The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 2982-2989

The Metabolic Syndrome in Survivors of Acute Lymphoblastic Leukemia of Pediatrics Patients at Zagazig University Hospitals

Abeer Atef Mohamed[1], Elhamy Rifky Abdelkhalek[1], Mohamed Refaat Beshir[1], Thoraya Hosny[2]
Departments of [1]Pediatrics and [2]Clinical Pathology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Abeer Atef Mohamed, **Mobile:** (+20)1098495077, **Email:** engisma3il1234@gmail.com

ABSTRACT

Background: Insulin resistance is considered to be of the major causes of the metabolic syndrome. There is a growing body of evidence showing that treatment for Acute Lymphoblastic Leukemia (ALL) has side effects.

Objective: The aim of the current work was to detect the prevalence of metabolic syndrome in survivors of childhood ALL to determine the relationship between metabolic syndrome and growth parameters in ALL survivors.

Patients and methods: This cross-sectional study included a total of twenty-four ALL survivors, attending at Pediatrics Hematology and Oncology Unit, Faculty of Medicine, Zagazig University Hospitals. Full clinical examination as well as laboratory investigations including estimation of serum insulin, total cholesterol, triglycerides, HDLc, LDLc, fasting plasma glucose were done for all patients.

Results: Obesity was significantly higher among metabolic syndrome (MS) cases. Patients with metabolic syndrome in ALL showed greater systolic and diastolic blood pressure than those without metabolic syndrome. It was found that children with metabolic syndrome had higher fasting plasma insulin levels and fasting plasma glucose levels than those without the syndrome. ALL patients who had metabolic syndrome had higher triglyceride levels than those without MS.

Conclusion: It could be concluded that ALL survivors are at an elevated risk for metabolic syndrome, as the increased risk for obesity and disturbed lipid profile in those patients.

Keywords: Metabolic Syndrome, Acute Lymphoblastic Leukemia, Survivors.

INTRODUCTION

One-fourth of all cases of juvenile cancer are attributed to hematological malignancies, the most frequent type of cancer in children **(1).** Using modern treatment methods, the 5-year survival rate for ALL has increased from practically zero in the 1950s to almost 80% **(2)**. As the number of ALL survivors grows, the negative effects of their therapy become more obvious. Surviving patients have been shown to have numerous endocrine/metabolic side effects, such as low growth hormone, gonadotropin, and thyroid hormone secretion, as well as metabolic syndrome **(3).**

The metabolic syndrome is a group of diseases all linked to insulin resistance that includes abdominal obesity, high blood sugar, high cholesterol, and high blood pressure **(4).** Children with obesity, metabolic syndrome, and type 2 diabetes are at greater risk for cardiovascular disease and diabetes mellitus, according to research **(5).** Metabolic syndrome in healthy children and adolescents with modified Adult Treatment Panel (ATP) III criteria ranges from 2.0-11.5 percent in developed nations **(5).**

30% of obese and overweight patients evaluated by Cruz *et al.* had the metabolic syndrome, according to their findings **(6).** It has long been hypothesized that obesity and its metabolic consequences such as insulin intolerance and dyslipidemia are caused by a growth hormone deficiency (GH). **Talvensaari *et al.*** found in their study that long-term survivors of childhood cancer had lower GH secretion, which was linked to metabolic issues **(7).**

The purpose of this study was to find out if metabolic syndrome is common among childhood ALL survivors and if so, what effect it has on growth parameters.

PATIENTS AND METHODS

This cross-sectional study included a total of twenty-four acute lymphoblastic leukemia survivors, attending at Pediatrics Hematology and Oncology Unit, Faculty of Medicine, Zagazig University Hospitals. This study was conducted between March 2020 to November 2020.

Acute myocardial infarction diagnosis was based on clinical symptoms, elevated cardiac biomarkers (CK, CK-MB, and Troponin), and 12-lead electrocardiogram results.

Inclusion Criteria:

- Both sexes below 18 years of age.
- Pediatric cancer survivors who were treated at Zagazig University's hematology/oncology unit using the regimen in place.
- ALL survivors for a minimum of 2 years after the end of chemotherapy provided that, they were below (age of 18 years) at time of diagnosis of having cancer.
- In remission.

Exclusion Criteria

- ALL survivors above the age of 18.
- Children affected by any illness other than cancer e.g., TB, Diabetes.
- Patients who had a relapse of leukemia.
- Children who had undergone bone marrow transplantation.
- Pre-existing cognitive, psychological or communication disorders in children.

Received: 26/1/2022
Accepted: 27/3/2022

- Study participation would be in jeopardy for children with unstable physical conditions, as judged by the healthcare staff.

***Ethical Consideration*:**

This study was ethically approved by Zagazig University's Research Ethics Committee. Written informed consent of all the participants' parents was obtained and submitted them to Zagazig University (ZU-IRB#6873). The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

All study groups underwent the following:

1. **History taking:** Full history was collected and protocols of treatment of ALL, as well as family history.
2. **Clinical examination:** General examinations, vital signs, in addition to anthropometric measures; weight (kg), height (m), BMI (kg/m^2) grouped by age and gender. Patients with a BMI of 25-30 were considered overweight. Patients with BMI a BMI >30 were considered obese. Waist circumference (cm) and blood pressure (mmHg) were measured.
3. **Laboratory investigations** including estimation of serum insulin, total cholesterol, triglycerides, HDLc, LDLc, fasting plasma glucose and CRP were done for all patients.

Following the revised version of ATP III [8]:

A kid was said to have metabolic syndrome if three or more of the following criteria were present: (1) A waist circumference over the 95th percentile for either gender or age indicated obesity. (2) Triglycerides readings more than 115 mg/dL. (3) A fasting blood glucose level above 110 mg/dl. (4) Blood pressure levels were considered hypertensive if they were greater than the 90th percentile for their age, gender, and height. (5) HDL-C levels of less than 40 mg/dL. (6) A single fasting insulin level of 24 mu/L or above and an assessment of insulin sensitivity using the expression FI were necessary to identify hyperinsulinemia.

Statistical analysis

The IBM SPSS software programme version 20.0 was used. The range (minimum and maximum), mean, standard deviation, median, and interquartile range were used to characterise quantitative data (IQR). In order to determine the significance of the acquired results, a 5-percent threshold was used. It was a Chi-square test. For categorical variables, chi-square correction for more than 20% of cells with anticipated count less than 5 was required, Student t-test: to calculate the quantities of data of normal distribution and to compare between two studied groups. P value < 0.05 was considered significant.

RESULTS

The mean age at time of diagnosis was 8.6±2.36 years (5- 15 years), and the mean age at remission was 11.34±2.55 years (Range 7-17 years). At presentation, the mean age of children was 13.58±2.39 years. The interval mean was 2.25±0.58 years, consanguinity was founded in 29.2%, and family history was founded in 16.7%. Regarding sex, we had 10 males (41.7% and 14 females (58.3%), the male: female ratio was 0.7 **(Table 1).**

Table (1): Socio-demographic data distribution among the studied group (N=24).

Age at diagnosis/years		**Mean± SD**	**8.6±2.36**
		Median (Range)	**8.0 (5-15)**
Age at remission/years		**Mean± SD**	**11.34±2.55**
		Median (Range)	**10.0 (7-17)**
Age at presentation/years		**Mean± SD**	**13.58±2.39**
		Median (Range)	**13.0 (9-18)**
Interval		**Mean± SD**	**2.25±0.58**
		Median (Range)	**3.0 (2-5)**
		N	**%**
Consanguinity	**-VE**	**17**	**70.8**
	+VE	**7**	**29.2**
Family history	**-VE**	**20**	**83.3**
	+VE	**4**	**16.7**
Sex	**Female**	**14**	**58.3**
	Male	**10**	**41.7**
	Total	**24**	**100.0**

Weight and height were distributed as **39.04±13.58 kg** and **139.91±10.53 cm** respectively and BMI and WC were distributed as **19.41±6.12 kg/m^2** and **72.6±15.04 cm** respectively, 13.0% of the studied group were above the 95.0% percentile **(Table 2).**

Table (2): Anthropometric measures distribution among the studied group (N=24).

Weight (kg)	**Mean± SD**	**39.04±13.58**	
	Median (Range)	**32.0 (23.0-88.0)**	
Height (cm)	**Mean± SD**	**139.91±10.53**	
	Median (Range)	**136.0 (123.0-161.0)**	
BMI (kg/m^2)	**Mean± SD**	**19.41±6.12**	
	Median (Range)	**17.55 (11.4-36.63)**	
WC (cm)	**Mean± SD**	**72.6±15.04**	
	Median (Range)	**70.0 (57.0-115.0)**	
		N	**%**
BMI according to 95.0% percentile	**Normal**	**20**	**83.3**
	High	**4**	**16.7**
WC according to 95.0% percentile	**Normal**	**20**	**83.3**
	High	**4**	**16.7**
	Total	**24**	**100.0**

12.5 % of the studied group had high blood pressure **(Table 3).**

Table (3): Blood pressure measures distribution among the studied group (N=24)

		N	**%**
Systolic Blood pressure (mmHg)		**Mean± SD**	**100.78±14.58**
Diastolic Blood pressure (mmHg)		**Mean± SD**	**71.95±7.49**
		N	**%**
Blood pressure according to 95.0% percentile	**Normal**	**21**	**87.5**
	High	**3**	**12.5**
	Total	**24**	**100.0**

Distribution of Laboratory parameters, 25.0% had high FBG, 16.7% had high LDL, only one case had high cholesterol and 29.1% had high TG and 12.5% had low HDL and 16.7% were positive regard CRP**, Table (4):**

Table (4): Laboratory parameters distribution among studied group (N=24)

FBG (mg/dl)	**Mean± SD**	**97.95±3.85**	
Insulin (uIU/ml)	**Mean± SD**	**2.28±0.44**	
LDL (mg/dl)	**Mean± SD**	**121.34±18.8**	
Cholesterol (mg/dl)	**Mean± SD**	**184.95±11.4**	
Triglycerides (mg/dl)	**Mean± SD**	**98.69±7.58**	
HDL/ Cholesterol (mg/dl)	**Mean± SD**	**48.6±6.22**	
CRP (mg/L)	**Mean± SD**	**8.69±1.95**	
		N	**%**
FPG (mg/dl)	**<110 (-VE)**	**18**	**75.0**
	>110 (+VE)	**6**	**25.0**
LDL (mg/dl)	**<160 (-VE)**	**20**	**83.3**
	>160 (+VE)	**4**	**16.7**
Cholesterol (mg/dl)	**<200 (-VE)**	**23**	**95.8**
	>200 (+VE)	**1**	**4.2**
Triglycerides (mg/dl)	**<115 (-VE)**	**17**	**70.9**
	>115 (+VE)	**7**	**29.1**
HDL (mg/dl)	**>40 (-VE)**	**21**	**87.5**
	<40 (+VE)	**3**	**12.5**
CRP (mg/L)	**Negative**	**20**	**83.3**
	Positive	**4**	**16.7**
	Total	**24**	**100.0**

Only 4 cases (16.7 %) had metabolic syndrome **(Figure 1).**

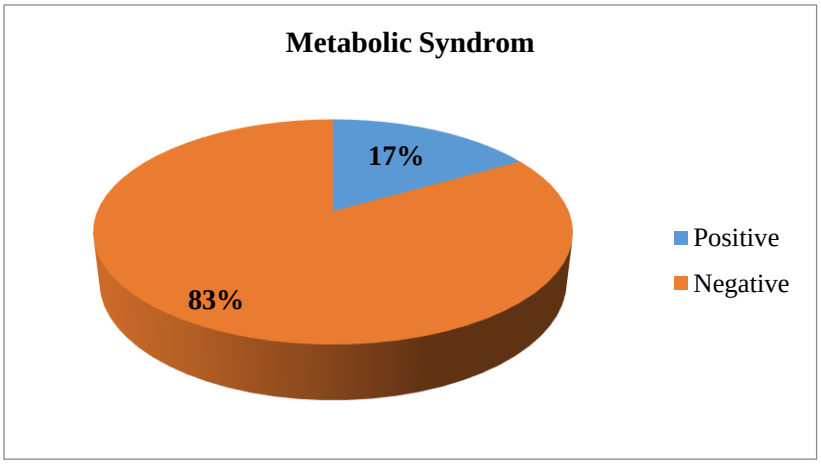

Figure (1): Metabolic syndrome distribution.

Weight, BMI, Waist, SBP, DBP were significantly higher among metabolic syndrome cases, and also Consanguinity, High BMI, WC, and BP were significantly associated with MS (**Table 5).**

Table (5): The relation between metabolic syndrome and basic demographic, anthropometric measures and blood pressure.

			Patients without MS	Patients with MS	t/ X^2	P
Age at Diagnosis (years)			**8.25±2.24**	**11.0±2.0**	**1.998**	**0.059**
Age at remission (years)			**10.74±3.11**	**13.01±4.12**	**1.741**	**0.082**
Age at presentation (years)			**12.95±4.18**	**15.16±4.96**	**1.857**	**0.071**
Interval (years)			**2.7±0.65**	**3.33±1.52**	**1.307**	**0.205**
Weight (kg)			**33.4±7.94**	**76.66±17.09**	**7.583**	**0.001****
Height (cm)			**138.3±10.07**	**150.66±7.5**	**2.026**	**0.056**
BMI (kg/m^2)			**17.3±2.38**	**33.42±4.5**	**9.787**	**0.001****
Waist Circumference (cm)			**67.75±6.96**	**105.0±14.79**	**7.477**	**0.001****
Systolic blood pressure (mmHg)			**96.0±6.99**	**132.66±11.01**	**7.925**	**0.001****
Diastolic blood pressure (mmHg)			**69.5±3.2**	**88.33±7.63**	**7.896**	**0.001****
Consanguinity	**-VE**	**N**	**16**	**1**		
		%	**80.0%**	**25.0%**		
	+VE	**N**	**4**	**3**	**4.88**	**0.027***
		%	**20.0%**	**75.0%**		
Family History	**-VE**	**N**	**17**	**3**		
		%	**85.0%**	**75.0%**		
	+VE	**N**	**3**	**1**	**0.61**	**0.43**
		%	**15.0%**	**25.0%**		
Gender	**Female**	**N**	**11**	**3**		
		%	**55.0%**	**75.0%**		
	Male	**N**	**9**	**1**	**0.47**	**0.31**
		%	**45.0%**	**25.0%**		
BMI	**Normal**	**N**	**20**	**0**		
		%	**100.0%**	**0.0%**		
	High	**N**	**0**	**4**	**23.0**	**0.001****
		%	**0.0%**	**100.0%**		
WC	**Normal**	**N**	**20**	**0**		
		%	**100.0%**	**0.0%**		
	High	**N**	**0**	**4**	**23.0**	**0.001****
		%	**0.0%**	**100.0%**		
BP	**Normal**	**N**	**20**	**1**		
		%	**100.0%**	**25.0%**		
	High	**N**	**0**	**3**	**16.7**	**0.001****
		%	**0.0%**	**75.0%**		

FBG, Insulin, LDL, Cholesterol, Triglycerides, and HDL Cholesterol were significantly higher among MS cases and also FBG abnormal LDL, Cholesterol, TG, HDL were significantly associated with MS **(Table 6).**

Table (6): the relation between metabolic syndrome and basic demographic, anthropometric measures and blood pressure.

			Patients without MS	Patients with MS	t/ X^2	P
FPG			**89.4±25.12**	**155.0±26.45**	**4.196**	**0.00****
Insulin(uIU/ml)			**2.15±0.28**	**3.16±0.31**	**5.702**	**0.00****
LDL(mg/dl)			**116.65±13.06**	**152.66±24.0**	**4.021**	**0.001****
Cholesterol(mg/dl)			**183.15±7.73**	**197.0±24.75**	**2.109**	**0.047***
Triglycerides(mg/dl)			**92.05±21.31**	**143.0±25.86**	**3.777**	**0.001****
HDL Cholesterol(mg/dl)			**49.8±5.10**	**40.66±8.32**	**2.685**	**0.014***
FPG	**Normal**	**N**	**18**	**0**		
		%	**90.0%**	**0.0%**		
	High	**N**	**2**	**4**	**13.2**	**0.001****
		%	**10.0%**	**100.0%**		
LDL	**Normal**	**N**	**19**	**1**		
		%	**95.0%**	**25.0%**		
	High	**N**	**1**	**3**	**10.36**	**0.003***
		%	**5.0%**	**75.0%**		
Cholesterol	**Normal**	**N**	**20**	**3**		
		%	**100.0%**	**75.0%**		
	High	**N**	**0**	**1**	**7.23**	**0.008***
		%	**0.0%**	**25.0%**		
TG	**Normal**	**N**	**17**	**0**		
		%	**85.0%**	**0.0%**		
	High	**N**	**3**	**4**	**10.85**	**0.002***
		%	**15.0%**	**100.0%**		
HDL	**Normal**	**N**	**19**	**2**		
		%	**95.0%**	**50.0%**		
	Low	**N**	**1**	**2**	**7.25**	**0.008***
		%	**5.0%**	**50.0%**		
CRP	**Negative**	**N**	**17**	**3**		
		%	**85.0%**	**75.0%**		
	Positive	**N**	**3**	**1**	**0.87**	**0.31**
		%	**15.0%**	**25.0%**		

DISCUSSION

Almost one-third of new occurrences of pediatric malignancy in Egypt are caused by juvenile acute lymphoblastic leukemia (ALL). The incidence of pediatric acute lymphoblastic leukemia (ALL) in Egypt's National Cancer Institute NCI, Cairo University is roughly four cases per 100,000 children per year. Men outnumber women by 2.3 to 1. 68.5 percent of the population is between the ages of 2 and 10 years. There has been an increase in the number of children who survive at least five years after being diagnosed with acute lymphoblastic leukemia (ALL). There is an elevated risk of long-term health problems for children who have survived cancer treatment, some of which present during or shortly after treatment, while others surface years after treatment [(8)].

More than half of the young Finnish cancer survivors (56 percent of whom had ALL) had multiple sclerosis, compared to zero in the control group [(9)].

This study showed that male to female ratio was 1:1.4, the percentage of male and female was 41.7% and 58.3% respectively.

This is contradicting with **Singh *et al.*** [(8)] who stated that men were (55.5 percent) and women were (45.5%). Males have a higher overall survival rate for surviving childhood.

In the current study, regarding consanguinity, it was founded in 29.2% of Several children were diagnosed with Acute Lymphoblastic Leukemia.

This result was in agreement with **Yahia *et al.*** [(9)] who found consanguinity (44%) in Egyptian Children with Acute Lymphoblastic Leukemia.

This study showed that family history was founded among 16.7% of children with Acute Lymphoblastic Leukemia.

The current findings were in line with those of the past **Zierhut *et al.*** [(10)] who stated that a correlation between ALL and a family history of cancer (39.6 percent).

Family history of cancer can provide insight into

the genetic (and/or shared environmental) basis of an illness. Several studies of ALL have examined the family history of the disease [11, 12].

In the present work, 16.7% of the studied group were above the 95.0% percentile (obese) according to BMI percentile.

The result was nearly agreed with **El-Rashedy *et al.*** [13], who studied the prevalence of obesity and overweight in a group of ALL survivors treated at Menoufia University, Egypt. A total of 35 pediatric survivors of ALL were analyzed. Both boys and females had their growth and WHO standard deviations shown. Having a BMI above the 95th percentile was considered obese. Obesity was more common in pediatric survivors of acute lymphoblastic leukemia (ALL) (45 percent).

Furthermore, research from the Childhood Cancer Survivor Study (CCSS) revealed that all-leukemia survivors (those who survived for at least five years after treatment) were more likely to be obese (31.7 percent) [14].

This study was in agreement with **Asner *et al.*** [15] and **Fang *et al.*** [16] who stated that pediatric ALL survivors had a much greater prevalence of obesity and a significantly higher BMI.

However, **Murphy *et al.*** [17] and **Aldhafiri *et al.*** [18] reported that ALL survivors patients had low weight and a significantly low body mass index and were considered undernourished.

Glucocorticoid medication, which can either enhance a patient's adiposity by inhibiting growth hormone release or develop leptin resistance, may be to blame for their obesity in ALL [19]. In other words, it's possible that the medication has an unintended side effect of increasing energy intake while decreasing energy expenditure during routine physical exercise [12].

This study showed that 12.5% of the studied group had elevated BP. This result was in line with **Ociepa *et al.*** [20] who set out to determine whether childhood ALL survivors had hypertension. Among childhood ALL survivors, raised blood pressure was shown to be as common as 37% of the time.

Current results were consistent with that of **Giordano *et al.*** [21] who found that patients with ALL had greater SBP and DBP than healthy individuals.

Acute lymphoblastic leukemia survivors have high blood pressure, however the cause of this condition is still a mystery. As a child's heart grows, it is thought to be particularly vulnerable to the harmful effects of chemotherapeutic drugs [20]. Administration of various cytostatic agents may directly or indirectly cause endothelial damage [22].

In the present work, 16.7% had high LDL, only one case had high cholesterol and 26.1% had high TG and 12.5% had low HDL.

This agreed with **Giordano *et al.*** [21] who stated that a statistically significant difference between ALL and the control group in terms of LDL-C and HDL-C levels. Endothelial dysfunction and the earliest atherosclerotic lesion can be triggered and progressed by dyslipidemia, especially in youngsters with risk factors [20].

This study showed that 16.7% of the studied group had metabolic syndrome.

This agreed with **Oudin *et al.*** [23] **"**from the French Leukemia in Childhood and Adolescents survivors' cohort" reported that 10.3 percent of patients had the metabolic syndrome.

This coincided with **Özdemir *et al.*** [24] how many people who survived acute lymphoblastic leukemia have MS (ALL). They observed that 2 (5.1%) of the survivors had MS, while 21 (42%) of the survivors were overweight/obese.

This is lower than **Zareifar *et al.*** [25] who in their research, which included 53 eligible participants, 21 (39.6 percent) got MS.

Aldhafiri and colleagues [18] Patients aged 9 and older had a prevalence of 7.1% and 5.4.4%, respectively, of MS, according to the IDF criteria and NCEP III-ATP guidelines.

Nineteen percent of overweight and obese survivors had MS by the NCEP III classification, and 7.1 percent had at least two components of MS [26].

By the IDF criteria, MS prevalence was 7.1% (3/42 survivors aged 10 years) while by the NCEP approach, it was 5.4% (3 out of 56)[27].

In the present work, there was no statistically significant difference between cases with metabolic syndrome and cases without metabolic syndrome regarding sex.

This is contradicting with **Reisi *et al.*** [28] who demonstrated that men were more likely than women to have metabolic syndrome (30% Vs 4.5%, p = 0.02).

The current study found that metabolic syndrome patients were considerably older at diagnosis and at follow-up.

This agreed with **Vernay *et al.*** [29] who found that the incidence of metabolic syndrome increases with age.

This was contradicting with **Zareifar *et al.*** [25] who analyzed data from the study reported that patients with and without multiple sclerosis had an average age of 9.77 years and a mean follow-up period of 40.3 and 42.3 months, respectively. However, when these numbers were compared, it appeared that the risk of MS development for ALL people receiving therapy may increase.

In the present work, obesity was significantly higher among MS cases. This agrees with **Karakurt *et al.*** [30] who found that ALL survivors have a high risk for obesity and MS.

Research in Iran found that 25 percent of ALL survivors were obese, and nearly three-quarters of those patients developed multiple sclerosis, which is similar to our findings [28].

These findings were consistent with **Kim *et al.*** [21] the researchers who found that obese and overweight children had a greater prevalence of

metabolic syndrome.

SBP and DBP were considerably greater in patients with metabolic syndrome compared to patients without metabolic syndrome, according to this study.

This agrees with **Reisi *et al.*** [28] who found that the SBP and DBP were considerably higher in cases with metabolic syndrome than in cases of metabolic syndrome without metabolic syndrome.

This is similar to the study conducted by **Oudin *et al.*** [23] who found patients with metabolic syndrome in ALL patients had higher systolic blood pressure compared without metabolic syndrome.

Cases with metabolic syndrome had insulin levels substantially higher than those without metabolic syndrome.

In **Friedman *et al.*** [32] study**,** they discovered that childhood cancer survivors had greater fasting plasma insulin levels than a control group.

Also, **Reisi *et al.*** [28] study, Children with metabolic syndrome had a considerably higher fasting plasma insulin level than those without the condition. Survivors of acute lymphoblastic leukemia (ALL) may have hyperinsulinemia as a result of obesity and the hepatotoxic effects of treatment. Diabetes can be exacerbated by obesity, which is a substantial independent risk factor. Nearly three-quarters of the metabolic syndrome survivors we studied had insulin resistance, and all of them were obese[33]**.**

Fasting blood glucose levels were considerably higher in patients with metabolic syndrome compared to patients without metabolic syndrome, according to a new study.

This agrees with **DeBoer *et al.*** [34] who found that patients with metabolic syndrome in ALL had more elevated fasting glucose levels.

Patients with metabolic syndrome had greater triglycerides than patients without metabolic syndrome. This agrees with **Oudin *et al.*** [23] who found Patients with metabolic syndrome in ALL patients had increased triglyceride levels compared without metabolic syndrome in ALL patients.

This agrees also with **Morel *et al.*** [35] who found that the prevalence of hypertriglyceridemia is frequently reported in ALL survivors who had MS.

Interestingly, **DeBoer *et al.*** [34] Patients with metabolic syndrome in ALL exhibited higher triglycerides and fasting glucose levels, as well as increased blood pressure, according to the study. They may be developing the metabolic syndrome, which is associated with an increased risk of cardiovascular disease in the general population.

In our study, LDL, Cholesterol, were significantly higher among MS cases while HDL is decreased. This agrees with **Morel and colleagues** [35] the prevalence of dyslipidemia, which includes high triglyceride and LDL cholesterol and low HDL cholesterol, was found to be 50% in childhood ALL survivors.

CONCLUSION

It could be concluded that ALL survivors are at an elevated risk for metabolic syndrome, as the increased risk for obesity and disturbed lipid profile in those patients.

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