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Original Research Article

Hematological and Analytical Study among Iraqi Patients with Acute Myeloid Leukemia

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Abstract: **Background:** Electrolytes and trace elements play an important role within human body such as protection against cellular oxidative stress. Production of proteins and synthesis stabilization of nucleic acid **Objective:** The purpose of this study was to assess the serum concentrations of electrolytes sodium, potassium, calcium, and some trace elements levels among newly diagnosed Iraqi patients with acute myeloid leukemia. **Patients and Methods:** This study was conducted at the National Center of Hematology/ Al-Mustansiriyah University and Ministry of Science and Technology/ Baghdad. During the period from October 2018 until the end of March 2019. Sixty newly diagnosed Iraqi patients with AML were enrolled in this study; their age range was (38-50) years and they were compared with 30 healthy subjects as control group. Serum levels of some electrolytes and trace elements were estimated by the atomic absorption spectrophotometer. **Results:** There was a significant decrease in sodium, manganese, iron, cobalt, cupper, and, zinc, while a significant increase was found in serum magnesium and chromium in patients with acute myeloid leukemia as compared to controls ($p < 0.05$). There was a significant decrease in serum sodium, potassium, calcium, magnesium, and manganese in males patients as compared to females, while serum iron, cobalt, cupper, chromium, and zinc levels were significantly increase in male patients when compared with the femal **. Conclusions:** The role of the trace elements in patients with acute myeloid leukemia may provide vital clue for the etiopathogenesis of the occurrence of leukemia. The decreased levels of some these elements in patients with acute myeloid leukemia when compared to normal may be sort of interaction with the serum levels that are reversed. It is then also possible to relate anemia, a consistent finding with these diseases. Thus the deciphered role of trace elements will enable to understand the etiopathogenesis, provide a rapid diagnostic facility and also create effective treatment modalities.

Keywords: Acute Myeloid Leukemia, Electrolytes, Trace Elements.

INTRODUCTION:

Leukemia is a malignant disease of white blood cells (WBC) occurs when cells residing in the bone marrow they become cancerous and their daughter cells crowd normal cells in the bone marrow or are released from the bone marrow and circulate in the blood. Generally, leukemia has been classified as myeloid or lymphoid, depending on the lineage of the original mutated cell (Tollerud, D. *et al* ., 2012; Harmon, D.E. 2012). There are two types of leukemia acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). Acute leukemia develops rapidly from early immature WBC and acute forms leukemia are categorized by the types of cells from which they arise (Willems, E. *et al* ., 2003).

Acute myeloid leukemia is a heterogeneous disease, categorized by numerous somatically acquired driver mutations, coexisting competing clones, and disease evolution over time (Lichtenegger, F. S. *et al* ., 2017).

Most of the clinical manifestations of AML reflect the accumulation of malignant, poorly differentiated myeloid cells within the bone marrow, peripheral blood and infrequently in other organs. The majority of patients presents with a combination of leukocytosis and signs of bone marrow failure such as anemia and thrombocytopenia (De Kouchkovsky, I., & Abdul-Hay, M. 2016). Fatigue, anorexia, and weight loss are common complaints; lymphadenopathy and

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organomegaly are not typically seen. If left untreated, death usually ensues within months of diagnosis secondary to infection or bleeding. The diagnosis of acute leukemia is recognized by the attendance of 20% or more blasts in the bone marrow or peripheral blood (DiNardo, C. D. *et al* ., 2016).

In addition, an acute-phase protein such as ferritin is linked to inflammation and may be improved in the occurrence of chronic inflammation such as AML (Nemeth, E., & Ganz, T. 2014).

Ferritin is a protein consisting of 24 subunits that is current in every cell type. It stores iron and releases it in a controlled manner (Kim, A. *et al* ., 2014). The amount of ferritin stored reflects the amount of iron stored. Ferritin serves to store iron in a nontoxic form to deposit it in a safe form and to transport it to areas where it is essential (ORINO, K.*et al* ., 2001).

Trace elements play a role in several metabolic and physiological routes in the human body (Isidori, A. *et al* ., 2014). Iron (Fe), zinc (Zn), copper (Cu) and manganese (Mn) are essential cofactors for several enzymes that play a role in maintaining DNA reliability. Additionally, they are complicated in membrane transport, nerve conduction and muscle contraction and also in the function of sub-cellular systems such as mitochondria, and also act as antioxidants (Wang, E.S. 2014). Therefore, differences in the optimum levels of these trace elements may unfavorably disturb biological progressions (Demir, C. *et al* ., 2011).

The aim of the study was to assess the serum concentrations of electrolytes sodium (Na), potassium (K), calcium (Ca), and some trace elements levels among newly diagnosed Iraqi patients with AML.

PATIENTS AND METHODS:

This study was conducted at the National Center of Hematology/ Al-Mustansiriyah University and Ministry of Science and Technology/ Baghdad. During the period from October 2018 until the end of March 2019. Sixty newly diagnosed Iraqi patients with AML were enrolled in this study; their age range was (38-50) years and they were compared with 30 healthy subjects as control group. Each patient assessed with full name, age, gender, body mass index (BMI), disease diagnosed, and medications received. Blood sample withdrawn and handled by EDTA tube and plain tube then processed in the laboratory to estimate complete blood count (CBC), hemoglobin (Hb), platelets (PLT), WBC, lymphocytes account, and neutrophils. Serum levels of electrolytes Na, K, and Ca were measured by easy kit analyzer. Levels of metals (Fe, Mg, Mn, Cu, Co, Cr, and Zn) were estimated by the atomic absorption spectrophotometer (AA670-Shimadzu, Japan).

Data Analysis:

To compare the significance of the difference in the mean values of any two groups, student's t-test was applied and $p \leq 0.05$ was considered statistically significant.

Results:

In table (1), there was an elevation in age and BMI in AML patients, but it was not statistically significant as compared to control group ($p < 0.61$, $p < 0.33$) respectively. The Hb, PLT, lymphocytes, and ferritin values of AML patients were significantly lower when compared with the control group, while WBC and neutrophils values were significantly higher in AML patients than in the control group ($p < 0.05$).

Table (1): Baseline characteristics and hematological parameters in AML patients and control

Parameters	Means±SD		*p*-value
	AML (n=60)	Control (n=30)	
Sex (M/F)	(30/30)	(16/14)	-
Age (years)	42.13±13.9	41.24±8.63	0.61
BMI (Kg/m^2)	28.17±4.21	26.32±4.14	0.33
Hb (g/dl)	8.71±1.72	13.2±1.13	0.01
PLT ($10^3/\mu l$)	23.17±3.56	216.8±18.14	0.0001
WBC ($10^3/\mu l$)	13.64±2.99	7.21±2.12	0.01
Neutrophils ($10^3/\mu l$)	24.16±2.34	8.31±3.21	0.001
Lymphocytes ($10^3/\mu l$)	6.27±1.17	18.31±3.21	0.01
Ferritin (ng/ml)	14.48±10.71	35.61±16.31	0.01

Table (2) shows a significant increase in Hb and ferritin levels in male when compared with female patients, while a significant decrease in PLT and WBC was found in male when compared with female patients, while neutrophils and lymphocyte a count show no significant difference between both genders of AML patients.

Table (2): Comparative of hematological parameters for both gender in AML patients

Parameters	Means±SD		*p*-value
	Male (n=30)	Female (n=30)	
Hb (g/dl)	12.12±2.41	8.28±1.03	0.05
PLT (10^3/µl)	18.14±3.81	28.20±3.31	0.05
WBC (10^3/µl)	7.23±2.14	18.05±1.52	0.05
Neutrophils (10^3/µl)	28.13±3.41	20.20±4.23	0.23
Lymphocytes (10^3/µl)	7.21±1.04	5.32±1.31	0.48
Ferritin (ng/ml)	17.31±9.81	11.31±6.62	0.05

Serum levels of metals and trace elements are illustrated in table (3). There was a significant decrease in Na, Mn, Fe, Co, Cu, and, Zn while a significant increase was found in serum Mg and Cr in AML patients as compared to controls ($p < 0.05$). There was a significant decrease in serum Na, K, Ca, Mg, and Mn in males patients as compared to females, while serum Fe, Co, Cu, Cr, and Zn levels were significantly increase in male patients when compared with the female, (table 4).

Table (3): Comparative of electrolytes and metals for AML patients and control

Parameters	Means±SD		*p*-value
	AML (n=60)	Control (n=30)	
Na (mg/dl)	131.30±12.93	142.55±2.58	0.05
K (mg/dl)	6.15±0.11	4.50±0.63	0.06
Ca (mg/dl)	11.32±1.47	12.30±0.12	0.08
Mg (mg/dl)	5.92±0.27	0.85±0.20	0.05
Mn (mg/dl)	0.75±0.24	1.58 ± 0.03	0.05
Fe (mg/dl)	30.0±12.30	108.30 ± 15.87	0.01
Co (mg/dl)	0.68± 0.18	1.48 ± 0.02	0.05
Cu (mg/dl)	0.75±0.18	1.50 ± 0.01	0.05
Cr (mg/dl)	4.0±0.70	0.68 ± 0.07	0.05
Zn (mg/dl)	0.47 ±0.70	0.58 ± 0.05	0.05

Table (4): Comparative of electrolytes and metals for both genders in AML patients

Parameters	Means±SD		*p*-value
	Male (n=30)	Female (n=30)	
Na (mg/dl)	125.9±19.27	136.7 ±16.6	0.05
K (mg/dl)	4.13±0.18	8.16 ±0.044	0.05
Ca (mg/dl)	9.03±1.63	13.63±1.30	0.05
Mg (mg/dl)	2.94±0.25	7.87±0.29	0.05
Mn (mg/dl)	0.32±0.21	1.28±0.28	0.05
Fe (mg/dl)	33.41±18.10	26.13±6.50	0.05
Co (mg/dl)	1.0±0.19	0.40±0.17	0.05
Cu (mg/dl)	1.12±0.22	0.46±0.14	0.05
Cr (mg/dl)	5.73±1.20	2.10±0.2	0.05
Zn (mg/dl)	0.69±0.45	0.25±0.9	0.05

DISCUSSION:

Leukemia originates from hematopoietic stem cells that miss their ability to differentiate normally for production of the mature blood cell (Riether, C. *et al* ., 2015).

In this study, Hb and PLT count were significantly lower in AML patients than controls. This finding was consistent with the results of Yamamoto, J.F., & Goodman, M.T. (2008). Other results in this study, lymphocytes in AML patients were significantly lower in patients than controls. This finding was consistent with the results of Chessel *et al* ., (1986).

However in this study, WBC and neutrophils count were significantly higher in AML patients than control. This result agreed with study of Wetzler *et al* ., (2012). This can be explained by the fact that in leukemia there is a clonal proliferation of malignant cells that may arise at any stage of maturation in the

bone marrow including lymphoid, myeloid or pluripotent stages (Wang, L. *et al* ., 2011).

In current study, there was no significant difference in the means of BMI in AML as compared to the control group. This finding was consistent with the results of Alizadeh *et al* ., (2011). This result could be related to the high metabolic rate of malignant cells, along with fever and body weight loss (Besa, E.C. *et al* ., 2013).

Sex-related differences in PLT count were described several studies. The mean PLT count was higher in women than men in all age classes. Subsequent studies confirmed that females have a slightly higher PLT count. In particular, no difference in the PLT count of men and women was found before the age of 15 years, whereas women had more platelets than men in the age range 15–64 years and over 64 years. In any case, sex-related differences in adults were only approximately 10% and much lower than those related to aging (Segal, J.B., & Moliterno, A.R. 2006; Biino, G. *et al* ., 2012).

As for age-related variability, also the mechanisms of sex-related differences in PLT count are unknown. However, the finding that women have a higher PLT count than men only after the age of 14 years suggests that puberty makes the difference. We can speculate that the reduction in body iron in females, which occurs in menstruating women and persists in the elderly (Shameer, K *et al* ., 2014), stimulates PLT production. However, the hormonal differences between men and women after puberty could also play a role. In particular, the observation that estrogens favor PLT formation in mouse supports this hypothesis, although no data in humans are available (Balduini, C.L., & Noris, P. 2014).

Under normal conditions, levels of serum ferritin show a close correlation with iron stores in liver biopsy samples. However, serum ferritin levels can be profoundly affected by the presence of inflammation, since serum ferritin is an acute-phase protein (Archer, N.M., & Brugnara, C. 2015). The acute-phase response is a major physiological defense reaction, whereby the body aims to restore physiological homeostasis in the face of inflammation. Serum levels of positive acute phase proteins including ferritin rise dramatically as part of the inflammatory response, mediated by increased expression of cytokines (Paul, B.T. *et al* ., 2017).

Many studies (Filippatos, T. D. *et al* ., 2005; Milionis, H. J. *et al* ., 1999) showed a low serum level of Na (hyponatremia) and K (hypokalemia). In this study, AML patients had hyponatremia but not hypokalemia. Patients in remission usually have normal serum electrolyte concentrations.

Hyponatremia, a serious electrolyte disorder associated with life-threatening neurological complications, is one of the most common electrolyte disorders associated with tumor-related conditions (Wakui, A. 1986). Hyponatremia is proposed to be due to an inappropriate production of antidiuretic hormone (vasopressin) by the leukemic cells (Udayakumar, N *et al* ., 2006).

In hematologic malignancy hypocalcemia is not common and results from various factors, including hypoalbuminemia, malabsorption, malnutrition, vitamin D deficiency and hypomagnesaemia, or chronic respiratory alkalosis. Tumor lysis with its high serum phosphorous concentrations caused deposition of calcium phosphate, thereby lowering serum calcium levels (Luciano, R.L., & Brewste, U.C. 2014).

This study found a higher levels of serum Mg in AML patients as compared to the controls. This agreed with the study of Alea *et al* .,., (2013) that found increased in serum Mg in all patients. Elevated serum Mg as a result of its release of malignant cells after cytotoxic therapy or its accumulation due to urate nephropathy which suggested an association between the deficiency of this element and the development of malignant disorders (Alwan, A. F. *et al* ., 2013).

Manganese is necessary for optimal biological function that is required as a cofactor for many enzymes. Manganeseassisted enzymatic antioxidant Mn-superoxide dismutase (Mn SOD) is an endogenous antioxidant enzyme it is function neutralize free radicals and prevent cellular damage (Parmalee, N.L., & Aschner, M. 2016). Increasing in free radical generation in leukemic patients and decreasing in the antioxidant defenses are indicative of oxidative stress involved in the pathogenesis of human leukemia (Lison, D. 2015).

In the current study, serum Mn showed significantly lower concentration in AML patients than control. In general observations of gender effect, it can be noticed that in male and female, serum Na, K, Ca, Mg, and Mn concentrations were more significant in AML females than males which might be referred to nutrition, health, work, location,….etc.

Cell lysis, due to chemotherapy, radiation, or leukemia itself, is an additional risk factor for developing iron overload. Treatment of secondary iron overload in AML patients remains, however, challenging (Hoeks, M. P. *et al* ., 2017). The Hb levels are often not sufficiently high to perform phlebotomies, while drug interactions or adverse events could hamper the use of iron chelation therapy which is should at least show a clear benefit on clinical outcomes like survival with an acceptable toxicity profile. Alternatively, more restrictive RBC strategies may help prevent secondary iron overload. Such restrictive strategies do not seem to have a direct negative impact on clinical outcomes in

patients with hematological malignancies (Tay, J. *et al* ., 2016). In this study, iron changed in both genders compared with controls. It is known that iron deficiency might be a results of one or more reason(s) such as poor diets, blood donation, infection, drugs, nutrition with non-rich of iron food beside other reasons were encounter to women child bearing age, pregnancy, bleeding, and disorder of breast feeding.

Cobalt is essential to mammals in the form of cobalamin (vitamin B12). Significantly lower concentration of cobalt in AML patients. Deficiency of Co leads to decreased availability of B12, and developed many symptoms and problems attributed to B12 deficiency, particularly pernicious anemia, nerve damage and a significant increase in the incidence of lymphatic and hematopoietic malignancies (Prashanth, L. *et al* ., 2015).

Regarding to the nutritional role of Cu and Zn and their important roles in metabolism regulation and their direct relation with cancers any significant changes in the level of these elements could be harmful to the body.

In this study, it was observed that there was a significant decrease in Cu concentration in AML patients compared with control. Some investigators combined between Cu deficiency and hematological and neurological abnormalities, they consider Cu deficiency is an established cause of hematological abnormalities but is frequently misdiagnosed (Sanaat, Z. *et al* ., 2011). Also, there was a significant decreasing serum Zn concentration in AML group compared with control is in agreement with previous data. The general trend towards slightly decreased Zn concentrations in malignant diseases agree with the experimental results obtained by implying that Zn deficiency is associated with the etiology of cancer (Halfdanarson, T. R. *et al* ., 2008). Chromium is a human carcinogen primarily by inhalation exposure in occupational settings. The need of Cr is for biosynthesis of glucose tolerance factor. The deficiency causes impairment of glucose tolerance while toxicity results in renal failure, dermatitis, and pulmonary cancer (Costa, M., & Klein, C.B. 2006).

In general and according to the present data, Co, Cr, Cu, and Zn can be considered as primary indications of AML in females. The presence of these elements in tissues even in low concentrations was proliferation marker. The change of tested elements in all samples can be attributed to different factors such as presence of other health problems, nutrients, social background, location, work, and specialty of woman life due to several disorders.

CONCLUSIONS:

The role of the trace elements in AML may provide vital clue for the etiopathogenesis of the occurrence of leukemia. The decreased levels of some these elements such as, Cu, Zn, and Fe in AML patients when compared to normal may be type of interaction with the serum levels that are inverted. It is then also probable to relate anemia, a consistent finding with these diseases. Thus the deciphered role of trace elements will allow to understand the etiopathogenesis, afford a rapid diagnostic ability, and also create operative treatment modalities.

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