# Serum endocan and endothelial dysfunction in childhood acute lymphoblastic leukemia survivors: a tertiary center experience

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## Abstract

**Background:** An increased risk of cardiovascular complications is reported in survivors of childhood acute lymphoblastic leukemia (ALL). Early identification of impaired vascular health may allow for early interventions to improve outcomes.

**Aim:** The study was conducted to assess the endothelial dysfunction in ALL survivors using a new marker, serum endocan, and measurement of the mean common carotid arteries intima media thickness (cIMT).

**Methods:** A case-control study was conducted on 100 childhood ALL survivors (aged 6–18 years), with 80 healthy age and sex-matched children as a control group. Lipid profile, hepatitis markers, and serum ferritin where measured, in addition to the measurement of serum endocan. and cIMT by B-mode high-resolution ultrasonography for all study participants.

**Results:** Triglycerides, total cholesterol, post prandial glucose, and serum ferritin were significantly higher in ALL survivors than controls ($p < 0.05$). Dyslipidemia was detected in 6% of ALL survivors. ALL survivors showed statistically higher serum endocan levels ($470.41 \pm 556.1$ ng/l, *versus*, $225.94 \pm 185.2$ ng/l, respectively) and increased cIMT levels compared with the control group ($0.650 \pm 0.129$ mm *versus* $0.320 \pm 0.095$ mm, respectively) $p < 0.05$. Serum endocan was positively correlated with cIMT and blood cholesterol.

**Conclusions:** The survivors of childhood ALL demonstrated an elevated level of serum endocan and increased cIMT. These can be used as predictors of endothelial dysfunction, and, as a consequence, the risk of developing premature atherosclerosis.

*Keywords:* acute lymphoblastic leukemia, carotid artery intima media thickness, childhood, endocan, endothelial dysfunction, survivors

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## Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. The introduction of multimodal risk-adjusted treatment and the improvement of tailored therapy achieved by collaborative studies has resulted in a growing number of childhood ALL survivors.[1]

Increased survival, is, however, accompanied by health problems due to chemo/radiotherapy sequelae and lifestyle changes.[2] Cancer survivors have a much higher risk of non-cancer-related mortality compared with age-standardized mortality rates. Cardiovascular disease (CVD) is the most common cause of this mortality.[3]

The development of CVD is initially characterized by endothelial damage, which is an early feature of atherosclerosis and vascular diseases in humans.[4] The role of endothelial dysfunction in the

development of CVD in ALL and other cancers has also been of interest. Several methods have been used to assess endothelial dysfunction. The average of the common carotid arteries intima media thickness (cIMT) is the gold-standard for evaluation of subclinical atherosclerosis.[5]

The endothelial-specific molecule, serum endocan, has been proposed as a vascular endothelial dysfunction biomarker which can contribute to endothelium-dependent pathological disorders.[6] Experimental evidence shows that endocan plays a role in regulating major physiological processes such as cell adhesion in chronic inflammatory disorders.[7]

There are few studies evaluating endothelial dysfunction in childhood ALL survivors using both serum biomarkers and measurements of cIMT.[8] In this study, we aimed to assess the endothelial dysfunction in ALL survivors using a new marker, serum endocan, in addition to the measurement of cIMT.

### Subjects and methods

This case-control study was conducted in 100 ALL survivors. These were 54 females and 46 males at Pediatric Oncology Clinic, Zagazig University Hospital, during routine follow-up visits in the period from May 2018 to June 2019. Thier ages range from 6 to 18 years. All patients had finished chemotherapy at least 24 months before enrollment in the study, and were treated according to a ALL Protocol adopted from CCG protocol. Patients who were on chemotherapy or radiotherapy, who demonstrated clinical evidence of CVD, or who had undergone bone marrow transplantation were excluded from the study. The control group comprised 80 sex- and age-matched healthy children. The study protocol was approved by the research and ethical committee of the Faculty of Medicine, Zagazig University, IRB approval number 3602. Written informed consent was taken from the parents or guardians of each participant.

All patients were subjected to a full medical history, with a special emphasis on a history of cardiovascular diseases; in addition, a thorough clinical examination included weight, height, body mass index (BMI), and vital signs, including heart rate and blood pressure (BP) monitoring. BP was measured 3 times at 2 min intervals in the right arm after 5 min of quiet sitting using a Dinamap automated sphygmomanometer. A mean systolic and diastolic reading was calculated from the 3 readings. Mean blood pressures were compared with age and height-matched data from the National Heart, Lung, and Blood Institute to calculate the systolic and diastolic percentile.[9]

Routine laboratory assessments included complete blood count, liver, and kidney function in addition to the measuerment of blood glucose by the glucose oxidase method.

Fasting blood samples were analyzed according to routine procedures for lipid profile, including total plasma cholesterol, triglycerides. High-density-lipoprotein (HDL) cholesterol levels were measured using an enzymatic colorimetric method with the Olympus AU 600 autoanalyzer using reagent from Olympus Diagnostics GmbH (Hamburg, Germany). Low-density-lipoprotein (LDL) cholesterol levels were calculated by the Friedewald formula. Hypercholesterolemia was defined as a fasting LDL cholesterol $\geq 3.4$ mmol/l and or the use of cholesterol-lowering medication.[10]

Serum endocan levels were analyzed in the serum samples by using an ELISA kit (Catalog no: EK0762, Boster Biological Technology Co., Ltd., USA) in accordance with kit procedures.

Vascular structure was determined by measurement of the common cIMT using GE Logiq P7 ultrasound machine, using a probe at high resolution 7.5 MHz.

The cIMT value considered for statistical analysis was the average of the right and left common carotid arteries measurements. The cIMT was measured using longitudinal images of the common carotid arteries, in which the leading edges of the lumen intima and media adventitia interfaces (the double line pattern) of the arterial wall represent intima-media-complex.

The cIMT measurements were always performed in the arterial segment devoid of atherosclerotic plaque. Atherosclerotic plaque is defined as a local cIMT of 1.5 mm or as a focal thickness encroaching into the arterial lumen of greater than 0.5 mm or 50% of the cIMT surrounding area.[11] Intima-media measurements were completed on each patient and control subject by a single observer to avoid interobserver variability.

Multivariate linear regression analysis was performed to determine the role of cardiovascular risk factors on the levels of serum endocan level and on cIMT.

### Statistical analysis

The data were analyzed using SPSS version 16.0 (SPSS for Windows, Version 16.0. Chicago, SPSS Inc). Continuous quantitative variables were expressed as the mean ± SD and median (range). A comparison of several groups' median was conducted using the Kruskal–Wallis test. Comparisons between two groups were conducted using the Mann–Whitney U test. Categorical qualitative variables were expressed as both absolute frequencies and relative (number and percentage) values. The comparison of several groups' median was conducted using the Chi–squared test. Odds ratios (ORs) and 95% confidence intervals (CIs) were used for risk assessement. The results were considered statistically significant when the $p$-value was $\leqslant 0.05$.

### Results

One hundred pediatric ALL survivors were included in this study. Their mean age was $10.75 \pm 2.87$ years (ranged from 6 to 18 years); 54% were females while 46% were males. The mean ± SD of follow up was $3.55 \pm 1.6$ years; the median follow up was 4 years with a range of 2–10 years.

The mean BMI was $18.04 \pm 2.86$ kg/m$^2$, with a range of 11.73–22.96 kg/m$^2$, with no significant difference between patients and controls ($p > 0.05$). No significant differences were found between ALL survivors and controls regarding systolic (SBP) and diastolic blood pressure (DBP). Eighty patients were diagnosed as B-lineage ALL and twenty patients had T-lineage ALL. The Mean ± SD of the cumulative dose of doxorubicin was $180.5 \pm 79.77$ mg/m$^2$ while the median (range) was 175 (100–405) mg/m$^2$.

ALL survivors had significantly higher serum cholesterol than controls (151.66 mg/dl *versus* 124.87 mg/dl; $p < 0.05$). Moreover, they had significantly higher serum triglyceride than controls (130.96 mg/dl *versus* 120.79 mg/dl; $p < 0.05$). HDL-cholesterol and LDL-cholesterol levels were lower in ALL survivors compared with controls; however, the

difference did not reach a statistically significant level, see Table 1.

The mean cIMT was significantly higher among ALL survivors than controls ($0.650 \pm 0.129$ mm, *versus* $0.320 \pm 0.095$ mm, respectively; $p < 0.05$). The mean serum endocran level was significantly higher in ALL survivors compared with controls ($470.41 \pm 556.1$ ng/l, *versus*, $225.94 \pm 185.2$ ng/l; $p < 0.05$).

Correlation analysis showed that serum endocan level was positively correlated with cIMT and DBP; in contrast, it was negatively correlated with HDL-cholesterol level ($p < 0.05$). On the other hand, there was no relationship between the serum endocan level and either demographic data, anthropometric data, or biochemical parameters, see Table 2.

Moreover, cIMT demonstrated a positive correlation with cholesterol, ($r = 0.447$, $p < 0.05$), LDL-cholesterol ($r = 0.331$, $p < 0.05$) and triglyceride ($r = 0.523$, $p < 0.05$) levels, see Table 3. No significant relationships were found between cIMT and any of the demographic data, anthropometric data, vital signs, or biochemical parameters.

In multivariate analysis, the following cardiovascular risk factors remained significant when correlating with serum endocan levels: SBP ($p = 0.022$), cholesterol ($p = 0.011$), HDL-cholesterol ($p = 0.002$), and LDL-cholesterol ($p = 0.005$), see Table 4.

In contrast, when these confounding factors were entered in a multivariate model to determine the association of these risk factors with carotid intima media, they lost significance; see Table 5.

### Discussion

Improved cure rates for childhood cancers have led to a growing population of survivors who are at risk for long-term complications from their disease and chemotherapy treatment; included within this is a high-risk for accelerated atherosclerosis.[12]

The available research on impaired vascular function among childhood ALL survivors is scarce. Most studies have primarily focused on adult survivors of cancer.[8,13] We conducted this study to evaluate endothelial dysfunction among childhood ALL survivors using the biomarker serum

**Table 1.** Clinical and biochemical characteristics of ALL survivors and controls.

| Demographic data | ALL survivors | | Controls | | p-value |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| Sex | | | | | |
| Male | 46 | 46 | 40 | 50 | 0.762 |
| Female | 54 | 54 | 40 | 50 | |
| Age (years) | | | | | |
| Mean ± SD | 10.75 ± 2.87 | | 9.67 ± 2.74 | | 0.07 |
| Range | 6–18 | | 5–14 | | |
| Weight (kg) | | | | | |
| Mean ± SD | 36.7 ± 9.52 | | 36.10 ± 12.21 | | 0.827 |
| Range | 15–55 | | 20–56 | | |
| Height (cm) | | | | | |
| Mean ± SD | 141.84 ± 15.75 | | 138.20 ± 13.99 | | 0.371 |
| Range | 110–165 | | 118–170 | | |
| BMI (kg/m$^2$) | | | | | |
| Mean ± SD | 18.04 ± 2.86 | | 18.41 ± 4 | | 0.67 |
| Range | 11.73–22.96 | | 13.22–26.63 | | |
| SBP | | | | | |
| Mean ± SD | 106 ± 6.22 | | 105 ± 5.12 | | 0.527 |
| Range | 95–120 | | 95–110 | | |
| DBP | | | | | |
| Mean ± SD | 63.7 ± 5.13 | | 63.25 ± 3.72 | | 0.723 |
| Range | 60–80 | | 60–70 | | |
| Cholesterol | | | | | |
| Mean ± SD | 151.66 ± 15.66 | | 124.87 ± 26.13 | | 0.000* |
| Range | 120–190 | | 35.5–140 | | |
| HDL-cholesterol | | | | | |
| Mean ± SD | 58.88 ± 13.30 | | 61.38 ± 10.83 | | 0.417 |
| Range | 15.4–68 | | 33–81 | | |
| LDL-cholesterol | | | | | |
| Mean ± SD | 56.24 ± 25.70 | | 67.44 ± 19.94 | | 0.055 |

*(Continued)*

**Table 1.** (Continued)

| Demographic data | ALL survivors | | Controls | | p-value |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| Range | 33.70–158 | | 21–110 | | |
| Triglycerides | | | | | |
| Mean ± SD | 130.96 ± 9.98 | | 120.79 ± 18.62 | | 0.004* |
| Range | 112–150 | | 66.7–140 | | |

*Statistically significant at $p < 0.05$.
ALL, acute lymphoblastic leukemia; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

**Table 2.** Correlation between endocan level and cardiovascular risk factors of ALL survivors.

| | Pearson's correlation | |
|---|---|---|
| | R-value | p-value |
| Age at diagnosis (years) endocan level | 0.084 | 0.560 |
| BMI endocan level | 0.144 | 0.318 |
| SBP endocan level | 0.279 | 0.050 |
| DBP endocan level | 0.314 | 0.026* |
| Cholesterol endocan level | 0.042 | 0.770 |
| HDL-cholesterol endocan level | 0.280 | 0.049* |
| LDL-cholesterol endocan level | 0.148 | 0.305 |
| Triglyceride endocan level | 0.038 | 0.793 |
| Fasting blood glucose endocan level | 0.198 | 0.169 |

*Statistically significant at $p < 0.05$.
ALL, acute lymphoblastic leukemia; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

endocan, in addition to assessing cIMT to predict early atherosclerotic lesions.

This study demonstrates that children surviving ALL are at an increased risk for impaired vascular function, manifested by increased cIMT and serum endocan.

Link *et al.*[14] found a significant increase in cIMT measurements at different sites in the carotid artery in 29 ALL survivors compared with controls. In addition, Chow *et al.*[13] examined the short term (2–60 months) effects of chemotherapy on endothelial function in 14 children and young adults age 7–21 years with a variety of diagnoses. They reported a significant decline in endothelial dependent dilation among patients compared with the control group. Dengel *et al.*[8] reported that leukemia survivors had a significant decline in endothelial function when measured by ultrasound imaging during brachial artery flow-mediated dilation. In addition, the authors reported that ALL survivors had reduced carotid compliance and distensibility indicating arterial stiffness.

A recent study published by Sadurska *et al.*[15] found that cIMT significantly increased in ALL

**Table 3.** Correlation between carotid intima media and lipid profile in ALL survivors.

| | Pearson's correlation | |
|---|---|---|
| | *R*-value | *p*-value |
| Age at diagnosis(years) cIMT | 0.015 | 0.916 |
| BMI cIMT | 0.182 | 0.205 |
| SBP cIMT | 0.052 | 0.720 |
| DBP cIMT | 0.147 | 0.310 |
| Cholesterol cIMT | 0.447 | 0.001* |
| HDL-cholesterol cIMT | 0.062 | 0.668 |
| LDL-cholesterol cIMT | 0.331 | 0.019* |
| Triglycerides cIMT | 0.523 | 0.000* |
| Fasting blood glucose cIMT | 0.078 | 0.590 |

*Statistically significant at $p < 0.05$.
ALL, acute lymphoblastic leukemia; BMI, body mass index; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

**Table 4.** Multivariate linear regression model to determine the role of cardiovascular risk factors of ALL survivors on endocan level.

| Cardiovascular risk factors | Coefficient | *p*-value | Overall significance of model |
|---|---|---|---|
| Age at diagnosis (years) | −75.8 | 0.500 | < 0.001* |
| BMI | 124.6 | 0.140 | |
| SBP | 157.7 | 0.022* | |
| DBP | 143.17 | 0.077 | |
| Cholesterol | 1.1 | 0.011* | |
| HDL-cholesterol | 100.3 | 0.002* | |
| LDL-cholesterol | 88.9 | 0.005* | |
| Fasting blood glucose | 202.9 | 0.065 | |
| Triglycerides | 6.110 | 0.757 | |

*Statistically significant at $p < 0.05$.
ALL, acute lymphoblastic leukemia; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

survivors in comparison with healthy controls. Chemotherapy for ALL has been reported to cause endothelial damage.[16]

The exact mechanism by which chemotherapy causes endothelial dysfunction is unknown; both *in vivo* and *in vitro* studies have shown that doxorubicin, one of the important chemotheraputic agents used in the treatment of several cancer including ALL. Doxorubicin causes apoptosis of vascular endothelial cells.[17,18] Apoptosis has been associated with reduced endothelial cell density and a decrease in the endothelial function as determined by acetylcholine infusion.[19] It has been speculated

**Table 5.** Multivariate linear regression model to determine role of cardiovascular risk factors of ALL survivors on carotid intima media.

| Cardiovascular risk factors | Coefficient | *p*-value | Overall significance of model |
|---|---|---|---|
| Age at diagnosis (years) | 0.005 | 0.782 | 0.001* |
| BMI | 0.023 | 0.071 | |
| SBP | −0.013 | 0.226 | |
| DBP | −0.023 | 0.060 | |
| Cholesterol | < 0.001 | 0.994 | |
| HDL-cholesterol | −0.002 | 0.604 | |
| LDL-cholesterol | −0.007 | 0.157 | |
| Fasting blood glucose | 0.009 | 0.597 | |
| Triglycerides | −0.004 | 0.192 | |

*Statistically significant at $p < 0.05$.
ALL, acute lymphoblastic leukemia; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

that chemotherapy-induced changes in the vessel wall could lead to permanent deficits in endothelial function.[8] Methotrexate, one of the most commonly used anti-leukemic agents, is associated with the elevation of plasma homocysteine.[20] It is believed that hyperhomocysteinemia leads to subsequent endothelial injury and endothelial dysfunction.[21]

Another explanation for the difference in endothelial function between ALL survivors and controls could be a difference in cardiovascular risk factors. The possible risk factors include obesity and metabolic syndrome. In our study, we found no statistically significant difference between ALL survivors and controls regarding body weight and BMI. Dengel *et al.*[8] reported similar findings, but they found childhood cancer survivors had significantly higher body fat than healthy controls. Several studies have reported an increased prevalence of overweight or obese cancer survivors.[22–24]

Previous researchers have suggested that an abnormal lipid profile, especially triglycerides, contributes to endothelial dysfunction, which was further hypothesized for adult survivors of childhood ALL.[8]

Nevertheless, dyslipidemia was documented in our study population. The higher values of triglycerides and cholesterol, in addition to the lower values of HDL- and LDL-cholestrol detected in ALL survivors as compared with controls, represent two of the criteria to define the metabolic syndrome in accordance with the International Diabetes Federation definition. Even more importantly, they are major risk factors for the onset of atherosclerosis and fatty liver.[25] Similarly, Giordano *et al.*,[26] reported in their study in childhood ALL survivors that ALL patients showed metabolic alteration even though obesity was not documented. ALL patients had significantly higher levels of triglycerides, in addition to total and LDL-cholesterol levels, compared with controls. HDL-cholesterol levels were lower in ALL patients compared with controls. Dyslipidemia has to be considered as a trigger for the initiation and progression of endothelial dysfunction and the earliest atherosclerotic lesions, especially in children with risk factors.[25]

Previous researchers have suggested that abnormal lipid profiles; in particular triglycerides, contribute to endothelial dysfunction. This has been further hypothesized for adult survivors of childhood ALL.[8,27,28]

The possible mechanisms of dyslipidemia in childhood cancer survivors include radiation therapy with or without growth hormone deficiency and corticosteroid therapy.[14]

Some of the chemotherapy medications may also cause serum lipid abnormalities. Cyclophosphamide causes impaired vascular lipoprotein lipase and hypertriglyceridemia in animal models.[29,30] Asparaginase is associated with a risk of pancreatitis and very high triglycerides levels.[31]

However, Jarvala *et al.*[4] found that triglycerides and other cardiovascular risk factors did not differ in ALL survivors compared with survivors. This suggests that differences in endothelial dysfunction may be due to ALL therapy itself.

The endothelium is an important regulator of vasodilation, inflammation, and enhanced thrombotic activity in addition to its important role in the development of hypertension, atherosclerosis, and CVD.[32,33]

Several studies have highlighted the role of serum endocan as one biomarker OF vascular endothelial dysfunction.[6,34,35] Endocan is synthesized and secreted by activated vascular endothelial cells and may play a role in regulating cell adhesion. Increased serum endocan levels in patients with subclinical or severe atherosclerosis are associated with endothelial activation and dysfunction.[6,36] Fortunately, our study is the first to examine the role of serum endocane as a marker of endothelial dysfunction in ALL survivors. In addition, we also examined the relationship between serum endocane and cIMT.

In our study, there is a significant increase in serum endocan in ALL survivors compared with the control group. Furthermore, there was a significant positive correlation between serum endocan levels and cIMT as well as the mean diastolic blood pressure. In addition, several authors have reported a positive correlation between serum endocan and cIMT in different diseases.[6,37–40]

## Conclusions

In conclusion, survivors of childhood ALL in the examined group demonstrated elevated concentrations of the new biomarker (serum endocan) and increased cIMT values, compared with controls, which may confirm the occurrence of endothelial dysfunction.

Serum endocan levels may provide more relevant information regarding the development and progression of atherosclerosis in subjects treated for childhood ALL.

A large prospective study aiming to follow up endothelial function in ALL survivors is urgently needed to provide aggressive management of risk factors and appropriate lifestyle interventions. Ultimately, this will improve cardiac-related mortality in this population.

## Limitation of the Study

The main limitation of our study was the relatively small sample size. Sample size was not calculated prior to study; instead, we recruited all those eligible to participate in the study over a period of one year.

Another limitation was the relatively short duration of follow-up. A longer follow-up is required to correlate the observed data with a higher incidence of CVD in long-term survivors from ALL. Moreover, we missed initial data at presentation (lipid profile and cIMT).

## Novelty Statement

Serum endocan is a new diagnostic biomarker for endothelial dysfunction. Few studies have evaluated its value in endothelial dysfunction in a small number of childhood ALL survivors. In the current study, we assessed its role *versus* the gold standard; measurement of the mean cIMT.

In this study we demonstrated endothelial dysfunction in survivors of childhood ALL. Serum endocan correlated well with the gold standard. cIMT, where both were elevated confirming endothelial dysfunction. Serum endocan can be used as a predictor of endothelial dysfunction, and, consequently, the risk of developing premature atherosclerosis.

## Authors' contributions

LS: set the idea of the study and designed the study.

LS, ER, NK: reviewed literature, drafted the manuscript.

LS: critically analyzed the data.

GK, MZ, WM: data collection and performed data analysis.

OG, GM, HS: performed the laboratory tests related to the work.

IL, BS: performed the radiological tests related to the work.

All authors reviewed and approved the manuscript for final publication.

## Ethical approval and consent to participate
This study was approved by the research and ethical committees of the participating hospitals. All parents of enrolled children signed written informed consent for participation of their children in the current study.

## Consent for publication
All parents of enrolled children signed written informed consent for publication of this current study.

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## Availability of data and materials
All data and materials related to the study are included in the current manuscript.

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