many inflammatory diseases, such as rheumatoid arthritis, arthritis, and diabetes, and the relationship between oxidative stress and

Xanthine Oxidase is still known that xanthine oxidase is strongly involved. (Khither *et al*., 2020; Bisset *et al*., 2021; Guergouri *et al*., 2021). Another measure looked at in this investigation LP was serum was tested and found to be unchanged because Mitoxantrone is an important anti-cancer agent, which is oxidatively activated by peroxidases (Rentsch *et al*., 1998). LPO is expressed in hormone-dependent mammary tumors (Duffy and Duffy, 1977) and, therefore, its interaction with mitoxantrone may be important for the clinical effectiveness of the drug.

CONCLUSIONS

It was noted from our study that the levels of Grx1 and MsrA have an important role in determining the condition of all patients, which can have a role in diagnosing the disease and as a therapeutic target as well as monitoring the progression of the disease. The results indicated that age, disease duration, and body mass index have a prominent impact on patients by increasing the severity of the injury.

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دور الكلوتاريدوكسين –1 وبعض انزيمات الاجهاد التأكسدي في مرضى سرطان الدم الليمفاوي الحاد

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الملخص

تم ربط علاقة الفسيولوجية المرضية لسرطان الدم بمركبات الأكسدة، اذ ان عدم التوازن بين مواد الاكسدة ومضادات الأكسدة تؤدي الى حصول حالة الاجهاد التأكسدي وهذا يقود الى زيادة تنشيط عوامل النسخ المختلفة لدى مرضى سرطان الدم وان علاج سرطان الدم والتشخيص يرتبط بشكل وثيق بالإجهاد التأكسدي وهو عامل مهم في ظهور المرض وتطوره. كان الهدف من هذه الدراسة هو قياس الكلوتاريدوكسين–1 كمضاد للأكسدة، وكذلك قياس انزيمات ميثيونين سلفوكسيد ردكتيز A، والمايلوبيروكسيديز، وكتاليز، والزانثين أوكسيديز وكلوتاثايون S–ترانسفيريز. في مرضى سرطان الدم الذين تتراوح أعمارهم بين سنتين وخمسة عشر عاما. ركزنا على نوع سرطان الدم الليمفاوي الحاد ومقارنتهم مع مجموعة السيطرة في نفس العمر لتقدير مستوى كلوتاردوكسين–1 وبعض انزيمات الاجهاد التأكسدي وتأثير العمر وزيادة فترة حدوث المرض، وكذلك تأثير مؤشر كتلة الجسم على المرضى. شمل هذا البحث 90 عينة، 64 مريضاً بسرطان الدم الليمفاوي الحاد و26 شخصاً سليماً. تم جمع العينات من مستشفى تعليمي مخصص لسرطان الدم لدى الأطفال في دهوك والموصل بالعراق في الفترة من سبتمبر إلى ديسمبر 2023.

لوحظ من هذه الدراسة، ان هناك ارتفاع مستويات انزيمات كلوتاردوكسين–1 والكتاليز وزانثين اوكسيديز وكلوتاثايون S–ترانسفيريز بشكل كبير في جميع المرضى مقارنة بالمجموعة السيطرة، لكن مستويات انزيمات ميثيونين سلفوكسيد ردكتيز A، والمايلوبيروكسيديز انخفضت بشكل ملحوظ إحصائيًا في جميع المرضى سرطان الدم الليمفاوي الحاد.

عند ملاحظة تأثير زيادة العمر على المرضى لوحظ ان هناك ارتفاع في انزيمات كلوتاردوكسين–1 والكتاليز والمايلوبيروكسيديز وزانثين اوكسيديز بشكل ملحوظ في مجموعات من جميع المرضى، ولكن مستويات ميثيونين سلفوكسيد ردكتيز A انخفضت بشكل كبير في جميع المرضى مع تقدم العمر. وان تأثير زيادة مدة المرض على المرضى لوحظ ان هناك زيادة في كلوتاردوكسين–1 وكلوتاثايون S–ترانسفيريز وان فعالية انزيم ميثيونين سلفوكسيد ردكتيز A لمدة 1 إلى 24 شهرًا ليس له فرق كبير بين المجموعات الثلاث ولكن في 25 إلى 36 شهرًا ارتفع بين المجموعات الثلاث، ومستوى انزيم المايلوبيروكسيديز من 1 إلى 24 شهرًا انخفض بشكل ملحوظ. أخيرًا في دراسة تأثير مؤشر كتلة الجسم على جميع المرضى، زادت مستويات انزيمات كلوتاردوكسين–1 والكتاليز والمايلوبيروكسيديز وزانثين اوكسيديز وكلوتاثايون S–ترانسفيريز بشكل ملحوظ إحصائيًا مع زيادة مؤشر كتلة الجسم، وانخفض انزيم ميثيونين سلفوكسيد ردكتيز A. لوحظ من خلال دراستنا أن انزيمي كلوتاردوكسين–1 وميثيونين سلفوكسيد ردكتيز A لهما دورا بارزا في تحديد مدى تأثر المرضى بمرض سرطان الدم الليمفاوي الحاد وشدته، والذي يمكن أن يكون له دور في علاج ومراقبة تطور المرض.

الكلمات الدالة: سرطان الدم الليمفاوي الحاد، الكلوتاريدوكسين، ميثيونين سلفوكسيد ريدكتيز، مؤشر كتلة الجسم، مدة المرض.