Evaluation of Some Biochemical Parameters and Hormones In Patients with Acute Myeloid Leukemia in Iraq

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Abstract
The effect of myeloid leukemia, especially acute myeloid leukemia (AML), has been widely noticed on the parameters of liver and kidney functions and the levels of certain hormones. This study aimed to evaluate a number of biochemical parameters of liver and kidney functions and hormones in Iraqi subjects with newly diagnosed acute myeloid leukemia. Eighty newly diagnosed AML adult patients (40 males and 40 females) and forty healthy individuals (20 males and 20 females) with an age range of 16-75 years were involved in this study during their attendance at the Hematology Department of Baghdad Teaching Hospital/ Medical city in Baghdad province from March 2019 to February 2020. Blood samples were collected from all subjects for the determination of serum levels of the parameters of liver function parameters, kidney function, lactate dehydrogenase (LDH), and Erythropoietin (EPO). The results showed that the serum levels of liver function parameters (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) had highly significant increases (p< 0.01) in AML patients (85.87±2.49, 53.93±1.76, 150.87±7.04 U/L, respectively) as compared to the control (30.58 ±2.04, 22.89 ±0.97, 75.51 ±2.12 U/L, respectively). Also, the level of kidney function parameters (blood urea, creatinine and uric acid) showed highly significant increases (p< 0.01) in AML patients (58.82 ±1.49, 1.831 ±0.05, 8.34 ±0.15 mg/dl, respectively) as compared to the control (31.10 ±1.03, 0.850 ±0.02, 4.81 ±0.14 mg/dl, respectively). In addition, the level of LDH showed a highly significant increase (p< 0.01) in the patients with AML (657.72 ±80.76 U/L) as compared to the control (166.05 ±6.15 U/L). Moreover, the level of EPO showed a highly significant increase (p<0.01) in the patients with AML (11763.80 ±329.46 pg/ml ) as compared to the control (316.94 ±34.42 pg/ml).

Key words: Liver and kidney function, AML, LDH, EPO.
Introduction

Leukaemia is a haematological malignancy that occurs when a certain aspect of the division or life span of a blood cell or its precursor is regulated incorrectly [1]. The cell uncontrollably begins to proliferate and forms a large cell population derived from a single cell [2]. Haematological malignancies are cancers that affect the blood, bone marrow, and lymph nodes. This classification includes various types of leukemia (acute lymphocytic (ALL), chronic lymphocytic (CLL), acute myeloid (AML), chronic myeloid (CML), myeloma, and lymphoma (Hodgkin’s and non-Hodgkin’s (NHL)) [3,4].

Leukaemia refers to unreigated proliferation without differentiation of the progenitor cells. A block of differentiation results in the accumulation of immature cells which fail to mature fully and then die. Proliferating immature cells, which are stopped in differentiation and escape immune surveillance, ultimately dominate the bone marrow and invade other tissues and organs, which can lead to death [5].

In AML, infiltration has been observed both in the tract of the portal vein and in the sinusoid of the liver; extremely large infiltration of leukemic liver cells can appear as a fulminant liver failure [6]. Aminotransferases are normally present in the serum in low concentration. These enzymes are released into the blood in greater amounts when there is damage to the liver cell membrane resulting in increased permeability [7, 8]. In the case of hepatic infiltration by leukemia cells, the activation of ALP and gamma-glutamyl transferase (GGT) is high [9].

Blood urea nitrogen (BUN) acts as an important sign for the condition of the disease. Compared to the control group, BUN levels were found to be elevated in leukemia patients [10]. Research studies have shown that not only AML and ALL but also other types of chronic leukemia, such as CLL and acute neutropenia, have been associated with the mortality of patients with leukemia [10,11]. The findings of a current study suggest that the measurement of BUN levels may be useful for predicting renal outcomes [12].

LDH is a cytoplasmic enzyme found in nearly all tissues, but at rising concentrations in muscles, liver, and kidneys. Moderate levels of this enzyme are also present in red blood cells [13]. The enzyme’s function is to catalyze the reversible conversion of lactate to pyruvate by reducing NAD to NADH and vice versa [14]. During cell damage, LDH is progressively elevated, due to a cellular disorder occurring in acute leukemia, along with overgrowth of normal malignant cells [15].

LDH is elevated in the cases of myocardial or pulmonary infarction, leukemia’s, hemolytic anemia, non-viral hepatitis, sickle - cell anemia, lymphoma, renal infarction, acute pancreatitis, and any case that results in the leaking of cytoplasm [16, 17].
Erythropoietin is a glycoprotein hormone released primarily by interstitial fibroblasts in the kidney, in the rate of 90%, in close association with peritubular capillaries and epithelial tubules [18,19]. Also, a limited contribution of 10% is conferred by the liver and other tissues, such as lung, brain, heart, spleen and, retina, which yield only modest levels depending on physiological and pathological changes [20]. EPO is produced in response to tissue hypoxia or severe anemia, where its main function is to control the process of blood production in the bone marrow [21, 22]. The present study was undertaken to assess the serum levels of liver and kidney function parameters, LDH, and EPO in a sample of Iraqi AML patients.

**Materials and Methods**

This study was conducted at the Hematology Department of Baghdad Teaching Hospital in Baghdad Medical City during the period from March 2019 to February 2020. Eighty adult newly diagnosed AML patients, including 40 males and 40 females, and forty healthy participants, including 20 males and 20 females, with an age range of 16-75 years were enrolled in this study.

Four ml of blood were collected from the cubical vein using 5 ml disposable needles and syringes. The blood was dispensed in a gel tube and left to clot for 10 minutes at room temperature, after which the serum was separated by centrifugation at 3000 rpm for 10-15 minute and preserved in deep freezer at -20 C before analysis. The kits of ALT, AST, ALP, blood urea, uric acid, and LDH (Siemens, Germany) are based on automated bichromatic endpoint method, while creatinine kit (Linear, Spain) was prepared based on manual measurement. The ELISA kit (Mybiosource, USA) used for the estimation of EPO hormone is designed for an accurate quantitative measurement. Statistical package for social science (SPSS/PC version 18) software was used to analyze the obtained data. Differences among means were computed using the t-test with a p-value ≤ 0.05.

**Results and Discussion**

The serum levels of liver function parameters (ALT, AST, ALP) showed highly significant increases (p≤ 0.01) in patients with AML (85.87±2.49, 53.93±1.76, and 150.87±7.04 U/L, respectively) as compared to the control (30.58 ±2.04, 22.89 ±0.97, and 75.51 ±2.12 U/L, respectively), as illustrated in table (1).

| Group       | Mean ± SE     |
|-------------|---------------|
|             | ALT U/L       | AST U/L       | ALP U/L       |
| Patients    | 85.87 ±2.49   | 53.93 ±1.76   | 150.87 ±7.04  |
| Control     | 30.58 ±2.04   | 22.89 ±0.97   | 75.51 ±2.12   |
| t-test      | 7.62 **       | 5.18 **       | 20.22 **      |
| p-value     | 0.0001        | 0.0001        | 0.0001        |

**Table 1-Levels of liver function parameters (ALT, AST and ALP) in the sera of AML patients and control.**

The present study found that the patients with myeloid leukemia had increased ALT and AST levels, which is consistent with previous studies that showed significant increased serum levels of both enzymes in patients with leukemia, viral hepatitis, and liver cirrhosis [23]. In leukemia patients, the high activity of these enzymes may be due to hepatic infiltration. An infiltrative disorder that results from a defect in the membranes of mitochondria and cytoplasm is proportional with increased levels of AST [24]. Increased ALT and AST levels in leukemia patients are caused by hepatic injury [25]. In addition, the elevation in the number of leukemic cells leads to an increase in the concentration of transaminase enzymes [26].

Moreover, in this study, the increase in ALP activity was similar to the results of earlier studies [27, 28], which reported that the increase in ALP activity could be due to either direct infiltration of leukemia cells into the liver as a result of damages in the mitochondrial and cytoplasmic membranes or to liver tissue damage due to a certain immune response. However, our results are not consistent with the findings of Lee et al. [29], who reported that the damaged liver cells fail to produce ALP.
The serum levels of kidney function parameters (blood urea, creatinine, and uric acid) were significantly increased ($p \leq 0.01$) in AML patients ($58.82 \pm 1.49$, $1.831 \pm 0.05$, $8.34 \pm 0.15$ mg/dl, respectively) compared with the control ($31.10 \pm 1.03$, $0.850 \pm 0.02$, $4.81 \pm 0.14$ mg/dl, respectively) as illustrated in Table-2.

**Table 2**: Levels of kidney function parameters (blood urea, creatinine and uric acid) in the sera of AML patients and control.

| Group     | Mean ± SE         | Blood urea mg/dl | Creatinine mg/dl | Uric acid mg/dl |
|-----------|-------------------|------------------|------------------|-----------------|
| Patients  | 58.82 ±1.49       | 1.831 ±0.05      | 8.34 ±0.15       |
| Control   | 31.10 ±1.03       | 0.850 ±0.02      | 4.81 ±0.14       |
| t-test    | 4.47 **           | 0.164 **         | 0.472            |
| p-value   | 0.0001            | 0.0001           | 0.0001           |

**: (p≤0.01).

The mean levels of serum urea and uric acid showed highly significant ($p \leq 0.01$) increases in the patient with AML as compared to the control. Our results agree with those of a previous study [30], which showed that serum urea and uric acid concentrations in patients with AML before treatment were statistically significantly higher than those in the control group. This is because uric acid in the serum is the result of the breakdown of the nucleic acids of leukemia cell and may be a marker of disease aggression [31,32].

High serum uric acid levels, including those observed in gout and articular degenerative disorders, as well as blood vessel inflammation and atherosclerosis, have been shown to play an important role in several disease states [33]. In patients with leukemia, multiple complications may cause clinically advanced hyperuricemia, including tumor lysis syndrome, drug adverse reactions, and renal dysfunction. Further research indicates that the increase in serum uric acid was caused by under-excretion due to renal dysfunction in some patients [32].

The level of creatinine demonstrated a highly significant increase in patients with AML compared with the control. This result agrees with that reported by an earlier work [34], which showed that creatinine level was highly significantly increased ($p<0.01$) in AML patients. Furthermore, because creatinine is an endogenous molecule, its metabolism is subject to interpersonal variations depending on various factors [35]. Creatinine is still the widely agreed criterion for the diagnosis of renal failure, but we must bear in mind that its importance represents the functioning of the kidney and not necessarily the existence of actual injury [36].

Other finding in this study revealed that serum LDH level had a highly significant increase ($p \leq 0.01$) in the patients with AML ($657.72 \pm 80.76$ U/L) as compared to the control ($166.05 \pm 6.15$ U/L), as shown in Table-3.

**Table 3**: Levels of LDH and EPO in the sera of AML patients and control

| Group     | Mean ± SE         | LDH U/L              | EPO pg/ml           |
|-----------|-------------------|----------------------|---------------------|
| Patients  | 657.72 ±80.76     | 11763.80 ±329.46     |                     |
| Control   | 166.05 ±6.15      | 316.94 ±34.42        | 937.76 **           |
| t-test    | 229.74 **         | 316.94 ±34.42        | 937.76 **           |
| p-value   | 0.0001            | 0.0001               | 0.0001              |

*: (p≤0.05), ** (p≤0.01).

This result agrees with those published by Elbossaty [37] and Merza et al. [38], who reported that the mean LDH level at presentation was extremely significantly increase as compared with the control. This may be due to a cancer burden activity that has reversed the function and turnover of leukemia cells. LDH level can be adopted as a useful tool, not only as a differentiation marker for different types of leukemia, but also for patient follow-up during the treatment time.
Increased cellular LDH activity represents a change towards anaerobic metabolism and increased glycolysis in the cytoplasm of malignant cells, followed by high cell turnover. However, lactate dehydrogenase is a key enzyme in the system of producing energy in tumor cells, stimulating the conversion of pyruvate to lactate under hypoxic conditions [39]. Because of its role in anaerobic metabolism, tumor cells grow even after rapid proliferation, leading to low oxygen conditions in the microenvironment of the tumor [40].

The serum level of EPO, the hormone of the kidney, showed a highly significant increase (p<0.01) in the patients with AML (11763.80 ±329.46 pg/ml ) compared with the control (316.94 ±34.42 pg/ml ), as shown in table (3). This result is in agreement with that of Molica et al. [41] in their study of patients with leukemia, who declared that the elevated level of EPO may be due to the disorder itself, which is characterized by an irregular proliferation of immature cells, called blasts, that may interfere with the development in the bone marrow of natural blood cells. Therefore, it contributes to erythrocytopenia, leukocytopenia, and thrombocytopenia. Also, many symptoms occur due to the suppression of natural blood cell components and the resultant anemia that causes increased development of EPO synthesis in the kidneys, leading to a significant increase in its serum level[42, 43].

Erythropoietin production is catalyzed both by anemia and low arterial oxygen compression. Therefore, it has been concluded that tissue oxygen compression regulates erythropoietin production. The increase in EPO concentration may be due to the fact that elderly people have an inadequate erythropoietin response, resulting in several consequences that may include decreased renal excretory function due to occult interstitial kidney dysfunction [44].

**Conclusions**

It can be concluded from the results of the present study that there were negative effects on the functions of liver and kidney as well as the serum levels of EPO and LDH in acute myeloid leukemia patients.

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