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Original Article

Serum Adiponectin and Resistin Levels in de Novo and Relapsed Acute Lymphoblastic Leukemia Children Patients

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Abstract

Background: Adipose tissue secretes a large number of adipocytokines such as leptin, resistin, and adiponectin. Many of these hormones and cytokines are altered in obese individuals and may lead to disruption of the normal balance between cell proliferation, differentiation, and apoptosis. The aim of our work was to investigate the disturbance of secretion of adiponectin and resistin in de novo and relapsed acute lymphoblastic leukemia (ALL) in Egyptian children and determine whether adiponectin and resistin are implicated in increased risk relapse compared to healthy individuals.

Methods: Measurements of adiponectin and resistin were performed at diagnosis, in 32 patients with de novo ALL aged 3 to 18 years (mean 9.8 y) and 19 children with relapsed ALL aged 5 to 17 (mean 9.9 yr). 10 apparently healthy children with matched age and sex were used as controls.

Results: Mean adiponectin levels were low ($P < 0.05$), whereas mean resistin levels were high ($P<0.05$) at diagnosis and relapsed ALL (compared to healthy controls). A significant decrease of adiponectin levels was observed in relapsed ALL compared to de novo ALL. In contrast resistin was significantly increased in relapsed ALL compared to de novo patients. Adiponectin in ALL subjects inversely correlated with resistin level ($r = -0.51$, $P < 0.001$).

Conclusion: Low adiponectin and high resistin level at diagnosis suggest their implication in ALL pathogenesis and may serve as potential clinically significant diagnostic markers to detect leukemic relapse.

Keywords: Acute lymphoblastic leukemia, Adiponectin, Resistin

Introduction

Leukemias strike males and females in all ages and represent about one-third of childhood cancers. The most common type is childhood acute lymphoblastic leukemia (also called acute lymphocytic leukemia or ALL). ALL is a fast growing cancer with an overproduction of abnormal immature white blood cells, called lymphoblasts or leukemic blasts. This type of leukemia usually affects children ages 1 - 10 years (1). Relapsed, recurrence leukemia can occur during therapy or after completion of treatment and represents the main cause for treatment failure (2).

In Egypt about four new cases of ALL per 100.000 children are diagnosed each year in the National Cancer Institute (NCI), Cairo University. It comprises about 30% of all pediatric malignancies and 70% of pediatric leukemia. In children between the ages of 2 and 10 ALL is the predominant form of leukemia with higher rates in males than females (3, 4).

Several studies confirm that altered secretion of the adipocytokines from adipose tissue is believed to increase the risk of various types of cancer. Leptin and adiponectin, adipocyte secreted hormones, are well-studied factors relation to malignancies. Leptin was found to be inversely associated with risk of chronic lymphocytic leukemia (CLL), however, no significant association between CLL and adiponectin (5). Among the pathophysiological mechanisms underlying the association between obesity and cancers are insulin resistance (6), low-grade systemic inflammation (7), and altered secretion of adipokines (8), though the mechanisms may differ between different types of cancer. The link between insulin resistance and cancer may be related to the compensatory hyperinsulinemia. High concentration of circulating insulin may signal cells to proliferate through different mechanisms either by directly signaling growth, or by increasing the levels of other more potent growth factors. Insulin-like growth factors (IGF) is one of the growth factors that have an important pathogenic role in cancers through promoting cell proliferation and decreasing apoptosis (6).

Adiponectin, a hormone exclusively derived from adipocyte and secreted in high concentration into the blood (9). Previous studies postulated an inverse relation between serum levels of adiponectin and the risk of breast, endometrial, prostate, colorectal, kidney cancer and acute myeloid leukemia (AML) in children (10-15).

Accumulating evidence suggests that adiponectin may have an important protective role in carcinogenesis through exerting an insulin-sensitizing (16), anti-inflammatory (17), and antiangiogenic effect (18). Moreover, it exerts direct anti-carcinogenic effects through the AMP-activated protein kinase (AMPK) system. The mechanism seems to involve cell cycle arrest through the up-regulation of p53 and p21 (19). Independent of AMPK activation, adiponectin decreases the production of reactive oxygen species (ROS) (20), which appears to cause decreased AMPK activation (21) leading to inhibition of cell proliferation.

Resistin is a member of cysteine – rich protein family. In human it is produced only in small amount by white adipose tissue (22) while relatively high levels of resistin mRNA are detectable in circulating mononuclear cells (23). Resistin may have an adiposity-independent role in breast carcinogenesis (24) and may be a good biomarker of gastric cancer (25). It also has a role in the relation between inflammation and insulin resistance (26). Although, it is well documented that adipose tissue dysfunction increases the risk of some types of cancer such as that of the colon, breast and prostate, only few studies have elucidated whether disturbances of adipocytokines are linked to ALL. Therefore, in our present study we evaluated the disturbance of adipose tissue hormonal secretion (adiponectin and resistin) in de novo and relapsed acute lymphoblastic leukemia among Egyptian children, determined whether this disturbance is implicated in recurrence of acute lymphoblastic leukemia, and investigated the correlation between adiponectin and resistin in both groups.

Materials and Methods

This study was conducted on 51 children patients suffering from ALL (29 males and 22 females); they were selected from Medical Oncology Center, Mansoura University. All subjects provided informed consent and the study protocol was approved by the Ethics Committee of the Mansoura University Hospitals. Patients were classified into:

De novo acute lymphoblastic leukemia group (de novo ALL): included 32 patients (18 male and 14 female) with age range (3 –18 years).

Relapsed acute lymphoblastic leukemia group (relapsed ALL): included 19 patients (11male and 8 female) with age range (5 - 17 years). Besides 10 healthy children (6 male and 4 female) with age range (5 - 18 years), served as a healthy control group.

Collection of the blood samples

Fasting blood samples were collected from patients and healthy controls. Samples were divided into two aliquots, the first contained; whole blood (with anticoagulant) for complete blood count and the other aliquot was allowed to clot at room temperature and the sera were separated by centrifugation at 3000 r.p.m. for 10 min. After separation the sera were stored at -70° C till assay.
All patients and control were subjected to:

- Complete blood count was done by Coulter counter (Cell Dyn 3500) and examination of Lishman or Wright-stained peripheral blood smears.
- Determination of serum Adiponectin level by Human Adiponectin/Acrp30 Quantikine ELISA Kit, which is Quantikine Colorimetric Sandwich ELISAs, catalog no. DRP300, purchased from R&D Systems, Inc. 614McKinley Place NE Minneapolis, MN55413 USA.
- Determination of serum resistin level by the Quantikine Human Resistin kit which is a quantitative sandwich enzyme immunoassay technique purchased from R&D Systems, Inc. 614McKinley Place NE Minneapolis, MN55413 USA (27).

Statistical analysis

Statistical analysis was carried out using SPSS 14.0 for Windows software. Variables were expressed as mean ± standard deviation (SD). Differences between groups were analyzed by an unpaired *t* test. The correlation coefficients between two variable parameters were determined by Pearson correlation test. Significance was assigned for *P* values as significant where $P < 0.05$.

Results

Complete blood counts data of studied participants are summarized and compared in Table 1. In both ALL groups (de novo and relapsed), red blood cell counts were significantly lower, whilst white blood cell counts were significantly higher compared with healthy controls ($P<0.05$). Additionally, relapsed ALL group has significant increase in white blood cell counts when compared with de novo ALL group ($P < 0.05$). Adiponectin and resistin levels of studied groups are expressed in mean ± S.D and shown in Table 2.

Table 1: General features and complete blood counts of different studied groups, data are expressed in mean ± S.D

	Control group	De Novo ALL	Relapsed ALL
No. of patients	10	32	19
Sex (M/F)	6/4	18/14	11/8
Age (year)	11.9±4.629	9.781±4.0698	9.947±3.597
Hemoglobin (g/dl)	12.27±1.385	10.0375±1.0188*	9.357±1.702*
RBCs (10^6//l)	4.17± 0.383	3.413±0.583*	3.236±0.578*
Leukocytes (10^3/l)	7.45±1.768	28.565±10.075*	33.821±10.417*$^{\phi}$
Platelets (10^3/l)	200.025±20.279	100.627±40.684*	100.475±50.845*

*significant difference ($P<0.05$) compared to control group
ϕ significant difference ($P<0.05$) compared to de novo ALL group

Table 2: Serum adiponectin levels in control group, de novo ALL and relapsed ALL. Data expressed as mean ± S.D

	Control group	De Novo ALL	Relapsed ALL
Adiponectin(ng/ml)	11.91±2.234	10.0313±1.934*	7.7316±1.083*$^{\phi}$
Resistin(ng/ml)	4.92±1.55	7.353±1.582*	9.784±1.656*$^{\phi}$

*significant difference ($P<0.05$) compared to control group
ϕ significant difference ($P<0.05$) compared to de novo ALL group

ALL groups (de novo and relapsed) showed significantly lower adiponectin levels 10.031 ± 1.934 and 7.731 ±1.083 (ng/ml) respectively compared with healthy controls 11.91 ± 2.234 ng/ml ($P < 0.05$), while exhibited significantly higher resistin levels 7.353 ±1.582 and 9.784 ± 1.656 (ng/ml) respectively in comparison with healthy controls 4.92± 1.55 (ng/ml). Moreover, a significant increase in resistin levels was observed in relapsed ALL group when compared with de novo ALL group ($P < 0.05$).

Pearson coefficient correlation showed inverse correlation between adiponectin and resistin levels in ALL groups (r = -0.51, $P < 0.001$, Fig. 1).

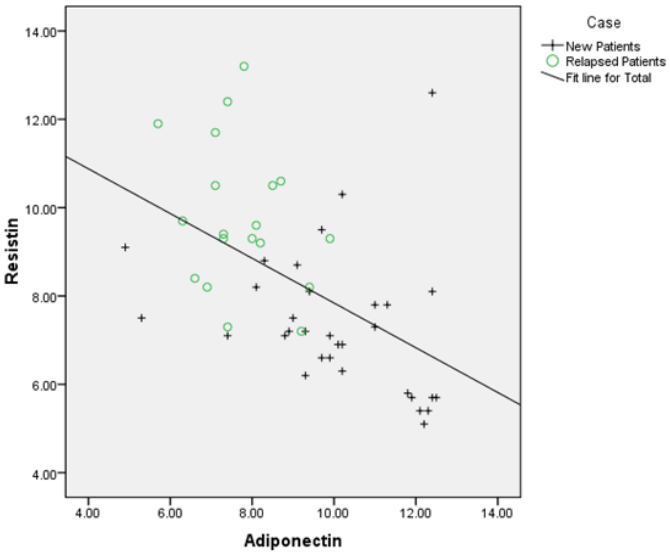

Fig. 1: Correlation between serum resistin and adiponectin levels in ALL patients (de novo & relapsed ALL)

Discussion

The current study addressed the hypothesis that dysregulation in adipocytokines has a potential role in carcinogenesis and cancer progression focusing on leukemia. The aim of this study was to evaluate adiponectin and resistin concentration in newly diagnosed and relapsed ALL children and whether the disturbance in those two adipokines is implicated in ALL relapse. We have identified that the level of adiponectin is decreased in de novo ALL children compared to healthy controls, its level also decreased in relapsed ALL compared to both healthy controls and de novo ALL patients. These findings are in agreement with the results obtained by Moschovi et al. (28) who confirmed the low plasma level of adiponectin at ALL diagnosis compared with controls. In an in vitro study (29) the authors have investigated the functions of adiponectin in haematopoiesis and found that adiponectin predominantly inhibits proliferation of myeloid cell lines, and induces apoptosis in myelomonocytic leukemia lines, but did not suppress proliferation of erythroid or lymphoid cell lines. This hormone has also been inversely associated with both adult forms of cancer that have been epidemiologically investigated, namely breast cancer (11, 30) and endometrial cancer (12, 31).

We also reported a decreased level of adiponectin in relapsed ALL compared to both healthy controls and de novo ALL patients. A possible explanation could be due to a direct effect of adipose tissue dysfunction on the leukemia itself, perhaps mediated by adiponectin and other adipocyte- derived hormones. Alternatively; it may be an adipocyte interaction with leukemia cells to impair chemotherapy of ALL as suggested earlier (32).

Adiponectin is a direct angiogenesis inhibitor that induces apoptosis in activated endothelial cells (18, 33). Similarly, decreased adiponectin level facilitates the development of cancer by preventing pathologic cell mitosis (34, 35). Additionally, adiponectin level is attributed to the further increase in production of inflammatory cytokines in the cachectic stage by cancer cell itself (36, 37). Leukemia per se causes a more intensive inflammatory process than malignancies of solid organs, with proinflammatory cytokines further suppressing adiponectin (28).

Our study also demonstrated that resistin level in Egyptian children with ALL was high in de novo compared to healthy controls, also in relapsed ALL resistin level was high compared to controls and de novo ALL. Resistin in ALL subjects was inversely correlated with adiponectin level (r = –0.51, $P<0.001$). These results would appear to align with results obtained by Moschovi et al. (28)

who showed that in children with ALL, resistin levels are high at diagnosis compared with controls. Moreover, correlations from their study suggested that leukemia related to inflammatory cytokines release serum lipids may stimulate leptin and resistin secretion and vice versa. Changes in adipose tissue and metabolism occur in multiple myeloma (MM), acute leukemia, and chronic lymphocytic leukemia (CLL) (38). They studied resistin level in serum of patients with hematologic malignancies and they found that resistin level was significantly higher in lymphoma patients than in chronic lymphocytic leukemia (CLL), acute leukemia and control groups.

Although only a few studies have analyzed resistin in patients with malignancies, the general properties of resistin could contribute to tumorigenesis (39). Resistin has been also shown to induce production of vascular endothelial growth factor receptor (VEGFR) and the formation of endothelial cell tubes (40). Moreover, resistin is seen mainly as an inflammatory factor (41) which is associated with TNF-α and IL-6, and may up regulate several adhesion molecules and cytokines (26).

Conclusion

We reported decreased adiponectin and elevated resistin levels in association with de novo and relapsed ALL in Egyptian children. This finding suggests the implication of both hormones in ALL pathogenesis which might be useful prognostic markers in guiding the treatment of ALL in the future.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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