# Measurement of Serum Lipid Profile Parameters, Blood Urea Nitrogen, Serum Uric Acid and Serum Creatinine Levels for Children with Acute Lymphoblastic Leukemia


- **Abstract**

**Introduction:** Leukemia is the commonest malignancy of childhood and is the causative of a third of childhood cancer deaths. Lipid abnormalities have been recognized in children with acute lymphoblastic leukemia (ALL). Kidney involvement in leukemia can be quite immense. This study aimed to investigate impact of childhood acute lymphoblastic leukemia and chemotherapy on serum lipid profile parameters and serum renal function tests and on body function.

**Materials and Methods:** eighteen pediatric ALL patients were enrolled. Serum blood lipid profile, blood urea nitrogen (BUN), serum uric acid (UA), and serum creatinine levels were measured during treatment.

**Results:** ALL was more among boys (61.11%) than girls. Of 18 cases, 14 (77.78%) were with low total cholesterol (TC), 2 (11.11%) with low triglycerides (TGs), all (100%) with low high-density-lipoprotein cholesterol (HDL-C), 14 (77.78%) with low blood urea nitrogen (BUN), and 2 (11.11%) with low serum uric acid (UA). Four (22.22%) were with high serum TGs, 6 (33.33%) with high serum very-low-density-lipoprotein (VLDL), 12 (66.67%) with high BUN, and 2 (11.11%) with high creatinine.

**Conclusions:** malignancies and chemotherapy recognizably affected serum lipid profile and serum renal function measurements and consequently adversely affected body. The specialist physician should be very careful in determining the dose of chemotherapy treatment,

otherwise the specialist physician may be held accountable and accounting in case of serious damage to health or death of patients.

**Keywords:** pediatric acute lymphoblastic leukemia, lipid profile, renal function

- **Introduction**

Leukemia is the commonest malignancy of childhood and is the causative of a third of childhood cancer deaths [1]. Leukemia can be identified as a neoplastic disease that includes the blood forming stem cells of bone marrow, spleen, and lymph nodes [2]. Eighty percent with acute leukemia have acute lymphoblastic leukemia; the remaining mostly have acute myeloid leukemia. Childhood chronic leukemia is almost seldom[3]. Acute lymphoblastic leukemia occurs from an acquired or a genetic injury to the DNA of a single cell in the marrow. The impacts of acute lymphoblastic leukemia involve uncontrolled and exaggerated growth and accumulation of cells called "lymphoblasts" or "leukemic blasts," which fail to act as normal blood cells. The existence of the leukemic blasts inhibits the production of normal cells. Therefore, when acute lymphoblastic leukemia is diagnosed, the number of healthy blood cells (red blood cells, white blood cells and platelets) is usually lower than normal [4].

Since the 1960s, a strategy of total therapy has implemented systemic therapy targets the primary disease site (the bone marrow), while intrathecal therapy is directed at leukemic cells within central nervous system (CNS) which would otherwise evade chemotherapy [3]. The coexistence of genetic polymorphisms in drug metabolizing enzymes, transporters, targets, and receptors, in the context of drug and non-drug effects, may cause high frequencies of unusual drug toxicities. Chemotherapeutic drugs can be cell cycle specific or cell cycle non-specific [5]. Ideally treatment includes four phases of chemotherapy: first remission-induction which targets quick eradication of at least 99% of the initial leukemic cell burden, resulting in prompt restoration of normal haemopoiesis; second consolidation and therapy directed at

central nervous system (CNS) which targets eradication of residual, drug resistant leukemic cells, lessening the hazard of relapse and reduction in danger of central nervous system (CNS) relapse; third intensification which aims reduction in relapse risk; and fourth continuation remedy [3].

Lipid abnormalities have been recognized in children with acute lymphoblastic leukemia (ALL) [6]. Leukemia is frequently with multiorgan system involvement. Kidney involvement in leukemia can be quite immensive [7].

This study aimed to measure serum lipid profile parameters, serum blood urea nitrogen, serum uric acid, and serum creatinine levels in children with acute lymphoblastic leukemia and investigate the impact of the disease and chemotherapy treatment on these biochemical markers levels and consequently body functions.



- **Materials and Methods**
- **Study Cases**

This study was conducted on eighteen pediatric patients [ eleven boys (61.11%) and seven girls (38.89%)] suffering from acute lymphoblastic leukemia who attended between October 2015 to December 2016 the Central Child Hospital in Baghdad, Iraq and all were diagnosed and under treatment in the hospital. Their ages ranged from five to twelve years old (7.67±0.48). All were subjected to multiple drug chemotherapy treatment which involved γ-tocopherol (γ TMT), vincristine (VCR), methotrexate (MTX), and 6-mercaptopurine (6-MP).

- **Blood Sampling**

An overnight fasting venous blood samples were drawn from all children while they were under remission-induction treatment. Serum total cholesterol (TC), serum triglycerides (TG),

serum high-density-lipoprotein cholesterol (HDL-C), , blood urea nitrogen (BUN), serum uric acid (UA), and serum creatinine levels were measured using kits (Randox) and read by autoanalyser device (Automated Mindray Ps 200). Serum very-low-density-lipoprotein (VLDL) levels were calculated according to the equation:

VLDL=TGs/5 [8].

Serum low-density-lipoprotein (LDL) levels were calculated using the equation:

LDL=TC-(HDL-C+VLDL) [8].

Table (1) shows the reference levels of biochemical tests according to the leaflets of the kits used.

Table (1): reference pediatric levels for biochemical tests used in this study

| Levels / Biochemical Test | Extremely Low Levels | Low Levels | Normal Levels | Borderline Levels | High Levels | Very High Levels |
|---|---|---|---|---|---|---|
| Serum Total Cholesterol (mg/dl) | - | <140 | <170 | 170-199 | ≥200 | - |
| Serum Triglycerides (mg/dl) | <10 | - | <150 | 150-199 | 200-499 | >500 |
| Serum HDL-Cholesterol(mg/dl) | - | - | >35 | - | - | - |
| Serum Very-Low-Density Lipoprotein (mg/dl) | | | 2-30 | | | |
| Serum Low- | - | - | <110 | 110-129 | >130 | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| density Lipoprotein (mg/dl) | | | | | | |
| Blood Urea Nitrogen (mg/dl) | - | - | 5-18 | - | - | - |
| Serum Uric Acid (mg/dl) | - | - | 2-6.5 | - | - | - |
| Serum Creatinine (mg/dl) | - | - | 0 -5 | - | - | - |

- **Ethical Consideration**

Informed consent was obtained from the children or their parents.

- **Statistical Analysis**

Statistical analysis was performed using SAS (Statistical Analysis System-version 9.0) [9].

- **Results**

Table (2): Serum biochemical mean levels for pediatric patients included in this study

| Biochemical Test | No. of cases & (%) | LowLevels (Mean±SE) | No. of cases & (%) | Normal Levels (Mean±SE) | No. of cases & (%) | Borderline Levels (Mean±SE) | No. of cases & (%) | High Levels (Mean±SE) |
|---|---|---|---|---|---|---|---|---|
| TC | 14 (77.78 %) | 93±9.25 | 2 (11.11% ) | 168±1 | 2 (11.11 %) | 178±1 | - | - |
| TGs | 2 (11.11 %) | 29±0.00 | 10 (55.56% ) | 98.60±4.40 | 2 (11.11 %) | 196±0.00 | 4 (22.22 %) | 317±59.47 |
| HDL-C | 18 (100% ) | 15.78±1.86 | - | - | - | - | - | - |
| LDL | 14 (77.78 %) | 48±4.33 | 4 (22.22% ) | 104±0.41 | - | - | - | - |
| VLDL | - | - | 12 (66.67% ) | 17.40±1.72 | - | - | 6 (33.33 %) | 55.33±9.09 |
| BUN | 2 (11.11 %) | 1.50±0.50 | 4 (22.22% ) | 12.00±2.94 | - | - | 12 (66.67 %) | 29.16±1.72 |
| Creatinine | - | - | 16 (88.89% ) | 0.19±0.02 | - | - | 2 (11.11 %) | 0.50±0.00 |
| UA | 2 (11.11 %) | 0.90±0.00 | 16 (88.89% ) | 3.35±0.20 | - | - | - | - |

NO.: number, (%): percentage, Mean±SE: Mean±Standard Error, TC: total cholesterol, TGs: triglycerides, HDL-C: high-density-lipoprotein cholesterol, LDL: low-density lipoprotein, VLDL: very-low-density lipoprotein, BUN: blood urea nitrogen, UA: uric acid

Of eighteen cases two (11.11%) showed low levels of total cholesterol, high-density-lipoprotein cholesterol, low-density-lipoprotein, normal levels of serum uric acid, serum triglycerides, very-low-density-lipoprotein, and high levels of blood urea nitrogen and serum creatinine. Another two cases (11.11%) showed low levels of serum total cholesterol, serum high-density-lipoprotein cholesterol, serum low-density-lipoprotein, normal levels of serum uric acid, serum creatinine, borderline levels of serum triglycerides, and high levels of blood urea nitrogen, and serum very-low-density-lipoprotein. Another two cases (11.11%) revealed low levels of serum high-density-lipoprotein, normal levels of serum total cholesterol, serum low-density-lipoprotein, serum uric acid, serum creatinine, and high levels of blood urea nitrogen, serum triglycerides, and serum very-low-density-lipoprotein. Two cases (11.11%) exhibited low serum high-density-lipoprotein, normal levels of serum triglycerides, serum low-density-lipoprotein, serum very-low-density-lipoprotein, borderline levels of serum total cholesterol, and high levels of blood urea nitrogen. Four cases (22.22%) demonstrated low levels of serum total cholesterol, serum high-density-lipoprotein, serum low-density-lipoprotein, and normal levels of serum triglycerides, serum very-low-density-lipoprotein, blood urea nitrogen, serum uric acid, and serum creatinine. Two cases (11.11%) showed low levels of serum total cholesterol, serum high-density-lipoprotein, serum low-density-lipoprotein, normal levels of serum triglycerides, serum very-low-density-lipoprotein, serum uric acid, serum creatinine, and high levels of blood urea nitrogen. Two cases (11.11%) showed low levels of serum total cholesterol, serum high-density-lipoprotein, serum low-density-lipoprotein, normal levels of serum uric acid, serum creatinine, and high levels of serum triglycerides, serum very-low-density-lipoprotein, and blood urea nitrogen. Finally two cases (11.11%) revealed low levels of serum total cholesterol, serum triglycerides, serum high-density-lipoprotein, serum low-density-lipoprotein, serum uric acid, blood urea nitrogen, and normal levels of serum creatinine, and serum very-low-density-lipoprotein.

Four (22.22%) out of eighteen children with acute lymphoblastic leukemia suffered from metabolic syndrome. Fourteen (77.78%) out of eighteen children with acute lymphoblastic leukemia suffered from the presence of renal leukemic disorders involvement.

**Discussion**

Childhood acute lymphoblastic leukemia (ALL) occurs more often in boys than in girls (male:female ratio, 55% to 45%) [10]. This is attributed to several genetic factors. The majority of children with acute lymphoblastic leukemia possess the precursor B cell type, which is positive for the CD10 and CD19 cell surface markers. About 15% of children with acute lymphoblastic leukemia will have the T cell (CD3 positive) phenotype [11]. These children tend to be male and older, with more frequent central nervous system (CNS) involvement and bulker illness, involving mediastinal masses. In the United Kingdom, girls with acute lymphoblastic leukemia now receive two years of treatment and boys three years, because boys have an increased risk of relapse which, to some degree, can be offset by a longer period of therapy [3].

Biochemical markers play an essential role in accurate diagnosis and also for assessing risk and adopting remedy that enhances clinical result [12]. National Institute of Health (NIH) 2001 identified a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological, pathologic processes, or pharmacologic responses to a therapeutic intervention [13].

Abnormal blood lipid levels have been correlated with different forms of malignancy including acute lymphoblastic leukemia (ALL) [6][14]. Halton *et al.* (2000) found altered blood lipid profile at the time of diagnosis of acute lymphoblastic leukemia comprised elevated triglycerides and reduced high-density-lipoprotein-cholesterol concentrations [14]. Considerable therapy-related changes in lipid profiles were recognized in children with acute

lymphoblastic leukemia during combination chemotherapy treatment for children with acute lymphoblastic leukemia [14]. Hypocholesterolemia has been noticed at diagnosis in patients with various forms of cancer. Previous studies have revealed an inverse relation between serum cholesterol and disease stage and mortality [15]. Although there was a trend for children with widespread tumors to have lower levels of cholesterol than those with localized tumors [14]. The explanation of low cholesterol levels before remedy is attributed to increase cholesterol synthesis and accumulation of cholesterol esters in tumor tissues and due to increase catabolism after therapy so it is regarded possible prognostic factor in malignancies as proposed in some studies [16]. Chemotherapy treatment can cause metabolic syndrome and among metabolic syndrome components hypertriglyceridemia and low-high-density-lipoprotein-cholesterol levels, i.e., dyslipidemia which is correlated with global cognitive impairment. Chemotherapy treatment exposure may result in neurocognitive impairment through direct or indirect effect on vascular function by causing metabolic syndrome [17].

Creatinine is a commonly used as measure of kidney function. The diagnosis of renal failure is often suspected when serum creatinine is greater than the upper limit of the normal interval. The higher values are noticed in leukemia. The most frequently determined clinical indices for predicting renal function depends upon level of urea in the serum. Increased blood urea nitrogen (BUN) is observed associated with kidney disease or failure. Decreased blood urea nitrogen (BUN) is seen in fluid excess, trauma, and malnutrition [12]. Malnutrition represents a major problem in children experiencing from cancer [18]. Methotrexate (MTX) functions by blocking the body's use of folic acid [19].

It is possible to have too little uric acid in blood which is a symptom of liver or kidney disease and it is a symptom of Fanconi syndrome, a disorder of the kidney tubules that blocks the absorption of substances such as glucose and uric acid. These substances are then passed in the urine instead. Fanconi anemia is one of the seldom inherited bone marrow failure

syndromes (IBMFS) with a very high cancer-predisposition, involving leukemia [20]. Li *et al.* (2015) demonstrated that folic acid therapy lowered uric acid concentrations in patients with mild to moderate hypertension [21]. These preliminary findings suppose that the acute response to the anticancer treatment may initiate chronic vascular dysfunction by the disruption of uric acid homeostasis [17]. The most adverse impact of methotrexate is kidney failure [19]. Acute renal failure has a wide variety of etiologies but when correlated with acute leukemia it is typically attributed to leukemic infiltration of the kidneys, septicemias, therapy-related side effects, metabolic changes arising from chemotherapy, and nephrotoxic drugs [22]. Acute renal failure in patients with hematological malignancies can present a principal clinical problem, and generally grows as a direct invasion of the hematological malignant cells, for example, obstruction of the ureters, or renal artery or vein thrombosis [23]. The kidney is the most common extrareticular and extrahematopoietic organ infiltrated by leukemia with infiltration seen in 60% to 90% of patients with hematologic malignancy [24]. Kidney dysfunction varies from asymptomatic to severe and demanding renal replacement therapy. In a series of 1200 autopsy cases, the prevalence of kidney infiltration was 54% in acute lymphoblastic leukemia (ALL). Kidney failure because of leukemic infiltration is rare. Glomerulopathies have been demonstrated in all hematologic malignancies [7].

- **Conclusion**

Acute lymphoblastic leukemia (ALL) incidence was more in boys than in girls. Acute lymphoblastic leukemia (ALL) children in most cases exhibited abnormal serum lipid profile parameters and abnormal serum renal function tests measured during treatment which attributed to hematologic malignancies of the disease and to chemotherapy toxicities and led to suffering of metabolic syndrome and/or kidney diseases and disorders in some pediatric patients. The toxicity of the treatment has clear adverse effects on the functions of the body

and studies have even shown that it may lead to death during treatment, so the specialist physician should be very careful in determining the dose of chemotherapy treatment, but the specialist physician may be held accountable and accounting in case of serious damage to health or death of patients.

- **References**

1- Clarke R, Bruell A, Bankhead C, Mitchell C, Phillips B, Thompson M. Clinical presentation of childhood leukemia: a systematic review and meta-analysis. Archives of Disease in Childhood. 2016; 101(10).

2- Banihashem A, Ghasemi A, Ghaemi N, Moazzen N Amirabadi A. Prevalence of transient hyperglycemia and diabetes mellitus in pediatric patients with acute leukemia. Iran J Ped Hematol Oncol. 2014; 4(1):5-10.

3- Mitchell C, Hall G, Clarke R. Acute leukemia in children: diagnosis and management. BMJ. 2009; 338:1491-1495.

4- Pui CH, Mullighan CG, Evans W, Ralling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood. 2012; 120(6): 1165-1174.

5- Perry M. Classical chemotherapy mechanisms, toxicities and the therapeutic window. Cancer Biology & Therapy. 2003; 2(4) Suppl 1: 52-54.

6- Hasan J. Lipid profiles in children with acute lymphoblastic leukemia on L-asparginase therapy. M J B U. 2010; 28(2):51-58.

7- Luciano R, Brewster U. Kidney involvement in leukemia and lymphoma. Advances in Chronic Kidney Disease. 2014; 21(1):27-35.

8- Hantoosh S, AL-Rubai H, Zageer D, AL-Musawi I. Association between age, body mass index, waist circumference, lipid profile parameters, and symptomatic bacterial urinary tract infection in Iraqi adult women. Asian J Pharm Clin Res. 2016; Vol. 9, Suppl. 3:57-60.

9- SAS. SAS/STAT. Users Guide for Personal Computer. Release 9.1. Cary, N.C., USA: SAS Institute, Inc.. 2010.

10- Hunger S, Muilighan C. Acute lymphoblastic leukemia in children. N ENG J MED. 2015; 373(16):1541-1552.

11- Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, Eden TO. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukemia: results of the UK Medical Research Council ALL97 randomized trial. Br J Haematol. 2005; 129:734-745.

12- Gowda S, Desai P, Kulkarni S, Hull V, Math A, Vernekar S. Markers of renal function tests. N Am J Med Sci. 2010; 2(4):170-173.

13- Ramachandran SV. Biomarkers of cardiovascular disease molecular basis and practical considerations. Circulation. 2006; 113:2335-2362.

14- Halton J, Nazir D, McQueen M, Barr R. Blood lipid profiles in children with acute lymphoblastic leukemia. Cancer. 1998; 83(2):379-384.

15- Williams RR, Sorlie PD, Feinleib M, McNamara PM, Kannal WB, Dawber TR. Cancer incidence by levels of cholesterol. JAMA. 1981; 245:247-252.

16- Umeki S. Decrease in serum cholesterol levels in advanced lung cancer. Respiration. 1993; 60(3):178-181.

17- Cheung Y, Edelmann M, Mulrooney D, Green D, Chemaitilly W, John N, Robison L, Hudson M, Krull K. Uric acid and neurocognitive function in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. Cancer Epidemiol Biomarkers Prev. 2016; 25(8):1259-1267.

18- Antillon F, de Maselli T, Gracia T, Rossi E, Sala A. Nutritional status of children during treatment for acute lymphoblastic leukemia in the Central American Pediatric Hematology Oncology Association: Preliminary data from Guatemala; Pediatric Blood. Cancer. 2008; 50:502-505.

19- Acqua T, Loucks R, Chang C, Brabetz B. A review of methotrexate for acute lymphoblastic leukemia. Student Research Conference. 2017.

20- Alter, B. Fanconi anemia and the development of leukemia. Best Pract Res Clin Haematol. 2014; 27(0):214-221.

21- Li H, Qin X, Xie D, Tang G, Zhang Y, Li J, Hou F, Wang X, Huo Y, Xu X. Effects of combined enalapril and folic acid therapy on the serum uric acid levels in hypertensive patients: a multicenter, randomized, double-blind, parallel-controlled clinical trial. Intern Med. 2015; 54(1):17-24.

22- Munker R, Hill U, Jehn U, Kolb HJ, Schalhorn A. Renal complications in acute leukemias. Haematologica. 1998; 83:416-421.

23- Sherief L, Azab S, Zakaria M, Kamal M, Aly A, Ali A, Alhady M. Renal presentation in pediatric acute leukemia. Medicine. 2015; 94(37):e1461.

24- Richmond J, Sherman RS, Diamond HD, Craver LF. Renal lesions associated with malignant lymphomas. Am J Med. 1962; 32:184-207.