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Research Article

Physiological and Chemical Study to Evaluation the Epidemiology of Acute Lymphocytic Leukemia for Patients without a Family History of Cancer in Karbala City, Iraq

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ABSTRACT
During the period from the beginning of February 2016 to the end of October 2017 in the Center of Oncology of Hematology of El-Hussein Medical city in Karbala, 30 samples were collected for patients with acute lymphocytic leukemia ranging between 1-13 years old (6,80 ± 3, 79) who didn't have a family history of any cancer infection before receiving chemotherapy. The study was divided into two sections based on sex. The study included 19 males aged (1 - 12 years) and 11 females aged (1- 13 years old). The results showed significant differences in the levels of trace elements (Fe), (Cu), (Zn) and (Ni) in the serum. There was significant difference (p = 0.00) between the healthy and the patients who didn't gain medicine. Also, significant differences were in levels of fe) and Cu (cu) in serum samples in the samples of males and females with their peers in the control group. There were also significant differences when comparing the sexes in each of the two study groups. The results also showed significant differences in zn Blood samples for male and female patients with acute lymphocytic leukemia and healthy individuals, while significant differences of Ni (ni) between males and females of the infected group and healthy males.

Keyword: *leukemia, trace elements.*

INTRODUCTION

The rate of infection with cancer has increased with a clear rise in the incidence of leukemia, which is the second most common cancer in 2017[1] after it was ranked seventh in 1989 (Ministry of Health, Iraqi Cancer Board, 1993), and leukemia is the number one cancer in children[2].

The incidence of leukemia varies according to age, sex, race and geographical distribution. 10 from 100,000 people develop leukemia every year, while acute lymphoblastic leukemia represents half of patients[3] Blood cancer is more in males than females[4]. The ratio of males to females is 2: 3 in acute leukemia and 1: 2 in lymphocytic leukemia, while 1.3: 1 in leukemia. Acute leukemia occurs in all age groups, while cases of acute myeloid leukemia occur in adults and increase with age. On the other hand, people in the age group between 40 and 60 years are the most vulnerable to infection with leukemia and finally reach the highest percentage of acute lymphocytic leukemia in children aged 3 to 7 years[5].

Several studies have indicated that changes in the level of trace elements have been associated with a wide range of minor health disorders such as hair loss, skin problems, digestive disorders, recurrent colds, sleep disturbances and unexplained tiredness of large and complex health problems such as cardiovascular disease, diabetes Long-term complications resulting from obesity, autism, Alzheimer's, and finally cancer and progress rapidly[6,7].

Iron (Fe) is one of the important trace elements for the survival of many vital processes in the body. Its body mass does not exceed 5 grams, 60% of which is concentrated in the blood, liver, kidneys and bone marrow[8]. Fe enters the structure of hemoglobin (the basal protein in the structure of the red blood cells that transport oxygen from the lungs to the cells of the body for the purpose of perpetuating the oxidation processes) and also enters the structure of Myoglobin[9]. Fe plays the role of the agent associated with a large number of oxidation and reduction enzymes and is transported in the blood by Transferrin and stored in the spleen by Ferritin[10]. imbalance level of Fe is a common health indicator for many genetic and non- genetic the most important of which are liver disorders, anemia caused by

Table 1: Numbers of Study Group Members and Their Age.

Subjects (n)	Age (Year) Mean± S.D.	Minimum - Maximum Age
Controls 30	5.96 ± 3.36	1-12
	6.70 ± 3.77	2-13
Patients 30	6.69 ± 3.94	2-12
	7.00 ± 3.65	2-13

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Table 2: Levels of serum-treated serum in all patients with diagnosis and healthy individuals.

Subjects (n)	Fe Mean ± S.D. Min.-Max. Range	Cu Mean ± S.D. Min.-Max. Range	Zn Mean ± S.D. Min.-Max. Range	Ni Mean ± S.D. Min.-Max. Range
Patients 30	6.548 ± 1.055 4.140 - 8.840 4.690	2.338 ± 0.592 1.140 - 3.280 2.140	0.933 ± 0.513 0.100 - 3.210 3.110	12.095 ± 7.889 1.580 - 46.940 45.360
Control 30	8.883 ± 1.064 6.560 – 10.770 4.210	3.522 ± 2.267 3.170 – 3.980 0.081	1.621± 1.493 1.290 – 8.390 8.100	28.046 ± 6.763 15.760 – 40.490 24.720
p	0.000	0.000	0.011	0.000

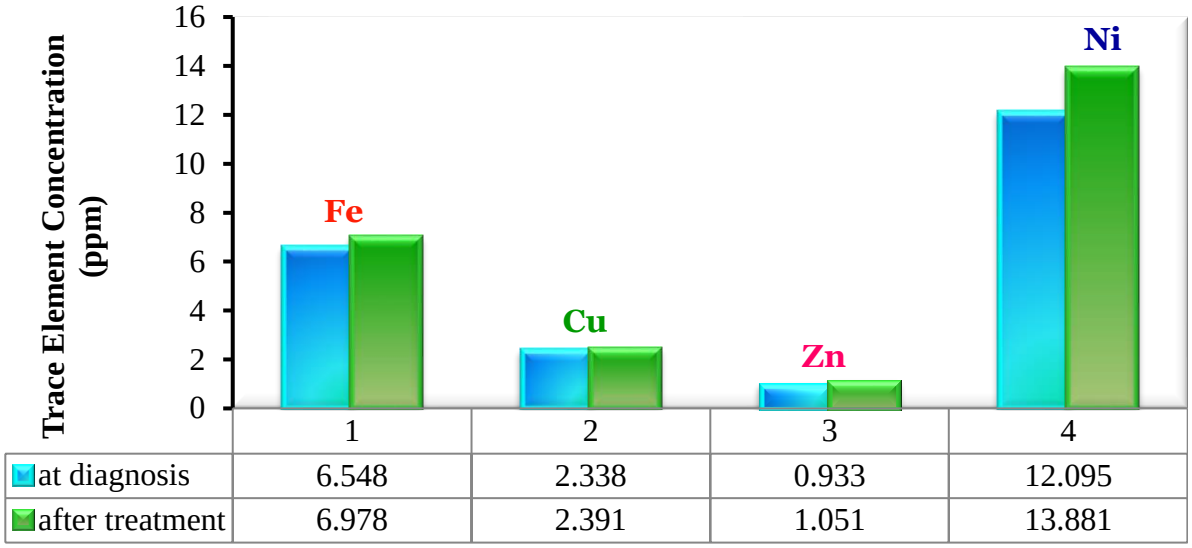

Figure 1: Levels of trace elements (Fe, Cu, Zn, and Ni) residing in the serum of the ALL-infected group at diagnosis and after treatment.

Table 3: Levels of Serum Resident in ALL Patients After Treatment and Control Group Members.

Subjects (n)	Fe (ppm) Mean ± S.D. Min.-Max. Range	Cu (ppm) Mean ± S.D. Min.-Max. Range	Zn (ppm) Mean ± S.D. Min.-Max. Range	Ni (ppm) Mean ± S.D. Min.-Max. Range
Patients 30	6.978 ± 1.209 4.420 – 9.870 5.450	2.391 ± 1.058 1.250 – 3.310 2.060	1.051 ± 1.081 1.037 – 4.930 4.560	13.881 ± 11.288 2.510 – 65.210 62.710
Control 30	8.883 ± 1.064 6.560 – 10.770 4.210	3.522 ± 2.267 3.170 – 3.980 0.081	1.621± 1.493 1.290 – 8.390 8.100	28.046 ± 6.763 15.760 – 40.490 24.720
p	0.000	0.000		0.000

Fe deficiency, chronic infections, malnutrition, and many types of cancers. Leukemia comes first.

Copper is one of the key trace elements in energy production through participation in oxidation and reduction processes[11] as well as its role in blood synthesis and hemoglobin control[12] Cu helps in metabolism, regulating blood pressure, speed of wound healing, protecting the body from sickle cell anemia and osteoporosis. It works with both Zn and vitamin C in flexible tissue work and plays an important role in regulating gene expression and preventing leukemia[13]. Decreased nutrient intake of CN or the breakdown of cytotoxic mechanisms leads to the emergence of many pathological symptoms ranging from minor neurological disorders and electrical signal transmission disorders in the central nervous system to bone marrow disorder, Blood and finally a lack of blood cell production[14,15]. The low level of Cu in the blood can be attributed to an inherited disease, as in Meknes's disease, in which the patient is diagnosed with the inability to absorb Cu in the intestine[16]. While creasing in concentrating of (Cu), often due to diseases such as Wilson Disease, in which Cu is subtracted across the bile and accumulates in the liver, kidney, and brain[17].

Table 4: Levels of the resident components of serum ALL patients before treatment and control group individuals.

Trace Element (ppm)	Subjects (n)				*p*
	Patients		Controls		
	30		30		
	Males	Females	Females	Males	
	18	12	19	11	
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	
	Min.-Max.	Min.-Max.	Min.-Max.	Min.-Max.	
	Range	Range	Range	Range	
Fe	6.278 ± 1.028	7.089 ± 1.093	8.625 ± 1.099	9.401 ± 1.064	*0.048*
	4.140-8.150	5.520-8.840	6.560-10.770	7.730-10.630	*For 1vs2*
	4.000	3.310	4.210	2.900	*0.058*
					For 3vs4
					0.000
					For 1vs3
					0.000
					For 2vs4
Cu	2.032 ± 1.046	2.952 ± 1.024	3.412 ± 1.016	3.743 ± 1.018	*0.000*
	1.140-2.760	2.470-3.280	3.170-3.680	3.460-3.980	*For 1vs2*
	1.620	1.081	1.052	0.520	*0.014*
					For 3vs4
					0.000
					For 1vs3
					0.000
					For 2vs4
Zn	1.019 ± 1.061	1.076 ± 1.017	1.540 ± 1.749	1.783 ± 0.825	*0.523*
	1.010-3.210	1.045-1.040	1.029-8.390	0.590-3.360	*For 1vs2*
	3.110	1.059	8.100	2.76	*0.545*
					For 3vs4
					0.574
					For 1vs3
					0.030
					For 2vs4
Ni	11.582 ± 4.138	14.121 ± 12.633	24.833 ± 5.532	34.472 ± 3.730	*0.442*
	3.680-18.960	1.580-46.940	15.760-33.320	30.100-40.490	*For 1vs2*
	15.270	45.360	17.560	10.390	*0.004*
					For 3vs4
					0.000
					For 1vs3
					0.000
					For 2vs4

There are about 2 grams of Zinc Zn in the adult human body is distributed by 25% in the muscles and 65% in the bones and There are about 2 grams of Zn zinc in the adult human body. Zn is present in all components of the cells and is concentrated in the nucleus. The gland, skin, and parts of the brain, pancreas, placenta, prostate, and sperm are rich in zinc[18]. Zn is an essential nutrient and clearly affects the metabolism of proteins, fats, carbohydrates and phosphorus in most organisms[19]. It is also important in the manufacture of nucleic acids, which controls the production levels of proteins in the cell[20]. One of the most important functions of Zn in the body is its host as cofactor Enzyme Cofactor in the whole system Holozyme of the enzymes known as the need for metal to perform the function, where Zn Cofactor of about 300 Enzyme. Zn is necessary for the stability of the fusion between the enzyme and the base material in some enzymes and in other enzymes Zn is the central ion of the effectiveness of these enzymes, but often Zn performs both functions as in the enzyme alcohol Dehydrogenase and the third possibility of zinc is to activate the effectiveness of some enzymes. Three enzymes are significantly affected by changes in Zn levels: Alkaline Phosphatase in the bones, Carboxypeptidase A in the pancreas, and Deoxythimidine Kinase in the subcutaneous tissues[21]. Zn participates in Krebs Cycle for energy production[22]. Zn interferes with vitamin E and, if present at a low level, vitamin E is ineffective and increases the Zn presence. It enables it to occupy the binding sites of Fe and Cu in fat and protein , As well as DNA, thus showing its direct physical capacity as an antioxidant, because the element Fe is an effective element in the process of oxidation and reduction and thus can be a highly effective roots of the H2O2, which analyzes the fat peroxides to the root of Peroxyl and Alloxyl and these roots working on fat oxidation[23,24].

Table 5: Levels of serum-treated serum in patients with ALL after receiving chemotherapy and control group individuals.

Trace Element (ppm)	Subjects (n)				*p*
	Patients		Controls		
	30		30		
	Males	Females	Females	Males	
	18	12	19	11	
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	
	Min.-Max.	Min.-Max.	Min.-Max.	Min.-Max.	
	Range	Range	Range	Range	
Fe	6.616 ± 1.099	7.703 ± 1.328	8.625 ± 1.099	9.401 ± 1.064	*0.000*
	4.420-7.870	5.730-9.870	6.560-10.770	7.730-10.630	*For 1vs2*
	3.450	4.140	4.210	2.900	*0.058*
					For 3vs4
					0.000
					For 1vs3
					0.000
					For 2vs4
Cu	2.098 ± 1.047	2.978 ± 1.020	3.412 ± 1.016	3.743 ± 1.018	*0.000*
	1.250-2.800	2.720-3.310	3.170-3.680	3.460-3.980	*For 1vs2*
	1.550	1.059	1.052	0.520	*0.014*
					For 3vs4
					0.000
					For 1vs3
					0.000
					For 2vs4
Zn	1.204 ± 1.096	1.075 ± 1.017	1.540 ± 1.749	1.783 ± 0.825	*0.255*
	1.037-4.930	1.055-1.098	1.029-8.390	0.590-3.360	*For 1vs2*
	4.560	1.043	8.100	2.76	*0.545*
					For 3vs4
					0.305
					For 1vs3
					0.027
					For 2vs4
Ni	12.925 ± 3.949	16.7940 ± 19.089	24.833 ± 5.532	34.472 ± 3.730	*0.242*
	6.850-21.590	2.510-65.210	15.760-33.320	30.100-40.490	*For 1vs2*
	14.740	62.710	17.560	10.390	*0.004*
					For 3vs4
					0.000
					For 1vs3
					0.000
					For 2vs4

Another important function of the two is to participate in the system and the oxidative breakdown of the cell membrane by free radicals occurs in the absence of Zn or its very small presence[25]. The mechanism by which Zn acts as an antioxidant is not known, but Zn of the process of building Metallothionein as well as the protein rich in amino acid Csystein, which acts as a stalker of free radicals[26. A] wide range of health symptoms coincide with decreased levels of Zn in the body. These symptoms are treated with food and dietary supplements containing this component[27]. Sickle cell anemia and dysfunction of T-lymphocyte cells are associated with deficiency Sharp in Zn[14].

Nickel is a trace element that acts as an adjunct to a number of enzymes, advanced by the antioxidant defense system[28]. Ni contributes as a key ingredient in building vitamin B12. Ni deficiency causes slow growth, fertility problems, Regulation of the work of other elements, as well as increased levels of growth disorder and inability to produce blood cells[29]. Nickel carbonate has been found to be one of the chemical compounds that stimulate the transformation of a normal cell into a cancerous cell. It is a highly toxic compound that travels from the lungs to breathe and is transferred to the blood, leading to brain degeneration leading to cancer[30].

MATERIALS AND METHODS

During the period from the beginning of February 2016 to the end of October 2017 in the Center of Oncology of Hematology of EL Hussein Medical city in the province of Karbala, 30 samples were collected for patients with acute lymphocytic leukemia ranging between 1-13 years old (6,80 ± 3, 79) who didn't have a family history of any cancer before receiving chemotherapy after receiving

Table 6: Relations between trace elements residing in control group serotypes.

r p	Trace Element (ppm)	Fe	Cu	Zn	Ni
	Fe	1	0.420 0.021	0.165 0.385	0.549 0.002
	Cu	0.420 0.021	1	-0.013 0.945	0.787 0.000
	Zn	0.165 0.385	- 0.013 0.945	1	0.089 0.641
	Ni	0.549 0.002	0.787 0.000	0.089 0.641	1

Table 7: relationship between surgical elements in sicks of the all group with disease.

r p	Trace Element (ppm)	Fe	Cu	Zn	Ni
	Fe	1	0.515 0.004	0.043 0.822	0.243 0.196
	Cu	0.515 0.004	1	-0.253 0.178	0.121 0.523
	Zn	0.043 0.822	-0.253 0.178	1	0.033 0.863
	Ni	0.243 0.196	0.121 0.523	0.033 0.863	1

official approvals and with the help of the medical staff supervising the patients in this center. The control group included 30 healthy individuals (18 males and 12 females). The current study was designed to investigate the levels of a number of trace elements in patients with acute lymphocytic leukemia when diagnosed and compared with healthy counterparts in the control group in order to identify the effect of the cancer infection at the levels of those elements and then follow the levels of those elements after receiving chemotherapy to identify the response of body for treatment.

The levels of Fe, Cu, Zn, and Ni were assessed in serological samples for both the group of children with acute lymphocytic leukemia and the group of healthy individuals using flamingo-atomic spectroscopy.

RESULTS AND DISCUSSION

The levels of trace elements (Fe, Cu, Zn and Ni) of vital importance in the serum of study patients were assessed at diagnosis and after treatment, as well as control group members using the atomic absorption spectrometry technique.

When comparing the results of the evaluation of the four trace element levels assessed in all patients with acute lymphocytic leukemia (ALL)) when the lesions were diagnosed with their control group samples, the four element levels were found to be lower in the patient samples than the healthy group, Student's t-test showed significant differences ($p = 0.000$) in Fe, Cu and Ni, while the difference was significantly less when evaluating the Zn level ($p = 0.011$) as shown in Table 2.

Despite the relatively high levels of trace elements residing in infected samples after treatment compared to their levels in diagnosis as shown in Figure 2, the statistical treatment of the results of patients' samples after receiving chemotherapy and comparing them with the control group showed that chemotherapy was not effective It isn't sufficient to raise the level of the four elements in the samples of the study samples from patients with acute lymphocytic leukemia to normal levels, where the levels of the elements present in the current work remained significantly lower ($p < 0.05$) compared to the healthy group (Table 3).

In order to investigate the potential differences in the levels of the four measurable elements resulting from the difference in sex, the results of the four components were compared between the two groups on the one hand and between the subgroups (patients and healthy) of the same sex on the other hand by applying the analysis of variance. ANOVA)

The results showed that there were significant differences between males and females when evaluating the levels of Fe ($p = 0.048$ and Cu ($p = 0.000$) respectively, while the study did not record similar results when comparing the levels of Zn and Ni in males and females in the group ($P = 0.014$ and Ni) ($P = 0.004$) in individuals in the control group. The levels of Fe and Zn were close to males and Healthy females.

When comparing the group of infected females (before starting treatment) with their healthy counterparts, the current study showed significant differences ($p = 0.000$) in Fe, Cu and Ni respectively, while the study failed to find statistically significant differences in Zn levels when compared Group of females infected with healthy ones (Table 4).

The results of the comparison between the males (males with acute lymphocytic leukemia when diagnosed with the disease and members of the male control group) were consistent with those observed when comparing the females of the two study groups. Excluding these results were observed when comparing the levels of Zn in the male groups A statistically significant difference was observed ($p = 0.030$) between these two groups, as shown in Table 4.

In order to monitor the effect of the treatment of each sex of patients with chemotherapy and to test its effect on the levels of trace elements, the implicit gender comparison was carried out after the group members received at least two doses of chemotherapy. On the other hand, the trace element levels of the two groups of patients Gender with their counterparts in control totals.

Table 5 indicates a high statistical variance in the levels of Fe and Cu between females and males in the current study group. Although the level of these two components increased after receiving chemotherapy (Figure 1), the female response was higher than that of males in this group. The highest levels of these two components were recorded in the female group as shown in Table 5. There were no significant differences between females and males with acute lymphocytic leukemia when evaluating the levels of Zn ($p = 0.255$) and Ni ($p = 0.242$)

Table 8: Relationships between trace elements residing in the vaccines of all patients with chemotherapy.

r p	Trace Element (ppm)	Fe	Cu	Zn	Ni
	Fe	1	0.656	-0.214	0.494
			0.000	0.256	0.005
	Cu	0.656	1	-0.438	0.223
		0.000		0.016	0.235
	Zn	-0.214	-0.438	1	-0.135
		0.256	0.016		0.477
	Ni	0.494	0.223	-0.135	1
		0.005	0.235	0.477	

respectively.

The study found a statistically significant difference (p = 0.000) when comparing the female and male patients with their control group for Fe, Cu and Ni, while the study failed to find a significant difference (p = 0.305) among female patients after receiving treatment and healthy females when evaluating level of Zn, While the difference in the levels of this component between healthy and unhealthy males was statistically significant (p = 0.027)

Table 6 shows statistically significant correlations (p = 0.021) between Fe and Cu where the levels of these two elements were correlated in 42% of control group samples. 55% of the control group samples were associated with positive correlation with a high level of significance (p = 0.002) when testing the relationship between Fe and Ni.

The current study showed a positive correlation with a significant statistical significance of 0.787 (r = p = 0.000) when studying the relationship between the Cu and Ni elements residing in control group samples (Table 6). On the other hand, the relationship between Zn and Cu and Ni, respectively to Morale.

The study showed that there was a statistically significant positive correlation between Fe and Cu only, whereas the correlative relationship between the other four measured components of the morale was absent. At the same rate as in control group results, but at a higher correlation level, the relationship between Cu and Zn was found to be negative in ~ 25% of the patients' samples prior to chemotherapy, as in Table 7.

After receiving chemotherapy, the percentage of samples positively correlated with both Fe and Cu was increased to 66% of the total samples of the study patients. It was observed that this correlation was highly consistent and meaningful (p = 0.000)

The number of samples positively associated with each other when evaluating the relationship between Fe and Ni was increased to 50% of the total number of specimens evaluated and at a significant level (p = 0.005). The results of the study showed a significant increase in correlation coefficient (r = -0.438) Consistency of recorded results resulting in increased statistical morale.

The relationship between the Zn and Fe elements as well as Zn and Ni was reversed (negative) (-0.214 and -0.135 with Fe and Ni respectively) after chemotherapy, thus it was opposite to the nature of the association of the Zn with two other elements in control group samples.

The results of the current study were consistent with a large number of studies that indicated a simultaneous decrease in Fe level with cancer incidence and overall progression[31] and with acute lymphocytic leukemia in particular[32], while the results were inconsistent with other studies[33].

Copper levels were low in samples with acute lymphocytic leukemia. These results were consistent with many studies of many types of cancerous and non-cancerous infections.

Zn affects the growth, development and safety of the immune system. Many studies have indicated that Zn deficiency can cause T cell dysfunction and weaken cellular immune function[34]. The results of the present study are consistent with a number of studies that have shown a significant reduction in Zn levels in acute lymphocytic leukemia patients compared to control group[35].

Despite the failure to obtain previous studies indicate the role of Nickel in the process of carcinogenicity or affected by the levels of progression of the stages of infection and the fact that previous research had indicated the role of this element only in stimulating the emergence of metabolic syndrome metabolic symptoms of gaining weight and high cholesterol, triglycerides and hypertension[27]. Another study indicated that those who had high levels of Nickel were less likely to develop pancreatic cancer by 33% to 95% compared to those who suffer from low levels of these elements in the body. Yet, the results of the current study is the starting point for Many of the special impact of business change in the level of nickel element in different body fluids during various pathological injuries.

CONCLUSIONS

Cancer negatively affects the natural balance of nutrients, including trace elements, in particular, due to a combination of factors including malnutrition, loss of appetite, vomiting and bad digestion and malabsorption. Characteristic feature of abnormal cellular transitions is the decline of the cancer cell's ability to synthesize a number of proteins. For a number of trace elements or influencing proteins indirectly in these proteins. The elements present in the present work except nickel are involved in being enzymatic accompaniments for a large number of enzymes that stimulate oxidation and reduction reactions, and are directly related to the oxidative stress of the cell.

RECOMMENDATIONS

Study of other trace element and their effect on the cancer patient. Study of genetic change of the cancer patient and their correlation with trace element

REFERENCE

1. Ministry of Health, Iraqi Cancer Board (2018). Results of Iraqi Cancer Registry 2017.

2. Ministry of Health, Iraqi Cancer Board (2008). Results of Iraqi Cancer Registry 1993.
3. Craig JIO, McClelland DBL, Ludlam CA. Blood disorders in Davidson's Principles and Practice 20th edn, Churchill Livingston Edinburgh, 2006, pp 999-1064.
4. Hoffbrand, A.V.; Pettit, J.E. and Moss, P.A.(2005). Essential Hematology, Blackwell Sceintific Publication, Oxford, ISBN 0-62305-153-1.
5. Ross, J. A.; Spector, L. G. and Davies, S. M. (2005). Biological basis of cancer and blood disorder. Etiology of childhood cancer: Recent reports. Pediatric Blood & Cancer, 45: 239–241
6. Ozgur ,E; Halit, D ; Erkan, D; Ramazan, E ; Tugba, G ;Canan, D ; Edip, G ;Nedim, Tand Mehmet, F ., (2013). Plasma Concentrations of Some Trace Element and Heavy Metalsin Patients with Metastatic Colon Cancer. Journal of Cancer Therapy, 4: 1085-109
7. Yang W. C., .(2015) Iron Metabolism and Leukemia Advanced Techniques in Biology & Medicine Adv Tech Biol Med 2015, 3:1
8. Yu Y., Kovacevic Z, Richardson DR (2007) Tuning Cell Cycle Regulation with an Iron Key. Cell Cycle 6: 1982-1994.
9. Yamanishi, H.;Kimura,S. and Yanagihara,T.(2005).Fully automated of Serum iron measurements.Clin.Chem.40.540-551.
10. Zuo X, Chen J, Zhou X, Li X & Mei G 2006. Levels of selenium, zinc, copper, and antioxidant enzyme activity in patients with leukemia. Biological trace element research. 114 (1-3): 41-53.
11. Gaetke, LM; Chow-Johnson, HS; Chow, CK. (2014). Copper: toxicological relevanceand mechanisms. Arch Toxicol. Nov; 88(11): 1929-38.
12. Khoshdel Z, Naghibalhossaini F, Abdollahi K, Shojaei S, Moradi M, Malekzadeh M. Serum Copper and Zinc Levels Among Iranian Colorectal Cancer Patients. Biol Trace Elem Res 2015;170:294-9. doi: 10.1007/s12011- 015-0483-4.
13. Angelova M, Asenova S, Nedkova V, & Koleva R. [2011]: Copper in the human organism. Trakia Journal of Sciences. Vol. 9, No. 1, p:88-98.
14. Labib HA, Hassanein M, Etewa RL. Serum copper is a simple but valuable prognostic marker in B-cell chronic lymphocytic leukemia. Int J Hematol 2014; 100:575-81. doi: 10.1007/s12185-014-1686-8.
15. Ozgur, E; Halit, D; Erkan, D; Ramazan, E ; Tugba, G ;Canan, D ; Edip, G ;Nedim, Tand Mehmet, F., (2013). Plasma Concentrations of Some Trace Element and Heavy Metalsin Patients with Metastatic Colon Cancer. Journal of Cancer Therapy, 4: 1085-1090
16. Mazdak H, Yazdekhasti F, Movahedian A, MirkheshtiN, Shafieian M. The comparative study of serum iron, copper, and zinc levels between bladder cancer patientsand a control group. Int Urol Nephrol. 2010; 42:89-93.
17. Molina-Lopez J; Florea, D; Herrera-Quintana, L; Adam, V; Kizek, R ; Quintero ,B and Planells, E et al. (2015). Biomarkers of Zn status associated to colorectal cancer pathogenesis. Journal of Metallomics and Nanotechnologies, 2: 11—18.
18. Carl A, Edward R, David E, & Barbara G. [2008]: Fundamentals of Clinical Chemistry. 6th Edition.
19. Johnson S. The possible crucial role of iron accumulationcombined with low tryptophan, zinc and manganese incarcinogenesis. Med Hypotheses. 2001;
20. Dar, N. A., Mir, M. M., I. Salam, et al., "Association be-tween Copper Excess, Zinc Deficiency, and TP53 Mu-tations in Esophageal Squamous Cell Carcinoma from Kashmir Valley, India: A High Risk Area," Nutrition and Cancer, Vol. 60, No. 5, 2008, pp. 585-591.
21. Stevens, A. & Lowe, J.(2000). Pathology, (2nd ed)., Mosby, London. Pp: 79-104
22. Yelinova V, Glazachev Y, Khramtsov V, Kudryashova L, Rykova V, Salganik R. Studies of human and rat bloodunder oxidative stress: changes in plasma thiol level, antioxidant enzyme activity, protein carbonyl content, andfluidity of erythrocyte membrane. Biochem Biophys ResCommun. 1996; 221:300-3.
23. Prasad A., Kucuk O. Zinc in cancer prevention.Cancer Metastasis Rev. 2002;21(3-4):291-5
24. Radhakrishnan, M., Hammond, G., Jones, P. B., Watson, A., McMillan-Shields, F., & Lafortune, L. (2013). Cost of Improving Access to Psychological Therapies (IAPT) programme: an analysis of cost of session, treatment and recovery in selected Primary Care Trusts in the East of England region. Behaviour Research and Therapy, 51, 37–45.
25. Lefta, A., A., Biochemical Evaluation of the Levels of Oxytocin Serotonin and Some Oxidative Stress Parameters in Sera of Patients with Morbid Obesity., M.S., Department of Chemistry / Faculty of Education for Girls/ University of Kufa (2017)
26. Shils, M. & Shike, M., 2006. Modern nutrition inhealth and disease. Lippincott Williams &Wilkins
27. Das K, Das S, & Dhundasi S. [2008]: Nickel, its adverse health effects and oxidative stress. Indian J Med Res. Vol. 128, p:412-425.
28. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: A systematic review of the literature. Am J Med Am J Med. 2004 Apr 5;116 Suppl 7A:11S-26S.
29. Nielsen F H. [2008]: Ultratrace elements possible importance for human: Au update. Hyper trace elements and disease. Vol. 101, p:355-376
30. Gambino, T.;Sit,H. and Lone ,J.(2005).Iron and iron binding capacity In leukemia patiants .Hemattology .9.44-48.
31. Kabat, G.;Rohan,T.and Salonen,R.(2007).Dose excess iron play arol in Carcinogenesis .Pub Med .18(10).1047-1053.
32. Percy,MJ.(2008).Again – of – function mutation in the HIF2A gene in the Familial erythrocytosis .N Eng J Med .8.162.200.
33. Hanna, J., Expression of CD95 in Acute Lymphocytic Leukemia (ALL) in Egyptian Children before and

after Treatment., J .Blood Disorders Transf .(2014), 6:1

34. Modaressi, A., Hadjibabaie, M., Shamshiri, A. R, Namdar, R., Abdollahi, M., & Ghavamzadeh, A. (2012). Trace elements (Se, Zn, and Cu) levels in patients withnewly diagnosed acute leukemia. IJHOSCR, 6, 5–10.