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Evaluation of the role of interleukin-35 in patients with acute myeloid leukemia

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Abstract:

Background:

This study aimed to evaluate the expression of cytokine 35 in AML patients and to investigate its role as biomarkers. It was also observed that the activity of acute myeloid leukemia was associated with the levels of lipoproteins in the blood.

Hypocholesterolemia is a metabolic disorder that can be seen in chronic diseases and malignant tumors. In this study, we aimed to evaluate the characteristics of the lipid profile of patients diagnosed with malignant acute myeloid leukemia compared to a healthy group matched for age and sex with diagnosed patients.

Method:

45 patients whose diagnosis of malignant blood disease (AML) was confirmed were recruited and the expression of interleukin-35 was studied in AML patients. Their lipid profiles were also studied before treatment. 42 healthy individuals were selected as a healthy group and the levels of total cholesterol, triglycerides (TG), were compared. low-density lipoprotein (LDL) and high-density lipoprotein (HDL)

Results:

The results showed a significant increase in interleukin-35,triglycerides and low-density lipoprotein levels and a significant decrease in high-density lipoprotein and very low-density lipoprotein levels in serumof patients compared to the healthy group. The results also showed a significant positive correlation for interleukin-35 with the values of triglycerides and low-density lipoprotein. Also, it was found that the effect of the diseases on males is higher than on females in general, and it showed that the age group most affected in adult patients is from 40 to 80 years. The results also showed and explained the effect of chemotherapy on patients with acute myelogenous leukemia compared to patients who did not receive chemotherapy.

Conclusion:

An increase in the values of interleukin 35 was observed for patients compared to healthy subjects. This study also proved that interleukin 35 can identify AML disease in healthy people due to its excessive expression. An increase in triglycerides in the blood was also observed, as well as a decrease in the level of total cholesterol, as well as a decrease in the values of (HDL) and (VLDL) in malignant blood tumors and an increase in the values of (LDL), that is, it must be taken into account that there may be chronic diseases and malignant tumors that cause accidental hypocholesterolemia and hyperlipidemia. There is a need for many studies on this subject to determine the effects of dyslipidemia. Hematology on pathogenesis and prognosis of disease in hematologic malignancies

Introduction:

Acute myeloid leukemia (AML) is a clonal disorder affecting hematopoietic stem cells (HSCs) and is characterized by the expansion of abnormal myeloid cells. AML arises from leukemia stem cells (LSCs) and is characterized by the uncontrolled proliferation and dedifferentiation of myeloid progenitors [1]. Acute myeloid leukemia is an aggressive malignant disease of the myeloid line of white blood cells characterized by the rapid proliferation of abnormal cells that accumulate in the bone marrow (BM) and

interfere with the production of normal blood cells[2]. AML is distinguished from other blood-related disorders by the presence of at least 20% of myoblasts in the bone marrow [3].

It is worth noting that acute myeloid leukemia is the most common form of acute leukemia in adults. The average age at diagnosis is 68 years. It is a disease that affects the elderly in general. The prognosis for these patients is still poor, with a 5-year survival rate of less than 10%. At the moment [4]

Almost all AML diseases that can be observed clinically are caused by genetic mutations, deletions, and chromosome translocations. In addition, we mention that AML can be diagnosed by immune phenotyping, biopsy, cytochemistry, and imaging tests [5].

IL-35

Numerous studies have demonstrated the potential role of cytokines in the treatment of various types of malignant diseases, including acute myeloid leukemia (AML), based on their ability to activate immune responses. In this context, different lines of evidence indicate that cytotoxic effector cells such as T cells and natural killer cells It can participate in protecting patients with acute myeloid leukemia from relapse[6].

The mechanism of action of cytokines in the tumor microenvironment is investigated by examining their direct effects on cancer cells in addition to their indirect actions through the regulatory functions of immune cells that stimulate or inhibit tumor progression [7].

It should be noted that interleukin 35 (IL-35) was discovered in 2007 and was recently identified in the family of interleukin 12 (IL-12).

Which plays a major role in the suppressive function of regulatory T cells [8] is able to effectively suppress T cell proliferation. An increasing number of studies have indicated that interleukin-35 plays an important role in controlling immune-related disorders.

It was reported for the first time that this cytokine is produced exclusively by regulatory T cells (Tregs), and recent studies have shown that interleukin-35 (IL-35) can also be produced by dendritic cells and B cells. It has also been shown that interleukin can also be produced by tissues. human carcinogenesis Accordingly, interleukin-35 has recently appeared as a new regulator of immune responses, and it plays an important role in the development of autoimmune diseases and cancer. Interleukin-35 has been overexpressed in a variety of cancers and may exert its function on both anti-tumor immune responses as well as directly on cancer cells. As studies have shown that interleukin-35 has a vital and targeted role for treating cancer, meaning that interleukin-35 can directly affect the survival of cancer cells and because of its heterogeneous, non-covalent nature [9]

Therefore, the concentrations of interleukin-35 were regulated in patients diagnosed with acute myeloid leukemia, old and new, compared to healthy subjects, which indicated that interleukin-35 has a role in pathophysiology, and therefore the involvement of this interleukin in promoting tumor progression by increasing cancer cell proliferation, angiogenesis, metastasis, and immune suppression and exhaustion of T cells. [7].

lipoproteins:

Lipoproteins are large molecular complexes that transport hydrophobic lipids (mainly triglycerides, cholesterol and fat-soluble vitamins) through body fluids to and from tissues where they can be used as an energy source or stored. Accordingly, plasma lipoproteins are classified into five main types, based on their relative density:

Chylomicrons, very low density lipoproteins (VLDL), low-density lipoproteins (LDL),

Intermediate Density Lipoproteins (IDL), High-density lipoproteins (HDL)

In recent years, the attention of researchers has been attracted towards studying the role of lipids in different types of malignant tumors. Low levels of lipids in the blood have been observed. Attempts have been made to explain hypolipoproteinemia in patients with active acute leukemia. It has been shown that due to the high rate of expansion and metabolism in Cancer cells will decrease cholesterol and other intracellular lipids in these cells. A lot of studies have been done taking into consideration the abnormalities of blood lipids in acute leukemia. Most of them have shown lower total cholesterol and elevated triglycerides in leukemia patients[10].

In this study, we aimed to evaluate the lipid profile of patients diagnosed with malignant acute myeloid leukemia compared to a healthy group.
By measuring the expression of interleukin-35 in (AML) patients in different clinical stages of malignancy

Materials and methods:

45 patients over the age of 18 years, males and females, who were hospitalized in the hematology wards at Ibn Sina Teaching Hospital in Nineveh Governorate between 2022-2023 were diagnosed with acute myeloid leukemia (newly diagnosed patients who did not receive chemotherapy, as well as those who were previously diagnosed and receiving treatment). The patients were diagnosed by blood film and bone marrow examination conducted by hematologists at Ibn Sina Teaching Hospital in Nineveh Governorate After explaining and obtaining permission from each patient, blood was drawn and a blood serum sample was obtained after placing it in the centrifuge in the private hospital laboratory, and then freezing the samples until the necessary number of samples is completed to conduct experiments and measurements on them. Where the lipid profile was evaluated. Total cholesterol (TC), High-density lipoprotein (HDL) cholesterol, triglycerides (TG), and low-density lipoprotein (LDL) cholesterol were also evaluated. and very low-density lipoprotein (VLDL) cholesterol

Ethical considerations:

Written informed consent was acquired from each patient before his or her participation in this study. Patients' selection and study protocol conformed to the Helsinki ethical guidelines and were approved by the Institutional Ethics Committee In its session held at the Department of Health on 29/6/2022 on the research project No. (2022111)

statistical analysis:

The results were analyzed statistically using Excel, the name of the test we used, SPSS version 18, and the type of test was T-test [11].

Results:

Table 1: Levels of interleukin-35 and lipoproteins

Biochemical parameters	Groups(Mean ± Standard Deviation	
	Control	Patient
Interleukin 35	198.73±36.26	1240.66±189.33*
Triglyceride mmol/L)	143.17±28.99	162.5±32.87*
Total Cholesterol mg/dL)	180.22±35.32	128.57±29.73*
High-density lipoprotein(mg/dl	46.58±7.98	25.97±5.43*
Low-density lipoprotein(mg/dl	76.87±19.67	104.96±24.85*
ry low-density lipoprotein(mg/dl)	32.43±7.18	30.24±6.90*
Atherogenic index	4.015±1.08	5.90±1.33*

*Indicate that there a significant difference at p≤0.05

In Table 1, a significant increase of interleukin-35 was observed in the patientesgroup compared to the control group, that interleukin-35 is from the IL-12 family. Reducing the anti-tumor effect and contributing to T-cell dysfunction. Promotes proliferation of AML blasts, indicating that IL-35 has an important role in the pathogenesis of AML [12]. This increase was also associated with clinical stages of malignancies and an increased cytokine level is a feature of leukemia that may support blast survival and metastasis. IL-35 consists of two subunits EB13, P35 as a previous study found that both interleukin-35 subunits and other associated subunits The IL-12 family (P28, P40) in the bone marrow of adults from AML patients was upregulated higher compared to the healthy group, as well as the expression of mRNA, p28 was upregulated in the group of patients, where the high expression of P35, EB-13, mRNA indicated to an increase in IL-35 at the gene level in adult AML patients [13]

Also, a study showed that interleukin-35 stimulated the formation of tumor blood vessels due to the accumulation of CD11b + Grl + myeloid cells in the tumor microenvironment. It was found that

overexpression of IL-35 in human cancer cells caused cell cycle arrest and thus suppression of cell growth. Furthermore, the authors also observed that IL-35 stimulated the initiation of apoptosis.[14]

TG

It is also noted in Table 1 that there is a significant increase in triglycerides for patients compared to healthy subjects, and a study indicated that increased blood lipids may be associated with APL in addition to weight gain for three possible reasons, one of which is directly related to weight gain and the other is related to the fusion protein RARa/PML

The other involves the induction of abnormal fat metabolism in patients

Concerning the RARa/PML fusion protein, galectin-12 is selectively and overexpressed in APL cells and this over expression is mediated by PPARY (a group of protein nuclear receptors that act as transcription factors that regulate the expression of genes). RAR activation leads to activation. This leads to increased secretion and degradation of TG-rich particles, causing accumulation of TG in the plasma. Since the PML protein was initially described as a tumor suppressor, studies investigating PML focused mainly on its roles in apoptosis, cell cycle regulation, and tumorigenesis. A study also found that FOXO1 stimulates a transport protein. microsomal triglycerides and lipoprotein C-III, which leads to activation of particle aggregation and inhibition of lipoprotein lipase Both are a cause of increased plasma TG. Also, a study indicated that many leukemia patients are prone to hypertriglyceridemia due to lifestyle habits such as excessive nutrient intake, low levels of exercise, and relatively low levels of participation in social activities[15].

LDL and cholesterol

Also, it was noted in Table 1 a rise in LDL levels of patients compared to healthy controls, that AML cells with high LDL uptake have low sensitivity to the regulatory effect of sterols on the expression of LDL receptors, and that AML cells secrete a growth factor that stimulates the expression of the LDL receptor. It could be a stimulation paracrine or autocrine mediation by this factor is responsible for the elevated uptake of LDL in AML cells. AML patients have decreased bile acid production, which may lead to cholesterol malabsorption and hypocholesterolemia. Many drug-resistant leukemia cell lines have an elevated uptake of LDL, which supports the idea of using LDL as a drug transporter.[16]

HDL and VLDL

Also, it was shown in Table No. 1 a significant decrease in the levels of HDL and VLDL in patients compared to healthy subjects. Early studies showed that some fats were less in AML cells, given that it is now known that fats play an important role in sending cell signals and regulating homeostasis and are often disturbed in malignant tumors. Recently, AML patients have been reported to have lower HDL cholesterol than any healthy controls. AML cells may show increased lipid catabolism. A study showed that pharmacological inhibition of fatty acid oxidation (FAO) delays the proliferation of AML cells cultured on a feeder layer of stromal cells. argument. [17]

The delayed degradation of the patient's VLDL indicates that it is a poor substrate for lipoprotein lipase, since the RC fatty acid chain length and the degree of unsaturated fraction of the triglyceride esters greatly influence the activity. The high percentage of LPLac of fatty acid in the patient's VLDL indicates that the combination Abnormal triglycerides lead to slower breakdown. [18]

Table 2: Relationship between interleukin-35 and lipoproteins

Biochemical parameters	Negative	Positive
Triglyceride mmol/L)		0.6032
Total Cholesterol mg/dL)	-0.3022	
High-density lipoprotein(mg/dl	-0.2876	
l Low-density lipoprotein(mg/dl		0.5234
very low-density	-0.2276	

lipoprotein(mg/dl)		
Atherogenic index		0.501

In Table 2, a significant correlation was observed between the values of interleukin-35 and the values of triglycerides and low-density lipoprotein for patients compared to the healthy group. The expansion of adipose tissue due to excessive energy intake is associated with many changes in tissue function and composition. In particular, dysfunctional fats are characterized by inflammation, It is primarily driven by the infiltration of inflammatory CD11c-polarized macrophages that express M1. Once the tissue is infiltrated, M1 macrophages and adipocytes establish a complex reciprocal communication network that includes cytokines and chemokines. A study revealed that changes caused by obesity in adipose tissue increase the expression of cytokines, adipokines, metabolites, and extracellular vesicles that affect the behavior of cancer cells and promote tumor growth. Inflammatory cytokines promote cancer cell invasion and metastasis [19].

Table 3 Shows the impact of the disease on the age group 40-80 years

Biochemical parameters	**Age group (Mean ± Standard Deviation)**			
	Age group(16-40)		**Age group (40-80)**	
	Control (n=34)	**Patient (n=18)**	**Control (n=16)**	**Patient(n=26)**
Interleukin35	220.74±43.36	1194.75±201.33*	184.22±40.54	1251.065±217.6*
glyceride mmol/L)	126.24±30.43	187.18±37.68*	147.30±25.94	227.25±40.27*
Total Cholesterol mg/dL)	170.96±35.98	135.68±31.88*	205.66±42.28	143.59±32.63*
High-density ipoprotein(mg/dl	47.58±7.58	24.32±5.16*	43.85±12.31	26.99±6.42*
Low-density ipoprotein(mg/dl	74.53±17.79	100.83±21.29*	78.31±16.92	116.33±23.32*
very low-density poprotein(mg/dl)	37.25±9.65	24.72±7.22*	45.41±10. 87	29.47±8.13*
therogenic index	3.72±0.91	6.12±1.19*	4.34±1.32	7.17±1.34*

* Indicates that there is a significant difference at the probability level $p \leq 0.05$

In Table 3, the effect of the disease on the age group (40-80 years) is shown. It is evident that older patients are more likely to develop comorbidities and lower performance status than younger patients. Also, a previous study noted that when compared to younger adult patients, acute myeloid leukemia in the older stage is likely to precede the stage of myelodysplasia and often has unfavorable cytogenetics, as if a study proves that the percentage of patients increased Much of the increase in unfavorable cytogenetics is attributed to a marked increase in the proportion of patients who have lost part or all of chromosomes 5 or 7, a finding seen in 34% of Elderly adult patients, and the Medical Research Center also reported a significant increase in acute myelogenous leukemia and the incidence of complex abnormal karyotypes in addition to abnormalities of chromosome 5 in older individuals, as well as there may be an accumulation of non-clonal mutational events in stem cells Thus, the development of leukemia in old stem cells may inevitably lead to a malignant tumor with greater genetic instability and clonal diversity. The presence of fewer normal stem cells to compete with malignant clones and repopulation of the marrow after treatment may also contribute to the worse outcomes observed in Older patients as well as the aging microenvironment may also influence the nature of the disease in the elderly is an additional issue of interest [20].

Table 4 Effect of gender on levels of interleukin-35 and other lipoproteins in patients with acute myeloid leukemia

	Man group (Mean ± Standard Deviation)	
Biochemical parameters	Famale group	Male group

	Control (n=26)	Patient(n=18)	trol 30)	ent(n=22)
Interleukin 35	211.73±43.87	1199.56±198.55*	.97±40.34	0±210.56*
Triglyceride mmol/L)	121.42±32.38	170.88±37.89*	.20±35.67	.63±40.59*
Total Cholesterol mg/dL)	177.53±35.71	148.44±31.87*	.89±33.71	.83±30.08*
High-density lipoprotein(mg/dl	48.57±7.86	24.39±5.90*	5±7.31	09±6.28*
l Low-density lipoprotein(mg/dl	86,23±20.3	100.57±22.58	7±17.69	.17±28.24
very low-density lipoprotein(mg/dl)	33.97±9.95	24.30±7.24*	8±10.72	6±9.66*
Atherogenic index	3.77±0.78	5.61±1.43*	±1.23	2±1.64*

* Indicates that there was a significant difference at the probability level P≤0.05

In Table 4, the results showed a significant increase in the male group compared to females, as studies showed a positive effect of the female sex on the overall survival of patients with acute myelogenous leukemia compared to males. A previous study explained that the loss of the Y chromosome in male patients with A primary link factor for AML leads to a shorter OS. Another study found that RUNX1 mutations are more common in males with AML and that these mutations are significantly associated with lower overall survival compared to females. As these studies showed that some genetic mutations and chromosomal deletions of weak prognostic importance may occur more frequently in males. Also, a study found that males are worse with AML than females, as many preclinical data indicated a positive effect of androgens as well as estrogens on causing AML. Androgens may facilitate the entry of certain viruses into cells, and AML may be caused by retroviruses as well, if this is the case. In the case, one might assume that males are more severely affected with AML than females, due to androgens enhancing the activity of the causative agent, due to the interaction of sex hormones on leukemia cell lines. Models of human diseases, for example, are confusing in terms of androgensWell-conducted studies extend the life of leukemia-infected mice and inhibit the proliferation of some patient-derived myeloid leukemia cell lines among others. On the other hand, selective induction has been demonstratedFurthermore, gonadotropins secreted from the pituitary gland have been shown to stimulate migration, adhesion, and proliferation of many human myeloid leukemia cell lines. Also of interest is the fact that some testis-specific genes show a pattern of Sex-dependent expression in AML blast cells.[21]

Table 5 Shows the effect of chemotherapy on the levels of interleukin-35 and other lipoproteins

Biochemical parameters	ups(Mean ± Standard Deviation	
	patients before chemotherapy	patients after chemotherapy
Interleukin 35	14.26±215.23	72.51±190.67*
Triglyceride mmol/L)	9.69±38.69	6.61±34.87*
Total Cholesterol mg/dL)	9.64±32.24	2.17±36.76*
High-density lipoprotein(mg/dl	89±8.67	33±9.19*
Low-density lipoprotein(mg/dl	27±20.23	23±19.86*
ry low-density lipoprotein(mg/dl)	51±10.14	91±12.27*
Atherogenic index	6±1.76	4±1.60*

* Indicate there was a significant difference at the probability level p≤0.05

In Table 5, the results after chemotherapy showed a decrease in the level of interleukin for patients, as it is known that the deformation of blood cells affects the flow of blood vessels and contributes to vascular complications. Hematology drugs have the ability to modify these complications if they change the deformation Blood cells reported the effect of chemotherapy on the mechanical properties of leukemia cells. In a previous study, AML cells were incubated with standard induction chemotherapy, and the stiffness of individual cells was tracked by atomic force microscopy. Upon exposure to chemotherapy, the

stiffness of leukemia cells increased by approx. Two orders of magnitude, which reduced its passage through microfluidic channels, as the rate of hardness increase depends on the type of treatment

Chemotherapy. Hardening occurred with cell death for all cell types examined as a result. The results of a previous study revealed that cell death caused by chemotherapy increases the stiffness of leukemia cells, which may affect vascular flow in the microcirculation. This remarkable association between cell death and increased Cell sclerosis may have implications for patients with AML and leukemia. It has also been hypothesized that alteration of the biophysical properties of leukemia cells by chemotherapy agents is a possible link..Also, a previous study showed that chemotherapy-induced cell death is associated with dynamic changes. in the actin cytoskeleton (actin reorganization in leukemia cell lines) [22]

Conclusion:

From this study, we demonstrated that serum levels of interleukin-35 may serve as a highly sensitive and specific diagnostic marker in AML, meaning that this cytokine could be a cause of disease progression. Also, an increase in triglycerides in the blood was observed, as well as a decrease in the level of total cholesterol, as well as a decrease in (HDL) and (VLDL) values in malignant blood tumors and an increase in (LDL) values

That is, it must be taken into account that there may be chronic diseases and malignant tumors that cause occasional hypocholesterolemia and increased blood fats.

Many studies on this topic are needed to determine the effects of dyslipidemia on pathogenesis and prognosis in hematological malignancies.

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